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Research Paper

New-Onset Refractory Status Epilepticus With Diffuse Cerebral Restricted Diffusion in Young Children: A Novel Clinical-Radiologic Presentation

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ABSTRACT

Background: New-onset refractory status epilepticus (NORSE) is a clinical presentation characterized by explosive-onset refractory status epilepticus (RSE) without evident etiology or active epilepsy, often leading to devastating epilepsy. There is heterogeneity in neuroradiographic findings for NORSE. We encountered a series of young patients with NORSE who had diffuse cerebral restriction in diffusion (DCRD) with similar radiographic appearances as acute encephalopathy with biphasic seizures and late restricted diffusion/acute leukoencephalopathy with restricted diffusion (AESD/ALERD). We explore clinical similarities and proposed pathophysiologic overlaps to highlight a novel clinical-radiologic presentation.
Methods: Retrospective review was completed for patients younger than five years meeting NORSE criteria and then screened for radiographic evidence of DCRD. Demographic, clinical, and outcome data were collected.
Results: Eleven patients met NORSE criteria, of whom seven displayed DCRD. Immunosuppressant management varied. All patients required multiple antiseizure medications and continuous infusions for RSE. Only one had an etiology identified (genetic). All but one patient developed diffuse, global, and progressive cerebral atrophy. Two patients died: one after prolonged seizure three years post-NORSE and another of unknown causes two months post-NORSE. Of five survivors, three have medically refractory epilepsy. Most survivors have severe disability.
Conclusions: We present a single-center case series of seven patients with NORSE and DCRD, akin to AESD/ALERD. Our patients differed clinically to AESD/ALERD in terms of seizure severity and poorer outcome. There is a need to develop biomarkers for specific NORSE phenotypes. The young child with NORSE and DCRD may represent a novel phenotype with a specific neuroradiographic signature that deserves further attention.

Introduction

The clinical presentation of new-onset refractory status epilepticus (NORSE) is rare and poses a diagnostic challenge, especially in young children. NORSE is characterized by an episode of explosive-onset refractory status epilepticus (RSE), which lacks a clear active metabolic, structural, toxic, or infectious etiology alongside the absence of pre-existing active epilepsy or related neurological disorders.[1] Patients who present with NORSE following fever in the preceding one to 14 days are classified as having febrile infection-related epilepsy syndrome (FIRES), a subcategory of NORSE.[1-3] Extensive diagnostic evaluation is necessary to determine the underlying etiology for NORSE; around 50% of NORSE cases remain cryptogenic.[4] Cryptogenic NORSE is usually refractory to classical immunotherapies, and patients are often left severely impaired with poorer outcomes.[5,6] In previous literature, the diagnosis of NORSE was reserved for adult patients, whereas

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the clinical presentation of FIRES was thought to be limited to pediatric patients.[3,7] However, clinical understanding has evolved so that both terms can be utilized in patients at any age,[8-10] including young children.

As the clinical definition of NORSE requires the absence of a pre-existent "active epilepsy," it is difficult to determine in young children whether their epilepsy has begun explosively. There are pediatric epilepsies that may present with an explosive onset in a previously typically developing child, such as *TANGO2*,[11] *PCDH19*,[12] *ALG6-CDG*,[13] and *POLG1*/Alpers-Huttenlocher syndrome.[14] Although there is paucity of data describing NORSE in young children, there exist sparse reports of NORSE and FIRES in patients younger than five years; the largest case series presents 21 children aged less than one year at the time of NORSE[15] including a case report of a genetic-associated NORSE secondary in a seven-month-old female.[12]

Neuroimaging, particularly brain magnetic resonance imaging (MRI), plays a key role in NORSE; it is indispensable to rule out structural etiologies for RSE, and is often performed serially throughout a patient's course, even in the chronic stage. Although there are no neuroradiologic stigmata of NORSE, 50% to 80% of patients have abnormal findings on MRI.[16-18] Reported findings typically include T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in the neocortex, basal ganglia, limbic system, mesial temporal region, splenium, claustrum, and periventricular white matter.[16] Restriction in diffusion as an ictal manifestation of RSE (not isolated to NORSE) has also been described in neocortical and/or in non-neocortical regions.[19] However, global restriction in diffusion as a neuroradiographic manifestation of NORSE has not been described.

We present a cohort of children aged less than five years with NORSE and global restriction in diffusion. We explore pathophysiologic reasons for this radiographic expression and compare with other pediatric conditions that present with seizures and diffuse global restriction in diffusion. We aim to amplify the spectrum of the clinical and radiologic presentation of NORSE in young children.

Methods

We performed a single-center retrospective review of all patients under age five years presenting from June 1, 2013, to July 12, 2023, with new-onset seizures refractory to antiseizure medications (ASMs), meeting clinical criteria for a NORSE diagnosis. We additionally searched for all patients under age five years who received pentobarbital; at our institution this medication is only utilized via continuous infusion (CI) for management of RSE (as opposed to sedation). Patient charts were reviewed to only include patients who had an episode of RSE as their first seizure presentation. We excluded patients with a history of epilepsy or neurological disorder and in whom there was a confirmed underlying etiology within 72 hours of presentation (i.e., bacterial meningitis, traumatic brain injury, acute ischemic stroke, etc.). We then selected patients who had evidence of global cerebral restriction in diffusion-weighted brain MRI, confirmed by official radiology report and secondarily confirmed by authors. We obtained information pertaining to demographic, laboratory studies, clinical course, paraclinical tests, and outcomes.

Institutional review board approval was provided to complete this study from Medical College of Wisconsin/Children's Wisconsin.

Results

Patient history and presentation

We screened 458 charts of patients aged under five years who presented with RSE. We found 11 patients who met clinical criteria for NORSE. We then screened for the presence of diffuse cerebral restriction on brain MRI, a finding noted in seven patients. These seven patients were included in the final study (Table 1).

The median age at NORSE presentation was seven months (interquartile range [IQR] 6 to 41). All patients were healthy prior to presentation. Four had a pre-existent fever prior to NORSE, meeting criteria for FIRES. All patients underwent a broad infectious, structural, and genetic evaluation. One patient had a biphasic course, presenting as RSE with relative initial improvement before worsening.

Acute hospital course, medications and therapies

A summary of each patient's clinical management and hospital course is listed in Table 2. All seven patients received multiple ASMs (median 5 [IQR 4 to 7]). All patients also received two or more CIs, the duration of which lasted a median of 11 days [IQR 8 to 15]. Six of the seven patients were trialed on the ketogenic diet in efforts to control persistent RSE. Some form of first-line immunotherapy was administered in four patients for presumed inflammatory contribution to seizures. Median duration of hospitalization and intensive care unit stay was 56 days [IQR 24 to 61] and 14 days [IQR 11 to 13], respectively.

Diagnostic evaluation

Diagnostic evaluation for all seven patients is listed in Table 1. After a broad general, infectious, and genetic evaluation, all but one case were deemed cryptogenic. Noonan syndrome was diagnosed in one child (Patient 4) and considered not to be causal of his RSE presentation. Patient 6 had a cryptogenic etiology for several years, until re-examination of whole genome revealed a homozygous 32.96-kb deletion that encompasses exons 3 to 9 of the *TANGO2* gene, causative of autosomal recessive *TANGO2* deficiency, also known as *TANGO*-related metabolic encephalopathy and arrhythmias.

Three patients had brain MRI performed upon arrival, which was normal in all. Eventually, all patients had either the MRI repeated or performed, and all had diffuse, global cerebral restriction in diffusion, sparing the basal ganglia in three (Table 3, Fig). Six patients had brain MRI performed in the chronic state of NORSE, wherein all but one (Patient 2) had diffuse, global cerebral atrophy that developed throughout hospitalization and NORSE course.

Outcomes

At the time of preparation of this manuscript, two patients have died, a mortality rate of 28.6% ($n = 2/7$). Patient 5 died after a prolonged seizure three years following initial NORSE presentation, and Patient 6 died of unknown causes two months after NORSE episode. Of the five patients who survived, three have medically refractory epilepsy, although all remain on ASMs. The majority of survivors ($n = 4/5$, 80%) have severe degree of disability with a Pediatric Cerebral Performance Category score of 4.

Discussion

We describe a single-center case series of seven young patients with NORSE with imaging findings notable for global cerebral restriction in diffusion. All patients were admitted to the pediatric intensive care unit with seizures that necessitated use of multiple ASMs and CIs for control of RSE and had prolonged hospitalizations. Outcomes were poor; two died and the five survivors had moderate to severe disabilities. Three of the surviving children have medically refractory epilepsy. After extensive diagnostic evaluation, all but one were considered cryptogenic. This dual presentation of NORSE

TABLE 1.
Demographics, Clinical Presentation, Diagnostic Evaluation Methods

Patient #	Age at Presentation (mo.)/Sex	Past Medical History/ Development	Family History of Epilepsy	Clinical Presentation /Mono- vs Biphasic	General Evaluation	Infectious Evaluation	Genetic Evaluation
1	12/M	None	Relatives with febrile seizures	Fever, RSE, brief CA during intubation/ monophasic	CT, MRI, LP, NTM, AC, LaPy, OAA	CSF study: MEP. *Parechovirus*, COVID-19	WES; mitochondrial DNA sequencing; SDDA
2	41/F	Speech delay	Uncle with tumor-related epilepsy	Emesis, rash, encephalopathy, RSE/ monophasic	CT, MRI, LP	CSF studies: MEP, AEP, HSV, arbovirus, West Nile, adenovirus, coxsackie, *Enterovirus*, HIV. Tick-borne panel, *Mycoplasma*, *Chlamydia*. Abs: *Brucella*, *Bartonella*, *Babesia microti*, Powassan	Pediatric disease sequencing panel with CNV detection
3	6/M	None	None	Fever, RSE, encephalopathy, hyperglycemia, hepatitis/monophasic	CT, MRI, LP, NTM, AC, LaPy, OAA, GDF-15	HSV	SDDA
4	48/M	Speech delay	Older sibling: seizures after neonatal encephalopathy	Fever, RSE, encephalopathy/ monophasic	CT, MRI, LP, NTM, AC, LaPy, OAA, GDF-15	CSF studies: MEP, AEP, HSV, *enterovirus*	SDDA; neonatal crisis sequencing panel with CNV detection
5	7/M	None	None	Fever, RSE, apnea/ monophasic	CT, MRI, LP, NTM, AC, LaPy, OAA	CSF studies: MEP, AEP, HSV COVID-19	WES, SDDA
6	3/F	None	Father with epilepsy	RSE, encephalopathy/ monophasic	CT, MRI, LP, NTM, AC, LaPy, OAA	CSF studies: MEP, AEP, HSV COVID-19	SDDA
7	6/M	None	Brother with epilepsy (same presentation)	RSE, apnea, CA, hypoglycemia/biphasic	CT, MRI, LP, NTM, AC, LaPy, OAA	CSF studies: MEP	WES, WG, SDDA

Abbreviations:
Ab = Antibody
AC = Acetylcarnitine
AEP = Autoimmune encephalitis panel
CA = Cardiac arrest
CNV = Clinical number variant
COVID-19 = Coronavirus disease 2019
CSF = Cerebrospinal fluid
CT = Computed tomography
F = Female
GDF-15 = Growth differentiation factor 15
HIV = Human immunodeficiency virus
HSV = Herpes simplex virus
LaPy = Lactate and pyruvate
LP = Lumbar puncture
M = Male
MEP = Meningoencephalitis panel
MRI = Magnetic resonance imaging
NTM = Neurotransmitter
OAA = Organic and amino acids
RSE = Refractory status epilepticus
SSDA = Epilepsy gene panel involving sequence and deletion/duplication analysis
WES = Whole exome sequencing
WG = Whole genome

and diffuse restriction in diffusion provides an opportunity to examine this novel clinical-radiologic presentation in a young cohort.

NORSE should be considered a description of a clinical presentation rather than a specific diagnostic entity. As such, this clinical presentation has a few associated reported phenotypes. For example, NORSE in children is typically preceded by a febrile illness (FIRES)[1,4,9] and cryptogenic NORSE is typically associated with worse outcomes and less response to immunomodulators.[6,20] However, there are far more heterogeneous findings, such as nonspecific and variable cytokine/chemokine expression,[21] and a broad spectrum of MRI abnormalities described, such as T2/FLAIR changes of the neocortical, limbic, basal ganglia, and claustrum regions.[4,17,18,22,23] At the time of preparation of this manuscript, there were no published reports of cerebral diffuse cytotoxic edema as a radiologic signature in patients with NORSE, a very notable finding in our young cohort highlighting a novel NORSE phenotype.

There are, however, other pediatric conditions that do not have RSE as such a prominent and severe clinical feature as in NORSE cases, are preceded by infections, and have recognizable clinical-radiologic features. Acute encephalopathy with biphasic seizures and late restricted diffusion (AESD) is characterized by acute encephalopathy, seizures, and diffuse cerebral restriction in diffusion predominant in the subcortical white matter. A biphasic course is described with a prolonged seizure and encephalopathy acutely, followed by apparent stability with regaining of consciousness,

TABLE 2.
Clinical Management and Hospital Course

Patient #	# ASM	# CI	Immunotherapy	Keto Diet	CI days	ICU days	Hospital days	ICU: Complications
1	5	2	None	Yes	9	12	32	Cardiac arrest for 5 min, ETT/intubation, presumed aspiration pneumonia, mild transaminitis
2	7	2	IVMP	Yes	11	14	61	ETT/intubation, G-tube placed
3	4	2	None	Yes	8	8	24	ETT/intubation, NGT placed, moderate transaminitis, hyperglycemia, hyperlactatemia, acidosis
4	5	3	IVIG, IVMP	Yes	15	25	66	ETT/intubation, G-tube placed, mild transaminitis
5	5	3	IVMP	Yes	31	46	58	ETT/intubation, G-tube placed, transaminitis on day of presentation only
6	4	2	None	No	8	11	18	ETT/intubation, anemia, mild coagulopathy, NGT placed, transaminitis on day of presentation only
7	7	3	IVMP	Yes	12	56	56	ETT/intubation, prolonged QT syndrome, NGT placed, moderate transaminitis, anemia

Abbreviations:
ASM = Antiseizure medication
CI = Continuous infusion
ETT = Endotracheal tube
G-tube = Gastrostomy tube
ICU = Intensive care unit
IVIG = Intravenous immunoglobulin
IVMP = Intravenous methylprednisolone
NGT = Nasogastric tube

then followed by a second phase of seizures and worsened encephalopathy.[24,25] Initial imaging may be normal, and cerebral restriction in diffusion may be notable by the third day after presentation. Restricted diffusion may spare the central regions or impact them.[24-26] In some cases, the biphasic course is not apparent. For these infants, the preferred term is acute leukoencephalopathy with restricted diffusion (ALERD), although there remains a great deal of overlap between both conditions.[26] In cases of ALERD, seizures on presentation are not always present, although clusters may be seen later in the hospitalization. Restriction in diffusion in AESD/ALERD may involve or spare the deep gray matter.[26]

Although our cohort was strikingly similar radiographically to AESD/ALERD, it differed in the clinical presentation. First, seizures in AESD/ALERD are not reported as universally severe and in some cases may never occur. In a series of 11 children,[24] only one had RSE and five did not have status epilepticus (SE). In a series of 43 children with a biphasic seizure course, only 21.4% and 31.4% were noted to be in SE after the first and second phases of seizures, respectively.[25] Conversely, seizures were the prominent clinical manifestation of our patients; all seven patients of our cohort had RSE that necessitated several CIs to ultimately control seizure activity. Another notable difference between our NORSE cohort and those previously published is the underlying etiology. All but one of our patients had a cryptogenic etiology, whereas ALERD-specific reports emphasize a preceding or intercurrent infection: one series found Dengue as the etiology in 45%[24] and another found human herpes virus-6 and influenza A as the most common etiology.[25]

Our cohort had poorer outcomes than those described in the AESD/ALERD literature. Two died, and of the five survivors, four had severe disability and one had moderate disability; no child returned to normal development. Only two children did not develop medically refractory epilepsy; however, they continued on multiple ASMs. We attributed our poor outcomes to the degree of cerebral restriction in diffusion; however, outcomes in two series of patients with ALERD are not universally poor despite diffuse cerebral cytotoxic edema. In a series of 11 children one died, six had varying degrees of cognitive impairment, and four had a normal outcome.[24] In a series of 43 patients the authors noted that no patient died and only few developed neurological sequelae.[25]

This presentation of concomitant NORSE with diffuse cerebral restriction in diffusion provides the opportunity to explore possible pathophysiologic overlaps between AESD/ALERD and NORSE. There are recent efforts to combine a group of clinical and radiological phenotypes, thought to be secondary to a neuroinflammatory response after childhood infections, under the umbrella term "infection-triggered encephalopathy syndromes."[27] Clinical presentations that have been considered under this umbrella term include AESD and FIRES as two separate entities, as well as acute necrotizing encephalopathy of childhood, acute fulminant cerebral edema, and mild encephalopathy with reversible splenial lesion.[27] These clinical presentations are hypothesized to be caused by indirect activation of microglia and astrocytes, secondary to nonspecific infections outside the central nervous system.[28]

More specifically, neuronal damage from excessive glutamate release is considered to play an important role in the pathogenesis of AESD/ALERD.[29] Under excitotoxic circumstances, astrocytes are responsible for metabolizing extracellular glutamate. When glutamate release exceeds astrocytic metabolic capacity (due to deficient astrocytes or excessive glutamate quantity), excess glutamate allows calcium entry to the postsynaptic neuron causing cellular death.[30] Elevated cerebrospinal fluid cytokines have also been reported in the ALERD literature,[31] strengthening the theory of an inflammatory/excitotoxic feedback loop. A similar pathophysiologic hypothesis of excessive hyperinflammatory response with

TABLE 3.
Patient Outcomes, Including Ultimate Diagnosis

PT	Survival	PCPC: Latest Follow-Up	MRI Results	Epilepsy Severity: Latest Follow-Up	Epilepsy Management: Latest Follow-Up	Ultimate Diagnosis
1	Yes	4: Severe disability	Day 1: Normal Day 5: Widespread restricted diffusion including basal ganglia affected 3-mo: Global cerebral volume loss, occipital lobe cortical laminar necrosis, decreased diffusion restriction in basal ganglia/thalamus	No seizures for the last 1 year period	Ketogenic diet ASMs: Phenobarbital	Cryptogenic
2	Yes	3: Moderate disability	Day 1: Not performed Day 3: Widespread restricted diffusion including basal ganglia affected 5 year: Normal MRI of the brain	Multiple daily seizures	Ketogenic diet ASMs: Felbamate, phenobarbital	Cryptogenic
3	Yes	4: Severe disability	Day 1: Not performed Day 4: Cortical and subcortical restricted diffusion, basal ganglia spared 1 year: Mild diffuse cerebral volume loss compatible with sequela of previous diffuse cytotoxic edema	1-2 seizures/mo	Corpus callosotomy ASMs: cannabidiol, topiramate, valproic acid	Cryptogenic
4	Yes	4: Severe disability	Day 1: Not performed Day 3: Cortical and subcortical restricted diffusion, basal ganglia spared (although demonstrated T2/FLAIR hyperintensities) 2.5 years: Significant diffuse cerebral volume loss, progressed. Small FLAIR hyperintensity in subcortical white matter. No acute edema	Seizure free for last 2 years	Ketogenic diet ASMs: felbamate, clobazam, phenobarbital	Cryptogenic*
5	No†	4: Severe disability	Day 1: Not performed. Day 4: Cortical and subcortical restricted diffusion, basal ganglia spared 3-mo: Diffuse cerebral and cerebellar volume loss with encephalomalacia	1-2 seizures/day	Ketogenic diet ASMs: clobazam, clonazepam, topiramate, valproic acid	Cryptogenic
6	No‡	3: Moderate disability	Day 1: Normal Day 5: Widespread restricted diffusion including basal ganglia affected	Breakthrough seizures within 1 mo following discharge	ASMs: levetiracetam, phenobarbital	Cryptogenic
7	Yes	4: Severe disability	Day 1: Normal Day 7: Widespread restricted diffusion including basal ganglia affected 8-mo: Evolution of diffuse encephalomalacia, progressive cerebral white matter volume loss, and in brainstem and cerebellum	Seizures every 45-60 minutes	ASMs: cannabidiol, phenobarbital, clonazepam, levetiracetam, lamotrigine	Genetic§

Abbreviations:
ASM = Antiseizure medication
FLAIR = Fluid-attenuated inversion recovery
MRI = Magnetic resonance imaging
PCPC = Pediatric Cerebral Performance Category
PT = Patient
* Noonan syndrome; pathogenic variant in *LZTR1*.
† Died 3 years post-NORSE.
‡ Died 2 months post-NORSE.
§ *TANGO2* deficiency.

innate immune activation causing potentiating RSE has been suggested for NORSE.[5,32,33] However, the diffuse restriction in diffusion as a paramount radiographic feature in NORSE has not yet been described.

MRI abnormalities are commonly seen in cases of NORSE[17,18] and broadly of SE.[19,34] In a study of 206 adult patients with SE, peri-ictal MRI abnormalities were documented in 45%. These abnormalities included localized restriction in diffusion and T2/FLAIR hyperintensities. In a subset of the 206 patients (n = 140) arterial spin labeling was performed, and ictal hyperperfusion was noted in 37%.[19] Ictal hyperperfusion is hypothesized to be a compensatory mechanism in response to increased metabolic demands during seizures.[19,34,35] Although the majority of peri-ictal MRI abnormalities in SE usually resolve, prominent diffusion in

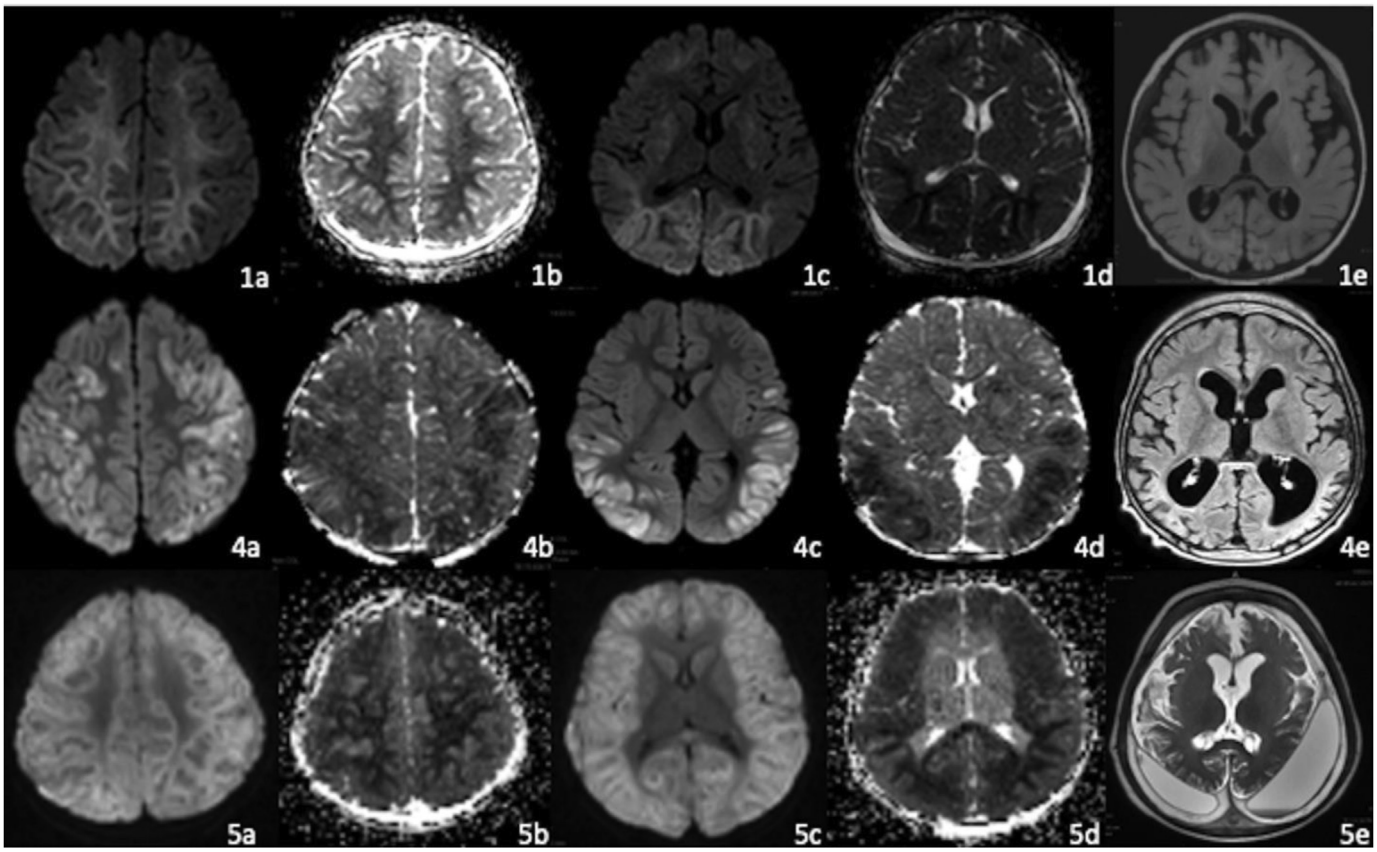

FIGURE. Radiographic representation of Patients 1, 4, and 5. Magnetic resonance imaging changes noted in Patients 1, 4, and 5. Diffusion-weighted imaging axial images (a and c) at different levels with corresponding apparent diffusion coefficient images (b and d). Restriction in diffusion is evident. These images were obtained on day 5 on Patient 1 and day 4 on Patients 4 and 5. Panels 1e and 4e represent fluid-attenuated inversion recovery axial images in the chronic state for Patients 1 and 4, respectively. Panel 5e represents T2-weighted axial image in the chronic state for Patient 5. Global atrophy of various levels of severity is appreciated with subdural fluid collections noted in Patient 5.

restriction suggestive of cytotoxic edema may be associated with subsequent brain tissue volume loss,[19,36,37] such as what we appreciated in our cohort in a cerebrally diffuse form.

MRI provides an opportunity to better understand the pathophysiology of SE and its effects on the brain leading to vasogenic and cytotoxic edema as the final expression of complex neurotransmitter trafficking failure and neuroinflammatory disturbances. It is hypothesized, that in the setting of SE, an imbalance of glutamate to gamma-amino butyric acid ratio provokes a hyperexcitatory milieu, oxidative stress, and perturbation of cellular metabolism. This leads to eventual mitochondrial injury and adenosine triphosphate dependent Na+/K+ pump failure culminating with calcium influx and intracellular cytotoxic edema leading to eventual restriction in diffusion.[34] Simultaneously, blood-brain barrier disruption may also occur, leading to more influx of potassium and/or leakage of serum proteins, which may cause central inflammation, vascularization, astrogliosis, and impaired potassium buffering with an eventual MRI signal of vasogenic edema.[34] Indeed, the blood-brain barrier has been imaged using dynamic contrast-enhanced MRI in a series of seven patients with NORSE and noted to be excessively permeable out of proportion to other neuroinflammatory conditions.[16]

More so, if the hyperexcitatory-hyperinflammatory cycle continues and perfusion is not maintained to support these exaggerated metabolic demands oxygen delivery may be inadequate.[34] We hypothesize that this radiographic appearance in our NORSE cohort is the culmination of exceeded astrocytic and vascular regulatory-compensatory capacity in young children, potentiating cellular death and thus cytotoxic edema with diffuse restriction in diffusion creating a toxic feedback loop of uncontrolled seizures and further neuronal death diffusely throughout the cerebrum.

There is a critical need for biomarkers that more rapidly detect inflammatory-mediated, potentially catastrophic neurological conditions such as NORSE. The ideal biomarker should have good clinical and analytical validity and conserve pathophysiologic reliability.[38] We propose the ideal biomarker to also have a rapid result turnaround time; in conditions such as NORSE/FIRES and AESD/ALERD the window to possibly modify the hyperexcitatory-hyperinflammatory milieu of which RSE is only a symptom may be very short. Despite international consensus for NORSE[9] recommending initiating first-line immunomodulatory treatment within the first 72 hours (95.8% agreement) and escalating to second-line immunotherapy if first-line is not efficacious (81.2% agreement), three patients in our cohort did not receive any immunotherapy. Of the four patients who received immunotherapy, none received targeted blockade of innate immune activation molecules (i.e., recombinant interleukin-1 receptor antagonists, tocilizumab, etc.). We hypothesize that timing of presentation impacted physician's rapid recognition of NORSE and familiarity with recommendations for first- and second-line immunotherapy; all but one patient (Patient 1) presented before publication of the international consensus guidelines for NORSE.[9] Furthermore, because of our patients' age, clinicians possibly conceptualized different mechanisms (hypoxic-ischemic injury, toxic, genetic) as explanatory for their presentation. We add this clinicoradiographic description as a biomarker to explore in young patients with NORSE.

Limitations

Our single-center study has limitations, commencing with our small sample size. Another limitation of this study was the difficulty in locating patients who fully met inclusion criteria; reporting chart terminology was inconsistent. Only three patient charts included utilization of "NORSE" terminology found with the International Classification of Diseases, 10th Revision, code "G41.8." Therefore, there is potential that we did not include patients particularly in the earlier years (2013 to 2017) of our study, before growing acceptance, knowledge, and utilization of "NORSE" and related terminology. We attempted to screen for patients receiving pentobarbital as a modality to find and include additional patients; however, some patients may still have been missed in screening.

Missed patients due to lack of written terminology may also be the case for the term "ALERD and AESD"; none of our patients had those terms applied. Patients with less ictal burden and ALERD/AESD, described most commonly in the literature, may have been excluded, which therefore biased our sample to patients with the most severe ictal expression of ALERD/AESD. Another limiting factor is the heterogeneity in diagnostic evaluation for our patients. For example, the only patient with an etiology for NORSE (Patient 6) had genetic testing repeated years after presentation, and he was the only one who had whole genome analysis. It is unknown if the remaining cryptogenic patients have etiologies yet to be uncovered by re-examination of genetic testing. Finally, we did not search for non-NORSE etiologies of RSE that had diffuse restriction in diffusion, thus limiting our ability to conclude that these imaging findings are a radiologic stigmata of NORSE in young patients.

Conclusions

We present a single-center case series of young patients with NORSE and diffuse cerebral restriction in diffusion akin to the clinicoradiologic phenomenon termed AESD/ALERD. We present clinical findings of both syndrome's phenotypes, highlighting similarities and differences in two conditions with potential pathophysiologic overlaps. There is a need to develop biomarkers for specific NORSE phenotypes, including novel neuroradiographic signatures. The young child with NORSE and diffuse cerebral restriction in diffusion may be a novel phenotype with a specific neuroradiographic signature that deserves further attention.

CRediT authorship contribution statement

Hope M. Reecher: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Niyati P. Mehta:** Writing – review & editing, Validation, Resources. **Namrata D. Patel:** Writing – review & editing, Validation, Resources. **Rachel A. Sawdy:** Writing – review & editing, Validation, Resources. **Raquel Farias-Moeller:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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