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REVIEW

Neuropathology of New-Onset Refractory Status Epilepticus (NORSE)

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Abstract

New-Onset Refractory Status Epilepticus (NORSE), including its subtype with a preceding febrile illness known as FIRES (Febrile Infection-Related Epilepsy Syndrome), is one of the most severe forms of status epilepticus. Despite an extensive workup (clinical evaluation, EEG, imaging, biological tests), the majority of NORSE cases remain unexplained (i.e., "cryptogenic NORSE"). Understanding the pathophysiological mechanisms underlying cryptogenic NORSE and the related long-term consequences is crucial to improve patient management and preventing secondary neuronal injury and drug-resistant post-NORSE epilepsy. Previously, neuropathological evaluations conducted on biopsies or autopsies have been found helpful for identifying the etiologies of some cases that were previously of unknown cause. Here, we summarize the findings of studies reporting neuropathology findings in patients with NORSE, including FIRES. We identified 64 cryptogenic cases and 66 neuropathology tissue samples, including 37 biopsies, 18 autopsies, and seven epilepsy surgeries (the type of tissue sample was not detailed for 4 cases). We describe the main neuropathology findings and place a particular emphasis on cases for which neuropathology findings helped establish a diagnosis or elucidate the pathophysiology of cryptogenic NORSE, or on described cases in which neuropathology findings supported the selection of specific treatments for patients with NORSE.

Keywords Autopsy · Biopsy · Epilepsy surgery · Febrile Infection-Related Epilepsy Syndrome (FIRES) · Neuropathology · New-Onset Refractory Status Epilepticus (NORSE)

Abbreviations

FIRES	Febrile Infection-Related Epilepsy Syndrome
NORSE	New-Onset Refractory Status Epilepticus
RSE	Refractory status epilepticus
SE	Status epilepticus

Introduction

Status epilepticus (SE) is the second most common neurological emergency, affecting around 40 per 100,000 people yearly [1]. Approximately 25% of SE cases are refractory to at least two appropriately chosen and dosed anti-seizure medications, known as refractory SE (RSE). New-Onset Refractory Status Epilepticus (NORSE) is one of the most severe clinical presentations of RSE. NORSE occurs in

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adults or children without active epilepsy and without a clear acute or active structural, toxic, or metabolic cause, with an estimated 3200 cases per year in the United States [2, 3]. Febrile Infection-Related Epilepsy Syndrome (FIRES) is a subset of NORSE that involves a prior febrile infection starting between 2 weeks and 24 h before the onset of SE [3]. The prognosis is often poor among NORSE patients, including a high rate of mortality, around 12% in children and even higher in adults (16–27%), prolonged stay in an intensive care unit (15–40 days), post-NORSE epilepsy, and other neurological sequelae including cognitive and behavioral effects [4–7].

In recent years, there has been an increased awareness and desire to understand the causes and mechanisms underlying NORSE onset and consequences. As of 2019, around 200 cases of NORSE had been published, allowing us to better appreciate its clinical presentation [8, 9]. While some cases of NORSE and FIRES might be caused by autoimmune or infectious encephalitis, or rare genetic disorders, the majority remain unexplained ('NORSE of unknown etiology' or 'cryptogenic NORSE') [4, 6, 10]. The etiological diagnostic workup usually includes clinical evaluation, continuous EEG monitoring, magnetic resonance imaging of the brain, and a broad spectrum of biological tests including cerebrospinal fluid evaluation, anti-neuronal antibodies testing, and sometimes CSF metagenomic testing (next-generation sequencing for detection of infectious organisms) or CSF plus serum cytokine studies. While there are some risks of performing a brain biopsy for intensive care patients, neuropathological analysis coupled with metagenomics has been previously found helpful in identifying the etiology of some otherwise unexplained encephalitides [11–13]. Such analysis could play a role in identifying NORSE etiologies and in guiding treatment decisions [14].

In the present review, we summarize the neuropathology findings described in biopsy, epilepsy surgery, or autopsy tissues from patients with NORSE. We place a particular emphasis on described cases for whom neuropathology findings helped establish a diagnosis or elucidate the pathophysiology of cryptogenic NORSE, and on cases in which neuropathology findings supported the selection of specific treatments for patients with NORSE.

Methods

We searched the PUBMED, Scopus, Google Scholar, and EBSCO databases for articles using the terms: NORSE, FIRES, "New-Onset Refractory Status Epilepticus" or "Febrile Infection-Related Epilepsy Syndrome", and neuropathology, biopsy, autopsy, or surgical specimen, individually and together in all different combinations. The references of the articles found were also screened for relevant publications. Only papers in English were included. We selected articles that describe neuropathology findings in the brains of patients with NORSE/FIRES (from autopsy, biopsy, or epilepsy surgery). As there was a significant lack of research material, we expanded the review search to include articles published before the proposed definitions for NORSE and FIRES as long as they reported data from patients with an unknown-etiology new-onset refractory SE [3].

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines (PRISMA) [15]. From 1983 to December 2022, 80 publications were identified, including many case reports and some case series (Fig. 1). We carefully scanned the publications to eliminate duplicate reports and cases inconsistent with the clinical definitions of NORSE/FIRES and retained 19 studies for this review.

Here, we summarize the neuropathology findings of those 19 studies with a total of 66 tissue samples from 64 cryptogenic NORSE patients. Next, we describe the neuropathology findings specifically for cases where the pathology report eventually pointed to a specific etiology (diagnostic evaluation) or otherwise directly impacted patient management.

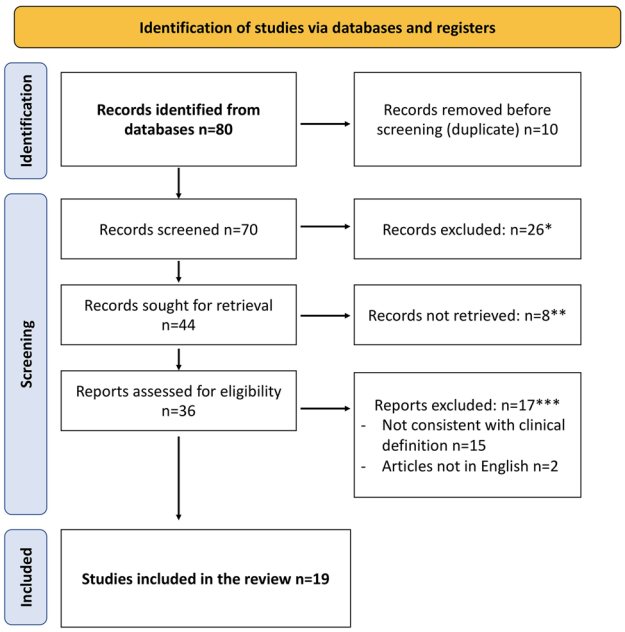

Fig. 1 PRISMA flow diagram. Records refer to search results, titles, or abstract screening. Reports refer to the full-text data screening. *Twenty-six records screened were excluded after abstract reviewing as data were not consistent with search criteria. **Eight records sought for retrieval were excluded as they corresponded to letters to editors or abstract conferences with no full text available. ***Seventeen reports assessed for eligibility were excluded as data were not consistent with NORSE/FIRES clinical definition or because the articles were not written in English

Neuropathology findings in human Status Epilepticus

One of the largest neuropathology reports on the brains of patients with SE dates back to 1983 [16]. It was a series of 290 people with epilepsy, of which 52 had, at some point in their lives, suffered from one or more recorded episodes of SE, with or without a discovered etiology [16]. Detailed neuropathology findings were provided for eight pediatric and 12 adult patients who died during the SE course. Among children, the most affected area was the hippocampus (primarily showing sclerosis of CA1, and in some cases features related to ischemic/hypoxic changes), followed by the cerebellum, which exhibited Purkinje cell loss and gliosis. The neurons of the thalamus (specific nuclei not specified) were also shown to be vulnerable, and some patients presented with diffuse areas of cortical necrosis [16]. Neuronal loss was frequently described as associated with the proliferation and activation of microglial cells and astrocytes. Similar neuropathology findings were found in adults, although they were generally less severe than in children.

While the above study did not only consider patients who experienced new-onset RSE from an unknown etiology, it provides the critical context of anatomic findings associated with prolonged seizures.

Neuropathology findings in human NORSE/FIRES

Neuropathology findings were described for 66 tissue samples collected from 64 NORSE cases, including 32 adults and 32 children. Fifty-one patients out of the 64 presented with brain abnormalities (80%), including 25 out of the 32 adults (78%) and 26 out of the 32 children (81%) (Table 1). Thirty-seven patients underwent a brain biopsy, 18 an autopsy, and seven an epilepsy surgery. Among them, one patient underwent a biopsy followed by an epilepsy surgery, and one patient underwent a biopsy followed by an autopsy (detailed biopsy results were not provided). The type of tissue analyzed was not precisely described for four cases and the neuropathology findings were not described for two autopsies and two biopsies.

Ten biopsies out of the 35 (29%) with detailed results showed normal findings. EEG, clinical findings, or imaging data guided the location of the biopsy. The absence of pathological findings did not guarantee a good outcome as reported in a six-patient retrospective study where patients with normal brain biopsy developed severe mental and physical disabilities as well as refractory post-NORSE epilepsy [17]. Three out of the 16 autopsies performed (19%) that included results were also reported unremarkable [18]. All patients ($n=7$) who underwent a resection of the epileptic focus presented with neuropathological abnormalities.

Representative examples of autopsy neuropathology findings in the hippocampus were provided for two patients in Figs. 2 and 3.

Neuronal loss

The most common neuropathology finding in autopsy tissues was the presence of neuronal loss, described in 11 out of the 16 cases [4, 17–25] (Fig. 2A-B). As previously reported in other types of SE in humans, the most affected area was the temporal lobe, specifically the hippocampus (6 patients out of the 11 cases, 55%) [16, 17, 21–23, 25]. Longitudinal MRIs of four patients showed a progressive increase in T2 signal intensity of the hippocampi bilaterally, and three of them had bilateral hippocampal atrophy on subsequent MRIs [17, 21–23]. The neurons of the cerebellar cortex (Purkinje cells) and the thalamus were also shown to be vulnerable, as shown in 5 (31%) and 4 cases (25%), respectively [17, 19, 21, 22]. The neuronal loss affected the pulvinar nuclei for two cases and the specific nuclei were not specified for the two others. Neuronophagia was described within the pulvinar nuclei of a 26-year-old man at autopsy [21]. He underwent four MRIs throughout his clinical SE course that showed restricted diffusion of the pulvinar nuclei, as well as bilateral medial temporal lobes and insulae. [21]. Neuronal loss was also reported in the dentate, inferior olivary, and pontine nuclei of a 6-year-old child who presented with a poor outcome after SE ended (tetraplegic as well as seizures, gastrostomy feeds, tracheostomy) and who died two years after SE onset [19]. This neuropathology finding was associated with diffuse brain stem atrophy without signal change on the MRI performed four months after SE onset [19]. Neuronal atrophy was reported in the neocortices and cingulate cortex for two and one patient, respectively [22, 23].

The brain biopsy findings were provided for 35 patients [4, 5, 17–19, 24, 26–31]. Only one of them revealed neuronal necrosis at the acute phase of the NORSE [30]. A second patient underwent a further resection of the seizure-onset zone in the temporal cortex also revealing neuronal necrosis [27]. Those data suggest neuronal loss might be identified in a broad piece of tissue or appear only late after SE onset. The absence of neuronal loss in the other biopsy tissues might also be related to the absence of representative material. As neuronal loss was observed in autopsy tissues from patients who died in the first month after SE onset [17, 19, 20], but not found in biopsy performed several months after SE onset [17, 26], we might suggest that this neuropathology finding is not time sensitive. Neuronal necrosis was also reported for two other patients who underwent a resection of the epileptic focus [24].

Table 1 Previously reported NORSE cases with neuropathological evaluation

Case series/report	Total number of NORSE patients	Number of NORSE patients with histopathological evaluation	Age category	Type of pathological evaluation	Total number of evaluations with specific etiology identified or treatment suggested by findings	Findings
Sahin et al. 2001 [30]	8	5	Children	5 biopsy (location not specified)	1	- 1: neuronal necrosis, gliosis - 2: multifocal gliosis **Diagnosis of human herpes virus 6 (HHV-6) encephalitis** - 3: leptomeningeal inflammatory infiltrate (inflammatory cell types not specified) - 4: gliosis - 5: gliosis
Baxter et al. 2003 [19]	6	4	Children	3 autopsy 1 biopsy	0	Autopsies: - 1: slight gliosis in the white matter - 2: neuronal loss and gliosis in the cerebellar cortex and thalamus* - 3: neuronal loss and gliosis in the olivary nuclei, pontine nuclei, and thalamus* Cerebral cortex biopsy: - ischemic cell changes in some neurons, reactive astrogliosis and scattered macrophages
Van Lierde et al. 2003 [17]	6	4	Adults	2 autopsy 2 biopsy	0	Autopsies: - 1: bilateral hippocampal sclerosis and deep cerebellar gray matter gliosis - 2: hippocampal neuronal loss and destruction of Purkinje cells Biopsies (right temporal and left orbitofrontal biopsies): 1 and 2: unremarkable
Wilder-Smith et al. 2005 [20]	7	2	Adults	2 autopsy	0	1 and 2: diffuse neuronal loss and gliosis

Table 1 (continued)

Case series/report	Total number of NORSE patients	Number of NORSE patients with histopathological evaluation	Age category	Type of pathological evaluation	Total number of evaluations with specific etiology identified or treatment suggested by findings	Findings
Costello et al. 2009 [4]	6	4	Adults	1 autopsy 1 biopsy 2 epilepsy surgeries	0	Autopsy: - 1: increased microglia and pyknotic neurons in both subicula and parahippocampal gyri. Diffuse neuronal injury with reactive microglia and astrocytosis. Right frontal brain and meningeal biopsy: - 1: gliosis and microglial activation Epilepsy surgeries: - 1: gliosis within the amygdala - 2: gliosis and microglial activation
Boyd et al. 2010 [21]	1	1	Adult	1 autopsy	0	Loss of pyramidal neurons in the hippocampi. Neuronophagia of neurons within the pulvinar nuclei.
Van Baalen et al. 2010 [31]	14	6	Children	6 biopsies (location not specified)	0	- 1: ischemic cortex damage, marked white matter edema, reactive gliosis - 2: no inflammatory changes or other specific findings - 3: gliosis - 4: rarefication of cornu ammonis cells - 5: neuronal damage in the left temporal lobe - 6: reactive gliosis
Kramer et al. 2011 [5]	77	13	Children	13 biopsy (location not specified)	0	Gliosis in 7 patients. Leptomeningeal inflammatory infiltrate for 1 patient (inflammatory cell types not specified). Unremarkable for 5 patients.

Table 1 (continued)

Case series/report	Total number of NORSE patients	Number of NORSE patients with histopathological evaluation	Age category	Type of pathological evaluation	Total number of evaluations with specific etiology identified or treatment suggested by findings	Findings
Juhasz et al. 2013 [27]	1	1	Adult	1 biopsy followed by epilepsy surgery	0	Left temporal lobe biopsy: - astrocytosis Epilepsy surgery: - neuronal necrosis, reactive astrocytosis, microglial activation, and sparse lymphocytic infiltration (CD45 +)
Ogawa et al. 2016 [22]	1	1	Child	1 autopsy	0	Atrophy of the temporal lobes with neuronal loss of CA1 and CA4 of bilateral hippocampi. Neuronal loss, gliosis and microglial activation in the amygdala, thalamus*, cerebellum, and in several neocortices.
Sato et al. 2016 [32]	1	1	Child	1 epilepsy surgery	1	Infiltration of the capillaries by neutrophilic leukocytes (T cells, microglia) in the area exhibiting severe spongiosis **Initiation of treatment with tacrolimus**
Villamar et al. 2017 [25]	1	1	Child	1 autopsy	1	Diffuse intraparenchymal inflammation with lymphocytic and polymorphonuclear cell infiltration, focal neuronophagia, rare neurons containing intracytoplasmic inclusions consistent with Negri bodies in the left parahippocampal cortex. **In situ RT-PCR of brain tissue positive for Rabies virus RNA**
Matar et al. 2017 [26]	1	1	Adult	1 biopsy (chronic phase)	1	Focal angiocentric mononuclear inflammatory cell infiltrates (T cells). **Diagnosis of angiitis of the central nervous system treated with cyclophosphamide.**

Table 1 (continued)

Case series/report	Total number of NORSE patients	Number of NORSE patients with histopathological evaluation	Age category	Type of pathological evaluation	Total number of evaluations with specific etiology identified or treatment suggested by findings	Findings
Dilena et al. 2019 [28]	1	1	Child	1 biopsy	1	Left posterior temporal lobe biopsy: Astrogliosis, prominent microglia activation and scattered CD8 + T cells. **Initiation of treatment with anakinra.**
Daida et al. 2020 [23]	1	1	Adult	1 autopsy	0	Neuronal loss and gliosis (hippocampus, amygdala, cingulate cortex, cerebellar cortex, neocortical regions). Few microglia in the cortex. Infiltration of macrophages in the spinal cord. Axonal loss and increased number of macrophages in the dorsal root ganglion and nerve roots of the cauda equina.
Gugger et al. 2020 [18]	20	5	Adults	3 autopsies 2 biopsies (location not specified)	0	Unremarkable
Mathhews et al. 2020 [33]	26	7	Adults	2 autopsies 1 biopsy (location not specified) Not detailed for the 4 others	3	1 Herpes Simplex Virus (on biopsy) 1 Candida encephalitis (on autopsy) 1 Hemorrhagic necrotizing leukoencephalopathy (on autopsy) Not detailed for the 4 remaining patients
Donnelly et al. 2020 [29]	1	1	Adult	1 biopsy	0	Frontal lobe cortex and subcortical white matter biopsy: Microglial activation,reactive CD3 + T cells, and hemosiderin deposition within the perivascular spaces.

Table 1 (continued)

Case series/report	Total number of NORSE patients	Number of NORSE patients with histopathological evaluation	Age category	Type of pathological evaluation	Total number of evaluations with specific etiology identified or treatment suggested by findings	Findings
Suchdev et al. 2021 [24]	5	5	Adults	1 autopsy *(after a biopsy with results not provided)* 1 biopsy 3 epilepsy surgeries	2	Autopsy: - extensive necrotizing vasculopathy; minimal lymphocytic infiltrate in perivascular parenchyma and leptomeninges; occasional CD45 + lymphocytes (T cells) Left middle temporal gyrus biopsy: - gliosis with astrocytosis and microglial activation (cortex and white matter) Epilepsy surgeries: - 1: gliosis and microglial activation with acute neuronal damage, sparse inflammation - 2: neuronal loss and necrosis in the hippocampus (CA1, subiculum), astrocytosis, microglial activation (CD68 +) and moderate infiltration by T cells **anti-GAD antibody encephalitis** **Initiation of treatment with PLEX and cyclophosphamide** - 3: focal parenchymal necrosis, lymphocytic infiltration with small vessel vasculitis, focal microglial activation **Diagnosis of lymphocytic vasculitis**

*Thalamic nuclei not specified

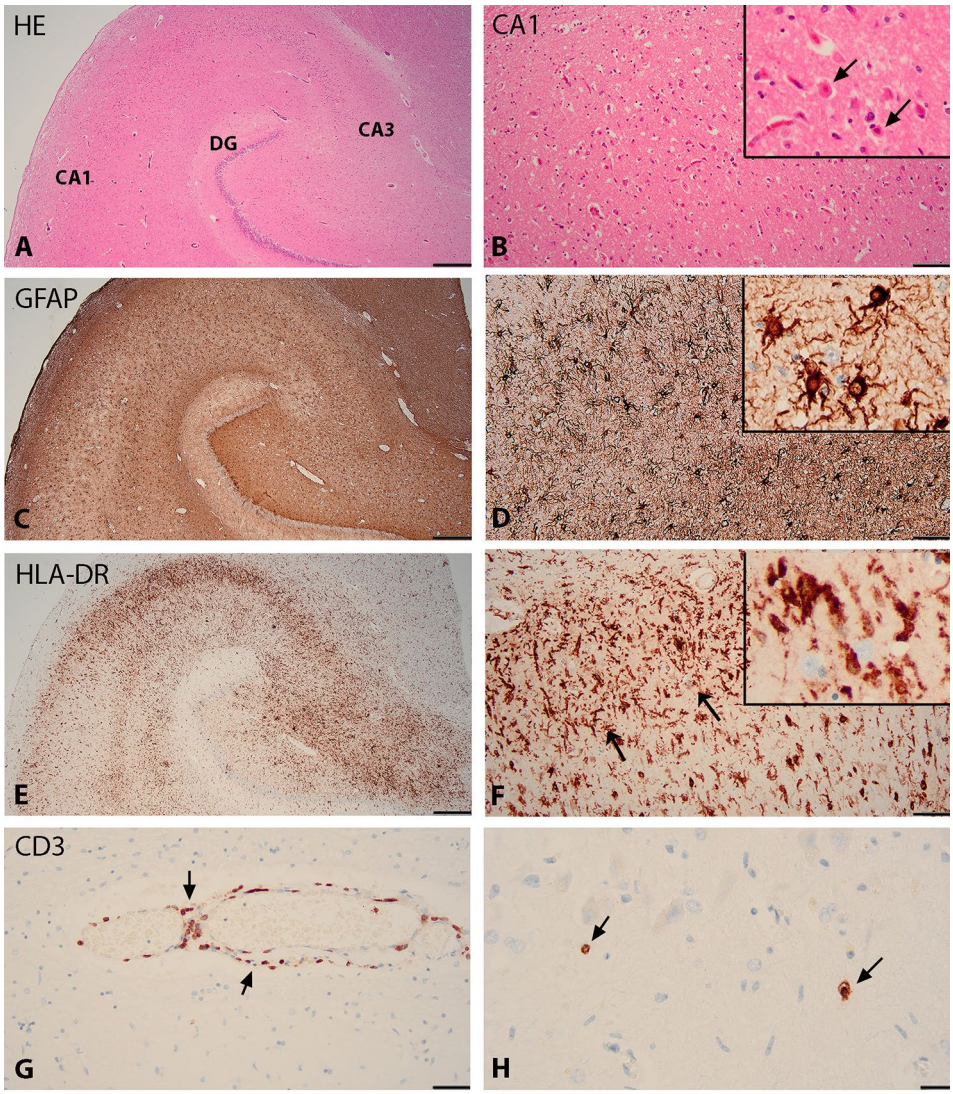

Fig. 2 Case 1: Histopathology of the hippocampus for a patient with NORSE of unknown etiology or cryptogenic NORSE. A 35-year-old male with no significant previous medical history presented with generalized epileptic seizures progressing to super-refractory status epilepticus. He died 6 days after developing status epilepticus with no known etiology found. Panels **A** and **B**: Hematoxylin and eosin (HE) staining of the hippocampus showing the loss of pyramidal neurons in CA regions, with severe ischemic changes, particularly in CA1; insert in B shows a high magnification of CA1 with eosinophilic, shrunken cytoplasm of residual neurons (arrows). Panels **C** and **D**: glial fibrillary acidic protein (GFAP) immunostaining shows strong astroglial expression throughout the different hippocampal subfields; insert in **D** shows a high magnification of astrocytes in CA1. Panels **E** and **F**: human leukocyte antigen-DR class II (HLA-DR) immunostaining shows strong immunoreactivity, particularly in CA1; insert in F shows a high magnification of HLA-DR positive cells in CA1 (arrows). Panels **G** and **H**: CD3 (cluster of differentiation 3) shows perivascular T-cells (arrows in G); only a few T-cells are detected in CA1 (arrows in H). DG, dentate gyrus. Scale bars in **A**, **C**, **E**: 500 µm; **B**, **D**, **F**: 100 µm; **G**, **H**: 50 µm

Gliosis

In contrast to neuronal loss, astrogliosis (typically assessed with GFAP immunostaining) was described frequently on autopsy and biopsy examinations in 9 out of the 16 autopsy cases (56%) and 19 out of the 35 biopsy cases (54%) [4, 5, 17, 19, 20, 22–25, 27, 28, 30, 31] (Fig. 2C-D). Astrogliosis was also described for all patients who underwent epilepsy surgery [4, 24, 27, 32]. Astrogliosis has been reported to affect several brain areas (cortex, hippocampus, thalamus [specific nuclei not specified], amygdala, cerebellar white and grey matter, neocortical regions) but with an unequal severity for patients and brain areas [4, 17, 19, 22, 23]. Except for three cases, all patients who underwent an autopsy that revealed neuronal loss also were found to have astrogliosis in the same brain areas [4, 17, 19, 20, 22, 23]. Astrogliosis is frequently reported in association with a

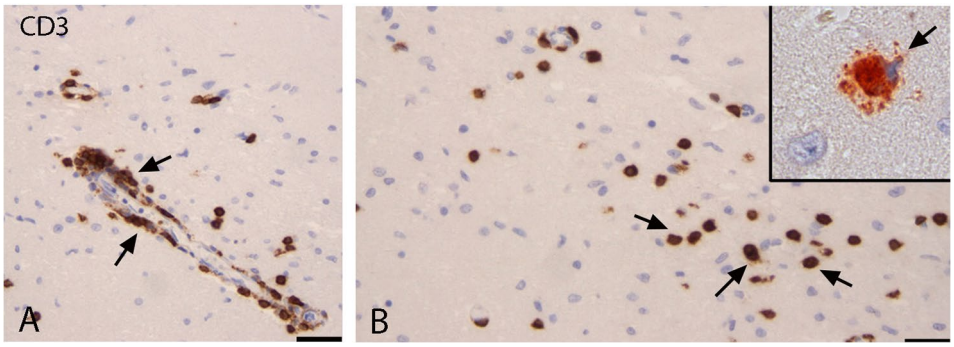

Fig. 3 Case 2: Histopathology of the hippocampus for a patient with FIRES (Febrile Infection-Related Epilepsy Syndrome). A 4-year-old girl with no significant previous medical history had a brief non-specific prodromal illness with mild fever. She then presented with generalized epileptic seizures progressing to super-refractory status epilepticus. The patient died 27 days after developing status epilepticus for which no underlying cause was found despite extensive investigation. Panels **A** and **B**: CD3 (cluster of differentiation 3) shows perivascular T-cells (arrows in **A**); intra-parenchymal T-cells are detected in CA1 (arrows in **B**); insert in **B** shows a cytotoxic lymphocyte with granzyme B positivity. DG, dentate gyrus. Scale bars in **A**, **B**: 50 µm

prominent microglial reactivity as reflected by strong and diffuse CD68 and HLA-DR immunostaining [4, 22, 24, 27, 28] (Fig. 2E–F).

Lymphocytic infiltration

Pathological examination showed infiltration by leukocytes for nine patients (epilepsy surgery n = 4; biopsy $n = 3$; autopsy $n = 2$) [24–29, 32] (Fig. 2G–H and 3A–B). Most lymphocytes observed were mononuclear, almost exclusively CD3 + T cells with a predominance of CD8 + T-lymphocytes [24, 26, 28, 29]. Infiltration was mostly angiocentric [24, 26, 32] (Fig. 2G–H and 3A–B). T-cell infiltration might be related to a central pro-inflammatory state and/or to a blood–brain barrier disruption [29, 32]. Immunoreactivity to matrix metalloproteinase-9, an extracellular protease contributing to the disruption of the blood–brain barrier, was evident in cortical vessel walls of one patient with CD8 + T-cell infiltration [32]. Hemosiderin deposition, indicating loss of vascular integrity and thus disruption of the blood–brain barrier, was noted within the perivascular spaces as well as in vessels of the cortex of another patient with CD8 + T-cell infiltration [29]. CSF pleocytosis was described for seven patients, with a white blood cell count ranging from 8 to 335 cells per µL, suggesting an ongoing inflammatory process [24–26, 29, 32]. However, readily identifiable CSF viral and bacterial etiologies were ruled out for all patients [24–26, 29, 32]. The two other patients had none or just one white blood cell per µL in the CSF [27, 28]. Nevertheless, inflammatory conditions cannot be ruled out: one of them presented specifically with increased brain expression of IL-1ß and IL-1R [27].

Diagnostic utility of neuropathology findings in patients with NORSE

For ten cases (16%), including four biopsies, three epilepsy surgeries, and three autopsies, the neuropathological analysis was reported as diagnostic of a specific etiology ($n = 7$) or having resulted in significant modification of the patient's management ($n = 4$).

An etiology was identified for seven patients based on neuropathology findings. Identified etiologies were infectious in four cases (herpes simplex virus encephalitis $n = 1$, human herpes virus 6 encephalitis $n = 1$, candida encephalitis $n = 1$, rabies encephalitis $n = 1$), vasculitis for two cases, and probably post-infectious for one other case with hemorrhagic necrotizing leukoencephalopathy [24–26, 30, 33]. It is worth noting that patients with infections diagnosed based on neuropathology findings had negative CSF testing and were therefore not treated with appropriate antimicrobials, likely resulting in a worse outcome [33]. None of the patients had evidence of malignancy, cortical dysplasia, or non-inflammatory vascular disease.

In four cases, brain biopsy/surgery findings enhanced rapid treatment modifications that were helpful for seizure cessation and improving patient outcomes [24, 26, 28, 32].

The first case is a 31-year-old female for whom initial MRI showed hyperintensities on FLAIR images involving bilateral mesial temporal lobes and for whom CSF analysis was suggestive of an inflammatory disorder [24]. She was first treated with high-dose pulse steroids and a first course of plasmapheresis without efficacy to resolve the RSE. Subsequently, she underwent a resection of the epileptogenic area. This intervention did not allow an immediate cessation of seizures. However, on histopathology, hippocampal neuronal loss and necrosis were associated with brain infiltration

by CD3 + T cells with a predominance of CD8 + T-lymphocytes [24]. Further investigation led to a diagnosis of anti-GAD antibody encephalitis. Based on those results, she was treated with another course of plasmapheresis followed by cyclophosphamide administration. Although not immediate, these interventions allowed a cessation of SE and the patient was discharged to a subacute rehab facility [24].

The second case is a previously healthy 11-year-old child who presented with a 4-day history of fever and received several anesthetics and antiseizure drugs as well as intravenous immunoglobulins and methylprednisolone pulse therapy to manage RSE from a suspected inflammatory underlying etiology [32]. Despite treatment, the patient's seizures increased in frequency and he underwent a left occipital lobectomy after two months of illness. The patient's seizures reduced in frequency after the surgery but he developed clusters of seizures occurring every 2–4 weeks. The neuropathological evaluation revealed infiltration of the capillaries by large numbers of neutrophilic leukocytes. CD8 + T cells and CD68 + microglia cells were also observed around vessels. These immune responses prompted clinicians to initiate treatment with tacrolimus to inhibit cytotoxic T-cell activity [32]. As a result, the patient's seizures decreased in frequency. While the impact of the left occipital lobectomy on the patient's improved seizure control can not be excluded, the authors suggested a benefit of tacrolimus. Indeed, discontinuation of tacrolimus triggered the recurrence of seizures, suggesting T cell involvement in post-NORSE epilepsy for this patient.

The third case is a 46-year-old man who was admitted with a diagnosis of refractory non-convulsive SE and showed an elevated protein level (747 mg/dL) and 51 white blood cells per µL in the CSF [26]. He received several antiseizure medications and anesthetics and was started empirically on intravenous steroids for suspicion of autoimmune encephalitis. After three days of steroids, the patient improved dramatically and was discharged on an oral prednisolone taper. Nonetheless, he could not return to work after a few months and presented with a significant MRI worsening. He, therefore, underwent a brain biopsy for further investigation [26]. The biopsy revealed many focal angiocentric mononuclear inflammatory cell infiltrates (predominantly T cells), allowing clinicians to suspect primary angiitis of the central nervous system [26, 34]. The patient was started on cyclophosphamide and dramatically responded to treatment [26].

The fourth case is a previously healthy 10-year-old child who presented with four days of fever followed by recurrent focal and generalized seizures that evolved into a RSE [28]. SE was partially controlled by anesthetics but each attempt to reduce sedation caused a relapse of SE. Evaluation of CSF revealed an elevated protein level (60 mg/dL) without associated cells. All viral, bacterial, autoimmune, mitochondrial, and metagenomic tests resulted in negative findings. High-dose steroids and immunoglobulins were administrated without efficacy, as well as the ketogenic diet. A brain biopsy was performed two months after SE onset and showed reactive astrogliosis, prominent reactive microglia, and a few scattered CD8 + T-lymphocytes [28]. These neuropathology findings combined with the negative results of metagenomic sequencing supported the decision to include anakinra, an IL-1R1 blocker, in the management of the patient for seven months. During this period, only two seizures occurred, and an improvement of the background EEG was observed [28]. After anakinra withdrawal, seizures and EEG epileptiform discharges reoccurred, suggesting the benefit of this treatment in patient management.

Discussion

The most frequent neuropathology findings reported in patients with NORSE were neuronal loss, reactive gliosis, and perivascular T-cell infiltration. Neuropathology findings allowed identifying a specific etiology and/or selecting a new treatment for 10/64 cases (16%).

Neuronal loss was frequently reported in autopsy tissues (69%) but found in only one of the biopsies done. In contrast, hippocampal surgeries performed on patients with pharmacoresistant temporal lobe epilepsy for several years after NORSE frequently revealed the damage pattern of hippocampal sclerosis, highlighted by neuronal cell loss and concomitant astrogliosis [35–37]. These results suggest that neuronal loss could be triggered by seizure persistence and might be considered a consequence of prolonged SE [24, 27, 35]. However, these results might also be explained by the lack of relevant or representative material to detect neuronal loss in biopsy specimens or be related to hypoxic insult during terminal illness [19, 24]. Indeed, neuronal loss was found in autopsy tissues from patients who died in the first month after SE onset [17, 19, 20, 25].

Although astrogliosis was reported for most patients with NORSE, this is not a specific feature. Prominent astrogliosis was previously described in patients with hippocampal sclerosis and in an animal model of SE before the occurrence of spontaneous seizures [35, 38–41]. Astrogliosis was particularly pronounced in regions with prominent neuronal loss [38]. Increasing evidence supports the role of astroglial cells in contributing to seizure development or seizure persistence [42–44]. Reactive astrocytes may shift towards a pro-inflammatory state, facilitating the production of inflammatory molecules and reactive oxygen species that trigger seizure persistence or recurrence [41, 45–48]. Increasing evidence shows that astrocytes may present different phenotypes during disease pathogenesis [49]. Single-cell and single-nucleus transcriptomic studies have unraveled

several stage-dependent transcriptomic states in Huntington and Alzheimer diseases, as well as in multiple sclerosis [50–52]. Further investigations are required to explore the phenotypic changes occurring in astrocytes for people with epilepsy. Seizures also likely play a role in astroglial cell activation, as reflected by the production of astroglial cell markers (S100-B, GFAP) quickly after seizures or SE onset, creating a potential feedback that exacerbates the pathological process [41, 53–56].

Microglia activation was frequently reported to be associated with astrogliosis and neuronal loss, both in autopsy and biopsy specimens from patients with NORSE. Microglia activation was previously described in patients with temporal lobe epilepsies with two distinct phenotypes based on the intensity of the neuronal loss [57]. Microglia activation and proliferation can contribute to cortical thinning, neurodegeneration, and subsequent cognitive sequelae [58, 59], as well as trigger further seizure development [59]. Emerging evidence highlights the bilateral signaling between microglia and astrocytes [60, 61]. In particular, microglia–via their molecular secretion of cytokines, chemokines, or nitric oxide–influence the function of reactive astrocytes, driving astrocytes from a neuroprotective to neurotoxic phenotype [60, 62–64]. The reactive astrocyte can thereafter contribute to seizure development and progression [41, 65, 66]. Similarly, astrocytes release molecules that regulate microglial function, either to promote microglial activation and motility [60, 67, 68], or to attenuate microglial activation and phagocytosis [69–72]. Together, this bidirectional crosstalk is crucial for maintaining a pro-inflammatory environment [60, 61]. By modulating GAP junctions or purinergic receptors, astrocyte-microglia crosstalk can play a major role in establishing network hyperexcitability after a brain insult and might contribute to post-NORSE epilepsy [73–75]. The previously described efficacy of anakinra treatment might result from the modulation of astroglial cell activation or direct effects of anakinra on neuronal excitability [28, 76–78]. The individual roles of microglia and astrocytes (with a broad spectrum of pathological changes or phenotypes ranging from pro-inflammatory to anti-inflammatory) deserve attention and further investigation.

Perivascular T-cell infiltration was reported for nine patients (14%). This feature was previously described in several limbic encephalitides such as GAD65 or Rasmussen encephalitides [79, 80]. The T-cell infiltration could be explained by a blood–brain barrier disruption during the SE course and a concomitant pro-inflammatory condition in patients with NORSE [29, 32]. As autoimmune encephalitis is the most identified cause of NORSE [6], the T-cell infiltration might highlight the underlying etiology [24, 79]. Treatment with tacrolimus or cyclophosphamide was found able to shorten SE duration and prevent the occurrence of post-NORSE seizures in some cases [24, 26, 32]. Those results suggest an involvement of T cells in NORSE consequences. As described in Rasmussen encephalitis, CD8 + T-cells may attack both neurons and astrocytes, thereby triggering neuronal loss and gliosis [80]. Treatment with tacrolimus, by preventing neuronal loss and gliosis, was able to reduce neurological deficits in patients with Rasmussen encephalitis [80]. However, tacrolimus was not found able to reduce seizure frequency for these patients [80]. Further studies will be required to establish the pathogenic role of those cells in patients with NORSE. Single-nuclei RNA sequencing analyses might be relevant to investigate the exact phenotype of T cell subpopulations, probing for markers of cytotoxic activity, with strong expression of granzyme B, as previously described in Rasmussen encephalitis [81, 82].

Neuropathology findings allowed for identifying an etiology underlying NORSE and/or guidance of treatment strategy for 16% of patients. We may expect a higher proportion of diagnostically informative results with a more consistent investigation of brain specimens for patients with NORSE. The systematic combination of neuropathology findings and new technologies, such as next-generation sequencing or single-nuclei analyses, may help identify NORSE etiologies [11].

Current data are limited by the absence of guidelines describing how to collect and analyze brain tissue from patients with NORSE. Additionally, this review focused only on articles written in English. Guidelines are needed to describe (i) how and when to perform brain tissue collection, preparation, staining, and storage (ii) what neuropathology findings to look at, and (iii) in which brain areas.

Conclusion

None of the neuropathology findings reported in the identified studies were specific to patients with NORSE. Systematic data that allow for more nuanced correlations between pathologic features and clinical presentation are crucial to help elucidate mechanisms of post-NORSE epileptogenesis, identify NORSE etiology and guide patient management. Guidelines for consistently evaluating brain samples will therefore be extremely valuable in advancing our understanding of NORSE/FIRES.

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Declarations

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