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Review

New onset refractory status epilepticus (NORSE)

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ABSTRACT

Purpose: To summarize the clinical features, suggested work-up, treatment and prognosis of new-onset refractory status epilepticus (NORSE), a condition recently defined as the occurrence of refractory status epilepticus (RSE) in a patient without active epilepsy, and without a clear acute or active structural, toxic or metabolic cause; and of the related syndrome of febrile infection-related epilepsy syndrome (FIRES), also recently defined as a subgroup of NORSE preceded by a febrile illness between 2 weeks and 24 h prior to the onset of RSE.

Method: Narrative review of the medical literature about NORSE and FIRES.

Results: NORSE and FIRES mainly affect school-age children and young adults. A prodromal phase with flu-like symptoms precedes the SE onset in two third of NORSE cases, and by definition in all FIRES. Status epilepticus usually starts with repeated focal seizures with secondary bilateralization. Most cases evolve to super RSE (SRSE) and have unfavorable outcome, with short-term mortality of 12–27%, long-term disability and epilepsy. No specific imaging or laboratory abnormalities have been identified so far that allows an early diagnosis and half of adult cases remain of unknown etiology. A standardized diagnostic algorithm is provided and. Autoimmune encephalitis is the most frequent identified cause. In the absence of specific diagnosis, immunotherapy could be tried in addition to antiepileptic treatment.

Conclusions: This review presents the rare but devastating syndrome of NORSE, including the subcategory of FIRES. Early recognition with complete work-up is primordial to identify the underlying cause and promptly start appropriate treatment.

1. Introduction and new definitions

New-onset refractory status epilepticus (NORSE) is a rare but devastating condition. Overall, approximately 200 cases of NORSE in adults [1–12] and 200 cases of FIRES in children [13–30] have been reported in the literature.

This term was used for the first time by Wilder-Smith et al [1] to describe cases of super refractory status epilepticus (SRSE) without a previous history of epilepsy and with no identifiable underlying cause. However, other definitions have been applied for the term in subsequent studies [2,3]. Similar conditions have also been described under various names in children, including severe refractory status epilepticus due to presumed encephalitis [31], idiopathic catastrophic epileptic encephalopathy presenting with acute onset intractable status [13], devastating epileptic encephalopathy in school-age children (DESC) [14], acute encephalitis with refractory repetitive partial seizures (AERRPS) [15] and febrile infection-related epilepsy syndrome (FIRES) [16], also called fever-induced refractory epileptic encephalopathy of school-age children [32] or fulminant inflammatory response epilepsy syndrome [33]. In the latter, the presence of a febrile episode prior to the onset of SE is by definition required. While fever often precedes the onset of seizures in adults with NORSE [4], its presence has never been required to make the diagnosis. Some authors have argued that NORSE and FIRES are distinct entities [34]. However, apart from age and fever, the two syndromes do in fact share many similarities (see below) and most authors now believe they are identical or at least belong to the same category of disease [35,36].

Until recently, the lack of a standardized terminology was a limitation to clinical research. This motivated the introduction of consensus definitions [36]. According to this recent proposal, NORSE is defined as a clinical presentation, in a patient without active epilepsy, with new onset of refractory status epilepticus (RSE) without a clear acute or active structural, toxic or metabolic cause [36]. It includes cases with a known etiology, when it is not easily identified by the

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recommended initial investigations by imaging (including brain MRI) and lumbar puncture (including PCR for HSV-1), which are typically obtained within 72 h after admission. This definition allows ruling out usual causes of status epilepticus (SE) such as acute strokes, brain masses, drug overdoses, etc. On the other hand, cases due to viral infection of CNS (except HSV1 encephalitis) or auto-immune encephalitis are included [36].

A definition of FIRES has also been proposed, defining it as a subgroup of NORSE preceded by a febrile illness between 2 weeks and 24 h prior to the onset of refractory status epilepticus, and removing any age criteria [36].

An etiology is identified in approximatively 50% of adult cases of NORSE. The majority of cases with a known etiology are due to sporadic or paraneoplastic auto-immune encephalitis [4]. In case series of children with FIRES, the cause is almost always unknown but the lack of etiological diagnosis was likely an inclusion criteria for these studies, introducing a selection bias [14,16,20,21]. Further, those series are small and the diagnostic work-up is variable and often incomplete. Also, many published cases predates the description of encephalitis caused by more recently identified antibodies to neuronal surface antigens, such as anti-gamma-amino-hydroxybutyric acid [GABA](A) receptors [13,14,18].

2. Epidemiology of NORSE and FIRES

NORSE and FIRES most frequently occurs in previously healthy young adults and school-aged children, although adults above 60 can also be affected. There is a female predominance in most adult series [1–4,12] while boys are more frequently affected than girls in pediatric series [37]. The incidence is unknown but it can be estimated that they represent up to 20% of cases of RSE [38,39]. It is likely that many cases have been previously mislabeled as “possible” or “presumed” viral encephalitis as they often fulfill the diagnostic criteria for these entities [31,40].

3. Clinical features and prognosis of NORSE and FIRES

In adults, a non-specific mild illness with gastro-intestinal, upper respiratory or flu-like symptoms precedes the onset of seizures in two-third of cases [4], and in up to 90% of cases of unknown cause [12]. Fever is documented in at least a third of adult cases of NORSE [34] and is by definition the rule in FIRES. [33,4,37].

This prodromal phase precedes the onset of seizure and SE by 1–14 days. [33,4,37] and the patient may be asymptomatic for a few days during the interval. Seizures are initially brief and infrequent, increasing within a few hours to days in frequency (up to hundreds per day) and evolving into SE, which usually requires ICU admission and anesthesia. The most frequent seizure type is focal seizure with secondary bilateralization [4,19,37].

3.1. EEG results

The EEG shows various kinds of sporadic or periodic epileptiform discharges, which can be lateralized, bilateral independent or multifocal, often involving the temporal and frontal regions. Generalized discharges have also been reported [14,4].

Recently, a retrospective analysis suggested that FIRES was characterized by three EEG findings: beta-delta complexes resembling extreme delta brush, seizure onset with prolonged focal fast activity, followed by the gradual appearance of well-formed rhythmic spike or spike-and-wave complexes, and shifting ictal activity [23]. These preliminary findings deserve further study and confirmation.

3.2. Laboratory and imaging results

About 70% of cases show an abnormal MRI with T2/FLAIR hypersignal located in limbic and/or neocortical areas, often bilaterally [4]. Basal ganglia [14] and peri-insular [20] involvement have also been reported. When repeated, a diffuse atrophy appears in one third of cases [18–20]. Two recent studies highlighted the presence of peculiar transient bilateral claustral T2/FLAIR changes in adult and children with NORSE or FIRES [5,41]. It is unclear if these findings are specific to these conditions, thus suggesting a specific pathogenic mechanism, or if they are merely the consequence of prolonged ictal activity.

Half to two-third of the cases of unknown etiology present mild CSF pleocytosis (less than 10 cells/μl) and slightly increased protein level [4,42],but these findings could result from the intense seizure activity rather than indicate an inflammatory or infectious etiology.

3.3. Outcome

Most cases of FIRES and NORSE evolve to SRSE, a category of SE associated with prolonged intensive care unit (ICU) stay and poor outcome [15,16,19,42].

The median duration of ICU stay in FIRES and NORSE ranges from 20 to 40 days in children [14,16,18,19] and 15 days in adults [4]. Mortality rate is around 12% in children [42] and reaches 16 to 27% in adults [2–4,6], with neurological sequelae in most survivors. Long-term outcome is often poor with half to two-third of the survivors developing cognitive impairment and functional disability, including vegetative state, and only a small proportion of patients being able to resume their previous life [13,15,16,4,17–21]. Drug-resistant epilepsy is the rule in most survivors. Factors associated with worse outcome include the duration of SE and the occurrence of medical complications [4]. One large retrospective study found that the use and duration of barbiturate coma was associated with worse outcome in children with FIRES [42]. Similarly, one study in adults with NORSE found that the number of anesthetic drugs used was associated with poorer outcome [4]. Given the retrospective and observational design of these studies, it is unclear whether this association indicates an independent effect of anesthesia and its complications or is rather due to the variability in severity and refractoriness. Prospective randomized controlled studies are required to settle this question.

4. Known etiologies and clues to these etiologies

According to recent definitions, NORSE etiology is either unknown (previously called cryptogenic) or an unusual cause is identified after an extensive work-up. Close to 200 uncommon causes of SE have been reported in the literature [38,43] and can be divided in 4 categories: inflammatory and autoimmune encephalitis, uncommon infectious encephalitis, genetic disorders and toxic disorders. As indicated above, the most frequent identified cause is autoimmune encephalitis [3,4,6], including sporadic and paraneoplastic cases, highlighting the importance of a complete auto-immune workup which should be early set up in case of RSE without a straightforward cause. The most frequently identified antibodies target the N-methyl-D-aspartate (NMDA) receptor and the voltage-gated potassium channel (VGKC) complex. No antibody has been found in pediatric cohort except some anecdotal cases [22,44–47]. One study found anti-glutamate receptor (GluR) epsilon 2 antibodies in the CSF of a few FIRES cases but their role and significance remain unknown [15].

Some clinical features can suggest a specific underlying etiology (Table 1). For instance, paraneoplastic limbic encephalitis, which is exceptional in children but occurs more frequently in adults, is characterized by cognitive impairment, behavioral changes, sleep disturbances, and seizures. Status epilepticus is usually not a prominent manifestation [38,48]. Anti-NMDA receptor encephalitis is the leading cause of autoimmune encephalitis, with 40% of patients being younger than age 18 years [49] and often starts with febrile illness. Then patients develop psychiatric symptoms, manifesting in children as behavioral disturbances and tantrums. Children are more likely to present

Table 1
NORSE: Prominent presentation features of the most frequent etiologies.

Categories	*	Most frequent findings	Clinical clues
Unknown	50%		No specific findings Prodromal mild febrile illness in 65% of cases Typically severe and prolonged SE
Inflammatory and auto-immune encephalitis	40%	Paraneoplastic limbic encephalitis (Anti-Hu, -Ma2/Ta, -CV2/CRMP-5, -amphiphysin, -VGCC, -mGluR5)	Cognitive, especially memory impairment, behavioral changes, temporal lobe seizures, sleep disturbance Hu: often more diffuse encephalomyelitis Ma2/Ta: hypothalamic dysfunction CV2/CRMP5: diffuse encephalomyelitis, chorea
		Surface-binding autoantibodies	
		Anti-NMDAr	Mostly young females Prodromal fever, short-term memory loss, psychiatric symptoms, hallucinations, oro-lingual dyskinesia, autonomic and respiratory failure *Children*: behavioral changes, movement disorders *EEG*: extreme delta brushes (50%)
		Anti-VGKC complex	Mostly elderly males LGI-1: limbic encephalitis, facio-brachial dystonic seizures, SIADH Caspr2: episodic ataxia
		Anti-GABA(B)r	Limbic encephalitis
		Anti-GABA(A)r	Multifocal neocortical encephalitis
		Anti-AMPAr	Prominent psychiatric symptoms, cerebellar ataxia
		Anti-Glycine-r	No specific features
		Anti-GAD	No specific features
		Steroid responsive encephalopathy with autoimmune thyroiditis	Rapid-onset dementia, myoclonus, stroke-like episodes Anti-TPO, anti-TG
Infectious encephalitis	10%	HSV1	Temporal involvement
		Enterovirus	Rash, acute lower motor neuron syndrome
		CMV	*Immunodeficiency*: Gastro-intestinal symptoms, retinitis, pneumonitis
		EBV	Adenopathies, ataxia
		VZV	*Immunodeficiency*: CNS lymphoma
		Mycoplasma pneumoniae	Rash
		Bartonella henselae	Respiratory symptoms, EEG: extreme spindles
		Arboviruses (West Nile virus, tick-borne virus etc..)	Children. Cat-scratch disease with skin lesion and regional adenopathy Flu-like episode; WNV: parkinsonism, acute lower motor neuron syndrome, EEG: triphasic waves
Genetic disorders	Rare	SCN1A	Dravet syndrome
		PCDH19	Epilepsy and mental retardation limited to female
		CADASIL	Migraine, strokes, visual problems, cognitive deterioration
		Mitochondrial disorders	Elevated CSF lactate and stroke-like episodes.
		MELAS	Occipital seizures, *epilepsia partialis continua*, liver failure, nystagmus, ataxia.
		POLG1	

*Proportions mainly reflect adult population. There is a lack of data in pediatric population.
Abbreviations: AMPAalpha-amino-3-hydroxy-5-méthylisoazol-4-propionate; GABA; gamma aminobutyric acid; CADASIL; cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Caspr2contactin associated protein 2; CMVcytomegalovirus; CNScentral nervous system; CSFcerebrospinal fluid; EBVEpstein-Barr virus; EEGelectroencephalogram; GADglutamic acid decarboxylase; HSVherpes simplex virus; LGI1Leucine-rich glioma inactivated 1; MELASsyndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; NMDA; N-methyl-D-aspartate; PCDHprotocadherin; POLG1mitochondrial DNA polymerase gamma; SIADHsyndrome of inappropriate antidiuretic hormone secretion; SCNneuronal voltage-gated sodium channel; SEstatus epilepticus; TGthyroglobuline; TPOthyroperoxydase; VGKCvoltage gated potassium channel-complex; VZVvaricella-zoster virus; WNVWest-Nile virus.

movement disorders, seizures and SE than adults. Rapid disintegration of speech and language, hyperactivity, and irritability are often seen, then progression to decreased responsiveness and severe catatonic stage, with typical oro-lingual dyskinesia and autonomic failure [48,50,51]. The EEG shows a specific pattern of 'extreme delta brushes' in 50% of cases [52,53]. Encephalitis with anti- VGKC complex (LGI1 or, more rarely Caspr2) antibodies are associated with limbic encephalitis and a syndrome of inappropriate secretion of antidiuretic hormone (SIADH).Pathognomonic facio-brachial dystonic seizures can occur in anti-LGI1 encephalitis. Rare pediatric cases of SE associated with an unspecified anti-VGKC complex antibody have been reported [54]. No specific findings have been demonstrated in cryptogenic NORSE cases. They broadly have similar clinical course than patients with NORSE caused by auto-immune encephalitis, albeit with a longer SE duration [4]. A retrospective study compared the clinical features of 11 cryptogenic NORSE with anti-NMDA receptor encephalitis and revealed more frequent prodromal fever, symmetric brain MRI abnormalities, had less frequent involuntary movements, absent psychobehavioral symptoms, and had more severe SE with ventilatory support requirement [12].

5. Current hypothesis for cases with unknown etiology

Despite an extensive, albeit variable, workup, half of adult NORSE cases remain cryptogenic. However, their clinical features do not differ much from autoimmune cases, suggesting a similar etiology. It is possible that some cryptogenic cases correspond to autoimmune encephalitis associated with antibodies not yet identified. In particular, the prevalence of CSF abnormalities was similar in both cryptogenic cases and cases with an autoimmune or infectious etiology.

In children, elevated levels of pro-convulsant cytokines (interleukin-6, e.g.) have been documented in the CSF, suggesting an inflammatory cause [55]. Those cytokines could be the consequence of a viral infection, explaining the previous febrile illness, and could occur in the setting of a genetic predisposition [33,25]. Genetic analyses have also been disappointing so far [56] but a recent study demonstrated an association with polymorphisms in the interleukin 1 receptor antagonist (IL1RN) gene [25], further suggesting an immune basis.

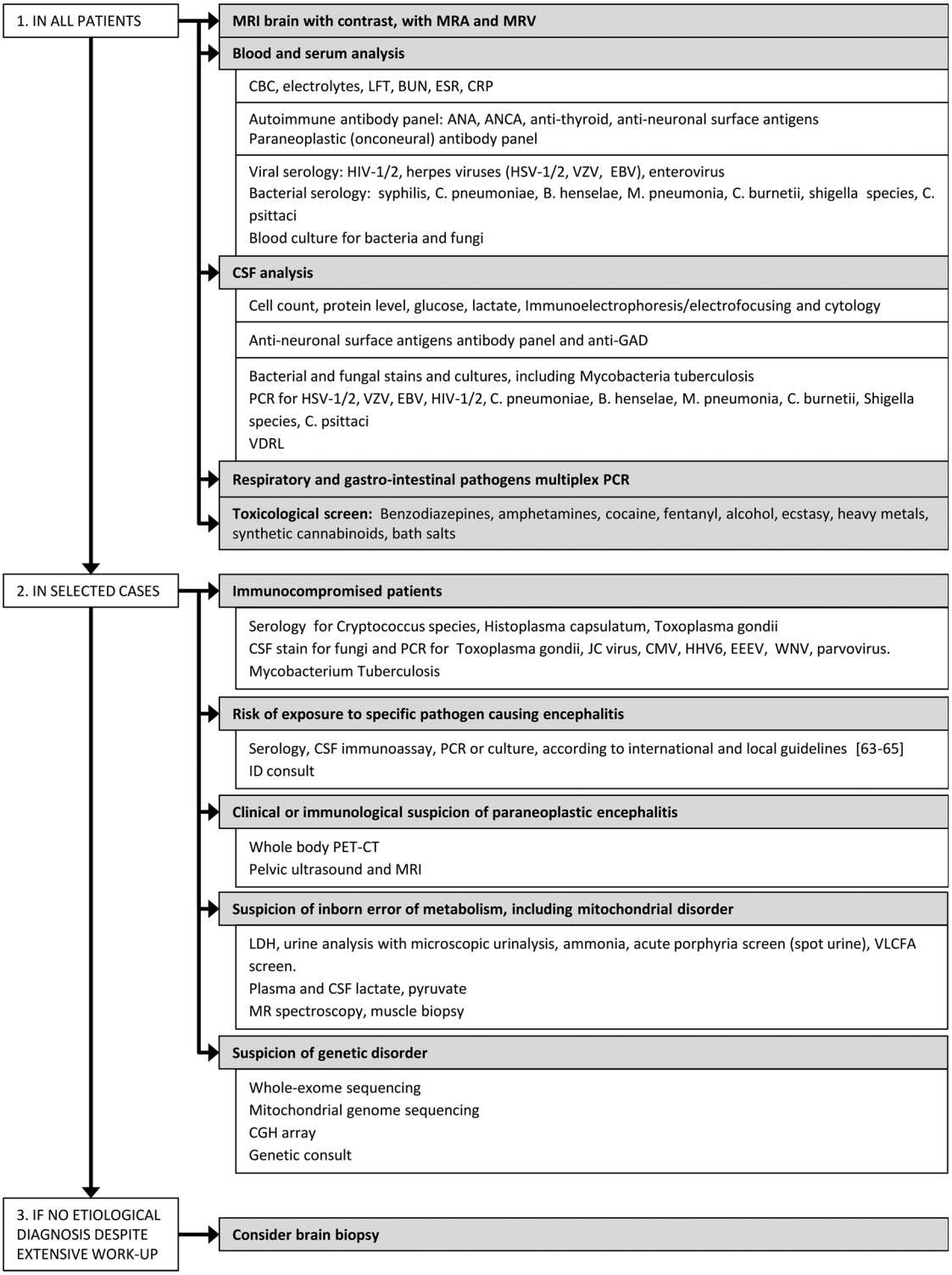

Fig. 1. Adapted from http://www.norseinstitute.org/definitions/http://www.norseinstitute.org/definitions/ [63–65].
ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies ; B. henselae: bartonella henselae; BUN: blood urea nitrogen; CBC: Complete blood count; C. burnetii: coxiella burnetii; CGH: comparative genomic hybridization; CMV: cytomegalovirus; CNS: central nervous system; C. pneumoniae: chlamydia pneumoniae; C. psittaci: chlamydia psittaci; CRP: C-reactive protein; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; EBV: Epstein-Barr virus; EEEV: Eastern equine encephalitis virus; EEG: electroencephalogram; ESR: erythrocyte sedimentation rate; GAD: glutamic acid decarboxylase; HHV: human herpesvirus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; ID: immunodeficiency; LDH: lactate dehydrogenase; LFT: Liver function tests; M. pneumonia: mycoplasma pneumonia; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; MRV: magnetic resonance veinography; PCR: polymerase chain reaction; PET-CT: positron emission tomography–computed tomography; VLCFA: very long chain fatty acid; VDRL: venereal disease research laboratory; VZV: varicella-zoster virus; WNV: West-Nile virus.

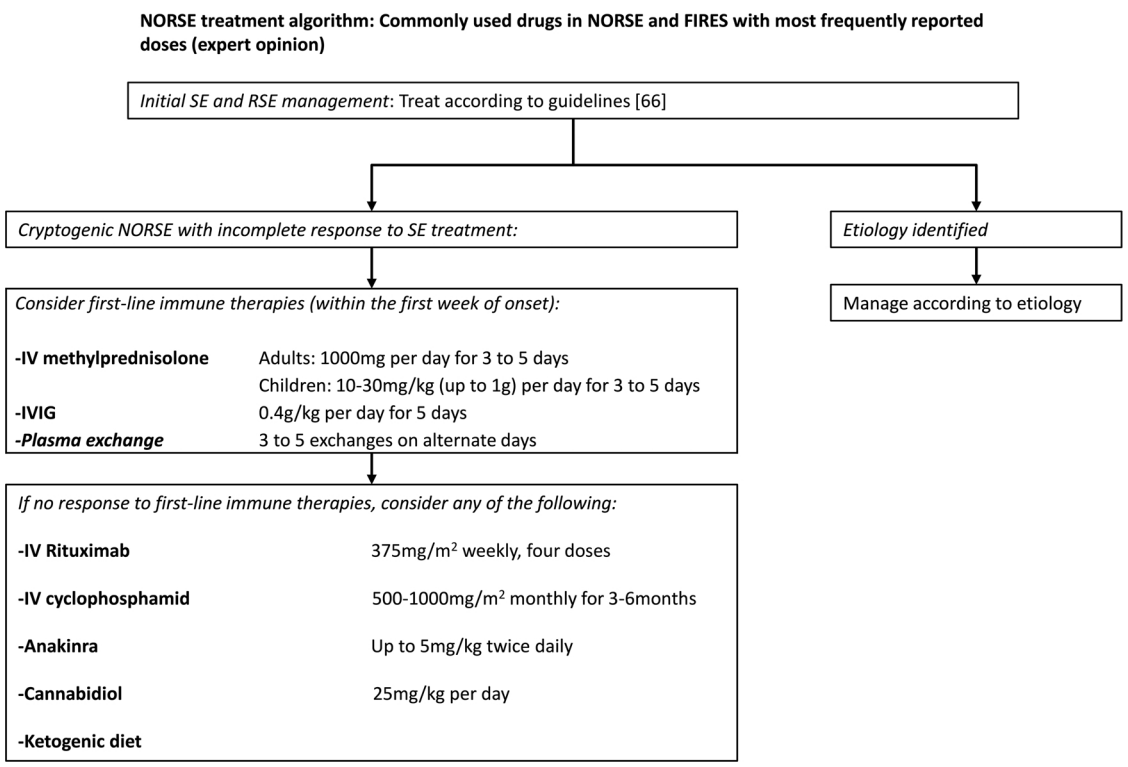

Fig. 2. NORSE treatment algorithm: Commonly used drugs in NORSE and FIRES with most frequently reported doses (expert opinion) [66].
Adapted from Gaspard et al, 2018 [39] and van Baalen et al, 2017 [10].
IV = intravenous; IVIG = intravenous immunoglobulin; RSE: refractory status epilepticus, SE: status epilepticus.

6. Diagnosis of NORSE and FIRES

In the absence of a specific diagnostic test, the diagnosis of NORSE and FIRES is made on clinical grounds after the initial workup rules out obvious causes of RSE, which usually takes 48–72 h.

Extensive investigations should then be performed to identify a rare cause of SE. These investigations should focus on autoimmune and uncommon infectious etiologies and take into account the specifics of each case. A diagnostic decision tree is available in Fig. 1 and on the NORSE institute website http://www.norseinstitute.org/definitions/.

No validated tests are available to distinguish FIRES from a febrile RSE, a very different entity with good outcome. Theoretically, children with febrile SE present high fever at SE onset while children with FIRES had fever within the two previous weeks.

Association between FIRES cases and elevated cytokine levels in the CSF or predisposing genetic factors [15,25] should be confirmed they can be used. Similarly the occurrence of peculiar MRI changes in the claustrum should be further explored as candidate diagnostic tests [5].

7. Treatment of NORSE and FIRES

Treatment with anti-seizure medications is often disappointing. At least 75% of patients require anesthetics in continuous infusion and prolonged burst-suppression coma is often unavoidable to stop the seizures. Status often resumes once the anesthetics are weaned off [33,37]. At least a third of patients require multiple anesthetic drugs to achieve seizure control [4,37].

In adults, some studies have suggested better outcome with immunotherapies. This hypothesis is supported by the fact that half of NORSE cases are caused by auto-immune encephalitis. Early immune therapy is then recommended by experts, as delaying treatment may contributes to worse outcome, as in auto-immune and viral encephalitis [39,57,58]. These include first-line (steroids, intravenous immunoglobulins, and plasma exchange) and second-line therapies (e.g., tacrolimus, rituximab, cyclophosphamide, anakinra). However prospective controlled studies are lacking

In children, immunotherapies seem less effective [15,47]. Multiple different therapeutic options have been reported in small case series and none seems to be superior, with the possible exception of the ketogenic diet [17,59]. Nabbout et al highlighted the efficiency of this therapeutic diet on 8 children, with 7 them showing improvement after 1 to 4 days of ketonuria. This treatment is already known to be efficient in RSE in children of any cause and experts recommend to start it as soon as possible, once FIRES is suspected, e.g., from second day of super-refractory SE [33]. The efficacy of the ketogenic diet in SRSE in adults, including possible cases of NORSE, has also been suggested [60].

Cannabidiol (CBD) is a recent potential alternative therapy in epilepsy and has been shown to improve seizure frequency and duration in 6 out of 7 children, mainly in the chronic phase. However only on was seizure free and all had cognitive sequelae [61].

Anakinra, a recombinant version of human Interleukin(Il)-1 receptor antagonist, was successful in a single case of a 32-months-old girl with FIRES who received 5 mg/kg twice daily. The drug was well tolerated and effective, leading to a dramatic seizure reduction on 3 separate occasions in the same patient, however no long-term follow-up is available [26,39].

Those therapeutic options, as well as hypothermia at 33 °C [62], ketamine, lidocaine, need to be validated by large and prospective studies. A suggested algorithm for the use of these therapies is presented in Fig. 2, with their suggested dosing.

8. Conclusion

NORSE and FIRES are rare but devastating epileptic disorders, occurring in previously healthy patients. Uncommon but treatable etiologies, such as autoimmune encephalopathies, can be identified in some patients, especially adults, motivating extensive investigations. However a majority of cases remain without a known etiology and little

is currently known about the underlying pathologic mechanism, although an inflammatory cause is suspected. Treatment is usually disappointing and outcome is often poor, although a minority of patients may resume their previous life. The ketogenic diet appears promising but requires larger prospective studies. The recent publication of consensus definitions will help future research, with the aims to understand the cause and to improve patient care.

Conflict of interest

The authors have no conflict of interest to declare.

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