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Advances in diagnosing and treating new-onset refractory status epilepticus (NORSE)

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Advances in diagnosing and treating new-onset refractory status epilepticus (NORSE)

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Editorial: Advances in diagnosing and treating new-onset refractory status epilepticus (NORSE)

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Editorial on the Research Topic
Advances in diagnosing and treating new-onset refractory status epilepticus (NORSE)

New-onset refractory status epilepticus (NORSE) is a rare but devastating condition describing a group of diseases and disorders that are characterized by *de novo* onset of uncontrollable seizures, so called refractory status epilepticus (RSE), without an identifiable acute or active structural, toxic, or metabolic cause (1). Febrile infection-related epilepsy syndrome (FIRES) is a subcategory of NORSE with the addition of prior febrile infection between 2 weeks and 24 h before the onset of RSE (1, 2).

Reliable numbers regarding its incidence are lacking, but occurrence has been estimated to be ~1–2 per 100,000 person years (3, 4). In case an etiology is found, such as autoimmune encephalitis, treatment can be directed at the underlying pathophysiology. However, therapeutic effects are often not sufficient, and in ~75% of patients, the underlying etiology remains unknown (5–7). Although plenty of studies have been published on NORSE and FIRES over the last decades, no high-level evidence exists on which to base diagnostic and treatment recommendations. Given the very poor prognosis with a mortality rate of 10–30% and severe sequelae in most surviving patients (8), this lack of evidence is troublesome. Hence, this Research Topic aimed at collecting novel research and findings on the matter in order to ease the effort of systematically assessing the body of evidence in future.

A detailed description of the clinical, etiological, electrophysiological neuroimaging and outcomes of new onset status epilepticus (SE) cases and their differences from SE developing in epileptic patients is reported by Benaiteau et al.. As NORSE/FIRES identifies a "clinical presentation," it could be sustained by many different etiologies, and more than 200 uncommon disorders have been described so far (9). Inflammatory/autoimmune and paraneoplastic causes reach up to 40% of all etiologies representing the most relevant group followed by infective unusual causes that represents up to 10%, while genetic, metabolic, and toxic causes are considered rare (10). However, assessing the genetic landscape of

NORSE/FIRES is an expanding field parallel to the improvement of the genetic tests and to the increase the knowledge of pathogenic variants related to epilepsy and SE in general.

Among genetic causes, mitochondrial diseases could play an important role both in children and adults. Astner-Rohracher et al. reported on a new pathogenic variant in FASTK2D presenting as NORSE in a young patient thus extending the phenotypical spectrum of FASTKD2-related mitochondrial disease. Overall, the role of genetic etiologies is evaluated by deCampo et al. in a single-center retrospective study on 25 children with FIRES over a 10-year period. None of the tests resulted as positive/causative, thus confirming the rarity of the genetic etiology. Nevertheless, the authors underline also the important aspect of the heterogenicity of the tests, thus giving a focus and a critical view on new diagnostic perspectives (deCampo et al.).

The diagnostic workup in general is a central aspect in NORSE/FIRES. In fact, it is known that after an extensive diagnostic work-up, ∼50% of cases remain with unknown etiology, thus representing "cryptogenic NORSE." Standardized and shared diagnostic algorithms are the basis for improving the management and trying to reduce the number of cryptogenic cases. In this view, recently, international consensus-based recommendations have been published by the International NORSE consensus group (11, 12). Sheikh and Hirsch reported and evaluated the recommendations for the in-hospital management of NORSE/FIRES patients in specialized centers, while an algorithm for the rapid identification and transfer of NORSE/FIRES patients to the most appropriate specialized center to ensure a rapid and appropriate treatment is discussed by Vinette et al..

Correct and rapid diagnoses are key in order to plan the appropriate treatment. As described by deCampo et al., there is now a trend toward increased use of immunomodulatory agents next to steroids and intravenous immunoglobulins as the most common treatment. It is important to note, however, that multiple agents are available and even more could be repurposed, making pre-clinical research immanent to further treatment options. To this end, the role of immunotherapy is addressed in the study of Cerovic et al., who developed an *in vitro* model of the mouse hippocampal/temporal cortex where epileptiform activity and drug-resistant seizures are exacerbated by neuroinflammation induction. In this model, the application of two immunomodulatory agents - anti-IL6 and anti-IL1—delayed the onset of epileptiform events and strongly reduced the ASM-resistant epileptiform activity. Their validated model highlights the therapeutic potential of anti-inflammatory agents in NORSE/FIRES (Cerovic et al.).

In addition to drug therapy, Sheikh and Hirsch mentioned the efficacy of ketogenic diet after early treatment with first-line immunotherapy. This notion is also supported by Nabbout et al., presenting a study of 16 patients treated with ketogenic diet. Next to their patients, the authors present a systematic meta-analysis of the published case, concluding high efficacy of ketogenic diet in patients with general RSE (with half the patients experiencing RSE cessation in 7 days) and also patients with NORSE in particular (Nabbout et al.).

In addition to medical drugs and ketogenic diet, neuromodulation offers an exciting possibility to treat NORSE as outlined by Jindal et al., Ritter and Selway, and Stavropoulos et al.. As pointed out by Ritter and Selway, vagal nerve stimulation (VNS) can be a viable treatment option, not only aiding status cessation but also enabling physicians to wean of anesthesia. Based on a systematic literature assessment as well as on two own cases, they describe several beneficial effects of VNS treatment in the chronic but notably also the acute phase of NORSE (Ritter and Selway). Of interest, one of the mentioned cases with VNS implantation from the same group is described in more detail by Jindal et al. further revealing that VNS can be safely used in a pregnant patient with NORSE. On a broader spectrum, the usage of VNS as well as electroconvulsive therapy and deep brain stimulation is investigated as part of a systematic literature review by Stavropoulos et al., showing that any of these could add to a successful treatment of NORSE and FIRES.

One of the ascribed benefits of neuromodulation techniques, such as VNS, is the lasting treatment of refractory epilepsy after cessation of status (Stavropoulos et al.). As revealed in a systematic review by Taraschenko et al., ∼41% of adult and 57% of children with NORSE will experience refractory seizure occurrence after the acute phase of NORSE. Together with cognitive disabilities and psychiatric disorders arising at the chronic state, these results highlight the importance of the topic at hand (Taraschenko et al.). Data on FIRES presented by Shrestha et al. as well as Shi et al. is even more troublesome. Shrestha et al. analyzed a multi-center case series of FIRES patients, demonstrating severe neurocognitive impairment even when patients received state of the art therapy. Shi et al. showed a similar severe outcome in a retrospective single-center study of 11 adult patients with cryptogenic FIRES. Four of them died in hospital. Among long-term survivors, another patient died and even though all survivors reached functional independence, they developed drug-resistant epilepsy or remote recurrent SE mostly associated with permanent damage of hippocampus and needing anti-seizure medications polytherapy.

With these last contributions stressing the aforementioned severity of NORSE/FIRES, this Research Topic aimed at collecting evidence to guide treatment and future research in this field. The major importance of early recognition of the syndrome itself and the identification of possible etiologies becomes apparent throughout all of the contributions. While genetic testing might yield important information regarding causes for NORSE, common multidisciplinary approaches toward a clear diagnosis at specialized centers is of immanent importance in order to enable rapid and accurate treatment initiation, that ultimately could prevent fatal or severe outcomes.

Author contributions

AT: Writing—original draft, Writing—review and editing. GG: Writing—original draft, Writing—review and editing. NG: Writing—review and editing. MS: Writing—review and editing. RW: Supervision, Writing—review and editing. JJ: Writing—review and editing.

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Conflict of interest

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Long-term outcomes of adult cryptogenic febrile infection–related epilepsy syndrome (FIRES)

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Background: Cryptogenic febrile infection-related epilepsy syndrome (FIRES) is a rare but catastrophic encephalopathic condition. We aimed to investigate the long-term outcome in adult cryptogenic FIRES.

Methods: This was a retrospective study based on the prospective database in the neuro-intensive care unit of a tertiary hospital in China. Consecutive adult patients with cryptogenic FIRES between July 2007 to December 2021 were included. Long-term outcomes included function independence, the development of drug-resistant epilepsy (DRE), remote recurrent status epilepticus (SE), anti-seizure medications (ASMs), and changes in the brain Magnetic Resonance Imaging (MRI).

Results: A total of 11 adult patients with cryptogenic FIRES were identified from 270 patients with SE. Four (36%) patients died in the hospital, with three of them withdrawing treatments, and one patient died 12 months after discharge. After the follow-up ranging from 12 to 112 months, 6 (55%) patients were still alive, and all of them achieved functional independence [modified Rankin Scale (mRS) 0-3]. 45% (5/11) patients developed DRE, 18% (2/11) had remote recurrent SE, and 55% (6/11) were on polytherapy with ASMs at the last follow-up. Most of the patients with initial normal or abnormal MRI had abnormalities in the hippocampus at follow-up, and most of the other MRI abnormalities found in the acute stage disappeared over time.

Conclusion: The outcome of adult cryptogenic FIRES is daunting. More than one-third of patients die in the hospital. Survivors of cryptogenic FIRES may regain functional independence, but they usually develop DRE and receive polytherapy of ASMs for a long time.

KEYWORDS

febrile infection-related epilepsy syndrome, adult, new-onset refractory status epilepticus, refractory status epilepticus, long-term outcome, case series

1. Introduction

Febrile infection-related epilepsy syndrome (FIRES) is a rare but devastating encephalopathic condition. FIRES was first reported in children as "acute encephalitis with refractory, repetitive partial seizures" (AERRPS), and the term FIRES was first used by van Baalen et al. to report 22 children with prolonged or recurrent seizures after fever (1, 2). In recent years, FIRES has also been reported in adults, and this term has been used to emphasize the acute *de novo* presentation of refractory status epilepticus (RSE) without clearly identifiable acute or active causes (3–5). The clinical characteristics of FIRES are similar to those of new-onset refractory status epilepticus (NORSE), and both are thought to involve fulminant neurogenic inflammation in the brain. Based on the latest consensus, FIRES is considered a subcategory of NORSE that requires a prior febrile infection starting between 2 weeks and 24 h before the onset of RSE (6).

The exact pathophysiology of cryptogenic FIRES remains poorly understood. Some preliminary studies suggest that FIRES may involve a dysregulated innate immune system activation (6–8). The inflammatory cascade triggered by non-specific infections lowers the seizure threshold and precipitates seizures which in turn induce a massive neurogenic inflammatory response (9). Fulminant neurogenic inflammation and seizures become a vicious cycle that together contributes to recurrent seizures and status epilepticus. Besides the anti-seizure medications (ASMs), some immunomodulatory and anti-inflammatory therapies are used in patients with FIRES. High-dose steroids, intravenous immunoglobulin (IVIG), plasmapheresis, therapeutic hypothermia, and interleukin-1 receptor antagonist were reported to be partially efficacious in FIRES (9–13), but robust evidence is lacking.

In the acute phase, approximately 12% to 22% of patients cannot survive FIRES/NORSE (9, 14). In the long term, only 18% of children with FIRES regain normal cognitive function, and more than 90% develop refractory epilepsy requiring lifelong treatment (9, 15, 16). However, the long-term outcomes of adult patients with cryptogenic FIRES remain unknown. Due to the lack of related studies, we conducted a case series study to investigate the long-term outcome in adult cryptogenic FIRES, including functional independence, seizure outcomes, and changes in brain images.

Abbreviations: AERRPS, acute encephalitis with refractory, repetitive partial seizures; ASM, anti-seizure medication; CBZ, carbamazepine; CIVADs, continuous infusion of intravenous anesthetic drugs; CSF, cerebrospinal fluid; CZP, clonazepam; DRE, drug-resistant epilepsy; EEG, electroencephalogram; FIRES, febrile infection-related epilepsy syndrome; IV, intravenous; IVIG, intravenous immunoglobulin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; MRI, magnetic resonance imaging; mNGS, Metagenomic Next-Generation Sequencing; mRS, modified Rankin Scale; MV, mechanical ventilation; NCSE, non-convulsive status epilepticus; NICU, neuro-intensive care unit; NORSE, new-onset refractory status epilepticus; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; RSE, refractory status epilepticus; SE, status epilepticus; TPM, topiramate; VPA, valproate.

2. Materials and methods

2.1. Study design

This study was a retrospective study based on a prospective database in the neuro-intensive care unit (NICU) at Xijing Hospital, China. This study was approved by the Ethics Committee of Xijing Hospital (KY20222115-C-1) and was conducted in compliance with Chinese laws and the Helsinki Declaration. Patients' consent was waived by the ethics committee.

2.2. Participants and definitions

The NICU database was searched between July 2007 to December 2021 for patients with cryptogenic FIRES. The inclusion criteria were as follows: (1) age 16 years or older; (2) status epilepticus (SE) refractory to at least 2 appropriately selected and dosed parenteral anti-seizure medications including a benzodiazepine (3, 17) with fever prior to the onset of RSE between 24 h and 2 weeks (6). Exclusion criteria were (1) active epilepsy or other preexisting relevant neurological disorder, and (2) SE due to a clear acute or active cause (6). Convulsive SE was defined as continuous or repetitive motor seizures without complete interictal recovery to clinical baseline (18). Non-convulsive SE (NCSE) was defined as a type of SE without prominent motor movements and manifested as neurological deficit, disturbance of consciousness and behavioral changes, and was diagnosed according to the Salzburg Consensus Criteria for NCSE (19).

2.3. Data collection

Collected clinical data included age, gender, medical history, prodromes, SE characteristics (worst type, duration, medications, treatment responses), findings of ancillary tests [cerebrospinal fluid (CSF) routine tests, CSF Metagenomic Next-Generation Sequencing (mNGS) test, CSF and peripheral blood autoantibody tests, peripheral blood Whole-Exome Sequencing test, tumor screening examinations, brain Magnetic Resonance Imaging (MRI), continuous electroencephalogram

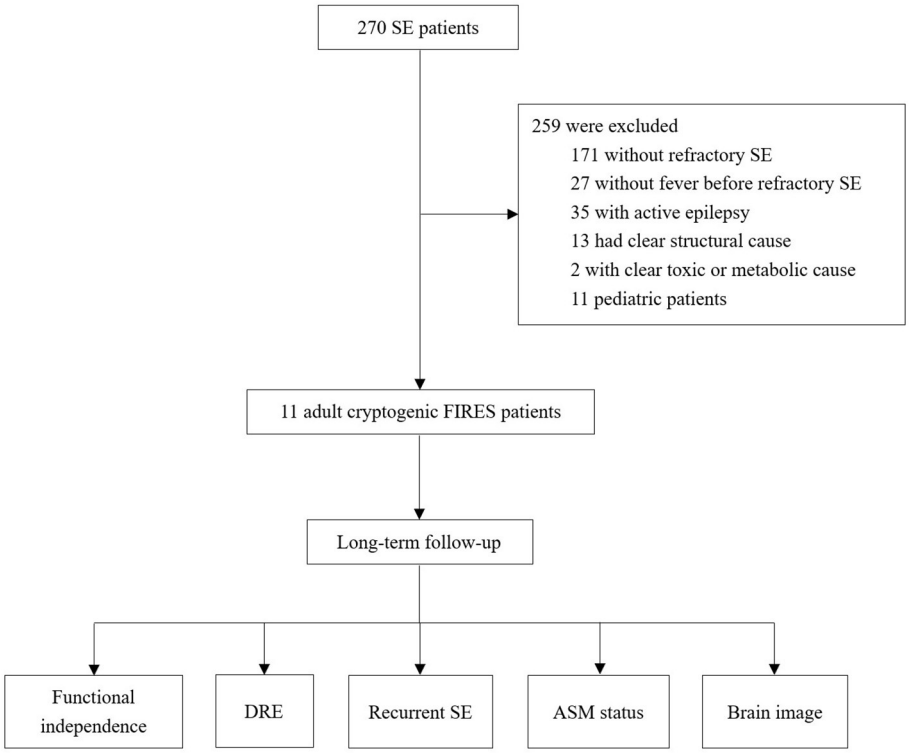

FIGURE 1
Flowchart of the study. SE, status epilepticus; FIRES, febrile infection-related epilepsy syndrome; DRE, drug-resistant epilepsy; AEM, anti-seizure medication.

(EEG)], and treatments and duration in NICU. A prodrome was considered as any symptom prior to SE onset between 24 h and 2 weeks. SE semiology was classified according to the latest guidelines of SE (18). The following antibodies were tested in all patients: anti-NMDA-R, anti-CASPR2, anti-AMPA1-R, anti-AMPA2-R, anti-LGI1, anti-LGI2, anti-GABA2-R, anti-Hu, anti-Yo, anti-Ri, anti-Mn2, anti-CV2, anti-Amphiphysin, anti-ANNA-3, anti-Tr, anti-PCA-2, and anti-GAD.

2.4. SE monitoring and management

All the patients received continuous EEG monitoring (Solar 2000 N, Solar Electronic Technologies Co., Ltd., Beijing, China) to guide anti-seizure treatments and detect non-convulsive seizures. The management of SE was controlled by the same group of neurologists according to the clinical guidelines (20, 21): the first-line treatments were benzodiazepines; the second-line agents were intravenous sodium valproate, phenobarbital sodium and levetiracetam; and the third-line treatments were continuous infusions of anesthetics (midazolam or/and propofol).

2.5. Outcomes

Long-term outcomes included function independence, the development of drug-resistant epilepsy (DRE), remote recurrent SE, ASMs, and changes in the brain MRI. Functional independence was defined as a modified Rankin Scale (mRS) score of 0–3. DRE was defined as the failure of adequate trials of 2 tolerated and appropriately chosen and used ASMs (whether as monotherapies or in combination) to achieve sustained seizure freedom (22). Remote recurrent SE was defined as any episode of SE after hospital discharge (23). Outcomes were assessed by a trained neurologist based on clinical data obtained from routine consultations in the outpatient clinic and telephone interviews. The last follow-up ended in November 2022.

3. Result

We identified 11 cases fulfilling our criteria among 270 cases with SE (Figure 1). The clinical characteristics were summarized in Table 1 and presented in detail in Supplementary Tables 1, 2. Age ranged from 17 to 35 years, and the median age was 24 years. A female predominance was observed (74% vs. 36%). All the cases remained cryptogenic despite an extensive workup.

The autoimmune antibody detection and CSF mNGS tests were negative in all patients. Most patients had negative findings in the Whole-exome sequencing test, and two patients had the heterozygous mutation in NFKB1 and ALDH7A1, respectively (Supplementary Table 2).

The median time from fever to RSE was 5 days, and other prodromes included headache (46%), gastrointestinal symptoms (18%), behavioral changes (9%), and confusion (9%) (Table 1). All the patients had NCSE with coma. Generalized (46%) seizure onset was more common than lateralized (27%) and multifocal (27%). The median time from the first seizure to SE was 2 h, and one patient started with SE. All the cases were super refractory SE, and the median duration of SE was 31 days.

Patients received a median of 6 ASMs in NICU. Continuous infusion of anesthetics was used in 91% of patients, and mechanical ventilation was used in all the patients. Immunotherapies were used in 91% of patients, including intravenous steroids (82%), IVIG (73%), plasma exchange (18%), and mycophenolate mofetil (MMF) (9%). Ketogenic diet and hypothermia were used in 27% and 18% of patients, respectively. The median length of NICU stay was 48 days. Four (36%) patients died in the hospital, and treatments were withdrawn in three of them at the request of their families: Patient 1 developed sepsis and severe liver and heart failure, Patient 3 developed severe anemia (hemoglobin 28 g/L) despite receiving blood transfusions for 13 consecutive days (possibly due to visceral hemorrhage), and Patient 4 developed refractory septic shock.

The median follow-up in this study was of 20 months, ranging from 12 to 112 months. At the last follow-up, 5 (45%) patients died (4 died in the NICU, and 1 died 12 months after NICU discharge), and 6 (55%) patients were alive (Figure 2). All of these FIRES survivors achieved functional independence. Five patients (45%) had recurrent seizures (mostly generalized) after NICU discharge with a frequency of 3–180 seizures per month (Supplementary Table 3). All of these patients developed DRE (45%), and 2 (18%) had remote recurrent SE (Figure 2). Among 7 NICU survivors, 6 (86%) patients were on polytherapy with ASMs at the last follow-up. Levetiracetam (86%) and phenobarbital (71%) were more commonly used than other ASMs, such as valproate, topiramate, and carbamazepine (Table 2). Eight (73%) patients had normal brain MRI during the acute phase, of whom 4 died in NICU and the other 4 developed brain MRI abnormalities (mainly in the hippocampus) at follow-up (Table 3). Three (27%) patients had abnormal MRIs during the acute phase. MRI lesions disappeared completely in 1 patient after 6 months and recovered partially in 2 patients after 1–5 months. Of the 7 patients with follow-up MRIs, 4 had abnormalities in the hippocampus, 1 had hydrocephalus, 1 had abnormal signals in temporal and occipital lobes, and 1 had a normal brain MRI. Among the four patients with abnormalities in the hippocampus, two patients had T2/FLAIR hyperintensity in the hippocampus, and two patients had hippocampal atrophy (one of them had global brain atrophy). The follow-up MRI images of these two patients were presented in Figure 3.

TABLE 1 Clinical characteristics of adult cryptogenic FIRES patients.

Characteristics	All cases ($n = 11$)
Age, years, median (IQR)	24 (21-30)
Male, *n* (%)	4 (36.4)
Time from fever to RSE, days, median (IQR)	5 (3-5)
Time form first seizure to SE, hours, median (IQR)	2 (1-5)
History of seizure, *n* (%)	1 (9.1)
Prodrome, *n* (%)	
Fever	11 (100.0)
Headache	5 (45.5)
Gastrointestinal symptoms	2 (18.2)
Behavioral changes	1 (9.1)
Confusion	1 (9.1)
Worst SE type, *n* (%)	
NCSE with coma	11 (100.0)
SE duration, days, median (IQR)	31 (15-77)
NICU management	
Number of anti-seizure medications, median (IQR)	6 (4-6)
Use of CIVADs, *n* (%)	10 (90.9)
Ketogenic diet, *n* (%)	3 (27.3)
Immunotherapies, *n* (%)	10 (90.9)
IV steroids, *n* (%)	9 (81.8)
IVIG, *n* (%)	8 (72.7)
Plasma exchange, *n* (%)	2 (18.2)
Mycophenolate mofetil, *n* (%)	1 (9.1)
Hypothermia, *n* (%)	2 (18.2)
Use of MV, *n* (%)	11 (100.0)
MV duration, days, median (IQR)	36 (10-77)
EEG features of seizures, *n* (%)	
Generalized onset	5 (45.5)
Lateralized onset, unilateral	3 (27.3)
Multifocal onset	3 (27.3)
Abnormal MRI, any, *n* (%)	3 (27.3)
NICU stay, days, median (IQR)	48 (22-78)
In-hospital death, *n* (%)	4 (36.4)

SE, status epilepticus; NCSE, non-convulsive status epilepticus; NICU, neurological intensive care unit; CIVADs, continous infusion of intravenous anesthetic drugs; MV, mechanical ventilation; IV, intravenous; IVIG, intravenous immunoglobulin.

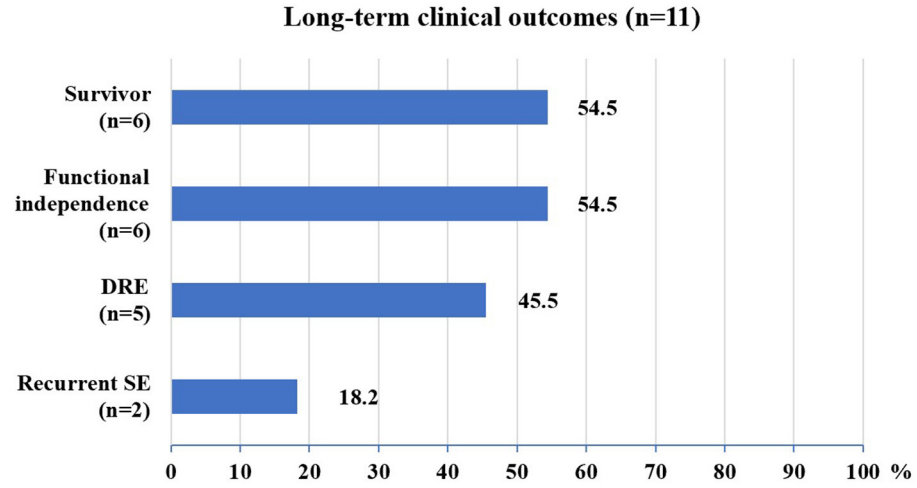

FIGURE 2
Long-term clinical outcomes of FIRES patients. DRE, drug-resistant epilepsy; SE, status epilepticus.

TABLE 2 ASM status of NICU survivors at the end of follow-up.

	NICU survivors (n = 7)
Treatment status, *n* (%)	
Monotherapy	1 (14.3)
Polytherapy	6 (85.7)
ASM, *n* (%)	
LEV	6 (85.7)
PB	5 (71.4)
TPM	3 (42.9)
CZP	3 (42.9)
VPA	2 (28.6)
LTG	2 (28.6)
PER	2 (28.6)
CBZ	1 (14.3)
OXC	1 (14.3)
LCM	1 (14.3)

ASM, anti-seizure medication; LEV, levetiracetam; PB, phenobarbital; TPM, topiramate; CZP, clonazepam; VPA, valproate; LTG, lamotrigine; PER, perampanel; CBZ, carbamazepine; OXC, oxcarbazepine; LCM, lacosamide.

4. Discussion

This is the first study reporting the long-term outcome of adult patients with cryptogenic FIRES. This case series study showed a long-term mortality rate of 45% for cryptogenic FIRES, with most survivors achieving functional independence but developing DRE, receiving polytherapy of ASMs, and developing hippocampal abnormalities in the long term.

The in-hospital mortality of adult FIRES in this study was 36%, much higher than that reported in pediatric studies (24). A multicenter study of 77 children with FIRES reported in-hospital mortality of 12% (9), and another study including 16 FIRES children from the pSERG (the United States Pediatric Status Epilepticus Research Group) database reported in-hospital mortality of 19% (25). The pSERG cohort also found that FIRES had a more prolonged course and worse outcomes compared to other types of NORSE in children, which is consistent with our findings in adults. In a multicenter study of 125 adults with NORSE, in-hospital mortality was lower for all-type NORSE (22%), NORSE with a clear cause (18%), and cryptogenic NORSE (27%) than for cryptogenic FIRES in this study (14). Their study also reported shorter durations of SE and ICU stay for all-type NORSE, NORSE with a clear cause, and cryptogenic NORSE compared to cryptogenic FIRES (36%) in this study. In a study of 26 NORSE adults (73% were cryptogenic), in-hospital mortality (23% vs. 36%), SE duration (17 vs. 31 days), and length of ICU stay (32 vs. 48 days) were also lower than in this study (26). These studies indicate that cryptogenic NORSE/FIRES is more severe than NORSE with a clear cause, and cryptogenic FIRES is even more severe than cryptogenic NORSE.

The long-term outcomes of adult FIRES were previously reported in a German study of 6 cases (27). In their study, only 1 case was cryptogenic, and the rest were due to autoimmune or parainfectious encephalitis. All these 6 patients achieved functional independence (mRS $\leq$ 3) but were found to have refractory epilepsy, brain atrophy, and severe memory impairment. Although the severity (e.g., SE duration and worst type) of FIRES patients in their study is unknown, their findings regarding functional outcomes and the development of refractory epilepsy are consistent with ours. With or without a clear cause, most adult FIRES survivors can regain the

TABLE 3 The initial and follow-up brain MRIs.

Patient	Initial		Follow-up	
	Time from onset, days	Location of abnormalities	Time from onset, months	Location of abnormalities
1	1	Normal	Death	-
2	10	Bilateral cingulate gyrus, frontotemporal and insular cortex	6	Normal
3	1	Normal	Death	-
4	2	Normal	Death	-
5	1	Corpus callosum, bilateral frontal parietal islands occipital lobe	11	Hydrocephalus
6	1	Normal	8	Bilateral hippocampi
7	10	Normal	72	Hippocampal atrophy and global brain atrophy
8	1	Normal	Death	-
9	1	Corpus callosum, bilateral hippocampi	1	Bilateral hippocampi
10	1	Normal	1	Bilateral temporal lobes and insulas, left occipital lobe
11	2	Normal	16	Bilateral hippocampal atrophy

ability to move unassisted. However, they usually develop MRI abnormalities in the hippocampus or mesial temporal lobes, and their quality of life is severely affected due to refractory epilepsy.

Patients with NORSE are more likely to develop DRE than patients with SE of all causes. In this study, 5 of 7 (71%) NICU survivors developed DRE, and 2 of them experienced remote recurrent SE. Two cohort studies of adult NORSE patients also showed high DRE rates of 75–80% in survivors (28, 29), while only 37% of patients with SE of all causes developed DRE (30). Children with FIRES have an even higher DRE rate of 93% (9). One possible reason is that there are more survivors of FIRES in children than in adults, and these survivors usually develop DRE in the long term. However, there is not much difference in the risk of remote recurrent SE between FIRES (29%) and all-cause SE (32%) (31).

Approximately 73% of patients with cryptogenic FIRES in this study had normal brain MRI scans in the acute phase, which is consistent with a rate of 61% in pediatric patients with FIRES (32). Lesions of FIRES on MRI usually involve the temporal lobe, basal ganglia, insula, and thalamus (27, 32). Previous case studies also found that T2/FLAIR hyperintense lesions appeared in bilateral claustrum on average 10 days after SE (29, 33). However, no claustrum abnormality was observed in our patients. In this study, most of the patients with initial normal or abnormal MRI had abnormalities in the hippocampus at follow-up, and most of the other MRI abnormalities found in the acute stage disappeared over time. In addition, previous pediatric and adult cases of FIRES showed that generalized brain atrophy and mesial temporal sclerosis were also frequently found in the chronic phase (27, 32).

Whether and how to give immunomodulatory therapies after the acute phase of cryptogenic FIRES is a clinical dilemma. DRE and cognitive impairment are major challenges after NICU discharge for patients, their families, and clinicians. Initially, we focused on treating DRE with various ASMs and did not give immunomodulatory therapies after NICU discharge. Recently, we tried immunomodulatory treatments for patients with cryptogenic NORSE/FIRES after NICU discharge, on the assumption that they may involve dysregulated innate immune system activation. Some patients were given MMF after the use of high-dose methylprednisolone and IVIG in the acute phase and continued to receive MMF for 1–2 years after discharge from NICU. Some patients received sirolimus and/or repeated cycles of IVIG after NICU discharge. The cycles of IVIG and the duration of sirolimus depend on the seizure outcomes. However, patients were often reluctant to continue treatment if their seizure control did not improve after 1–2 cycles of IVIG or after 3 months of sirolimus. In this study, Patient 6 received MMF and Patient 11 received repeated cycles of IVIG and sirolimus after discharge from NICU, but neither of them had improved seizure control. In addition, we are also gaining experience with

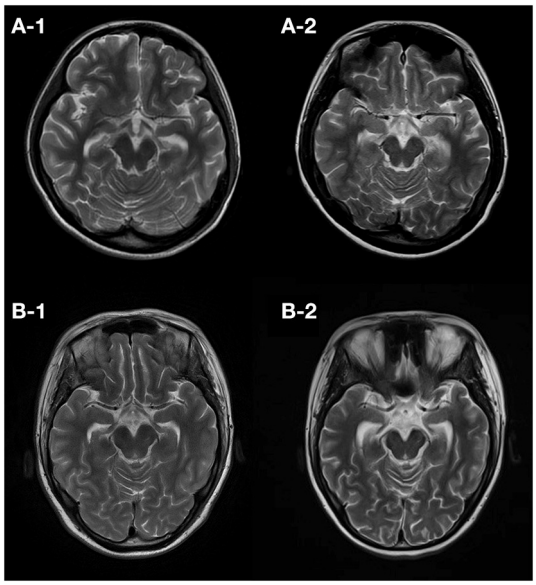

FIGURE 3
Follow-up T2 images of patients developing atrophy. Patient 7 had an initial normal brain MRI (10 days from onset) and showed hippocampal atrophy 50 days **(A-1)** and 72 months **(A-2)** later. Patient 11 also had an initial normal MRI (2 days from onset) and showed hippocampal atrophy 3 months **(B-1)** and 16 months **(B-2)** later.

rituximab, interleukin-1 receptor antagonists, and interleukin-6 antagonists in the post-acute phase of FIRES. The use of immunomodulatory therapy for cryptogenic FIRES after NICU discharge remains disputable and requires further randomized studies.

The limitations of this study include the single-center design and small sample size which reduce its generalizability. However, FIRES is a very rare condition, and this calls for further multicenter and international studies. The timing of brain MR in this study was highly variable, and it is unclear whether the MRI abnormalities found at follow-up were caused by FIRES or DRE. In addition, neuropsychological outcomes may also affect the quality of life, such as intellectual impairments and mental state, but they were not assessed in this study.

5. Conclusion

The outcomes of adult patients with cryptogenic FIRES are daunting. More than one-third of patients die in the hospital. Survivors of cryptogenic FIRES may regain functional independence, but they usually develop DRE and receive polytherapy of ASMs for a long time. Future studies are needed to answer many open questions on this clinical challenge.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Xijing Hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

XS and YW: data collection, interpretation, and analysis. XK and FYa: data checking. XS and FYu: drafting manuscript. YW, XW, and FYu: drafting review. WJ and FYu: study design and critical revision. WJ: study supervision and obtaining funding. All authors approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1081388/full#supplementary-material

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A case report: New-onset refractory status epilepticus in a patient with *FASTKD2*-related mitochondrial disease

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Objectives: New-onset refractory status epilepticus (NORSE) is associated with high morbidity and mortality. Despite extensive work-up, the underlying etiology remains unknown in 50% of affected individuals. Mitochondrial disorders represent rare causes of NORSE. Biallelic variants in *FASTKD2* were reported as a cause of infantile encephalomyopathy with refractory epilepsy.

Case description: In the study, we report a previously healthy 14-year-old with a new, homozygous *FASTKD2* variant presenting with NORSE. Following a seizure-free period of 7 years, he experienced another super-refractory SE and subsequently developed drug-resistant focal epilepsy, mild myopathy, optic atrophy, and discrete psychomotor slowing. Structural MRI at the time of NORSE showed right temporo-parieto-occipital FLAIR hyperintensity and diffusion restriction, with extensive right hemispheric atrophy at the age of 22 years. Whole-exome sequencing revealed a novel homozygous loss of function variant [c.(1072C>T);(1072C>T)] [p.(Arg358Ter);(Arg358Ter)] in *FASTKD2* (NM_001136193), resulting in a premature termination codon in the protein-coding region and loss of function of FASTKD2. Oxidative phosphorylation (OXPHOS) in muscle and skin fibroblasts was unremarkable.

Conclusion: This is the first case of a normally developed adolescent with a new homozygous loss of function variant in *FASTKD2*, manifesting with NORSE. The phenotypical spectrum of FASTKD2-related mitochondrial disease is heterogeneous, ranging from recurrent status epilepticus and refractory focal epilepsy in an adolescent with normal cognitive development to severe forms of infantile mitochondrial encephalopathy. Although mitochondrial diseases are rare causes of NORSE, clinical features such as young

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age at onset and multi-system involvement should trigger genetic testing. Early diagnosis is essential for counseling and treatment considerations.

KEYWORDS

new-onset refractory status epilepticus (NORSE), *FASTKD2* mutation, genetic epilepsies, mitochondrial disease, drug-resistant epilepsy

Introduction

New-onset refractory status epilepticus (NORSE) is defined as refractory status epilepticus (SE) in individuals without previous history of epilepsy and no identification of an underlying cause within 72 h (1). An association with preceding febrile illness is common and even required in the subcategory of febrile infection-related epilepsy syndrome (FIRES). NORSE is associated with high morbidity and mortality, and the outcome strongly depends on the underlying etiology (2). Standardized diagnostic work-up is performed to identify structural, toxic, metabolic, or inflammatory causes (3–6) with infectious and autoimmune etiologies as the leading cause (7, 8). However, in up to 50% of patients, no etiology can be identified (8) (cryptogenic NORSE).

Mitochondrial diseases (MDs) are rare causes of SE (9). Currently, disease-causing variants in over 300 genes located in both the mitochondrial and nuclear DNA are known to be associated with MDs, resulting in heterogeneous phenotypes (9).

Biallelic variants in *FASTKD2*, encoding the protein Fas-activated serine/threonine kinase domain-containing protein-2, localizing to the inner mitochondrial matrix, have been reported in six individuals and represent a rare cause of infantile encephalomyopathy with refractory epilepsy and/or status epilepticus (10–12). In this study, we report the first case of a normally developed adolescent with a new homozygous loss of function variant in *FASTKD2*, manifesting with NORSE.

Case description

The male patient was born as the second child to Caucasian parents with no known consanguinity or medical concerns after an uneventful pregnancy. His early motor development was unremarkable; he could walk at the age of 12 months and was athletic without rapid exhaustion during sports. In primary school, his fingers were observed in a peculiar positioning while writing, and his parents noted a "sloppy" gait and mild joint hypermobility, which were not further investigated. His performance at school was unremarkable. At the age of 14 years, he presented with NORSE at a district hospital in Salzburg, Austria (Figure 1). Three days before admission, he complained of left-sided blurred vision, headache, nausea, and high temperature of up to 38 degrees Celsius, qualifying the episode as FIRES. On the day of admission, his parents observed unsteady gait and psychomotor slowing for several hours, preceding a focal to bilateral tonic–clonic SE with head and eye deviation to the left. Administration of intravenous benzodiazepines (lorazepam, LZP 4 mg, diazepam, and DZP 16 mg) and antiseizure medication (ASM) (levetiracetam, LEV 2 g) led to the cessation of motor activity, but the impairment of consciousness persisted. The patient was intubated and transferred to the neurological intensive care unit (NICU) at the Paracelsus Medical University Hospital Salzburg, Austria. On arrival, he was comatose under anesthetic treatment without ictal motor activity or gaze deviation. Neurological examination revealed a subtle deformity of both feet with bilateral pes cavus. Acute brain MRI performed on arrival showed right temporo-occipital diffusion restriction, hyperperfusion, and hyperintensity in the FLAIR sequence (Figure 2). EEG concordantly revealed fluctuating lateralized periodic epileptiform discharges (LPEDs) over the same region, compatible with possible NCSE (13).

Initial laboratory testing and analysis of cerebrospinal fluid (CSF) identified no pathologies. Lactate levels in CSF and serum were within normal limits. Antiviral treatment with acyclovir and immunotherapy (immunoglobulins and corticosteroids) was started on day 1, but further extensive work-up of CSF revealed no infectious cause. Intravenous antiepileptic seizure medication (ASM) with LEV was established, and the patient could be weaned and extubated after 12 h. Thereafter, he presented with psychomotor slowing, slight anisocoria with mydriasis on the left side, and reported blurred vision. Because of repetitive focal impaired awareness seizures with head and eye deviation to the left, accompanied by clonic jerking on the left side, ASM was intensified (add-on lacosamide, LCM). Repeated EEG studies showed continuous slowing over the right posterior quadrant with frequently intermittent epileptiform discharges. MRI follow-up on day 5 demonstrated decreasing diffusion restriction and FLAIR hyperintensity in the right temporo-occipital region with mild right hippocampal swelling (Figure 2). Neural antibodies (anti-NMDA-R; anti-AMPA-R, anti-VKCC; LGI1/VGKC, anti-Yo, anti-Ri, anti-Hu, anti-CV2, anti-GABA-A/B, anti-MAG, and anti-Tr), and anti-thyroid antibodies (thyroperoxidase-TPO, thyrotropin-receptor-TRAK, thyroglobulin-TAK) were negative, as were mitochondrial diagnostics, including Sanger Sequencing for m.3243A>G ("MELAS"), m.8344A>G ("MERFF") mitochondrial DNA point mutations, and of the entire *POLG* and *FXN* (Friedreich's ataxia) genes.

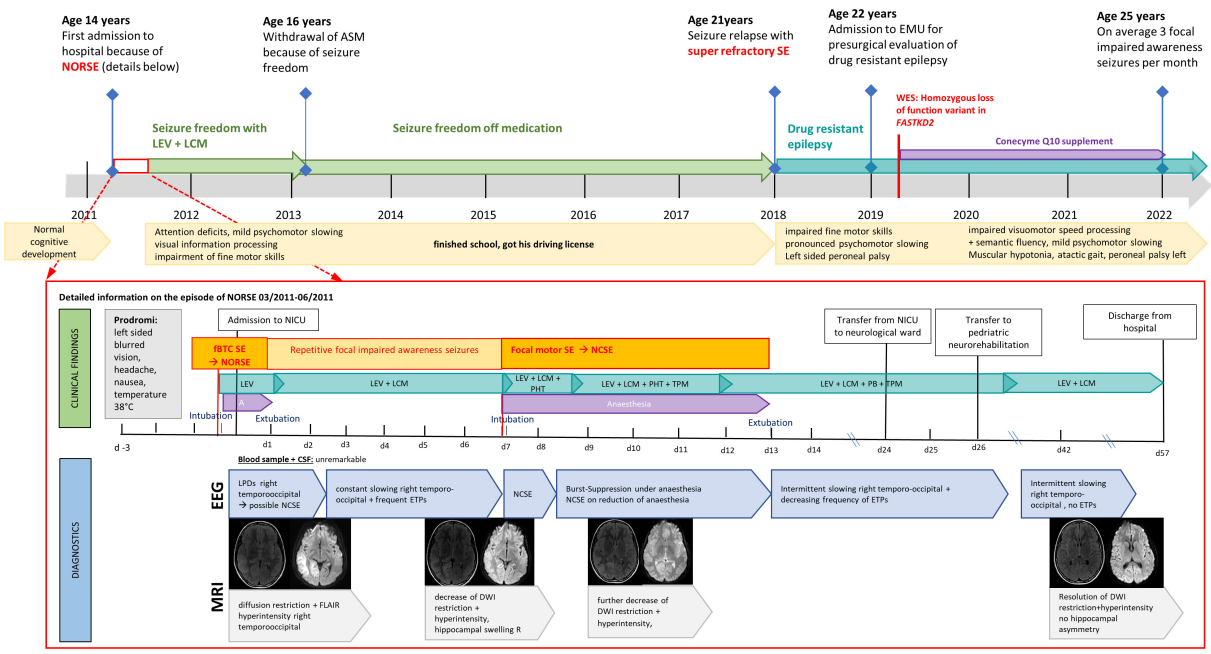
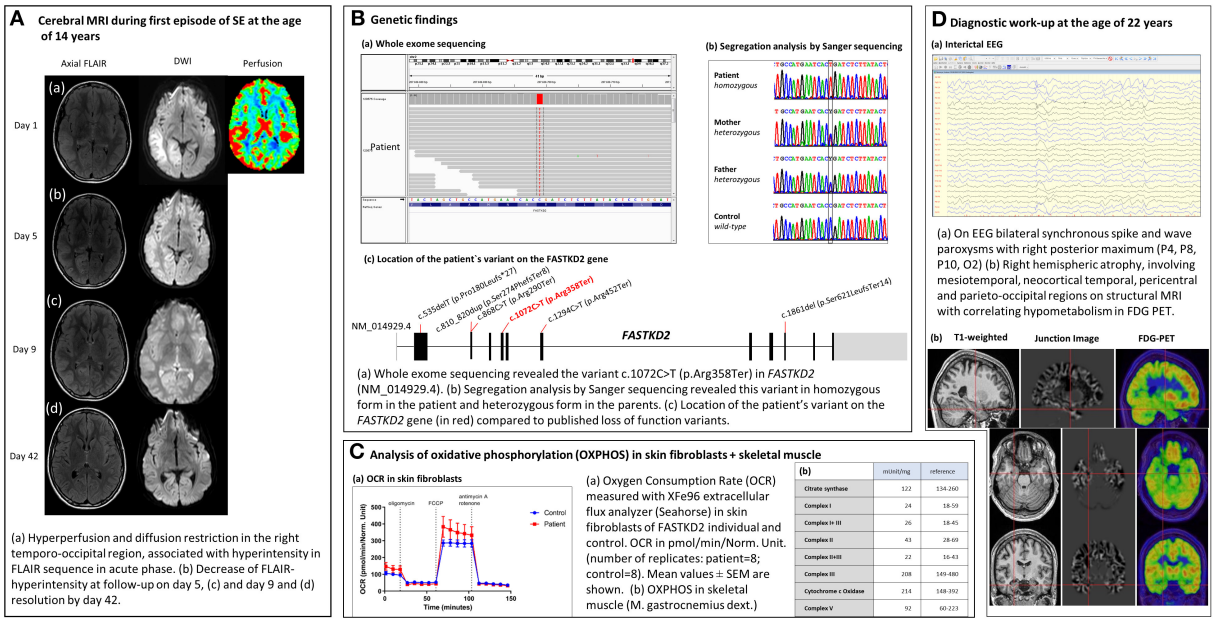


FIGURE 1
Diagnostic findings in a patient with FASTKD2 related mitochondrial disease presenting with new onset refractory status epilepticus (NORSE).



(b)	mU/U/ng	reference
Citrate synthase	122	134-260
Complex I	24	18-59
Complex I+ III	26	18-45
Complex II	43	28-69
Complex II+III	22	16-43
Complex III	208	149-480
Cytochrome c Oxidase	214	148-392
Complex V	92	60-223

FIGURE 2
Timeline: Clinical course of a patient with FASTKD2 related mitochondrial disease.

On day 7, the patient developed another focal motor SE with the impairment of consciousness and left-sided clonic, resistant to benzodiazepines and IV ASMs (LEV, LCM, phenytoin, and PHT). EEG showed lateralized periodic epileptiform discharges over the right hemisphere, with spatiotemporal evolution consistent with NCSE. Anesthetic treatment with thiopental was re-established with clinical and electrographic seizure recurrence on the withdrawal of anesthesia. SE persisted despite anesthetic treatment (switch to midazolam/ketamine), immunotherapy, high-dose magnesium, and intensified IV

ASM (add-on topiramate, switch from PHT to phenobarbital). After 5 days, SE ceased on day 13, and the patient was gradually weaned from anesthetics. Thereafter, he showed slight ataxia, incomplete hemianopia to the left, vertical oscillatory nystagmus, slurred speech, and psychomotor slowing. He remained seizure free under high-dose ASM polytherapy (LEV, LCM, TPM, and PB), and neurological deficits improved gradually. MRI follow-up on day 9 showed a further decrease in diffusion restriction and FLAIR hyperintensity in the right temporo-occipital region (Figure 2). EEG gradually improved with persistent slowing over the right posterior quadrant but decreasing frequency of epileptiform discharges. Visual fields were normal, but vertical oscillatory nystagmus and discrete vertical palsy persisted. The patient had pronounced deficits in all cognitive domains, which gradually improved and were close to the lower normal age-adjusted range 3 months after discharge (see Supplementary material). ASMs were tapered down, and the patient remained seizure-free under dual therapy (LEV and LCM). MRI follow-up on day 42 demonstrated a resolution of diffusion restriction and FLAIR hyperintensity in the right hemisphere without hippocampal asymmetry. Intermittent slowing over the right posterior quadrant without epileptiform discharges persisted on EEG. Eleven weeks after admission, he was discharged from hospital with mild residual impairment of fine motor skills and attention deficits. Despite extensive diagnostic work-up, no underlying cause for the patient's new-onset epilepsy first manifesting with NORSE could be identified. ASMs were withdrawn after 2 years of seizure freedom; he finished school and got his driving license after 5 years of seizure freedom off medication.

Aged 21 years, after 7 years of seizure freedom, the patient relapsed with a super-refractory bilateral tonic–clonic SE treated at a community hospital in Carinthia, Austria (Figure 1). He developed a propofol infusion syndrome and septic multiorgan failure, treated with high-dose catecholamines, intermittent continuous veno-venous hemodialysis, and broad-spectrum antibiotics. SE was terminated after more than 6 weeks with gradual weaning from the ventilator after 2 months. He was discharged from hospital 3 months after admission with residual left-sided peroneal palsy, impaired fine motor skills, and pronounced psychomotor slowing.

Subsequently, the patient developed drug-resistant epilepsy with focal onset aware and impaired awaresse seizures despite high-dose polytherapy (LEV 4500 mg per day, LCM 1200 mg per day, and PHT 300 mg per day) and was admitted to our epilepsy-monitoring unit for presurgical evaluation aged 22 years (Figure 1).

Diagnostic assessment

At the time of admission, the patient (22 years) presented with mild psychomotor slowing, discrete myopathy, spastic ataxic gait, and peroneal palsy on the left. Ictal and interictal EEG showed bilateral synchronous sharp waves with a maximum over the right posterior temporal to parieto-occipital head region. Structural MRI according to the in-house epilepsy protocol revealed an extensive right hemispheric atrophy involving mesiotemporal, neocortical temporal, pericentral, and parieto-occipital regions with correlating hypometabolism in fluorodeoxyglucose (FDG)-positron emission tomography (PET) (Figure 2).

Because of the multisystemic nature of the disease, mainly involving the central nervous system, muscles, and eyes, an MD was suspected. ECG detected a right-bundle branch block, and echocardiography was unremarkable. Baseline lactate levels in serum and CSF were normal, and bicycle ergometry detected no lactate increase during exercise. Abdominal ultrasound, liver and renal function were unremarkable. Ophthalmological examination showed slight bilateral optic atrophy. Muscle MRI revealed hyperintensity and atrophy in both gastrocnemii muscles with right-sided predominance. Electromyography showed signs of discrete myopathy.

Oxidative phosphorylation (OXPHOS) was evaluated in fresh muscle and skin fibroblasts (14) (Figure 2). Evaluation of OXPHOS in muscle (M. gastrocnemius right) revealed normal activities of the respiratory chain complexes I [24 mUnit/mg (18–59 mUnit/mg)], II [43 mUnit/mg, (28–69 mUnit/mg)], III [208 mUnit/mg, (149–480 mUnit/mg)], IV (cytochrome-C-oxidase) [214 mUnit/mg, (148–392 mUnit/mg)], V [92 mUnit/mg, (60–223 mUnit/mg)], and citrate synthase [122 mUnit/mg, (134–260 mUnit/mg)]. Oxygen consumption rate (OCR) was measured by Seahorse XFe96 analyzer in cultivated skin fibroblasts of the FASTKD2 individual and control. No decrease in either basal or maximal respiration could be detected (Figure 2).

Considering the patient's medical history and clinical findings, genetic testing was extended (Figure 2). Whole-exome sequencing from leucocyte-derived DNA was performed using a SureSelect Human All Exon V6 kit (Agilent). The coding regions were enriched, followed by sequencing as 100-bp paired-end runs on a HiSeq 4,000 (Illumina). Reads were aligned to the human reference genome (UCSC Genome Browser build hg19) using the Burrows–Wheeler Aligner (v.0.7.5 a) (15). Single-nucleotide variants, small insertions, and deletions were detected with SAMtools (version 0.1.19). Based on the assumption of autosomal recessive inheritance, variants were prioritized with a minor allele frequency of <0.1%, and *de novo* variants were prioritized with a minor allele frequency of <0.01%. As a result of this, we discovered a new homozygous loss of function *FASTKD2* variant [c.(1072C>T);(1072C>T)] [p.(Arg358Ter);(Arg358Ter)]. For confirmation and investigation of its segregation, the *FASTKD2* variant was investigated by targeted Sanger sequencing using the following forward primer 5'-CAGCACAAGACCCTGTCTCA-3' and reverse primer 5'-CTGGAGGTCTTTGCAGGACT-3'.

The new *FASTKD2* variant is a non-sense mutation, resulting in the introduction of an in-frame premature termination codon (PTC) into the protein-coding gene sequence and, subsequently, loss of the function of FASTKD2 (NM_001136193). Both parents are heterozygous carriers of this variant (Figure 2). According to the ACMG criteria, (16) the FASTKD2 variant is classified as "pathogenic" (score: 11, PVS1: very strong, PP5: moderate, and PM2: supporting). In the database ClinVar, this variant has been reported as "likely pathogenic" (allele ID: 1675474).

Based on these findings, genetic counseling at the Department of Neuropediatrics was performed, and treatment options were discussed. As no causal therapy is available for this rare mutation, lifestyle modifications with a structured daily routine, a healthy diet, aerobic sports, and sufficient periods of rest were emphasized. Coenzyme Q10 supplement and ketogenic diet were established, but the latter was stopped as no improvement in seizure frequency could be achieved, and the diet was not well-tolerated by the patient.

The patient is currently aged 25 years and suffers from an average of three focal onset aware and impaired awareness seizures per month, despite ongoing high-dose ASM polytherapy (LEV 3,250 mg per day, PHT 300 mg per day, LCM 600 mg per day, and PER 12 mg per day). No focal to bilateral tonic–clonic seizures or SE occurred since diagnosis. Neurological examination and neuropsychological assessment showed no deterioration of cognitive function or neurological deficits at the last follow-up, with persistent mild psychomotor slowing, impairment of semantic fluency, and visuomotor processing speed.

Discussion

In this study, we describe a patient with a new biallelic homozygous *FASTKD2* variant associated with NORSE and recurrent RSE. The discovered *FASTKD2* variant is a non-sense mutation, resulting in the introduction of an in-frame PTC into the protein-coding gene sequence and, subsequently, loss of function of FASTKD2. FASTKD2 is a protein located in the inner mitochondrial matrix and is presumably involved in mitochondrial ribosomal assembly, mtRNA stabilization, and translation (17, 18). Isolated complex IV deficiency and decreased COX staining were detected in one patient with FASTKD2-related MD (11). FASTKD2 and helicase DDX28 are also required for 16S rRNA-binding during ribosome assembly in mitochondria (17), and loss of function variants in *FASTKD2* were associated with the impairment of OXPHOS complexes I–IV and ATPase (17, 18). *In vitro* studies of immortalized lymphocytes of two individuals with FASTKD2-related MD (12) detected reduced 16S rRNA expression and decreased activity of OXPHOS-complexes-containing-mtDNA subunits, suggesting that defective mtRNA translation might lead to multiple OXPHOS complex deficiency other than complex IV (12). In our patient, as in one other patient presenting with a late onset comparatively mild phenotype (10), OXPHOS was unremarkable in skeletal muscle and skin fibroblasts, suggesting a possible correlation between disease severity and alterations of OXPHOS.

To date, only six patients with FASTKD2-related MD have been published (summarized in Table 1) (10–12). The first two reported cases were siblings from consanguineous parents with early onset severe encephalomyopathy and refractory epilepsy (11). The underlying mutation was a homozygous nonsense mutation in the *KIAA0971* gene, encoding for the FASTKD2 protein. A biochemical analysis revealed highly decreased COX function in the muscle mitochondria of one patient and lymphocytes of the other. A completely different phenotype with late disease onset at the age of 15 years and MELAS-like clinical presentation without developmental delay was described in a third patient with FASTKD2-related MD (10). A compound heterozygous mutation (p.R205X and p.L255P) in the *FASTKD2* gene was discovered in this patient, and no alterations of OXPHOS were detected by the analysis of skeletal muscle. The latest report on FASTKD2-related MD described three patients with infant-onset encephalomyopathy with moderate neurodevelopmental delay. Three different novel *FASTKD2* mutations (c.808_809insTTTCAGTTTTG, homoplasmic mutation c.868C>T, and heteroplasmic mutation c.1859delT/c.868C>T) were discovered in these patients, all of them leading to truncated FASTKD2 variants, lacking the C-terminus RNA-binding domain. A mitochondrial function analysis in immortalized lymphocytes revealed multiple OXPHOS deficiencies not isolated to complex IV in two of those patients.

In summary, the genetic and phenotypical spectrum of published cases with FASTKD2-related MD is highly variable, with age at disease onset ranging from 6 months to 15 years. Developmental delay was a leading symptom in all but one patient (10), ranging from moderate delay in early motor milestones to severe deterioration of psychomotor function with the inability to walk or speak following normal development (11). In contrast, psychomotor development was unremarkable in our patient, and no cognitive decline or progression of neurological symptoms was detected at the last follow-up. Muscular hypotonia (11, 12) and bilateral optic atrophy (10, 11) were common findings observed in three published cases as well as in our patient. Furthermore, different from our patient, elevated lactate levels in serum or CSF were measured in all previously published cases but one. Epileptic seizures with subsequent development of refractory epilepsy are the leading symptom in our patient and represented the first clinical symptom in five of six previously published cases. Recurrent SE was reported in two patients (10, 11); however, this is the first case manifesting with NORSE. In addition, involvement of basal ganglia with extrapyramidal symptoms and correlating hyperintensity in globus pallidus (3/6 bilateral; 1/6 unilateral) on

TABLE 1 Comparison of published cases with FASTKD2-related mitochondrial disease (FASTKD2-MD).

	Patient 1 Ghezzi et al. (11)	Patient 2 Ghezzi et al. (11)	Patient 3 Yoo et al. (10)	Patient 4 Wei et al. (12)	Patient 5 Wei et al. (12)	Patient 6 Wei et al. (12)	Patient 7 Astner-Rohracher et al. (19)
FASTKD2 mutation	Homozygous non-sense mutation in the KIAA0971 gene p.R416X + p.R416X	Homozygous non-sense mutation in the KIAA0971 gene p.R416X+ p.R416X	Compound heterozygous mutations p.R205X (c.613C>T) + p.L255P (c.764T>C)	Homozygous mutation at p.L270fs*11 (c.808_809insTTTCAG TTTTG)	Homozygous mutation p.R290 (c.868C>T)	Two compound heterozygous mutations at c.1859delT/c.868C>T and p.S621Lfs*14/p.R290	Homozygous mutation p.[Arg358Ter]; [Arg358Ter] (c.[1072C>T]; [1072C>T])
Ethnics/nationality	Bedouin (Israel) sister	Bedouin (Israel) Brother	Korean	Chinese	Chinese	Chinese	Austrian
Consanguinity	Yes (first degree cousins)	Yes (first degree cousins)	No	No	Yes	No	No
Sex	Female	Male	Male	Female	Female	Female	Male
Age at disease onset	7 months	1 year	15 years	6 months	22 months	1 year	14 years
First symptom	Fever associated seizure	Fever associated subacute neurological deterioration (Muscle hypotonia, extrapyramidal movements left>right)	Generalized tonic clonic seizure	Axial hypotonia + dyskinesia	Seizure	Seizure	Focal to bilateral tonic clonic seizure -> refractory SE (NORSE)
Developmental delay	Delayed development from age 7 months, at age 14 y: follows simple commands, 20 words vocabulary, can sit, is not able to walk	Deterioration of neurological development from age 1 year, at 4 years bed-ridden with neither communication nor any voluntary activity.	No	Delayed motor development, able to sit at the age of 9 months, walks at the age of 3	Yes, no further information given	Delayed development from the beginning, unable to sit until 7 months and walk until 22 months of age	No
Status epilepticus (SE)	No	Repeated SE	1st SE at age 18 y, 2nd SE at age 26 y	No	No epilepsy	No	Refractory SE at age 14 y and age 21 y
Clinical manifestations	Developmental delay, Myoclonic and gelastic seizures, optic atrophy, spastic left-sided hemiparesis	Developmental delay, refractory seizures with repeated SE, optic atrophy, muscle hypotonia, extrapyramidal symptoms	Stroke-like episode with visual field deficit left, epilepsy, Bilateral optic atrophy	Developmental delay, axial hypotonia, dyskinesia	Dyskinesia, unconscious shaking of hands, occasional convulsions at 3 years	Nystagmus, hypotonia, slurred speech, diminished deep tendon reflexes in the lower limbs.	Refractory status epilepticus twice, drug-resistent focal epilepsy, mild psychomotor slowing, myopathy, spastic atactic gait
Brain MRI	MRI at age 7 months: Generalized Symmetric atrophy CT at age 5y: Right hemispheric atrophy	MRI at age 1 y: Hyperintensity left nucleus caudatus, globus pallidus, and crus cerebri CT at age 2.5 y: Generalized atrophy, more pronounced on the left basal ganglia, bilateral dilatation of ventricles + basal cysternae	Right occipital lobe infarction	MRI at age 14 months:high T2 signal intensity in bilateral globus pallidus, medulla oblongata, and mesencephalon	MRI at age 9 years:bilateral symmetrical hyperintensity in globus pallidus	MRI at age 1 year 8 months:Brain atrophy, bilateral symmetrical hyperintensity signals in globus pallidus, putamen, and caudate nucleus MRI at age 2.5 years: T2 hyperintensity bilateral basal ganglia and cerebral atrophy	MRI at age 14 years: Diffusion restriction and FLAIR hyperintensity right temporo-occipital MRI at age 22 years: atrophy right temporo-parietal

(Continued)

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TABLE 1 (Continued)

	Patient 1 Ghezzi et al. (11)	Patient 2 Ghezzi et al. (11)	Patient 3 Yoo et al. (10)	Patient 4 Wei et al. (12)	Patient 5 Wei et al. (12)	Patient 6 Wei et al. (12)	Patient 7 Astner-Rohracher et al. (19)
EEG	Bilateral epileptiform discharge left > right	Right hemispheric attenuation + triphasic waves over left hemisphere	Slowing right hemisphere, sharp transients right parieto-occipital region	Not performed	Abnormal (not specified)	Not reported	Bilateral synchronous spike and wave with right posterior maximum
Lactate level	Serum 2.4–3.2 mM (normal < 1.8 mM)	CSF 3.8 mM (normal < 1.8 mM),	Serum 2.2 mM (normal< 1.6 mM)	Serum 3.4 mM (normal < 2.1 mM)	Normal: 1.9 mM (normal < 2.1 mM)	Serum 6.3 (normal < 2.1 mM)	Serum 2.2 mmol/l CSF 2.2 mmol/l (normal 1.1–2.2 mmol/l)
Abdominal sonography	Normal	Normal	Normal	Not performed, laboratory testing normal	Not reported	Not reported	Normal
Renal function	Normal	Normal	Normal	Normal	Not reported	Not reported	Normal
Specific therapy	Not reported	Not reported	Coenzyme Q10	Not reported	Not reported	Not reported	Coenzyme Q10
Echocardiography	Normal	Normal	Normal	Not reported	Hypertrophic cardiomyopathy, sinus tachycardia	Not reported	Normal
Optic nerve	Bilateral opticatrophy	Bilateral opticatrophy	Bilateral opticatrophy	Not reported	Not reported	Not reported	Bilateral mild atrophy of temporal fibers
Muscle biopsy	COX activity reduced to 21% of controls, other respiratory chain complexes: normal	Not performed	SDH, COX, mGT stain: normal	Not performed	Not performed	Not performed	COX, citrate synthase, respiratory chain complexes I, II, III, V: normal
Skin fibroblasts	Normal activity of MRC	Normal activity of MRC					OCR: no decrease of basal or maximal respiration
Immortalizedlym phozytes	Not performed	Decreased COX activity		16s-rRNA 30% lower compared to controls; 8.5-fold higher extracellular lactate generation	16s- rRNA 54% lower compared to controls; 4.3-fold higher extracellular lactate generation	Not performed	Not performed
Visual evoked potentials	Not performed	Not performed	Delayed	Not performed	Not performed	Not performed	Not performed

COX, cytochrome C oxidase; mGT, modified Gomori trichrome; MRC, mitochondrial respiratory chain complex; NORSE, new-onset refractory status epilepticus; OCR, oxygen consumption rate; SE, status epilepticus; SDH, succinate dehydrogenase.

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brain MRI was described in half of the patients. Global brain atrophy on MRI was seen in three individuals, and one patient with early onset disease developed left-sided hemiparesis with concordant severe unilateral right hemispheric brain atrophy (11). Unilateral brain atrophy with posterior maximum was also found in our patient without focal neurological deficits. Cardiac involvement with hypertrophic cardiomyopathy and sinus tachycardia was detected in one patient with moderate early onset encephalomyopathy, whereas the cardiological work-up of our patient, as of the other published cases, revealed no pathologies.

The case we report here adds to the phenotypical spectrum of FASTKD2-related MD. Clinical presentation with late-onset disease manifesting with NORSE is unique. Biochemical findings and genetic profiles differ from previously reported cases. The discovered variant has not been described previously and, in contrast to other cases, no alterations of OXPHOS could be detected. However, due to tissue specificity, unremarkable findings in skeletal muscle and skin fibroblasts do not exclude alterations of OXPHOS in other tissue/organs. Furthermore, a correlation between disease severity and alterations in OXPHOS can be hypothesized. Altogether, this case emphasizes the heterogeneous phenotypical spectrum of MDs and further contributes to understanding the complexity of FASTKD2-related MDs.

Epilepsy is a common symptom of mitochondrial disease (20), but the underlying pathophysiological mechanisms leading to SE are incompletely understood. Bioenergetic failure with the subsequent collapse of ionic gradients leading to apoptotic cell death and oxidative stress with the overproduction of reactive oxygen species might play an important role in seizure perpetuation. However, the role of mitochondrial dysfunction in SE is more complex, including immune dysfunction and impaired mitochondrial dynamics (9). The pathophysiological mechanisms leading to NORSE in our patient can only be hypothesized. Even in the absence of evidence for the impairment of OXPHOS, bioenergetic failure, and oxidative stress are probably among the leading causes.

Despite the sparse literature relating NORSE to MD (8), clinical features such as seizures, optic atrophy, cardiomyopathy, increased serum or CSF lactate, and MRI abnormalities should raise suspicion of an underlying MD in individuals presenting with NORSE or new-onset complex epilepsies. Exome or genome-wide genetic testing, including both nuclear and mtDNA, should be considered even in the absence of other clinical findings. Identifying the exact (genetic) diagnosis is key for proper counseling and treatment considerations. A ketogenic diet seems promising for seizures in certain MD subtypes (21), and pathomechanism-based treatment options are increasingly available (22). To date, no targeted therapy is available for FASTKD2-MD. However, therapeutic strategies suppressing PTCs and restoring the deficient protein function show good results in other diseases (23) and might also be a promising approach in our case of FASTKD2-MD. Future research might enable tailored therapy that influences seizure control and disease progression in these patients.

Furthermore, frequently used drugs in the treatment of (NOR)SE, such as valproic acid (VPA), propofol, or thiopental, should be used with caution due to the increased risk of hepatic failure and propofol infusion syndrome in certain MD subtypes, especially VPA in POLG-related MD. In our patient, the earlier genetic diagnosis could have prevented the development of propofol infusion syndrome.

Future research and international collaborations and registries are needed, especially in these cases of rare and complex genetic epilepsies, to gain knowledge on clinical course, treatment response, and prognosis. This is essential to guide future treatment decisions and counseling of patients and their families.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AA-R contributed to the study concept, data acquisition, and drafting of the manuscript. MM, GK, and ER contributed to the data acquisition. FR, ML, SW, and JM contributed to the data acquisition and drafting of the manuscript. CN contributed to the drafting of the manuscript. MA contributed to data acquisition. ET contributed to the study concept and the drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AA-R reports travel support and speaker's honoraria from Eisai, outside the submitted work. ML reports a travel grant from UCB Pharma and a speaker's honorarium from Eisai, outside the submitted work. GK reports travel support from UCB, Eisai and Cyberonics and speaker's honoraria from Eisai, outside the submitted work. CN reports consulting honorarium from Epilog NV, outside the submitted work. ET reports personal fees from EVER Pharma, Marinus, Argenx, Arvelle/Angelini, Epilog, Medtronic, MedScape, Bial–Portela & C[a], NewBridge, GL Pharma, GlaxoSmithKline, Hikma, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Genzyme Sanofi, GW Pharmaceuticals/Jazz, and Actavis outside the submitted work; his institution has received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Osterreichischer Fond zur Wissenschaftsforderung, Bundesministerium fur Wissenschaft und Forschung, and Jubilaumsfond der Österreichischen Nationalbank outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1063733/full#supplementary-material

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Seizure burden and neuropsychological outcomes of new-onset refractory status epilepticus: Systematic review

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Background: Long-term sequelae of the new onset refractory status epilepticus (NORSE) include the development of epilepsy, cognitive deficits, and behavioral disturbances. The prevalence of these complications has been previously highlighted in case reports and case series: however, their full scope has not been comprehensively assessed.

Methods: We conducted a systematic review of the literature (PROSPERO ID CRD42022361142) regarding neurological and functional outcomes of NORSE at 30 days or longer following discharge from the hospital. A systematic review protocol was developed using guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results: Of the 1,602 records for unique publications, 33 reports on adults and 52 reports on children met our inclusion criteria. They contained the description of 280 adults and 587 children of whom only 75.7 and 85% of patients, respectively had data on long-term follow-up. The mean age of adult and pediatric patients was 34.3 and 7.9 years, respectively; and the longest duration of follow up were 11 and 20 years, respectively. Seizure outcomes received major attention and were highlighted for 93.4 and 96.6% of the adult and pediatric NORSE patients, respectively. Seizures remained medically refractory in 41.1% of adults and 57.7% of children, while seizure freedom was achieved in only 26 and 23.3% of these patients, respectively. The long-term cognitive outcome data was provided for just 10.4% of the adult patients. In contrast, cognitive health data were supplied for 68.9% of the described children of whom 31.9% were moderately or severely disabled. Long-term functional outcomes assessed with various standardized scales were reported in 62.2 and 25.5% of the adults and children, respectively with majority of patients not being able to return to a pre-morbid level of functioning. New onset psychiatric disorders were reported in 3.3% of adults and 11.2% of children recovering from NORSE.

Conclusion: These findings concur with previous observations that the majority of adult and pediatric patients continue to experience recurrent seizures and suffer from refractory epilepsy. Moderate to severe cognitive disability, loss of functional independence, and psychiatric disorders represent a hallmark of chronic NORSE signifying the major public health importance of this disorder.

KEYWORDS

chronic NORSE, febrile infection epilepsy-related syndrome (FIRES), refractory seizures, encephalopathy, cognitive failure, mood disturbances, functional outcomes, seizure outcomes

1. Introduction

New onset status epilepticus (NORSE) and its subcategory Febrile Infection Related Encephalopathy Syndrome (FIRES) have been described in adult and pediatric patients under various terms starting as early as 1950's. The term NORSE was coined by Wilder-Smith in 2005; the definition and clinical criteria were formalized in 2018 (1–3). NORSE encompasses various clinical presentations of *de novo* recurrent refractory seizures without evidence of acute structural, metabolic, or toxic causes (3). The true incidence of NORSE is unknown; however, it may constitute up to 20% of all cases of refractory status epilepticus (4, 5). NORSE most frequently occurs in previously healthy young adults and school-aged children; however, older individuals, including septuagenarians, have also been affected. In adult case series, a higher prevalence has been reported in women. This contrasts with pediatric case series where NORSE predominantly affects boys (1, 6–9). An etiology is identified in up to 50% of the adult patients with NORSE, most of whom suffer from primary or paraneoplastic autoimmune encephalitis (7). On the other hand, paraneoplastic and autoimmune NORSE is rare in children (10–12).

A prodromal phase has been reported in 60–100% of patients with NORSE. The prodrome precedes the onset of seizures and status epilepticus (SE) by 1–14 days (7–9, 13) and includes fever, a cardinal diagnostic criterion of FIRES, in 34–91% of patients (7–9). Other prodromal symptoms include headache, mild gastrointestinal or upper respiratory illness, and behavioral disturbances (7, 8). Electroencephalogram (EEG) abnormalities are present in all NORSE patients, and seizures are detected in more than 88% of patients undergoing continuous video EEG monitoring (7, 8). Brain magnetic resonance imaging (MRI) as well as laboratory examination of serum and cerebrospinal fluid (CSF) for the presence of autoantibodies or abnormal immunoglobulin indexes are routinely performed and are frequently abnormal (7–9).

Strides have been made in evidence-based care for NORSE patients. Criteria for the diagnosis of NORSE has been introduced and accepted by the neurology community (3). In addition, evidence- and experience-based recommendations for the management of patients with NORSE have been published by experts from the International NORSE Consensus Group (14, 15). While significant progress has been made in delineating the diagnostic and treatment approaches for NORSE, less emphasis has been placed on studying clinical outcomes, including the long-term sequalae, after the hospital discharge. Further, the literature focuses primarily on seizure outcomes, as refractory epilepsy represents the most significant disability in survivors of NORSE (1, 2, 6–12, 16–99). However, over two-thirds of patients experience moderate to severe cognitive disability following hospitalization or remain in a vegetative state (5, 6, 92, 93, 99). Reports concerning functional limitations after NORSE are sparse and include components of formal functional assessment or narrative descriptions of impaired academic performance or activities of daily living (1, 2, 6–12, 16–99). The emergence of psychiatric and behavioral disturbances after NORSE have also been described; however, the full spectrum of these complications have not been systematically assessed outside of the time of hospitalization.

In this study, we conducted a systematic review of literature on NORSE and compiled data on the neurological and psychiatric outcomes of NORSE at 30 or more days following hospitalization. The long-term outcomes of SE and refractory SE have been documented in recent systematic reviews where the patient symptoms were assessed starting as early as 30 days after the discharge (100–102). Consistent with previously set criteria (100–102), we considered to use a 30-day mark as an appropriate interval after which the outcomes of SE were considered "long-term." Given that some of these complications may improve over time, we did not restrict the length of follow-up after hospitalization in these reports. We disaggregated the findings in adult and pediatric patients and summarized the key demographic and clinical features of these cohorts. The purpose of this systematic review is to tackle the special circumstance of *de-novo* SE and highlight the spectrum of neurocognitive disabilities in patient recovering from NORSE.

2. Methods

The systematic review protocol was developed using guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (103) and registered in the International Prospective Register of Systematic Reviews (PROSPERO, Center for Reviews and Dissemination number CRD42022361142) (104).

2.1. Search strategy

Literature searches were initially carried out from May 30–June 1, 2021, and later updated with the final update on October 13, 2022. MEDLINE (EBSCOhost), CINAHL (EBSCOhost), APAPsycINFO (EBSCOhost), EMBASE (embase.com, version including 1974-present), Scopus, and the Cochrane Library (including the Cochrane Database of Systematic Reviews and The Cochrane Central Register of Controlled Trials, wiley.com) were searched from inception to the final search date. The search strategy was developed by a librarian (C.S.) in consultation with epileptologist with research interest in neuroimmunology and clinical subspecialty in autoimmune epilepsy (O.T.). Each database search included terms representing the "long-term follow-up" and "NORSE" concepts (see complete search strategies available at https://digitalcommons.unmc.edu/search/14). The "long-term follow-up" concept was represented by a variety of subject headings and keywords. Since none of the databases we used had a subject heading for the "NORSE" concept, this concept was represented by keywords and key phrases alone. The following alternate names and acronyms for NORSE were considered during search strategy development: new-onset refractory status epilepticus, NORSE, febrile infection-related epilepsy syndrome, FIRES, febrile illness-related epilepsy, fever-induced refractory epileptic encephalopathy, idiopathic catastrophic epileptic encephalopathy, severe refractory status epilepticus owing to presumed encephalitis, devastating epilepsy in school-age children, DESC, acute non-herpetic encephalitis with refractory repetitive partial seizures, acute encephalitis with refractory repetitive partial seizures, AERRPS, *de novo* cryptogenic refractory multifocal febrile status epilepticus. The search strategies were designed to retrieve records containing any of these names listed and to retrieve records containing any of the listed acronyms if the record in question also contained a word beginning with one of the following word

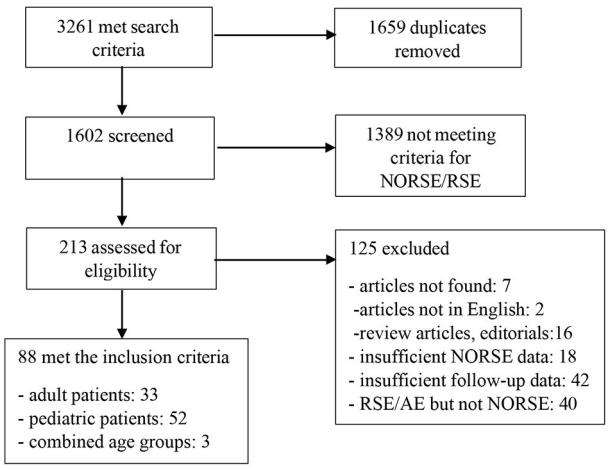

FIGURE 1
Search strategy flow diagram.

trunks: epilep, convul, or seizur. Since no funds were available for translation, English- language filters were applied. Conference abstracts, editorials, and review articles were separated from other search results when filters allowed.

2.2. Study selection and quality assessment

The database searches retrieved 3,261 total records (142 from CINAHL, 24 from the Cochrane Library, 637 from EMBASE, 911 from MEDLINE, 306 from PsycINFO and 1,241 from Scopus, Figure 1). All search results were imported into RefWorks and 1,659 duplicate records were removed using RefWorks' and Zotero duplicate detection tools. A total of 1,602 unique publications remained for title/abstract review (Figure 1). The titles and abstracts were reviewed by two independent neurologists (S.P. and N.G.) for the inclusion criteria and selected articles were chosen for full review. Disagreements between reviewers and inquiries by reviewers were resolved by another reviewer. Reports on other types of SE that did not fulfill the criteria of NORSE as well as those with outcomes reported at <30 days following the discharge were excluded. Case reports and case series were evaluated based on completeness and quality of reporting and were excluded if they did not provide the pertinent information (105).

2.3. Data extraction

Data extraction was performed using a standardized template. In addition to basic demographic data, the following outcomes were extracted: duration of follow-up, proportion of patients with seizures controlled with anti-seizure medications (ASM) or other treatments, proportion of patients with refractory seizures and recurrent SE, presence and severity of acquired cognitive disability with specific reference to memory impairment. In addition, functional outcomes assessed with Modified Rankin Scale (mRS), Clinical Global Impressions of Improvement Scale (CGI-I), Pediatric Cerebral Performance Score (PCPS), or Glasgow outcome score (GOS) at the last follow-up visit and proportion of patients with acquired neurological comorbidities, psychiatric complications, and learning disabilities were extracted.

2.4. Data analysis

Age was determined through weighted means, when possible. The sex distribution, proportions of patients with seizures, SE, cognitive failure, and other comorbidities were assessed when possible. Comparisons of results between the age groups were descriptive only and not statistically assessed. The summaries were disaggregated for the adult patients (19 years and older), the children, and the mixed age cohort. Given that the age range of patients in the individual reports was broad, the outcomes for various age groups could not be stratified. Similarly, given that the range of follow-up time was broad in the individual reports and these intervals were largely non-overlapping, the outcomes for the specific time intervals were not assessed.

3. Results

3.1. Demographic patient characteristics

From 1,602 publications identified by the search, 1,389 reports were excluded after the initial title and abstract screening as they did not meet criteria for NORSE/refractory status epilepticus (RSE), and 213 reports were selected for full manuscript review (Figure 1). Of these 213 articles, 33 studies in adults and 52 studies in children met the inclusion criteria (Figure 1). Three reports contained findings for adult and pediatric age groups. Collectively, the reports contained a description of 280 adult and 587 pediatric patients of which the data on the long-term seizure and cognitive outcomes were available for 212 (75.7 %) adult and 499 (85%) pediatric patients, respectively. In two studies that did not disaggregate findings by age (166 patients total), the data on long-term outcomes were available in 127 (76.5%) patients (51, 59).

In the adult group, the mean age of patients was 34.3 years, and the majority (77.6%) were female. The working diagnosis of NORSE was established in 146 (68.9%) patients, FIRES in 9 (4.3%) patients, new onset super refractory SE (NOSRSE) in 17 (8%) patients, RSE and superrefractory SE (SRSE) in 17 (8%) patients, autoimmune anti-NMDA receptor encephalitis in 2 (0.9%) patients, unspecified autoimmune encephalitis in 19 (8.9%) patients, and acute encephalitis with repetitive recurrent partial seizures (AERRPS) or presumed limbic encephalitis in 2 (0.9%) patients. Pertinent laboratory findings in these patients included the autoantibodies against NMDA receptors (28), $GABA_A$ receptors (1), $GABA_B$ receptors (2), voltage gated potassium channel complex (VGKC, 7), contactin-associated-protein (CASPR,1), type 1 anti-neuronal nuclear protein (ANNA-1, anti-Hu, 1) and GAD-65 proteins (8) in the serum or CSF; however, the tumor status of patients was not consistently recorded. In the large case series on NORSE, paraneoplastic antibodies in patients with confirmed malignancies included anti-Ro (1), anti- NMDA receptor (9), anti-VGKC (3), anti-Hu (3), anti-voltage gated calcium channel (VGCC,

2) antibodies and collapsing response mediator protein 5 (CRMP-5, 1) (5). The identification of infectious agents, including Epstein-Bar virus and other pathogens (Cytomegalovirus, Herpes simplex virus, human immunodeficiency virus, *Mycoplasma pneumoniae*, *Treponema pallidum, Toxoplasma gondii*, Varicella zoster virus, West Nile virus) were reported in 14 patients. Collectively, the etiology of NORSE appeared to be established in 37.7% of 106 patients described in articles meeting our inclusion criteria. Other findings in adult patients were signal abnormalities on the MRI (4) or mass spectroscopy (1) of the brain.

In pediatric studies, the mean age of patients was 7.9 years, and 42.5 % were female. The diagnosis of NORSE or FIRES were established in 149 (29.8%) and 237 (47.4 %) of patients, respectively. Other diagnoses included AERRPS in 35 (7%) patients, devastating encephalopathy in school age children (DESC) in 14 (2.8%) patients, hemiconvulsion-hemiplegia syndrome (HHE) in 35 (7%) patients, SE-related presumed encephalitis in 19 (3.8%) patients, *Mycoplasma pneumoniae* encephalitis in 5 (1%) patients, anti-NMDA receptor encephalitis in 3 (0.6%) patients, as well as anti-GAD encephalitis, steroid-responsive encephalopathy and associated autoimmune thyroiditis (SREAT) or SRSE in 1 patient each (0.2%). The pertinent findings in patients' evaluation included presence of autoantibodies in the serum and CSF specimens in 19 (3.2%) patients. The antibodies against NMDA receptors (2), $GABA_A$ receptors (1), AMPA-GluR3 receptors (1), and GAD-65 protein (6) as well as elevated serum and CSF anti-thyroid peroxidase (TPO) antibodies (1) were documented along with the increase of CSF cytokines such as tumor necrosis factor and interleukins 6 and 10 (1). Genetic deficiencies (5) and secondary hemophagocytic lymphohistiocytosis (3) were also recorded as the possible etiologies of NORSE. Brain MRI examinations were abnormal in 31 patients and revealed various degrees of cortical atrophy (10), signal changes in the claustrum (1), temporal cortical regions (2), and cerebellum (1) as well as bilateral hippocampal atrophy (1).

In two large reports that collectively included 127 adult and pediatric patients, the proportion of female patients was smaller than male (41.7%); but the age of participants was not consistently provided (51, 59). The autoimmune antibodies were not identified in serum and CSF of these patients. The cortical and hippocampal signal abnormalities on brain MRI were reported in 27 patients.

3.2. Seizure outcomes

The duration of follow-up in the adult group ranged from 30 days to 11 years. Seizure outcomes were reported in 198 out of 212 patients (93.4%, Supplementary Table 1). Of these, 10 (5.1%) patients become seizure-free and discontinued the ASMs, while 28 (14.1%) and 15 (7.6%) patients were seizure-free when receiving the ASMs alone or ASM in combination with other treatments, respectively. In the 10 patients who were seizure-free, the treatment status was not reported. Medically refractory epilepsy was diagnosed in 82 (41.4%) patients for whom other treatment approaches were tried, including immunotherapies [steroids, intravenous immunoglobulin (IVIG), tacrolimus, mycophenolate mofetil, rituximab, anakinra, plasma exchange, cyclophosphamide] in various combinations (25) as well ketogenic diet (5), modified Atkin's diet (3), neurostimulation (2) and focal cortical resections (5). Delayed recurrent SE was reported in two patients.

In the pediatric group, the duration of follow-up ranged from 30 days to 20 years. Seizure outcomes were reported for 482 (96.6%) patients (Supplementary Table 2). Forty-seven patients (9.8%) were seizure free without ASMs, while 66 (13.7%) patients achieved seizure control with ASMs alone or when treated with ASMs combined with ketogenic diet. The treatment status in an additional 27 patients was not recorded, although they were reported to be seizure free. Medically refractory epilepsy was documented in 278 (57.7%) patients of whom 34 patients required therapies beyond ASMs, including steroids (3), IVIG (5), tocilizumab (2), anakinra (2), and ketogenic diet (12). Neuromodulation (7) and focal resections (2) were also listed among the treatments for refractory seizures. Recurrent SE was reported in 8 patients.

3.3. Cognitive outcomes

Cognitive outcomes at 30 days or later following the hospital discharge were reported for 22 (10.4%) of the adult patients included in the reviewed literature; most of these patients were described in case reports (Supplementary Table 1). Most of the studies assessed cognitive outcomes subjectively. All available data on neuropsychological testing, including the formal test scores are provided in Supplementary Tables 2, 3. At the last follow-up, 3 patients (13.6%) had normal cognition, 2 (9.1%) had mild cognitive impairment, and 4 (18.2%) and 2 (9.1%) had moderate or severe degrees of cognitive impairment, respectively. Three patients (13.6%) remained in a vegetative state; however, the time of assessment (10 months) was only documented for one patient. Memory impairment was reported in 12 patients (54.5%). Four (33.3%) of these had moderate or severe impairment. Specific reference to working or visual memory impairments were made in 2 patients. Mild naming deficits (1) and persistent impairment of processing speed and verbal memory function (1) were also reported at the last follow-up.

Reports concerning pediatric patients elaborated on cognitive outcomes after hospital discharge more frequently than reports concerning adults. The assessment of cognitive status was documented in 68.9% of all 344 included pediatric patients with NORSE (Supplementary Tables 2, 3). Seventy-eight patients (22.7%) have experienced complete cognitive recovery. Mild impairment was diagnosed in 42 children (12.2%), while moderate and severe loss were noted in 60 (17.4%) and 50 (14.5%) of children, respectively. Thirty patients (8.7%) have remained in a vegetative state. The degree of intellectual disability was not specified in 94 (27.3%) children. References to specific memory impairment were made in reports concerning 19 patients of whom 8 had a severe memory loss. Delayed motor, social, and verbal development were noted in 1 child described in a case report.

3.4. Functional outcomes and activities of daily living

In adult reports, mRS scores and activities of daily living data were included in 123 (58%) and 13 (6.1%) of patients, respectively (Supplementary Table 1). In 37 (30%) patients, the specific values of

mRS were provided and were as follows: 23 patients (30.1 %) with scores of 0–1, 27 (22.5%) with scores of 2–3, and 24 (19.5%) with scores of 4–6. Eight patients had no formal assessment but were noted to return to baseline or had good recovery and have remained autonomous in their day-to-day functioning. Three patients had not regained consciousness. The GOS was reported in 9 (4.2%) patients of whom 2, 1, and 6 had scores of 5, 3, and 1, respectively (Supplementary Table 1). A report of 14 patients had only narrative characterization of the activities of daily living. Eight of these 14 patients were described as being independent and 6 patients as needing assistance. Other assessments included mentioning of a patient's ability to resume previous academic activities (1) and another patient's referral to a supervised nursing facility (1).

Pediatric patients' functional outcomes as assessed with mRS, PCPS, CGI-I, pediatric GOS, and GOS were reported in 61 (12.2%), 63 (12.6%), 5 (1%), 18 (3.6%), and 16 (3.2%) patients, respectively (Supplementary Table 2). There were 6, 2, and 6 patients with the mRS scores of 0–1, 2–3, and 4–6, respectively. Sixty-three patients were assessed with PCPS. Favorable outcomes, defined as score ≤ 2, were noted in 12 (19.1%) children while unfavorable outcomes (i.e., score >3) were noted in 51 (80.9%) patients. The outcomes assessed with CGI-I were distributed as follows: favorable (i.e., score of 2–3) in 3 patients, and without change (i.e., score 4) in 2 patients. The subdomains of communication and autonomy were reported in 5 patients. Pediatric GOS was used in two studies to assess outcomes with a score of 1 and 4 corresponding to the good recovery and vegetative state, respectively. There were 4, 3, 7, and 4 patients with scores of 1, 2, 3, and 4, respectively. Three other studies utilized GOS with scores that were defined differently such that 5 was consistent with good recovery and 2 was consistent with vegetative state. Scores of 5, 4, 3, and 2 were reported in 7, 4, 1, and 4 patients, respectively. Of 87 patients, for whom the activities of daily living were characterized, 55 (63.2%) were independent and 32 (36.8%) required assistance. In the narrative descriptions of the functional status, there were reports of resuming premorbid academic activities (3), having some academic difficulties (14), requiring special education (1), developing learning disabilities (10), having attention deficits and executive dysfunction (2), and developing severe developmental delay (5).

3.5. Acquired psychiatric comorbidities and neurological deficits

The emergence of new onset psychiatric disorders in adult survivors of NORSE were reported in only 7 (3.3%) patients (Supplementary Table 1). These manifestations included schizophrenia (1), attention deficit disorder (2), Capgras syndrome (1), psychomotor agitation (1), and personality changes (2). Various neurological deficits were reported in 6 patients and included bilateral lower extremity weakness and mild ataxia (1), right hemiparesis and dysphasia (1), mild receptive dysphasia (1), and moderate language impairment (1) as well as unspecified gait disturbance (1).

The description of psychiatric complications of NORSE were more common in the pediatric literature and were provided for 56 (11.2%) of all included children (Supplementary Table 2). Reports concerning 56 of the pediatric patients mentioned behavioral disturbances of various severity: 13 developed aggression, 2 suffered from emotional lability, 4 had apathy, and 1 had conduct disorder. Mild or severe attention deficit hyperactivity disorder and various manifestations of attention impairment were diagnosed in 9 patients and an autism spectrum disorder was reported in 1 patient. One child attempted suicide. Various neurological sequalae of NORSE were described in 108 (21.6%) children. Specifically, the long-term motor deficits included hemiplegia (35, 32.4%), unspecified motor impairments (36, 33.3%) and unilateral tongue weakness (1, 0.01%). Other impairments included visual field deficits (1), peripheral neuropathy (2), ataxia (3), choreoathetoid movements (1), and tremor (3). Language deficits were reported in 20 (18.5%) patients. One of these children improved after the initiation of responsive neurostimulation.

4. Discussion

In the present study, we systematically reviewed and summarized the literature on the long-term neurological and psychiatric outcomes of NORSE in adult and pediatric patients who survived longer than 30 days after hospital discharge. We found that seizure status is assessed in over 90% of patients who had the data on the long-term outcomes. However, the cognitive outcomes were only included in one tenth of these reports in adults and nearly two-thirds of the reports concerning children. Functional outcomes were included in more than 60% of studies of adults and more than 25 % of studies of children. Unfortunately, the functional outcomes were measured using four different outcome scales limiting our ability to synthesize study results into an understanding of the overall scope of associated disability. New onset psychiatric disorders were under-reported and were only included in a small proportion of the reports. Overall, these findings reflect the lack of standardization for the reporting of outcomes, particularly for reporting symptoms other than seizures, and may also reflect a gap in the care of these patients after the initial hospital encounters.

4.1. Seizure outcomes

Consistent with previous observations, in this systematic review, we found that majority of adults and children with NORSE will continue to have seizures 30 days or later after the hospital discharge. Of those who continue to have seizures, 41.1% of adults and 57.7% of children will remain refractory to either conventional ASDs used alone or in combination with immunotherapies, ketogenic diet, and neurostimulation. The pathogenesis of recurrent seizures in NORSE is not clear. Several proposed mechanisms of uncontrolled seizure generation during the acute phase of NORSE included aberrant signaling in the interleukin (IL)-1 and toll-like receptor (TLR)-mediated pathways, overactivation of the NLRP3 inflammasome as well as functional or genetic deficiency of IL-1 receptor antagonist activity (48, 67, 106–113). These mechanisms can also be involved in late seizure recurrence in survivors of NORSE. Of note, chronic epilepsy in cryptogenic NORSE develops without a latent period which is distinct from the post-infectious epilepsies associated with viral or bacterial pathogens (10, 114).

4.2. Cognitive outcomes

Our findings add to those of previous studies that showed only a small proportion of patients have achieved their pre-morbid cognitive function after they were discharged from the hospital (9). Nearly one-third of adults or children continue to suffer from moderate and severe intellectual disability. In a case series of 14 pediatric patients with NORSE, all children attended special education in the later course, and seven patients had severe cognitive failure. The primary impairment involved deficits in frontal lobe function and was manifesting as the lack of motor and speech initiative, major slowness, perseveration, and poor attention (9, 10). While there were no specific patterns in neuropathological findings in NORSE, gliosis, laminar cortical necrosis, and diffuse cortical atrophy are the shared common features (1, 6, 99, 115, 116). Moreover, various degrees of persistent inflammation and structural changes such as mesial temporal sclerosis may contribute to the severity of cognitive phenotype.

Chronic cognitive disability after NORSE represents the major public health problem. Since many patients are previously healthy, severe cognitive impairment or vegetative states after NORSE are devastating. A need exists for comprehensive chronic care that includes cognitive rehabilitation for patients and respite for caregivers. The mechanism of cognitive failure in NORSE is unclear, but it is likely linked to the severity and duration of seizures (91). In subtypes of autoimmune encephalitis that can manifest as NORSE (e.g., anti-NMDA receptor encephalitis), antibodies were found to be directly pathogenic for memory failure and seizures. However, the pathogenesis of epileptic encephalopathy in other antibody-mediated or cryptogenic NORSE is not clear (7, 117, 118). The lack of the uniformed objective measurements of cognitive function noted in the reviewed literature represents a major shortcoming of this research. More systematic and comprehensive objective testing of survivals is needed in future studies.

4.3. Functional outcomes and activities of daily living

We found that a comprehensive approach in documenting the functional outcomes in survivors of NORSE were lacking. Further, only one-fourth of the children and 60% of adults in our study had their functional outcomes assessed and reported. While the mRS was the most common outcome scale applied in adult patients, there were three additional outcomes scales used in pediatric patients. Such inconsistent data availability in outcomes particularly for the pediatric patients introduce a potential bias and limits definitive conclusions. In the recent systematic analysis of functional outcomes in autoimmune encephalitis, it was established that mRS had poor sensitivity for cognitive disability and mood disturbances in encephalitis at follow-up (119). There was an additional focus on the academic performance and other aspects of social functioning in children, which were consistently underreported in the adult literature. Given that many patients with NORSE have now survived for several decades, a more standardized approach in categorization of their functional abilities is needed to monitor their recovery and develop guidelines for individualized rehabilitation.

4.4. Acquired psychiatric comorbidities and neurological deficits

Psychiatric comorbidities, including recurrent psychosis are frequently encountered in severe epileptic encephalopathies (120); however, the prevalence of mental illness in association with recent refractory SE is unknown. Multiple factors could contribute to the development of psychosis and depression in patients recovering from NORSE, including the individual vulnerability to the effects of ASDs or immunotherapy as well as prolonged brain hypoxia (121). The presence of specific autoimmune antibodies (such as anti-AMPA or anti-NMDA receptor antibodies) in NORSE with established etiologies can guide the anticipation of chronic psychiatric sequalae (122). The accounts of new onset psychiatric disorders in only 3.3 and 11.2% of the adults and pediatric patients with chronic NORSE likely reflects underreporting and insufficient attention to these comorbidities on the part of neurologists involved in care of these patients.

4.5. Limitations

Our study has several limitations. We found that the majority of reports on long-term outcomes of NORSE are focused on seizure status while other domains of the neurological and psychiatric health were assessed and commented on inconsistently. This likely represents a reporting bias and underreporting in various relevant health domains for the most severely disabled patients (e.g., those in vegetative state) and those whose seizures were under better control. This limits our conclusions regarding the prevalence of multiple manifestations of chronic NORSE other than seizures. Given the retrospective and observational design of most reviewed studies, it is unclear whether the severity of SE and its refractoriness can be linked to any of the reported outcomes. This impedes our progress in understanding the mechanisms of cognitive failure and development of psychiatric comorbidities in NORSE. Given that the analysis in specific age categories in pediatric patients was not feasible, the outcomes of SE at different stages of brain development and the effects of age-related compensatory abilities have not been accounted for. Likewise, the inability to disaggregate the data into the specific duration of follow-up precluded the analysis of outcomes at different stages of recovery from NORSE. Lastly, we acknowledge the selection and information bias that was not specifically assessed in this systematic review.

5. Conclusions

We found that most patients with chronic NORSE continue to experience recurrent seizures, and seizure treatment and reporting remain the main focus of the literature. Documentation of cognitive disability, loss of functional independence, and onset psychiatric manifestations have been inconsistent and should be interpreted with caution given the methodological limitations. While challenging to implement due to the rarity and geographic dispersion of NORSE, future prospective studies may help provide high-quality evidence to guide the management and rehabilitation of these patients.

Author contributions

OT: conceptualizing the study, drafting of the manuscript for content, and major role in the analysis and interpretation of data. SP: main role in the acquisition and analysis of data. CS: main role in the acquisition and analysis of data as well as study design. YP: acquisition and analysis of data. NG: drafting of the manuscript and main role in the acquisition and analysis of data as well as study design. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1095061/full#supplementary-material

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Specific profiles of new-onset vs. non-inaugural status epilepticus: From diagnosis to 1-year outcome

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While new-onset status epilepticus (NOSE) is a harbinger of chronic epilepsy, prospective medical data are sparse in terms of specifying whether the evolution of status epilepticus (SE) and seizure expression in NOSE resembles what occurs in patients who have already been diagnosed with epilepsy [non-inaugural SE (NISE)] in all aspects apart from its inaugural nature. The aim of this study was to compare the clinical, MRI, and EEG features that could distinguish NOSE from NISE. We conducted a prospective monocentric study in which all patients ≥18 years admitted for SE over a 6-month period were included. A total of 109 patients (63 NISE and 46 NOSE cases) were included. Despite similar modified Rankin scores before SE, several aspects of the clinical history distinguished NOSE from NISE patients. NOSE patients were older and frequently had neurological comorbidity and preexisting cognitive decline, but they had a similar prevalence of alcohol consumption to NISE patients. NOSE and NISE evolve in the same proportions as refractory SE (62.5% NOSE, 61% NISE) and share common features such as the same incidence (33% NOSE, 42% NISE, and $p = 0.53$) and volumes of peri-ictal abnormalities on MRI. However, in NOSE patients, we observed greater non-convulsive semiology (21.7% NOSE, 6% NISE, and $p = 0.02$), more periodic lateral discharges on EEG ($p = 0.004$), later diagnosis, and higher severity according to the STESS and EMSE scales ($p < 0.0001$). Mortality occurred in 32.6% of NOSE patients and 21% of NISE patients at 1 year ($p = 0.19$), but with different causes of death occurring at different time points: more early deaths directly linked to SE at 1 month occurred in the NOSE group, while there were more remote deaths linked to causal brain lesions in the NISE group at final follow-up. In survivors, 43.6% of the NOSE cases developed into epilepsy. Despite acute causal brain lesions, the novelty related to its inaugural nature is still too often associated with a delay in diagnosing SE and a poorer outcome, which justifies the need to more clearly specify the various types of SE to constantly raise awareness among clinicians. These results highlight the relevance of including novelty-related criteria, clinical history, and temporality of occurrence in the nosology of SE.

KEYWORDS

status epilepticus, new-onset status epilepticus, new-onset refractory status epilepticus (NORSE), peri-ictal MRI abnormalities, outcome, epilepsy, refractory status epilepticus (RSE)

1. Introduction

It is interesting to note that recent acronyms and definitions of status epilepticus (SE) include the following references to time and the novelty of occurrence: *new-onset* status epileptic (NOSE) (1), *new-onset* refractory SE (NORSE) (2, 3), *late-onset* absence SE (4), and *subacute* encephalopathy syndrome in alcoholics (SESA) (5). Could the mode of onset, novelty, and temporal context be key to understanding SE? What makes NOSE a specific clinically relevant pathological entity that is distinguishable from other types of SE, i.e., non-inaugural SE that occurs in patients with epilepsy (NISE)?

Only recently have the temporality of onset and novelty become an integral part of the definitions of SE. Since the pioneer definitions of SE (4), many "mechanistic" or "operational" definitions of SE have been proposed (4, 6–10). Until now, they have been exclusively based on semiology (convulsive or non-convulsive, generalized or focal, etc.). The temporal dimension has long been considered regarding the duration of SE but not in the context of its onset. Operationally, NOSE is defined as "prolonged seizures lasting *more than 5 min* or the presence of recurrent seizures without return to baseline in between *in patients with no previous history of epilepsy*" (11). However, this definition remains non-consensual. SE nosology is constantly evolving due to the clinical heterogeneity of its semiology, a complex poorly understood pathophysiology (12, 13), multiple etiologies (14), and difficulties conducting prospective studies.

Clarifying the definition of NOSE is essential as the incidence is significant. Approximately half of all adult cases of SE (up to 59%) are inaugural in non-epileptic patients (15–20). The incidence of NOSE was found to be 16.3/100,000 to 36/100,000 adults per year depending on the cohort and whether or not the new ILAE 2015 definition and classification of SE was taken into account (21, 22). However, despite the incidence, knowledge of the clinical, EEG, and MRI spectrum of NOSE in adults is mostly based on retrospective data (11, 20, 23–25).

One of the few consensual elements concerning NOSE is a poor prognosis and a possible progression to refractory SE (i.e., NORSE) (24, 26–28). Mortality in 1 month is 20–61% depending on the cohort. Factors of poor prognosis are the age of the patient [especially over 65 years (11)], etiology, and the duration of the SE (15–17, 23, 24, 29, 30). Tracheal intubation and co-infections are additional factors of adverse outcomes (23).

In survivors, a poor prognosis for NOSE also suggests the onset of a chronic illness. More than 58% of survivors may experience seizures, mainly related to acute or progressive brain injury, the duration of SE (significant threshold at 24 h) being the only independent predictor of the development of chronic epilepsy after SE (27). Paradoxically, some series also showed that progression to NORSE had no influence on functional outcome or mortality at the last follow-up, while SE semiology (non-convulsive vs. convulsive and loss of consciousness) or age above or equal to 65 did not predict progression to NORSE (11).

If NOSE is a precursor to chronic epilepsy, it could be hypothesized that its presentation resembles NISE in all aspects apart from its inaugural nature. However, the medical literature is unable to demonstrate this. None of the studies cited above investigated the discriminating features between NOSE and NISE. In addition, little information is available on the paraclinical aspects associated with NOSE, and the most recent publications frequently focused on the refractory subtype of these *de novo* SE (2, 3, 31).

Although it is now well-established that NOSE can develop into epilepsy, to our knowledge, there is no prospective trial that compares the clinical, MRI, and EEG patterns that may distinguish NOSE from NISE. Does the mechanism that leads to epilepsy result in a specific clinical pattern of SE? Are there imaging and electrophysiological criteria that distinguish NOSE from NISE? Do NOSE and NISE progress similarly and have the same prognosis?

To clarify these questions, we conducted a prospective monocentric study to multimodally compare NOSE and NISE at baseline (before SE), during SE, and at follow-up in 1, 3, and 12 months. The aims of this study were (1) to compare clinical and paraclinical (brain imagery and electrophysiological recordings) features of NOSE (including NORSE) and NISE; (2) to study the outcome of SE at 1, 3, and 12 months as well as the prognostic factors; and (3) more specifically to analyze peri-ictal MRI abnormalities. We hypothesized that NOSE and NISE each have their own specificities, particularly in terms of outcomes. We hoped to identify new markers for positive diagnosis and the prognosis of inaugural SE.

2. Methods

2.1. Design and population

Our work is a prospective, observational, descriptive, single-center study (Figure 1). We collected clinical, neuroradiological, and electrophysiological data for each patient admitted consecutively to Toulouse University Hospital from December 2015 to June 2016 (1) for SE and (2) SE not clinically diagnosed immediately on admission but subsequent to the first EEG. To select these patients, all EEGs performed during this period and all requests for EEGs for SE were screened. The inclusion criteria were a diagnosis of SE confirmed by a neurologist, exclusion of post-anoxic SE, age of 18 years and older, and non-refusal to participate in the study. The use of the data in our study was approved by the Regional Ethics Committee at Toulouse University Hospital (CPP Sud-Ouest no. 04-1215).

2.2. SE definitions and classifications

Epilepsy is defined as a lasting predisposition to generate seizures and the cognitive, behavioral, psychological, and social consequences of this condition (32). NOSE was defined as the occurrence in patients without a history of SE or uncured epilepsy (cured epilepsy is the absence of seizures in the absence of treatment for more than 5 years). The following functional and semiological definitions were used for either NOSE or NISE.

Abbreviations: ASM, Anti-seizure medication; CSF, Cerebrospinal fluid; EEG, Electroencephalogram; EMSE, Epidemiology-based mortality score in status epilepticus; FLAIR, Fluid-attenuated inversion recovery; GPDs, Generalized periodic discharges; MRI, Magnetic resonance imaging; mRS, Modified Rankin Scale; NCSE, Non-convulsive status epilepticus; NOSE, New-onset status epilepticus; NORSE, New-onset refractory status epilepticus; NIRSE, Non-inaugural refractory status epilepticus; NISE, Non-inaugural status epilepticus; PLDs, Periodic lateralized discharges; PMAs, Peri-ictal MRI abnormalities; SE, Status epilepticus; SESA, Subacute encephalopathy with seizures in alcoholics; STESS, Status epilepticus severity score.

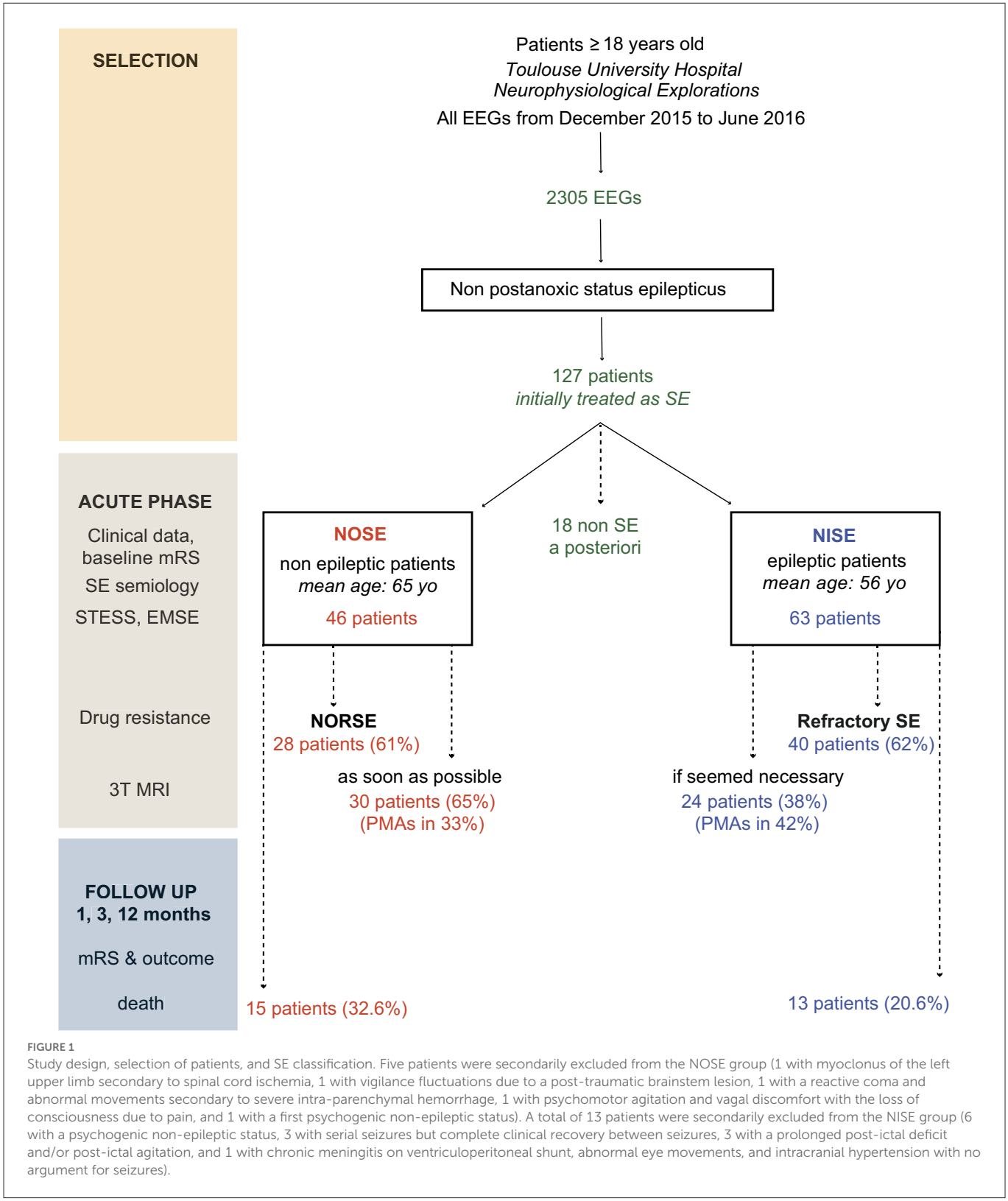

FIGURE 1
Study design, selection of patients, and SE classification. Five patients were secondarily excluded from the NOSE group (1 with myoclonus of the left upper limb secondary to spinal cord ischemia, 1 with vigilance fluctuations due to a post-traumatic brainstem lesion, 1 with a reactive coma and abnormal movements secondary to severe intra-parenchymal hemorrhage, 1 with psychomotor agitation and vagal discomfort with the loss of consciousness due to pain, and 1 with a first psychogenic non-epileptic status). A total of 13 patients were secondarily excluded from the NISE group (6 with a psychogenic non-epileptic status, 3 with serial seizures but complete clinical recovery between seizures, 3 with a prolonged post-ictal deficit and/or post-ictal agitation, and 1 with chronic meningitis on ventriculoperitoneal shunt, abnormal eye movements, and intracranial hypertension with no argument for seizures).

The definitions used for *generalized* and *focal convulsive* SE were (10, 21, 33) the occurrence of at least two epileptic seizures in a short interval without complete recovery of a stable neurological status between seizures; ictal clinical or electrical activity lasting 5 min or more for generalized seizures and 10 min or more for focal seizures; serial seizures; and seizures followed by a coma or persistent confusion.

The definition used for *non-convulsive* SE (NCSE) was based on the Salzburg consensus criteria (34, 35). We considered that an NCSE was *certain* if there was an association with an acute

qualitative or quantitative alteration of consciousness without prominent motor symptoms *or* persistent after a clinical seizure with motor manifestation, not otherwise explained, *and* electrical confirmation by EEG (pattern of epileptiform discharges at a frequency >2.5 Hz present for more than 10 recorded seconds). When epileptiform discharges were present <2.5 Hz in the worst 10-s epoch or there was no epileptiform discharge but only continuous rhythmic delta-theta activity >0.5 Hz, the following secondary criteria were fulfilled: (a) typical spatio-temporal evolution or (b) subtle clinical ictal phenomena were present during the patterns, or (c) a clear clinical *and* EEG improvement after intravenous administration of an appropriately chosen anti-seizure medication (ASM) was documented.

2.3. Clinical data

In the acute phase, we collected the following data: age, gender, personal history, modified Rankin score (mRS) before SE (at baseline), medications, clinical symptoms of the seizures observed *during* SE, and *post-ictal* deficit. Severe and life-threatening complications were specified: respiratory distress, including infectious pneumonia, hemodynamic instability (systolic blood pressure <90 mmHg; the need for vasoamines), and traumatic complications.

SE duration was calculated or estimated through a combination of clinical and EEG data. SE was considered refractory if it persisted 30 min after the introduction of a first- and second-line ASM (9, 36) and super-refractory if it persisted at least 24 h after the start of general anesthesia (37, 38).

The etiologies and/or contributing factors of SE were classified according to the ILAE Task Force definition: acute etiologies, sequelae or old structural abnormalities, progressive etiologies, known epileptic syndromes, and unknown etiologies (21, 39). SE severity was rated by two scales, namely, the Status Epilepticus Severity Score (STESS) (40) and the Epidemiology-Based Mortality Score in Status Epilepticus (EMSE) (41).

The cognitive status of non-epileptic patients before SE was estimated using the long version (a 26-item questionnaire) of the IQ CODE (42). In the literature, the threshold chosen for diagnosing dementia is 3.4/5 (43).

The chronology of follow-up was 1, 3, and 12 months to detect early, medium-term, and late complications, respectively (mRS, onset of recurrent epileptic seizures or new SE, and death). Cognitive complaint and focal neurological deficit were specified at 3 months.

2.4. Electrophysiological data

Scalp-EEGs (9–21 surface electrodes, 256 Hz sampling rate) combined with video and ECG were recorded with the Deltamed system (Natus Medical Incorporated). At least 20 min were recorded for each patient (12 patients were monitored for several hours). The time period between the first EEG and the onset of symptoms was noted. EEG recordings were analyzed by clinical electrophysiologists (JC, MB, MD, RD, and LV). EEGs were classified as "normal," "sedation EEG," "ictal," or "post-ictal" EEG. Epileptic activities were divided into "periodic discharges," "rhythmic delta discharges," and "paroxysmal abnormalities" (i.e., spikes, polyspikes, and spikes-and-waves) (21).

2.5. MRI

We used two 3T imagers (Magnetom Skyra, Siemens Healthcare and Achieva, Philips Medical System) in the clinical neuroradiology department. An MRI was performed urgently as soon as the patient's condition allowed, ideally within 72 h of the diagnosis of NOSE and if considered necessary for the care of patients with NISE. A minimum of the following sequences was performed: DWI, ADC mapping, fluid-attenuated inversion recovery (FLAIR), T1 with gadolinium, and gradient-recalled echo T2*. The presence of PMAs in DWI and FLAIR sequences, the volume of PMAs in DWI, the presence and type of old cerebral lesions, and SE etiology were analyzed by a trained neuroradiologist and neurologist (FB and MB). When other lesions (peritumoral edema, gliosis, acute stroke, etc.) could explain the abnormalities in DWI and FLAIR, these were not considered as PMAs.

We semi-automatically quantified the PMA volume in DWI using OLEA software in a one-shot analysis with manual correction [Olea Sphere® version 2.3, cutting thickness of 3 or 4 mm, technique validated for ischemic stroke (44)]. The PMA volume was estimated using the average of three different segmentations for each patient. The standard zones of the magnetic susceptibility artifact were systematically trimmed.

If an MRI control was required, it was scheduled on the same 3T machines within 3 months of the SE.

2.6. Statistical analyses

To compare the NOSE and NISE groups, we used the chi-square test for qualitative variables, except when the theoretical numbers were <5, in which case, Fisher's test was used. To compare quantitative variables, we used the Wilcoxon test. To limit the risk of type-1 errors associated with multiple comparisons, we corrected the alpha values using the Bonferroni method. The alpha values to be considered are indicated below the figures or tables (in general, the alpha value = 0.05/90). Due to the inherent heterogeneity of clinical data and the multiple comparisons made, we considered "tendencies" for $p < 0.05$ but above the corrected threshold. We only considered significant p-values below the corrected alpha values. For *post-hoc* analyses, Tukey's test was used (p-values automatically adjusted for multiple comparisons).

To study the impact on outcome (mRS) at different timestamps for predictive factors such as the presence or absence of PMA, drug resistance, or status epilepticus, we performed multiple linear regressions. We used linear mixed-effects models in which the variable "patient" was considered a random effect. The variables "measurement time" (baseline, first month, third month, and twelfth month), drug resistance (1/0), with or without PMA (1/0), and new-onset status epilepticus (1/0) were considered as fixed effects. Finally, Pearson correlations were performed. The corrected p-value was considered for the significance threshold for linear mixed-effect models, and the Pearson correlation was 0.017 (0.05/3).

3. Results

3.1. A large prospective cohort of SE including NOSE and NISE

During the 6 months, 2,305 EEGs were performed, allowing the inclusion of 127 patients who had been treated for SE. A total of 18 patients initially considered as having SE were excluded after revision of the diagnosis *a posteriori*: five patients from the NOSE group and 13 epileptic patients from the NISE group. Therefore, 109 patients (46 NOSE and 63 NISE cases) were finally included (Figure 1).

3.2. Clinical history distinguishing NOSE and NISE patients

Clinical data are presented in Table 1. Despite a similar level of autonomy on the mRS before SE, patients experiencing NOSE tended to be older ($p < 0.01$, alpha = 0.0006). The same proportion of excessive alcohol consumption, psychiatric history, and use of psychotropic drugs was found in both groups. Alcohol abuse or dependence was directly involved in 5 NOSE patients and 6 NISE patients. The IQ code before SE was obtained for the NOSE group only: 28/46 (61%) patients had a score of ≥3.4/5, which is above the threshold indicating significant cognitive impairment that affects autonomy in daily life. All patients in the NISE group had been on ASM (median = 1, min = 1, max = 5). In total, 24 of 57 NISE patients (42%) had a history of SE (data are lacking for six subjects). Epilepsy was considered stabilized (seizure-free patients) for 38 of 59 patients before the onset of SE (data are lacking for four patients).

3.3. A higher frequency of acute brain lesions on imagery in NOSE

Acute brain lesions on imagery were significantly more frequent in the NOSE group (n = 10, $p < 0.0001$, and alpha = 0.0006). This included three severe traumatic brain injuries, three infectious diseases (pneumococcal meningitis, HSV1 herpes meningoencephalitis, and empyema with extensive cerebral venous thrombosis), 1 posterior reversible encephalopathy syndrome, 1 inflammatory cerebral amyloid angiopathy, 1 junctional ischemic stroke (M1 stenosis), and 1 undetermined meningoencephalitis leading to NORSE. Cases of acute brain etiologies in NISE patients were 2 severe head traumas (one of which was due to acute alcohol intoxication) and 1 ischemic stroke during meningioma surgery.

Progressive etiologies were all already known before SE in the NISE group and included a large majority of brain tumors (5 glioblastomas, 3 meningiomas, 2 brain metastases, and 1 cerebral lymphoma) and 1 patient with Alzheimer's disease and cerebral amyloid angiopathy, whereas 5 of 7 were discovered during SE evaluation in the NOSE group (2 glioblastomas, 1 brain metastases due to small cell lung cancer, 1 brain lymphoma recurrence, 1 cerebral cavernoma, and 2 cases of Alzheimer's disease).

Remote brain lesions were mainly post-traumatic and of a vascular, ischemic, or hemorrhagic nature.

3.4. Other heterogeneous acute factors that trigger NOSE and NISE

Other acute triggers could be associated and included forgetting ASM for 13 NISE patients (20.6%), sleep deprivation (4 NISE patients), stress (2 NISE patients), fever/sepsis (5 NOSE and 8 NISE patients), and drugs that lower the epileptic threshold (4 NOSE and 6 NISE patients). Among the 4 patients in the NOSE group with no etiology found at the time of SE, two were chronically heavy consumers of cannabis.

3.5. Beyond novelty or a history of epilepsy, a different expression of NOSE and NISE

NOSE tended to be diagnosed later, with a maximal delay in the diagnosis of 15 days (vs. 30 h for NISE, $p = 0.06$, alpha = 0.0006) and a median of 60 min for NOSE vs. 10 min for NISE, resulting in diagnostic and therapeutic delays ($p = 0.006$ and $p = 0.09$, respectively, alpha = 0.0006) (Table 1). SE duration was heterogeneous: on average 62 h for NOSE vs. 23 h for NISE ($p = 0.33$). In both groups, SE lasted ≥24 h in one-third of the patients and if associated with severe complications required resuscitation management in 35% of the cases. The mean duration of hospitalization was 13 days for the NOSE group [min = 4, max = 96, median = 10 days] and 10 days for the NISE group [min = 1, max = 117, median = 7 days]. Progression to refractory SE was not significantly different between the groups ($p = 0.93$).

The following heterogeneous types of SE were encountered in both NOSE and NISE: generalized convulsive, focal convulsive, initially non-convulsive, or secondary generalized convulsive in similar proportions (Table 1). However, secondary non-convulsive SE tended to be more prevalent in NOSE than in NISE (21.7% in NOSE, 6% in NISE, $p = 0.02$, alpha = 0.0006). NOSE patients tended to have more post-ictal focal neurological deficits and a greater number of severe complications, especially hemodynamic complications ($p = 0.04$ and alpha = 0.0006).

SE severity was significantly higher in NOSE than in NISE. STESS and EMSE scores were above the poor prognosis threshold in 78% of NOSE vs. 36.5% of NISE patients (36/46 ≥ 3/6 vs. 23/63; $p < 0.0001$; alpha = 0.0006) and 63% vs. 28.5% (29/46 ≥ 64/255 vs. 18/63; $p < 0.0001$; and alpha = 0.0006), respectively.

3.6. Different proportions of poor outcomes between baseline and the last follow-up in NOSE and NISE

There was no global effect of the inaugural or non-inaugural nature of SE on the outcome ($p = 0.373$) according to a mixed-effects model. Nevertheless, there was an interaction between the type of SE and the mRS at baseline, and in 1, 3, and 12 months ($p < 0.017$). This suggests that mRS between baseline and 12 months changes at a different speed between the two groups of patients (Figures 2, 3). For NISE patients, mRS at baseline was only different from the mRS at 12 months (Tukey's HSD test, diff = 1.05, and $p = 0.0005$). For NOSE patients, the mRS at baseline was different from the mRS at 1 month (Tukey's HSD test; diff = 1.28; and $p = 0.0033$), 3 months (Tukey's

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TABLE 1 Clinical characteristics of NOSE and NISE patients.

	Total SE	NOSE	NISE	*p*
	n = 109	*n* = 46	*n* = 63	
Female gender	52 (47.7%)	21 (45%)	31 (49%)	0.71
Age (years)	60	65.7 (22–101)	56.3 (15–90)	0.01^
Neurologic history	65 (60%)	24 (52%)	41 (65%)	0.49
Cured epilepsy	3	3 (6.5%)	0	0.14
Severe cranial trauma	29	7 (15%)	12 (19%)	0.58
Stroke	23	15 (32.6%)	8 (12.7%)	0.01
Cerebral hemorrhage	11	2 (4.3%)	9 (14 %)	0.11#
Cerebral tumors	14	2 (4.3%)	12 (19%)	0.02
CNS infections	3	0	3 (4.7%)	0.26#
Psychiatric history	24 (22%)	10 (21.7%)	14 (22%)	0.95
Alcohol abuse	24 (22%)	8 (17.4%)	16 (25%)	0.32
Daily use of psychotropic drugs	44 (40%)	17 (37%)	27 (43%)	0.54
IQ code ≥ 3.4/5	–	28 (60.9%)	–	
Modified Rankin Scale before SE				
0–1	38	18 (39%)	20 (31.7%)	0.55
2–3	61	22 (47.8)	39 (62%)	0.2
4–5	10	6 (13%)	4 (6.3%)	0.39
SE type				
Generalized convulsive	39 (35.5%)	16 (34.7%)	23 (36.5%)	0.85
Focal convulsive	44 (40%)	20 (43.5%)	24 (38%)	0.57
Non-convulsive	26 (24%)	10 (21.7%)	16 (25.5%)	0.66
Secondary non-convulsive	14 (12.8%)	10 (21.7%)	4 (6%)	0.02
Secondary generalized convulsive	29 (26.6%)	14 (30.4%)	15 (24%)	0.44
Median time between SE and diagnosis (min-max)	30 min (0–15 d)	60 min (0–15 d)	10 min (0–30 h)	0.006^
Median time between SE and therapeutic care (min-max)	90 min (0–15 d)	90 min (10 min–15 d)	60 min (5 min–30 h)	0.09^
Average number of ASMs needed to stop SE (min-max)	3 (1–7)	3 (1–7)	2.7 (1–6)	0.24^
ASMs used for SE				
Benzodiazepines	95 (87%)	41 (89%)	54 (85.7%)	0.81
Phosphenytoin	45 (41%)	25 (54%)	20 (31.7%)	0.03
Broad spectrum ASM	68 (62%)	27 (59%)	41 (65%)	0.63
Narcotics	34 (32%)	19 (41.3%)	15 (23.8%)	0.08
Severe complications	42 (38.5%)	23 (50%)	19 (30%)	0.057
Respiratory	30 (27.5%)	15 (32.6%)	15 (24%)	0.42
Hemodynamic	20 (18%)	13 (28.2%)	7 (11%)	0.04
Trauma-related	13 (12%)	6 (13%)	7 (11%)	0.99
Intensive care	39 (35.5%)	16 (35%)	23 (36%)	0.85
Ventilated-intubated	26 (24%)	13 (28%)	13 (20%)	0.49

(Continued)

TABLE 1 (Continued)

	Total SE $n = 109$	NOSE $n = 46$	NISE $n = 63$	p
Post-ictal vigilance disorders	72 (66%)	34 (73.9%)	38 (60%)	0.2
Focal post-ictal neurological deficit	76 (70%)	37 (80.4%)	39 (62%)	0.06
STESS median	3/6	4/6	2/6	<0.0001
Poor outcome threshold ≥ 3/6	59 (54 %)	36 (78%)	23 (36.5%)	
EMSE median	58/255	67/255	50/255	<0.0001
Poor outcome threshold ≥ 64/255	47 (43 %)	29 (63%)	18 (28.5%)	
Average SE duration (min-max)	40 h (15 min–41 d)	62 h (15 min–41 d)	23 h (30 min–8 d)	0.33
Pharmacoresistance				
Refractory SE	68 (62%)	28 (61%)	40 (62.5%)	0.93
Super-refractory SE	9 (8%)	5 (11%)	4 (6%)	0.49[#]
SE etiologies				
Acute etiologies	25 (23%)	20 (43.5%)	5 (7.9%)	<0.0001
Acute cerebral injury on MRI	13 (12%)	10 (21.7%)	3 (4.8%)	0.01
Remote etiologies	41 (37.7%)	14 (30.4%)	27 (42.9%)	
Without acute trigger	16 (14.7%)	7 (15.2%)	9 (14.3%)	0.73
Remote with acute trigger	25 (23 %)	7 (15.2%)	18 (28.6%)	0.09
Progressive etiologies	17 (15.6%)	7 (15.2%)	10 (15.8%)	0.93
Defined electroclinical syndromes	22 (20%)	1 (2.1%)	21 (33.3%)	<0.0001
With acute trigger	12 (11%)	1 (2.1%)	11 (17.4%)	0.01
Unknown/cryptogenic	4 (3.7%)	4 (8.7%)	0	0.029[#]
Mortality				
At 1 month	11 (10%)	7 (15.2%)	4 (6.4)	0.20[#]
At 3 months	16 (14.7%)	11 (24%)	5 (8%)	0.02
At 1 year	28 (25.7%)	15 (32.6)	13 (20.6%)	0.19

Psychotropic drugs included benzodiazepines and hypnotics, serotonin reuptake inhibitors, and neuroleptics. ASM include levetiracetam, sodium valproate, lacosamide, lamotrigine, carbamazepine, oxcarbazepine, eslicarbazepine, topiramate, phenobarbital, ethosuximide, gabapentine, zonisamide, phenytoin, stiripentol, clobazam, and clonazepam. Broad spectrum ASM used for SE treatment were levetiracetam, lacosamide, and sodium valproate in the majority of the cases and perampanel and oxcarbazepine occasionally. Cured epilepsy is the absence of seizures in the absence of any treatment for over 5 years. Alpha = 0.05/90 = 0.0006.

[#]Fisher's test, ^Wilcoxon test, or otherwise chi-square test.

HSD test, diff = 1.46, and $p = 0.0006$), and 12 months (Tukey's HSD test, diff = 1.76; and $p = 0$).

Finally, in NOSE and NISE combined, we observed positive correlations between outcomes at the final follow-up (mRS at 12 months) and in descending order on both the STESS (Pearson correlations, $r = 0.455$, $p = 1^{-06}$, and alpha < 0.017) and EMSE scores (Pearson correlations, $r = 0.326$, $p = 0.0006$, and alpha < 0.017) as well as the duration of SE (Pearson correlations, $r = 0.217$, $p = 0.002$, and alpha < 0.017).

There was a recurrence of SE in 13 patients with NOSE (28.2%) and in 15 patients with NISE (23.8%) at 1 year but at different times: there was a recurrence in the first month in 7 cases of NOSE but only in 1 case of NISE (Fisher test, $p = 0.01$). For patients who did not die during the acute phase of SE, 17 of 39 patients with NOSE developed epilepsy (43.6%) and 29 of 52 patients with NISE had a recurrence of seizures in the year following SE (55.7%, data lacking for 11 patients). In survivors at 3 months, there was a cognitive complaint in 57% of the NOSE patients (57%) vs. 71% of the NISE patients and a focal (motor of language) deficit in 26% of NOSE and 43% of NISE cases.

3.7. Different causes of death at different time points in NOSE and NISE

At the final follow-up, mortality was observed in 32.6% of NOSE vs. 20.6% of NISE patients ($p = 0.19$). However, rates of death varied according to time points (Figure 3). This occurred within the first month in 15% of NOSE patients and 6% of NISE patients. The cumulated rate increased to 24% and 8% at 3 months ($p = 0.02$ and alpha = 0.0006; Table 1). The patients who died in 1 year all had refractory SE except for 1 NOSE and 2 NISE cases (25 refractory SE/28 deaths, 89%). The causes of death were diverse and variable according to the time.

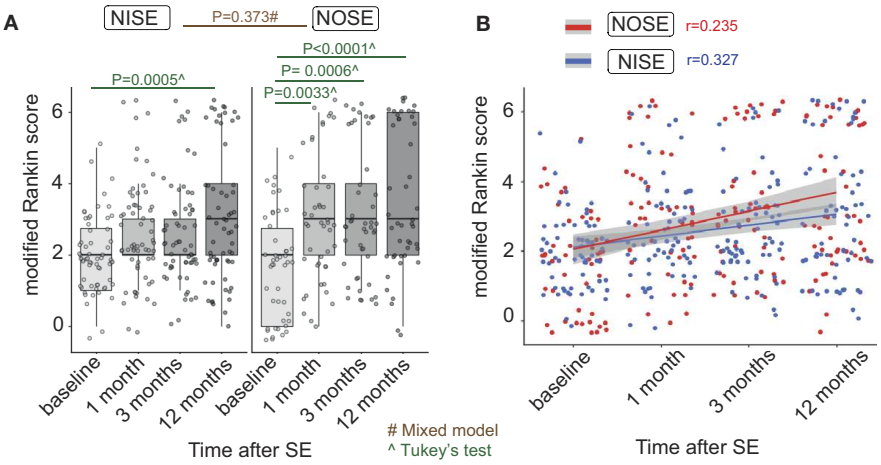

FIGURE 2
Outcome assessed by mRS between baseline and 12 months changes in different proportions in NOSE and NISE. **(A)** Individual mRS at each time point in NOSE and NISE groups. NISE patients had an average mRS of 2.02 at baseline, 2.6 at 1 month, 2.6 at 3 months, and 3.06 at 12 months. In contrast, NOSE patients had an average mRS of 2.02 at baseline, 3.3 at 1 month, 3.47 at 3 months, and 3.78 at 12 months. Therefore, we performed *post-hoc* analyses on these two groups independently. **(B)** Correlations between time after SE and outcome (Pearson correlations, $r = 0.376$ in the PMA group, $r = 0.252$ in the non-PMA group). Alpha = 0.05/3 = 0.017.

In the NISE group, at 1 month, death was related to the direct consequence of a refractory SE (1 patient), to the causal lesion induced by SE (2 patients with glioblastomas), and to a probable SUDEP (1 patient); at 3 months to invalidity (one 90-year-old patient); and at 1 year, to brain tumors (3 patients with glioblastomas and 2 patients with brain metastases), and to invalidity (3 patients with multiple pathologies).

In the NOSE group, at 1 month, death was related to the direct consequence of SE (five 54- to 95-year-old patients with organ failure after NORSE), at 3 months, to organ failure in super-refractory SE (one 56-year-old man) and to invalidity after SE in a context of multiple pathologies (three 72- to 91-year-old patients), and at 1 year, to glioblastoma (1 patient) and to progressive invalidity (three 62- to 101-year-old patients).

3.8. The same proportion of refractory NOSE and NISE

We observed similar numbers of pharmacoresistant NOSE and NISE cases (62% and 61%, respectively). According to the mixed-effects model, there was no global effect of refractoriness on the outcome, but there was an interaction between refractoriness and the time of the mRS assessment. This indicates that between baseline and 12 months, mRS changed in different proportions in refractory and non-refractory SE (considering both NOSE and NISE). Refractory SE had an average mRS of 2.01 at baseline, 3.08 at 1 month, 3.24 at 3 months, and 3.60 at 12 months. Non-refractory SE had an average mRS of 2.01 at baseline, 3.08 at 1 month, 2.58 at 3 months, and 2.97 at 12 months. Considering that the time of mRS assessment had a different effect on refractory and non-refractory SE, we analyzed these two groups independently. For refractory SE, baseline mRS was different from the mRS at 1 month (diff = 1.06, $p = 0.003$), 3 months (diff = 1.24, $p = 0.0004$), and 12 months (diff = 1.6, $p = 0$). For non-refractory SE, mRS after SE was different from baseline only at 12 months (diff = 0.95, $p = 0.002$).

3.9. No discriminating value for peri-ictal MRI abnormalities

A total of 54 patients (30 NOSE and 24 NISE cases) had a 3T MRI during the initial hospitalization for SE (MRI performed within the first 72 h of admission in 35 patients). MRI revealed an acute brain etiology in 9 patients with NOSE (30%), none in NISE patients, and old brain lesions in 18 patients in each group (66%).

PMAs were demonstrated in 20 patients (incidence of 37%, 10 patients in each group; Figures 1, 4, 5A). PMAs were present in 5 NOSE patients who responded to ASM, 5 NORSE, 6 refractory NISE, and 4 non-refractory NISE patients who experienced prolonged SE (180, 240, 700, and 2,000 min, respectively). The distribution of PMA and their aspect on the different MRI sequences were comparable in the 2 groups (Figure 4, Table 2). We noted the following two exceptions: a temporal punctiform gadolinium enhancement in two patients with non-refractory NOSE and a hyperintensity of the claustrum in one NOSE patient corresponding to SESA (Figure 4). There was no significant difference in PMA volume (Figure 5B, $p = 0.36$) between the 2 groups, but there was an outlier in the NISE group with a much higher volume than the others at 290 cc.

3.10. Relationship between PMA and outcome

According to the mixed-effects model for NOSE and NISE combined, there was no global effect of the occurrence of PMA on the outcome ($p = 0.22$). Nevertheless, there was an interaction between

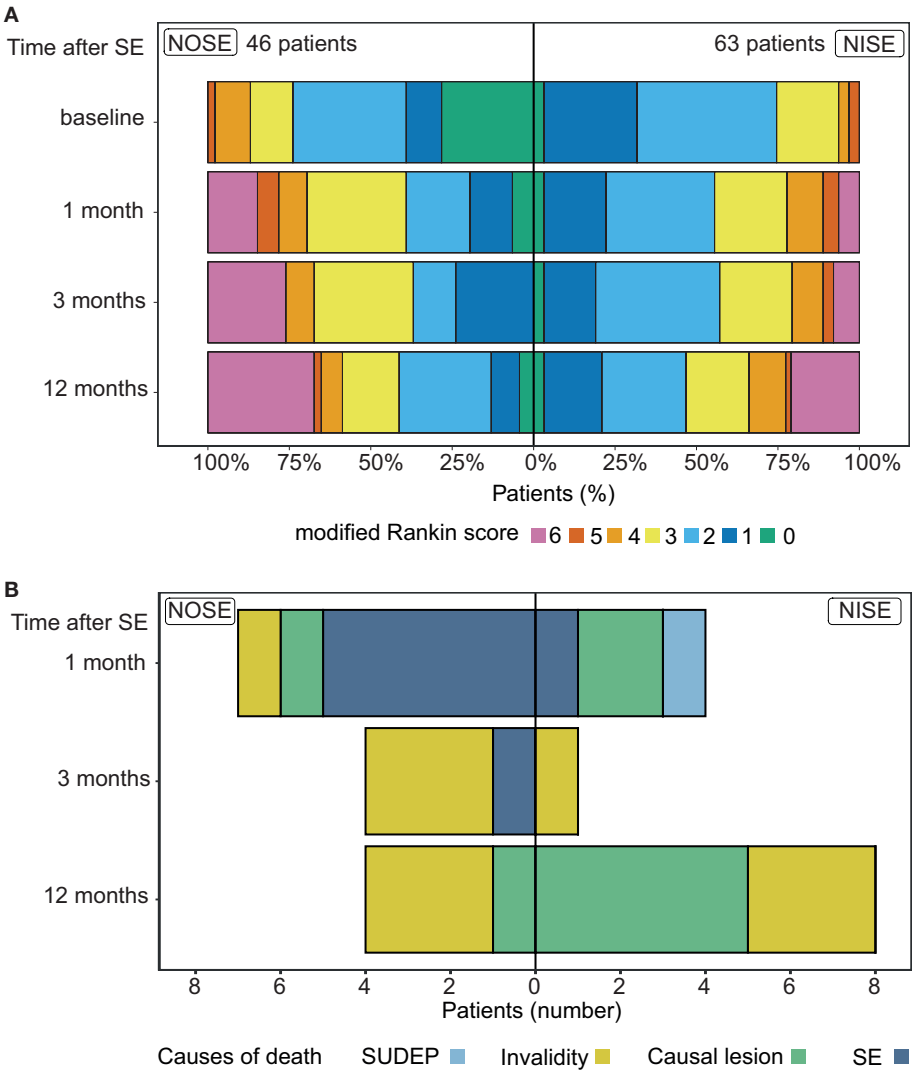

FIGURE 3
Outcome and causes of mortality in NOSE and NISE. **(A)** Outcome (mRS) changes in each group at each time point. Proportions of patients in NOSE and NISE groups for each mRS value. **(B)** Causes of mortality at each time point in NOSE and NISE groups.

the occurrence of PMA and the moment of mRS assessment (baseline, at 1, 3, and 12 months; $p = 0.000$), which suggests that between baseline and 12 months, mRS changed in different proportions in the two groups of patients (Figure 5C). We analyzed PMA and non-PMA groups independently using Tukey's HSD tests. For patients with PMA, the mRS at baseline was different from the mRS at 1 month (diff = 1.55 and $p = 0.02$) and at 12 months (diff = 2.1 and $p = 0.001$). In patients without PMA, mRS at baseline was different from mRS at 1 month (diff = 0.73 and $p = 0.01$), 3 months (diff = 0.89 and $p = 0.001$), and 12 months (diff = 1.18 and $p = 0$) (Figure 5D).

Concerning PMA changes during follow-up (7 of 10 patients with PMA in each group had an MRI control at 3 months), we noted a complete regression of PMA in only 5 patients (2 NOSE and 3 NISE cases) despite systematic normalization of the DWI due to the persistence of FLAIR hyperintensity in 8 patients (4 NOSE and 4 NISE cases) and the appearance of focal atrophy in 7 patients (5 NOSE and 2 NISE cases).

3.11. EEG patterns of periodic lateral discharges are more prevalent in NOSE

The median time before the first EEG was similar in both groups (~17 h). Different types of ictal abnormalities recorded on EEG are summarized in Table 3, and examples are provided in Figure 6. We analyzed spikes, spike-and-wave patterns, rhythmic delta discharges, and periodic epileptiform activities without identifying any specific type of epileptic activity that could be related to either NOSE or NISE. However, periodic lateralized activities tended to be more frequent in NOSE ($p = 0.004$ and alpha = 0.0006).

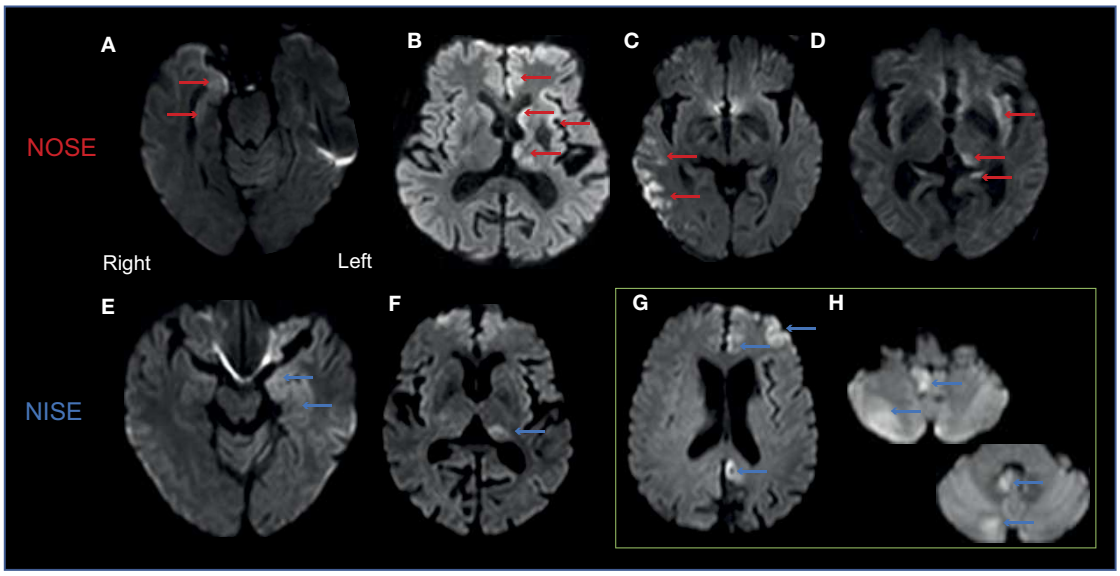

FIGURE 4
Generally similar patterns of PMA in NOSE and NISE. Examples of axial DWI views in 4 patients. **(A)** Right medial temporal hyperintensity in an 86-year-old woman with focal convulsive refractory NOSE. **(B)** Left thalamic, caudate nucleus, and frontal cortex hyperintensities in a 56-year-old man with generalized convulsive secondary non-convulsive super-refractory NOSE. **(C)** Right temporo-parietal cortex hyperintensity in a 79-year-old man with refractory generalized convulsive secondary non-convulsive NOSE. **(D)** Claustrum hyperintensity in the left hemisphere associated with a homolateral pulvinar and hippocampal hyperintensity in a 69-year-old alcoholic male with pharmacosensitive non-convulsive NOSE (SESA). **(E)** Left medial temporal hyperintensity in a 48-year-old man with pharmacosensitive focal non-convulsive NISE. **(F)** Left pulvinar hyperintensity in a 70-year-old man with pharmacosensitive focal non-convulsive NISE. **(G, H)** Right cerebellum hyperintensity and contralateral cortical hyperintensity in a 63-year-old man with a non-convulsive super-refractory NISE.

4. Discussion

Our study reveals a paradox: NOSE was more severe with more patients experiencing a poor outcome at the last follow-up but was not more refractory than NISE. Causes of death also differed at different time points of follow-up, with more early deaths directly linked to SE at 1 month in the NOSE group and more remote deaths related to causal brain lesions at the final follow-up in the NISE group.

We are aware of the limitations of our study: the clinical heterogeneity of the patients, heterogeneous types of SE and etiologies, outliers, MRI performed only in approximately half of the patients, and the difficulty assessing the kinetics of PMA. However, such limits are inherent in this type of prospective research precisely because of the severity of SE that can limit inclusion. Including more than 100 patients is rare and we were able to provide longitudinal data, without any patients lost to follow-up. Moreover, when available, MRI was always performed at a high resolution (3T) and within relatively homogeneous time frames.

4.1. NOSE patients are older than NISE patients at the onset

There is an undeniable fragility in NOSE patients at the onset: 61% had a preexisting cognitive decline (IQ Code $\geq$ 3.4). This fragility was not limited to the NOSE group: two-thirds of the patients had a significant disability (mRS $\geq$ 2) in both groups. The mean age of the patients in our study was 60 years, similar to the ages in previous cohorts: 60–65 years according to the cohort (15, 17, 23, 24, 45–47). However, NOSE generally occurs in older subjects (65 years vs. 56 years in NISE patients). Therefore, it is interesting to note that epileptic and non-epileptic patients were comparable in the literature for neurological and psychiatric history, previous psychotropic drug use, and alcohol abuse or dependence (16, 17, 24, 48). In particular, SESA was not overrepresented in NOSE.

4.2. NOSE is not more refractory than NISE but tends to be more severe

In both groups, SE was long, lasting $\geq$24 h in one-third of our patients, and if associated with severe complications required resuscitation management in 35% of the cases. This is consistent with previous studies in which the duration of SE was $\geq$ 24 h in 24–33% of the cases (15, 16) and only 7% of SE lasted <30 min (45).

In our study, the proportions of pharmacoresistance in SE (more than 60% of the cases in both groups) contrast with the 20–40% of refractoriness reported in the literature (16, 17, 45, 48, 49), although we used the same definitions of drug resistance and clinical management according to the national recommendations for therapeutic escalation (33).

However, as in the literature, NOSE was more severe than NISE. Indeed, the severity scales of NOSE were higher ($p < 0.001$), the duration was longer (62 vs. 23 h on average), and the diagnostic

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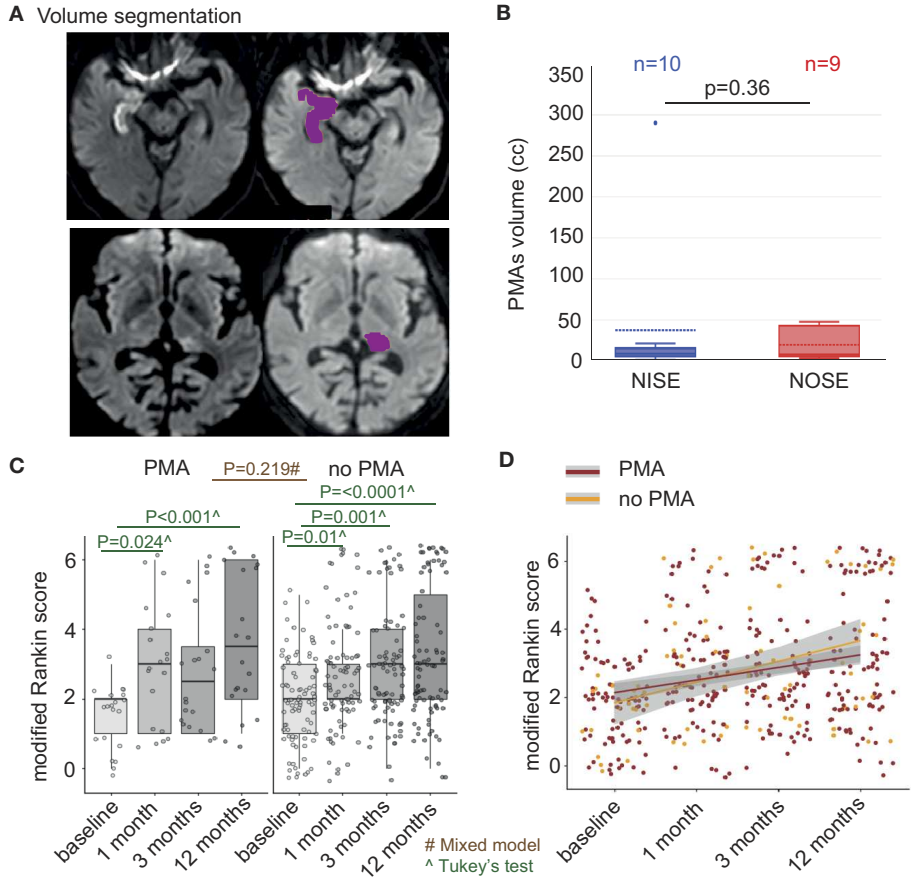

FIGURE 5
PMA volumes are similar in NOSE and NISE patients and PMA is related to prognosis. **(A)** PMA volumetry in DWI sequences. Semi-automatic quantification in one-shot analysis by OLEA (PMA is circumscribed in purple; colors were changed for purposes concerning the figure). Right mesial temporal hypersignal including the hippocampus (upper panel) and left posterior thalamic hypersignal (bottom panel). **(B)** Mean PMA volumes in each group. The two groups had a similar PMA volume ($p = 0.36$); note that there was an outlier in the NISE group with a much higher volume than the others at 290 ml, with a hypersignal in DWI of the majority of the left hemisphere cortex, the thalamus and at 7 days a right cerebellar diaschisis of partial NCSE secondarily generalized in a 52-year-old man institutionalized for encephalopathy evolving since childhood. **(C)** Individual mRS in patients with PMA and those without PMA. Patients with PMA had an average mRS of 1.5 at baseline, 3.1 at 1 month, 2.8 at 3 months, and 3.6 at 12 months. Patients without PMA had an average mRS of 1.5 at baseline, 2.2 at 1 month, 2.8 at 3 months, and 2.7 at 12 months. **(D)** Correlations between PMA evolution and outcome (mRS) at different time points (Pearson correlations, $r = 0.376$ in the PMA group, $r = 0.252$ in the non-PMA group). Alpha = 0.05/3 = 0.017.

tardiness was greater (60 vs. 10 min) resulting in a therapeutic delay. NOSE patients had more post-ictal focal neurological deficits (80% vs. 62% in NISE) and more serious complications (50% vs. 30% in NISE), especially hemodynamic complications. The length of hospital stay was also longer for NOSE patients than for NISE patients, on average 3 days. This is in line with the previously identified prognostic factors of SE, such as the age of the patient, the rapidity of the diagnosis and suitable therapeutic management, and the duration and etiology of SE (15–17, 19, 24, 47, 50, 51).

4.3. NOSE becomes secondarily non-convulsive more often than NISE

In our cohort, 36.7% of the SE were non-convulsive (NCSE), whereas NCSE accounts for 25% of the SE in the literature (21, 22, 52). NCSE is frequent (up to 47% of the SE managed in the Intensive Care Unit (53, 54) but is underestimated due to the misleading and non-specific clinical features. In fact, the diagnosis is mainly based on the EEG, and quite frequently there is a diagnostic delay and high pharmacoresistance in nearly one-third of the cases (55–58). NCSE has been associated with a longer duration and a worse prognosis than the other subtypes of SE, especially when it is inaugural because of its frequent refractoriness (50). The mortality rate of the inaugural NCSE [nearly 69% of NCSE in some cohorts (58)] can be as high as 40%, whereas it is ∼10% for the other SE (59).

4.4. In line with novelty, more acute brain lesions occur in NOSE

In a recent retrospective cohort including 85 NOSE patients, the main etiologies were acute symptomatic NOSE in 53.9%, unknown in 25.9%, progressive in 11.8%, and remote in 9.4%. For adults below the age of 60 years, the main etiology remained unknown (36.3%) followed by autoimmune-related SE (16.4%), while in the elderly (≥60 years), the primary etiology was central nervous system

TABLE 2 MRI results in NOSE and NISE groups.

	NOSE	NISE	*p*
	n = 30 (65%)	*n* = 24 (38%)	Chi^2 test
Time of MRI in relation to SE			
Peri-ictal	11	9	1
Postictal	15	12	0.82
Remission of epileptic symptoms	5	3	1#
Within 72 h after admission	23 (77%)	11 (46%)	0.04
Acute lesions (related to SE) visible on MRI, other than PMA	9 (30%)	0	0.01
Old brain lesions (anterior to SE) visible on MRI, other than PMA	18 (56%)	18 (75%)	0.38
PMA visible on MRI	10 (33%)	10 (42%)	0.53
MRI sequences allowing PMA visualization			
Diffusion hyperintensity	9	10	1#
ADC restriction	8	7	1#
FLAIR hyperintensity	8	8	1#
Gadolinium contrast enhancement	2	0	0.47#
Perfusion increase	3/12 (2 without PMA)	4/18 (1 without PMA)	1#
PMA location			
Cortex	9	4	0.057#
Hippocampus	8	6	0.63#
Amygdala	7	3	0.18#
Thalamus	3	4	1#
Pulvinar	3	3	1#
Claustrum	1	0	1#
Crossed cerebellar diaschisis	0	2	0.47#
Average PMA volume in cc (min-max)	20 (3.2–47.6)	31.4 (1.9–290)	0.36^

PMA, peri-ictal MRI abnormalities.
#Fisher's test; ^Wilcoxon test, or otherwise chi-square test. Alpha = 0.05/90 = 0.0006.

infection (23.3%) followed by cerebrovascular disease (20%) and intracranial tumors (20%) (23). In the 89 patients reported by Santamarina et al. (mean age of 69 years), NOSE had an acute etiology for 66.3% of the patients (46.1% brain lesions and 20.2% toxic/metabolic causes), a remote or progressive etiology for 19.1% of the patients, and remained cryptogenic for 14.6% of the patients (27).

If the etiologies overlap with these references, we emphasize different proportions according to these causes in our cohort (perhaps related to the fact that our NOSE cohort was smaller). The etiology of NOSE was acute in 43.5% of the cases vs. 8% in NISE ($p < 0.0001$), including an acute cerebral etiology in 21.7% of NOSE vs. 4.8% of NISE cases ($p = 0.01$). The etiology remained unknown in only 8.7% of the NOSE cases. However, by systematically comparing them to NISE, our results highlight the etiologies shared by both types of SE. For instance, we observed no autoimmune encephalitis, whereas this was the etiology for epilepsy in two NISE patients. We also noted 3 cases of non-convulsive NOSE that met the subacute encephalopathy and seizures in alcoholics (SESA) criteria (5, 60, 61), all with PMA on ictal MRI.

4.5. Poor outcome between baseline and last follow-up is more frequent in NOSE

To the best of our knowledge, the only study that has prospectively compared NOSE and NISE was restricted to 122 patients >60 years old with convulsive SE. It showed that comorbidities, a low Glasgow scale score, and an inaugural nature were poor prognostic factors (62). By including younger subjects and all types of SE, we were able to demonstrate the frailty and older age of NOSE subjects.

We also observed that the mRS increased at each assessment time in both groups. However, after *post-hoc* analyses, baseline mRS (before SE) for NOSE was statistically different from mRS at 1, 3, and 12 months, while for NISE, it was only different from mRS at 12 months.

In our cohort, 43.6% of the NOSE patients who survived developed epilepsy in the ensuing months. For Santamarina et al., it was close to 58.7% (27), which highlights the relevance of long-term maintenance of an ASM after SE. A total of 25.7% of patients had

TABLE 3 EEG patterns during NOSE and NISE.

	NOSE $n = 46$	NISE $n = 62$	p
Median time before 1st EEG	17 h	17 h	0.89^
Average time before 1st EEG (min-max)	39 h (3 h–384 h)	29 h (2 h–360 h)	
1st EEG conclusions			
Ictal	17 (37%)	25 (40%)	0.77
Postictal	22 (48%)	29 (47%)	0.85
Neurosedation	6 (13%)	4 (6.5%)	0.32#
Normal	1 (2%)	4 (6.5%)	0.39#
Epileptic and other pathological activities			
Epileptic discharges	14 (30%)	21 (34%)	0.74
Paroxysmal abnormalities	18 (39.1%)	23 (37%)	0.94
Spikes	15	14	0.23
Spike-and-wave patterns	5	16	0.06
Rhythmic delta discharges	10 (21.8%)	14 (22.6%)	0.96
Periodic activities	18 (39.1%)	8 (13%)	0.003
PLD	17	8	0.004
GPD	1	0	0.43#
Burst suppressions	0	2 (3.2%)	0.51#
EEG leading to SE diagnosis			
Generalized convulsive	0	1 (1.6%)	0.87#
Focal convulsive	5 (10.8%)	3 (4.8%)	0.40
Non-convulsive	12 (26%)	8 (13%)	0.12
Mean number of EEGs after the 1st one (median; min–max)	2 (1; 0–10)	2 (3; 0–16)	0.85
Long-term EEG monitoring	6 (13%)	6 (9.7%)	0.79

#Fisher's test; ^Wilcoxon test, otherwise chi-square test. PLD, periodic lateralized discharges; GPD, generalized periodic discharges.
Alpha = 0.05/90 = 0.0006.

a recurrence of SE during follow-up, including 28.2% NOSE cases [twice the rate found in a previous prospective cohort (45)]. There were more early recurrences of SE in NOSE patients ($p = 0.01$), probably associated with difficulty in controlling the initial SE and the underlying etiology.

We noted a high frequency of focal neurological deficits (34.4%) and cognitive complaints (70%) in both groups at 3 months but which were higher for NISE. Cognitive consequences are frequently reported in the literature and have a significant impact on quality of life (50, 63, 64). Therefore, in the clinical management of any SE, it would be relevant to conduct psychometric and standardized cognitive assessment some distance in time after NOSE and NISE to propose cognitive remediation adapted to these fragile patients.

4.6. Different causes of remote and early deaths in NOSE and NISE

The overall mortality of our population was high: 10%, 17%, and 26% at 1, 3, and 12 months, respectively. These rates are comparable to the mortality found in cohorts with any type of SE (NOSE and NISE, excluding post-anoxic encephalopathies) (17, 48) or even studies including only refractory SE with 24.5–25.4% mortality at 1 year (38, 65). Similarities to these rates can probably be explained by the high drug resistance in our cohort. In specific NORSE cohorts, mortality reached 22% (3, 28).

In our study, a higher global proportion of death was observed in NOSE than in NISE. The absence of statistical difference at the final follow-up does not exclude differences at distant time points and may reflect different mechanisms: more early deaths in the NOSE group directly linked to SE at 1 month and more remote deaths linked to causal brain lesions in the NISE group at final follow-up. In addition, it has been previously shown that NOSE is associated with a 15-fold increase in the risk of death in those older than 60 years (66).

4.7. For all SE in general, patients with PMA have a poorer prognosis at the last follow-up

The description and location of PMA in our cohort were comparable to previously published data (67–71): DWI hyperintensity with a moderate ADC restriction and FLAIR

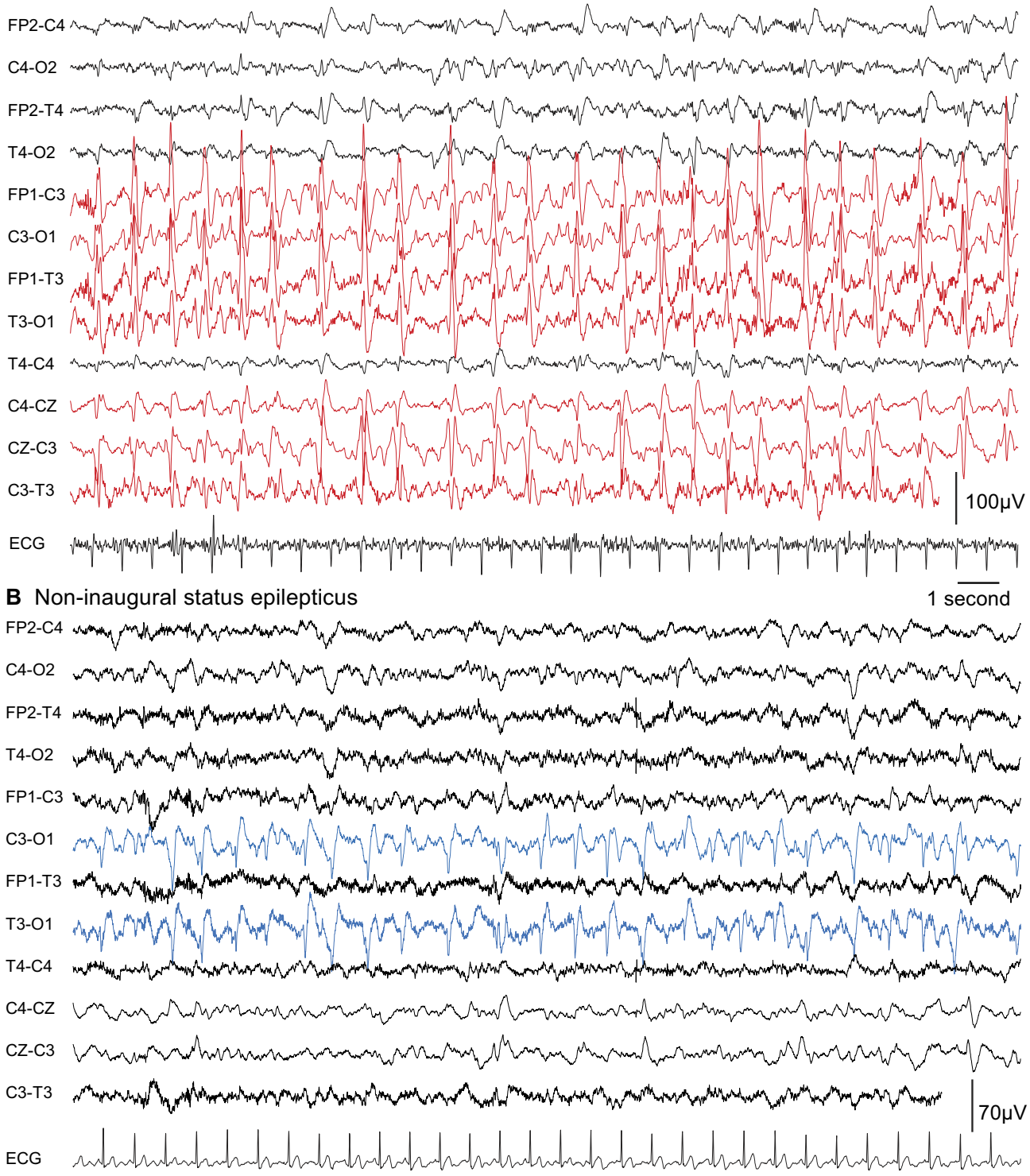

FIGURE 6
Two examples of EEG patterns that can be observed in NOSE and NISE. PLDs could be observed in the two types of SE but were more prevalent in NOSE. Here on the left hemisphere. **(A)** NOSE in a 56-year-old man (chronic psychiatric disorders and alcoholism with decompensated cirrhosis, left cerebral middle artery ischemic sequelae) who presented with a generalized convulsive SE, which became secondarily non-convulsive and super-refractory (SE lasted 41 days until death). PMAs were observed on MRI on the left hemisphere. **(B)** NISE in a 63-year-old man who presented with refractory non-convulsive SE (SE lasted 8 days). A context of stroke sequelae in the left middle cerebral artery region due to atheroma, alcoholism, and urinary tract infection. PMA was observed on MRI. After an initial stay of 54 days, there was an SE recurrence in 80 days leading to death in 4 months.

hyperintensity, preferentially in the hippocampus, the cortex, the amygdala, and the thalamus. In our cohort, both NOSE and NISE had PMAs that were comparable in appearance, location, and volume. These results are important because contrary to common belief, PMAs are not exclusive to NORSE and in general and are not exclusive to NOSE. The overall incidence of PMAs (37%) is close to the incidences found in studies that did not consider only abnormal MRI: 27.5% (25), 28% (72), and 42.5% (67). The incidence of PMAs was somewhat higher in the NISE group (42% vs. 33%) but their MRIs were performed later than those for NOSE patients. This difference could be due to the kinetics of the occurrence of PMAs.

A significant correlation has already been described between the presence of PMAs and the presence of PLDs on EEG with vigilance in the acute phase of SE, but no association was found with patient age, comorbidity, or mortality (25). Our clinical experience suggests that there is a very good anatomical correlation between the clinical symptoms of SE, the site of EEG abnormalities, and the location of PMA when present. Post-ictal motor deficits have also been more frequently associated with PMAs (53.3%) than with normal MRI (34.4%) (67). In our data, the outcome at the last follow-up changed in different proportions in the patients with PMA and those without PMA, while no correlation exists between PMA volume and mRS during follow-up. There does not appear to be any specific feature (volume, locations, and change) of PMAs that can distinguish a peri-ictal from a post-ictal state. Rapid brain imagery is recommended in the etiological assessment of any SE (10, 33). Our results highlight that in addition to the diagnostic potential and the identification of acute lesions, MRI provides prognostic information that may prove valuable in long-term patient management.

In the neuroimaging studies cited above, MRI monitoring was not systematic and completion time was extremely variable (interval of up to 1 year between the two MRIs) (68–70). In our study, MRI time was more homogeneous at ∼3 months and complete reversibility of PMA was noted in 36% of patients. Although diffusion was normalized, FLAIR hyperintensity was found in 57% of patients and focal atrophy in 50% of patients, predominantly in the temporal-hippocampal regions. These sequelae raise questions about the epileptogenic value and the clinical consequences of these permanent structural abnormalities.

4.8. Periodic lateral discharges are more frequent in NOSE than in NISE

We observed a tendency for more periodic lateral discharges (PLDs) in NOSE, while the median time before the first EEG was similar in both groups. Despite a later diagnosis in NOSE, accessibility to EEG was not different for NOSE and NISE, which is a crucial point to remember in clinical practice. PLDs were indicative of the presence of a cortical brain lesion and associated with more frequent vigilance disorders as previously described (73). PLDs were also associated with high morbidity and mortality in studies conducted in the eighties or nineties (74–76). We were unable to determine whether there is a PLD pattern (morphology, periodicity, and amplitude) specific to each type of SE. Further studies that analyze the appearance of PLDs according to the etiology, lesion, and type of SE are warranted.

4.9. NORSE vs. non-inaugural refractory SE

NOSE was not more refractory than NISE. Unfortunately, our data were not sufficient to highlight specificities between the particular cases of NORSE and non-inaugural refractory SE (NIRSE).

Are there certain etiologies that are particularly represented in refractory SE? In other series that focused specifically on the NORSE subgroup, the most common etiology was autoimmune encephalitis, while 52% of the cases of NORSE remained cryptogenic (3, 28, 31, 77). No autoimmune encephalitis was identified in our NOSE cohort although this etiology was repeatedly suspected and sought, while two cases of autoimmune encephalitis were included in our NISE group with a refractory SE. Two patients in our cohort met the criteria for cryptogenic NORSE: the first died within a few days despite appropriate resuscitative management while the second patient had severe cognitive impairment and loss of autonomy at 3 months.

Moreover, our data were not sufficient to isolate specific patterns of PMA between NOSE and NORSE. However, particularities in three patients should be noted: a case of claustrum hyperintensity in the NOSE group corresponding to SESA with non-refractory NCSE. In a recent study, claustral changes were reported as infrequent, occurring in 9.1% of NORSE patients (78) although the etiology for NORSE patients with claustrum involvement has not yet been elucidated. The claustrum sign has been associated with an aggressive refractory form of SE in particular cases of FIRES with cryptogenic etiology (78, 79) but never with SESA as far as we know. Two NISE patients presented with crossed cerebellar diaschisis with involvement of the cortex and the pulvinar ipsilateral to the refractory SE. Some identical cases have been described in the literature with reversible damage or the appearance of cerebellar atrophy associated with an unfavorable clinical course (80–84).

5. Conclusion

NOSE and NISE evolved in the same proportions as refractory SE and shared common patterns, such as the same types of PMAs on MRI. However, NOSE was distinguishable by the severity, a more fragile and older population at onset, and a frequent non-convulsive semiology. The causes of death differed in the early and late stages (at 1 year) in NOSE and NISE. Despite acute causal brain lesions, the inaugural character was still too often associated with a delay in diagnosis in SE, which justifies the need to more clearly specify the types of SE to constantly raise awareness among clinicians. These results also highlight the relevance of including novelty-related criteria, clinical history, and the temporality of occurrence in the nosology of status epilepticus.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Regional Ethics Committee at Toulouse University

Hospital (CPP Sud-Ouest no. 04-1215). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MB and JC: writing of the manuscript, major role in data acquisition and study design, data analysis and interpretation, and expert analysis of EEG. LV: revision of the manuscript, expert analysis of EEG, data analysis and interpretation, major role in the study design, and help with data acquisition. MD, FR, and RD: expert analysis of EEG and revision of the manuscript. EB: revision of the manuscript, data analysis, and interpretation. FB: expert analysis of MRI, major role in study design, and help with data acquisition. LG: statistical analyses and revision of the manuscript. VW: support for figures and statistical analyses. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Long-term neuropsychological outcomes in children with febrile infection-related epilepsy syndrome (FIRES) treated with anakinra

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Background: Febrile-infection related epilepsy syndrome (FIRES) is a rare epilepsy syndrome in which a previously healthy individual develops refractory status epilepticus in the setting of a preceding febrile illness. There are limited data regarding detailed long-term outcomes. This study aims to describe the long-term neuropsychological outcomes in a series of pediatric patients with FIRES.

Methods: This is a retrospective multi-center case series of pediatric patients with a diagnosis of FIRES treated acutely with anakinra who had neuropsychological testing at least 12 months after status epilepticus onset. Each patient underwent comprehensive neuropsychological evaluation as part of routine clinical care. Additional data collection included the acute seizure presentation, medication exposures, and outcomes.

Results: There were six patients identified with a median age of 11.08 years (IQR: 8.19–11.23) at status epilepticus onset. Anakinra initiation was a median of 11 days (IQR: 9.25–13.50) after hospital admission. All patients had ongoing seizures and none of the patients returned to baseline cognitive function with a median follow-up of 40 months (IQR 35–51). Of the five patients with serial full-scale IQ testing, three demonstrated a decline in scores over time. Testing results revealed a diffuse pattern of deficits across domains and all patients required special education and/or accommodations for academic learning.

Conclusions: Despite treatment with anakinra, neuropsychological outcomes in this series of pediatric patients with FIRES demonstrated ongoing diffuse neurocognitive impairment. Future research will need to explore the predictors of long-term neurocognitive outcomes in patients with FIRES and to evaluate if acute treatment interventions improve these outcomes.

KEYWORDS

new-onset refractory status epilepticus, NORSE, febrile infection-related epilepsy syndrome, FIRES, neuropsychological outcomes, cognitive outcomes, anakinra

Introduction

New-onset refractory status epilepticus (NORSE) is a clinical presentation in which previously healthy individuals develop refractory status epilepticus without a clear structural, toxic, or metabolic cause. Febrile infection-related epilepsy syndrome (FIRES) is a subset of NORSE that is preceded by febrile illness 24 hours to 2 weeks prior to the onset of status-epilepticus (1). Children with FIRES will present after a febrile illness with new seizures that rapidly progress to refractory or super refractory status epilepticus that can last for several weeks despite treatment with at least two intravenous antiseizure medications and continuous infusions (2, 3). Limited published literature to date suggests that of patients who survive the acute phase, nearly all have ongoing drug-resistant epilepsy with the majority not returning to prior baseline function (4, 5).

No etiology is identified in the majority of FIRES cases, but there is growing evidence that there may be an immune-mediated process following an initial infection (6). A preceding febrile illness can trigger intrathecal overproduction and release of proinflammatory cytokines, which activates mechanisms of innate immunity in the central nervous system (7). This immune activation increases neuronal excitability, leading to epileptogenesis (8). Status epilepticus itself can trigger proinflammatory processes and neuroinflammation which further promotes neuronal hyperexcitability and triggers ongoing seizures (9, 10). This hypothesized immune activation has led to the use of immune therapies such as steroids, intravenous immunoglobulin (IVIG), and plasma exchange in the treatment of FIRES, though typically with low response rates (11). One particular proinflammatory cytokine, interleukin-1 beta (IL-1β) has been implicated in experimental models of status epilepticus (12). Anakinra is an interleukin-1 receptor antagonist (IL-1Ra) used in FIRES that has been shown to reduce seizures in the acute phase (5, 6, 13) and is recommended for consideration in the treatment of patients with FIRES (14, 15).

Published data regarding the long-term neurocognitive outcomes in patients with FIRES is limited. Despite reports of acute benefit with anakinra, there are no prior studies describing long-term cognitive outcomes in this population. This study aims to describe the long-term neuropsychological and seizure outcomes in a series of pediatric patients with FIRES treated with anakinra.

Materials and methods

This is a multicenter retrospective case series of six patients with a diagnosis of FIRES treated with anakinra. Treating physicians identified patients with FIRES onset between December 2015 and December 2019. Inclusion criteria included patients <18 years old with a diagnosis of FIRES treated with anakinra in the acute hospital admission with available neuropsychological testing at least one year after refractory status epilepticus onset. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Colorado School of Medicine (16). Data collected included past medical and family history, lab and imaging results during the acute hospital course, as well as seizure frequency, antiseizure medications and other treatments (i.e., neuro-modulatory therapy) during the acute hospital course, and at each follow-up neuropsychological testing time point. Neuropsychological testing was completed as part of routine clinical care across three academic medical centers. Testing measures varied by institution, age of the patient at the time of assessment, and ability to complete measures. For analysis, tests were grouped into neuropsychological domains, and scores described between and within categories. The Colorado multiple institutional review board (COMIRB) approved this study.

Descriptive data analysis included frequencies and percentages for categorical variables. Continuous variables are reported in median and interquartile ranges. A pre-determined sample size was not calculated due to descriptive nature of study and small number of available patients.

Results

There were six patients identified with a median age of 11.08 years (Interquartile range (IQR) 8.19–11.23) at status epilepticus onset. All patients met the diagnostic criteria for FIRES with a preceding fever starting at least 24 hours prior to status epilepticus onset. Initial brain MRI was normal in three patients and non-specific inflammation such as T2/FLAIR hyperintensities occurred in three patients. Completion of genetic testing occurred in five patients and was negative or non-diagnostic in all these children. All patients had autoimmune antibody testing completed in cerebrospinal fluid (CSF), as well as in serum in five patients. This was negative in all patients except for one with a low-titer serum glutamic acid decarboxylase 65 (GAD65) (0.09 nmol/L; normal <0.02 nmol/L) only after treatment with IVIg. Four children had CSF cytokine testing, which were all elevated (Table 1). During the acute phase, all patients received treatment with pentobarbital and obtained burst-suppression on EEG. The median duration of burst suppression was 120 hours (IQR 63–348). All patients received treatment with intravenous immunoglobulins (IVIg) and five patients received corticosteroids. These treatments were prior to anakinra in four patients and concurrent with anakinra in two. The median time to initiation of anakinra was 11.0 days (IQR 9.25–13.50). One patient received treatment with tocilizumab following anakinra; this case was previously published and is included in this series to report additional long-term outcome data (17). Five patients received treatment with phenobarbital during the acute period. There were ongoing seizures at last follow-up for all patients with variable frequency ranging from multiple per day to monthly. All patients continued to take a median of 3.5 (IQR 2–5) daily antiseizure medications at the time of their last neuropsychological evaluation. Two patients also received treatment with neuromodulation (vagus nerve stimulation or responsive neurostimulation). Brain MRI results in the long-term follow-up phase revealed a combination of hippocampal volume loss, including mesial temporal sclerosis, and / or diffuse cerebral or cerebellar volume loss (Table 1). Additional information regarding specific cytokine testing results, duration of treatment with anakinra, antiseizure medication exposure, and seizure outcomes are available in Table 1.

TABLE 1 Patient characteristics and medical history.

Patient	Age at onset (years)	ICU length of stay (days)	CSF cytokine elevations	Time in burst suppression (hours)	# ASM attempted during inpatient admission	Immune-modulatory treatment besides anakinra	Time to anakinra start (days)	Time on anakinra (days)	Seizure burden prior to anakinra	Seizure burden at hospital discharge	Seizure burden at last evaluation	ASM at last cognitive evaluation	Rescue medication frequency at last cognitive evaluation	Follow-up MRI results (months since onset)
1	11	40	IL-1B, IL-4, IL-5, IL-6, IL-8, IL-10, IFN-γ	48	9	Corticosteroids IVIg Plasmapheresis	14	83	100 per day	1 per month	2.5 per month	Clobazam Lacosamide Phenobarbital	1 every 6 months	Low hippocampal volume with concern for unilateral mesial temporal sclerosis (51 months)
2	11	16	IL-1, IL-4, IL-6, IL-8, IL-10	72	7	Corticosteroids IVIg	16	46 – later restarted	18 per day	2 per month	1 per day	Clobazam Valproic acid	Monthly	Progression of cerebral and cerebellar volume loss, unilateral hippocampal volume loss and asymmetric T2 signal (40 months)
3	11	31	Not checked	60	9	Corticosteroids IVIg	19	Remains on anakinra	52 per day	1 per month	1 per day	Lacosamide Brivaracetam VNS Bilateral hippocampal RNS	Infrequent	Slight increase in moderate to marked cerebellar volume loss (81 months)
4	11	55	Not checked	408	10	IVIg	9	26	22 per day	1-2 per week	1 per week	Clobazam Lacosamide Phenobarbital Levetiracetam Lorazepam	3 per month	Right greater than left diffuse atrophy; left greater than unilateral hippocampal volume loss (58 months)
5	7	60	IL8, IL5, IP-10 (CXCL10)	720	8	Corticosteroids IVIg	50	Remains on anakinra	4 per week	0	Daily	Clobazam Lacosamide Levetiracetam Perampanel Decadron VNS	None	Stable mild generalized volume loss, unchanged likely mesial temporal sclerosis that is asymmetric (50 months)
6	6	53	IL-2, IL-4, IL-6, IL-8, IL-10	168	9	Corticosteroids IVIg	5	15	42 per day	1–2 per week	2 per day	Phenobarbital Levetiracetam Epidiolex Rufinamide Oxcarbazepine	2–3 per month	Right mesial temporal sclerosis with mild generalized atrophy (27 months)

IL, interleukin; IFN-γ, interferon gamma; ICU, intensive care unit; CSF, cerebrospinal fluid; ASM, antiseizure medications; VNS, vagus nerve stimulation; RNS, responsive neurostimulation.

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Patients had serial neuropsychological testing repeated between 1 and 4 times after status epilepticus onset with a median follow-up of 40 months (IQR 35–51 months). The testing measures completed for each patient during follow-up are available in Supplementary Table 1. None of the six patients returned to baseline functioning after onset of FIRES, according to physician report and pediatric cerebral performance category (PCPC). PCPC was normal for all patients prior to FIRES onset with all patients demonstrating decline in function to a score of moderate to severe disability at last follow-up (Table 2). There was one patient (patient 2) who had improvement in PCPC score over time with a change from the category of severe disability to moderate disability. This patient also had an improvement in full-scale IQ score from initial testing (Figure 1). Full-scale IQ testing for one patient (patient 5) demonstrated average IQ scores, although there was a decline in scores between follow-up time points. The remainder of patients demonstrated IQ scores that were between the ranges of low average to extremely low. Of the five patients with serial IQ testing, three patients demonstrated a decline in full-scale IQ scores over the follow-up period.

Overall, patients demonstrated a diffuse pattern of deficits across domains at the last follow-up time point (Figure 2). Deficits included verbal and non-verbal reasoning and visual spatial abilities, as well as memory deficits. Language weaknesses encompassed both receptive and expressive language impairment. Additionally, visual motor integration, fine motor speed and dexterity were each below age expectations, and weaknesses occurred across varying aspects of attention and executive functioning. Reading skills ranged from extremely low to average. Longitudinal testing demonstrated preservation of these skills over time, without evidence for decline or loss of skills. While longitudinal data was not available for other areas, there was a slight trend for lower math calculation skills when compared to reading. Spelling was more variable.

Parent, and in some cases, teacher report questionnaires (ABAS-3, BASC-3, and Vineland-3) were suggestive of concerns for symptoms of executive functioning deficits, psychosocial difficulties and overall adaptive functioning weaknesses in at least two patients. Parent or teacher BASC-3 questionnaires were completed in three children and suggestive of clinically significant hyperactivity. In two children, there was also indication of internalizing symptoms, including increased anxiety, somatization, or depression. At last follow-up, all patients continued to present with neuropsychological impairments and required special education services/interventions and/or accommodations for academic learning (Table 2).

Discussion

In this series of pediatric patients with FIRES treated acutely with anakinra, neuropsychological testing does not suggest a pattern of specific neurocognitive deficits, but rather a global decline in functioning. There is evidence that some patients continue to have further neurocognitive decline over time, although some patients demonstrate stable neuropsychological scores or improvement. All patients required educational support and interventions during the long-term follow-up period.

These findings are concordant with data supporting that super-refractory status epilepticus causes worse neurological outcomes and lower rates of return to baseline cognitive function than non-super-refractory status epilepticus (18). One study reported that 58% of patients with NORSE had neurocognitive deficits, of which 30% were severe (19). This is consistent with the current case series in which all patients demonstrate neurocognitive deficits including two patients classified as severe based on PCPC category. All patients in this series had return of speech and independent ambulation although no patients returned to their neurocognitive baseline, and all had some degree of disability at follow-up.

In general, patients had full-scale IQs below normal, and three patients showed a decline in full-scale IQ during period of long-term follow-up. This aligns with a previous study in which all patients with devasting epileptic encephalopathy in school-aged children (DESC) with prolonged status epilepticus had IQs below normal at follow-up, and serial follow-up neurocognitive testing showed progressive decline of intellectual functioning (19). At follow-up in another series of children with FIRES only 18% of survivors returned to normal function at last follow-up, although this classification also included the presence of learning disabilities (4). Poor cognitive outcomes were associated with younger age at FIRES onset and longer duration of induced burst suppression coma (4). The current case series reflects this with the youngest patients at FIRES onset exhibiting the second and third largest declines in IQ over the follow-up period with one of these patients also spending the longest time in burst suppression. However, this case series is not powered to statistically make comparisons between exposures. Three patients demonstrated ongoing decline in serial full-scale IQ over time. This decline may be multifactorial and related not only to initial FIRES presentation with refractory status epilepticus but also partly due to ongoing seizure activity in the chronic phase, medication effect, and factors related to the underlying etiology and pathophysiology of FIRES that need further exploration. However, it is also important to note the variability in serial full-scale IQ testing in this case series with one patient improving over time. This suggests that recovery of neurocognitive function can occur for some patients and highlights the importance of rehabilitation programs to maximize this potential.

When further evaluating domains of neuropsychological function this case series identified concern in all domains including verbal and non-verbal memory and visual spatial skills, as well as language weaknesses with very low receptive and expressive language scores and reduced fine motor speed and dexterity. Concordant with the present findings, neuropsychological testing in children with convulsive status epilepticus show decreased memory scores compared to a healthy control group (20). Though this study did not compare FIRES patients to a control group, all patients in this study had a verbal and visual memory score at last follow-up that fell in the bottom two quartiles. Additionally, there are prior reports of FIRES patients presenting with impairments in word finding, fluency, knowledge of words, and semantic comprehension (4, 19, 21).

Attention and executive functioning are also greatly impaired in patients with a diagnosis of FIRES. Executive function deficits are also seen in patients with drug-resistant frontal and temporal

TABLE 2 Patient outcome measures according to physician report.

Patient #	PCPC at admission	PCPC at discharge	PCPC at last follow-up	Return to neurocognitive baseline	Ambulation	Return of speech	Return to school	Additional academic supports
1	1	3	3	No	Independent	Yes	Yes	Medical day program followed by IEP, special education classes
2	1	4	3	No	Independent	Yes	Yes	Medical day treatment program
3	1	4	4	No	Independent	Yes	Yes	Homebound tutor
4	1	4	4	No	Independent	Yes	Yes	Special education classes, IEP
5	1	3	3	No	Independent	Yes	No	Special education classes
6	1	3	3	No	Independent	Yes	Yes	1:1 paraprofessional or tutor

PCPC, Pediatric Cerebral Performance Category; IEP, individualized education plan.

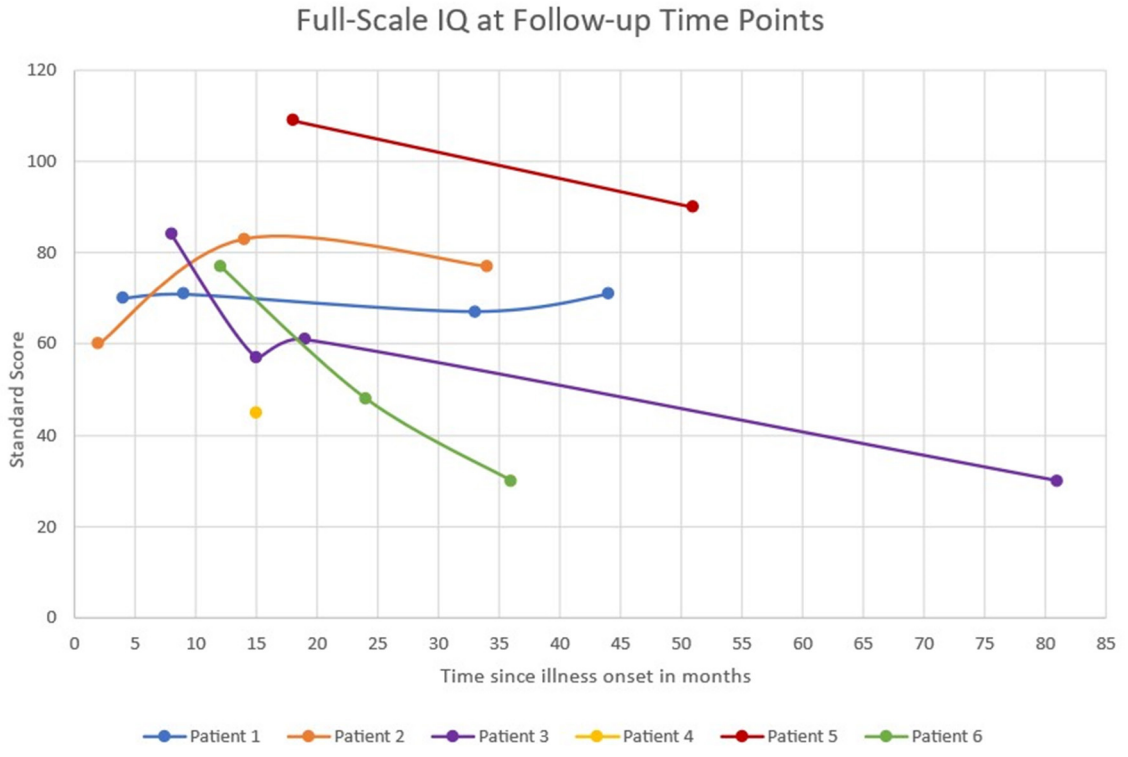

FIGURE 1
Full-scale IQ scores at serial follow-up time points. Full-scale IQ score categories: Average 90–109, Low average 80–89, Borderline 70–79, Extremely low <69.

epilepsy and reduced impulse-inhibition in patients with temporal lobe epilepsy (22). These findings and those in the present case series may be in part due to ongoing drug-resistant epilepsy, localization of seizure onset, and cerebral dysfunction in the chronic phase of FIRES with multiple daily antiseizure medications.

Academic achievement was among the best performing domains for patients in this case series. This aligns with reports of higher scores for specific academic skills (such as arithmetic, spelling, reading recognition, and reading comprehension) relative to academic performance in patients with traumatic brain injury.

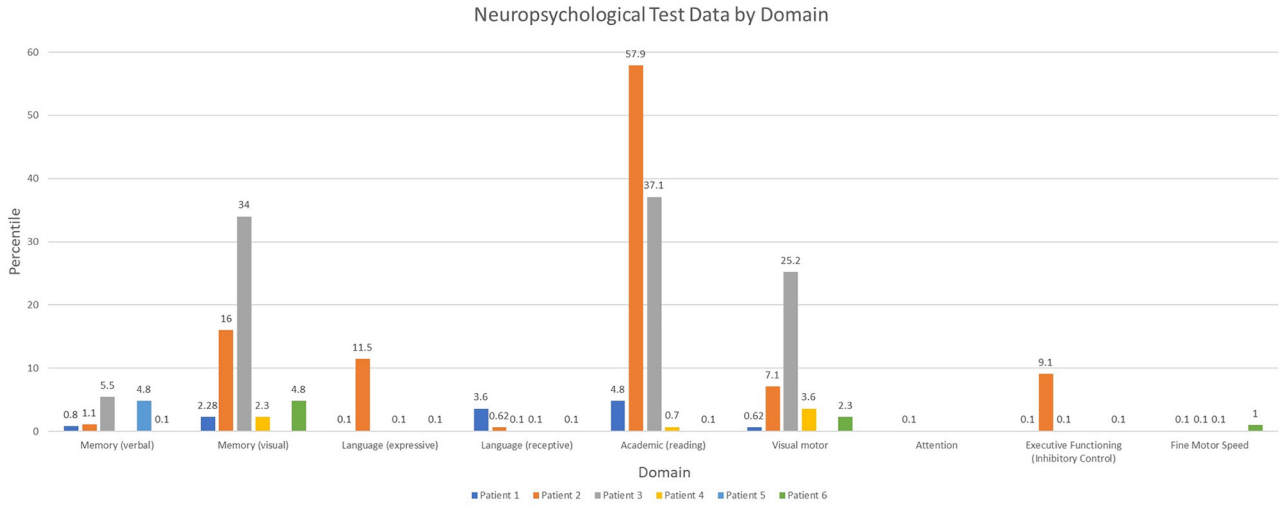

FIGURE 2
Neuropsychological test data by domain at the time of last assessment.

Cognitive and behavioral deficits that impact performance may mediate this discrepancy (23).

Social and emotional functioning results were variable on parent report suggesting concerns for internalizing (attention, anxiety, depression) or externalizing (hyperactivity, aggression, conduct problems) for some patients although not all. In a prior study of children with DESC, all patients presented with emotional and behavioral disorders that included fits of anger, aggressiveness, agitation, apathy, and withdrawal behaviors (19). Another study of patients with convulsive status epilepticus found that approximately one-third of patients scored above the clinical cut-off on at least one behavioral scale (24). It is therefore reasonable to consider that these behavioral impairments may influence reports of academic performance in relation to academic skills. It is important to evaluate and address behavior and social-emotional functioning in the clinical care of patient with FIRES.

Most patients in this case series returned to some form of education but all had special education needs. This is reflected in the literature with prior reports of FIRES needing special education classes (19) and half of children with convulsive status epilepticus having special educational needs (21).

Overall, the described changes in cognitive function have multiple proposed explanations including the location of seizures, initial refractory status epilepticus, ongoing drug-resistant epilepsy, as well as antiseizure medication exposure in the acute and chronic phase of FIRES treatment. Additional causative considerations include the impact of the underlying pathophysiology of FIRES and status epilepticus. Seizures in children with FIRES often have a focal onset in both temporal-perisylvian areas of the brain, then spread to the frontal lobes (9, 25). PET scans show hypometabolism in the temporoparietal and orbitofrontal cortices (25). Damage in these areas is consistent with cognitive deficits found in FIRES, most commonly language, memory, behavior, and frontal lobe function. Follow-up brain imaging in this case series demonstrates diffuse atrophy and mesial temporal sclerosis or hippocampal volume consistent with prior reports in the chronic phase (26). These findings may additively contribute to cognitive impairments and future research evaluating serial magnetic resonance imaging (MRI) of the brain with long-term neurocognitive outcomes is warranted.

Antiseizure medication themselves can also contribute to cognitive and behavioral deficits. During the acute and chronic phases of FIRES patients receive treatment with multiple antiseizure medications as shown in this cohort with all patients receiving treatment with at least two antiseizure medications at the time of their last follow-up testing. Specifically high dose phenobarbital has been proposed in the acute treatment of FIRES (14) and in our cohort five patients received this treatment acutely with two patients remaining on phenobarbital at the last follow-up neuropsychological testing visit. Phenobarbital has been associated with an IQ that is on average 8.4 points lower than placebo in children with febrile seizures, as well as reduced performance on IQ when compared to valproic acid (27–29). There are additional antiseizure medications that can also be associated with cognitive and behavioral changes, such as topiramate or levetiracetam (29, 30). Overall, the cognitive and behavioral side effects of antiseizure medications may explain *some* of the cognitive deficits seen in this study population, although antiseizure medications are unlikely to account for the full extent of decline compared to baseline function prior to onset of FIRES.

One limitation of this study is small sample size, as FIRES is a rare pediatric condition, and only patients treated with anakinra were included. Additionally, because this was a multicenter, retrospective study, neuropsychological testing could not be standardized across all sites and patients, so patients received various neuropsychological tests at various timepoints. In some cases, alternative testing procedures were utilized as a result of the patient's cognitive limitations (e.g., use of WNV instead of WISC-V or WASI-II in a patient that presented with severe language deficits). While there was often no direct comparison of scores between or within patients, percentiles could be compared within the same category of neuropsychological tests. This allowed for an adequate understanding of patients' neurocognitive functioning at last follow-up compared to their peers. However, standardized

serial monitoring of neuropsychological outcomes would be beneficial as part of routine follow-up care for patients with FIRES.

Future prospective studies of patients with FIRES in which standardized neuropsychological assessments are completed at set follow-up points would allow for a more direct analysis of change in neurocognitive function over time. This should be correlated with detailed neuroimaging and electrographic data to better understand these outcomes over time. It would also be helpful to include a comparative control group of patients not treated with anakinra to better determine any potential benefits of anakinra on neuropsychological outcomes. Ongoing multicenter collaboration and family engagement are encouraged to meet these objectives.

Conclusions

In summary, long-term follow-up of FIRES patients treated with anakinra demonstrates significant neurocognitive impairment across all neuropsychological testing domains with variable stability of scores over time. This reflects and builds upon neuropsychological data available in the literature. Future research needs to better understand the predictors of long-term neurocognitive outcomes and influence of acute treatment interventions. There is a need for standardized long-term serial neuropsychological assessments for all patients with FIRES and NORSE. It is recommended that this be incorporated into a multidisciplinary approach including not only neurologists and epilepsy specialists, as well as rehabilitation, neuropsychology, and mental health team members to support maximal neurocognitive recovery and support.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Colorado Multiple Institutional Review Board (COMIRB). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

EW, GB-S, EM, and KE contributed to the conception and design of the study. EW and KE developed the database. CS, KB, CV, SN, EW, and KE completed data collection. AS, EW, GB-S, and KE performed data review and analysis. EW and AS wrote the initial drafts of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

EM serves on the advisory board for Sobi.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1100551/full#supplementary-material

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An *in vitro* model of drug-resistant seizures for selecting clinically effective antiseizure medications in Febrile Infection-Related Epilepsy Syndrome

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Introduction: FIRES is a rare epileptic encephalopathy induced by acute unremitting seizures that occur suddenly in healthy children or young adults after a febrile illness in the preceding 2 weeks. This condition results in high mortality, neurological disability, and drug-resistant epilepsy. The development of new therapeutics is hampered by the lack of validated experimental models. Our goal was to address this unmet need by providing a simple tool for rapid throughput screening of new therapies that target pathological inflammatory mechanisms in FIRES. The model was not intended to mimic the etiopathogenesis of FIRES which is still unknown, but to reproduce salient features of its clinical presentation such as the age, the cytokine storm and the refractoriness of epileptic activity to antiseizure medications (ASMs).

Methods: We refined an *in vitro* model of mouse hippocampal/temporal cortex acute slices where drug-resistant epileptic activity is induced by zero Mg^{2+}/100 μM 4-aminopyridine. Clinical evidence suggests that acute unremitting seizures in FIRES are promoted by neuroinflammation triggered in the brain by the preceding infection. We mimicked this inflammatory component by exposing slices for 30 min to 10 μg/ml lipopolysaccharide (LPS).

Results: LPS induced a sustained neuroinflammatory response, as shown by increased mRNA levels of IL-1β, CXCL1 (IL-8), TNF, and increased IL-1β/IL-1Ra ratio. Epileptiform activity was exacerbated by neuroinflammation, also displaying increased resistance to maximal therapeutic concentrations of midazolam (100 μM), phenytoin (50 μM), sodium valproate (800 μM), and phenobarbital (100 μM). Treatment of LPS-exposed slices with two immunomodulatory drugs, a mouse anti-IL-6 receptor antibody (100 μM) corresponding to tocilizumab in humans, or anakinra (1.3 μM) which blocks the IL-1 receptor type 1, delayed the onset of epileptiform events and strongly reduced the ASM-resistant epileptiform activity evoked by neuroinflammation. These drugs were shown to reduce ASM-refractory seizures in FIRES patients.

Discussion: The neuroinflammatory component and the pharmacological responsiveness of epileptiform events provide a proof-of-concept validation of this *in vitro* model for the rapid selection of new treatments for acute ASM-refractory seizures in FIRES.

KEYWORDS

drug-refractory status epilepticus, neuroinflammation, antiseizure medications, immunomodulatory drugs, cytokines

1. Introduction

Febrile Infection-Related Epilepsy Syndrome (FIRES) is a "subcategory of New-Onset Refractory Status Epilepticus (NORSE)" that requires a prior febrile infection, with fever starting between 2 weeks and 24 h prior to onset of refractory status epilepticus (SE). NORSE is defined as a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other pre-existing relevant neurological disorder, and without a clear acute or active structural, toxic, or metabolic cause (1). After ineffectiveness of first and second line ASMs on acute seizures, at least 75% of FIRES patients require continuous infusion of anesthetics to stop seizures, with frequent relapses when anesthetics are discontinued (2–5).

FIRES etiopathogenesis remains unknown, however, both experimental and clinical research strongly suggest that neuroinflammation is a key precipitating factor. In particular, a febrile infection would trigger a self-perpetuating dysregulation of innate immunity involving glial cells and neurons in susceptible individuals (2). The neuroinflammatory response in FIRES patients is reflected by a storm of cytokines and chemokines, such as IL-1β, IL-6, TNF and IL-8 (6–9) in the CSF, as well as by reactive microglia and astrocytes (10) and increased expression of IL-1β and IL1 receptor type 1 (IL-1R1) in brain tissue (11). Activation of neuroinflammatory signallings in the brain promotes seizures in animal models (12, 13), thus suggesting that the cytokine storm contributes to the onset and perpetuation of seizures in FIRES.

Based on this evidence, new immunomodulatory/anti-inflammatory drugs in clinical use for other indications have been recently shown to reduce seizures in FIRES patients, such as systemic administration of anakinra or tocilizumab, or intrathecal dexamethasone (6, 14) [*reviewed in* (3, 15)]. In particular, these interventions were effective on unremitting seizures, also shortening the duration of mechanical ventilation, intensive care and hospital stay, and improving neurological outcomes (6, 14) [*reviewed in* (3, 15)].

There is a large arsenal of anti-inflammatory drugs to be repurposed for their therapeutic potential in NORSE/FIRES for stopping ASM-refractory seizures, thus preventing the long-term neurological consequences. There is urgent need, therefore, of developing experimental tools for rapid test of new drugs and for identifying molecular targets.

Since no validated experimental models for FIRES are as yet available, we set up a new *in vitro* model of drug-resistant seizures in FIRES. The model did not have to mimic the etiopathogenesis of FIRES, which is still unknown, but to provide a simple tool for rapid throughput screening of new therapies that target pathological inflammatory mechanisms in FIRES.

To this aim, we exposed hippocampal/temporal lobe slices from naïve mice of an age that approximates the clinical condition (16), to an inflammatory challenge. This challenge occurred before slices were exposed to hyperexcitable conditions evoking ASM-resistant seizures. Our data provide a proof-of-concept validation of this *in vitro* model for selecting treatments for the acute ASM-refractory seizures in FIRES.

2. Materials and methods

2.1. Animals and brain slice preparation

We used 28–30-day old male C57BL6/N mice. All procedures involving animals and their care were conducted in accordance with the principles set out in laws, regulations, and policies governing the care and use of laboratory animals: Italian Governing Law (D.lgs 26/2014; Authorisation n.19/2008-A issued March 6, 2008 by Ministry of Health); Mario Negri Institutional Regulations and Policies (Quality Management System Certificate—UNI EN ISO 9001:2008—Reg. N° 8576-A); the NIH Guide for the Care and Use of Laboratory Animals (2011 edition) and EU directives and guidelines (EEC Council Directive 2010/63/UE). Experiments were reviewed and approved by the intramural Animal Care and Use Committee, and by the Italian Ministry of Health.

Mice were killed by cervical dislocation. Brain was rapidly removed from the skull and horizontal brain slices (350 μm) from both hemispheres were cut with a vibratome (Leica VT 1000S) in ice-cold modified artificial cerebrospinal fluid (aCSF, mM): 87 NaCl, 2.5 KCl, 1 NaH_2PO_4, 75 sucrose, 7 $MgCl_2$, 24 $NaHCO_3$, 11 mM D-glucose, and 0.5 mM $CaCl_2$. Then, slices were transferred into the incubating chamber and submerged in aCSF containing (mM): 130 NaCl, 3.5 KCl, 1.2 NaH_2PO_4, 1.3 $MgCl_2$, 25 $NaHCO_3$, 11 D-glucose, 2 $CaCl_2$, and constantly bubbled with 95% O_2 and 5% CO_2 at room temperature. Slices were incubated in this condition for at least 1 h before starting the experiment.

2.2. High-density CMOS microelectrode array recordings

Recordings were performed using CMOS-microelectrode array (MEA) BioCamX (3Brain GmbH, Lanquart, Switzerland) at room temperature and slices were continuously perfused with oxygenated aCSF at a rate of 2 ml/min.

The recording array allowed simultaneous extracellular recordings from 4,096 electrodes at a sampling rate of 10 kHz per channel. The channels were arranged in a 64 × 64 array configuration and each square pixel measured 21 × 21 μm. The size of the recording area on the chip was suitable for recording from the entire hippocampal/cortical slice. Once the slice was positioned on the chip, it was held in place with a custom-made anchor of platinum wire and nylon mash.

The epileptiform activity was triggered by slice perfusion for 40 min with aCSF containing zero (0) Mg^{2+} and 100 μM 4-aminopyridine (4-AP) (17, 18), and consisted of synchronized field potentials (FPs) occurring at different frequency rates. Slices were preincubated for 30 min with aCSF alone or with the addition of 10 μg/ml lipopolysaccharide (LPS) before perfusion with the ictogenic cocktail. LPS was washed out for 5 min with aCSF before slice perfusion with 0 Mg^{2+} + 100 μM 4-AP (Supplementary Figure 1A). The tested drugs were added to the perfusion solution as shown in Supplementary Figures 1B, C (*see below*). Activity was recorded during 10 min sessions (T1 = 0–10 min; T2 = 20–30 min from the start of 0 Mg^{2+} + 100 μM 4-AP perfusion). FPs were detected using BrainWave5 software (3Brain) as follows: high and low threshold were set at

+200 μV and −200 μV, energy window 40 ms, refractory period 5 ms and maximum wave duration 500 ms.

We classified the epileptiform activity evoked 0 Mg^{2+} + 100 μM 4-AP into three major categories: (1) *ictal events* consisting of synchronous and repetitive field potentials (FPs) discharges (>5 s) with frequency >1 Hz (*see tracing in* Figure 3A); (2) *status epilepticus* (SE)-like events consisting of repetitive FPs with frequency ranging between 0.8–1.3 Hz and lasting >5 min (*see* Figure 3A); (3) interictal events consisting of synchronous single or repetitive FPs (<5 s). FP bursts were identified by a minimum of three FPs/burst with an interval between FPs ≤1 s.

At the beginning of the experiment, a digital image of the slice was taken trough a stereomicroscope. During the *post-hoc* analysis of the epileptiform activities, the digital image was overlayed on the activity map to identify the active areas in the slice. For quantification of epileptiform activity (FP frequency, amplitude and burst duration; incidence of ictal and SE events), we focused the analysis on the most active area in the whole hippocampal/cortical slice, as determined by activity map and the corresponding raster plot (e.g., Figures 2A, B). FPs measures were reckoned by averaging the values from each electrode in the active area. *Post-hoc* analysis showed that the most active areas were randomly distributed among hippocampus and temporal cortex in the various experimental groups.

2.3. Drug application

Slices were incubated for 30 min in aCSF or LPS (+5 min washout), then 0 Mg^{2+} + 100 μM 4-AP perfusion was started. After recording recurrent epileptiform events for at least 10 min, slices were perfused with the selected ASMs (dissolved in the ictogenic cocktail) at their maximal therapeutic plasma concentration in humans (4) for 40 min: phenytoin 50 μM, phenobarbital 100 μM, sodium valproate 800 μM (Sigma-Aldrich, USA), midazolam 100 μM [Accord Helathcare Italia srl (19); n = 5–7 slices/drug from 3 to 5 mice]. The experimental protocol is described in Supplementary Figure 1B. For testing the immunomodulatory drugs, slices were pre-incubated with LPS in aCSF (30 min + 5 min washout), then perfused for 15 min with aCSF ± anakinra [22 μg/ml; 1.3 μM; Swedish Orphan Biovitrum AB (Sobi), Stockholm, Sweden] or chimeric mouse/rat anti-IL-6R antibody (14.7 μg/ml; 100 μM; Genetech Inc., San Francisco, CA, USA). Then, 0 Mg^{2+} + 100 μM 4-AP was perfused (± drugs) for 40 min (n = 6 slices /drug from 3 to 5 mice).

2.4. RTqPCR

We used an independent set of slices to determine the neuroinflammatory response to 10 μg/ml LPS. After 30 min LPS incubation, slices were washed out in aCSF for either 30 min or 60 min (n = 7–10 slices/time point). At the end of washout, slices were collected and snap-frozen in liquid nitrogen, then stored at −80°C until analysis. Tissue was homogenized in Qiazol Lysis Reagent (Qiagen, Hilden, Germania) and total RNA isolated using the miRNeasy Mini kit (Qiagen) according to manufacturer's instructions. The concentration and purity of RNA were determined at 260/280 nm using a high-speed microfluidic UV/VIS spectrophotometer QIAxpert (Qiagen) and the integrity and quality of RNA were evaluated by 4200 Tapestation (Agilent Technologies, Santa Clara, CA, USA). cDNA was synthesized from 800 ng RNA using the high-capacity cDNA reverse transcription kit (Applied Biosystems, Waltham, Massachusetts, USA) following the manufacturer's protocol (Applied Biosystems). RT-qPCR experiments were run in triplicate for each sample using 384-well reaction plates and an automatic liquid handling station (epMotion 5075LH, Eppendorf, Hamburg, Germany) on an Applied Biosystems 7900HT System (Applied Biosystems). mRNA expression was analyzed using QuantiFast SYBR Green PCR Master Mix (Qiagen). The designed primers are reported in Table 1. Data were normalized using geometric mean of 2 independent housekeeping genes (*s2Vb* and *Actb*). Cycle threshold (CT) values were obtained using manual threshold.

TABLE 1 Primer sequence.

Gene	Primer sequence	
	Forward	Reverse
Actb	GCCCTGAGGCTCTTTTCCAG	TGCCACAGGATTCCATACCC
s2Vb	AGCATGTCACTGGCCATCAA	CCCAATCCCTATGCCTGAGAT
Il1rn	AACCACCAGGGCATCACAT	CTTGCCGACATGGAATAAGG
Il1b	TGCCACCTTTTGACAGTGAT	GATGTGCTGCTGCGAGATT
Tnf	TGAACTTCGGGGTGATCG	GGTGGTTTGTGAGTGTGAGG
Cxcl1	ACCGAAGTGATAGCCACACTC	TCCGTTACTTGGGGACACC

2.5. Statistical analysis

Statistical analysis was performed by GraphPad Prism 8 (GraphPad Software, USA) for Windows using raw data. Data are presented as bargrams with individual values, and mean ± SEM. Non-parametric tests were chosen due to the low power of normality tests when the sample size is small. In each experiment, statistical analysis is reported in the respective figure legend. Differences between groups were considered significant for values of $p < 0.05$. Sample size was *a priori* determined based on literature data and previous experience with the 0 Mg^{2} +100 μM 4-AP model.

3. Results

3.1. Neuroinflammation *in vitro* model

We refined an *in vitro* model of epileptiform activities in hippocampal/temporal cortex slices from naive mice induced by 0 Mg^{2+} + 4-AP. The aim was to mimic the unresponsiveness of epileptiform events to ASMs (17), as observed in FIRES patients. We added the prototypical immune-inflammatory agent LPS to reproduce the cytokine storm that precedes seizure precipitation in FIRES.

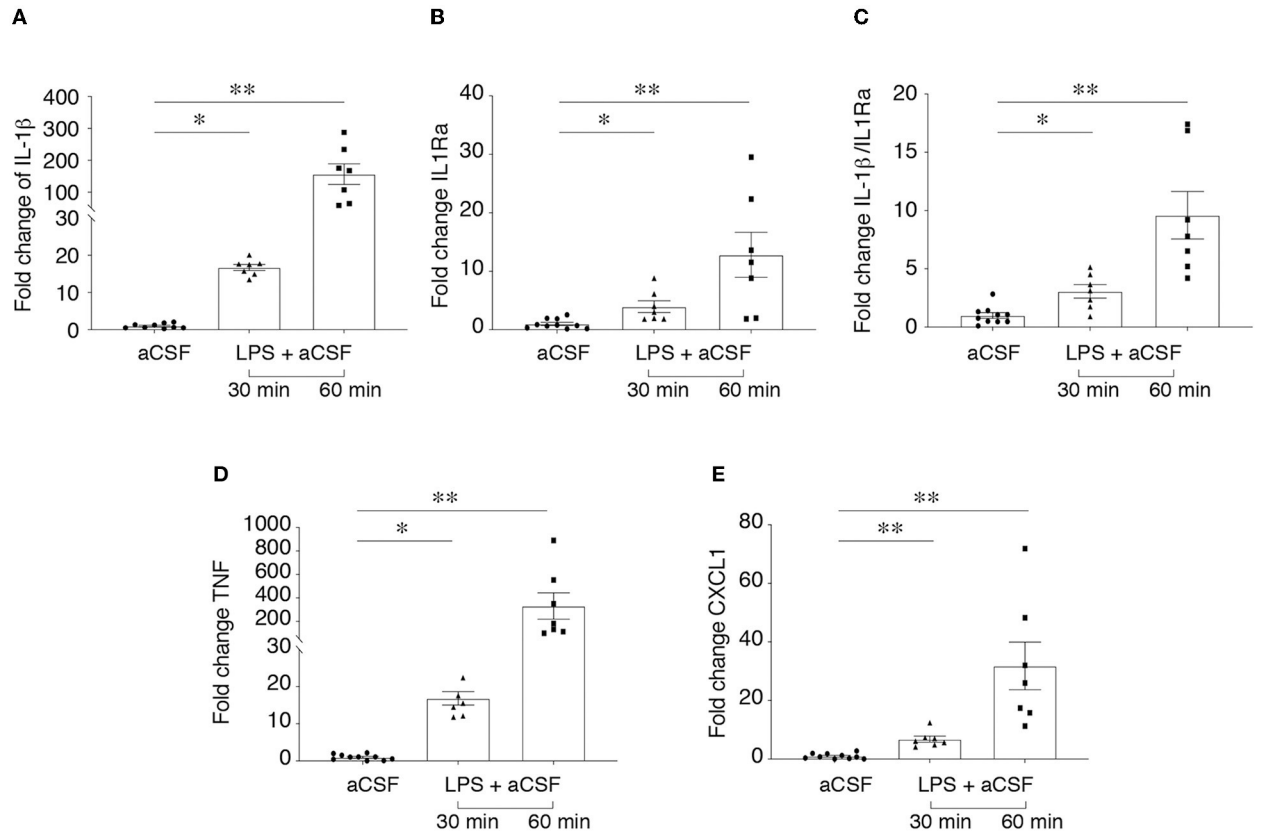

FIGURE 1
LPS-induced neuroinflammation in hippocampus/temporal cortex slices. RT-qPCR analysis of cytokine mRNA **(A–E)** in hippocampal/temporal cortex slices incubated with aCSF alone or with 10 μg/ml LPS for 30 min, followed by 30 min or 60 min washout in aCSF. Reference genes were *s2Vb and Actb*. Data are presented as fold-increase vs. control value in aCSF incubated slices (mean ± SEM and single values). *$p < 0.05$, **$p < 0.01$ vs. aCSF by Kruskal–Wallis test followed by Dunn's multiple comparison test.

Figure 1 shows a significant induction of ictogenic cytokines mRNA, namely *Il1b* **(A)**, *Tnf* **(D)** and *Cxcl1* **(E)** in brain slices after 30 min incubation with 10 μg/ml LPS. This induction was evident after 30 min LPS washout ($p < 0.05$; $p < 0.01$ vs. aCSF) and persisted after 60 min washout ($p < 0.01$ vs. aCSF). *Il1rn* (B) was also induced at both time points ($p < 0.05$; $p < 0.01$ vs. aCSF) although to a minor extent as compared to *Il1b* transcript. Accordingly, *Il1b*/*Il1rn* ratio **(C)** was significantly increased ($p < 0.05$; $p < 0.01$) compared to aCSF incubated slices, thus denoting a predominance of proinfammatory vs. antiinfammatory cytokines.

3.2. Exacerbation of epileptiform activity by neuroinflammation

Epileptiform activity (activity map and raster plot are depicted in Figures 2A, B, D, E) was quantified during 10 min recording at two sequential time points (T1= 0–10 min, Figures 2A, B and T2 = 20–30 min, Figures 2D, E) from the start of 0 Mg^{2+} + 4-AP perfusion. Pre-incubation for 30 min with LPS exacerbated epileptiform activity in slices (Figures 2B, E vs. Figures 2A, D): bargrams show an increased frequency of FPs ($p < 0.05$ vs. 0 Mg^{2+} + 4-AP alone) and FP burst duration ($p < 0.05$) at T1 (Figure 2C) and T2 (Figure 2F), without affecting the amplitude of recorded events. Moreover, the incidence SE events (Figure 3A; see Section 2.2 for definition) observed in 0 Mg^{2+} + 4-AP bathed slices was significantly increased by four-fold on average in LPS pre-incubated slices (Figure 3B; $p < 0.05$).

3.3. ASM-resistance of epileptiform activity is increased by neuroinflammation

We tested the effect of specific ASMs that classically fail in FIRES patients, namely 800 μM sodium valproate, 50 μM phenytoin, 100 μM phenobarbital and 100 μM midazolam on 0 Mg^{2+} + 4-AP-evoked epileptiform activities in LPS-pre-exposed vs. naïve slices (Figure 4). Epileptiform events were quantified at T2 = 20–30 min after the beginning of drug perfusion (*protocol in* Supplementary Figure 1B). In slices exposed to 0 Mg^{2+} + 4-AP (Figure 4A), both phenytoin ($p < 0.05$), phenobarbital ($p < 0.01$) and midazolam ($p < 0.05$) partially reduced the frequency of FPs with residual epileptiform activity still detected, while sodium valproate was ineffective. In LPS-preincubated slices exposed to 0 Mg^{2+} + 4-AP (Figure 4B), only phenobarbital and midazolam partially reduced the frequency of FPs ($p < 0.05$; $p < 0.01$)

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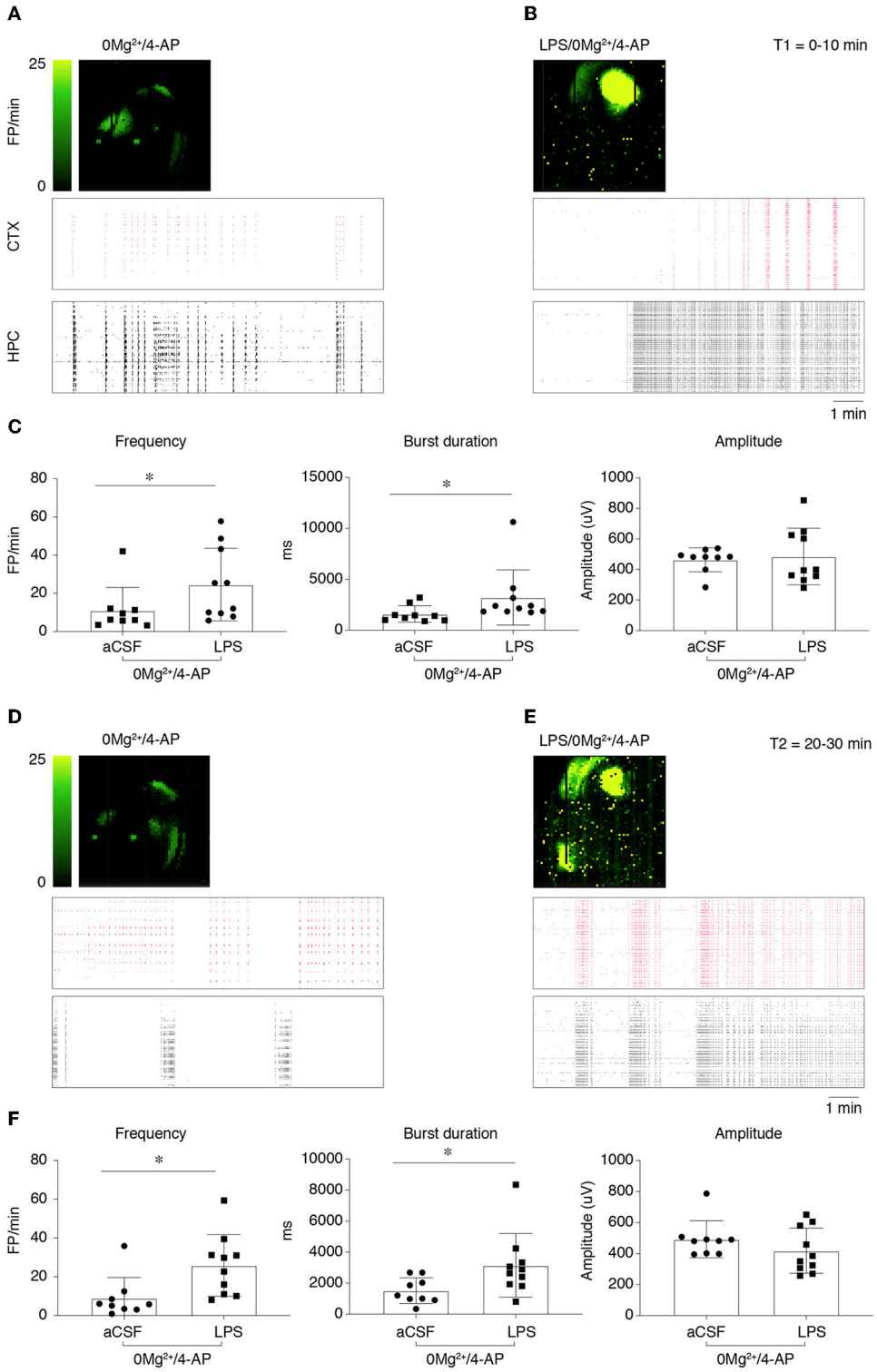

FIGURE 2
Lipopolysaccharide effect on epileptiform activity in hippocampus/temporal cortex slices. **(A, B)** Depict representative activity maps (*first row*; higher field potential, FP, frequency corresponds to lighter green color) and raster plots (*second and third rows*) of epileptiform activity recorded in the temporal cortex (CTX) or hippocampus (HPC) during 0 Mg^{2+}/100 μM 4-AP perfusion alone **(A)** or in slices pre-incubated with LPS [**(B)**; 10 μg/ml LPS for 30 min, followed by 5 min washout], then exposed to 0 Mg^{2+}/100 μM 4-AP for 40 min. **(C)** Reports quantification of epileptiform activity (FP frequency, burst duration and amplitude) *during T1* (0–10 min from the start of 0 Mg^{2+}/4-AP perfusion) reckoned in the area of higher activity (as shown by activity map/raster plot) in each slice. **(D, E)** Depict representative activity maps and raster plots *during T2* (20–30 min from the start of 0 Mg^{2+}/4-AP perfusion). **(F)** Reports quantification of epileptiform activity during T2 reckoned in the area of higher activity in each slice. Data are presented as mean ± SEM and single values (0 Mg^{2+} + 4-AP, $n = 9$ slices; LPS + 0 Mg^{2+} + 4AP, $n = 10$ slices). *$p < 0.05$ vs. 0 Mg^{2+}/4AP by Mann–Whitney test.

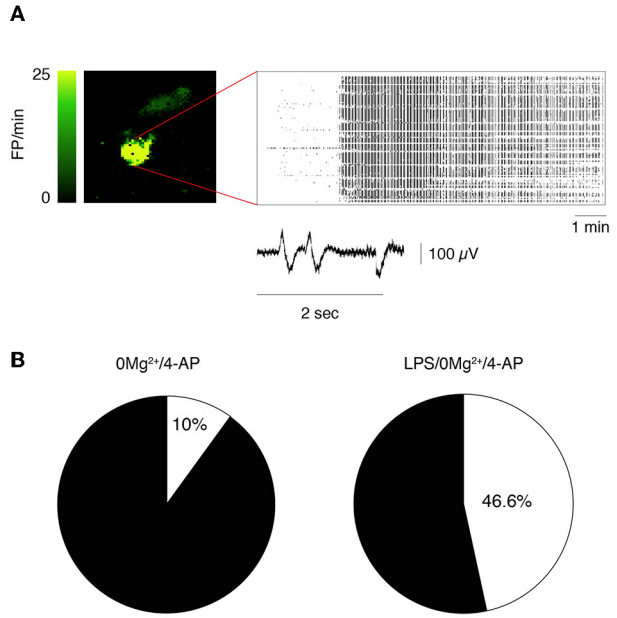

FIGURE 3
Incidence of status epilepticus in LPS-treated slices. **(A)** Depicts a representative activity map (higher FP frequency corresponds to lighter green color) and raster plot showing a status epilepticus (SE) event in hippocampus. Enlarged tracing depicts FPs from one representative electrode. **(B)** Shows the incidence of SE events in 0 Mg^{2+}/4-AP exposed slices ± LPS (10 μg/ml LPS for 30 min, followed by 5 min washout). 0 Mg^{2+} + 4-AP, $n = 9$ slices; LPS+0 Mg^{2+} + 4AP, $n = 10$ slices. $p < 0.05$ vs. 0 Mg^{2+}/4AP by Chi-square test.

while both phenytoin and sodium valproate were ineffective. The respective activity maps and raster plots are depicted in Figures 4D, E.

Since FP frequency analysis encompassed all epileptiform activities, we specifically analyzed *ictal events* and *SE events* (see Section 2.2 for definition) during 20–40 min perfusion. Notably, we found that while ASMs fully inhibited these activities in slices exposed to 0 Mg^{2+} + 4-AP (64% incidence in aCSF vs. 0% with ASMs), the same ASMs were only partially effective in LPS-pre-exposed slices (Figure 4C). In particular, ictal and SE events occurred in 86% of LPS-pre-exposed slices, in 57% of sodium valproate slices (4/7), in 33% of phenytoin and midazolam slices (2/6) and in 20% of phenobarbital slices (1/5 slices; Figure 4C).

These results indicate that seizure resistance to ASMs is exacerbated in LPS pre-treated slices.

3.4. Immunomodulatory drugs inhibit ASM-resistant epileptiform activity in lipopolysaccharide treated slices

We investigated the effect of anakinra and the anti-IL-6R antibody on epileptiform activity in LPS-treated slices. To this aim, we modified the experimental protocol to take into account the time that the immunomodulatory drugs may require to counteract neuroinflammation. Thus, we perfused slices with aCSF containing the immunomodulatory drug for 15 min *prior* to switching to 0 Mg^{2+} + 4-AP perfusion solution. As for ASMs, the immunomodulatory drugs were perfused for further 40 min (Supplementary Figure 1C), and epileptiform events were measured during 20–30 min (T2). As depicted in Figures 5A, B, both immunomodulatory drugs showed similar effects by significantly delaying the time to onset of the first FP ($p < 0.05$; $p < 0.01$ vs. LPS/0 Mg^{2+} + 4-AP) and by reducing FP frequency ($p < 0.05$; $p < 0.01$ vs. LPS/0 Mg^{2+} + 4-AP). The respective activity maps and raster plots are depicted in Figure 5C. Importantly, ictal events and SE events in LPS/0 Mg^{2+} + 4-AP (83% incidence; Figure 4C) were abolished by both anakinra and the anti-IL-6R antibody (0% incidence: *depicted in* Figure 5C, HPC).

4. Discussion

We described a refined *in vitro* model of epileptiform activities induced in hippocampal/temporal cortex slices of naive mice by 0 Mg^{2+} + 4-AP (17). We choose this model since the evoked epileptiform events showed limited responsiveness to first and second line ASMs (17), as observed in FIRES patients (3–5). Moreover, the model used mouse hippocampal/temporal cortex slices, including subiculum, perirhinal and the entorhinal cortices. This circuitry is crucially involved in the epileptiform activity and neuropathology of FIRES, as shown by EEG and MRI studies. Finally, we used MEA recording for monitoring epileptiform events over the entire limbic circuitry.

To mimic salient clinical features of FIRES, we modified the original model (17) by taking into account the age of onset of FIRES and the cytokine storm. In particular, since the incidence of FIRES is higher in school-age children and young adults (although it may occur at any age), we used acute slices from 28 to 30-day old mice that approximates grade school age-puberty in humans (16). Moreover, the original model lacked the immune/inflammatory challenge which precedes seizure precipitation in FIRES. Thus, we preincubated slices for 30 min with the prototypical inflammatory agent LPS. This condition induced a prominent neuroinflammatory response in the slices that persisted after LPS washout for the entire time of electrophysiological recording. LPS-induced neuroinflammation included the induction of cytokines with both *in vitro* (20) and *in vivo* ictogenic properties, such as IL-1β, TNF (21, 22) and CXCL1 (23). In particular, the ratio of IL-1β to its receptor antagonist IL-1Ra was significantly increased by LPS vs. naïve slices, supporting a failure of endogenous antiinfammatory mechanisms to resolve neuroinflammation (13). A deficit in antiinflammatory mechanisms was described in epileptic foci of patients with ASM-resistant seizures (24), in the hippocampus of animal models of SE (13, 22) and patients with FIRES (25).

In accordance with the increased level of ictogenic cytokines/chemokines, LPS exacerbated the epileptiform activity evoked by 0 Mg^{2+} + 4-AP by increasing the frequency and burst duration of FPs, as well as the incidence of ictal/SE events. This evidence is in accordance with the increased frequency of evoked epileptiform discharges induced by LPS in immature rat hippocampal slices (18). Differently from our study, however, Gao et al. added LPS *after* epileptiform discharges occurred, and no

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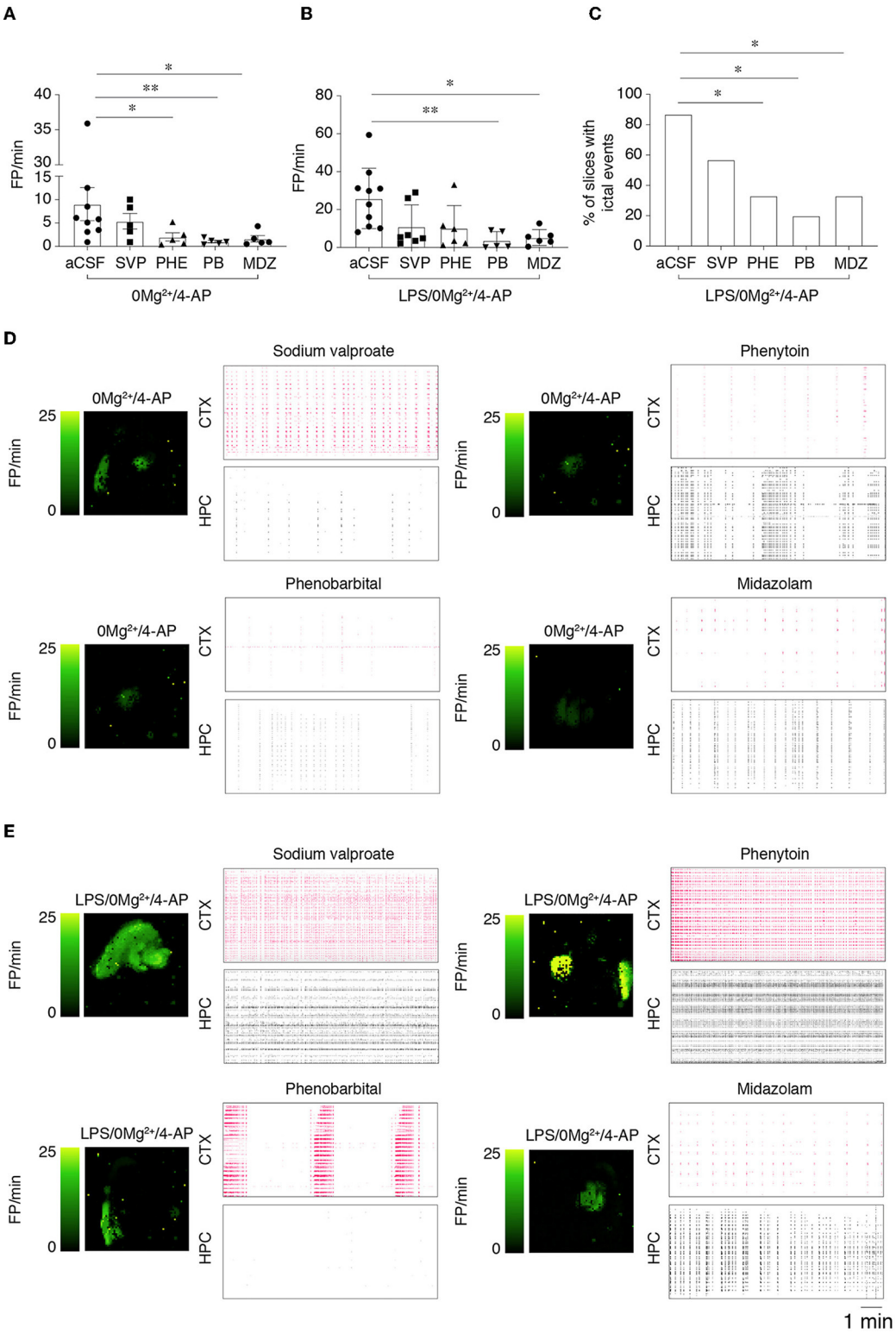

FIGURE 4
Effect of ASMs on epileptiform activities. **(A, B)** Show the effect of 800 μM sodium valproate (SVP), 50 μM phenytoin (PHE), 100 μM phenobarbital (PB) and midazolam (MDZ, 100 μM) on field potential (FP) frequency in slices perfused with 0 Mg^{2+}/4-AP **(A)** or pre-treated with LPS **(B)** (10 μg/ml LPS for 30 min, followed by 5 min washout), then exposed to 0 Mg^{2+}/100 μM 4-AP for 40 min. Quantification of epileptiform activity was done *during T2* (20–30 min from the start of 0 Mg^{2+}/4-AP perfusion) in the area of higher activity in each slice. Data are presented as mean ± SEM and single values ($n = 5–7$ slices/experimental group) *$p < 0.05$; **$p < 0.01$ by Mann–Whitney test vs. respective control slices (aCSF, no ASMs added). **(C)** Shows the incidence of the combination of ictal and SE events in LPS-pretreated slices in the various experimental groups. *$p < 0.05$ vs. 0 Mg^{2+}/4AP by Chi-square test. **(D, E)** Depict representative activity maps (higher FP frequency corresponds to lighter green color) and raster plots in temporal cortex (CTX) and hippocampus (HPC) after addition of the various ASMs to slices perfused with 0 Mg^{2+}/4-AP ± LPS. SVP, sodium valproate; PHE, phenytoin; PB, phenobarbital, MDZ, midazolam.

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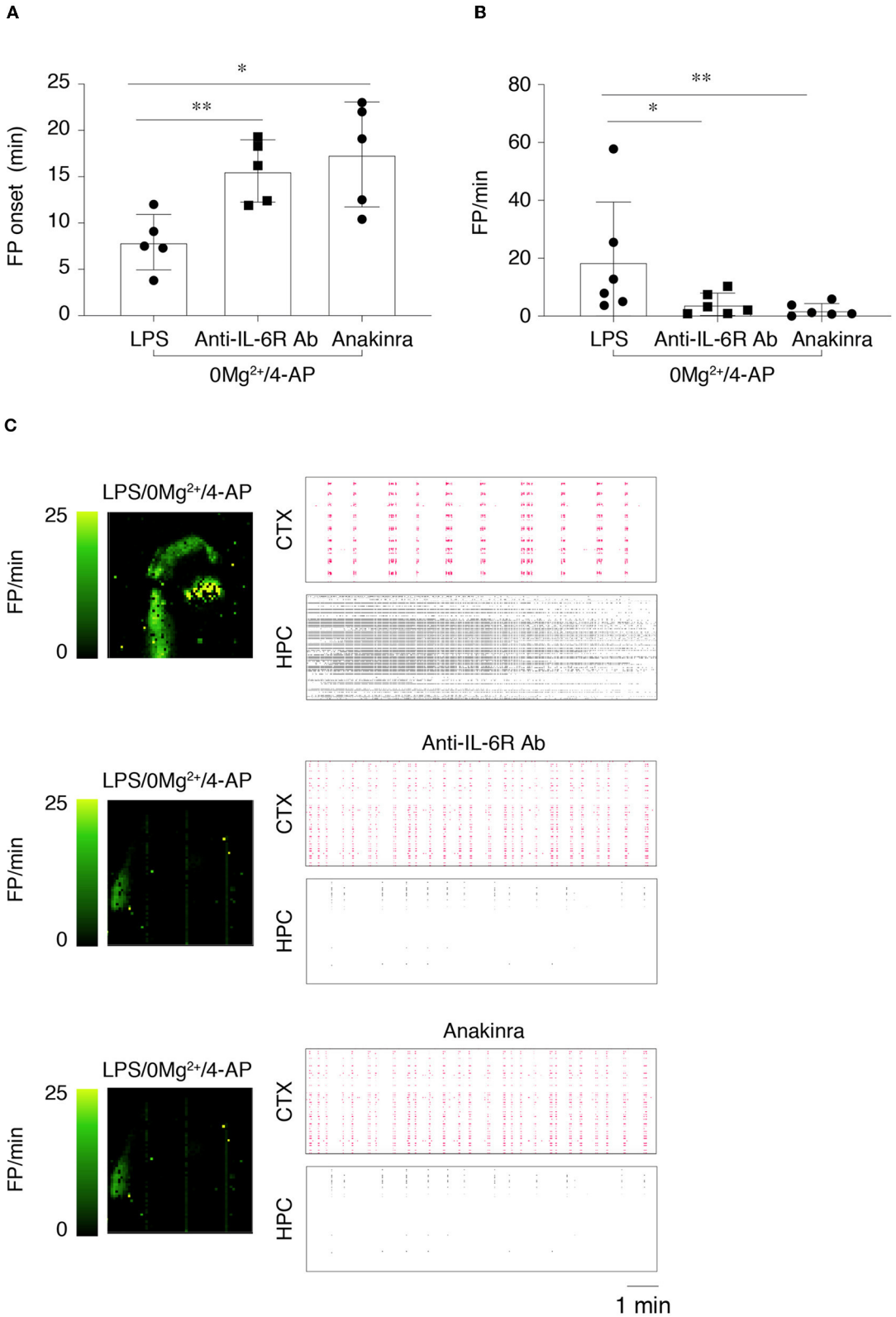

FIGURE 5
Effects of anti-IL-6R antibody and anakinra on epileptiform activity in lipopolysaccharide-treated slices. **(A, B)** The onset of the first field potential (FP) event **(A)** and FP frequency **(B)** in the various experimental groups ($n = 6$ slices/group). FP frequency was calculated *during T2* (20–30 min from the start of 0 Mg^{2+}/4-AP perfusion). Slices were preincubated with aCSF containing LPS (10 μg/ml for 30 min, followed by 5 min aCSF washout), then perfused in aCSF ± anti-mouse IL-6R Ab (100 μM) or ± anakinra (1.3 μM) for 15 min followed by 0 Mg^{2+}/4-AP ± drugs for 40 min. *$p < 0.05$; **$p < 0.01$ by Mann–Whitney test vs. respective control slices (aCSF, no added drugs). **(C)** Depicts representative activity maps (higher FP frequency corresponds to lighter green color) and raster plots in temporal cortex (CTX) and hippocampus (HPC) in slices perfused with 0 Mg^{2+}/4-AP+LPS with or without the immunomodulatory drugs.

drugs were tested. We provide, therefore, a new model for seizures in FIRES, where neuroinflammation contributes to the severity of epileptiform activity.

To determine the pharmacological responsiveness of seizures developing in the LPS-exposed slices, we tested the antiictogenic activity of specific ASMs that classically fail in FIRES patients, namely midazolam, phenytoin, phenobarbital and sodium valproate (4). Each ASM, used at its maximal therapeutic plasma concentration in humans, showed only a partial effect in reducing FPs in naïve slices exposed to 0 Mg^{2+} + 4-AP. Notably, in slices where neuroinflammation was induced by LPS, the refractoriness of epileptiform events to ASMs was exacerbated. In fact, phenytoin and sodium valproate were both ineffective on FP frequency, and midazolam and phenobarbital were only partially effective. Importantly, the incidence of ictal and SE events was increased in LPS-treated slices (86.6 vs. 64% without LPS). Moreover, these events were suppressed by ASMs in slices not pre-exposed to LPS, while they were only partially reduced by midazolam, phenobarbital and phenytoin, and unresponsive to sodium valproate, in LPS-exposed slices.

Next, we tested the effect of two immunomodulatory drugs, namely the anti-mouse IL-6R antibody (corresponding to tocilizumab in humans) and anakinra (recombinant human IL-1Ra) on epileptiform activity exacerbated by LPS. These drugs showed therapeutic effects on seizures and improved neurological outcomes in FIRES patients [*reviewed in* (3)]. Both immunomodulatory drugs at concentrations reflecting their maximal plasma or CSF therapeutic levels (26–28) drastically reduced epileptiform activities in LPS-treated slices, and abolished SE events. Thus, this refined *in vitro* model mimics both ASM-resistant seizures and their sensitivity to immunomodulatory drugs in FIRES. To maximize the rapidity of drug testing, we focused our analyses on the most active area (either hippocampus or temporal cortex, as shown by activity maps/raster plots) in the slice. Moreover, the epileptiform activity was quantified starting 20 min after perfusion of the ictogenic cocktail, when the epileptiform events were stably expressed and the drugs had time to act on their targets.

We propose this model as a first screening test to rapidly select potentially effective drugs for ASM-refractory seizures in FIRES patients. A limitation of the *in vitro* model is that it does not allow to control for drug penetration through the blood brain barrier and for PK/PD/toxicity issues which require to be addressed in an *in vivo* model. Recently, LPS-primed adult mice with increased hippocampal cytokine levels (e.g., IL-1β, TNF, IL-6) were shown to develop a more severe pilocarpine-induced SE compared to naïve mice. Similarly to our *in vitro* model, SE was refractory to various ASMs (29). Thus, this mouse model may represent a second step for *in vivo* validation after drug selection in the slice model.

Notably, the slice model reinforces the evidence that neuroinflammation in the limbic system exacerbates seizures and contributes to the mechanisms of ASM-resistance. Accordingly, in mouse model of SE refractory to benzodiazepines, the co-administration of anakinra and diazepam terminated SE (30). Drugs blocking the P2X7 receptors, which results in inflammasome inhibition, relieved SE resistance to various ASMs in mice (31). Our *in vitro* model, therefore, allows testing whether drug-resistance is relieved by combining antiinflammatory drugs with ASMs. Understanding whether neuroinflammation is a factor involved in seizure severity and refractoriness to ASMs would prompt early addition of anti-inflammatory drugs to the conventional treatment protocols in FIRES patients.

In conclusion, the *in vitro* experimental data support that cytokine pathways, mediated for example by IL-1β, TNF and CXCL1/IL-8, are involved in ASM-resistant seizures in FIRES. These factors can be targeted by drugs with immunomodulatory properties, such as anakinra and tocilizumab, or by new investigational drugs against other inflammatory targets that are emerging in the preclinical literature (32, 33). Since the etiopathogenesis of FIRES is still unknown, this model mimics the pharmacological response of seizures to clinically used drugs in FIRES patients. The model, therefore, could facilitate drug screening before *in vivo* testing, allowing a faster path to the clinical use of new effective treatments for FIRES that are urgently needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was reviewed and approved by Mario Negri Institute Animal Care and Use Committee, and by the Italian Ministry of Health.

Author contributions

MC and MDN conducted the experiments and analyzed the data. IC conducted RT-PCR experiments and analyzed the data. AV supervised the study and together with MC designed the experiments and wrote the manuscript. All authors have read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1129138/full#supplementary-material

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Investigating the genetic contribution in febrile infection-related epilepsy syndrome and refractory status epilepticus

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Introduction: Febrile infection-related epilepsy syndrome (FIRES) is a severe childhood epilepsy with refractory status epilepticus after a typically mild febrile infection. The etiology of FIRES is largely unknown, and outcomes in most individuals with FIRES are poor.

Methods: Here, we reviewed the current state-of-the art genetic testing strategies in individuals with FIRES. We performed a systematic computational analysis to identify individuals with FIRES and characterize the clinical landscape using the Electronic Medical Records (EMR). Among 25 individuals with a confirmed FIRES diagnosis over the last decade, we performed a comprehensive review of genetic testing and other diagnostic testing.

Results: Management included use of steroids and intravenous immunoglobulin (IVIG) in most individuals, with an increased use of immunomodulatory agents, including IVIG, plasma exchange (PLEX) and immunosuppressants such as cytokine inhibitors, and the ketogenic diet after 2014. Genetic testing was performed on a clinical basis in almost all individuals and was non-diagnostic in all patients. We compared FIRES with both status epilepticus (SE) and refractory status epilepticus (RSE) as a broader comparison cohort and identified genetic causes in 36% of patients with RSE. The difference in genetic signatures between FIRES and RSE suggest distinct underlying etiologies. In summary, despite the absence of any identifiable etiologies in FIRES, we performed an unbiased analysis of the clinical landscape, identifying a heterogeneous range of treatment strategies and characterized real-world clinical practice.

Discussion: FIRES remains one of the most enigmatic conditions in child neurology without any known etiologies to date despite significant efforts in the field, suggesting a clear need for further studies and novel diagnostic and treatment approaches.

KEYWORDS

febrile infection-related epilepsy syndrome, new onset refractory status epilepticus, refractory status epilepticus, pediatric epilepsy, genetics

1. Introduction

Febrile infection-related epilepsy (FIRES) is a rare and often catastrophic neurological condition characterized by refractory status epilepticus (RSE) that is preceded by a febrile illness occurring 2 weeks to 24 h prior to onset of seizures (1). Historically, FIRES was described in the pediatric population, but it is now recognized to occur in adults as well (2). FIRES describes a subcategory of individuals with new onset refractory status epilepticus (NORSE), a clinical presentation characterized by *de novo* onset RSE that has no identifiable active structural, toxic, or metabolic cause (1). While NORSE and FIRES represent a small fraction of all patients with RSE, they represent one of the most severe forms, with prolonged hospitalizations frequently followed by cognitive impairment and intractable epilepsy or death.

The underlying etiology for FIRES remains elusive. In some cases, an autoimmune or viral form of encephalitis is identified, although in most cases no underlying cause is identified. These cases are designated as cryptogenic and are an area of active investigation (1). A fulminant aberrant inflammatory response in the central nervous system has been proposed as a unifying mechanism (3, 4). SE may induce a proinflammatory cascade, with several of these molecules further promoting proconvulsant activity which becomes refractory to treatment (5, 6). Furthermore, reported abnormal imaging findings have been variable and nonspecific (7, 8).

Among studies focused on elucidating the etiology of FIRES, there has been an increased focus on potential underlying genetic factors as causative etiologies, though no genetic factors have ever been definitively identified. The lack of genetic explanation in FIRES stands in stark contrast to the genetic landscape of epilepsy more broadly in which the genetic yield is up to 33% with different forms of genetic testing (9, 10). Studies exploring genetic etiologies of SE and RSE indicate a subset of various genes that are associated with SE (11, 12). However, there are fewer recognized genes and validated variants associated with RSE (13, 14).

Given the rarity of NORSE and FIRES, a consistent barrier to identifying genetic etiologies is the limited population from which data can be systematically analyzed. While there have been reports of individuals with FIRES or NORSE having variants in genes associated fever-sensitive epilepsies or metabolic diseases, (15–19) many of these variants have not been confirmed to be explanatory, further contributing to the air of enigma regarding FIRES. A genetic susceptibility to immune dysregulation through variants in the cytokine pathway has also been suggested (15) but systematic genetic studies have not replicated these findings (20, 21). Recently, we published exome findings on 50 individuals with FIRES and did not identify any disease-causing genetic variants, including in candidate genes (21). Human leukocyte antigen (HLA) sequencing in a previous cohort of 29 individuals with FIRES previously failed to identify prominent HLA genes (21). Consequently, the role of genetics as an etiology or predisposition for FIRES remains inconclusive.

Therefore, in this retrospective study, we aimed to further delineate the genetic etiology of FIRES, as well as SE and RSE more generally. We used natural language processing (NLP) methods to identify children diagnosed with FIRES at a large tertiary center and systematically reviewed the genetic testing completed as part of their clinical care to identify a potential genetic etiology for FIRES. To determine how the genetic yield of FIRES fits within the broader landscape of children with non-FIRES related SE and RSE, we examined broader cohorts of children diagnosed with SE or RSE as their first presentation of seizure.

2. Methods

2.1. Identification and inclusion of individuals with FIRES

This was a retrospective single-center observational study performed at Children's Hospital of Philadelphia (CHOP). Individuals with FIRES were identified through NLP of free-text patient notes from the Electronic Medical Records (EMR) between 2013 and 2023 using the search terms "Febrile infection-related epilepsy" or "FIRES" or "new-onset refractory status epilepticus" or "NORSE" with "febrile infection." Some individuals in our study were initially admitted to outside institutions prior to transfer to CHOP as a tertiary care center. We included these patients as we had access to shared EMRs from their hospitalizations at the time of their subsequent presentations to CHOP. We manually reviewed the selected charts to confirm the diagnosis of FIRES based on formal consensus criteria (1).

The following definitions were used. Status epilepticus (SE) was defined as 5 min or more of continuous clinical seizure activity or recurrent seizure activity without recovery between seizures. Refractory status epilepticus (RSE) was defined as SE persisting despite administration of at least two appropriate parenteral medications including a benzodiazepine, without a specific duration required. We used consensus guideline definitions of NORSE and FIRES (1). NORSE was defined as *de novo* onset of RSE without an identifiable acute or active structural, toxic, or metabolic cause. FIRES was considered a subcategory of NORSE requiring prior febrile illness starting between 2 weeks and 24 h before onset of RSE (with or without fever at onset of status epilepticus). Individuals were excluded if: (1) there was no documentation of preceding illness, remote history of illness without documentation, or lack of outside records to confirm preceding febrile illness; (2) the word "FIRES" was included in the chart but referred to family history or to a publication that included the search term or the differential diagnosis where FIRES was ultimately dismissed; or (3) the clinical history did not align with the formal consensus definition for FIRES. Accordingly, three individuals with NORSE but without sufficient clinical information to diagnose FIRES based on the characteristics defining FIRES described above were excluded. This study was completed and approved by the Institutional Review Board at CHOP.

2.2. Clinical and treatment data

We manually reviewed demographic and clinical data of 25 individuals with FIRES, including information on hospital admissions and genetic workup (see below). For each patient, we reviewed their prior medical and developmental history, history of preceding illness with fever, and age at time of hospitalization for FIRES and at discharge. For treatment strategies, all children were placed on anesthetic infusions during their hospital course (midazolam, pentobarbital, ketamine); however, detailed records about the dates of administration were limited so we focused only on whether anesthetic

infusions were administered, number of anti-seizure medications at discharge, and the use of anti-inflammatory and immunomodulatory agents including intravenous immunoglobulin (IVIG), steroids, plasmapheresis (PLEX), and other immunomodulatory agents.

2.3. Genetic testing

For individuals with confirmed diagnoses of FIRES, a comprehensive review of patient records was performed to identify elements of their diagnostic workup for FIRES, with particular attention to the timing and type of genetic testing. Previous genetic testing was identified in the EMR and stored as laboratory results, external media uploads, or within recent neurology and genetic clinical notes. Lastly, a free text search of medical charts was performed with the key words: "*SCN2A*," "*POLG*," "gene," "karyotype," "microarray," "epilepsy panel," "exome," and "mito." Cases where genetic testing was performed but reports were not available for review were noted. We documented the type of genetic test (single gene sequencing, karyotype, microarray, whole exome sequencing, mitochondrial genome sequencing), results, report date, coding and protein variant change, inheritance, and variant pathogenicity. Of note, genetic testing of individuals with FIRES spanned several years and tests were sent to and interpreted by different diagnostic labs, according to the discretion of the ordering provider. In the context of ongoing gene discovery, genes included on the gene panels have been variable depending on the year and may not have included more recently discovered genes.

2.4. Cohorts for mapping the genetic etiologies of SE and RSE more broadly

To characterize the clinical and genetic landscape of individuals with SE and RSE more broadly we used two cohorts: (1) 32,112 individuals with epilepsy in the Pediatric Epilepsy Learning Health System (PELHS) and (2) 1,894 individuals with presumed or confirmed genetic epilepsies at CHOP. First, using the PELHS cohort, we mapped the genetic and clinical landscape of non-FIRES RSE through systematic evaluation of the EMR, capturing more than 4.5 million full-text health care notes spanning 203,369 total patient-years. We limited our search in this cohort to the first presentation of RSE, as subsequent encounters with RSE documented in the patient notes could refer to a new RSE event or history of prior RSE. We assessed the overall distribution of RSE onset in this larger cohort and contrasted it with the wider distribution of onset in FIRES.

Secondly, in order to generate an understanding of genes that may be implicated in SE and RSE more broadly, we further delineated the genetics of children with SE and RSE using a dataset comprised of 1,894 individuals with presumed genetic epilepsy and neurodevelopmental disorders and characterized the genetic yield of SE. This resulted in 1,158 individuals in the CHOP cohort with SE. When performing NLP on patient notes to capture phenotypes such as the presence of certain seizure types of neurological features, we only parsed notes prior to a genetic diagnosis if applicable. The rationale was to control for bias associated with clinical impressions following a molecular diagnosis. For example, individuals with *PCDH19*-related disorders might have "status epilepticus" in their patient charts due to a general clinical description of *PCDH19*-related disorder, rather than the patient's specific phenotype.

In our cohort of 1,894 individuals with presumed genetic epilepsies, we then focused only on individuals with a known genetic diagnosis who presented with RSE at first seizure presentation (i.e., no prior history of epilepsy) in order to identify genetic etiologies associated with a NORSE-like presentation. We identified 208 individuals with RSE from NLP. Seventy-five of these individuals had a genetic diagnosis. Twenty-two of the 75 individuals presented with RSE at their first seizure presentation. We then manually reviewed patient charts of this smaller cohort and excluded the following: (1) individuals who did not have true RSE (e.g., in whom "refractory" referred to seizure action plans embedded in the chart rather than the clinical history); (2) individuals who had a pre-existing diagnosis of epilepsy; (3) one individual in whom the genetic diagnosis did not correlate with the RSE presentation; and (4) neonatal-onset RSE. We focused on genetic etiologies associated with RSE after the neonatal period to serve as a closer comparison group to FIRES/NORSE. This left us with four individuals carrying three separate genetic diagnoses. This subgroup also included two additional individuals. The first was the twin of another individual who had the same clinical presentation (4 months earlier) and was diagnosed with the same genetic condition. The second had been previously excluded from our FIRES database as she did not meet FIRES diagnostic criteria. This left six individuals who had presented with RSE as first seizure presentation and who were ultimately diagnosed with a genetic epilepsy syndrome.

Lastly, we aimed to better understand phenotypic differences between individuals with SE at first onset of seizures, including subgroup of individuals with RSE, due to a genetic etiology versus individuals without a genetic diagnosis. We calculated odds ratios with 95% confidence intervals using Fisher's exact test, stratifying individuals with and without an identified genetic etiology. Phenotypic associations between the two subgroups are presented as a phenogram, a previously published method that allows us to visualize the overall constellation of a selection of phenotypic features and severity of clinical presentations between groups (22–24).

3. Results

3.1. Individuals with FIRES can be identified from the EMR in a large tertiary health network

Using NLP methods, we identified 201 individuals. We then filtered out individuals where FIRES was used in: (1) the context of a publication reference that contained the word "FIRES" or for conditions that have been documented to be associated with FIRES or NORSE, or (2) patients for which a referral note was written but the individual was never evaluated at CHOP. This resulted in 59 individuals for manual chart review. Thirty-four individuals were excluded due to an alternative diagnosis, not meeting criteria for FIRES, or a remote history of FIRES with absence of documentation of the illness. There were eight individuals diagnosed with FIRES but excluded because of a lack of clinical information (see Supplementary Table 1). There were six patients with a presumed diagnosis of NORSE, but only three had sufficient clinical documentation to confirm diagnosis. One of these

patients was also diagnosed with MOG encephalitis. Notably, one patient had a diagnosis of *PCDH19*; however, for this individual there was insufficient documentation for further study (see Supplementary Table 2). Following exclusion after manual review, there were 25 individuals diagnosed with FIRES with sufficient clinical histories (Figure 1).

In the 25 individuals with FIRES, the median age of onset of SE was 7.25 years (IQR 5.06–9.84 years; Figure 2A). Eleven individuals (44%) were female. Twenty individuals (80%) had no significant prior medical history. Of the five individuals with a prior medical history, one individual had a history of two simple febrile seizures that occurred more than 1 year prior, as well as recurrent urinary tract infections. Other medical conditions included autism, attention deficit hyperactivity disorder, concussion diagnosed 2 weeks prior to seizure onset, and celiac disease (Table 1). Twenty-four (96%) were developmentally typical prior to seizure onset. Eight individuals (32%) had fever and fatigue as the preceding symptoms prior to seizure onset, while eight individuals (32%) had headaches, with two of these individuals also presenting with altered mental status. Five individuals (20%) had gastrointestinal symptoms of vomiting and/or diarrhea, and one individual also had a rash. Four individuals (16%) had upper respiratory infection prodromal symptoms. Five individuals had an identified bacterial or virus (*rhinovirus/adenovirus/Bartonella*, *Mycoplasma*, *Metapneumovirus*, *rhinovirus/parvovirus*, *E. coli* urinary tract infection). Three individuals were ultimately diagnosed with autoimmune encephalopathy with anti-thyroid encephalitis (anti-thyroid peroxidase antibodies), Sjogren's syndrome, and catastrophic antiphospholipid syndrome.

The median duration of hospitalization before discharge or transfer of care was 1.3 months (IQR 27–81 days). One individual remained hospitalized due to social factors and had been in the hospital for a duration of 2.8 years up to the time of inclusion. All children were noted to have some form of cognitive, speech, or physical impairment at the time of discharge (Table 1). Six (24%) individuals died before hospital discharge. One individual that was diagnosed with FIRES died 7 years later, due to cardiac arrest secondary to a variant in *SCN5A*.

3.2. Treatment in FIRES has changed across the years

All individuals were placed on anesthetic infusions for treatment of seizures during their hospitalization. Of the 19 individuals

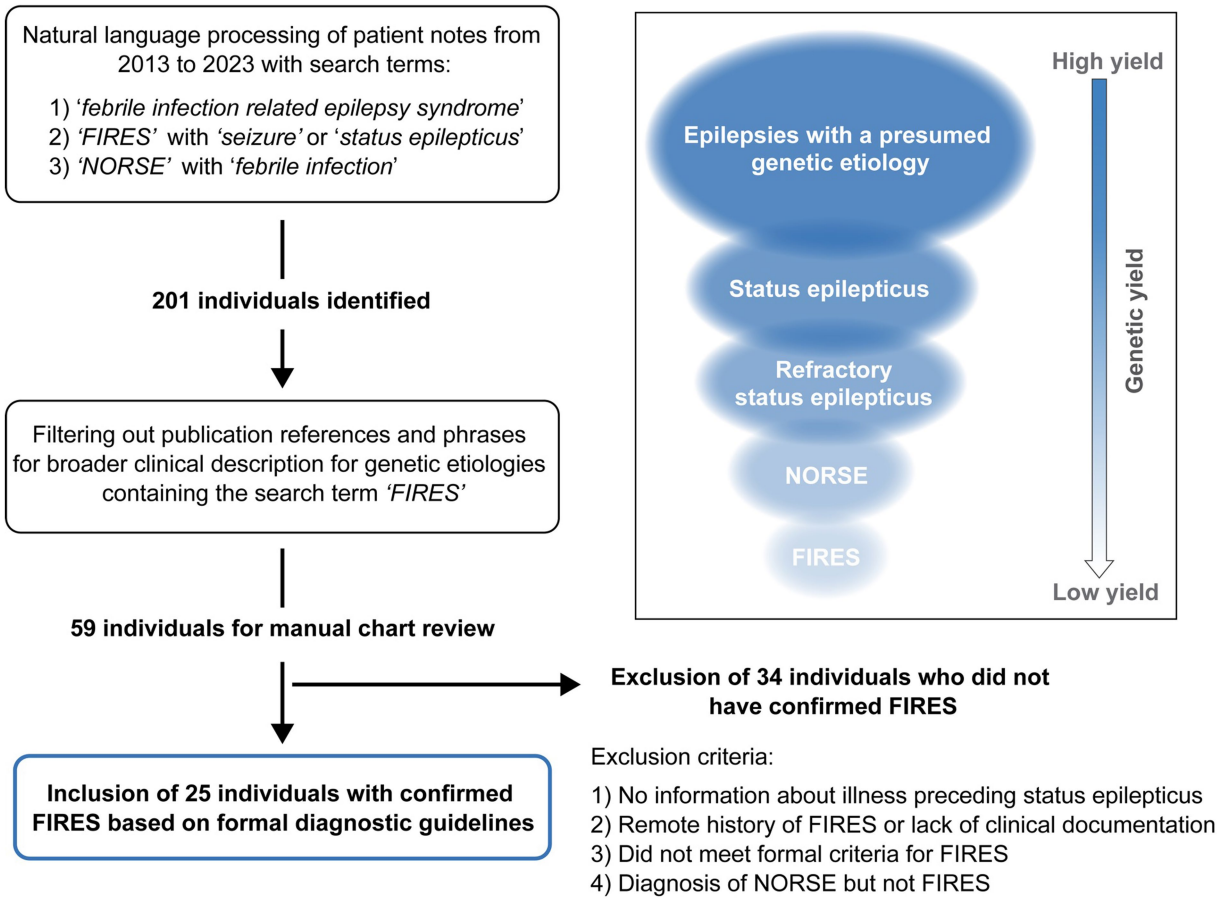

FIGURE 1
Framework for the identification of individuals with Febrile Infection Related Epilepsy Syndrome (FIRES). Natural language processing was applied across a large pediatric institution Electronic Medical Record database followed by manual chart review, leading to identification of 25 individuals with confirmed FIRES based on formal consensus criteria. FIRES is a subset of New Onset Refractory Status Epilepticus (NORSE), showing the hierarchy of FIRES and NORSE with broader subgroups of individuals with SE related epilepsies and epilepsies with a presumed underlying genetic cause (inset).

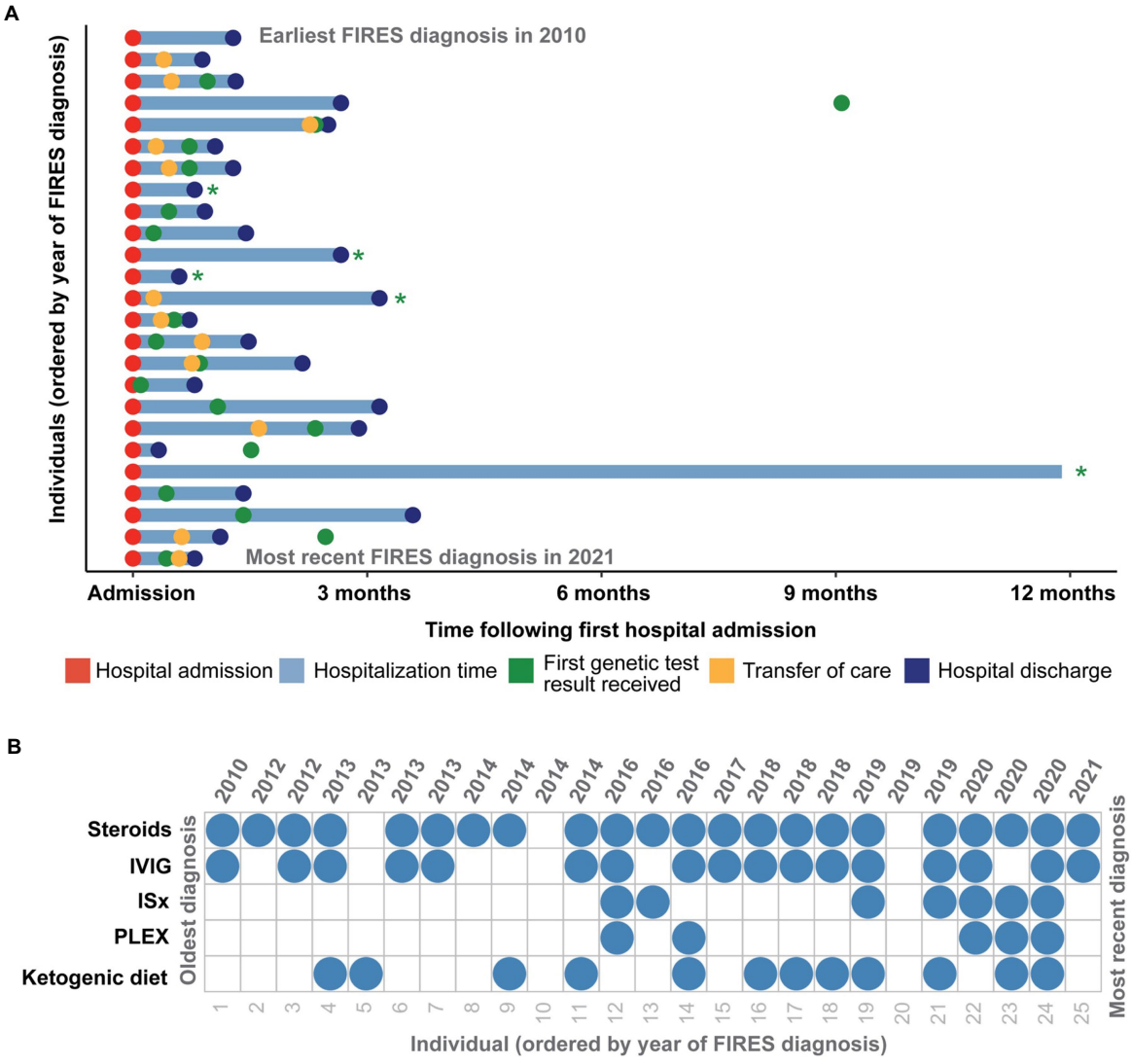

FIGURE 2
Clinical histories of 25 individuals with FIRES identified in the Electronic Medical Records (EMR), highlighting in **(A)** time at hospital admission and discharge in addition to transfer of care and time of first genetic test results received in the first year following first status epilepticus event. Individuals whose genetic testing results were received more than a year after first hospital admission are indicated with a green asterisk. **(B)** Overview of treatment strategies for each individual presenting with FIRES, ordered by year of FIRES diagnosis, showing common use of steroids and intravenous immunoglobulins (IVIG) and an increased use of immunosuppressants (ISx) and plasmapheresis (PLEX) after 2014.

discharged, all individuals were on anti-seizure medications (ASMs) with a median of three ASMs (IQR 3-4). Specific ASMs are listed in Table 2. Twenty-two (88%) individuals received some form of immunotherapy (IVIG, steroids, PLEX, immunomodulatory agents). Twenty-two (88%) received steroids, seventeen (68%) received IVIG, seven (28%) received immunomodulatory agents (included anakinra, tocilizumab, rituximab, cyclophosphamide and hydrochloroquine), and five (20%) received PLEX (Figure 2B). Twelve (48%) individuals were initiated on the ketogenic diet during their hospitalization. While there was a heterogeneous pattern of treatment strategies over time (Figure 2B), we found that there was increased use of ketogenic diet and immunomodulating therapies in addition to steroids and IVIG after 2014. However, when assessing clinical histories, we did not find any significant difference in mortality, length of hospitalization, or number of ASMs at discharge in individuals who were hospitalized before versus after this year.

3.3. Genetic testing is heterogeneous in FIRES and does not reveal underlying genetic etiology

Twenty-three (92%) individuals received genetic testing (Figure 3). Fifteen individuals received the results of testing during their hospital admission, and eight received results of genetic testing after discharge. Among the 23 with genetic testing, eight (35%) received single gene testing, eight (35%) received karyotypes, 12 (52%) received SNP chromosomal microarrays (two of whom did not have

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TABLE 1 Demographics and clinical histories of 25 individuals with FIRES.

Participant	Year diagnosed with FIRES (age, years)	Sex	Prior medical diagnoses	Development	Prodromal symptoms[a]	Positive findings[b]	Hospital duration (months)	Death before discharge
1	2010 (7.35 years)	F	None	Normal	Headache		1.28	N
2	2012 (5.06 years)	M	None	Normal	URI		0.89	N
3	2012 (7.81 years)	M	None	Normal	Headache, Altered mental status		1.32	Y
4	2013 (11.9 years)	M	concussion 2 weeks prior	Normal	Headache, Altered mental status		1.28	Y
5	2013 (9.21 years)	M	None	Normal	URI		2.50	N
6	2013 (18.7 years)	F	None	Normal	none	*Mycoplasma* IgM/IgG+	2.66	N
7	2013 (10.8 years)	M	None	Normal	Headache		1.05	N
8	2014 (0.63 years)	F	None	Normal	GI	*Metapneumovirus*; *SCN5A*	2.66	N[c]
9	2014 (6.52 years)	M	ADHD	Normal	URI	+Rhino/parvovirus	1.44	N
10	2014 (3.39 years)	F	None	Normal	Fatigue		0.79	N
11	2014 (8.47 years)	F	None	Normal	Headache		0.92	Y
12	2016 (4.96 years)	M	None	Normal	Fatigue		3.16	N
13	2016 (12.38 years)	F	None	Normal	None	Sjogren's syndrome	0.59	N
14	2016 (8.07 years)	M	None	Normal	Headache		0.72	Y
15	2017 (2.39 years)	F	2 febrile seizures, recurrent UTI	Normal	Fatigue	*E. coli* + UTI	1.48	N
16	2018 (5.95 years)	M	None	Normal	URI/Sinusitis		2.17	N
17	2018 (2.79 years)	M	None	Normal	GI		3.16	N
18	2018 (6.61 years)	F	None	Normal	Headache		0.79	N
19	2019 (7.25 years)	M	Autism	Autism	None		34.3	N
20	2019 (2.59 years)	M	None	Normal	GI	*Adeno/Rhinovirus, Bartonella*	0.33	N
21	2019 (9.84 years)	M	None	Normal	Headache		2.89	Y
22	2020 (17.0 years)	F	Celiac disease	Normal	GI	Lupus cerebritis/ Catastrophic APS syndrome; +GAD antibodies	1.11	Y
23	2020 (6.88 years)	F	None	Normal	GI, Rash		3.58	N
24	2020 (6.34 years)	F	None	Normal	None	Anti-TPO	1.41	N
25	2021 (16.7 years)	M	None	Normal	None		0.79	N

ADHD, attention deficit/hyperactivity disorder; UTI, urinary tract infection; URI, upper respiratory infection; GI, gastrointestinal symptoms; APS, antiphospholipid; GAD, anti-glutamic acid decarboxylase; TPO, thyroid peroxidase; IVIG, PLEX, steroids, immunomodulatory.[a]All patients had fever per consensus guidelines for FIRES.
[b]Determined to be not causative for FIRES.
[c]Death occurred 7 years after discharge.

additional testing), 18 (78%) received epilepsy panels, 13 (57%) received exomes, and 11 (48%) received mitochondrial sequencing. One individual also received Fragile X testing, and three individuals had an exome reanalysis performed. No individuals in our cohort received whole genome sequencing, although some families were offered this testing (see Supplementary Table 3).

Systematic review of genetic testing revealed no genetic etiology for FIRES. Six individuals' genetic testing revealed a total of nine pathogenic or likely pathogenic variants, but none were considered explanatory for FIRES. Individuals 9, 10, 14, and 25 had single, heterozygous pathogenic or likely pathogenic variants in autosomal recessive genes identified on epilepsy panels or exome sequencing and were not considered explanatory. Exome sequencing revealed that Individual 2 harbored a heterozygous pathogenic variant in *SCN5A*, associated with autosomal dominant cardiac conduction system dysfunctions and cardiomyopathy, and Individual 24 had a heterozygous pathogenic variant in FLG, associated with autosomal dominant eczema. Mitochondrial genome sequencing revealed that

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TABLE 2 Treatment strategies in FIRES.

Participant	Year diagnosed with FIRES (age, years)	IVIG	Steroids	PLEX	Immunomodulators	Ketogenic diet	ASMs[a] at discharge	Number of ASM at discharge
1	2010 (7.35 years)	Y	Y	N	N	N	CZP, PRM, RUF	3
2	2012 (5.06 years)	N	Y	N	N	N	LEV, VPA	2
3	2012 (7.81 years)	Y	Y	N	N	N	Deceased	Deceased
4	2013 (11.9 years)	Y	Y	N	N	Y	Deceased	Deceased
5	2013 (9.21 years)	N	N	N	N	Y	CLB, LAC, ZNS	3
6	2013 (18.7 years)	Y	Y	N	N	N	LEV, PHB, PHT, TPM	4
7	2013 (10.8 years)	Y	Y	N	N	N	LEV, LAC, CLB	3
8	2014 (0.63 years)	N	Y	N	N	N	PHB, LEV, CLB	3
9	2014 (6.52 years)	N	Y	N	N	Y	LEV, PHB, TPM, CBD	4
10	2014 (3.39 years)	N	N	N	N	N	LEV, VPA, CZP	3
11	2014 (8.47 years)	Y	Y	N	N	Y	Deceased	Deceased
12	2016 (4.96 years)	Y	Y	Y	Rituximab, Cytoxan	N	PHB, LEV, LAC, CLB	4
13	2016 (12.38 years)	N	Y	N	Rituximab, hydroxychloroquine	N	LEV, CLB, LAC	3
14	2016 (8.07 years)	Y	Y	Y	N	Y	Deceased	Deceased
15	2017 (2.39 years)	Y	Y	N	N	N	LEV	1
16	2018 (5.95 years)	Y	Y	N	N	Y	PHB, TPM, CLB	3
17	2018 (2.79 years)	Y	Y	N	N	Y	BRV, VPA, CBD, CLB, TPM, PHB	6
s18	2018 (6.61 years)	Y	Y	N	N	Y	RUF, LAC, PHB, CLB	4
19	2019 (7.25 years)	Y	Y	N	Anakinra	Y	CBD, TPM, LAC	3
20	2019 (2.59 years)	N	N	N	N	N	LAC, OXC	2
21	2019 (9.84 years)	Y	Y	N	Anakinra, tocilizumab	Y	Deceased	Deceased
22	2020 (17.0 years)	Y	Y	Y	Rituximab, cyclophosphamide, Anakinra	N	Deceased	Deceased
23	2020 (6.88 years)	N	Y	Y	Anakinra, tocilizumab	Y	PHB, CLB, LAC, LEV, VPA, ZNS, RUF	7
24	2020 (6.34 years)	Y	Y	Y	Anakinra	Y	PRP, CLB, LEV, OXC, PHB	5
25	2021 (16.7 years)	Y	Y	N	N	N	VPA, LEV, CZP	3

[a]BRV, brivaracetam; CBD, cannabidiol; CLB, clobazam; CZP, clonazepam; LAC, lacosamide; LEV, Levetiracetam; OXC, oxcarbazepine; PHB, Phenobarbital; PHT, fosphenytoin; PRM, Perampanel; RUF, rufinamide; TPM, topamax; VPA, valproate; ZNS, zonisamide.

individual 14 had a likely pathogenic variant in MT-TK detected at ~4% heteroplasmy in blood and 3% heteroplasmy in brain tissue. Mitochondrial MT-TK variants are most associated with myoclonic epilepsy with ragged-red fibers (MERRF) syndrome at heteroplasmy levels markedly greater than in this individual (25) therefore, it is unlikely that this variant was explanatory for this individual's clinical features.

We reviewed variants of unknown significance (VOUS) to identify candidate genes, but none were identified. There were 36 total VOUS revealed across all testing modalities. Genetic testing *via*

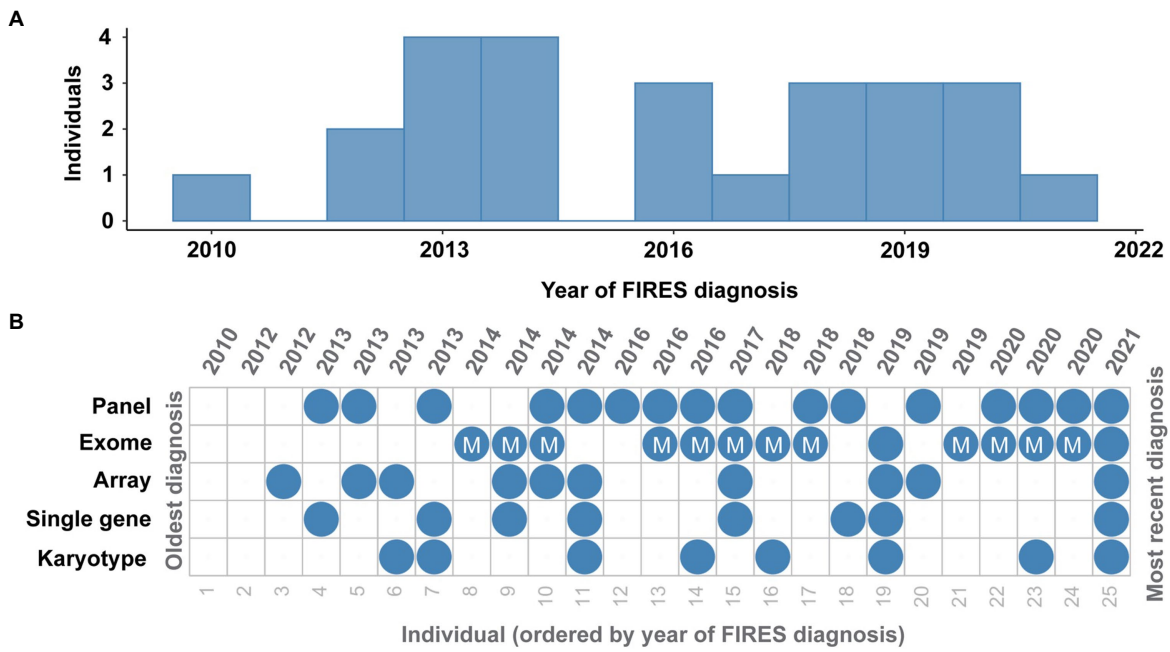

FIGURE 3
Genetic testing in FIRES has been heterogeneous over the years. **(A)** Distribution of FIRES diagnoses in the past decade. **(B)** Overview of genetic testing including karyotype, single gene testing, microarray, whole exome sequencing (with mitochondrial testing indicated), and gene panel in 25 individuals with FIRES, ordered from the oldest diagnosis in 2010 to most recent diagnosis in 2021.

Whole Exome Sequencing with mitochondrial DNA sent in 2014 revealed a *de novo* VOUS in *ITPR1*, associated with autosomal dominant Gillespie syndrome and adult-onset spinocerebellar ataxia, in Individual 9 which did not fit the phenotype for FIRES. Exome sequencing revealed biallelic, compound heterozygous VOUSs, with confirmed inheritance from each parent respectively, in *SPTBN5*. This gene was a candidate gene at the time of this individual's exome sequencing. While *SPTBN5* has since been identified as causative of an autosomal dominant disorder characterized by developmental differences and seizures (26), this gene has not yet been fully validated, and thus the variants found in our patient remain of uncertain clinical significance. Furthermore, given that all known affected individuals with *SPTBN5* had *de novo* variants, this finding is unlikely to be relevant to the diagnosis of Individual 9. In summary, no genetic etiology was identified for any patient presenting with FIRES.

3.4. Characterization of common genetic etiologies in individuals with SE and RSE suggest at a distinct genetic architecture underlying FIRES

As all genetic testing performed in our FIRES cohort was non-explanatory, we expanded the scope of our study to assess the genetic landscape of a broader group of individuals with SE and RSE, aiming to elucidate how FIRES fits more broadly into the context of SE and RSE. First, we identified 959 individuals with presence of RSE documented in 166,301 time-stamped patient encounters in a broader cohort of 32,112 individuals with childhood epilepsy (Figure 4A). The highest proportion of individuals had onset of RSE during the first 3 months of life, which contrasts with the distribution of onset in our cohort of individuals with FIRES.

Second, to better understand the genetic landscape of individuals presenting with RSE as well as SE more broadly, we examined our CHOP cohort, narrowing to evaluate only those individuals who had experienced SE or RSE. This yielded a genetic etiology for 36% of cases (Figure 4A). Regarding the occurrence of SE, >80% of individuals carrying certain genetic diagnoses, including *KCNT1*, *DEPDC5*, and *NPRL3*, had at least one occurrence of SE prior to the genetic diagnosis. For other common genes in our cohort, including *STXBP1*, *SCN1A*, *KCNQ2*, *SCN2A*, fewer than 50% of individuals had at least a one-time presentation with SE prior to genetic diagnosis.

In our CHOP cohort of individuals with SE, we searched for and curated for a smaller subgroup of individuals who presented with RSE as the initial presentation of seizures as a comparative population to individuals with FIRES. After filtering the dataset and excluding individuals following manual review, we identified six individuals with RSE on initial seizure presentation who ultimately were diagnosed with a genetic disorder (Figure 4B). These individuals do meet criteria for NORSE by consensus guidelines. These included one individual with *PCDH19*, two individuals with *CACNA1A*, two twin sisters with homozygous variants in *RANBP2*, and one individual with *KCNA2*. Each of these individuals presented prior to the age of 24 months, and only one presented with RSE after the age of 12 months. Each had genetic testing sent within a week of presentation, except for the individual with *PCDH19,* for whom data are not available (see Supplementary Table 4).

Finally, we performed a phenotypic analysis comparing clinical features such as neurodevelopmental and other epilepsy phenotypes between SE associated with genetic diagnosis ($n = 389$) and idiopathic (non-FIRES) SE ($n = 769$). Individuals with identified genetic etiologies

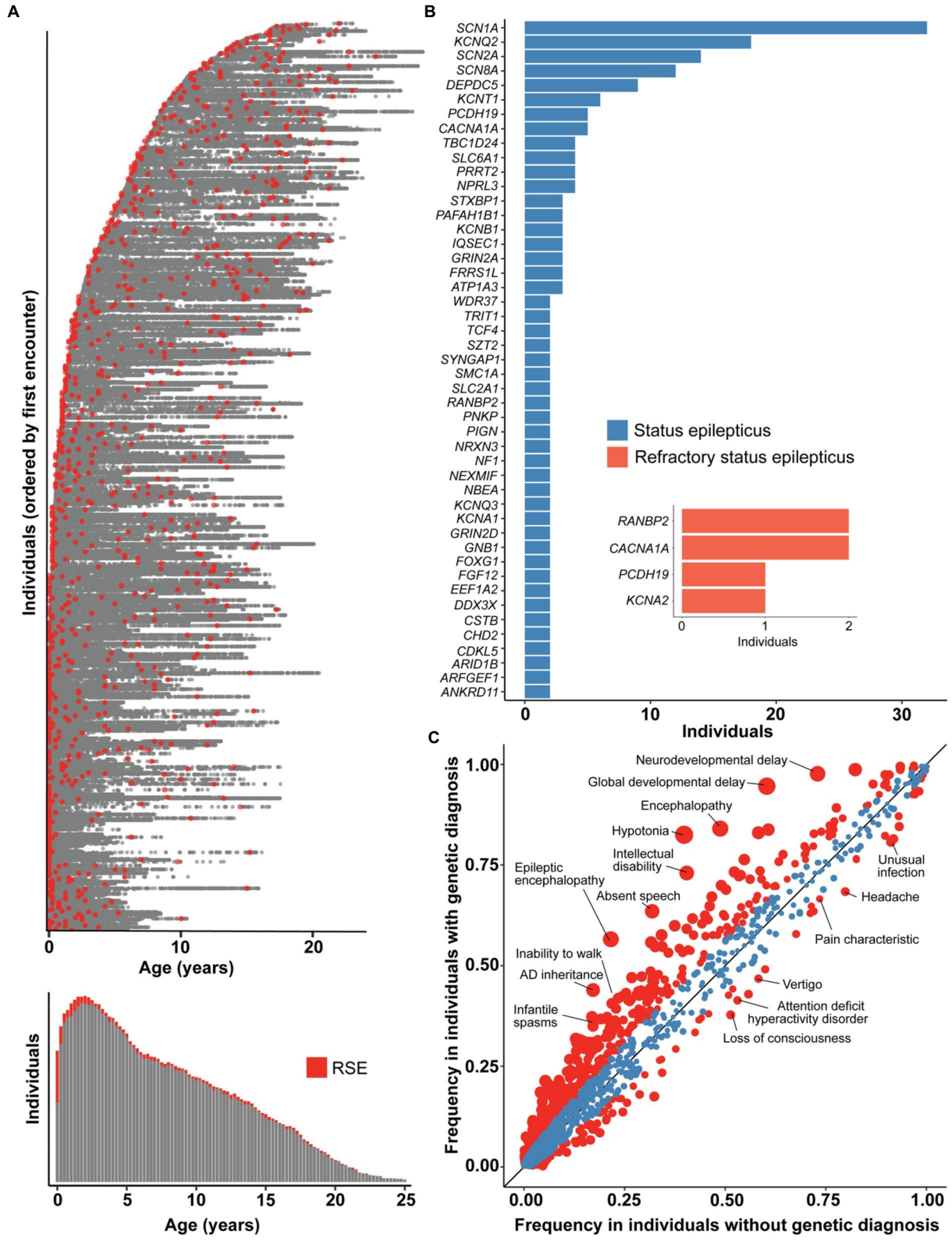

FIGURE 4
The genetic architecture of status epilepticus and refractory status epilepticus (RSE) differs from FIRES. **(A)** 166,301 time-stamped encounters from the Electronic Medical Records (EMR) across 959 individuals identified with RSE in a broader cohort of 32,112 individuals with childhood epilepsy, showing in red the encounters at which RSE was first documented for each individual. Only the encounter of first RSE onset is captured for each individual, as later encounters with RSE documented could either refer to a new or prior RSE event, and we found that the majority of individuals presenting with RSE have onset within the first 3months of life. **(B)** Status epilepticus and RSE in the most common genetic etiologies in a cohort of 1,894 individuals with known or presumed genetic epilepsies. NLP was performed only on patient notes prior to a genetic diagnosis to adjust for bias in clinical

(Continued)

FIGURE 4 (Continued)
impression following a molecular diagnosis. Inset shows numbers of individuals with genetic diagnoses who presented with RSE as first seizure presentation. **(C)** Clinical features in 1,158 individuals with status epilepticus stratified by individuals with a genetic diagnosis (n=389) compared to individuals without a genetic diagnosis (n=769), highlighting a difference in overall disease severity between the two subgroups. Red indicates phenotypic features with nominal significance (p<0.05) while size of points indicate −log10(p-value). The landscape of FIRES were distinct from both subgroups, with characteristic severe clinical presentations and no currently identified genetic etiology.

were more likely to have hypotonia (OR 7.13, 95% CI 5.25–9.77), global developmental delay (OR 11.49, 95% CI 7.21–19.24), and epileptic encephalopathy (OR 4.72, 95% CI 3.60–6.21). Individuals without an identified genetic diagnosis had a two-fold higher risk of headache (OR 1.83, 95% CI 1.37–2.44), attention deficit hyperactivity disorder, (OR 1.63, 95% CI 1.24–2.06) and memory impairment (OR 2.09, 95% CI 1.40–3.18; Figure 4C). This highlights the higher frequency of certain neurological clinical features in individuals with genetic epilepsies.

4. Discussion

FIRES is a rare and severe condition characterized by new onset RSE that presents following a febrile illness prior to seizure onset with an unknown pathophysiology and etiology. Previous studies have sought to understand an underlying genetic cause of FIRES. However, thus far findings remain mixed and inconclusive, despite phenotypic commonalities and clinical overlap with other developmental and epileptic encephalopathies. This finding is surprising, given the overall genetic landscape of epilepsy, where yield for genetic testing is 33% (9, 10). Here, we mapped the landscape of 25 individuals with FIRES, providing an overview of the clinical and treatment histories across 75 cumulative patient-months. We then examined the genetics of broader cohorts of individuals with SE or RSE to better understand how FIRES fits into the conceptual framework of genetic and genetic predispositions in epilepsy.

4.1. Clinical presentation and treatment of children with FIRES

Our cohort consisted of 25 individuals who met clinical criteria for FIRES. The initial clinical symptomatology described in this cohort is in line with other previously published series in children (18, 27): at onset, children were largely school age, were neurodevelopmentally typical, and exhibited prodromal symptoms prior to onset including confusion, headache, gastrointestinal symptoms, or mild febrile illness/upper respiratory infection. In four individuals, a viral pathogen was identified. Three individuals were diagnosed with an autoimmune condition. All patients had prolonged hospitalizations and a biphasic course characterized by an initial acute catastrophic phase followed by a chronic phase, with refractory epilepsy and some degree of neurological impairment.

Treatment for FIRES was also similar to previously published cohorts (3, 27, 28). All children received anesthetic infusions during the initial presentation and required ASMs at the time of discharge. The vast majority of children received steroids and IVIG. Despite the reported efficacy for ketogenic diet (4, 28) only approximately half of these patients received the diet, although the number of individuals with ketogenic diet increased across the years. PLEX was also commonly administered but not as frequently as steroids or IVIG. Notably across years, there was increased use of immunomodulatory agents including the recombinant version of human IL1RA, anakinra, and the IL-6 pathway antagonist tocilizumab, roughly corresponding to their introduction as a potentially efficacious treatment for FIRES in 2016 and 2018, respectively (29, 30). While there was no change in mortality, hospitalization duration, or number of ASMs at discharge, interpretation of this change in clinical practice was limited in this study due to the relatively low number of individuals with FIRES and the differences in the timing at which all immune-related medications were administered.

4.2. Absence of known etiologies in FIRES

First, despite a comprehensive review of genetic testing and review of all variants in our cohort of 25 individuals with FIRES, no genetic etiologies were identified. These negative findings are in agreement with our current understanding of FIRES as described in published literature and through ongoing efforts of etiological discovery (20, 21). While there are select reports of variants in *SCN1A*, *PCDH19*, *POLG*, *DNM1*, *KCNT1*, and *SCN2A* linked to FIRES, none of these variants are considered explanatory for the patients' disease or upon closer review, the clinical presentation does not meet criteria for FIRES (15–17, 31–34). Consequently, despite the high yield for genetic findings in up to 33% of individuals with epilepsy, genetic yield in FIRES is 0% at this time.

The low yield of genetic testing in FIRES may suggest a novel genetic mechanism, polygenic etiology, or alternative etiologies. Inflammatory or autoimmune causes may contribute to the etiology of FIRES, however, given consistently poor outcomes and response to immunomodulatory medications, the latter is unlikely to be the sole explanatory mechanism. It is likely that the underlying etiology is multifactorial and involves a constellation of dysfunctional pathways such as cytokine-mediated inflammation, mitochondrial dysregulation, genetic susceptibility, and environmental exposures. Yet, while it is critical to consider that individuals presenting with RSE may in fact have distinct clinical disorders, the homogeneity of phenotype and consistent absence of genetic findings in FIRES points to a conceptual difference that characterizes FIRES as a singular clinical entity and distinguishes this cohort from both genetic and other forms of idiopathic SE and RSE.

4.3. Conceptual differences between FIRES and epilepsies associated with SE/RSE

While distinct in some features, FIRES is similar to other forms of developmental epileptic encephalopathies such as *STXBP1* and *CKDL5*, in that almost universally all individuals have poor outcomes with a similar phenotypic landscape with cognitive, speech and motor

impairment. However, a clinical characteristic that may distinguish FIRES from other forms of RSE is age of onset (Figure 4A). As we found in our broader cohort of 959 individuals with RSE, the highest proportion of individuals with genetic RSE had onset within the first 3 months of life, highlighting the importance of genes that are variably expressed at different ages and developmental stages. Individuals with FIRES, on the other hand, typically have onset in childhood, with an age of onset ranging from 7.6 months to 18.7 years in our cohort.

To better understand the genetic landscape of SE/RSE more broadly, we aimed to provide an in-depth overview of the landscape in non-FIRES epilepsies associated with SE and RSE. In broadening our cohort to include non-FIRES SE and RSE, we attempted to capture individuals along a gradient of disease severity and onset of seizure presentation, first capturing any individuals prior to genetic diagnosis who were documented to have SE, followed by narrowing our comparison cohort to individuals with RSE, and then only to individuals who had no other seizures prior to the onset of RSE. First, we found that the relative frequency of SE in specific genetic etiologies varies. The underlying architecture of SE is well established, with over 100 genes identified with conditions including inborn errors of metabolism and congenital disorders, structural malformations, mitochondrial disorders, and infantile/childhood onset epileptic encephalopathies, among others (11, 35). We then narrowed in on individuals without pre-existing epilepsy diagnoses who presented with RSE as their first seizure episode, in order to more closely compare these individuals to children with FIRES. Accordingly, we narrowed in on a much smaller cohort of individuals with RSE who were ultimately diagnosed with genetic conditions and demonstrated that the frequency of genetic diagnoses occurs on a gradient, with fewer and fewer genetic etiologies identified as we narrow our cohort and approach NORSE-like and FIRES-like presentations.

Through comparison with a larger SE/RSE cohort, we demonstrate that there are more recognized genes associated with RSE that require further investigation. As neonatal-onset RSE is clinically and biologically distinct from RSE following the neonatal period, we excluded individuals with neonatal onset RSE secondary to variants in genes such as *SCN2A* and *KCNQ2* in assessing genetic etiologies associated with first time presentation of RSE. We subsequently identified four genes that were implicated in individuals with NORSE-like RSE: *CACNA1A*, *RANBP2*, *PCDH19*, and *KCNA2*. However, none of these individuals had FIRES, and the lack of substantial evidence in the explanatoriness of these genes in individuals with confirmed FIRES further highlight the complexity of genetic testing and interpretation, underscoring the critical need for ongoing genetic testing in order to generate more evidence for gene and variant validity.

4.4. Comprehensive genetic testing in FIRES

While we have demonstrated an absence of identifiable causative etiologies with our current understanding in our FIRES cohort, the presumed genetic contribution points to the critical need for further elucidation of the underlying genetic landscape to identify pathogenic mechanisms in RSE/SRSE. We show that genetic testing has been heterogeneous throughout the years, particularly with regard to timing of initial test as well as choice of first genetic test. Testing has also been sent to different labs based on provider preference and year of testing; furthermore, in the setting of ongoing gene discovery in the epilepsies, there have been differences in the genes included on different panels over the years depending on when genes were discovered and implicated in human epilepsy. Despite, or arguably because of the dynamic genetic landscape, genetic testing remains critical for FIRES.

Firstly, we argue that genetic testing should be performed as early as possible in the course of the patient's illness and hospital admission. Although FIRES is distinct from first presentations of genetic SE/RSE, there may be phenotypic commonalities at disease onset. Thus, addressing the genomic delay and sending for genetic testing earlier could have important implications in altering the management course significantly, allowing for more targeted therapies and avoiding unnecessary and potentially harmful immunomodulatory medications. Even negative genetic testing may aid in narrowing diagnostic differentials, given that individuals with FIRES have been consistently shown not to have a genetic etiology identified from genetic testing.

Secondly, in the era of active gene discovery whereby alternative genetic testing modalities are not fully comprehensive, including gene panels, which exclude candidate genes for epilepsy and neurodevelopmental disorders, Whole Exome Sequencing with mitochondrial DNA stands as the most comprehensive, efficient, and cost-effective testing and has been considered the gold standard for diagnostic testing. While we have the capability to perform NGS, this has not been routinely done as demonstrated in our cohort, and even under recent consensus guidelines, genetic testing was not recommended as an initial test but only as a later tier of testing (36). Given ongoing efforts in gene discovery and gene curation, continued testing *via* WES may allow for the identification of candidate genes or novel, previously unrecognized genes implicated in seizure susceptibility/epileptogenesis, gene expression/regulation, cellular dysfunction, or immunological dysregulation, which may help in guiding targeted therapies for FIRES and preventing the devastating sequelae.

5. Limitations

To investigate the overall clinical and genetic landscape of SE and RSE, we leveraged a computational approach based on Natural Language Processing (NLP) for extracting unstructured clinical data. The automatic assessment of clinical text poses challenges in clinical interpretation of large-scale datasets and requires consideration of potential biases. For example, for individuals with a genetic diagnosis, we were limited to assessing clinical features only prior to the diagnosis to prevent "note contamination," or the bias when phenotypes associated with the genetic diagnosis more broadly is captured in the patient chart and does not necessarily describe or is inaccurate to the specific patient. Furthermore, identification of individuals with FIRES and distinguishing RSE from SE required subsequent manual chart review. In the latter case, we had to review on an individual basis to confirm critical details of case presentations. Nevertheless, we demonstrate that a data-driven method can facilitate the identification of individuals that meet predefined criteria such as FIRES or RSE across a large EMR database and healthcare system that captures dynamic medical care over the years, allowing us to identify 25 individuals who were ultimately determined to meet FIRES criteria and 6 individuals with inaugural RSE secondary to a genetic diagnosis.

Another limitation of our study was the limited analysis of longitudinal clinical data, including the characterization of epilepsy histories and developmental trajectories over time following the initial presentation of FIRES. This included analysis of detailed medication histories. While anesthetic infusions were captured in our center's medical records, we did not have data to the level of a minute or hour time scale for the initial presentations of patients who were admitted to an outside institution at disease onset prior to transfer of care to our center. Accordingly, we were not able to reconstruct medication landscapes for these patients. Thus, while our study revealed a trend toward increased use of ketogenic diet and immunomodulatory agents, interpretation of outcomes and efficacy of treatment strategies were limited due to a small sample size and high variability in the administration of the various therapies. Given the importance of understanding real-world clinical care, the reconstruction of medical treatment following hospital admission will be clinically meaningful. Nevertheless, in our study, we provide an objective picture of the heterogeneity in medical treatment using real-world data, including genetic testing in our cohort over the last decade for individuals with FIRES. We point to the importance of an early and comprehensive genetic work-up and the need for future studies to focus on assessment of longitudinal outcomes and trajectories in FIRES, which can be stratified by treatment strategies.

6. Conclusion

In our study, we analyzed the phenotypic and genetic landscape of febrile-infection related epilepsy syndrome (FIRES) and introduced a conceptual framework outlining the identification and assessment of clinical histories of 25 individuals with FIRES through a computational approach in the EMR. Comparing FIRES to other epilepsies characterized by SE, we identified a gradient of diagnostic yield and genetic diagnosis and a spectrum of disease severity associated with RSE and NORSE-like presentations (Figure 1, inset). We demonstrated a new paradigm for the consideration of genetic epilepsy, where identifiable genetic etiologies become increasingly rare with the increasing severity of seizure presentation, from SE to RSE, culminating in NORSE, and FIRES. This phenotypic pathway analysis points to a delineation of FIRES from similar conditions associated with explosive onset of epilepsy and RSE and highlights the critical need for future studies investigating underlying etiologies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study involving human participants were reviewed and approved per the Institutional Review Board at Children's Hospital of Philadelphia. Written informed consent from the patients or patients legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

DC, JX, AK, and IH contributed to the writing of the manuscript and figures. AG was responsible for data pulling using systematic computational analysis. DC conducted the manual review of all patients with FIRES. AK and JX conducted the analysis for larger cohorts in this study. KS, SR, and AK were responsible for interpretation of genetic testing from our CHOP and FIRES cohort. PG, MR, and NA were involved in the editing of this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articless/10.3389/fneur.2023.1161161/full#supplementary-material

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Early identification of NORSE and transfer to care setting with appropriate supports: A proposed algorithm

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New-onset refractory status epilepticus (NORSE) is a clinical presentation where an individual develops refractory status epilepticus without active epilepsy, or related neurological conditions. A subset of these individuals has a preceding fever and would be diagnosed with febrile infection-related epilepsy syndrome (FIRES). The underlying etiology of this condition varies and includes autoimmune and viral encephalitides. These conditions require multiple specialized health care teams working collaboratively and specific resources for investigation of the underlying etiology and management to provide optimal patient care. In this paper, we provide: (1) recommendations upon early recognition of NORSE and FIRES, (2) guidance on the resources needed to optimally provide care, and (3) guidance on considerations to initiate transfer of patients to a more specialized medical center. Additional recommendations for resource-austere centers without the ability to transfer such patients are also discussed. These recommendations are only for adult patients with NORSE as pediatric patients may require additional special considerations.

KEYWORDS

NORSE, FIRES, status epilepticus, epilepsy, neurocritical care

1. Introduction

New-onset refractory status epilepticus (NORSE) can be defined as a clinical presentation in a patient without active epilepsy or other existing relevant neurological disorder, with new onset of refractory status epilepticus in the absence of a clear acute or active structural, metabolic, or toxic cause. Refractory status epilepticus (RSE) is a condition where continuous or recurrent seizures do not stop with standard anti-epileptic medications (1). The duration of seizure activity required to diagnose status epilepticus varies by type of seizure. Generalized convulsive status epilepticus involves at least 5 min of continuous seizure activity or repeated seizures without return to baseline in-between lasting at least 5 min. The timepoint at which this prolonged seizure activity may result in long term consequences is believed to be at 30 min. Focal status epilepticus is defined by 10 min or more of focal seizure activity with impaired awareness, with the possibility for long term consequences to arise after 60 min. Nonconvulsive status epilepticus occurs when seizure activity is present for 10 or more minutes lacking prominent motor symptoms (2). Status epilepticus is considered refractory if "persisting despite administration of at least 2 appropriately selected and dosed parenteral medications including a benzodiazepine. There is no specific

seizure duration required" (1). NORSE has a subset of cases meeting the definition for febrile infection-related epilepsy syndrome (FIRES), where a febrile illness precedes the onset of refractory status epilepticus by 24 h to 2 weeks (1).

Although the prevalence of NORSE has not been studied and identified, the annual incidence of refractory status epilepticus is estimated to be 3.0–7.2 per 100,000 adults per year (3, 4). One study showed 20% of cases of refractory status epilepticus did not have a clear etiology after initial investigations (5), thereby making NORSE a rare condition. Despite its incidence, there is significant associated morbidity and mortality (5), and thus early recognition, identification, and transfer to an appropriate care-setting are paramount.

2. Early recognition

A prodromal period can precede the onset NORSE by a couple of weeks and often includes non-specific symptoms such as confusion, fever, fatigue, headache, gastrointestinal, or respiratory symptoms. It is estimated that this prodromal period is present in ~60% of cases (5). Individuals may then develop infrequent seizures which evolve into status epilepticus (6).

NORSE should be a diagnostic consideration in individuals presenting with new onset recurrent seizures evolving into status epilepticus with no known history of epilepsy and no clear identifiable etiology after initial blood work, CSF studies, and brain imaging has been completed.

There are several identified predictors of prolonged refractory status epilepticus. These include the presence of acute brain lesions, increased severity of status epilepticus (measured using the status epilepticus severity score [STESS] (7)), non-convulsive status epilepticus with coma, and increased serum albumin levels at onset of status epilepticus (8). STESS alone was found to be predictive of outcome and includes age, history of seizures, seizure type, and degree of impaired consciousness (7). The presence of these predictors may serve as a flag for clinicians, as each day of status epilepticus is associated with increased risk of mortality (8). As these predictive markers were identified in a more general population of individuals with status epilepticus, is unclear if they hold similar predictive value in the subset of those with NORSE and FIRES. It is plausible that considering NORSE top-of-mind in the differential diagnosis of new status epilepticus may aid in early recognition and clinical considerations for transfer, especially in resource-austere settings.

3. Investigations and treatment requirements

While it is of prime importance to provide airway and cardiovascular/blood pressure support and to halt seizures as soon as possible to prevent further neurologic injury, further consideration must be given to other aspects, including monitoring for breakthrough or nonconvulsive seizures and searching for an underlying etiology; especially one that can be treated. Once the patient is reasonably stabilized, consideration should be given to transferring the patient to a tertiary care center where more specialized investigations and care can be implemented.

An important aspect of a higher-level of care includes the multidisciplinary team, and ability to case conference about such patients with actionable diagnostic and treatment strategies. Centers with neurocritical care expertise are also uniquely qualified to monitor and treat these complex patients. Consultant teams are essential for the co-management of these cases. These services include Neurology with expertise in epilepsy and Internal Medicine and its subspecialties, who may be needed to help manage the multi-system effects of prolonged seizure activity and complications of antiseizure treatments including anesthetics (9). Individuals who continue to have seizures refractory to available therapies or sustain significant complications benefit from early involvement of palliative care for symptom management, bereavement support for the patients' family, and possibly end of life care (10–12).

Furthermore, specialized neuro-focused centers play an important role in the recovery phase where multidisciplinary team members such as physiotherapy, occupational therapy, speech language pathology, and rehabilitation medicine can collaboratively address the ongoing needs of patients who survive the acute phase of this illness. The burden of critical illness on NORSE patients is an important consideration with individuals exhibiting prolonged hospital stays, with a median ICU stay of 26 days (13, 14), often with neurological sequalae including altered cognition and development of epilepsy (12, 15, 16).

From an investigation standpoint, readily available access to continuous scalp EEG monitoring with video and MR imaging are important aspects of care. Having access to specialized diagnostic tests including autoimmune, paraneoplastic antibody testing, viral PCR testing may aid in early diagnosis (or lack thereof) of underlying etiology. In a significant proportion of cases, no etiology is identified, rendering their classification as cryptogenic (5), although with increasing recognition of various autoimmune etiologies the cryptogenic category is diminishing. In addition to standard treatment, some patients with NORSE may benefit from immunomodulatory therapies, such as corticosteroids, intravenous immunoglobulins, or plasma exchange, particularly if the underlying cause is thought to be autoimmune or inflammatory. The provision of some of these services (e.g., plasma exchange) is a challenge in austere settings.

In resource-austere settings where transfer to a comprehensive center is not possible, substitution of modalities of investigation and/or virtual care may be considered. Critical care settings without subspecialized expertise, CT imaging instead of MRI to rule out gross structural lesions, and serial routine EEGs instead of continuous monitoring can be considered (Table 1).

4. Proposed algorithm for recognition and transfer

When a patient is identified as having ongoing seizure activity, beyond the timepoints required for meeting criteria of status epilepticus (2), and after administration of an appropriately dosed parenteral benzodiazepine and another appropriate medication for treating status epilepticus (1) a diagnosis of refractory epilepticus is made. Specialized critical care services are crucial for providing optimal care to patients with NORSE, as this condition requires prompt and aggressive treatment in an ICU setting. Early transfer is also important because the critical care management of NORSE patients has potentially life-threatening complications that can arise

TABLE 1 Resources needed to provide optimal care for NORSE patients in the acute phase of their illness.

Well-resourced settings	Recommended timing after seizure onset	Substitutions for consideration in resource-austere settings
Medical services and healthcare professionals		
Critical care specialists with neurocritical care expertise	Immediate	Critical care specialists
Neurologically-trained nurses and house staff	Immediate	
Neurologists with expertise in epilepsy	Within 24 h	Experienced Neurologists
Internal medicine subspecialty services (Rheumatology, Immunology, Gastro-enterology, Nephrology, Cardiology)	As needed. Variable timing of initiation guided by any relevant rheumatologic/immunologic findings on investigations, complications that may arise during hospital course, and immunologic therapies considered	Dedicated anesthetists
Palliative care –neurology specific	As needed. Variable timing of initiation guided by the need for reevaluating goals of care, enhancing focus on comfort care, and/or supporting patient's family and healthcare team	Palliative care. Recommend expert consultation, virtual or with transfer of care
Management		
Securing airway and hemodynamic stabilization	Immediate (0–5 min)	
Parenteral anti-seizure and anesthetic medications, inhalational anesthesia, hypothermia	First line (benzodiazepine): 5–15 min Second line: 20–40 min Third line: 40–60 min	Anti-seizure medications administered *via* alternative routes (PR, IM, NG tube) or intravenously
Consider empiric antibiotic and antiviral coverage (e.g., for HSV)	Within 24 h	
Immune-modulating/suppressive therapies	Consider within 72 h, with expert consultation, with first-line treatment of IV methylprednisolone or IVIG	Recommend expert consultation, virtual or with transfer of care
Ketogenic diet	Consider within the first week. The earliest the ketogenic diet can be considered in (S)RSE is after failure of first-and second-line antiepileptic drugs	Recommend expert consultation, virtual or with transfer of care
Monitoring for complications, (e.g., hypotension, ileus, pneumonia)	Continuous throughout ICU admission	
Investigations		
Initial blood work, including: -CBC, electrolytes (with extended electrolytes), creatinine, liver enzymes. -Point of care glucose -Toxicology screen -Blood cultures	Immediate (0–5 min)	
Additional blood work, including: -Viral and bacterial serologies -Autoimmune panel: ANA, ANCA, Anti-thyroid, anti-neuronal surface antigens -Paraneoplastic antibody panel	Within 24 h.	
MRI brain with contrast	Within 48 h.	CT head
Continuous EEG monitoring, automated EEG, preferably with video	Within 24 h.	Repeated routine EEGs
Lumbar puncture with CSF testing for: -Cell count, protein, glucose, lactate, viral PCR, bacterial and fungal culture, cytology, autoimmune and paraneoplastic panels	Within 48 h	
If ongoing seizure activity, recommended transfer timepoints:		
Transfer within:	If needed to obtain:	
24 h	MRI brain, EEG	
48–72 h	Continuous EEG monitoring, neurocritical care expertise	
72 h and beyond	Immunosuppressive treatments (e.g., IVIG, plasmapheresis, anakinra), ketogenic diet	

The final column outlines possible substitutions in resource-limited settings.
HSV, herpes simplex virus; IV, intravenous; IVIG, intravenous immune globulin; CBC, complete blood count; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; MRI, magnetic resonance imaging; EEG , electroencephalogram; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RSE, refractory status epilepticus; SRSE, super refractory status epilepticus. References: (13, 17–20).

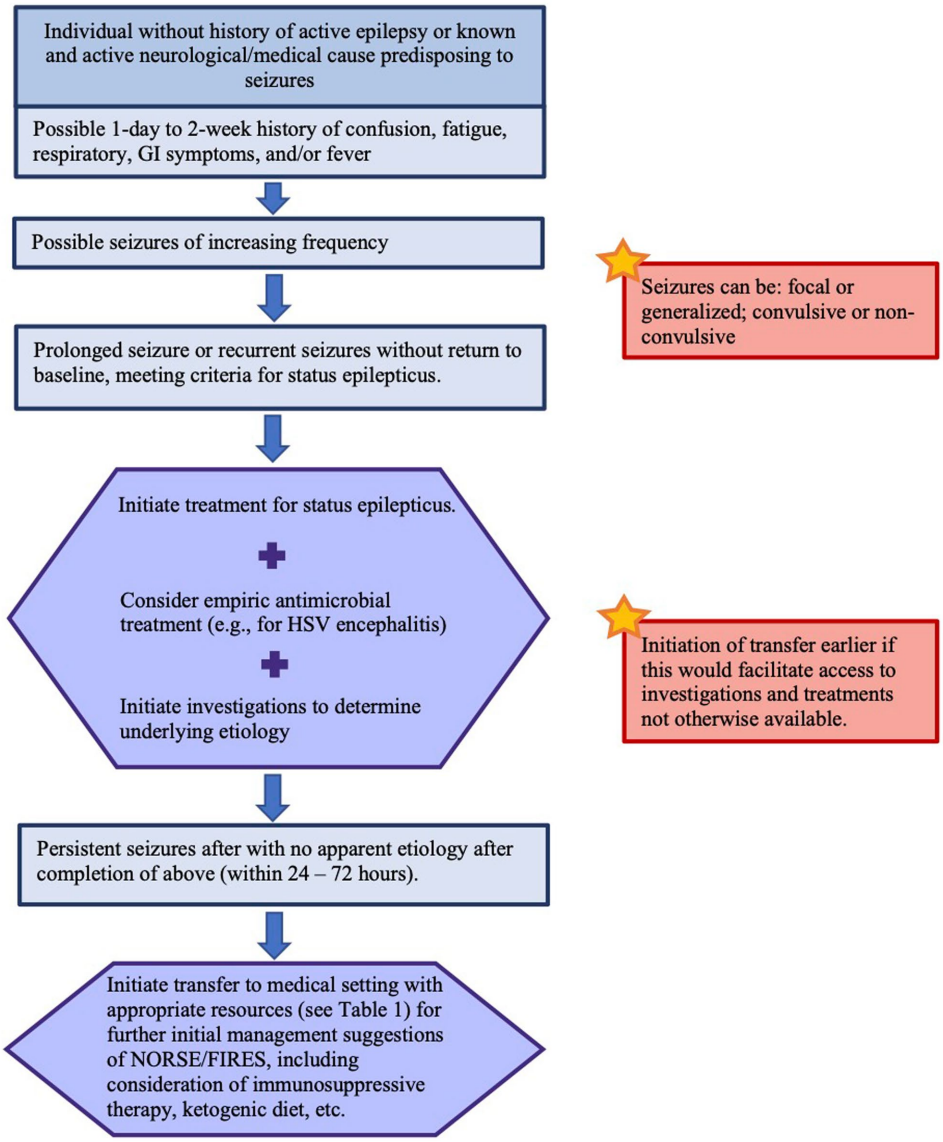

FIGURE 1
Proposed algorithm for recognition of NORSE/FIRES and transfer to a medical setting with appropriate resources. Please refer to reference (13) for details on recommended management of status epilepticus. Please refer to references (17, 20) for detailed recommendations on investigations and management of NORSE/FIRES.

such as respiratory failure (severe acute respiratory distress syndrome [ARDS]), cardiac complications (from seizure or anesthetics), gastro-intestinal complications, and metabolic disturbances.

When transferring a patient with NORSE to a specialized critical care facility, special considerations with attention to airway patency, adequate circulatory support, and provision of seizure-stabilizing medications and equipment for transport are necessary. A trained medical team with expertise in critical care and neurology should oversee the transfer, with appropriate monitoring and interventions in place to manage any potential complications that may arise during transport.

Early transfer should be facilitated, when possible, especially in cases where a transfer would enable access to essential tests (e.g., MRI, cEEG, neurocritical care, use of volatile anesthetics in the ICU for sedation or seizure suppression), and neuromodulatory treatment options (IVIG, plasma exchange, biologic treatments). Early transfer is especially important when nonconvulsive status epilepticus is suspected or there is lack of access to routine and serial EEG given the morbidity and mortality associated with prolonged status epilepticus (8). See Figure 1 for a proposed algorithm for identification and early transfer (13, 17).

5. Conclusion

Overall, early identification of NORSE and associated conditions such as FIRES is essential to initiate appropriate investigations and management. Optimal patient care involves a multidisciplinary approach and numerous investigations and treatments. We advocate for early transfer to a specialized center with these resources with the aim of mitigating the known risks and downstream complications of NORSE. These recommendations

pertain to adult patients as pediatric patients may require additional special considerations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

HK conceived this manuscript and oversaw direction and planning. SV wrote the first draft of this manuscript in consultation with HK and GY. All authors contributed to the content of this manuscript and were involved in editing this work.

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Conflict of interest

The authors declare that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Ketogenic diet for super-refractory status epilepticus (SRSE) with NORSE and FIRES: Single tertiary center experience and literature data

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Background and purpose: Ketogenic diet (KD) is an emerging treatment option for super-refractory status epilepticus (SRSE). We evaluated the effectiveness of KD in patients presenting SRSE including NORSE (and its subcategory FIRES).

Methods: A retrospective review of the medical records was performed at the Necker Enfants Malades Hospital. All children with SRSE in whom KD was started during the last 10 years were included. A systematic search was carried out for all study designs, including at least one patient of any age with SRSE in whom KD was started. The primary outcome was the responder rate and Kaplan–Meier survival curves were generated for the time-to-KD response. As secondary outcomes, Cox proportional hazard models were created to assess the impact of NORSE-related factors on KD efficacy.

Results: Sixteen children received KD for treatment of SRSE, and three had NORSE presentation (one infectious etiology, two FIRES). In medical literature, 1,613 records were initially identified, and 75 were selected for review. We selected 276 patients receiving KD during SRSE. The most common etiology of SRSE was acute symptomatic (21.3%), among these patients, 67.7% presented with NORSE of immune and infectious etiologies. Other etiologies were remote symptomatic (6.8%), progressive symptomatic (6.1%), and SE in defined electroclinical syndromes (14.8%), including two patients with genetic etiology and NORSE presentation. The etiology was unknown in 50.7% of the patients presenting with cryptogenic NORSE, of which 102 presented with FIRES. Overall, most patients with NORSE benefit from KD ($p < 0.004$), but they needed a longer time to achieve RSE resolution after starting KD compared with other non-NORSE SRSE ($p = 0.001$). The response to KD in the NORSE group with identified etiology compared to the cryptogenic NORSE was significantly higher ($p = 0.01$), and the time to achieve SE resolution after starting KD was shorter ($p = 0.04$).

Conclusions: The search for underlying etiology should help to a better-targeted therapy. KD can have good efficacy in NORSE; however, the time to achieve SE

resolution seems to be longer in cryptogenic cases. These findings highlight the therapeutic role of KD in NORSE, even though this favorable response needs to be better confirmed in prospective controlled studies.

KEYWORDS

NORSE, New-Onset Refractory Status Epilepticus, FIRES, febrile infection-related epilepsy syndrome, SRSE, super refractory status epilepticus, ketogenic diet, KD

1. Introduction

Status epilepticus (SE) is a potentially life-threatening condition resulting either from the failure of the natural homeostatic suppressing mechanisms responsible for seizure termination or from the initiation of mechanisms leading to abnormally prolonged seizure activity (1). About 31%−43% of the patients with SE are not controlled with first- and second-line treatments and enter in refractory SE (RSE), requiring intravenous anesthetic drugs (2). About 15% of the patients will progress further to super-refractory SE (SRSE), defined as SE that persists for more than 24 h after the initiation of anesthesia or recurs on the reduction or withdrawal of anesthetic drugs (3).

New-Onset Refractory Status Epilepticus (NORSE) is the clinical presentation describing a patient without active epilepsy or other preexisting relevant neurological disorder occurring without age limitation. It is characterized by *de novo* onset of RSE without a clear acute or active structural, toxic, or metabolic cause (4). The diagnosis of FIRES, an identified syndrome within NORSE, requires a prior febrile infection starting between 2 weeks and 24 h before RSE onset (with or without fever at SE onset) (4, 5). NORSE is a rare disorder (4). In Germany, the annual reported incidence and prevalence of FIRES in pediatric age are estimated to be 1:1,000,000 and 1:100,000, respectively (6). Patients presenting with NORSE or FIRES usually have a very poor prognosis, with mortality rates of 12%−27% and severe neurological sequelae, including cognitive impairment, functional disability, and drug resistant epilepsy in most survivors (7–9).

NORSE etiologies include viral or autoimmune causes. Cases with no identified cause after extensive evaluation are considered as "cryptogenic NORSE" or "NORSE of unknown etiology" (5).

So far, there is currently no high evidence to guide NORSE and FIRES treatment since most therapeutic approaches come from expert opinions and few case reports.

The ketogenic diet (KD) is an established, effective non-pharmacological treatment for drug-resistant epilepsy (10), and in the last decade, an increasing number of studies reported on the efficacy and tolerability of KD in intensive care units (ICU) as an emerging treatment option for SRSE (7, 11–13).

We reported our experience at a pediatric single tertiary center on the use of KD in patients with SRSE, specifically assessing the response in those with NORSE presentation. Our results were combined with the evidence provided by a systematic review of the literature. Finally, we aimed to evaluate the effectiveness of KD in patients presenting with SRSE and NORSE, using time to treatment response as the outcome measure, and to assess the impact of NORSE related characteristics on KD efficacy.

2. Methods

2.1. Study population

A retrospective review of the medical records was performed at the Necker Enfants Malades Hospital from April 2010 to October 2020. All children with SRSE in whom KD was started as adjunctive therapy were included. For each participant, we recorded and analyzed the following variables: age at SRSE onset, gender, previous history of epilepsy, SRSE etiology, number of treatments prior to KD, time lapse from SRSE onset to KD initiation, fasting at KD initiation, KD ratio, time to achieve ketosis from KD initiation, KD efficacy to stop SRSE, time to SRSE resolution after KD initiation, length of KD, side effects, number of antiseizure medications (ASMs) at hospital discharge, time of follow-up, and outcomes. We identified patients with NORSE presentation, specifying those with FIRES or with NORSE with unknown etiology.

2.2. Search strategy and study selection

A systematic review was performed in the electronic databases MEDLINE (PubMed), EMBASE, and Cochrane Library, with the following search terms: "ketogenic" AND ("refractory status epilepticus" OR "super refractory status epilepticus" OR "intensive care unit" OR "new onset refractory status epilepticus" OR "NORSE" OR "febrile infection related epilepsy syndrome" OR "FIRES").

The relevant studies have been selected with no date restriction, including children and adult patients. The reference lists of the included articles were also searched manually to find any additional eligible papers. The search was up to date as for the 2nd October 2022.

The results of this systematic review were reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (14).

All study designs with individual details, including at least one patient of any age with SRSE in whom KD was started, have been included. Duplicate records were excluded. Reviews, meta-analyses, editorials, commentaries, and expert opinions were excluded. Titles and abstracts were screened for study eligibility, and full-text articles were reviewed by SM and PDL. Any disagreement was resolved by discussion with a third review author (RN).

For each selected study, the following data were extracted on individual bases when available: age at SRSE onset, gender, previous

history of epilepsy, etiology of SRSE, number of treatments (ASMs and anesthetic agents) prior to KD start, other treatments (i.e., steroids) prior to start KD, the time lag from SRSE onset to KD initiation, fasting at KD initiation, KD ratio, time to achieve ketosis, KD efficacy to stop SRSE, time to SRSE resolution after KD initiation, length of KD, side effects, number of treatments at hospital discharge, time of follow-up, and outcomes. Patients with NORSE presentation were selected, specifying those with FIRES or with NORSE with unknown etiology.

2.3. Data analysis

Demographic and SE characteristics were summarized by standard descriptive measures.

The primary outcome was the responder rate, defined as clinical and electroencephalographic (EEG) resolution. Kaplan–Meier survival curves were generated for the time-to-KD response. As secondary outcomes, Cox proportional hazard models were created to assess the impact of the following factors on KD efficacy: age at SRSE onset, gender, previous history of epilepsy, etiology, the clinical presentation with NORSE/FIRES, number of treatments prior to KD, the time lag from SRSE onset to KD initiation, fasting at KD initiation, KD ratio, time to achieve ketosis from KD initiation, and side effects. A p-value $\leq$ 0.05 was considered statistically significant. Data were analyzed using STATA/IC version 15 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Single center experience

Overall, 16 children (six female) receive KD for treatment of SRSE at the Necker Enfants Malades Hospital. The median age at SRSE onset was 2 years old (IQR: 1–3, range: 1 month−10 years). Before admission for SRSE, 9/16 (56.2%) had a history of epilepsy. SRSE was due to defined epileptic syndromes in six patients (37.5%), and 6/16 (37.5%) had a progressive symptomatic cause. One patient had acute symptomatic etiology of SRSE due to cerebral anoxia. The remaining presented with NORSE due to infectious encephalitis (n = 1) and FIRES (n = 2) of unknown etiology. Before KD initiation, they received a median number of ASMs and anesthetics of 4 (IQR: 3–5; range: 2–7), and other treatments, including steroids (n = 2), IVIg (n = 1), and vitamin therapy (n = 2). The median delay from SRSE onset to KD initiation was 2.5 days (IQR: 2–7; range: 1–20).

KD was effective in achieving SRSE cessation in 5/16 (31.25%), after a median time from starting KD of 4.5 days (IQR: 1.5–16; range: 1–30). Side effects due to KD treatment were detected in 7/16 (43.75%), 3/16 died during the acute phase of SRSE, while at hospital discharge, 12/16 (75%) patients had ongoing seizures and received a median number of ASMs of 1 (IQR: 1–3; range: 1–5).

Table 1 summarizes patients' characteristics and details on KD administration, while Table 2 summarizes the response to KD and outcomes.

3.2. Literature systematic review

One thousand six hundred thirteen records were initially identified. Two hundred and twelve were retrieved for detailed assessment, of which 75 were included in the review (Figure 1). The selected studies were retrospective observational studies (n = 21) (7, 11, 13, 15–32), single cases (n = 43) (33–75), and small case series (n = 10) (76–85); only one study is a prospective, open-label, single-arm observational study (86). There were no randomized or non-randomized clinical trials. All included studies were considered to have a high risk of bias related to the retrospective study design, patient selection and data collection, ascertainment bias, missing data, and reporting of the results.

Table 3 summarizes patients' characteristics and details on KD administration and Table 4 summarizes the response to KD and outcomes.

3.2.1. Individual data extraction and analysis of the literature

Overall, the included studies described 276 patients, both of pediatric and adult age, receiving KD during SRSE. One hundred twenty-three/245 (50.2%) were female (information detailed in 71 studies). The majority of reported patients were children (208/276; 75.3%). The median age at SE onset was 9.1 years old [interquartile range (IQR)]: 5.2–20 years; range: 1.2 months−73 years; information available in 73 studies].

3.2.2. Etiology details

The most common etiology of SRSE was acute symptomatic (59/276; 21.3%), among these patients, 67.7% (40/59) presented with NORSE of immune (25/40; 62.5%) and infectious (15/40; 37.5%) etiologies. Other etiologies were remote symptomatic (19/276; 6.8%), progressive symptomatic (17/276; 6.1%), and SE in defined electroclinical syndromes (41/276; 14.8%), including two patients with genetic etiology and NORSE presentation. The etiology was unknown in 50.7% of the patients (140/276) presenting with NORSE, of which 102 presented with FIRES.

3.2.3. Treatment details and response to ketogenic diet

Overall, the median time duration of SRSE before KD initiation was 9 days (IQR: 5.2–20; range: 1–73; information available in 56 studies), the median number of treatments (ASMs and anesthetics) prior to KD was 6 (IQR: 5–8; range: 2–14; information detailed in 69 studies), and 143/276 (51.8%) patients also received other treatments prior KD mostly including immunotherapy (133/143; 93%).

KD was considered effective in 197/276 (71.4%) patients after a median time from KD initiation of 6.5 days (IQR 4–9, range 1–28). Overall, the total length of KD was 60 days (IQR 21–180; range: 3–900) in responders and non-responders patients (information available in 47 studies).

In patients with NORSE presentation (182/276, 65.9%), the median time of duration of SRSE before KD initiation was 15 days [interquartile range (IQR): 9–28; range: 2–420], and the median

TABLE 1 Necker Enfants Malades Hospital experience: patients' characteristics.

Patient	Age at SE onset	Gender	Previous history of epilepsy	Etiology	Treatments before KD	Duration of SE prior KD (days)	Fasting at KD initiation	KD ratio	Time to reach steady ketosis (days)
1	5 years	F	Yes	SE in defined electroclinical syndrome (DEE)	2 ASMs/anesthetics	4	Yes	4:1	4
2	10 years	M	Yes	Progressive (Alpers syndrome)	3 ASMs/anesthetics	1.5	No	4:1	1
3	3 years	M	No	Progressive (mitochondrial defect)	6 ASMs/anesthetics, IVIg	20	No	4:1	1
4	13 months	M	Yes	Progressive (Chediak Higashi syndrome)	4 ASMs/anesthetics	1.5	No	4:1	1
5	16 months	F	Yes	Progressive (Alpers syndrome)	7 ASMs/anesthetics, steroids	9	No	4:1	4
6	3 years	M	No	Acute (NORSE: infectious encephalitis)	5 ASMs/anesthetics	2	No	4:1	1
7	19 months	M	Yes	SE in defined electroclinical syndrome (Dravet syndrome)	3 ASMs/anesthetics	2	No	4:1	1
8	3 years	M	No	SE in defined electroclinical syndrome (neuro-cutaneous melanosis)	5 ASMs/anesthetics	1	Yes	4:1	1
9	2 years	M	No	Acute (Cerebral anoxia)	2 ASMs/anesthetics	2	No	4:1	1
10	2 years	F	Yes	SE in defined electroclinical syndrome (Dravet syndrome)	5 ASMs/anesthetics	4	No		3
11	4 years	F	No	Unknown (FIRES)	4 ASMs/anesthetics	5	No		1
12	2 months	M	No	Unknown (FIRES)	6 ASMs/anesthetics, vitamins	2	No		0
13	2 months	M	Yes	SE in defined electroclinical syndrome (EIMFS)	4 ASMs/anesthetics	2	Yes		1
14	1 month	F	No	Progressive (mitochondrial defect)	3 ASMs/anesthetics, pyridoxine	3	No		0
15	2 years	M	Yes	SE in defined electroclinical syndrome (Dravet syndrome)	4 ASMs/anesthetics, steroids	11	Yes		2
16	13 months	F	Yes	Progressive (mitochondrial defect)	4 ASMs/anesthetics	13	No		2

ASMs, antiseizure medications; DEE, developmental and epileptic encephalopathy; EIMFS, epilepsy of infancy with migrating focal seizures; FIRES, febrile infection-related epilepsy; Syndrome KD, ketogenic diet; NORSE, now onset refractory status epilepticus; SE, status epilepticus.

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TABLE 2 Necker Enfants Malades Hospital experience: response to KD and outcome.

Patient	KD efficacy to stop SE	Time to SE resolution (days)	Total length of KD (days)	Side effects	No. ASMs at discharge	Outcome
1	Yes	1	570	None	4	Ongoing seizures
2	Yes	1.5	1,500	None	2	Ongoing seizures
3	No	20	16	None	/	Dead
4	Yes	1.5	7	Vomiting	2	Ongoing seizures
5	No	9	16	Hypoglycemia	4	Ongoing seizures
6	No	2	12	None	/	Dead
7	No	2	4	Hypoglycemia	1	Ongoing seizures
8	Yes	1	9	None	2	Ongoing seizures
9	Yes	2	3	None	1	Ongoing seizures
10	No	4	16	Hypoglycemia	/	Dead
11	No	5	8	Hypoglycemia	2	Ongoing seizures
12	No	2	5	None	1	Ongoing seizures
13	No	2	3	Hypoglycemia	5	Ongoing seizures
14	No	3	10	None	1	Ongoing seizures
15	No	11	20	None	2	Ongoing seizures
16	No	13	90	Weight loss	3	Ongoing seizures

ASMs, antiseizure medications; KD, ketogenic diet; SE, status epilepticus.

number of other treatments prior to KD was 7 (IQR: 5–8; range: 2–16). KD was considered effective in 117/182 (64.3%) after a median time from KD initiation of 8 days (IQR 6–21, range 1–30).

Overall, adverse effects due to KD were reported in 124/276 (44.9%) patients.

3.2.4. Outcomes

Twenty-seven out of 276 (9.7%) patients died during the acute phase of SRSE, while 7/276 (2.5%) died after achieving SE cessation. At the latest follow-up with a median length after SE cessation of 10 months (IQR 3.3–18, range 9 days−156 months), 50/242 (20.6%) patients achieved seizure freedom, 46/242 (19%) suffering from ongoing seizures, while 44/242 (18.2%) had ongoing seizures associated with cognitive impairment, and 33/242 (13.6%) had cognitive impairment alone (information available in 63 studies). Overall, 88/90 (97.7%) with ongoing seizures received a median number of ASMs of 3 (IQR: 3–4, range: 1–10; information available in 36 studies).

3.3. Ketogenic diet effectiveness and influencing factors

For this analysis, we considered the literature cases in addition to our center cases. The data of 255/292 (82.9%) patients were available for Kaplan–Meier survival curves.

The probability to achieved SRSE cessation after KD initiation is 50.53% at 7 days [95% confidence interval (CI): 44.15–56.57], 33.16% at 14 days (95% CI: 27.21–39.22), and further decreases to 26.34% at 21 days (95% CI: 20.77–32.22), and 25.24% at 28 days (95% CI: 19.73–31.10).

The KD responder rates are different in children compared to adults (HR: 1.47, 95% CI: 1.04–2.06; $p < 0.02$). The median time to achieve SRSE cessation after starting KD is 8 days in children (IQR: 6–16; range: 1–30) and 5.5 days in adults (IQR 3–10; range 1–30).

A previous history of epilepsy implies a greater likelihood of KD efficacy in achieving SRSE cessation (HR: 1.54, 95% CI: 1.11–2.12; $p = 0.009$). The detection of known etiology implies a favorable response to KD (HR: 1.70, 95% CI: 1.26–2.30; $p < 0.0001$); in this regard, patients with an acute symptomatic cause of SRSE have a greater likelihood of KD efficacy (HR: 1.58, 95% CI: 1.13–2.23; $p = 0.008$).

Otherwise, even though most patients with NORSE benefit from KD (117/185, 63.2% achieving SRSE cessation, $p < 0.004$), they needed, however, a longer time to achieve SE resolution after starting KD compared with other non-NORSE SRSE (HR: 0.60, 95% CI: 0.44–0.81; $p = 0.001$; Figure 2). At the Kaplan–Meier survival analysis, the probability of achieving NORSE cessation after KD initiation was 56.13% at 7 days (95% CI: 48.02–63.48), 40.51% at 14 days (95% CI: 32.58–48.28), 32.75% at 21 days (95% CI: 25.20–40.50), and 31.12% at 28 days (95%CI: 23.66–38.85). The response to KD in the NORSE group with identified etiology compared to the cryptogenic NORSE was significantly higher ($p = 0.01$), and the time to achieve SE resolution after starting KD was shorter (HR: 1.56, 95% CI: 1.01–2.38; $p = 0.04$; Figure 3).

Overall, the number of treatments before KD initiation has a negative impact on the responder rate (HR: 0.93, 95% CI: 0.88–0.98, $p = 0.01$), while the time from SRSE onset to KD initiation does not significantly impact KD efficacy (HR: 0.99, 95% CI: 0.99–1.00, $p = 0.23$).

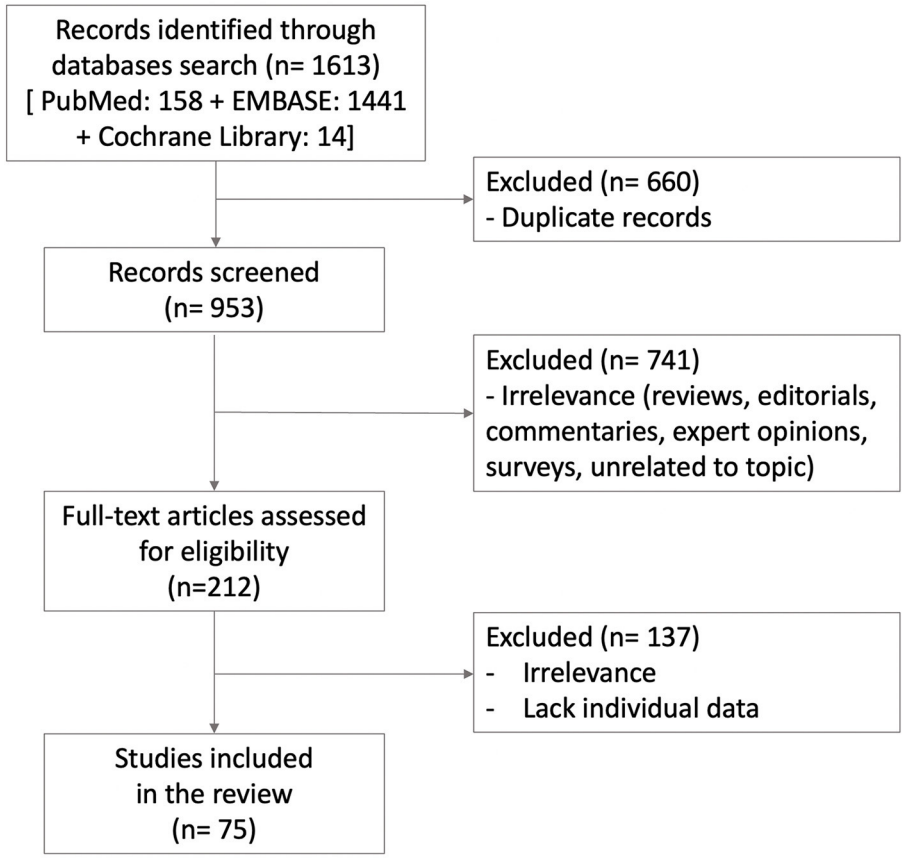

FIGURE 1
Flow diagram of the study selection process.

Side effects of KD negatively impact the probability to achieve SRSE cessation after KD initiation (HR: 0.60, 95% CI: 0.44–0.81, $p = 0.001$). Other KD related factors such as fasting before diet initiation, KD ratio, time to reach ketosis, and total length of KD, do not impact the likelihood of KD efficacy in achieving SRSE cessation.

4. Discussion

SRSE is a major neurological emergency, and the therapeutic interventions aim to reduce its duration, mortality, as well as short- and long-term comorbidities. NORSE (with its subcategory FIRES) is one of the most common causes of SRSE. Therapeutic alternatives are scarce, and the use of anesthetic agents as symptomatic treatment could worsen the outcome due to systemic complications that often co-occur. So far, there is currently no high-level evidence to guide NORSE management since most of the therapeutic approaches come from expert opinions and few cases. A few studies and case series on immunotherapy with monoclonal antibodies efficacy have been reported so far (40, 43, 47, 53, 59, 87), but their effectiveness has still to be assessed in large cohort studies.

NORSE outcomes are influenced mainly by non-modifiable variables such as age and underlying etiology, though complications from the NORSE status itself, treatments, and length of stay in ICU also contribute to morbidity and mortality.

KD is an emerging treatment option for RSE and SRSE (88), and most published evidence has shown high efficacy rates (12, 13, 89). The multiple mechanisms of action make KD a good therapeutic option in these conditions. The anti-seizure effect of KD may be due to multiple mechanisms involving neurotransmitters, mitochondria, gut microbiota, DNA methylation, ion channels, inflammation, and G-protein coupled receptors. It mimics ASMs polytherapy (88), and several of these mechanisms can occur rapidly, while others, such as the effects on mitochondria, gut microbiota, and DNA methylation, are likely long-term.

Many case reports and case series have demonstrated the potential efficacy and safety of KD for the acute treatment of SRSE; however, the quality of these studies remains scarce.

More literature reports the use of KD in children compared to adults, but studies on the adult population have shown higher efficacy rates (87.5 vs. 66.8%; $p = 0.001$) and a shorter time to achieve SE cessation after starting KD. This discrepancy is probably due to more refractory cases being over-represented in the childhood population.

In this systematic review, about half of patients experiencing SRSE, a cause has been identified, and almost a quarter have a previous history of epilepsy. However, half of the cases elude any easily detectable etiology, and previously healthy individuals

TABLE 3 Systematic review: summary of patients' characteristics and KD administration.

References	Study design	Population	Age at SE onset (years)	Gender	Previous history of epilepsy	Etiology	No. of ASMs & anesthetics before KD	Other treatment before KD	Duration of SE prior KD (days)	Fasting at KD initiation	KD ratio	Time to reach steady ketosis (days)
Aydemir and Kandula (33)	Case report	1 adult	27	M	0%	Unknown 100% (NORSE)	10	Immunotherapy, Electroconvulsive therapy	16	–	–	–
Chomtho et al. (15)	Retrospective observational	14 children	Median 7 (IQR 8 months−9 years, range 2 months−13.6 years)	F 50%, M 50%	35.7%	Acute 28.5% (NORSE: HSV and Rickettsia encephalitis, anti-NMDAR encephalitis); SE in defined electroclinical syndrome 35.7% (PLP deficiency, LGS, epilepsy due to focal cortical dysplasia); progressive 7.3% (RE); unknown 28.5% (NORSE/FIRES)	Median 6 (IQR 5–8, range 3–9)	Steroids 64.3%, IVIg 42.8%, pyridoxine 71.4%, PLP 35.7%, PLEX 7.1%, cyclophosphamide 7.1%, hypothermia 7.1%, epilepsy surgery 14.3%	Median 6 (IQR 5–9, range 4–14)	–	variable	Median 3.5 (IQR 2–7, range 1–9)
Dutta et al. (34)	Case report	1 adult	35	F	0%	Acute (hypoxic brain injury)	8	No	14	–	MCTKD	3
Giménez-Roca et al. (35)	Case report	1 adult	39	F	100%	SE in defined electroclinical syndrome (IGE)	10	MPN, IVIg	30	–	–	–
Luo et al. (36)	Case report	1 child	2.3	M	0%	Unknown (FIRES)	7	No	17	–	3.1	–
Orlandi et al. (37)	Case report	1 Adult	38	F	0%	Unknown (NORSE)	12	Allopregnanolone, magnesium sulfate, hypothermy, PLEX, IVIg, MPN	133	–	–	–
Perulli et al. (38)	Case report	1 child	11	F	0%	Unknown (FIRES)	12	MPN, IVIg, PLEX	32	–	–	7
Sivathanu et al. (39)	Case report	1 child	7	M	0%	Acute (NORSE in anti-GAD 65 encephalitis)	7	IVIg, MPN, RTX	9	–	4:1	2
Varughese et al. (40)	Case report	1 child	0.6	F	100%	SE in defined electroclinical syndrome (PCDH19)	3	–	3	–	–	–
Allen et al. (41)	Case report	1 adult	19	M	100%	SE in defined electroclinical syndrome (UBE2A deficiency syndrome)	11	Steroids	81	–	–	7
Anand et al. (76)	Case series	3 adults and 1 child	Median 25.5 (IQR 15.5–43.5, range 7–60)	F 25%, M 75%	50%	Acute 25% (stroke); SE in defined electroclinical syndrome 25% (LGS); remote 25% (post-encephalitis); unknown (NORSE) 25%	Median 6 (IQR 5–6.5, range 4–7)	Steroids (12.5%)	Median 3 (IQR 2–14, range 2–14)	–	4:1 (75%)	Median 3 (IQR 2–4.5, range 2–5)
Baba et al. (42)	Case report	1 child	8	F	0%	Unknown 100% (FIRES)	6	Steroids, IVIg	6	–	4:1	3
Breu et al. (16)	Retrospective observational	8 children	Median 1.12 (IQR 0.08–6.88, range 0.03–12.28)	F 50%, M 50%	62.5%	SE in defined electroclinical syndrome 50% (Ohtahara syndrome, IS due to SCN2A pathogenic variant, TSC); progressive 37.5% (Alpers syndrome); Unknown 12.5% (FIRES)	Median 5 (IQR 2.5–7, range 1–7)	Steroids (12.5%)	Median 6 (IQR 1.5–9, range 1–42)	–	4:1	Median 2.8 (IQR 1.14–8.52, range 1–17.9)
Camões et al. (77)	Case series	3 adults	Median 20 (IQR 20–38, range 20–38)	F 66.6%, M 33.3%	0%	Acute 33.3% (head trauma), unknown 66.6% (NORSE)	–	–	Median 5 (IQR 4–9, range 4–9)	Yes (48 h)	4:1 (100%)	Median 4.5 (IQR 1–8, range 1–8)

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TABLE 3 (Continued)

References	Study design	Population	Age at SE onset (years)	Gender	Previous history of epilepsy	Etiology	No. of ASMs & anesthetics before KD	Other treatment before KD	Duration of SE prior KD (days)	Fasting at KD initiation	KD ratio	Time to reach steady ketosis (days)
Donnelly et al. (43)	Case report	1 adult	26	F	0%	Unknown (NORSE)	14	MPN, RTX, L salpingo-oophorectomy, hypothermia, electroconvulsie therapy, PLEX, pyridoxine	56	–	–	–
Katz et al. (44)	Case report	1 adult	29	F	0%	Unknown 100% (NORSE)	20	Steroids, IVIg, PEX, CYC, empiric bilateral partial oophorectomy	28	–	5:1	9
Kaul et al. (45)	Case report	1 adult	65	M	0%	Acute (subarachoid hemorrhage)	5	No	25	–	2.3:1	4
Schoeler et al. (13)	Retrospective observational	8 children	Median 7 (IQR 6.6–9.6, range 5.8–10.8)	F 25%, M 75%	0%	Unknown 100% (FIRES)	Median 9 (IQR 8–14, range 8–16)	Immunotherapy	Median 13 (IQR 11.5–15, range 6–24)	–	4:1 (62.5%), 5:1 (12.5%), 3.1 (25%)	Median 3 (IQR 2–7.5, range 1–12)
Aurangzeb et al. (46)	Case report	1 adult	22	M	0%	Unknown 100% (NORSE)	9	Immunotherapy	27	–	–	0
Chee et al. (47)	Case report	1 child	14	F	0%	Unknown 100% (FIRES)	9	Steroids, IVIg, hypothermia, tocilizumab	–	–	–	–
Chiu and Datta (48)	Case report	1 child	11	M	0%	Acute 100% (Childhood primary angiitis of the CNS)	6	Steroids, IVIg, cyclophosphamide	24	–	4:1	–
Gupta et al. (49)	Case report	1 child	0.3	F	100%	SE in defined electroclinical syndrome 100% (Ohtahara syndrome due to AIMP1 pathogenic variant)	12	–	4	–	4:1 (100%)	2
Koessler et al. (50)	Case report	1 child	16	F	0%	Progressive 100% (Alpers syndrome)	9	Steroids, IVIg	9	–	4:1 (100%)	5
Noviawaty et al. (51)	Case report	1 adult	38	M	0%	Unknown 100% (NORSE)	9	Steroids	49	–	4:1 (100%)	5
Vallecoccia et al. (52)	Case report	1 adult	34	M	0%	Unknown 100% (NORSE)	10	Steroids, PEX, IVIg, tocilizumab	49	–	–	–
Wang et al. (17)	Retrospective observational	10 children	Median 9 (IQR 7–10, range 5–13)	F 60%, M 40%	0%	Unknown 100% (FIRES)	Median 3 (IQR 3–4, range 2–4)	–	Median 9 (IQR 6–20, range 2–22)	3 days	4:1 (100%)	Median 6 (IQR 3–10, range 1–14)
Arayakarnkul and Chomtho (18)	Retrospective observational	13 children	Median 8.3 (IQR 1.7–9.8, range 0.2–13.5)	F 46.1%, M 53.8%	30.8%	Acute 37.5% (intracranial hemorrhage, NORSE: infectious encephalitis, autoimmune encephalitis); progressive 7.7% (RE), SE in defined electroclinical syndromes 23.1% (PLP deficiency, LGS), unknown 23% (NORSE/FIRES)	Median 8 (IQR 7–9, range 5–12)	Steroids 69.2%, pyridoxine 84,6%, PLP 53.8%, IVIg 46.1%, hypothermia7.7%, PEX 7.7%	–	12 h	–	Median 2 (range 1.3–4.6)
Dilena et al. (53)	Case report	1 child	10	M	0%	Unknown (FIRES)	10	Steroids, IVIg, Mg	–	–	–	–
Francis et al. (19)	Retrospective observational	11 adults	Median 46 (IQR 31–72, range 21–73)	F 45.4%, M 54.5%	45.4%	Acute 63.6% (NORSE: anti-NMDAR encephalitis; intracranial hemorrhage, cardiac arrest, stroke, intracranial hemorrhage, ethanol withdrawal); remote 27.3% (traumatic brain injury sequelae); SE in defined electroclinical syndromes 9%	Median 3 (IQR 2–3, range 2–8)	–	Median 1 (IQR 0–2, range 0–3)	–	–	Median 1 (IQR 0–2, range 0–5)

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TABLE 3 (Continued)

References	Study design	Population	Age at SE onset (years)	Gender	Previous history of epilepsy	Etiology	No. of ASMs & anesthetics before KD	Other treatment before KD	Duration of SE prior KD (days)	Fasting at KD initiation	KD ratio	Time to reach steady ketosis (days)
Park et al. (20)	Retrospective observational	14 children, 2 adults	Median 8 (IQR 5–13.5, range 0.1–40)	F 37.5%, M 62.5%	12.5%	Acute 12.5% (NORSE: HSV encephalitis, enteroviral encephalitis), remote 12.5% (hypoxic ischemic encephalopathy), SE in defined electroclinical syndromes 12.5% (FLE, hemimegalencephaly), Unknown 62.5% (FIRES)	5 ASMs (range 2–8); 2 anesthetics (range 1–3)	None	Median 23 (IQR 12–33.5, range 3–420)	–	–	–
Peng et al. (21)	Retrospective observational	7 children	–	F 57%, M 43%	0%	Unknown 100% (FIRES)	Median 6 (IQR 5–7, range 5–7)	Steroids 71.4%, IVIg 100%, PEX 57%	Median 11 (IQR 4–15, range 3–31)	None	4:1 (42.8%), 3:1 (28.6%), 3:2 (14.3%), 2:5 (14.3%)	Median 3 (IQR 1–5, range 1–11)
Arya et al. (22)	Retrospective observational	14 children	–	–	14.2%	Acute 7.1% (NORSE: possible autoimmune encephalitis), remote 7.1% (MCD), SE in defined electroclinical syndromes 7.1% (TSC); unknown 78.5% (NORSE/FIRES)	–	Steroids 14.2%, IVIg 14.2%, PEX 21.4%, pyridoxine 7,1%, VNS 14.2%	Median 13 (IQR 5–18, range 3–39)	–	4:1 (78.6%), 3:1 (7.1%), 3:5 (7.1%), 5:1 (7.1%),	Median 2 (IQR 1–3, range 1–10)
Blunck et al. (54)	Case report	1 adult	42	F	100%	Remote (cerebral palsy)	11	SGLT2 inhibitor	–	24 h	4:1	20
Lee and Chi (23)	Retrospective observational	7 children	Median 11.2 (IQR 5.7–11.7, range 1.2–17.8)	F 71.4%, M 28.5%	0%	Unknown 100% (FIRES)	–	Steroids 28.5%	–	–	–	–
Cervenka et al. (86)	Prospective observational	15 adults	Median 47 (IQR 25–63, range 18–82)	F 66.6%; M 33.3	40%	Acute 40% (anoxic ischemic injury, intracranial hemorrhage, encephalitis, haemorrhagic infarct); progressive 6.6% (glioblastoma multiforme); SE in defined electroclinical syndromes 20% (LGS, focal epilepsy); unknown 33.3% (NORSE)	Median 8 (IQR 6–9, range 5–12)	Steroids 26.6%, PEX 33.3%, CYC 6.6%	Median 10 (IQR 5–19, range 2–39)	24 h (20%)	4:1 (100%)	Median 2 (IQR 1–7, range 1–16)
Farias-Moeller et al. (24)	Retrospective observational	9 children	Median 5 (IQR 5–8, range 2–8)	F 66.6%, M 33.3%	11.1%	Progressive 11.1% (CNS hemophagocytic lymphoistiocytosis), SE in defined electroclinical syndrome 11.1%; Unknown 77.8% (FIRES),	Median ASMs 4 (IQR 3–4); median anesthetic agents 2 (IQR 2–3)	Steroids 88.8%	Median 13 (IQR 10–16, range 7–41)	8 h (11.1%)	4:1 (77.7%), 3.1 (11.1%), 2.75:1 (11.1%)	Median 3 (IQR 3–4, range 2–13)
Fox et al. (55)	Case report	1 child	6	F	0%	Acute (FIRES)	8	Steroids, IVIg, PEX, biotin, folinic acid, pyridoxine, L-carnitine	–	–	–	–
Uchida et al. (56)	Case report	1 adult	20	F	0%	Acute (NORSE: anti-NMDAR encephalitis)	7	Steroids; IVIg, ovariectomy	–	–	–	–
Appavu et al. (57)	Case report	1 child	8 months	F	100%	SE in defined electroclinical syndrome (DEE due to TBC1D24 pathogenic variant)	3	None	–	–	–	–

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TABLE 3 (Continued)

References	Study design	Population	Age at SE onset (years)	Gender	Previous history of epilepsy	Etiology	No. of ASMs & anesthetics before KD	Other treatment before KD	Duration of SE prior KD (days)	Fasting at KD initiation	KD ratio	Time to reach steady ketosis (days)
Appavu et al. (57)	Retrospective observational	10 children	Median 8 (IQR 3.5–15, range 2–16)	F 40%, M 60%	40%	Acute 40% (PCDH19, GABRG2, anti-NMDAR encephalitis, mycoplasma post-infectious encephalitis), progressive 10% (RE), SE in defined electroclinical syndrome 30% (LGS, DR GE, non-ketotic hyperglycinemia), unknown 20% (NORSE/FIRES)	Median 5.5 (IQR 4–6, range 3–8)	MPN, IVIg, PLEX, ACTH 40%	Median 18 (IQR 8–28, range 1–45)	–	4:1 (90%), 5:1 (10%)	Median 5.5 (IQR 2–8, range 1–13)
Chiusolo et al. (58)	Case report	1 child	8	M	100%	SE in defined electroclinical syndrome (GE and ASD)	8	Clozapine, steroids, IVIg	–	–	3:1	3
Kenney-Jung et al. (59)	Case report	1 child	32 months	F	0%	Unknown (FIRES)	8	Steroids	6	–	4:1	47
Mirás Veiga et al. (60)	Case report	1 child	4	M	0%	Unknown (FIRES)	6	MPN, IVIg	4	–	–	–
Amer et al. (61)	Case report	1 adult	21	F	0%	Acute (NORSE: anti-NMDAR-encephalitis)	6	Steroids, IVIg, PEX	–	–	4:1	–
Caraballo et al. (78)	Case series	2 children	23 and 17 months	M 100%	100%	Progressive 50% (PME), SE in defined electroclinical syndrome 50% (myoclonic epilepsy)	5 and 4	Steroids 100%	15 and 21	24 h (100%)	4:1	–
Cash (62)	Case report	1 adult	50	M	0%	Remote (hypoxic ischaemic brain injury)	10	None	36	–	4:1	–
Cobo et al. (79)	Case series	4 children	Median 8.5 (IQR 3–12, range 0.16–13)	F 25%, M 75%	50%	SE in defined electroclinical syndrome 50% (EIMFS, TSC), unknown 50% (NORSE)	7 (range 7–8)	Pyridoxine, pyridoxal-5-phosphate, folinic acid 25%; IVIg 25%	Median 28 (IQR 19.5–51.5, range 19–67)	0%	4:1 (50%), 3:1 (25%), 2:1 (25%)	Median 5
Fung et al. (80)	Case series	4 children	Median 12 (IQR 7–16, range 6–16)	F 50%, M 50%	0%	Acute 50% (VGKC associated encephalitis, possible autoimmune encephalitis), unknown 50% (FIRES)	Median 6.5 (IQR 6–7, range 6–7)	PLEX 50%, vitamin B6 and folinic acid 50%	Median 17.5 (IQR 14.5–19.5, range 12–21)	–	4:1 (100%)	–
Incecik et al. (63)	Case report	1 child	16	F	100%	Remote (cerebral palsy)	8	Steroids, IVIg	–	–	–	–
Lin et al. (64)	Case report	1 child	6.3	M	0%	Unknown (NORSE)	6	None	2	0%	4:1	1
Moriyama et al. (65)	Case report	1 child	9	F	0%	unknown (FIRES)	4	None	15	0%	3:1	1
Barros et al. (66)	Case report	1 child	7	M	0%	Acute (NORSE: anti-NMDAR-encephalitis)	12	MPN, IVIg, PLEX, RTX	–	–	–	–
Caraballo et al. (26)	Retrospective observational	10 children	Median 8 (IQR 5–10, range 0.5–16)	F 40%, M 60%	0%	Unknown 100% (NORSE/FIRES)	3	IVIg 100%	–	100%	4:1	3
Fung (67)	Case report	1 child	16	F	0%	Acute (NORSE: encephalitis)	3	None	18	–	4:1	–
Gedik et al. (68)	Case report	1 child	5	M	0%	Acute (NORSE: meningoencephalitis)	11	IVIg	27	–	–	–
Matsuzono et al. (69)	Case report	1 adult	22	M	0%	Unknown (FIRES)	9	Steroids	155	–	–	–

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TABLE 3 (Continued)

References	Study design	Population	Age at SE onset (years)	Gender	Previous history of epilepsy	Etiology	No. of ASMs & anesthetics before KD	Other treatment before KD	Duration of SE prior KD (days)	Fasting at KD initiation	KD ratio	Time to reach steady ketosis (days)
O'Connor et al. (27)	Retrospective observational	5 children	Median 9 (IQR 5–9, range 0.83–10)	F 40%, M 60%	40%	Progressive 40% (Alpers syndrome, mitochondrial defect), SE in defined electroclinical syndrome 20% (GE), Unknown 40% (NORSE/FIRES)	Median 8 (IQR 5–9, range 5–9)	IVIg 40%	Median 10.5 (IQR 4.5–18, range 3–21)	0%	4:1	Median 5 (IQR 2–5, range 1.5–8)
Singh et al. (81)	Case series	2 children	7 and 10	F 50%, M 50%	0%	Unknown 100% (FIRES)	7	Steroids 100%	13 and 3	No	4:1 and 6:1	2 and 20
Thakur et al. (28)	Retrospective observational	10 adults	Median 33.5 (IQR 28–48, range 23–51)	F 60%, M 40%	10%	Acute 90% (anoxic ischemic injury, NORSE: infectious encephalitis, autoimmune encephalitis), remote 10% (cortical dysplasia)	Median 7.5 (IQR 5–12, range 5–13)	Steroids 50%	Median 21.5 (IQR 17–45, range 2–60)	70%	4:1 (90%), 3:1 (10%)	Median 3 (IQR 1–6, range 0.5–7)
Caraballo et al. (82)	Case series	2 children	12 and 9.5		0%	Unknown 100% (FIRES)	2 and 5	Immunotherapy 50%	–	–	–	–
Sort et al. (83)	Case series	3 children	Median 10 (range 3–11)	F 33.3%, M 66.6%	33.3%	Progressive 33.3% (mitochondrial defects), unknown 66.6% (HHE, FIRES)	Median 8 (range 6–9)	Steroids 66.6%, IVIg 33.3%, hypothermia 33.3%, PLEX 33.3%	Median 7 (range 5–47)	–	5:1 (33.3%)	Median 12 (range 1–17)
Strzelczyk et al. (70)	Case report	1 adult	21	F	100%	Progressive (Lafora disease)	8	Steroids, magnesium	15	–	4:1	3.5
Martikainen et al. (71)	Case report	1 adult	26	F	0%	Progressive (Alpers syndrome)	3	–	7	–	LGIT (low glycemic index treatment)	–
Vaccarezza et al. (29)	Retrospective observational	5 children	Median 6 (IQR 4–12, range 1–14)	F 66.6%, M 33.3%	0%	SE in defined electroclinical syndrome 20% (DR structural FE), unknown 80% (HHE, FIRES)	Median 7 (IQR 7–8, range 5–8)	Steroids 20%, IVIg 60%	Median 30 (IQR 18–45, range 15–52)	100%	4:1	2.5
Cervenka et al. (72)	Case report	1 adult	49	M	0%	Acute (NORSE: cerebral inflammation)	12	PLEX, epilepsy surgery	57	–	4:1	11
Ismail and Kossoff (2011)	Case report	1 child	14	F	0%	Unknown (FIRES)	10	None	60	–	4:1	2
Kramer et al. (7)	Retrospective observational	7 children	Median 6 (IQR 5–9, range 4–9)		0%	Unknown 100% (FIRES)	Median 6 (IQR 4–8, range 2–13)	Steroids 42.8%, IVIg 71.4%, PLEX 14.3%, vitamin B6 14.3%, Folinic acid 14.3%	–	–	–	–
Nam et al. (30)	Retrospective observational	4 children, 1 adult	Median 10 (IQR 8–14, range 4–40)	F 60%, M 40%	0%	Acute 100% (NORSE: infectious encephalitis)	Median 8 (IQR 8–10, range 5–11)	None	Median 30 (IQR 30–120, range 15–420)	–	4:1	
Kumada et al. (84)	Case series	2 children	3 and 5	F 100%	100%	SE in defined electroclinical syndrome 50% (FLE), remote 50% (subcortical band heterotopia)	7 and 3	–	390 and 150	–	4:1	3
Nabbout et al. (31)	Retrospective observational	9 children	Median 6 (IQR 5–7, range 4–8)	F 55.5%, M 44.4%	0%	Unknown 100% (FIRES)	Median 5 (IQR 4–6, range 3–7)	Steroids 77.8%	Median 17 (IQR 8–30, range 4–55)	100%	4:1	Median 3 (IQR 2–3, range 0–4)
Wusthoff et al. (85)	Case series	2 adults	34 and 29	F 50%, M 50%	50%	Acute 50% (NORSE: infectious encephalitis), progressive 50% (RE)	8 and 10	IVIg 50%, steroids 50%	20 and 101	50%	4:1	8 and 10

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TABLE 3 (Continued)

References	Study design	Population	Age at SE onset (years)	Gender	Previous history of epilepsy	Etiology	No. of ASMs & anesthetics before KD	Other treatment before KD	Duration of SE prior KD (days)	Fasting at KD initiation	KD ratio	Time to reach steady ketosis (days)
Villeneuve et al. (11)	Retrospective observational	4 children, 1 adult	Median 8 (IQR 3–10, range 1–18)	F 60%, M 40%	100%	Acute 20% (NORSE: infectious encephalitis), remote 20% (Sturge Weber syndrome), progressive 20% (Ito syndrome), SE in defined electroclinical syndrome 40% (cryptogenic epilepsy)	Mean 2.7	None	–	100%	4:1	–
Bodenant et al. (74)	Case report	1 adult	54	M	100%	SE in defined electroclinical syndrome (FE)	10	–	31	–	4:1	–
Baumeister et al. (75)	Case report	1 child	10	M	100%	SE in defined electroclinical syndrome (FE)	6	–	–	48 h	4:1	2
François et al. (32)	Retrospective observational	6 children	–	–	0%	Remote 100% (postencephalitic)	Mean 6 (range 3–10)	–	Median 11 (IQR 8–75, range 8–75)	100%	3.1/4.1	2

ACTH, adrenocorticotropic hormone; ASMs, antiseizure medications; CNS, central nervous system; CYC, cyclophosphamide; DEE, developmental and epileptic encephalopathy; DR, drug resistant; EIMFS, epilepsy of infancy with migrating focal seizures; FE, focal epilepsy; FIRES, febrile infection-related epilepsy syndrome; FLE, frontal lobe epilepsy; GAD, antiglutamic acid decarboxylase; HHE, Hemiconvulsion-Hemiplegia-Epilepsy syndrome; HSV, herpes simplex virus; GE, generalized epilepsy; IGE, idiopathic generalized epilepsy; IQR, interquartile range; IVIg, intravenous immunoglobulins; KD, ketogenic diet; L, left; LGS, Lennox-Gastaut syndrome; MCD, malformations of cortical development; Mg, magnesium; MPN, methylprednisolone; NMDAR, N-methyl-D-aspartate receptor; No, number; NORSE, new onset refractory status epilepticus; PLEX, plasma exchange; PLP, pyridoxal-5-phosphate; PME, progressive myoclonic epilepsy; RE, rasmussen encephalitis; RTX, Rituximab; SE, status epilepticus; TSC, tuberous sclerosis complex; VCKC, voltage-gated potassium channel.

develop prolonged NORSE without a readily identifiable explanation. Overall, patients with SRSE of known etiology appear to present a better response rate and a shorter time to achieve SRSE cessation after starting KD. SE occurring during the course of epilepsy syndromes, such as genetic and structural epilepsies, may benefit from KD in 75% of the cases. Furthermore, patients with SRSE of remote etiology were also reported as responders to KD in 62.5% (11, 26, 64, 74). Patients with SRSE due to progressive etiologies such as mitochondrial diseases (71) are good candidates for KD to be introduced early. Other etiologies involving immune-mediated pathways, such as Rasmussen encephalitis and autoimmune encephalitis with SRSE were reported to benefit of KD (18, 19, 28, 56, 57, 61, 66, 80, 85). In this regard, the presumed immune etiology in FIRES and NORSE cases, based on the activation of an inflammatory cascade, makes these conditions possible specific targets for KD (90). In this systematic review, NORSE, and its subcategory FIRES, are common causes of SRSE, but these difficult-to-treat conditions imply a longer time to achieve SE resolution after starting KD compared to other SRSE. This might be due to the addition of specific treatment tailored for etiologies and the high level of cases remaining without an etiology (cryptogenic NORSE) or where etiology was much delayed.

The etiology remains unexplained in about two-thirds of the cases of NORSE, representing the so-called "cryptogenic NORSE." The most identified cause in adult patients is autoimmune encephalitis, while infections are the prevalent etiology in pediatric patients (91).

The analysis of literature data combined with our single center experience highlighted a more favorable response to KD and a shorter SE duration in the NORSE group with identified etiology compared with NORSE of unknown etiology. These findings highlight the alternative therapeutic role of KD in patients affected by NORSE and FIRES, even though this favorable response needs to be better evaluated and confirmed in prospective controlled studies assessing both seizure control and functional outcome. The detection of an underlying cause may also allow an early treatment at the pathogenic level, which may reduce the risk of irreversible sequelae in the long-term. The recent international consensus recommendations for the management of NORSE, including FIRES, provides diagnostic and therapeutic algorithms to aid clinicians in patient care (92, 93). The consensus recommends the initiation of the KD in the first week, or if not already given, KD should be considered in prolonged and severe cases, emphasizing the importance of starting KD very early in the course of NORSE. These management recommendations may allow a faster and more tailored diagnostic process and improve treatment to allow better outcomes.

The main limiting factor for the use of KD in NORSE might be the time lag for efficacy, ketosis is usually reached within 24–72 h, and seizure reduction within the first week in the majority of the patients. This time lag could be challenging to accept in a severe condition such as NORSE.

Another impeding factor for the initiation of KD highlighted by several panelists of the consensus (92) is the limited availability and the lack of experience in its administration, particularly in adult patients. However, the expertise on KD in adult neurology is still increasing, and the number of adult patients with epilepsies, mostly of genetic etiology, treated with KD is on the rise.

TABLE 4 Systematic review: response to KD and outcomes.

References	KD efficacy to stop SE	Time to SE resolution (days)	Total length of KD (days)	Side effects	No. ASMs at discharge	Follow-up (months)	Outcomes
Aydemir and Kandula (33)	0%	90	24	None	6	2	Baseline functional status
Chomtho et al. (15)	92.9%	Median 11 (IQR 7–14, range 4–17)	–	Electrolyte imbalance (85.7%), hypercalciuria (71.4%), hypertriglyceridemia (64.3%), hypoglycemia (21.4%)	–	–	Seizure free 85.7%, Dead 14.3%
Dutta et al. (34)	100%	10	90	None	–	3	Neurorehabilitation
Giménez-Roca et al. (35)	100%	32	–	None	–	–	Baseline functional status
Luo et al. (36)	0%	42	36	None	4	1	Mild DD
Orlandi et al. (37)	0%	187	13	Elevation of liver and pancreatic enzymes	4	42	Severe ID, tetraparesis, DR epilepsy
Perulli et al. (38)	100% (with Anakinra)	48	105	None	3	3	Moderate ID
Sivathanu et al. (39)	100%	3	90	None	3	12	Mild delay
Varughese et al. (40)	0%	52	49	None	5	6	Mild delay
Allen et al. (41)	100%	7	–	None	3	24	–
Anand et al. (76)	100%	Median 6 (IQR 3.5–8, range 2–9)	Median 31 (IQR 24–166, range 18–300)	None	Median 2 (IQR 2–2.5, range 2–3)	Median 1 (IQR 1–10, range 1–10)	–
Baba et al. (42)	100%	–	15	Elevated liver and pancreatic enzymes	2	15	Neurological sequelae
Breu et al. (16)	75%	Median 1.5 (IQR 1–5, range 1–15)	–	Dehydration (12.5%), dystrophia (12.5%), constipation (25%), flatulence (12.5%), hypertriglyceridemia (25%), hyperlipasemia (12.5%), high ketosis (12.5%), diarrhea (25%), pancreatitis (12.5%), catecholamines (12.5%), hepatopathy, hypercholesterinemia (12.5%), reduced drinking (12–5%), weight loss (12.5%), paralytic ileus (12.5%)	–	Median 5 (IQR 3–12, range 3–12)	Dead (62.5%), seizure free after epilepsy surgery (12.5%), daily seizures (12.5%), monthly seizures (12.5%)
Camões et al. (77)	66.6%	Median 14 (IQR 13–15, range 13–15)	Median 32 (IQR 11–41, range 11–41)	Hypoglycemia (66.6%), gastric statis (33.3%), hypertriglyceridemia (33.3%), ileus (33.3%), septic shock (33.3%)	–	–	Seizure freedom (66.6%), dead (33.3%)
Donnelly et al. (43)	0%	84	14	Elevated liver enzymes	2	2	Mild ID
Katz et al. (44)	100%		45	None	–	7	cardiac arrest, relapse of SE
Kaul et al. (45)	100%	29	14	None	–	1	Neurorehabilitation

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TABLE 4 (Continued)

References	KD efficacy to stop SE	Time to SE resolution (days)	Total length of KD (days)	Side effects	No. ASMs at discharge	Follow-up (months)	Outcomes
Schoeler et al. (13)	62.5%	Median 19 (IQR 12–31, range 12–35)	Median 21.5 (IQR 16.5–68.5, range 12–383)	Loose stool (62.5%), hyperketosis (37.5%), weight loss (12.5%), elevated amylase and lipase (25%), elevated lactate dehydrogenase (12.5%), hypoglycemia (12.5%), metabolic acidosis (50%), hypertriglyceridemia (37.5%)	–	–	Dead (37.5%), daily seizures and severe ID (25%), weekly-monthly seizure and learning difficulties (25%)
Aurangzeb et al. (46)	0%	–	3	None	–	10	mRS 3, ongoing focal seizures
Chee et al. (47)	0%	–		–	4	4	Seizure freedom, mild neuropsychological impairment
Chiu and Datta (48)	100%	–	86	–	5	18	Seizure freedom, mild neuropsychological impairment
Gupta et al. (49)	100%	10	–	None	–	–	–
Koessler et al. (50)	100%	7	60	Elevated liver enzymes (100%)	2	3	Death after 3 months
Noviawaty et al. (51)	100%	2	68	None	7	12	Ongoing seizures, severe ID
Vallecoccia et al. (52)	0%	–	7	Intolerance and high gastric residual volume (100%)	–	–	–
Wang et al. (17)	80%	Median 8 (IQR 7–15, range 2–30)	Median 165 (IQR 36–240, range 8–365)	Arrhythmia (10%), urinary stones (30%), hematuria (10%)	Median 4 (IQR 3–4, range 0–5)	–	Ongoing seizures and ID (90%)
Arayakarnkul and Chomtho (18)	92.3%	Median 9 (IQR 6.5–11.5, range 6–16)	–	–	–	Median 83 (IQR 57–96, range 15–231)	Dead 15.4%, epilepsy surgery 7.7%, seizure free 77%
Dilena et al. (53)	0%	–	21	–	5	36	Severe ID, seizure improvement with Anakinra
Francis et al. (19)	100%	Median 5 (IQR 2–9, range 2–15)	–	Metabolic acidosis 63.6%, hypoglycemia 18.2%, bowel perforation 9%, infection 9%, elevated liver enzymes 9%, hyponatremia 9%	Median 3 (IQR 3–6, range 2–10)	–	Neurological sequelae 82%
Park et al. (20)	56.2%	6.5 (range 1–28)	Median 61.5 (IQR 30–82.5, range 4–474)	Regurgitation 25%, constipation 12.5%, hypertriglyceridemia 12.5%, aspiration pneumonia 37.5%, nausea 6.2%, vomiting 12.5%, kidney stones 6.2%, metabolic acidosis 6.2%, hypoproteinemia 12.5%, elevated liver enzymes 6.2%	–	–	Ongoing seizures (62.5%), severe ID (18.7%), moderate ID (12.5%), mild ID (50%)
Peng et al. (21)	85.7%	Median 5.5 (IQR 4–6, range 1–10)	Median 90 (IQR 60–90, range 60–330)	Diarrhea (57%), hyperlipidemia (57%), transient hyperamylasemia (14.3%)	Median 4 (IQR 3–4, range 3–4)	Median 14 (IQR 11–31, range 4–40)	Seizure freedom (28.6%), ongoing seizures (57%)
Arya et al. (22)	85.7%	Median 7 (range 7–14)	–	Bowel disturbances 7.1%, Weight loss 7.1%, hypertriglyceridemia 7.1%	Median 5 (IQR 3–5, range 2–7)	–	–

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TABLE 4 (Continued)

References	KD efficacy to stop SE	Time to SE resolution (days)	Total length of KD (days)	Side effects	No. ASMs at discharge	Follow-up (months)	Outcomes
Blunck et al. (54)	0%	–	36	–	8	4	Dead
Lee and Chi (23)	0%	–	–	Elevated liver enzymes 71.4%	Median 4 (IQR 3–5, range 1–5)	Median 31 (IQR 13–74, range 6–89)	Dead 28.5%, ongoing seizures 71.4%, moderate-severe ID 71.4%
Cervenka et al. (86)	73.3%	Median 5 (IQR 3–8, range 0–30)	Median 28 (IQR 15–52, range 4–630)	Hyponatremia 6.6%, constipation 13.3%, metabolic acidosis 26.6%, hyperlipidemia 13.3%, hypoglycemia 13.3%, weight loss 6.6%	–	Median 6 (range 6–21)	Death 33.3%, ongoing seizures 33.3, seizure freedom 20%, lost to FU 13.3
Farias-Moeller et al. (24)	55.5%	Median 7	Median 90 (IQR 30–150, range 7.5–180)	Hypertriglyceridemia 22.2%, pancreatitis 11.1%	Median 3	Median 3	Ongoing seizures 55.5%, cognitive deficits 100%
Fox et al. (55)	–	–	–	None	–	–	Ongoing seizures, severe ID
Uchida et al. (56)	100%	–	–	None	–	–	–
Appavu et al. (57)	100%	–	–	None	–	–	Ongoing seizures
Appavu et al. (57)	90%	Median 8 (IQR 3–15, range 1–30)	–	Ketoacidosis, hypophosphatemia, hypokalemia 10%	Median 3 (IQR 3–4, range 1–5)	Median 12 (IQR 4–29, range 1–39)	Death 10%, ongoing seizures 50%, seizure freedom 30%
Chiusolo et al. (58)	0%	–	8	Elevated liver enzymes	9	4	Ongoing seizures
Kenney-Jung et al. (59)	0%	–	92	–	4	12	Chronic epilepsy
Mirás Veiga et al. (60)	0%	–	–	Liver failure	–	3	Ongoing seizures, cognitive deficits
Amer et al. (61)	100%	–	–	–	3	–	–
Caraballo et al. (78)	100%	7	365 and 180	None	1 and 2	12 and 6	Ongoing seizures 50%, lost to FU 50%
Cash (62)	100%	–	–	None	4	3.7	–
Cobo et al. (79)	75%	–	Median 75 (IQR 51–103, range 28–130)	Nephrolithiasis 25%, asymptomatic hypoglycemia 25%, constipation 25%, gastroesophageal reflux 25%	Median 1 (IQR 0.5–2, range 0–3)	Median 2.5 (IQR 1.7–7.7, range 1–13)	Seizure freedom 25%, ongoing seizures 75%
Fung et al. (80)	25%	–	Median 10 (IQR 9.5–10.5, range 9–11)	Hypoproteinemia 25%, vomiting 25%, increase breakthrough seizures 25%	–	Median 2 (IQR 1–4.5, range 1–6)	Refractory epilepsy and cognitive deficits 75%, seizure freedom 25%
Incecik et al. (63)	0%	–	–	–	4	5.5	–
Lin et al. (64)	100%	1.5	90	Weight loss, intermittent diarrhea	5	3	Ongoing seizures
Moriyama et al. (65)	100%	3	26	Protein losing enteropathy		7.4	ongoing seizures, cognitive deficits

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TABLE 4 (Continued)

References	KD efficacy to stop SE	Time to SE resolution (days)	Total length of KD (days)	Side effects	No. ASMs at discharge	Follow-up (months)	Outcomes
Barros et al. (66)	0%	–	–	–	4	24	ongoing seizures, cognitive deficits
Caraballo et al. (26)	70%	6	Median 270 (IQR 60–540, range 7–1080)	Pancreatitis 20%, severe vomiting and hypoglycemia 10%	–	–	–
Fung (67)	0%	–	10	None	–	–	–
Gedik et al. (68)	0%	–	–	–	–	2	Seizure freedom
Matsuzono et al. (69)	100%	25	–	None	–	10	Seizure freedom, cognitive deficits
O'Connor et al. (27)	100%	Median 5 (IQR 2–5, range 2–8)	Median 405 (IQR 360–495, range 360–540)	None	–	Median 13.5 (IQR 12–16.5, range 12–18)	Ongoing seizures 80%, death 20%
Singh et al. (81)	100%	8	120	None	2 and 3	12 and 18	Ongoing seizures, cognitive deficits
Thakur et al. (28)	90%	3	Median 16 (IQR 13–23, range 4–41)	Hypertriglyceridemia 20%, acidosis 10%	Median 4 (IQR 3–4, range 2–6)	–	Seizure freedom 10%, ongoing seizures 40%, death 20%
Caraballo et al. (82)	50%	–	–	–	–	–	Ongoing seizures
Sort et al. (83)	66.6%	1 and 13	Median 21 (range 15–28)	Weight loss 33.3%, hypertriglyceridemia 33.3%	Median 3	Median 6 (range 1–14)	Death 33.3%, ongoing seizures 33.3%, lost to FU 33.3%
Strzelczyk et al. (70)	100%	4	–	None	–		Ongoing seizures
Martikainen et al. (71)	100%	5	60	None	1	2	Seizure freedom
Vaccarezza et al. (29)	80%	Median 2 (range 1–3)	Median 365 (range 10–720)	Diarrhea 40%, hypokalemia 20%	–	Median 12.1 (range 0.3–24)	Death 20%, ongoing seizures 60%, lost to FU 20%
Cervenka et al. (72)	100%	11	90	None	3	3	Seizure freedom
Ismail and Kossoff (2011)	100%	10	150	None	3	5	Ongoing seizures
Kramer et al. (7)	14.3%	2	–	–	–	–	Death 14.3%, cognitive deficits 85.7%
Nam et al. (30)	100%	Median 8 (IQR 7–14, range 3–19)	Median 150 (IQR 30–240, range 30–480)	Hypertriglyceridemia 20%, constipation 80%, gastroesophageal reflux 40%, aspiration pneumonia 20%	–	Median 5 (IQR 3–8, range 1–16)	Ongoing seizures 40%

(Continued)

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TABLE 4 (Continued)

References	KD efficacy to stop SE	Time to SE resolution (days)	Total length of KD (days)	Side effects	No. ASMs at discharge	Follow-up (months)	Outcomes
Kumada et al. (84)	100%	5 and 10	570 and 120	None	–	18 and 4	Ongoing seizures 50%, seizure freedom 50%
Nabbout et al. (31)	77.8%	Median 5 (IQR 4–6, range 4–6)	540	–	–	18	Death 11.1%, ongoing seizures 88.9%
Wusthoff et al. (85)	100%	6 and 4	365	None	3 and 4	12	Seizure freedom 50%, lost to FU 50%
Villeneuve et al. (11)	80%	Median 2.5 (IQR 1.5–6.5, range 1–10)	Median 180 (IQR 30–130, range 21–360)	Severe vomiting 80%, asthenia 60%, severe anorexia 20%, non-symptomatic hypoglycemia 80%, drowsiness 60%	–	Median 6 (IQR 2–12, range 1–20)	–
Bodenant et al. (74)	100%	6	77	None	4	2.5	Death
Baumeister et al. (75)	0%	–	3	Fatal propofol infusion syndrome	6	–	Death
François et al. (32)	50%	–	Median 79 (range 9–98)	Weight gain 33.3%, height-weight stagnation 66.6%, digestive disorder 66.6%, hypoglycemia 33.3%, renal lithiasis 16.6%, asthenia 83.3%, sinus dysfunction of central origin 16.6%, cardiac arrest (hypokalemia) 16.6%	–	Median 0.3 (range 0.3–2)	Seizure freedom 50%

ASMs, antiseizure medications; DD, developmental delay; DR, drug resistant; FU, follow-up; ID, intellectual disability; IQR, interquartile range; KD, ketogenic diet; mRS, Modified Ranking scale; No, number; SE, status epilepticus.

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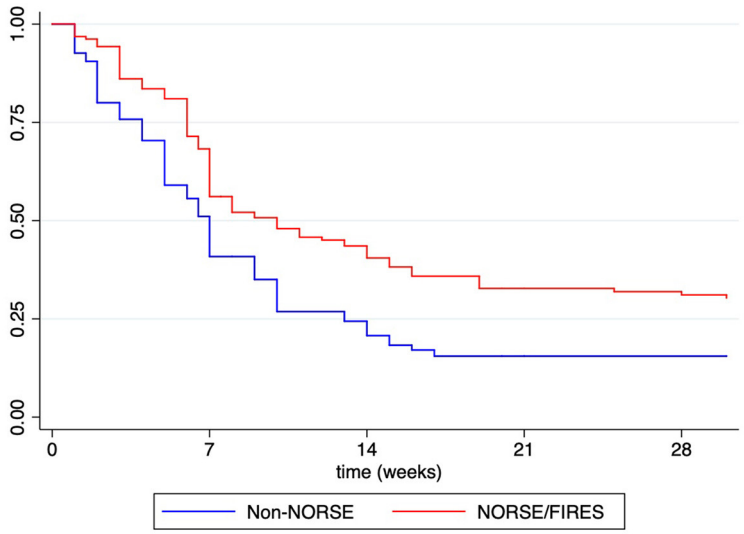

FIGURE 2
Kaplan–Meier survival estimates for probability to achieved RSE cessation after KD initiation in patients with NORSE/FIRES presentation vs. non-NORSE (other SRSE).

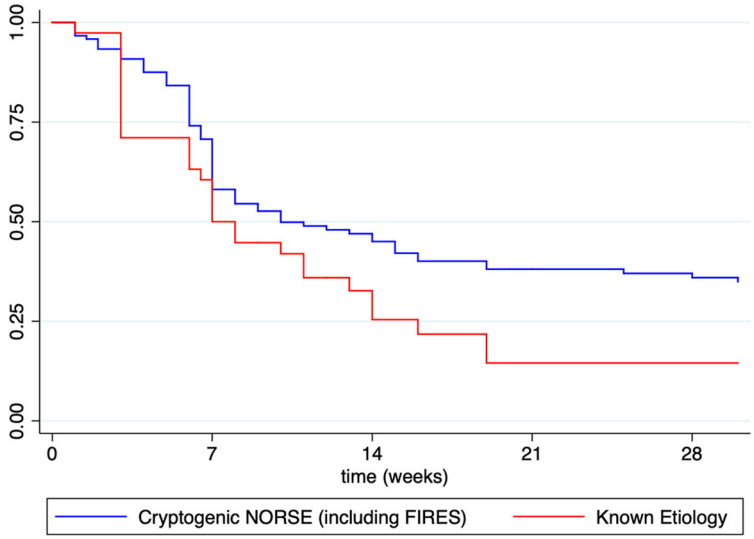

FIGURE 3
Kaplan–Meier survival estimates for probability to achieved NORSE cessation after KD initiation in patients with known etiology vs. cryptogenic NORSE (including FIRES).

The KD is well-tolerated with low rates of side effects in the ICU setting, highlighting that the diet has a safe profile and should be implemented in these settings. The most frequently reported side effects are easily manageable gastrointestinal or biochemical abnormalities, and the few serious adverse events reported in the literature are not necessarily attributable to KD.

The feasibility of implementing the KD in ICUs may be challenging also due to intensive care procedures, the possible occurrence of severe adverse events, and the concurrent administration of glucose-containing medications. A multidisciplinary team, including experienced physicians and dietitians, and standardized protocols should be warranted in these settings to overcome these issues. Most survivors have long-term sequelae in terms of drug-resistant epilepsy and poor functional outcomes, mostly related to the length of stay in the ICU and underlying etiology.

Due to its emergent and rare nature and the heterogeneity of the causes, randomized controlled treatment trials in NORSE are scanty. Literature data on KD in SRSE and NORSE comes mainly from retrospective observational studies, small case series, and anecdotal case reports that mainly report the good efficacy of the diet and rarely detail its failure.

These studies have inherent limitations and heterogeneity in etiology, protocols, and assessment criteria. Treating NORSE involves multiple medications and treatments given together, making it difficult to impute SRSE termination to a single therapeutic agent directly. In this regard, it is difficult to assess the primary therapeutic effect of KD or its synergistic action with other treatments. Furthermore, in some patients receiving concurrent medications targeting an underlying etiology, the resolution of SRSE cannot be directly attributed to the KD only. In this regard, the evidence of these reports shares the same weakness with all third-line treatments in RSE and SRSE, where no agent has achieved a high level of evidence-based medicine (3).

Although promising, the current results should be interpreted with caution due to the inherent bias, confounding factors, and small sample size of the included studies.

Evidence-based medicine is dramatically lacking to date, particularly in critical situations such as ICUs. In this regard, prospective, randomized controlled trials are needed to better assess KD as third-line therapy in managing RSE and preventing SRSE, mostly in patients with NORSE presentation. They should evaluate KD effectiveness in these specific settings, identify predictors of treatment response, and determine a ratio-responsive relationship of treatment. Outcomes should be assessed in the short-term, considering SE resolution, and in the long-term, evaluating subsequent seizure burden and neurological functioning.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

RN and SM contributed to the study concept, data acquisition and analysis, and drafting of the manuscript. PD contributed to the data acquisition and drafting of the manuscript. OD and MO contributed to the study concept, data acquisition, and drafting of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Perspective: Vagal nerve stimulation in the treatment of new-onset refractory status epilepticus

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Introduction: Resistance to drug therapy is a major hurdle in new-onset refractory status epilepticus (NORSE) treatment and there is urgent need to develop new treatment approaches. Non-drug approaches such as neuromodulation offer significant benefits and should be investigated as new adjunct treatment modalities. An important unanswered question is whether desynchronizing networks by vagal nerve stimulation (VNS) may improve seizure control in NORSE patients.

Main text: We present a summary of published NORSE cases treated with VNS and our own data, discuss possible mechanisms of action, review VNS implantation timing, stimulation setting titration protocols and outcomes. Further, we propose avenues for future research.

Discussion: We advocate for consideration of VNS for NORSE both in early and late stages of the presentation and hypothesize a possible additional benefit from implantation in the acute phase of the disease. This should be pursued in the context of a clinical trial, harmonizing inclusion criteria, accuracy of documentation and treatment protocols. A study planned within our UK-wide NORSE-UK network will answer the question if VNS may confer benefits in aborting unremitting status epilepticus, modulate ictogenesis and reduce long-term chronic seizure burden.

KEYWORDS

febrile infection-related epilepsy syndrome (FIRES), new onset refractory status epilepticus (NORSE), vagal nerve stimulation (VNS), neuromodulation, refractory status epilepticus (RSE)

1. Introduction

New-onset refractory status epilepticus (NORSE) and its subcategory febrile infection-related epilepsy syndrome (FIRES) are rare, devastating clinical presentations with <500 cases reported in the literature to date (1, 2). They are associated with high case fatality, long-term morbidity and their treatment is not supported by controlled studies (1, 2). Resistance to drug therapy is a major hurdle in managing this group of patients and there is urgent need to develop new treatment approaches. Functional disability is present in up to two thirds of NORSE survivors and subsequent chronic epilepsy is the norm (2–5), but individual reports and our own experience indicates that some people do have good cognitive and functional outcomes, even after prolonged status epilepticus (6). Whether desynchronizing networks by vagal nerve stimulation (VNS) may improve seizure control remains an unanswered question. Long-term studies of VNS in drug-refractory patients have

demonstrated a >50% seizure reduction in up to 60% of patients (7, 8) but the evidence base for VNS having the potential to interrupt refractory status epilepticus acutely is low (Class IV) (9). Additionally, whether VNS modulates brain activity directly through electrical stimulation, or also indirectly, via modulation of the immune system, is not completely understood. We first evaluate the current evidence behind the use of VNS in adult and pediatric NORSE cases, then present our own center's experience and propose avenues for future research.

2. Key VNS anti-ictal and anti-epileptogenic mechanisms of action

The anti-ictal and anti-epileptogenic mechanisms of action of VNS have been studied extensively in both humans and animal models and comprise stimulation of serotonergic and noradrenergic centers in the brainstem (10), norepinephrine binding in the limbic system (11) and modulation of cortical γ-Aminobutyric acid (GABA) A receptor density (12). These studies however, have not explored the mechanism of action of VNS in models of status epilepticus, and it is unknown whether the same mechanisms are responsible for the acute or subacute interruption of status, as in the long-term reduction of chronic seizures. In this respect, it is interesting to note, that in a human study seizures that were acutely stimulated using VNS had a reduced ictal spread as well as reduced impact on cardiovascular function (13). It is also unknown, whether VNS stimulation early during status epilepticus may prevent the process of epileptigenesis to some extent. It is also conceivable, that the changes in receptor occupancy and density induced by VNS may act synergistically and over the longer-term with concomitantly administered antiseizure medicines (ASM), such as benzodiazepines. More recent developments have seen VNS being used as anti-inflammatory treatment: preclinical evidence suggests that VNS may regulate cytokine expression by upregulating High mobility group box protein 1 (HMGB1) through activation of the cholinergic anti-inflammatory pathway (CAP), a loop formed of ascending vagus afferents, autonomic brain stem, forebrain cortical structures and descending vagus efferents [reviewed in (14)]. Therefore, application of VNS in NORSE patients may provide an immediate and controllable way to modulate ictogenesis and further brain injury due to unremitting seizures and inflammation.

3. Reported cases of VNS use in NORSE/FIRES

We searched ClinicalTrials.gov, and PubMed databases using the following search strategy (Supplementary Figure 1 Search criteria): ("VNS" OR "vagal nerve stimulation" OR "vagus nerve stimulation") AND ("New-onset refractory status epilepticus" OR "NORSE" OR "FIRES" OR "Febrile infection-related epilepsy syndrome"), including cases summarized in previous systematic reviews (9, 15). We reviewed individual case descriptions and excluded patients that did not fulfill the current definitions of NORSE and FIRES (1). Reports included individual case reports and case series; four reports were published as abstracts only (16–18). The amount of detail included in the cases reviewed varied substantially and the description of VNS stimulation parameters and titration protocols was not uniform. Of the 15 cases of NORSE treated with VNS identified (Table 1), 10 were adult (age range 19–49 years) and five pediatric cases (age range 17 months—14 years), nine were male and six female. Eight cases fulfilled criteria for the subtype FIRES, including all five pediatric cases. An etiology was identified in six adult cases [four NMDAR encephalitis (17, 18, 20, 23), one Human Parvovirus B19 infection (25), one AntiGluR encephalitis (22)], eight cases described negative investigation results and could be classified as cryptogenic (cNORSE) (16, 18–21, 24, 25). When documented, patients had tried multiple antiseizure medications (seven cases, average >5) and anesthetic agents (10 cases, average >3) with propofol, ketamine and midazolam the most commonly used anesthetic agents in order of frequency of use. Five patients were started on the ketogenic diet (16, 17, 19), without aborting status epilepticus, although adequacy of ketosis was never documented. In nine cases, a trial of immunosuppression was described, with most patients undergoing a combination regime of pulsed steroids [six cases (6, 16, 18–20, 22)], followed by ivIg [six cases (6, 16, 18–20, 22)], Plasma exchange [four cases (6, 16, 22, 25)] or Rituximab [two cases (19, 25)].

3.1. Timing of VNS implantation and titration protocols

VNS was implanted in the acute phase of NORSE in five cases (range 14–30 days from onset), in the chronic phase of treatment-resistant epilepsy (TRE) in seven cases (range 43 days—9 years from onset, Table 2). For the purposes of this article, we defined the acute phase of NORSE, as occurring within the first 30 days of NORSE onset, hypothesizing this to be the phase of acute inflammation and epileptogenesis, based on our experience and the available literature on clinical, electrographic and imaging evolution in NORSE (2–4). Details of VNS parameters and titration paradigms are summarized in Table 2. When documented, VNS was activated either on the same day of implantation or within the first 2 weeks after implantation: output current was rapidly increased (range 0.25–0.75 mA/24 h) to peak amplitudes of 0.5–3 mA achieved over 7–21 days. The most commonly used initial stimulation frequencies were 20–30 Hz, pulse widths of 250–500 μs, the latter later widened to 750 μs. Duty cycle settings started in the "conventional" range (30 s on/3 min off) with increases every 2–7 days. Whilst most cases remained in the conventional cycling range, the fastest cycling documented was 7s on/14s off (24). VNS resulted in a significant clinical change in 10 cases, an average of 16.3 days after implantation when documented (range 3–42 days). Eight reports documented the last drug modification or intervention before status cessation, albeit this was performed long before the 24 h suggested by Redecker et al. (26) as the most appropriate measure for the evaluation of efficacy of an ASM in the treatment of SE: in one case Perampanel was added (16), one case had Perampanel and Topiramate introduced (19), one completed a course of Rituximab on the same day as seizures were aborted and hence may have drawn additional benefit from previous Rituximab treatments (20),

TABLE 1 Patient characteristics, details of VNS implantation and stimulation parameters in published NORSE cases.

References	Age (year)	Diagnosis/etiology	Duration of NORSE before VNS	Day of VNS activation after implantation	Day of clinical change after implantation	VNS settings at clinical change	Seizure outcome	Last intervention before seizure reduction
Bonardi et al. (6)	14	FIRES, cryptogenic	43 days	0	29	OC = 2.25 mA; DC = 16%	Cessation of status	CBD
Luo et al. (19)	1 year 5 months	FIRES, cryptogenic	14 days	15	42	OC = 3mA, PW = 750 μs, ON = 14s, OFF = 1.8 min	Cessation of status	PRP and TPM
Espino et al. (20)	37	FIRES, cryptogenic	30 days	0	7	OC = 1.75 mA, F = 20 Hz, PW = 250 μs, ON = 30 s, OFF = 30 min	Abortion of SE but lifelong epilepsy	Rtiuximab
Espino et al. (20)	33	NORSE, NMDAR encephalitis	9 years	–	–	–	Initial improvement but then no change in seizure frequency	–
Kurukumbi et al. (21)	25	cNORSE	8 days	–	3	–	Seizure free day 3, recurrence of seizures day 6	Magnet swiping 2mA, 60s on
Yamazoe et al. (22)	24	FIRES, anti-GluR encephalitis	14 months	4	10	OC = 0.5mA, PW = 500 μs, ON = 21s, OFF = 3 min, DC = 12%	Seizure free at 2 months, recurrence after 3 months, seizure free at 1 year	None
Alsaadi et al. (23)	46	FIRES NMDAR encephalitis	110 days	0	7	OC = 2.5 mA, ON = 30 s, OFF = 5 min		None
Hoang et al. (16)	40	cNORSE	Unknown	–	–			PRP
Howell et al. (24)	14	cNORSE	14 days	–	–	OC = 1.75mA	–	–
Howell et al. (24)	9.2	cNORSE	–	–	–	–	Seizure reduction by 30%–40%	–
Howell et al. (24)	8.3	cNORSE	–	–	–	–	Seizure reduction by 30%–40%	–
Lin and Ko (17)	19	NORSE, NMDAR encephalitis	Weeks	–	–	–	–	–
Lin and Ko (17)	49	cNORSE	Months	–	–	–	–	–
Shatzmiller et al. (18)	19	NORSE, NMDAR encephalitis	–	–	–	–	–	Cyclophosphamide
Skaff and Labiner (25)	27	NORSE, Human Parvovirus B19 infection	>52 days	–	–	–	Cessation of status	–

CBD, cannabidiol; DC, duty cycle; —, not documented; NORSE, new-onset refractory status epilepticus; FIRES, febrile infection-related epilepsy syndrome; OC, output current; PRP, perampanel; PW, pulse width; TPM, topiramate; VNS, vagal nerve stimulation.

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TABLE 2 Summary of outcomes in published NORSE cases treated with VNS.

References	Outcome	Adverse events due to VNS	Last time point of review	ongoing numbers of ASM	Chronic epilepsy	cognitive outcome	level of function
Bonardi et al. (6)	Alive	Coughing and tachycardia, current reduced to 1.75 mA	12 months	Multiple	8 months seizure free	Normal and fluent speech, resumed home schooling	Walking with assistance
Luo et al. (19)	Alive	–	166 days	4 (TPM, VPA, LEV, PER)	Seizure free	Verbal and social behind normal limits	Walk without assistance
Espino et al. (20)	Alive	–	730 days	–	Daily FIAS	Moderate global cognitive and mild emotional involvement, affecting her social life	—-
Espino et al. (20)	Alive	–	2 years after implantation or 11 years after NORSE	–	12 seizures/d	Cognitively impaired	On disability support
Kurukumbi et al. (21)	Death due to comorbidities d17	–		–			
Yamazoe et al. (22)	Alive	–	1 year	–	Seizure free	Severely impaired	Wheelchair assistance
Alsaadi et al. (23)	Alive	–	8 months	0	–	Mild-moderate cognitive impairment	–
Hoang et al. (16)	Alive	–	1 ms after PRP	5	–	–	Not documented, discharge to IP Rehab
Howell et al. (24)	Died d29 in multiorgan failure, no inflammation on postmortem					–	–
Howell et al. (24)	Alive	–	23 years	2–4	–	Mild-mod ID language and memory deficits normal behavior	
Howell et al. (24)	Alive	–	26y	2–4	–	Mod ID language and verbal memory deficits Mild behavior disorder	
Lin and Ko (17)	Alive	–	–	–	–	–	–
Lin and Ko (17)	Alive	–	–	–	–	–	–
Shatzmiller et al. (18)	Alive	–	–	–	–	–	–
Skaff and Labiner (25)	Alive	–	–	–	–	–	–

FIAS, focal impaired awareness seizures; LEV, levetiracetam; PER, perampanel; TPM, topiramate; VNS, vagal nerve stimulation; VPA, valproate.

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one four pulses of cyclophosphamide (18) and one commenced on CBD oil (21), whilst in two cases VNS was the documented last intervention.

3.2. Outcomes

Cessation of super-refractory status was ascribed to VNS in two cases implanted in the acute (19, 20) and two in the chronic phase (21, 23). Status epilepticus is defined as refractory when it does not respond to first-line benzodiazepines and second-line antiseizure medicines, requiring general anesthesia: if refractory status persists or recurs 24 h or more after general anesthesia or recurs on withdrawing anesthetic medication it is defined as super-refractory (27, 28). Improvement in seizures but then recurrence was documented in two cases (20, 21), no effect in one (24), whilst sustained seizure reduction was documented in three cases: by 30%−40% in two (24), in one enabling weaning of anesthetic agents and leaving the ICU (23). Long-term outcomes were available for 12 cases (summarized in Table 2) and were documented between 1 month−26 years after implantation: two cases implanted in the acute phase died due to multiorgan failure or comorbidities (21, 24). Three patients were documented as seizure-free survivors, seven have ongoing chronic epilepsy (16, 20, 21, 24, 25). Bradycardia as side effect of Vagal Nerve Stimulation was the only adverse event due to VNS documented in one case (24). Functional outcomes were documented in eight survivors: the best cognitive outcome was documented in a 14-year old female (21) who resumed home schooling with normal and fluent speech. In both patients implanted in the acute and chronic phase, cognitive outcomes ranged from at least mild to severe cognitive impairment, whilst the only case described as walking without assistance was implanted in the chronic phase.

4. King's college hospital experience

Two adult cases of NORSE were implanted at our center:

Case 1—Late implantation of VNS in TRE phase of NORSE

A 54-year old female was implanted in the chronic phase of NORSE (day 67 from onset) and had failed multiple standard antiseizure medications, anesthetic agents and trials of immunosuppression (steroids, ivIg, Plasma Exchange). Our patient had also undergone an unsuccessful trial of electroconvulsive therapy and repetitive transcranial magnetic stimulation. VNS was switched on immediately after insertion, initial stimulation started with 0.5 mA output current, and gradually increased to 2 mA, 30 Hz, 500 μS, with a duty cycle of 35% (30 s ON and 1.1 min OFF). Case Ictal activity on EEG resolved on day 2 after implantation, allowing gradual tapering of clonazepam and anesthetic agents, and leaving the ICU. She died 46 days after VNS implantation due to an obstructed tracheostomy and cardiac arrest.

Case 2—Early implantation of VNS in acute phase of NORSEin pregnancy

A 30-year old pregnant female in the first Trimester of pregnancy was implanted with VNS in the acute phase (day 26 from onset) of NORSE possibly linked with drug overdose. She had also failed multiple standard antiseizure medications, anesthetic agents and trials of immunosuppression including Anakinra. VNS was switched on the day of implantation with initial output current of 0.25 mA. Output current was further uptitrated to 1 mA in the following 72 h, and increased to 1.25 mA on day 7 post-op. Our patient experienced improvement of myoclonic jerks from day 7 post-implantation and became seizure-free from day 20 post implantation. She regained functional independence during inpatient rehabilitaton, delivered a premature but healthy baby at 33 weeks and has remained seizure free to date (last reviewed 8 months from onset).

5. Discussion and perspectives for future research

Studying rare and complex diseases such as NORSE in the real clinical world is challenging, as patients may be subject to multiple and concomitant interventions and the presence of publication bias toward cases with good outcomes is very likely. Due to the paucity of cases and the variable amount of information available within each report, the level of evidence supporting the use of VNS in NORSE is low. Nevertheless, we feel that from the cases summarized in the previous sections and our experience, some general conclusions can be drawn: overall, VNS was a well-tolerated intervention without significant adverse effects in the short or long term, both in cases implanted acutely or in the TRE phase, supporting its safety even in pregnancy. Whilst it is not possible to determine a stimulation threshold effect leading to seizure cessation, most patients had VNS switched on either immediately or within the first few weeks of implantation at conventional—not high frequency—cycling rates and the output current increased over a short period of time (days to weeks). In the three cases, including ours (22, 23), where VNS was the last intervention before seizure cessation, clinical changes occurred within 7–10 days of implantation and benefit was sustained long term, in keeping with a recent meta-analysis of the effect of VNS in refractory status epilepticus (9). Beneficial effects reported include not only cessation of status but also the ability to wean anesthesia and assess patients's level of consciousness and neurological status. These positive effects were reported when VNS is implanted both in the acute and TRE phase. Since most if not all NORSE survivors go on to develop chronic epilepsy (2, 4, 5), we suggest that implanting VNS in NORSE should always be considered for its chronic neuromodulatory effect to reduce seizure burden in the long term and may also aid reducing ASM burden. Whether earlier implantation allows earlier control of status by acutely desynchronizing ictal rhythms and limiting seizure spread, and whether it would lead to better functional outcomes is unknown and should be put to the test in future trials. At King's College Hospital, a Charles Sykes Memorial Grant is supporting the set up of a multi-center "N-of-1 trial" series to study the efficacy and mechanism of action of VNS in the treatment of NORSE. N-of-1 trials are considered to be among the most relevant and rigorous study designs for assessing individual patent's treatment efficacy in rare diseases, such as NORSE, where a conventional randomized trial design would not be feasible. We will embed this study into a UK-wide NORSE network (NORSE-UK), including all major tertiary neuroscience centers in the UK, and would welcome international collaborators. Our research will develop

electrophysiological and serological biomarkers to predict and monitor response to VNS in NORSE, and may become relevant for the treatment of other drug resistant forms of SE.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

LMR and RS designed the work. LMR wrote the manuscript. Both authors revised the manuscript, read and approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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A practical approach to in-hospital management of new-onset refractory status epilepticus/ febrile infection related epilepsy syndrome

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New-onset refractory status epilepticus (NORSE) is "a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic, or metabolic cause." Febrile infection related epilepsy syndrome (FIRES) is "a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 h before the onset of refractory status epilepticus, with or without fever at the onset of status epilepticus." These apply to all ages. Extensive testing of blood and CSF for infectious, rheumatologic, and metabolic conditions, neuroimaging, EEG, autoimmune/paraneoplastic antibody evaluations, malignancy screen, genetic testing, and CSF metagenomics may reveal the etiology in some patients, while a significant proportion of patients' disease remains unexplained, known as NORSE of unknown etiology or cryptogenic NORSE. Seizures are refractory and usually super-refractory (i.e., persist despite 24h of anesthesia), requiring a prolonged intensive care unit stay, often (but not always) with fair to poor outcomes. Management of seizures in the initial 24–48h should be like any case of refractory status epilepticus. However, based on the published consensus recommendations, the first-line immunotherapy should begin within 72h using steroids, intravenous immunoglobulins, or plasmapheresis. If there is no improvement, the ketogenic diet and second-line immunotherapy should start within seven days. Rituximab is recommended as the second-line treatment if there is a strong suggestion or proof of an antibody-mediated disease, while anakinra or tocilizumab are recommended for cryptogenic cases. Intensive motor and cognitive rehab are usually necessary after a prolonged hospital stay. Many patients will have pharmacoresistant epilepsy at discharge, and some may need continued immunologic treatments and an epilepsy surgery evaluation. Extensive research is in progress now via multinational consortia relating to the specific type(s) of inflammation involved, whether age and prior febrile illness affect this, and whether measuring and following serum and/or CSF cytokines can help determine the best treatment.

KEYWORDS

new-onset refractory status epilepticus, febrile infection related epilepsy syndrome, anakinra, tocilizumab, rituximab, super-refractory status epilepticus, neuroinflammation, autoimmune encephalitis

Introduction

Status epilepticus (SE) is a neurologic emergency. A third of patients fail to respond to benzodiazepines and one other anti-seizure medication (ASM) and are, therefore, by definition (failing two ASMs), classified as having refractory status epilepticus (RSE) (1, 2). Attempts at seizure control are accompanied by simultaneous evaluation for the underlying etiology, the targeted treatment of which is essential to stop the seizures. In a significant minority of patients, an extensive diagnostic workup fails to reveal the cause of SE. This group represents two-thirds of *de novo* refractory status epilepticus (3).

A multinational panel of experts defined new-onset refractory status epilepticus (NORSE) as "a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic, or metabolic cause. This includes patients with viral or autoimmune causes. If no cause is found after extensive evaluation, this is considered 'cryptogenic NORSE'." Febrile infection-related epilepsy syndrome (FIRES) is "a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 h before the onset of RSE, with or without fever at the onset of SE. This applies to all ages. There may or may not be fever at the onset of SE (4)." Patients with FIRES account for the majority (~90%) of pediatric NORSE (5). The rarity of NORSE and the varied etiologies (when one is identified) have challenged impactful research in understanding the therapeutics. Numerous case reports, series, and reviews have been published (6), but there have been no randomized controlled trials to guide management.

A 2017 survey of neurointensivists showed that two-thirds of responding institutions did not have a protocol for evaluating and managing NORSE, a quarter of respondents would not perform autoimmune work-up, and a third would never use Intravenous immunoglobulins (IVIG) (7). In the absence of direct evidence guiding management and the variability in management practices shown in this survey, standardization of terminology was felt to be an important first step, followed by consensus recommendations for clinical management. Standardized terminology was proposed for NORSE and FIRES at the first International NORSE/FIRES Symposium in 2017 in Salzburg, Austria, conducted before the 6th Colloquium on Status Epilepticus and Acute Seizures, resulting in the definitions above (4). A recent Delphi study attempts to guide management; this was conducted to map the existing literature and multinational, multidisciplinary expert opinion to a list of consensus recommendations for treating NORSE/FIRES in all age groups (8). After a literature review, 48 experts rated the recommendation statements regarding diagnosis, treatment, and research directions on a scale of 1 (strong disagreement) to 9 (strong agreement). The consensus was reached (the statement was appropriate) if it received a median score of ≥7, whereas inappropriate if the median score was three or less. The analysis of evidence was mapped to the results of each statement included in the Delphi study. However, the evidence supporting most recommendations is limited; thus, these are intended to be considerations rather than strict guidelines.

Methods

Relevant articles from the annotated reference list of over 130 articles on NORSE/FIRES maintained by the NORSE institute were chosen for a detailed review (6). This list was last updated in July 2022 with input from the authors and other members of the NORSE Institute. In addition, Pubmed and Google Scholar searches were performed using the search terms "NORSE," "FIRES," "new-onset refractory status epilepticus," "febrile infection-related epilepsy syndrome," "refractory status epilepticus," and "super-refractory status epilepticus" to generate the updated articles for review, including those published after July 2022. Permission was obtained to use the tables listing diagnostic evaluation on the NORSE institute website, and these were revised based on the updated article review. A flowchart was created to show an algorithmic approach to evaluating and managing NORSE/FIRES based on the information obtained from the review of the articles.

Diagnostic approach

Acute management of adults with NORSE/FIRES should be primarily directed by neurointensivists when available and in consultation with a multidisciplinary team, including epilepsy, rheumatology, and immunology, at a center with the capability for continuous EEG monitoring (cEEG) and ideally at a tertiary care center with expertise in RSE, including NORSE (8, 9). By the time NORSE is suspected, the initial evaluation, including blood counts, chemistry, liver/renal function parameters, electrolytes, toxicology screen, CNS imaging, and preliminary CSF analysis, have been done and have failed to determine a cause for the RSE. There have been a few papers published suggesting a timed approach to the evaluation and management of NORSE/FIRES (9, 10). In Figure 1, we incorporate the suggestions from these papers to the most recent consensus recommendations obtained via the Delphi methodology and a literature review to create a comprehensive algorithm to guide the diagnosis and management of NORSE/FIRES (8, 9).

Blood/CSF investigations

Table 1 section 1 lists the tests to consider in the initial evaluation of blood/serum/CSF. Section 3 of Table 1 shows the additional blood/serum tests to consider if, on history, any high-risk features are suspected, such as an immunocompromised state or geographic, seasonal, or occupational exposure. Additional testing may be necessary for specific possible zoonotic exposures (shown in section 4 of Table 1) or exposure to drugs and toxins (section 5). This aligns with the expert consensus to obtain a comprehensive infectious evaluation in all patients, including cultures and viral and bacterial serology relevant to the geographic region and season (sections 1–3) (8, 9). In addition to the above, the expert consensus recommends obtaining the following tests in all or most patients in the initial 48 h (8): Comprehensive rheumatologic evaluation (section 9), evaluation for inborn errors of metabolism in young children (section 10), autoimmune and onconeural antibody panel (section 9), and extra blood and CSF samples for storage for future analysis (e.g., cytokine and genetic analyses) (section 11).

Additional CSF testing

CSF cytokines may serve as markers of disease progression and may help choose treatment (8, 9, 27). A strong suggestion towards the involvement of innate immunity in the pathogenesis of FIRES was

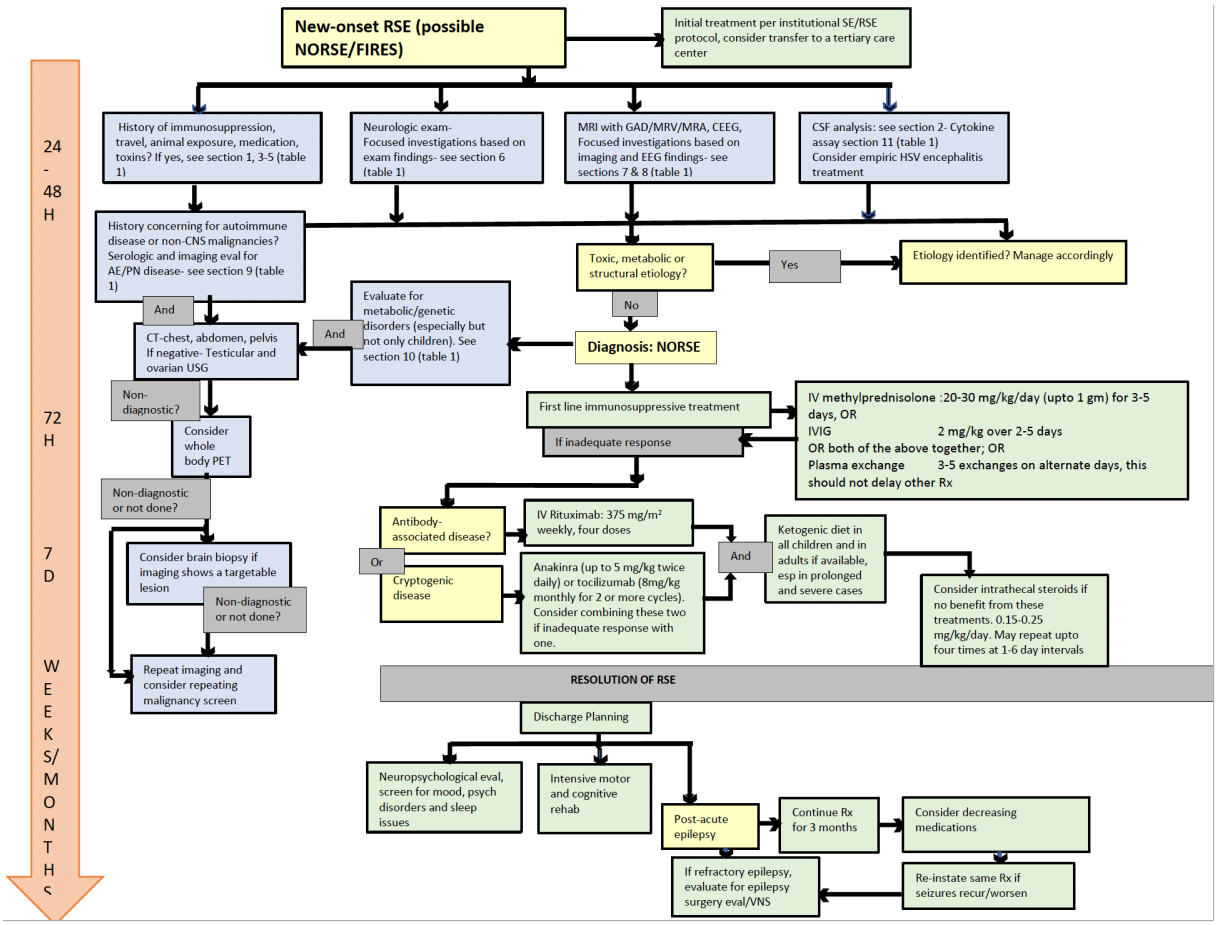

FIGURE 1
Flow diagram for evaluation and management of NORSE/FIRES. NORSE, new onset refractory status epilepticus; FIRES, febrile infection-related epilepsy syndrome; SE, status epilepticus; RSE, refractory status epilepticus; GAD, gadolinium; MRV, magnetic resonance venogram; MRA, magnetic resonance angiography; CEEG, continuous EEG; USG, ultrasonography; PET, positron emission tomography; HSV, herpes simplex virus; VNS, vagus nerve stimulator. Diagnostic consideration. Diagnostic procedure. Treatment. Outcome assessment. Clinical management timeline.

shown in a prospective case-control study of FIRES in children that showed a selective upregulation of proinflammatory cytokines (IL-6) and chemokines (IL-8/CXCL-10) in FIRES when compared against the control groups of inflammatory and non-inflammatory CNS disorders (11). In contrast, most T-cell-associated cytokines (IL-2, IL-17A, etc.) and homoeostatic chemokines (CCL21, CXCL12, etc.) remained unchanged or were downregulated.

Another study showed Th1-associated cytokines and chemokines to be elevated in FIRES compared to a broader network of cytokine and chemokine elevation in encephalitis (28).

In a single patient, elevated CSF proinflammatory cytokines (IL-8 and IL-6) before treatment normalized after anakinra when seizure control was obtained as well (29). Although CSF and serum levels of endogenous IL-1R antagonist are elevated in FIRES, a functional deficiency likely fails to block the IL-1R signaling as reported in the CSF of this single patient. Anakinra treatment can overcome this deficiency as post-treatment CSF showed a robust suppression of IL-1R signaling in response to IL1β (12). Other studies have shown seizure termination after administering IL-1 antagonists (such as anakinra) and IL-6 blockers, such as tocilizumab (13), in patients with NORSE. Thus, although no randomized trials or other definitive studies have been performed, CSF cytokine assay should be considered in all patients to help assess and characterize neuroinflammation, follow disease severity and progression, and guide the selection of targeted immunotherapies (section 11, Table 1).

Metagenomic next-generation sequencing is a comprehensive evaluation of microbial and host genetic material (DNA/RNA) in the CSF that aims to identify the presence of any non-human genetic material (i.e., infectious agents). This has largely been used in research, mostly related to encephalitis, and is now available for clinical use (14). Whenever possible, extra CSF should be stored for future autoimmune antibody testing, cytokine assay, and metagenomic analysis.

Imaging

MRI brain with gadolinium should be performed in all patients without contraindications within 48 h of presentation (8). Additional testing with MR or CT venogram/angiography should be performed if there is a suspicion of vascular malformations, cerebral venous

TABLE 1 List of heterogeneous etiologies of NORSE/FIRES and the diagnostic tests to consider (4, 8, 9, 11–26).

Section 1: Initial metabolic/infectious work up

Blood:

- CBC, BMP, LFT, BUN, Electrolytes (Ca, Mg, Phos), ESR, CRP, bacterial and fungal cultures

Serum:

- RPR-VDRL, HIV-1/2 immunoassay with confirmatory viral load if appropriate, PPD placement, IgG and IgM testing for *Chlamydia pneumoniae*, *Bartonella henselae*, *Mycoplasma pneumonia*, *Coxiella burnetii*, *Shigella* species, and *Chlamydia psittaci*
- Anti-neuronal surface antibody panel and onconeural antibodies (see below)
- Cytokines (see below)

Nares:

- Respiratory viral DFA panel

Section 2: CSF studies

- Cell count and differential count, protein, glucose, lactate and pyruvate (ratio lactate/pyruvate). Bacterial and fungal stains and cultures.
- PCR for HSV1, HSV2, VZV, EBV, HIV, *C. pneumoniae*, *B. henselae*, *C.burnetti*, *C psittaci*, *Shigella* species, VDRL, M Tb PCR.
- Immunoelectrophoresis/electrofocusing and cytology
- Anti-neuronal surface antibody panel and onconeural antibodies (see below)
- Cytokines (see below)
- Store CSF for metagenomic next-generation sequencing

Section 3: Focused testing for high-risk features

Recommended in immunocompromised patients:

- Serologic: IgG *Cryptococcus* species, IgM and IgG *Histoplasma capsulatum*, IgG *Toxoplasma gondii*
- Sputum: M Tb Gene Xpert (molecular test for tuberculosis)
- CSF: Eosinophils, silver stain for CNS fungi, PCR for JC virus, CMV, EBV, HHV6, EEE, Enterovirus, Influenza A/B, HIV, WNV, Parvovirus. Listeria Ab, Measles (Rubeola), Toxoplasma IgG
- Stool: Adenovirus PCR, Enterovirus PCR

Recommended if geographic/seasonal/occupational risk of exposure:

- Serum: buffy coat and peripheral smear (for parasitic infections such as malaria, babesiosis, toxoplasmosis etc.), Lyme EIA with IgM and IgG reflex, *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Baylisascaris procyonis*
- Serum and CSF: samples to CDC DVBID Arbovirus Diagnostic Laboratory, CSF and serum Rickettsial disease panel, Flavivirus panel, Bunyavirus panel
- Other optional: see attached table for further geographical/zoonotic risk factors

Section 4: Additional zoonotic/geographic exposure considerations

Ingestion:

- Unpasteurized milk: Tick-borne virus, *C. burnetii*
- Star fruit: caramboxin, oxalic acid

Geographical factors:

(residence, recent travel)

- Africa: West Nile virus
- Australia: Murray Valley Encephalitis virus, Japanese Encephalitis virus, Hendra virus, Eastern Equine virus, Western Equine virus, Venezuelian Equine virus
- Central and South America: Saint-Louis virus, *Rickettsia* spp. West Nile virus, Tick-borne virus, *Ehrlichia chaffeensis*/*Anaplasma phagocytophilum*
- Europe: Japanese virus West Nile virus
- India, Nepal: Tick-borne virus
- Middle East, Russia, Southeast Asia, China, Pacific Rim: Japanese virus, Tick-borne virus, Nipah virus

Seasonal factors:

- Late summer/early fall or winter: arboviruses, enteroviruses, influenza virus

Animal exposure:

- Cats—*B. henselae*, *T. gondii*
- Horses—Eastern Equine virus, Western Equine virus, Venezuelian Equine virus, Hendra virus
- Raccoons—*Baylisascaris procyonis*
- Rodents—*Bartonella Quintana*, Eastern Equine virus, Western Equine virus, Tick-borne virus, Powassan virus, LaCrosse virus
- Sheep and goats—*C. Burnetii*
- Swine—Japanese virus, Nipah virus

Insect exposure, including travel to infested area:

- Mosquitoes: EEE, WEE, Venezuelan Equine virus, Saint-Louis virus, Murray Valley virus, Japanese virus, West Nile virus, La Crosse virus Tick-borne virus, Powassan virus, *Rickettsia* spp.
- Ticks: *E. Chaffeensis*/*A. Phagocytophilum*

(Continued)

TABLE 1 (Continued)

Section 5: Status epilepticus caused by drugs, toxins, or related to medical intervention

Drugs:

- Antibiotics: cephalosporins, carbapenems, quinolones isoniazid, mefloquine, chloroquine
- Antidepressants/antipsychotics: bupropion, tricyclic antidepressants especially amoxapine, selective serotonin reuptake inhibitors, venlafaxine, lithium
- Chemotherapy: platinum-based agents cytarabine, gemcitabine irinotecan interferon-alpha, interleukin-2
- Humanized monoclonal antibodies: bevacizumab, ipilimumab, rituximab, infliximab
- Tyrosine kinase inhibitors: imatinib, pazopanib, sorafenib, sunitinib, GMCSF, ifosfamide
- Immunosuppressive and immunomodulatory drugs: cyclosporine, tacrolimus, sirolimus, intravenous immune globulins, anti-TNF-alpha (etanercept), anti-lymphocyte globulin, high-dose steroids, immune checkpoint inhibitors, CAR-T cell related encephalopathy syndrome (CRES) with Chimeric Antigen Related-T cell therapy
- Other medications: lindane, permethrin, flumazenil, 4-aminopyridine (dalfampridine), sulfasalazine, theophylline, anti-histamines, opiates (morphine, tramadol)

Complementary and alternative medicines:

- Borage oil, neem oil

Environmental toxins:

- Lead, aluminum star fruit (oxalic acid, caramboxin), organophosphates, organochlorines and pyrethroids

Biotoxins:

- Scorpion toxin, anatoxin, ciguatoxin, domoic acid and cyanide

Substances:

- Benzodiazepines, amphetamines, cocaine, fentanyl, alcohol, ecstasy, heavy metals, synthetic cannabinoids, bath salts, LSD, heroin, PCP, marijuana

Consider:

- Extended opiate and overdose panel

Section 6: Neurologic exam

- Acute lower motor neuron syndrome: Japanese Encephalitis virus, West Nile virus, Tick-borne virus, Enterovirus (serotype 71, coxsackie)
- Acute parkinsonism: Japanese virus, Saint-Louis virus, West Nile virus, Nipah virus, *T. Gondii*
- Prominent oro-lingual dyskinesias, catatonia, neuropsychiatric and autonomic dysfunction: anti-NMDA receptor encephalitis
- Facio-brachial dystonic seizures, piloerection, paroxysmal dizzy spells and hyponatremia: anti-LGI-1 encephalitis
- Stiff person syndrome, hyperekplexia: anti-GAD 65
- Mood changes and movement disorder: anti-mGLU-R
- Sensory neuronopathy/autonomic dysfunction: ANNA-1/anti-Hu
- Stiff person syndrome, progressive encephalomyelitis with rigidity and myoclonus, transverse myelitis: anti-amphiphysin antibody, anti-glycine
- Ataxia—Epstein-Barr virus, mitochondrial disorder

Section 7: EEG findings

- Extreme delta brush: anti-NMDA receptor encephalitis
- Frontal-central slow wave contralateral to tonic-dystonic seizures: anti-LGI1 encephalitis
- Extreme spindles: *M. pneumoniae*
- Parieto-occipital epileptiform discharges and seizures: mitochondrial disorder including POLG1, PRES

Section 8: MRI findings

- Prominent mesial temporal lobe involvement: paraneoplastic and autoimmune limbic encephalitis, anti-VGKC complex encephalitis (e.g., anti-LGI-1, anti-CASPR2)
- Basal ganglia: Saint-Louis encephalitis virus, La Crosse virus, Murray Valley virus, acute necrotizing encephalopathy of childhood (RANBP2 mutation)
- Posterior reversible encephalopathy syndrome (PRES) images: symmetrical cortical and subcortical hyperintense signals on T2 and FLAIR-weighted images in the parieto-occipital lobes of both hemispheres
- Stroke-like images: POLG1, MELAS

Section 9: Auto-immune/paraneoplastic

Serum and CSF paraneoplastic and autoimmune epilepsy antibody panel:

- Antibodies to LGI-1, CASPR2, Ma2/Ta, DPPX, GAD65, NMDA, AMPA, GABA-B, GABA-A, glycine receptor, anti-Tr, amphiphysin, CV-2/CRMP-5, Neurexin-3alpha, adenylate kinase, anti-neuronal nuclear antibody types 1/2/3 (Hu, Yo and Ri), Purkinje cell cytoplasmic antibody types 1,2, GFAP-alpha, anti-SOX1, N-type calcium channel Ab, PQ-type calcium channel

Other serologies:

- ANA, ANCA, anti-thyroid antibodies, anti-TG anti-dsDNA, ESR, CRP, ENA, SPEP, IFE, antibodies to Jo-1, Ro, La, Scl-70, RA factor, ACE, anti-endomysium antibodies, cold and warm agglutinins
- Optional: consider storing extra frozen CSF and serum for possible further autoimmune testing in a research lab

Neoplastic:

- CT chest/abdomen/pelvis, scrotal ultrasound, mammogram, pelvic MRI, CSF cytology and flow cytometry
- Optional: bone marrow biopsy; whole body PET-CT; cancer serum markers.

(Continued)

TABLE 1 (Continued)

Section 10: Metabolic/genetic
Metabolic:
See section 1
• Ammonia, porphyria screen (spot urine), plasma and CSF lactate and pyruvate
• Consider: Vitamin B1 level, B12 level, pyridoxine, folate, CPK, troponin; tests for mitochondrial disorder (lactate, pyruvate, MR spectroscopy, muscle biopsy), tests for MAS/HLH (serum triglycerides and sIL2-r)
Genetic:
• Screens for MERRF, MELAS, POLG1 and VLCFA screen. Consider ceruloplasmin and 24-h urine copper
• Consider whole exome or whole genome sequencing (also look for gene polymorphisms in IL1B, IL6, IL10, TNFA, IL1RN, SCN1A and SCN2A), mitochondrial genome sequencing, CGH array and genetics consult
Section 11: Cytokine assay
• Cytokine assay for quantitative measure of-IL-1β, IL-1Ra, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-17A, CCL2/MCP-1, CCL3/MIP-1α, granulocyte colony stimulating factor (G-CSF), vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α), interferon gamma IFN-g
• Consider repeating the analyses during SE course

sinus thrombosis, reversible cerebral vasoconstriction syndrome, CNS vasculitis, etc. Prominent mesial temporal lobe involvement may be seen in autoimmune and paraneoplastic limbic encephalitis, such as anti-VGKC complex encephalitis (15). Prominent basal ganglia involvement may be seen in viral encephalitides such as La-Crosse virus encephalitis (see section 8, Table 1 for others), but can also occur with anti-LGI-1 encephalitis, acute necrotizing encephalopathy of childhood (related to mutations in RANBP2), and other conditions (16–18). Stroke-like images may be seen in POLG1-related CNS disease and other mitochondrial disorders such as MELAS. All of those conditions (and many others) can present as NORSE.

Repeat MRI later during the hospitalization and in outpatient follow-up should be considered in all patients. This helps monitor disease evolution for any new MRI changes, which may help indicate the etiology and/or aid in prognostication. A higher proportion of patients will show abnormalities on follow-up imaging than the initial imaging, as shown in a retrospective FIRES study where the follow-up brain MRIs were abnormal in 87% of studies; in contrast, initial MRI showed abnormalities in 38% of patients (30). Repeat MRI also helps in assessing long-term changes due to the underlying disease or as a result of prolonged seizures. Progressive brain atrophy was seen in all 19 patients with super-refractory status epilepticus in a prospective study, where the degree of atrophy correlated with the SE duration but did not correlate with functional outcomes (31). Repeat MRI may help in assessing disease prognosis as well. Higher grades of periventricular white matter changes, leptomeningeal enhancement on the initial MRI, and hippocampal atrophy on later MRIs predicted poor functional outcomes in one large series, as did extra-temporal lesion extension, including the claustrum (31–33). A 13-patient series of NORSE with limbic encephalitis from Korea observed that on follow-up imaging, 10/13 had extra-temporal lesion extension, most commonly to the claustrum (32). This was seen in all patients in another 31-patient series from Italy, about ten days after SE onset (often not present on the first scan), in the form of T2/FLAIR hyperintensity in bilateral claustra (34). While this sign was initially thought to be a part of the imaging changes related to prolonged ictal activity due to its observation in unusually severe cases of refractory status epilepticus, further studies are needed to clarify this. The two studies described here have shown a higher prevalence than any previous series. All patients in the study from Korea and 50% of those in the study from Italy had evidence of limbic encephalitis; autoimmunity has been proposed as a likely mechanism and a reason for the high prevalence of claustrum involvement in these studies. In our experience, the claustrum sign appears to be much less common in North America, but this warrants further investigation, regardless.

Magnetic resonance spectroscopy (MRS) should be considered in cases where inborn errors of metabolism (including mitochondrial disease) are suspected. Malignancy screening (CT of the chest, pelvis, and abdomen) should be performed in most or all patients with cryptogenic NORSE/FIRES, especially in adults. If negative, this should be followed by a testicular/ovarian ultrasound. Malignancy screening should include whole-body positron emission tomography (PET) when other testing remains negative, especially (but not only) in older adults (Figure 1) (8, 9).

Continuous EEG

Continuous EEG monitoring is necessary for the diagnosis of non-convulsive seizures and for monitoring treatment effects with various medications. Certain EEG findings may point to the etiology, such as extreme delta brush in autoimmune encephalitides, particularly anti-NMDA receptor encephalitis (35), extreme spindles in *Mycoplasma pneumoniae* related infections (36), and parieto-occipital location of seizures and discharges in mitochondrial diseases (37). Tonic-dystonic seizures preceded by a contralateral frontal-central slow wave (~580 ms and amplitude ~71 μV) on EEG are seen in anti-LGI-1 encephalitis (19, 20).

Genetic testing

The multinational expert panel agreed that genetic testing, including mitochondrial gene testing and neuroinflammation panel (38), should be considered early in young children and should be considered at some point in most patients with

cryptogenic NORSE/FIRES. This may be followed by whole exome sequencing (8, 9), as several rare genetic and mitochondrial disorders can cause status epilepticus. Mitochondrial disorders associated with mutations of the genes encoding the presynaptic dynamin 1-like protein (DNM1L) and the catalytic subunit of mitochondrial DNA polymerase gamma (POLG1) have been seen in NORSE (39–44). Mutations of genes encoding neuronal channels such as *SCN1A*, *SCN2A*, and *SCN10A* have also been associated with NORSE (45–47). However, despite phenotypic similarities with certain genetic epilepsies, extensive genetic evaluation for candidate genes *PCDH19*, *SCN1A*, and *POLG* mutations was unrevealing in a cohort of pediatric FIRES patients (48). Another study of exome sequencing in 50 individuals (29 patient-parent trios and 23 single probands) with pediatric FIRES showed no pathogenic variants in genes associated with epilepsy or neurodevelopmental disorders; HLA sequencing in 29 patients did not show any allelic associations when compared against 529 population controls (49).

Brain biopsy

Brain biopsy should be considered when a targetable lesion is identified by neuroimaging (and is not likely to be secondary to seizure activity) and avoided if there is no targetable lesion (8, 9). Neuropathology has been reported only rarely; when diagnostic, the findings have shown herpes simplex encephalitis, candida encephalitis, acute disseminated encephalitis vasculitis, necrotizing vasculopathy, and lymphocytic infiltration related to anti-GAD antibody disease (50, 51).

Only 15/197 (7.6%) patients were reported to have undergone a brain biopsy in a recent systematic review of NORSE/FIRES. In a series of 22 children with FIRES, only a third had a brain biopsy, and these revealed non-specific findings (52). In the absence of radiological lesions to target, the diagnostic yield of a brain biopsy was thought to be low by the expert panel. When brain biopsy is performed, metagenomic next-generation sequencing should be considered on the tissue for infectious disease evaluation, including for rare, unsuspected organisms.

Treatment approach

Attempts at controlling status epilepticus should run parallel with disease modification efforts of the presumed disease, even when the etiology is unknown. Acute treatment of seizures should be similar to treatment of RSE in any situation. However, in patients without a clear explanation for SE in the first day or two, one should strongly consider first-line immunotherapy in the form of steroids, IVIG, or plasmapheresis; the consensus recommendations are to start these within the first 72 h of the onset of RSE (8, 9).

Seizure suppression

Anti-seizure medications

The initial management of status epilepticus should be guided by local/institutional guidelines or published guidelines (53, 54). For convulsive status epilepticus, benzodiazepines are the first-line treatment. Levetiracetam, valproate, and fosphenytoin were equally efficacious as the second-line ASM for convulsive status epilepticus in the ESETT trial (55). If there is a concern for mitochondrial disorders, valproate should be avoided. Other ASMs available in an intravenous form for rapid administration, which are often appropriate for early use, include lacosamide, phenobarbital, and brivaracetam. If the parenteral medications fail to control the seizures, enteral medications can also be tried (via a nasogastric tube). Continuous EEG monitoring is required to manage these patients, even those beginning as convulsive SE, as the seizures virtually always become nonconvulsive. The medications that do not show efficacy should be discontinued to avoid the accumulation of ASM burden with the potential side effects from the polypharmacy. There is no data to suggest what specific anti-seizure medications or a combination might be effective in this setting. However, published expert consensus suggests treating seizures in patients with NORSE/FIRES the same as with other causes (8).

Anesthetics

Anesthetic drug use should be similar to treatment of RSE in other conditions during the initial 48 h of NORSE/FIRES management (8, 9). Current data do not support using one anesthetic agent over any other. The commonly used anesthetics are midazolam, propofol, pentobarbital, thiopental, and ketamine. High-risk patients should be monitored to avoid and treat propofol infusion syndrome (56). Propofol, pentobarbital, and thiopental should be used with caution in mitochondrial disorders due to possible association with hepatic dysfunction (42). Limited data have shown favorable hemodynamics with ketamine, or at least less hypotension than with other anesthetics (57). Pentobarbital or thiopental is usually considered after other anesthetics fail, as they are associated with hypotension, electrolyte abnormalities, infections, and ileus.

The neurocritical care society guideline for evaluating and managing status epilepticus discusses the dosing considerations for the above-described anesthetic agents (58). There are no high-quality data to support the intensity and duration of anesthetic agents. The titration of the anesthetic agent is guided by continuous EEG, with the goal being the suppression of seizures or a background pattern of burst suppression. Titration to suppression-burst was associated with a lower frequency of seizure recurrence than titration to suppression of seizures; however, it was also associated with a significantly higher frequency of hypotension in a meta-analysis (59) Neither the choice of the anesthetic agent nor the titration goal was associated with differences in the overall outcome. The guidelines recommend seizure control for 24–48 h before a gradual taper of the anesthetics with ASMs in place for maintenance; recurrence of seizures post-anesthetic wean warrants resumption of anesthesia, likely at a higher dose (58). While the usual goal is to suppress most or all seizures, if aiming for suppression burst, experts recommend an interburst interval of 10 s and to wean anesthetic over 6–12 h. A recent retrospective study of propofol used for RSE showed that a shorter trial at higher doses might be more effective and safer than the recommended therapeutic coma duration (60). In this study, the duration of an initial therapeutic coma longer than 35 h was associated with a higher risk of seizure recurrence following the anesthetic wean.

These findings align with a previous retrospective study of midazolam in RSE that showed lower mortality for a higher dose of midazolam (2.9 mg/kg/h) than a lower dose (0.4 mg/kg/h) (61). However, earlier retrospective studies have found therapeutic coma to be associated with poor outcomes, but the confounding effect of the refractoriness of SE (that required anesthetic use) could explain the poor outcomes. Therapeutic coma in the setting of focal status epilepticus, especially with fully or partially maintained awareness, has been argued against due to similar concerns shown in another study that looked at outcomes in generalized vs. focal status epilepticus (62). Expert recommendations favor managing focal status epilepticus without significant impairment of consciousness without anesthetics (63).

Ketogenic diet

The expert panel recommends starting the ketogenic diet in the first week of hospitalization in children still in RSE. It should be considered in all prolonged and severe cases, including in adults, if not already given in the first week. If enteral administration is not possible, parenteral administration should be considered (if expertise is available for guidance) (8, 9). The ketogenic diet was shown to effectively control seizures within a few days of ketonuria in a pediatric FIRES series (64, 65) and was the only therapeutic agent that possibly shortened the acute phase in a retrospective study of 77 children with NORSE (66). Retrospective studies of refractory and super-refractory status epilepticus in adults and children have shown the ketogenic diet to be effective with only mild side effects (67, 68). The feasibility of a ketogenic diet in adults with RSE in the intensive care setting has been shown in some reports; however, the institutional expertise may vary even at tertiary care centers (69, 70).

Disease modification

Steroids are the first-line immunologic agent and should be started within 72 h of admission, preferably earlier if the initial etiologic workup is complete. Methylprednisolone 20–30 mg/kg per day (max 1 gm) should be given for 3–5 days intravenously. Intravenous immunoglobulins can be an alternative to steroids (see Figure 1 for doses) or can be administered simultaneously with steroids (9). The response to first-line immunotherapy is often incomplete. Once infections are excluded, second-line immunologic treatment should start within seven days of the onset of RSE, but it has the potential to improve outcomes even if administered after several weeks. Rituximab is recommended if an antibody-mediated disease is suspected or confirmed. In cryptogenic NORSE, IL-1R antagonists or IL-6 antagonists should be used, at least based on the current (limited) state of knowledge (8, 9). There is not high-quality data supporting second-line immunotherapy use other than anecdotal experience. Additionally, the results from case reports and series should be interpreted cautiously due to the confounders of publication bias and a natural disease course. The expert panel recommendation is based on experience with these agents in other neuroinflammatory disorders and risk-benefit assessment. The evidence does not support using a specific agent for second-line immunotherapy.

Anakinra is a recombinant interleukin-1 receptor antagonist used to treat rheumatoid arthritis, Still's disease, and cryopyrin-associated periodic syndromes. Multiple case reports have shown the benefit of anakinra in NORSE/FIRES patients that fail first-line and second-line immunotherapy (71–73). A retrospective study of 25 children treated with anakinra for FIRES showed association of treatment with shorter duration of mechanical ventilation, ICU and hospital length of stay. One treatment discontinuation was noted due to infection (74). Anakinra has also been used in other CNS inflammatory disorders. Four out of twelve adult patients receiving anakinra for various cerebral autoinflammatory disorders (including primary progressive multiple sclerosis, ADEM, autoimmune encephalitis, NORSE) etc. showed good outcomes following treatment, and none had any serious adverse events (75, 76). Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor, which has been used in rheumatoid arthritis, giant cell vasculitis, and cytokine release syndrome. In a 7-patient series of NORSE, treatment with tocilizumab was effective for 6/7 patients that failed conventional immunotherapy, including rituximab (13). One was attributed to NMDA antibodies, but the rest were cryptogenic. All patients had a prolonged course ranging from 16–75 days and failed multiple drugs and three anesthetic agents. Adverse events included severe infections in 2 and leukopenia in 3. Outcomes were not significantly different from other series, but the authors argue that this series was likely biased by including prolonged and severe cases; earlier administration of tocilizumab may have the potential for better outcomes. In cryptogenic cases of NORSE, failure of benefit with anakinra does not preclude a trial of tocilizumab, and vice-versa (77, 78).

In a series of the chronic phase of FIRES, anakinra was effective in 3/5 patients with a significant reduction in seizure burden without additional serious adverse effects. One patient had to be switched to tocilizumab due to inefficacy. This was studied against a control group that included nine patients, and only one had mild improvement in seizure frequency in a 6-month follow-up period (78–80). Randomized controlled studies are necessary to shed further light on the efficacy of disease-modifying treatment but are challenged by the rarity of this condition.

Other treatments: neuromodulation/ cannabidiol/hypothermia/intrathecal steroids

Non-invasive and invasive neuromodulation methods are feasible as a treatment option for super-refractory status epilepticus, including NORSE. Transcranial magnetic stimulation, electroconvulsive therapy, vagus nerve stimulation, and deep brain stimulation have all been sporadically used to manage super-refractory status epilepticus with variable benefits (80).

Similarly, there are isolated case reports of positive results with responsive neurostimulation with and without focal brain resection for super-refractory status epilepticus and NORSE/ FIRES (81, 82). Current evidence does not support cannabidiol or hypothermia as a first or second-line treatment (8, 9). Functional outcomes were no different between the hypothermia and control groups in a randomized control trial for convulsive SE (83, 84). It has been reported to be effective in a few cases, but the level of

evidence is likely inadequate to justify the risks at the current time (85, 86). Lastly, intrathecal steroids have been used: In a study of six children with FIRES, a shorter time from disease onset to treatment with intrathecal dexamethasone correlated with a shorter ICU stay and mechanical ventilation with no serious adverse events (87). Intrathecal steroids have the potential to shorten the acute stage of the disease, but further studies are needed.

Palliative care

NORSE is a heterogeneous condition whose etiology remains unidentified in many patients leaving the prognosis uncertain. Physicians should keep open communication with family regarding prognosis and the uncertainty involved. The palliative care team can effectively facilitate these conversations with the family and many other aspects of care and should be involved early. It is important to recognize that consulting palliative care does not mean that aggressive treatment is being abandoned; i.e., palliative care is not equivalent to hospice care. Due to the involvement of multiple specialists over a long period of time, identifying a lead physician that integrates all the data to present to the family is desirable (88, 89).

Discharge planning

Most patients will benefit from intensive motor and cognitive rehabilitation before a home disposition. Many will need ongoing immunologic treatments and multiple anti-seizure medications (ASMs) to manage pharmacoresistant epilepsy. Some patients (those with cryptogenic NORSE) will benefit from an ongoing evaluation with repeat imaging, including brain MRI and consideration of repeat imaging for malignancy screen. In those with poor seizure control, surgical evaluation for epilepsy surgery should be considered (Figure 1).

Outcomes/chronic disease

Mortality during the acute phase is seen in 13%–30% of adults and children (40, 90). Of the survivors, about two-thirds develop epilepsy (higher in pediatric series and lower in adults), with about half being drug resistant (40, 91). Poor functional outcomes are seen in about two-thirds of survivors. Studies of children with FIRES have shown that functional outcomes improve in most patients over time, with good outcomes (though usually not return to baseline) seen in two-thirds of the survivors at the last follow-up. A good outcome has been reported despite a prolonged therapeutic coma lasting for several months during the acute hospitalization (92).

Most patients need anti-seizure medications at discharge. If no clinical seizures are seen for three months following discharge, medication taper can be attempted with the goal of discontinuation. Prolonged EEG (24–72 h), usually performed in the outpatient setting (ambulatory EEG), can guide medication taper. For patients with continued drug-resistant epilepsy, immunotherapy (rituximab/anakinra/tocilizumab) should be continued at discharge, with a re-assessment of the need at three months. Patients who continue to have seizures despite use of ASMs, with or without immunotherapy, should be evaluated for epilepsy surgery, including neuromodulation.

Conclusion

NORSE, including its subtype of FIRES, is a rare and often devastating condition that presents with refractory and often super-refractory status epilepticus. The etiology is heterogeneous, with no definite one found in the majority of cases, but inflammation with activation of innate immunity is likely an important component of the pathophysiology in many cases, especially the cryptogenic ones. Early treatment with first-line immunotherapy and timely introduction of the ketogenic diet and IL-1R/IL-6 antagonists should be considered in most super-refractory patients. The current evidence to support these treatments is limited, but several multinational research efforts are ongoing to help elucidate the pathogenesis and to study treatment options systematically. One such collaboration resulted in the creation of the NORSE Institute and an active biobank that is collecting and analyzing samples from patients with NORSE/FIRES around the world.[1] The same website provides frequently-updated resources for clinicians, researchers, patients and families.

Author contributions

ZS conceptualized the manuscript framework, did a literature review, drafted the manuscript, created the figure, and edited the tables. LH edited and revised the manuscript and contributed to the figure and tables. All authors contributed to the article and approved the submitted version.

Conflict of interest

ZS is a member of the medical and scientific advisory board of the NORSE institute. LH has received consultation fees for advising from Accure, Aquestive, Ceribell, Eisai, Marinus, Medtronic, Neurelis, Neuropace, and UCB; royalties from Wolters-Kluwer for authoring chapters for UpToDate–Neurology and from Wiley for coauthoring the book Atlas of EEG in Critical Care by Hirsch and Brenner; and honoraria for speaking from Neuropace, Natus, and UCB. He serves as the co-chair of the medical and scientific advisory board of the NORSE institute.

Publisher's note

1 https://www.norseinstitute.org/

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Safe and effective implantation and use of vagal nerve stimulation in new-onset refractory status epilepticus in early pregnancy: a case report

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Introduction: The management of new-onset refractory status epilepticus (NORSE) in pregnancy may be complicated by anti-seizure medication (ASM) polytherapy-associated teratogenicity. We aim to demonstrate the safety and efficacy of vagal nerve stimulation (VNS) in a pregnant patient presenting with NORSE.

Case description: A 30-year old female, at 5-weeks' gestation presented with drug-refractory myoclonic status epilepticus, responsive only to high levels of anesthetic agents. The severity of seizures did not allow extubation, and the patient remained ventilated and sedated. VNS was implanted 26 days after seizure onset. The immediate post-operative output was 0.25 mA, which was rapidly titrated up to 0.5 mA the next morning, and to 0.75 mA that afternoon. This was further increased to 1.0 mA on 3rd day post-operation, and to 1.25 mA 7 days post-op. Myoclonic jerks diminished significantly 7 days post-op, allowing extubation. Twenty days after VNS implantation, no myoclonic jerks were observed. There was also a notable neurological improvement including increased alertness and mobility, and ability to obey commands. Drug overdose was subsequently found to be the most likely etiology of her NORSE. An early pregnancy assessment 17 days after VNS implantation showed a normally sited pregnancy, normal fetal heart activity and crown-rump length. The patient remained seizure free, gained functional independence and delivered a premature but otherwise healthy baby at 33 weeks' gestation.

Conclusion: NORSE is challenging to manage, further compounded in pregnancy due to the teratogenicity of ASMs and ASM polytherapy. This is the first case-study to report the safe implantation and use of VNS during the first trimester of pregnancy for the management of NORSE.

KEYWORDS

NORSE, VNS, pregnancy, outcomes, status epilepticus

1. Introduction

Status epilepticus (SE) is a life-threatening neurological emergency with a significant mortality and morbidity. New-onset refractory status epilepticus (NORSE) is "a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other pre-existing relevant neurological disorder, with new-onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause. This includes patients with viral or autoimmune causes. If no cause is found after extensive evaluation, this is considered "cryptogenic NORSE" or "NORSE of unknown cause"" (1). It represents ∼20% of all refractory status epilepticus cases, and although rare, it can be fatal and often leads to poor neurological outcomes (2). NORSE typically presents in young healthy people, with a viral illness-like prodrome (3).

Although several treatments such as anti-seizure medications (ASMs), anesthetic agents, immunosuppressive treatments, and neuromodulation have been suggested, consensus on optimal management is only now emerging. Management is further compounded in pregnant patients due to the teratogenicity of several anti-seizure medications (ASMs). In these patients, neuromodulation with vagal nerve stimulation (VNS) is an attractive option, as it may help avoid the use of ASM polytherapy. The successful use of VNS for NORSE has been documented in previous case reports/series (4–8), however, there are no reports of VNS use in NORSE in pregnancy. This case is the first to report on the safe and effective use of VNS in NORSE in early pregnancy.

2. Case description

2.1. Initial management

Our patient was a 30 year-old female, 5-weeks pregnant at presentation, with no history of epilepsy or neurological disease. She was brought to her local emergency department (ED) after she was found shaking and unresponsive by her partner. The seizure lasted for more than 1 h, and was aborted by 10 mg diazepam given by ambulance paramedics. Seizures recommenced in ED and were refractory to intravenous (IV) lorazepam (4 mg) and levetiracetam 1 g. She was subsequently intubated in ED and started on a propofol infusion (100 mg/h). CT head and lumbar puncture on admission were both unremarkable. Magnetic resonance imaging (MRI) and Magnetic resonance venogram (MRV) conducted on day two after onset were normal. The day after admission, the propofol infusion was held, which restarted seizure activity. The seizures started as distal limb myoclonic jerks in the upper and lower limbs, and then progressed to stimulus-sensitive (touch and sound), generalized myoclonus. Sedation was recommenced with propofol, fentanyl (200 micrograms/h) and midazolam (10 mg/h), and the levetiracetam dose was increased to 1.5 g BD. Clobazam 5 mg BD was also added. Generalized myoclonus/myoclonic jerks continued while she was on propofol, fentanyl, clobazam, levetiracetam, and midazolam. Obstetric input was sought, and phenytoin (100 mg TDS), lacosamide (100 mg BD), topiramate (100 mg BD) were added, in sequence. She was pulsed with methylprednisolone from day 5 of presentation.

2.2. Pre-operative management in our epilepsy center

Seven days after initial presentation, the patient was transferred to our center with ongoing right arm and left leg myoclonic jerks and head movements suggesting ongoing status epilepticus. Two hundred milligram biotin and pyridoxine 50 mg were commenced on arrival.

The patient's lumbar puncture was repeated on day 7 when she was admitted to our center and she was found to be HSV negative, and aciclovir was stopped. MRI head (Figure 1A) and spine were also repeated (day 11 after onset) and were unremarkable. On admission to our center metabolic, CSF virology, and autoimmune and paraneoplastic panels were all negative (detailed in Table 1), as were QuantiFERON-TB Gold, and blood, CSF and sputum cultures. Vitamin B12, folate and serum ferritin were normal. At this point, a diagnosis of NORSE was suspected, and the patient was managed as such.

The patient also underwent three EEGs: soon after admission to the local hospital CCU, a prolonged study after admission to our center, and after VNS implantation (Table 1; Figure 1B).

Propofol weaning was attempted again, 9 days after onset but this led to increased myoclonic jerks and it was reintroduced. Perampanel 6 mg was commenced via a nasogastric tube 11 days after onset. Five sessions of plasmapheresis (PLEX) were commenced 12 days after presentation. The patient was started on Anakinra (100 mg daily) after the last PLEX. Propofol was cross-tapered with ketamine (2.5 mg/kg/h) to reduce the risk of propofol infusion syndrome as the ketogenic diet as started. The ketogenic diet was commenced 22 days after onset, and Levetiracetam was switched to Brivaracetam (100 mg BD).

An CT chest abdomen and pelvis was performed and ruled out trophoblastic disease or ovarian teratoma.

Whilst there had been no collateral history or evidence of overdose, the toxicology panel conducted on admission to her local hospital, which was made available to us 20 days after onset, demonstrated grossly elevated levels of morphine, fentanyl, pregabalin, and cocaine. Two past admissions for ecstasy and pregabalin overdose also came to light. Based on these results, possible anoxic brain injury was considered although subsequent MRI Brain scans did not show any evidence of hypoxic injury.

Due to refractoriness of her myoclonus on weaning sedation, an unremarkable MRI brain study and difficulty in assessing her level of consciousness off sedation, the Epilepsy Surgery MDT agreed on VNS implantation. VNS was implanted 26 days after seizure onset.

2.3. VNS implantation and outcome

2.3.1. Outcome of status epilepticus

The clinical outcomes post-VNS implantation have been outlined in Table 2. The VNS was switched on day 0 with immediate post-operative settings 0.25 mA, 30 Hz, 500 μs, 30 s on, 5 min off, Duty cycle 10%. VNS output was increased till day 7 post-op according to Figure 2. All other parameters stayed the same. No intraoperative or post-operative complications were noted. Two days post-operatively, myoclonic jerks were still occurring,

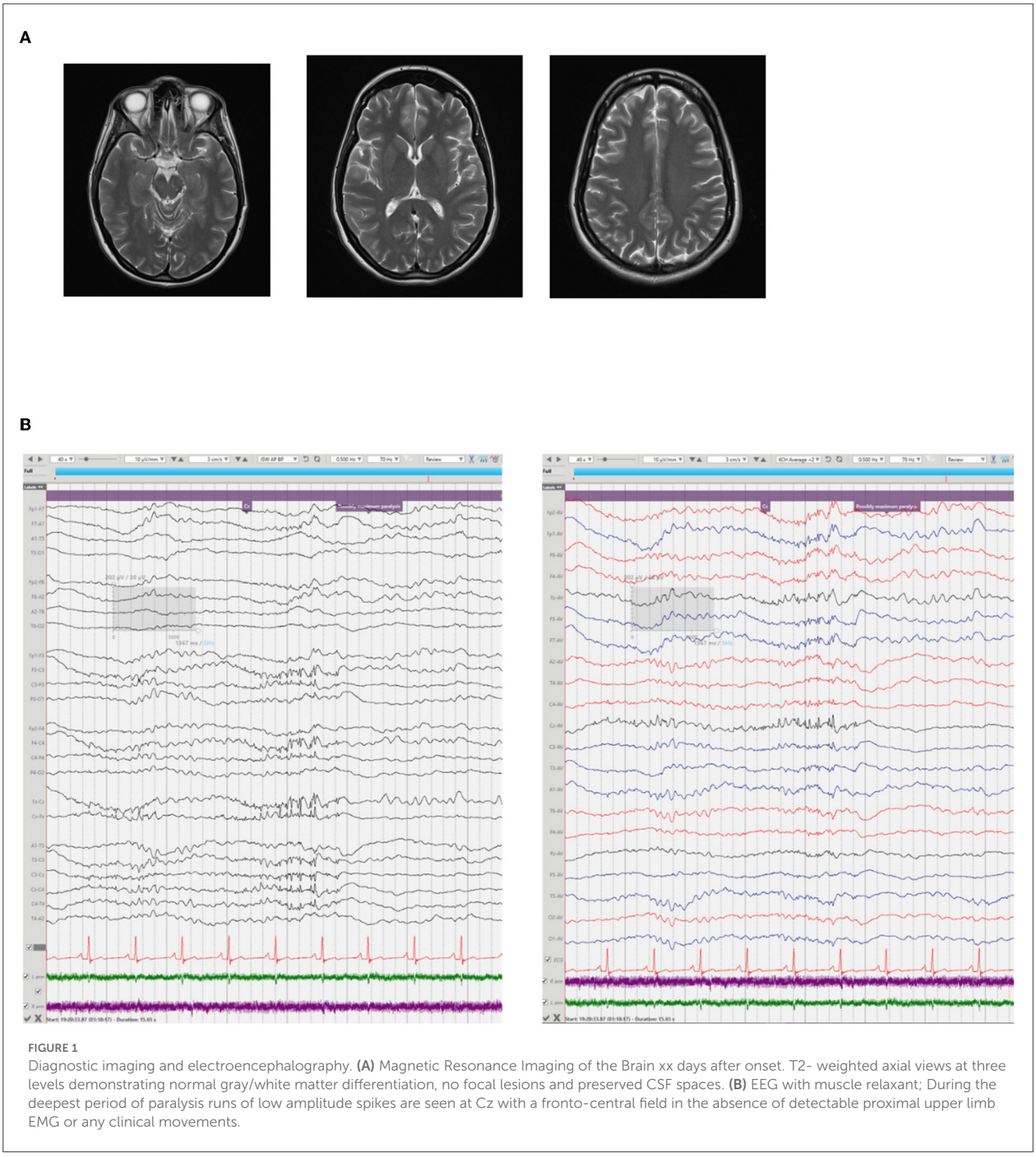

FIGURE 1
Diagnostic imaging and electroencephalography. **(A)** Magnetic Resonance Imaging of the Brain xx days after onset. T2- weighted axial views at three levels demonstrating normal gray/white matter differentiation, no focal lesions and preserved CSF spaces. **(B)** EEG with muscle relaxant; During the deepest period of paralysis runs of low amplitude spikes are seen at Cz with a fronto-central field in the absence of detectable proximal upper limb EMG or any clinical movements.

but eye opening to voice and apparent purposeful movements (including reaching for the tube) were noted. On day 3 post-operatively slow ketamine weaning was started. The patient was extubated on day 5 post-op. Semi-purposeful movement in all four limbs was noted, and the stimulus-sensitive myoclonic jerks had diminished significantly. Midazolam was stopped. No myoclonus was noted 7 days post-op. The patient was discharged to a neurology ward in our center. Anakinra, the ketogenic diet, and prednisolone were weaned. Thirteen days after VNS implantation, the patient demonstrated full passive range of motion in all limbs. After 18 days, normal power was noted in all limbs (MRC 4+/5). Nineteen days later the GCS had improved to 15/15. The patient showed comprehensible speech, and was oriented to place and person. Twenty days after VNS implantation, no myoclonic jerks were noted, and the patient was transferred back to her local hospital for further rehabilitation. Four months after VNS implantation, occasional, inconsistent tremors in upper and lower limbs were noted thought to be either a functional overlay or enhanced physiological tremor: these movements were clinically distinctively different from myoclonic jerks, were distractable and

TABLE 1 Summary of investigations.

Investigation	Results
CSF findings	
CSF NMDA receptor antibodies	Negative
CSF analysis	Negative
CSF glycine	Normal
CSF oligoclonal bands	Negative
CSF lactate	Raised
CSF virology (including CMV, adenovirus, HSV 1 and 2, EBV, enterovirus and varicella zoster virus)	Negative
Serum findings	
Metabolic panel (including Zn, Cu Se, Mg, Ca and phosphate)	Normal
Serum GAD	Negative
Glycine antibodies	Negative
Cytokine innate (including IL1-beta, IL6, TNF-alpha, and IL8)	Normal
NMDA receptor antibodies	Negative
Plasma Acyl Carnitine	Negative
Neuronal antibodies (including Hu, Ri and Yo antibodies)	Negative
Diabetes antibodies (including glutamic acid decarboxylase, IA2 and zinc transporter 8 antibodies)	Negative
Anti-CASPR2 antibodies	Negative
Anti-LGi1 antibodies	Negative
Amphiphysin	Negative
Anti-AMPA-1, AMPA-2 and GABA antibodies	Negative
Imaging and telemetry findings	
MRI head	No radiological evidence for explanation of NORSE, no claustrum sign bilaterally, basal ganglia normal bilaterally.
TVS ultrasound (before VNS implantation)	Gestational sac, yolk-sac and embryo present Fetal heart activity present: 171 bpm Both ovaries normal Crown-rump length normal
CT chest abdomen and pelvis	No evidence of malignancy No features of trophoblastic disease or ovarian teratoma
Transabdominal ultrasound (after VNS implantation)	Uterus: anteverted, normal Fetal heart activity present: 169 bpm Crown-rump length: 60 mm Amniotic fluid normal No free fluid Ongoing normally sited pregnancy
EEG on presentation to our center	Included withdrawing sedation and introducing muscle relaxant Interictal EEG showed continuous slow, generalized; at times rhythmic and stimulation induced, background suppression, spikes, central (Cz > C3 = C4, rare spread to Fz/F3/F4/Fp1/Fp2), and eta-delta complexes (rare, seen with stimulation). The patient is still in status epilepticus, by virtue of the existence of midline spikes and myoclonus, both spontaneous and clearly stimulus induced, with clear examples of EMG correlate following central small spikes, confirming a cortically driven process. There is however an improvement as both clinical and EEG changes appear much less prominently after stimulation and interictal midline discharges are less frequent and less prominent.
EEG after VNS implantation	Overall picture appears to be one of stimulus sensitive multifocal myoclonus. There is a clear increase in cortical spiking during the more major attacks and clear correlation of the jerks and spikes suggesting this is cortical rather than of brainstem origin.

could be voluntarily suppressed. A repeat EEG performed at about 5 months from hospital admission did not capture the tremor-like movements; it showed background slowing and occasional spikes with no clinical correlate (no motor manifestations). Five months after VNS implantation, no further seizures or focal neurology were reported. The patient continued to take clonazepam and perampanel and mobilized using a Sara Steady sit-to-stand aid. Fatigue and low mood were reported.

2.3.2. Pregnancy outcome

Except for a minor vaginal bleed lasting 2 days, pregnancy was uneventful: repeat fetal monitoring by ultrasound at day 17, 4 and 5 months after VNS implantation and a fetal anomaly scan were unremarkable and a spontaneous vaginal delivery was planned. The patient experienced preterm premature rupture of membranes (PPROM) at 33 + 2 weeks gestation, and went into preterm labor with transverse fetal lie and fetal bradycardia. The baby was delivered via emergency cesarean section under spinal anesthesia, and admitted to the neonatal ICU due to prematurity, but was discharged without neonatal concerns. Our patient made an unremarkable obstetric recovery.

3. Discussion

We present a case of a 5-weeks pregnant 30-year old female who presented with NORSE. Etiology remained unresolved, although drug overdose leading to subtle hypoperfusion was considered. VNS implantation on the 26th day after presentation was followed by reduction and eventually resolution of seizure activity.

This case highlights the safety and effectiveness of VNS use in pregnant patients presenting with super-refractory status epilepticus, and specifically, NORSE. Ultimately, our experience

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TABLE 2 VNS titration, clinical and electrographic progress.

Day	Event
Day 26	VNS implantation Post-operative VNS output: 0.25 mA
Day 27	VNS output increased to 0.50 mA VNS output increased to 0.75 mA Myoclonic jerks still occurring Eye opening to voice Apparent purposeful movements
Day 28	VNS output increased to 1.00 mA Slow ketamine weaning started Prolonged EEG: overall picture appears to be one of stimulus sensitive multifocal myoclonus. There is a clear increase in cortical spiking during the more major attacks and clear correlation of the jerks and spikes suggesting this is cortical rather than of brainstem origin.
Day 30	Patient extubated Semi-purposeful movements noted in all limbs Stimulus-sensitive myoclonic jerks diminished significantly Midazolam stopped
Day 32	VNS increased to 1.25 mA No myoclonus noted Patients commenced on folic acid 5 mg OD and vitamin D 10 micrograms OD
Day 33	Patient discharged to neurology ward in our center
Day 38	Full passive range of motion in all limbs
Day 43	Early pregnancy assessment by obstetrics team Fetal heart activity normal Normal crown-rump length Gestational age: 12 weeks + 3 days Concluded that pregnancy was developing normally
Day 44	Normal power in all limbs noted (MRC 4+/5)
Day 45	GCS 15/15 Speaking and comprehensible Oriented to person and place
Day 46	No myoclonic jerks noted Patient discharged to her local hospital for further neurorehabilitation
4 months after VNS	Obstetric decision that no additional fetal monitoring required Midwives have no specific clinical concerns about pregnancy. Occasional tremors in upper and lower limbs but they are inconsistent and can be stopped when the patient concentrates
5 months after VNS	No further seizures Continues on clonazepam and Permapanel No focal neurology Patient remains fatigued Mobilizing using Sara Steady Sit-to-stand aid Concomitant low mood Fetal ultrasound, including anomaly scan, normal Delivery plan: spontaneous vaginal delivery
6 months after VNS	Preterm premature rupture of membranes at 33 weeks gestation Transverse fetal lie and fetal bradycardia Category 1B cesarean section with spinal anesthesia to deliver baby Baby premature but otherwise healthy [Apgar scores = 3 (1 min), 7 (5 min), 8 (10 min)] Baby floppy at birth and heart rate <60 bpm, however, increased to >100 bpm after 5 inflation breaths within 3 min of life Baby breathing became regular after 3 min of life Oxygen saturation >95% by 5 min of life Baby pink and well-perfused, normal breath and heart sounds, soft abdomen Obstetric review concluded patient is making good operative recovery Baby remained on continuous positive airway pressure (CPAP) for 48 h after birth Enteral feed started for baby on day 5 after birth MRI head for baby—normal

suggests that VNS implantation can be considered early in pregnancy to facilitate seizure cessation and reduce the need for multiple ASMs, many of which are teratogenic, especially when administered together.

The use of VNS in pregnancy, and the corresponding obstetric and fetal outcomes are crucial to study, however, it is important to note that in all reported studies except one, VNS was implanted before conception. Moreover, in all studies, VNS was used to control long-standing epilepsy or reduce the need for ASM polytherapy. The acute implantation of VNS in pregnancy (specifically the first trimester) to control NORSE or super-refractory status epilepticus has not previously been reported. One study found that although the rate of obstetric interventions was higher than the average pregnant population, there was no VNS-related teratogenicity in the fetus (9), with normal mean Apgar scores and birth weights for the infants. Only 1/26 infants had a major malformation: the mother was managed with four ASMs, suggesting that VNS could potentially reduce the number of ASMs used and thus contribute to reducing the teratogenicity associated with ASM polytherapy. In another study following five pregnancies, four outcomes were positive, and one ended in a spontaneous abortion (10). No teratogenicity or VNS-related complications were observed during pregnancy or delivery. A further study followed a patient in whom VNS was implanted 2 months before conception, and decreased her seizure frequency significantly (11). Lastly, in a case series, three out of four patients had obstetric complications needing cesarean sections. Six out of seven babies were healthy; one had intellectual disabilities (12). Only, one case report outlines a patient in whom VNS was implanted during the 3rd trimester of pregnancy (13). The device was activated immediately without any complications and drastically improved seizure control. The patient delivered a healthy baby at 37 weeks' gestation via a cesarean section. Two overarching conclusions can be suggested from these cases—fetal outcomes are generally positive, however, obstetric complications might be increased in pregnant patients with VNS: the latter can be multifactorial, with epilepsy being a significant factor and spontaneous abortion and prepartum complications being strongly linked to ASM polytherapy. Our patient did not experience any obstetric complications after VNS implantation before delivery, and delivered a premature but otherwise healthy baby via a cesarean section in keeping with the literature reviewed.

The mechanism by which VNS controls seizure activity is relatively unknown. Uncertainty surrounding VNS function might raise concerns about its safe use in pregnancy, especially considering its apparent effects on neuroendocrine functions, and its influence on the ovaries and uterus. VNS can activate the hypothalamus, which is a key structure in the hypothalamic-pituitary-gonadal axis (14). However, while ascending fibers of the vagus nerve can activate the hypothalamus, they do not have an apparent effect on the downstream target organs (15).

Whilst contradictory evidence exists as to whether the vagus nerve can directly influence pelvic organ function (15, 16), other studies suggest it has little impact on pregnancy (14).

A further concern could arise due to a possible malfunctioning of the device during pregnancy, however one case demonstrated

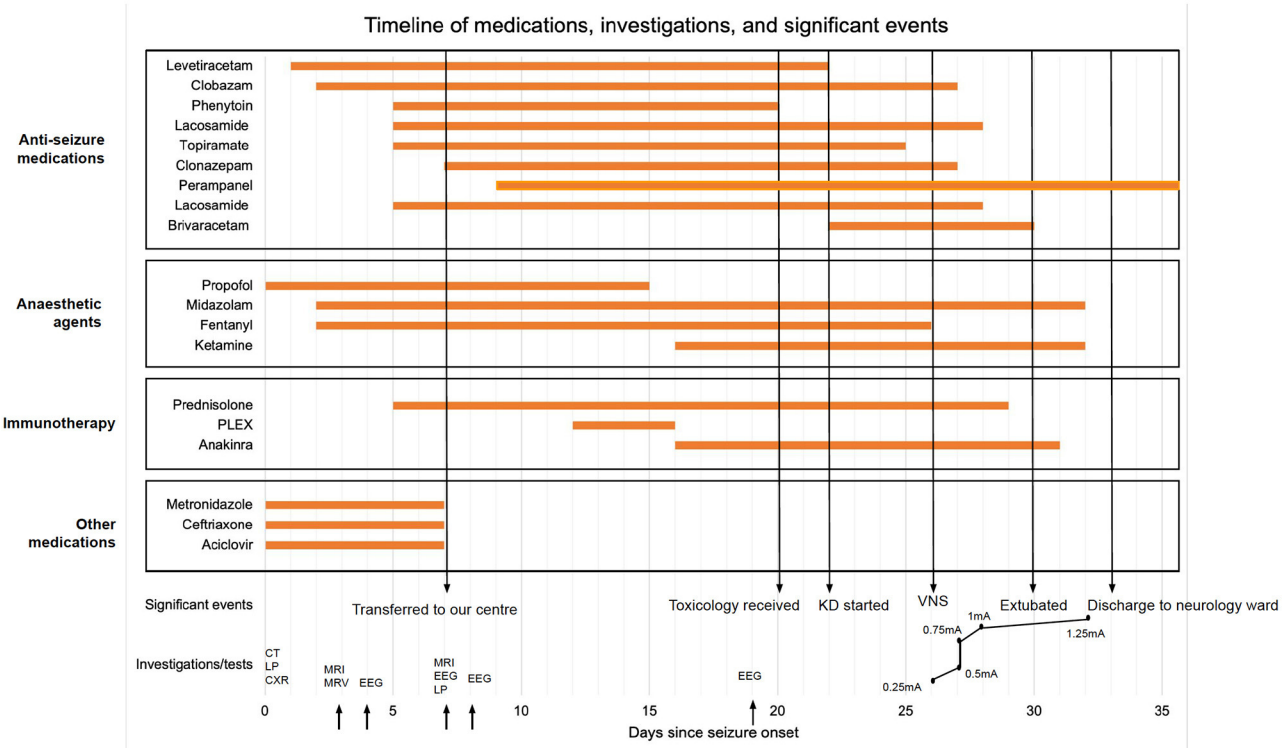

FIGURE 2
Timeline of care; KD, ketogenic diet; VNS, vagal nerve stimulation; CT, computed tomography; LP, lumbar puncture; CXR, chest x-ray; MRI, magnetic resonance imaging; MRV, magnetic resonance venogram; EEG, electroencephalogram.

that suboptimal functioning during organogenesis period did not lead to any morphological abnormalities in the fetus (17), while another study observed no malfunction of VNS during pregnancy or after birth (18). Our patient did not experience any VNS malfunctioning from implantation to discharge to her local hospital, and until she delivered her baby.

A final safety concern includes the rapid rate at which VNS is titrated up in NORSE. In our patient, the VNS current was increased from 0.25 to 1.25 mA within 7 days of implantation, an increase which would otherwise be spread out across several weeks. This did not negatively impact the patient or the fetus. Stimulus-related side-effects such as coughing, hoarseness and throat pain were not reported. The fast titration of VNS has been documented in other case reports outlining the use of VNS in NORSE (4–8), however, it had not been reported in pregnant patients presenting with NORSE.

Due to the severity of the patient's condition, multiple interventions were trialed in a short timeframe, including introduction of a ketogenic diet, Brivaracetam, Anakinra, and plasmapheresis. There is a possibility that one or more of these measures could have contributed to seizure termination. However, the following evidence supports VNS treatment being the main contributor to status cessation:

Adequate ketosis requires sustained blood ketone levels above 0.5 mmol/L. Our patient's blood ketones remained consistently under 0.5 mmol/L, except for one instance where they reached 1.4 mmol/L, confirming that adequate ketosis was not achieved, which reduces the likelihood of seizure termination due to a ketogenic diet. Furthermore, the patient's myoclonus did not recur when the ketogenic diet was stopped.

Brivaracetam is unlikely to have caused seizure cessation; one review investigating the use of Brivaracetam in SE found that the longest time to seizure termination with Brivaracetam was 24 h, and <50% of SE patients responded to Brivaracetam (19). Although, Anakinra and plasmapheresis have been successful in managing NORSE, any therapeutic effects would have become apparent in the first 7 days after initiation.

Our patient experienced a nearly immediate and sustained positive response when VNS was switched on; this also allowed ketamine weaning to be commenced, which had not previously been possible with any other therapeutic interventions.

Another point to address is the apparent improvement noted on EEG on day 19. This could be attributed to the introduction of Ketamine; however, the patient remained in intractable SE despite this, indicating that Ketamine alone could not provide seizure freedom.

Our case-report and subsequent literature-search suggest that acute VNS implantation is a safe and effective therapeutic option in pregnant patients presenting with NORSE. The patient experienced notable neurological recovery without significant or long-term obstetric or fetal compromise. Our findings are especially important because they highlight how VNS might significantly reduce seizure activity and increase favorable outcomes in a scenario which otherwise carries a poor prognosis.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained for the publication of this case report.

Author contributions

MJ: conceptualization, writing—original draft, writing—reviewing and editing, visualization, investigation, and methodology. LD and JW: investigation and writing—reviewing and editing. RG, SB, MA-C, and RS: investigation. LM: conceptualization, investigation, methodology, writing—reviewing and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1183080/full#supplementary-material

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Neuromodulation in new-onset refractory status epilepticus

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Background: New-onset refractory status epilepticus (NORSE) and its subset of febrile infection-related epilepsy syndrome (FIRES) are devastating clinical presentations with high rates of mortality and morbidity. The recently published consensus on the treatment of these conditions includes anesthetics, antiseizure drugs, antivirals, antibiotics, and immune therapies. Despite the internationally accepted treatment, the outcome remains poor for a significant percentage of patients.

Methods: We conducted a systematic review of the use of neuromodulation techniques in the treatment of the acute phase of NORSE/FIRES using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: Our search strategy brought up 74 articles of which 15 met our inclusion criteria. A total of 20 patients were treated with neuromodulation. Thirteen cases represented FIRES and in 17 cases the NORSE remained cryptogenic. Ten had electroconvulsive therapy (ECT), seven had vagal nerve stimulation (VNS), and four had deep brain stimulation (DBS); one patient had initially VNS and later DBS. Eight patients were female and nine were children. In 17 out of 20 patients, the status epilepticus was resolved after neuromodulation, while three patients died.

Conclusion: NORSE can have a catastrophic course and the first treatment goal should be the fastest possible termination of status epilepticus. The data presented are limited by the small number of published cases and the variability of neuromodulation protocols used. However, they show some potential clinical benefits of early neuromodulation therapy, suggesting that these techniques could be considered within the course of FIRES/NORSE.

KEYWORDS

new-onset refractory status epilepticus (NORSE), febrile infection epilepsy-related syndrome (FIRES), neuromodulation, deep brain stimulation (DBS), electroconvulsive therapy (ECT), vagal nerve stimulation (VNS)

Introduction

The Neurocritical Care Society has described status epilepticus (SE) as one of the most frequent neurological emergencies defined as a seizure with 5 min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures (1). SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which leads to prolonged seizures (2). SE has an incidence ranging between 8.52 and 41/100,000/year according to a recent review (3). This significant discrepancy between the different studies could be attributed to different study methodologies, populations, geographical representation, and also different SE definitions. A study in adults using the latest definition for SE from the International League Against Epilepsy (ILAE) found an incidence of 36.1/100,000 adults per year (4).

The mortality incidence of this condition increases dramatically when it persists and becomes refractory (RSE) or super refractory SE (SRSE). RSE is defined as the persistence of SE after the administration of two parenteral medications including a benzodiazepine and its termination requires general anesthesia (2, 5). SRSE is defined as the persistence of SE for 24 hours after administration of anesthesia, which could be uninterrupted or "recurring while on or after withdrawal of anesthesia, requiring anesthetic reintroduction" (5, 6). About 20% of the RSE cases will evolve to SRSE (7), which has a mortality rate of 30–50% in different studies (6, 8), and thus a rapid diagnostic assessment and appropriate treatment are of major importance for the best possible outcome.

New-onset refractory status epilepticus (NORSE) is defined as a "clinical presentation, not a specific diagnosis, characterized by de novo onset of RSE that may progress toward SRSE, in a patient without active epilepsy or other pre-existing relevant neurological disorders, and without an identifiable acute or active structural, toxic, or metabolic cause" (5). In the same article, febrile infection-related epilepsy syndrome (FIRES) has been defined as a subset of NORSE "requiring a febrile illness starting between 2 weeks and 24 h before the onset of RSE, with or without fever at the onset of SE" (5). There are no age restrictions to both NORSE and FIRES. Historically, several syndromes have also been used to describe similar cases of fever preceding RSE, such as de novo cryptogenic refractory multifocal febrile status epilepticus (9), idiopathic catastrophic epileptic encephalopathy (10), severe refractory status epilepticus owing to presumed encephalitis (11), devastating epilepsy in school-age children (12), acute non-herpetic encephalitis with refractory repetitive seizures (13), acute encephalopathy with inflammation-mediated status epilepticus (14), and acute encephalitis with refractory repetitive partial seizures (15). In a review of 249 cases named under these nomenclatures, Ismail and Kossoff (16) concluded that they represent the same clinical entity of FIRES.

NORSE remains without an identifiable cause in 50–73% of the cases and typically is called cryptogenic NORSE (17–19). It is a devastating condition with a mortality rate between 10 and 30% and about two-thirds of the survivors will have functional and cognitive impairment (20). Epilepsy persists after SE resolution in about 80% of the patients (18). In a retrospective review of 130 patients with NORSE, 22% of affected patients died in the hospital, and 62% had a poor outcome on discharge (19). Cryptogenic NORSE has even poorer outcomes (18). Various treatment options have been described in the literature apart from the common SE treatment with benzodiazepines, antiseizure drugs, and anesthetics. These include immune therapies such as methylprednisolone, therapeutic plasma exchange (TPE), and intravenous immunoglobulin (IVIG); hypothermia, ketogenic diet, second-line immunomodulatory treatments (anakinra, rituximab), surgical resection, and neuromodulation. However, no standardized approach existed until the international consensus recommendations for the management of NORSE/FIRES that were published recently (21). The treatment suggestions and their timeline are described in detail (22). Besides the antiseizure medications, the anesthetics, and the management of possible infection, there is a suggestion for initiation of first-line immunotherapy (corticosteroids or IVIG) within 72 h if basic infections have been excluded. Ketogenic diet and second-line immunotherapies should be initiated within 7 days of NORSE/FIRES onset. The guidelines do not include any neuromodulation technique during the acute phase of NORSE/FIRES based on the existence of limited data (21, 22). Although the authors suggest vagal nerve stimulation (VNS) for the post-acute phase, they do not suggest deep brain stimulation (DBS). Nevertheless, it is stated that there is no evidence of lack of efficacy for the latter (21, 22).

The need for complementary non-pharmacological treatments has been described in general for SRSE (23) and applies with higher importance to NORSE/FIRES as they can have potentially catastrophic consequences for the patient. There is a small number of published cases where neuromodulation was used for the treatment of NORSE/FIRES. Both non-invasive (electroconvulsive therapy [ECT]) and invasive techniques (VNS and DBS) have been applied. Other non-invasive techniques such as transcranial magnetic stimulation (TMS), transcranial direct electrical stimulation (tDCS), and external VNS have not been reported for NORSE/FIRES.

Non-invasive neuromodulation techniques

Electroconvulsive therapy (ECT) was primarily used in the past to treat patients with severe major depression, schizophrenia, catatonia, and many other mental disorders with high efficacy (24–28), but recent reviews have demonstrated good outcomes when used to abolish RSE or SRSE (29, 30). This non-invasive technique involves transcutaneous electrical stimulation of the cerebral cortex to induce a generalized seizure under EEG monitoring with general anesthesia. The ECT stimulus intensity and duration (pulse width) are determined by the patient's seizure threshold through trial and error, which affects efficacy, response speed, and severity of adverse cognitive effects (31). There are three types of electrode placement: bifrontal, bitemporal, and right unilateral (left unilateral for left-handed patients). Bitemporal placement is preferred in urgent clinical situations due to its higher speed of response, while right unilateral placement in situations where minimizing retrograde amnesia is a concern (27). The aim is to increase the patient's seizure threshold, potentially by 80% with bilateral ECT or 40% with unilateral ECT over one treatment course (32).

Invasive neuromodulation techniques

Vagal nerve stimulation (VNS) is an add-on treatment approved by the National Institute for Health and Care Excellence (NICE) for children and adults suffering from drug-resistant epilepsy (33). A pulse generator with a battery is implanted in the left subclavicular area and is connected with a 43-cm lead wire to two platinum/iridium helical electrodes attached to the left vagus nerve. An external programming system is used to control stimulation parameters (34). The reported early complications include bradycardia/asystole during the implantation procedure, peritracheal hematoma, and infections (3–8%) (34).

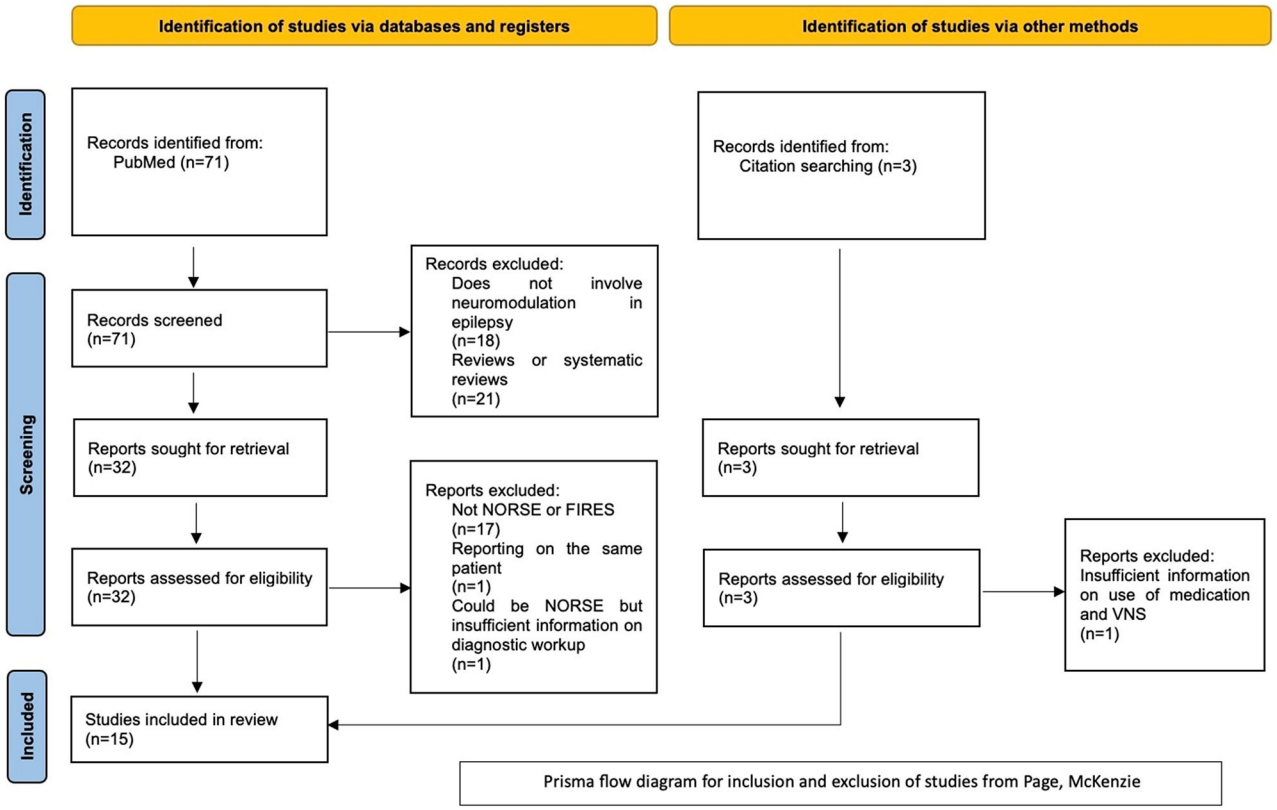

FIGURE 1
PRISMA flowchart for choice of included studies.

Deep brain stimulation (DBS) is an invasive neuromodulation technique approved by the United States Food and Drug Administration (FDA) for treating movement disorders (such as Parkinson's disease, essential tremor, and dystonia), treatment-refractory obsessive-compulsive disorder, chronic pain, and epilepsy (35–37). NICE has approved only anterior thalamic nucleus DBS for the treatment of refractory epilepsy in adults when pharmacological options have failed and resective surgery is contraindicated (38). The apparatus consists of electrodes with multiple contacts implanted to specifically targeted deep brain structures and connected through a subcutaneous wire to a pulse generator implanted on the chest wall. Stimulation parameters consisting of electrical (voltage or constant current) pulses with different amplitudes, frequencies, and pulse widths are controlled by an external wireless device (39). In patients with drug-resistant epilepsy, RSE, or SRSE, the electrodes are commonly implanted at the anterior or centromedian thalamic nucleus (37, 40). Possible hardware-related complications include lead migration or fracture, internal pulse generator malfunction, and skin erosion. As stated in a recent review (41), the most frequent complication is infection related to the implantation (≈5%).

This systematic review aims to present the available data about the possible benefits of using neuromodulation techniques as an add-on non-pharmacological treatment in cases of NORSE/FIRES.

Methods

This systematic review was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (42). The inclusion criteria were full-length articles written in English. These could be original articles, letters to the editor, or case reports/series. Articles containing overlapping data from previously published original articles, conference abstracts, and review articles were excluded. The studied population is patients with NORSE or FIRES who had treatment with any neuromodulation technique during the acute phase, defined as being still in SE, in the intensive care unit (ICU), and under sedation. NORSE cases with fever at the admission but without declaring when the fever started were considered as NORSE and not as FIRES because it was unclear whether the fever had started at least 24 h before the onset of RSE. Moreover, we have included cases where the authors did not use the terms NORSE or FIRES, but they have described the clinical details and testing approach and the condition could fit the current NORSE/FIRES definition. Articles without basic information about diagnostic or treatment approaches were excluded (Figure 1). Good outcome was considered the termination of SE irrelevant to the final outcome for the patient.

The search strategy is described in detail in Appendix 1.

Results

This review includes data from a total of 20 patients, but one patient underwent both VNS and DBS (43). Therefore, there were 21 neuromodulation treatments administered across 15 studies. The neuromodulation techniques used were ECT (n = 10), VNS (n = 7), and DBS (n = 4). Twelve out of 20 patients were male. Nine out of 20 patients were children (<18) and all except two (44, 45) had a diagnosis of FIRES. Seven out of 20 patients presented with NORSE, and the etiology was confirmed only in three (45–47) out of 20, with all the other cases remaining cryptogenic. A complete breakdown of demographics and outcomes is illustrated in Table 1. In cases where the patient experienced a good outcome, the time from neuromodulation until the improvement was reported heterogeneously. Some studies reported time before weaning anesthetics without any clinical or electrical seizure recurrence, some others reported the time before the discharge of the patient from neurointensive care, while others reported when SE was resolved.

The mean duration from NORSE onset to the application of neuromodulation was 56 days with a median of 30 days. Eighteen out of the 20 patients had improvement after neuromodulation [21 treatments, as one patient had VNS which failed, followed by successful DBS (43)], defined as resolution of SE and/or being able to step down from ICU. One of the patients with a resolution of SE after neuromodulation died from other comorbidities (48). The mean time from initiation of neuromodulation until SE resolution was 14 days and the median was seven days (for timings related to each neuromodulation technique see Table 1).

Regarding the overall outcomes, of the 17 survivors, 11 had persistent epilepsy (43–45, 49–54), 12 had cognitive and/or motor dysfunction (43, 45–47, 49–53, 55, 56), and one remained in a vegetative state (50).

TABLE 1 Basic demographics and outcomes.

Age, years, mean (range)	ECT	28.6 (3–77)
	VNS	22.9 (3–46)
	DBS	10.5 (5–17)
	Entire cohort	**23.8 (3–77)**
Neuromodulations (n = number of patients)	ECT	10
	VNS	7
	DBS	4
Gender (n = number of patients)	Males	12
	Females	8
NORSE or FIRES (n = number of patients)	NORSE	7
	FIRES	13
Etiology (n = number of patients)	Known (Encephalitis, CVID*)	3
	Cryptogenic	17
	Total	**20**
Clinical and/or EEG improvement after neuromodulation (n = number of neuromodulation treatments)	Yes	18
	No	3
	Total	**21**
Median number of days from NORSE onset to the initiation of neuromodulation (N = 20; range 5–435)	ECT	30
	VNS	22**
	DBS	47
	Entire cohort	**30**
Median number of days from initiation of neuromodulation to SE resolution (N = 17; range 0–61)	ECT	8.5
	VNS	7**
	DBS	8
	Entire cohort	**7**

*Common variable immunodeficiency-associated encephalomyelitis.
**One case patient had VNS very late in the course of NORSE (day 435) (47). When this outlier is excluded, the median number of days from NORSE onset until the treatment with VNS was 14, and from initiation of VNS treatment until SE termination was 5.

Results by type of neuromodulation technique

ECT was performed in 10 patients and was successful in resolving SE in nine of those cases (44, 51–54, 56). VNS was implanted in seven patients and was successful in resolving SE in five of those cases (43, 46–49, 55, 57). DBS was implanted in four patients; all of them had implantation at the centromedian thalamic nucleus (CMN-DBS) with a 100% success rate (43, 45, 50) (Figure 2). Overall, neuromodulation techniques led to improvement in 18 out of 20 patients. VNS was discontinued for the patient from the Howell et al. (57) case study, who did not show any improvement and died of multiorgan failure. SE was never resolved for patient 2 from the Kamel et al. study (53), who also died due to multiple comorbidities, including multi-antibiotic resistant hospital-acquired pneumonia and acute renal failure. Figure 3 shows the time from the onset of SE until the initiation of neuromodulation and the period before the resolution of SE after starting treatment with neuromodulation. No neuromodulation technique could be suggested as superior to the others. Details about the case-by-case timeline for initiation of neuromodulation and the final outcomes are presented in Table 2.

Medications administered

Both the mean and median number of drugs (including immune therapies and ketogenic diet) used in every patient was 14. Fourteen patients received immune therapies but only five patients received second-line immune therapies [three had anakinra (43, 49) and two had rituximab (50, 51)]. Figure 4 shows a complete list

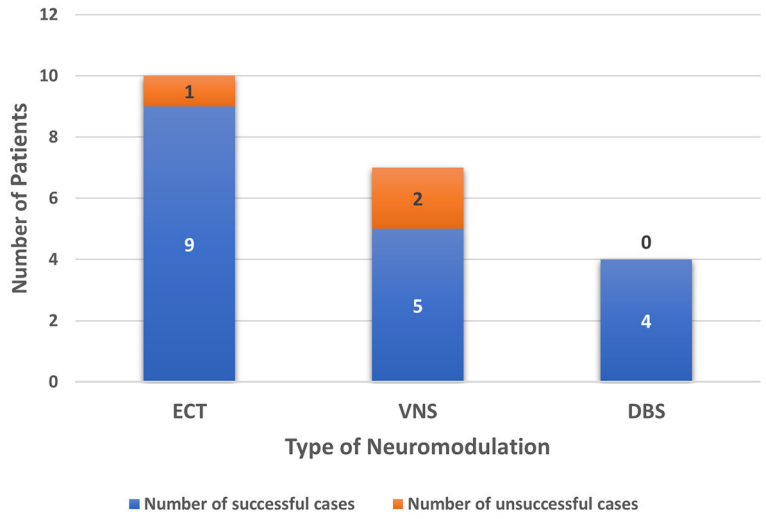

FIGURE 2
Number of patients reported for each type of neuromodulation including outcome.

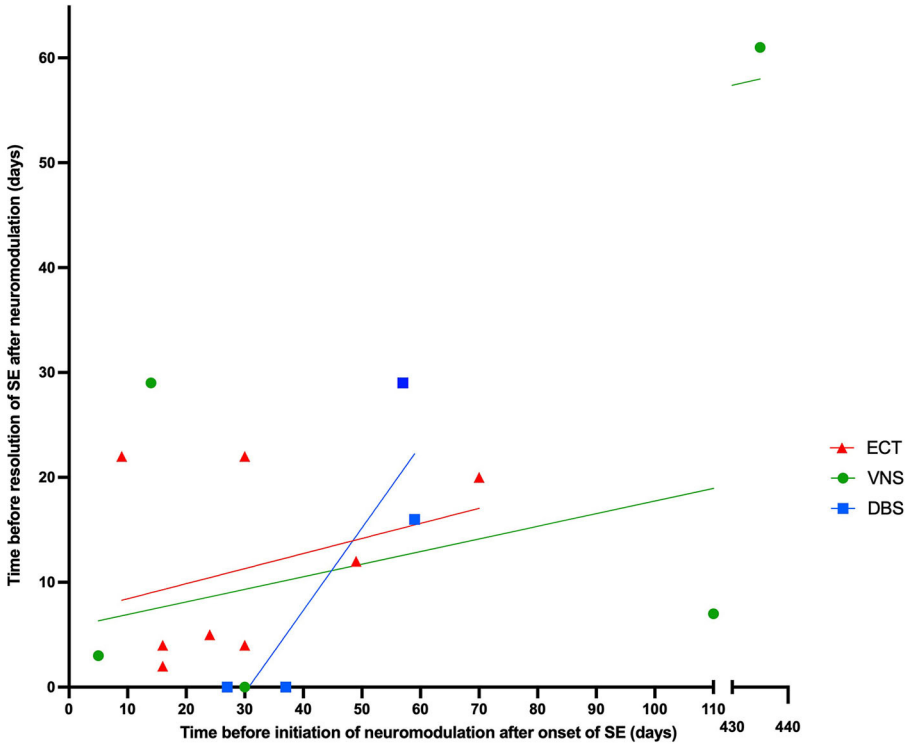

FIGURE 3
The relationship between time before initiating neuromodulation after onset of SE and time before resolution of SE after neuromodulation, categorized by type of neuromodulation technique.

of other medications and treatments that were used, as well as the percentage of patients administered each, across the 15 studies included in this review. The most used anti-epileptic drugs were levetiracetam (90%) and sodium valproate/valproic acid (85%), while intravenous immunoglobulin (70%) and steroids (65%) were the most common for first-line immune therapies.

Discussion

NORSE/FIRES represent a devastating condition with high mortality rates and poor neurocognitive outcomes (58). The necessity of rapid effective treatment is reflected in the timeline of the current therapeutic consensus (22). It is suggested that

TABLE 2 Characteristics of the patients, timelines for neuromodulation initiation, and outcomes.

Authors/patient number	Type of NMD	Age	Gender	NORSE/FIRES	Etiology	Time from NORSE onset to initiation of NMD (days)	Time before resolution of SE after initiating NMD (days)	Outcome after NMD (D = days after onset of SE)
Kurukumbi et al. (48)	VNS	25	Male	NORSE	Unknown	5	3	No SE or ES reported for 72 h after 3 days of VNS, succumbed to multiple comorbidities on D14
Alsaadi et al. (46)		46	Male	NORSE	Anti-NMDAR encephalitis	110	7	Weaned off midazolam after 1 week of VNS without any clinical or electrical seizures recurrences
Luo et al. (55)		3	Male	FIRES	Unknown	14	29	D43 seizure-free
Yamazoe et al. (47)		24	Male	FIRES	Anti-GluR autoimmune encephalitis	435**	61	Seizures completely disappeared after 2 months of VNS except for occasional eye deviation seizures
Howell et al. (57)/Pt. 7		14	Male	FIRES	Unknown	14	No improvement	No improvement over 15 days of VNS, died on D29 due to multiorgan failure
Espino et al. (49)/Pt. 1		37	Female	FIRES	Unknown	30	0	Cessation of SE 7 days after VNS implanted, but never seizure-free
Lehtimäki et al. (45)	DBS	17	Male	NORSE	CVID-associated encephalomyelitis	59	16	Resolution of SE and stepped down from neurointensive care on D75
Sa et al. (50)/Pt. 1		9	Male	FIRES	Unknown	27*	0	Almost abolishment of generalized seizures immediately after DBS implantation, seizure-free 33 days after (received anakinra 16 days after DBS)
Sa et al. (50)/Pt. 2		5	Male	FIRES	Unknown	37*	0	Almost abolishment of generalized seizures immediately after DBS implantation, which stopped completely 4 days later, remaining frequent focal seizures
Hect et al. (43)	VNS then DBS	11	Female	FIRES	Unknown	57	29	D85 onwards largely seizure-free, no abnormalities on serial EEG before discharge
Nath et al. (44)	ECT	3	Female	NORSE	Unknown	24	5	Seizure freedom lasted several hours to a day after each ECT treatment, persisted after fifth treatment, recurrence of 1–2 seizures a week later, resolved following two additional treatments except for some focal motor seizures
Kamel et al. (53)/Pt. 1		32	Female	NORSE	Unknown	30*	4***	SE resolved after 5 days (four ECT treatments)

(Continued)

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TABLE 2 (Continued)

Authors/patient number	Type of NMD	Age	Gender	NORSE/FIRES	Etiology	Time from NORSE onset to initiation of NMD (days)	Time before resolution of SE after initiating NMD (days)	Outcome after NMD (D = days after onset of SE)
Kamel et al. (53)/Pt. 2	ECT	41	Female	FIRES	Unknown	30*	No improvement	Seizures continued, died several days after initiating ECT due to multiple comorbidities
Kamel et al. (53)/Pt.3		26	Female	NORSE	Unknown	70*	20***	After fourth ECT treatment, seizure frequency decreased, SE resolved after another four treatments
García-López et al. (52)/Pt. 1		4	Male	FIRES	Unknown	60	Unknown	SE resolved after seven ECT treatments, kept having seizures
García-López et al. (52)/Pt. 2		32	Female	FIRES	Unknown	16	2	SE resolved after two ECT treatments, 2 months afterwards had auditory focal seizures without impairment of consciousness about every 10 days
García-López et al. (52)/Pt. 3		77	Female	NORSE	Unknown	16	4	SE resolved after four ECT treatments, living normal life without sequelae after discharge
Mirás Veiga et al. (56)		4	Male	FIRES	Unknown	49	12***	After 14 sessions, SE stopped, and EEG showed less frequent epileptiform activity
Tan et al. (54) Pt. 2		36	Male	FIRES	Unknown	9	22	Motor seizures resolved 2 weeks after eight ECT treatments
Chan et al. (51)		31	Male	FIRES	Unknown	30*	22	After first course of ECT, no sustainable improvement; second course given 8 days later; EEG stopped having ictal changes 10 days later

*Days after admission used, as onset of SE unknown.

**Corpus callosotomy performed after 14 months of SE (failed to terminate SE), VNS implanted 9 days after (~435 days since onset of SE).

***Duration of successful ECT treatment was used, but SE could have been resolved earlier.

NMD, Neuromodulation; VNS, Vagus nerve stimulation; DBS, Deep brain stimulation; ECT, Electroconvulsive therapy; NORSE, New-onset refractory status epilepticus; FIRES, Febrile infection-related epilepsy syndrome; Anti-NMDAR, Anti-N-methyl-D-aspartate receptor; Anti-GluR, Anti-glutamic acid receptor; CVID, Common variable immunodeficiency; SE, Status epilepticus; ES, Electrographic seizures; EEG, Electroencephalogram.

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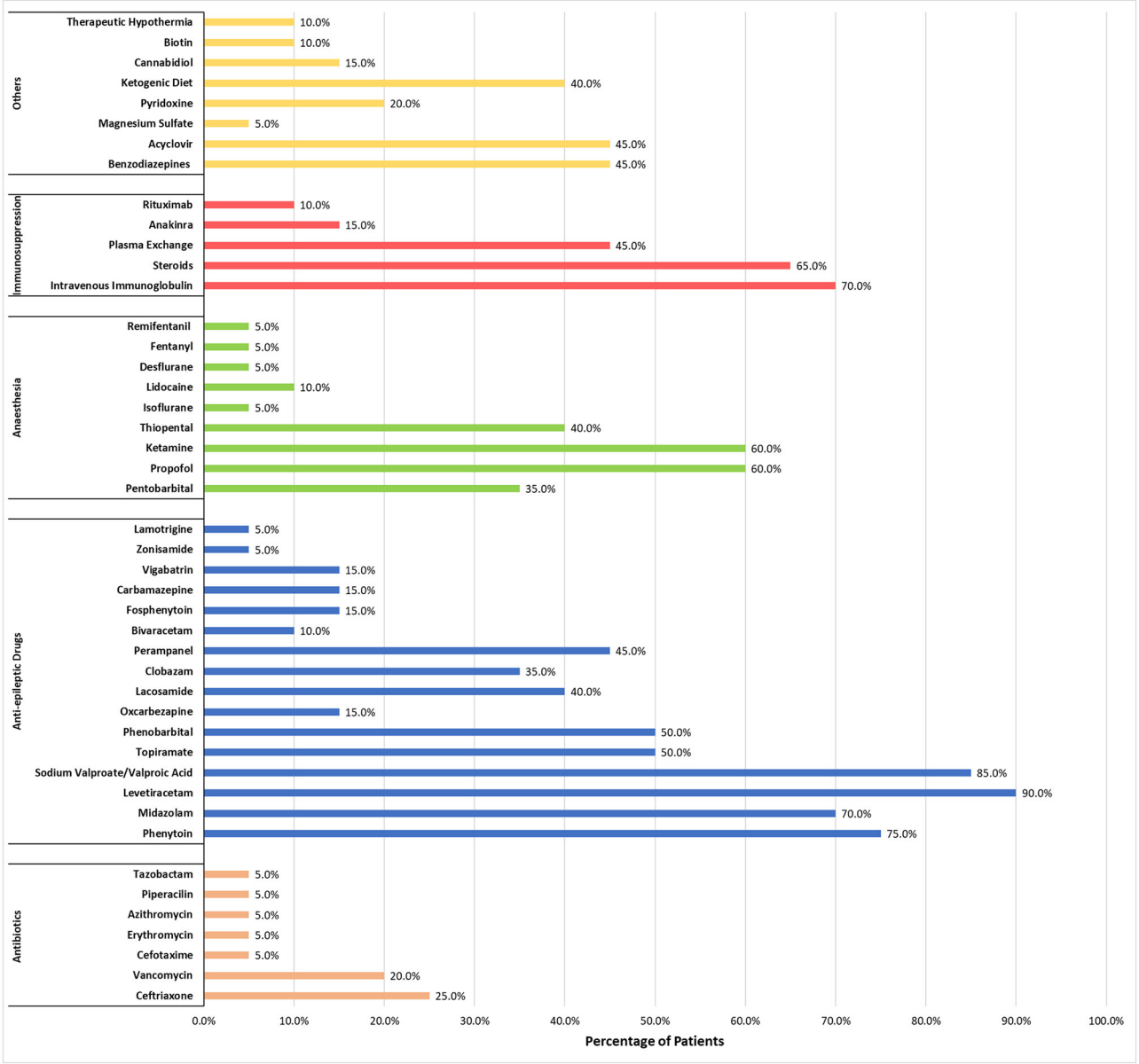

FIGURE 4
Percentage of patients who received each medication or treatment during management of NORSE/FIRES.

the poor outcome of NORSE, in both adults and children, is attributed to a combination of the duration of SE and the high rate of medical complications due to prolonged ICU stay and the high numbers and doses of anesthetics and antiseizure drugs required (19, 59, 60). It remains unclear whether this in fact is a consequence of the refractoriness of these cases, but on any occasion, the aim should be to reduce the iatrogenic burden. This could be supported by the adjunctive use of non-pharmacological techniques including neuromodulation.

The data collected in this review show that 18/20 NORSE/FIRES cases had a SE resolution after a trial of neuromodulation. Although the evidence is based on a small number of case reports/series with significant variability in time of application and techniques, neuromodulation techniques for these conditions appear to show potential benefit. Reasonably, the question arises regarding the proper time for consideration of a neuromodulation technique. The data in Figure 4 might suggest that SE resolution could happen earlier when the application of neuromodulation is performed closer to the date of NORSE onset, but the number of cases is very low and there are clear outliers. Based on these observations, we suggest that neuromodulation techniques, when available, could be considered earlier in the course of NORSE when the standard treatments have failed. Non-invasive neuromodulation techniques could be applied initially followed later by invasive neuromodulation techniques if SE continues. Even the possibility to use a different invasive technique if the first one was not associated with a good outcome has been reported. In one published case (43),

unsuccessful VNS was followed by CMN-DBS with termination of SE.

Despite extensive diagnostic assessment, about 49.9% of the cases remain cryptogenic, creating difficulty in establishing a standardized treatment approach. Furthermore, it has been published that cryptogenic NORSE can be predicted by the use of a score with a sensitivity and specificity at 93.9% and 100% respectively without the need to wait for all the results of extensive antibody testing (61). In our review, 85% ($n = 17$) of the cases who had neuromodulation for NORSE/FIRES are cryptogenic, a percentage which is much higher than the described general cohorts of NORSE. This could be explained by the fact that neuromodulation is probably used later and as a last resort in cases where the diagnosis remains unclear and there is no benefit from standard treatments. As shown in this systematic review, 14/17 of the cryptogenic cases improved after neuromodulation, indicating that these techniques could start being considered as an add-on treatment option when the standard diagnostic testing returns without results and SRSE persists. Neuromodulation would not be expected to have interactions with the pharmacological treatments and thus it could be used as an add-on without necessarily waiting long for an established outcome of the other treatments, especially if the timepoint of 7 days has passed and initiation of second-line immune therapies have not provided benefit.

An immune-mediated inflammatory mechanism is considered responsible for many NORSE/FIRES cases and immune therapies are commonly used. According to the recent consensus, these should start within the first 72 h from SE onset and be followed by second-line immune therapies within the 1st week if SE has not been resolved (22). In a review of 161 patients with NORSE, 87.5% received immune therapy; however, the outcomes remained poor with mortality rates of 16.5% and 10.3% for NORSE and FIRES, respectively. A good functional outcome, when checking between immune therapies, was highest for treatment with glucocorticoids (40.4%) and second-line immune therapies showed less efficacy (rituximab, cyclophosphamide) which could be explained by the application to already refractory cases (62). In our review, immune therapy was administered in 16 out of 20 patients. A variety of immune therapies were used across different reports (a complete list can be found in Figure 4). As SRSE persisted, trials of neuromodulation were started, which were associated with good outcomes in 14 patients (43–47, 49–54, 56, 57). All four patients who did not receive immunotherapy also showed improvement after neuromodulation (48, 53, 55). Given the prolonged effect of immune therapies, it would be hard to conclude whether the positive outcomes were caused exclusively by neuromodulation but in three cases where neuromodulation (DBS) was stopped after the improvement, there was a recurrence of SE which was again resolved when neuromodulation was restored (45, 50).

The use of neuromodulation techniques in the management of RSE/SRSE remains inconsistent as we have previously described (63). This is also true for the literature data we present in this systematic review which suggests that three neuromodulation techniques (ECT, VNS, and DBS) have shown some encouraging results. The evidence is based on limited data, without a consensus for a common protocol of neuromodulation application. The variability is caused by different available techniques at each center, distinct expertise, and cost. Furthermore, NORSE is a clinical presentation, not a specific disease, and there is significant diversity regarding the causes. Importantly, the mechanisms by which neuromodulation affects SE are not elucidated.

ECT is a long-used treatment option for psychiatric disorders, with several theories for its mechanism of action. Although distinct from the other neuromodulation techniques since the applied stimulation is not chronic, studies in different neurological conditions have shown that ECT can have a neuromodulatory effect by modification of resting state functional connectivity and regional gray matter volume (64). Animal studies have shown that many biologic processes can be altered, causing changes in neuroendocrine function, levels of neurotransmitters, neuroplasticity, and epigenetics (65). Internalization of NMDA receptors has also been described in rats' hippocampus after ECT (66). VNS was introduced in 1988, has been tested in clinical trials, and, since then, it has been implanted in thousands of patients with drug-resistant epilepsy. Despite being used for more than 30 years, the mechanism of action is not entirely elucidated. There are suggestions that VNS influences the limbic structures' function by altering the concentration of GABA and glutamate (67). Norepinephrine and serotonin levels can also be influenced by VNS function through impact on the locus coeruleus and the dorsal raphe nuclei (68). Moreover, changes in the brain's functional connectivity have been proposed as another possible effect of VNS. Recent studies have shown that changes in synchronization in specific frequency bands are different between responders and non-responders (69). Alteration of functional connectivity was also seen in a study using data from stereo-EEG recordings in patients with VNS. The connectivity could be either increased or decreased but was found decreased in the only patient who was a VNS responder (70). Similarly, the way DBS exerts its effects remains obscure. A major difference from other neuromodulation techniques is that a specific brain region is directly stimulated. It is not clarified whether the therapeutic effect is caused by the stimulation of neurons, glial cells, or fibers (71) by inhibition mediated by activation of GABAergic afferents or the inactivation of voltage-gated currents (71, 72).

These suggested mechanisms possibly reflect a change in excitation/inhibition balance which might facilitate the early termination of SE. However, immunological changes have also been described as a result of neuromodulation. More specifically, the effects of anterior thalamic nucleus DBS on plasma pro-inflammatory cytokine IL-6 and the anti-inflammatory cytokine IL-10 on a population with drug-resistant epilepsy were explored recently (73). The authors found that the IL-6/IL-10 ratio decreased significantly over time following DBS treatment and responders had an increase in IL-10. In the same direction, there is evidence that VNS can have an impact on inflammatory disorders by evoking a protective decrease in pro-inflammatory cytokines and the pro- and anti-inflammatory cytokine balance can indicate a positive outcome of VNS (74, 75). As the available data about NORSE/FIRES grows, it appears that autoimmune encephalitis is the most common cause and cryptogenic NORSE cases are possibly immune-mediated, but unidentified autoantibodies or inadequate work-up cause a failure in cause establishment. Moreover, elevated pro-inflammatory cytokine/chemokine levels are found in many cases (76). The second-line immune therapies for NORSE interfere with inflammation-related interleukin

action. Based on these observations, new studies exploring the possible anti-inflammatory effect and possible synergistic action of neuromodulation techniques would be of great interest and could possibly improve understanding of the delayed effect seen in a big number of cases.

This review has several limitations. The number of patients who have undergone neuromodulation for NORSE/FIRES is too low to provide robust results and allow guidance. Moreover, there is a high chance of significant reporting bias with successful neuromodulation cases being more likely to be submitted for publication compared to the ones where neuromodulation did not provide benefit. Furthermore, the grouping of cases under the umbrella of NORSE/FIRES might not be entirely accurate due to differences in diagnostic algorithms used in different centers and for some older cases. Similarly, the treatment approaches present major differences between patients, and this would be expected to have an impact on the published outcomes. Despite these drawbacks, we believe that this work provides meaningful data for neuromodulation treatment consideration in NORSE/FIRES.

Conclusion

This systematic review attempts to present the available data on the use of neuromodulation for the treatment of NORSE/FIRES. Three neuromodulation techniques have been reported for NORSE/FIRES cases with encouraging outcomes, either with non-invasive (ECT) or with implantable devices (VNS and DBS). DBS caused the termination of SRSE in all four cases, but no neuromodulation technique appeared clearly superior to the others. The goal of neuromodulation remains the termination of SRSE as early as possible, aiming to reduce mortality; however, there is no evidence of differences in long-term outcomes. The application of neuromodulation has not been tested through randomized, prospective controlled clinical trials, as has most of the other available treatments for this devastating condition, but the existing data show some potential benefit of neuromodulation therapy, suggesting that these techniques could be considered within the course of NORSE.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

IS, JK, and AV wrote the manuscript. JK and IS performed the literature review. JK performed the search and prepared the graphs. All authors reviewed and approved the final version of the manuscript.

Conflict of interest

AV has received honorarium for lectures and consultancy from Medtronic Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1195844/full#supplementary-material

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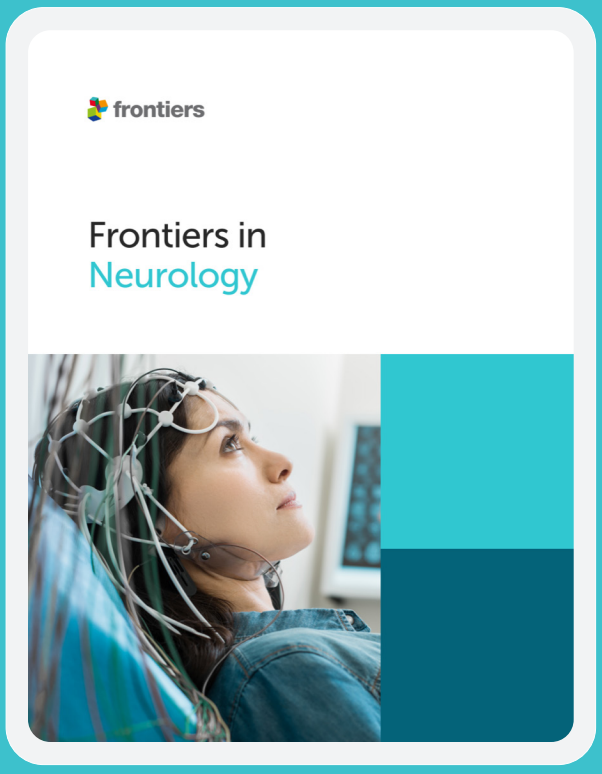

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