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REVIEW ARTICLE

Unraveling the enigma of new-onset refractory status epilepticus: a systematic review of aetiologies

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Abstract

Background and purpose: New-onset refractory status epilepticus (NORSE) is a clinical presentation, neither a specific diagnosis nor a clinical entity. It refers to a patient without active epilepsy or other pre-existing relevant neurological disorder, with a NORSE without a clear acute or active structural, toxic or metabolic cause. This study reviews the currently available evidence about the aetiology of patients presenting with NORSE and NORSE-related conditions.

Methods: A systematic search was carried out for clinical trials, observational studies, case series and case reports including patients who presented with NORSE, febrile-infection-related epilepsy syndrome or the infantile hemiconvulsion-hemiplegia and epilepsy syndrome.

Results: Four hundred and fifty records were initially identified, of which 197 were included in the review. The selected studies were retrospective case–control (n = 11), case series (n = 83) and case reports (n = 103) and overall described 1334 patients both of paediatric and adult age. Aetiology remains unexplained in about half of the cases, representing the so-called 'cryptogenic NORSE'. Amongst adult patients without cryptogenic NORSE, the most often identified cause is autoimmune encephalitis, either non-paraneoplastic or paraneoplastic. Infections are the prevalent aetiology of paediatric non-cryptogenic NORSE. Genetic and congenital disorders can have a causative role in NORSE, and toxic, vascular and degenerative conditions have also been described.

Conclusions: Far from being a unitary condition, NORSE is a heterogeneous and clinically challenging presentation. The development and dissemination of protocols and guidelines to standardize diagnostic work-up and guide therapeutic approaches should be implemented. Global cooperation and multicentre research represent priorities to improve the understanding of NORSE.

KEYWORDS
Febrile-infection-related epilepsy syndrome, infantile hemiconvulsion-hemiplegia and epilepsy syndrome, NORSE, seizures, status epilepticus

INTRODUCTION

Status epilepticus (SE) is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms leading to abnormally prolonged seizure activity [1]. It is an important neurological emergency and a potentially life-threatening condition [2]. Current treatment protocols are based on a three-stage approach, with benzodiazepines generally recommended as first-line agents, intravenous antiseizure medications as second-line and anaesthetics as third-line [3]. Refractory SE (RSE) is defined as a failure of first-line therapy with benzodiazepines and one second-line treatment with antiseizure medications, and in super-refractory SE (SRSE) status continues or recurs despite the use of anaesthetics for longer than 24 h [4,5].

Almost half of patients experiencing SE suffer from known epilepsy, and an obvious cause can be identified in many others [6–8]. Some cases, however, elude any easily detectable aetiology and previously healthy individuals develop prolonged RSE without a readily identifiable explanation. This form of presentation has been given different terms and acronyms suggesting a separate entity or disease. The lack of a clear concept of the nosology and the absence of standardized terminology has hampered multicentre investigations and generated confusion in the literature and at the bedside. Recently, a consensus definition has been proposed to clearly define new-onset RSE (NORSE) and other related disorders [9]. The multidisciplinary group of experts highlighted that NORSE is 'a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other pre-existing relevant neurological disorder, with a new onset of RSE without a clear acute or active structural, toxic, or metabolic cause' [9]. Febrile-infection-related epilepsy syndrome (FIRES) is a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 h prior to the onset of RSE, with or without fever at SE onset [9]. There is no age limitation for NORSE or FIRES, and both adults and children can present NORSE and FIRES.

In recent years, NORSE has become increasingly well recognized, and progress has been made in aetiological characterization with different causes identified in many cases. This study aims to systematically review the currently available evidence about the aetiology of NORSE and NORSE-related conditions.

METHODS

The results of this systematic review are reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Synthesis Without Meta-analysis (SWiM) in systematic reviews extension [10,11]. The relevant studies were identified through MEDLINE (accessed by PubMed as of April 2021, week 1). The search terms were combinations of the following: 'new onset refractory status epilepticus', 'febrile infection related epilepsy syndrome', 'devastating epileptic encephalopathy school aged children', 'acute encephalitis refractory repetitive partial seizures', 'fever induced refractory epileptic encephalopathy school aged children', 'idiopathic catastrophic epileptic encephalopathy presenting acute onset intractable status', 'severe refractory status epilepticus presumed encephalitis' and 'infantile hemiconvulsion hemiplegia epilepsy syndrome'. The full search strategy is outlined in the Supporting Information. Additional data were sought at the NORSE institute website (http://www.norseinstitute.org). There were no date limitations or language restrictions; English-language titles and abstracts were used if authors were not proficient enough in the published language to screen for inclusion of the studies or extract relevant data. The protocol was not registered previously.

The following types of studies were considered for inclusion: randomized or non-randomized clinical trials; observational case–control, cohort or cross-sectional studies; case series or case reports. Reviews, meta-analyses, editorials, commentaries and expert opinions were excluded. Studies were included if patients met the diagnostic criteria for NORSE or FIRES [9]. To take into account the phenotypic similarities with FIRES that have been reported worldwide in the literature under different terms over time [12], the following diagnoses were also considered: idiopathic catastrophic epileptic encephalopathy presenting with acute onset intractable status [13]; severe refractory status epilepticus because of presumed encephalitis [14]; devastating epileptic encephalopathy in school-aged children [15]; acute encephalitis with refractory, repetitive partial seizures [16]; fever induced refractory epileptic encephalopathy in school-aged children [17]. The Infantile Hemiconvulsion-Hemiplegia and Epilepsy syndrome (IHHE) was also included as this entity has recently been included amongst the NORSE-related conditions and defined as 'a specific syndrome in a patient <2 years old, presenting as NORSE with unilateral motor seizures, high grade fever at the time of onset of refractory status epilepticus, and unilaterally abnormal acute imaging, followed by hemiparesis lasting at least 24 h and excluding definite infectious encephalitis' [9]. Participants of any age, that is, paediatric and adult patients, sex and ethnicity were eligible. Two review authors (CR, SS) independently assessed studies for inclusion and any disagreement was resolved by discussion with a third review author (SL). The following information from included studies was extracted: first study author and age of publication, number and demographics of participants, diagnostic work-up and aetiologies identified in individual patients. The risk of bias of any included clinical trial was assessed using the RoB 2 tool [18], whilst it was not assessed individually for other study types (observational studies and case series/case reports) that, instead, were considered at high risk of bias [19].

RESULTS

Four hundred and fifty records were initially identified. Two hundred and sixty-five studies were retrieved for detailed assessment, of which 197 were included in the review (Figure 1). The selected studies were retrospective case–control ($n = 11$), case series ($n = 83$)

and case reports (n = 103); there were no randomized or non-randomized clinical trials. All included studies were considered to have a high risk of bias related to the retrospective design, selection of participants, ascertainment of exposure, data collection and missing data, and reporting of results.

The studies overall described 1334 patients both of paediatric and adult age. The list of references to included studies can be found in the Supporting Information.

The diagnostic evaluations reported across the studies are shown in Figure 2. The work-up performed to identify the underlying aetiologies differed markedly between the studies and great heterogeneity can be observed in the type of investigations adopted to evaluate the patients. Infectious and autoimmune/paraneoplastic panels were the most commonly performed diagnostic examinations being reported in 157/197 (79.7%) and 120/197 (60.9%) studies, respectively; genetic tests were described in 36 (18.3%) of the included studies. Amongst the advanced brain imaging techniques, brain positron emission tomography and single-photon emission computed tomography were the most often utilized, being reported in 16/197 (8.1%) and 7/197 (3.6%) studies. Amongst histopathological examinations, cerebral biopsy was the most frequent required and performed in 15/197 (7.6%) studies. Available details about autoimmune and infectious panels, advanced imaging techniques, genetic tests and histopathological analyses performed within the diagnostic work-up of the studies are summarized in Table S1.

In the included reports, the aetiology of NORSE remained unknown in the majority of cases; the most frequent causes identified in patients described in the studies were autoimmune and infectious disorders. The aetiologies recognized in all studies included in the review are shown in Table 1.

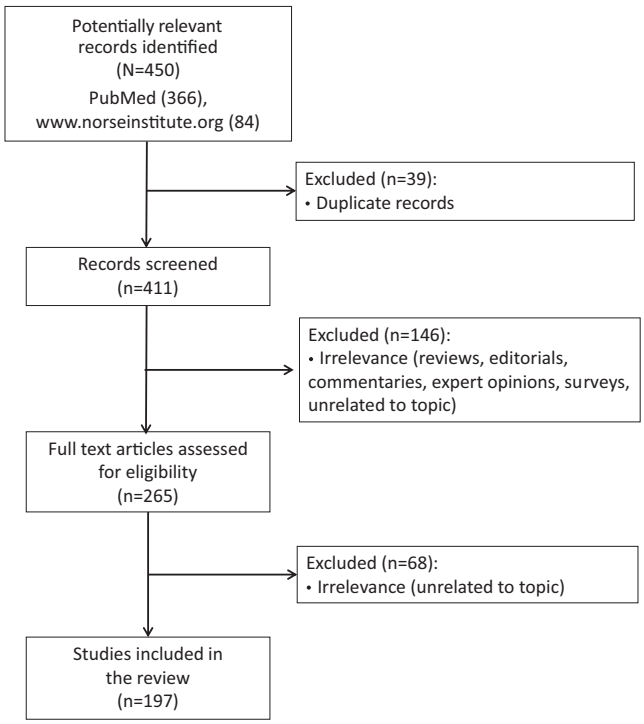

FIGURE 1 Flow diagram of the study selection process

DISCUSSION

New-onset refractory status epilepticus is a heterogeneous presentation of a variety of conditions and diseases. Based on the cohort studies with the largest population both in the paediatric and adult age groups, aetiology remains unexplained, despite an extensive, albeit variable diagnostic work-up, in about half of the cases representing the so-called 'cryptogenic NORSE' (c-NORSE) [20,21]. Amongst adult patients with symptomatic rather than c-NORSE, the most commonly identified cause is autoimmune encephalitis, either non-paraneoplastic or paraneoplastic. Different antibodies against neuronal surface or intracellular antigens have been associated with subtypes of autoimmune encephalitis, and their pathogenicity varies.

Antibodies directed against neuronal cell surface antigens are directly pathogenic, and they include antibodies against the *N*-methyl-D-aspartate receptor (NMDAR), leucine-rich glioma-inactivated 1 (LGI1) and γ-aminobutyric acid B receptor ($GABA_BR$) [22]. Although

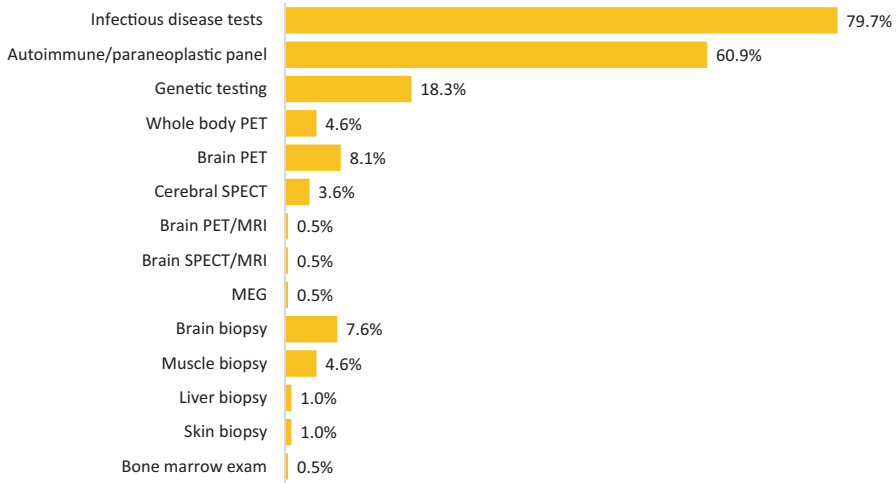

FIGURE 2 Diagnostic work-up in included studies. Laboratory, instrumental and histopathological tests reported as part of the diagnostic work of patients with NORSE and NORSE-related conditions. Percentages of studies out of the 197 included are shown. MEG, magnetoencephalography; MRI, magnetic resonance imaging; NORSE, new-onset refractory status epilepticus; PET, positron emission tomography; SPECT, single photon emission computed tomography

TABLE 1 Main characteristics of all studies included in the review and aetiologies identified in patients with NORSE and NORSE-related conditions

Study	Study design	Population	Prodromes	Aetiology
Acharya et al., 2015 [79]	Case report	Male, 45 years==		Triazophos poisoning
Agarwal et al., 2015	Case report	[a]Male, 4 years	Sinus infection, fever	Unknown
Agarwal et al., 2018	Case report	Male, 23 years	Fever, painless complete vision loss	Infection by simian virus 40
Akbik et al., 2020	Case series	Male, 76 years Female, 63 years Male, 71 years Male, 61 years	Headache, encephalopathy	Unknown Posterior reversible encephalopathy syndrome HSV encephalitis Checkpoint inhibitor-induced autoimmune encephalitis
Akiyama et al., 2020	Case report	Male, 84 years		Encephalitis associated with anti-$GABA_B$ receptor antibodies (in small cell lung cancer)
Al-Khateeb et al., 2019	Case report	Male, 41 years	Blurry vision, headache	Antiphospholipid syndrome
Alkhachroum et al., 2020	Case series	*N* = 12		Unknown
Alparslan et al., 2017	Case report	[a]Male, 8 years	Fever, upper respiratory infection	Unknown
Appavu et al., 2016	Case series	[a]*N* = 1 *N* = 1	Fever	Unknown Unknown
Appenzeller et al., 2012 [38]	Case series	[a]*N* = 15, male:female = 8:7, median age 6 (range 3–15) years	Fever (1/15) Febrile rhinovirus bronchitis (1/15) Febrile tonsillitis (1/15) Febrile upper respiratory infections (3/15) Subfebrile temperature, vomiting and headache (1/15) Febrile parvovirus B19 infection (1/15) Febrile pneumonia (1/15) Fever and headache (2/15) Febrile pharyngitis (1/15) Febrile enteritis (2/15) Febrile cervical lymphadenitis (1/15)	Unknown; one potentially functionally relevant mutation in *POLG* affecting a splice site variant (c.1251-5C>G) was identified
Arayakarnkul et al., 2018	Case series	*N* = 10, male:female = 5:5, age range 1.7–13.5 years	Fever	[a]Unknown (3/10) Steroid-responsive encephalopathy associated with autoimmune thyroiditis (2/10) Neuropsychiatric systemic lupus erythematosus (1/10) Encephalitis associated with anti-NMDAR antibodies (1/10) HSV encephalitis (1/10) Rickettsia encephalitis (1/10) Rasmussen encephalitis (1/10)
Aurangzeb et al., 2019	Case series	Male, 22 years Female, 18 years Female, 31 years Male, 75 years Male, 39 years Female, 27 years Male, 71 years	Flu-like symptoms, headache, abdominal discomfort, diarrhoea Fever, headache, nausea, sores on lips Fever, abdominal pain, vomiting Feeling drowsy Vomiting, fever Fever, myalgia, headache, neckache, confusion Subacute cognitive deterioration	Unknown Unknown Unknown Cortical damage/gliosis secondary to subarachnoid haemorrhage Unknown Unknown Encephalitis associated with anti-GAD and $GABA_BR$ antibodies
Baba et al., 2021	Case report	[a]Female, 8 years	Fever, diarrhoea, anorexia	Unknown

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Babi et al., 2017 [81]	Case report	Male, 40 years		Exposure to synthetic cannabinoids
Baxter et al., 2003 [13]	Case series	[b]*N* = 6, male:female = 4:2, age range 5 months to 6 years	Non-specific symptoms suggestive of infection (4/6), fever (2/6)	Unknown
Boyd et al., 2010	Case report	Male, 26 years	Headache, fever, myalgias	Unknown
Boyd et al., 2012	Case report	Female, 22 years	Fever, malaise	Unknown
Brunker et al., 2020	Case report	Male, 18 years	Flu-like symptoms, fatigue	CSF positivity of anti-GAD antibodies
Byler et al., 2014	Case report	[a]Male, 5 years	Fever, coryza, diarrhoea	Unknown
Cantarín Extremera et al., 2020 [71]	Case report	[a]Male, 9 years	Fever	Increased serum and CSF IL-6 levels; heterozygous variant of uncertain significance in *RELN*
Capizzi et al., 2015	Case report	[a]Female, 15 years	Fever, asthenia, upper respiratory tract infection	Unknown
Caputo et al., 2017	Case report	[a]Female, 13 years	Fever	Encephalitis associated with $GABA_AR$ antibodies
Caraballo et al., 2013	Case series	[a]*N* = 12, male:female = 8:4, mean age 8.5 (range 2–13.5) years	Fever and upper respiratory tract infection (9/12) Fever and gastroenteritis (3/12) Headache, drowsiness, confusion	Unknown
Carranza Rojo et al., 2012	Case series	[a]*N* = 10, age range 3–14 years	Fever (10/10) Confusion (8/10) Upper respiratory tract infection (1/10) Vomiting (4/10) Rash (1/10)	Unknown
Chalhub et al., 1977	Case report	Male, 3 months	Upper respiratory tract infection, fever	Coxsackie A9 enteroviral infection
Chan et al., 2018	Case report	Male, 31 years	Fever, myalgia, upper respiratory symptoms, cough	Unknown
Cho et al., 2019	Case report	Male, 76 years	Acute confusional state	Encephalitis associated with anti-SOX1 antibodies (history of stage IIIB squamous cell lung cancer)
Choi et al., 2019	Case series	*N* = 13, male:female = 7:6, median age 45 (IQR = 33–50.5) years	Myalgia (9/13) Fever (8/13) Headache (5/13) Upper respiratory tract infection symptoms (4/13) Nausea/vomiting (3/13) Acute memory impairment or confusion (12/13)	Unknown
Chou et al., 2016	Case report	[a]Female, 12 years	Fever and upper respiratory tract infection	Unknown
Clarkson et al., 2019	Case control	[a]*N* = 7, male:female = 5:2, age range 1.5–16 years	Febrile illness	Elevated levels of IL-1RA and IL-1β in the serum and CSF Functional deficiency in IL-1RA inhibitory activity Multiple variants within intronic sequences and a silent mutation in exon 6 of *IL1RN*

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Collaborative Group for Fever-induced Refractory Epileptic Encephalopathy in School-aged Children, 2012	Case series	[c]*N* = 13, male:female = 6:7, median age 8.3 years	Fever	Unknown
Costello, 2009	Case series	*N* = 6, male:female = 2:4, average age 28.5 (range 24–36) years	Fever and coryzal symptoms (i.e., nasal congestion, sore throat, myalgias) (4/6) Persistent dry cough (2/6)	Unknown
Dahaba et al., 2010	Case report	[d]Female, 14 years	Fever, upper respiratory tract infection	Unknown
Daida et al., 2020	Case report	Female, 28 years	Fever, disturbance of consciousness, automatisms, oral dyskinesia, upward-directed gaze palsy	Encephalitis associated with anti-ganglioside antibodies (IgG-GD1a, GT1b, GQ1b)
Dara et al., 2006	Case report	Female, 31 years		Newly diagnosed systemic lupus erythematosus (possible lupus cerebritis)
Deshmukh et al., 2019 [86]	Case series	*N* = 5, male:female = 4:1, age range 56–83 years		Carotid artery stenting
Dilena et al., 2019 [41]	Case report	[a]Male, 10 years	Fever, upper respiratory tract infection	Unknown; serum testing for anti-basal ganglia antibodies showed the presence of antibodies against a still unidentified 150 kDa antigen
Dillien et al., 2016 [68]	Case report	Female, 27 years	Flu-like syndrome	Serum positivity for antibodies against Japanese encephalitis virus Heterozygous single nucleotide variant in the sequence c.1280A>G [p.Lys427Arg] of *SMC3*
Donnelly et al., 2021	Case report	Female, 26 years		Unknown
Dono et al., 2020	Case report	Male, 81 years	Fever, mild dyspnoea, dry coughing	Post SARS-CoV-2 autoimmune encephalitis
Eaton et al., 2019	Case report	Male, 19 years	Nausea, headache	Positivity for anti-GAD antibodies
Eaton et al., 2021 [92]	Case report	Male, 26 years	Headache, intermittent diplopia, weight loss	Primary leptomeningeal melanomatosis
Eguchi et al., 2019	Case report	Male, 33 years	Fever, fatigue	Unknown
Farias-Moeller et al., 2017	Case series	[a]*N* = 7, male:female = 4:3, mean age 8 (range 5–16) years	Non-specific febrile illness (upper respiratory tract infection with odynophagia or, less often, a gastrointestinal illness)	Unknown
Farias Moeller et al., 2018 [33]	Case series	[a]*N* = 5, male:female = 3:2, median age 4.5 (IQR 4.5–12.5), range 4–16 years	Non-specific febrile illness	Unknown; secondary hemophagocytic lymphohistiocytosis in three cases
Fatuzzo et al., 2019	Case report	[a]Female, 29 years	Febrile episode	Unknown
Ferlisi et al., 2020 [69]	Case report	Female, 28 years; mild form of Axenfeld–Rieger syndrome		Unknown

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Fisher et al., 2020	Case series	[a]*N* = 8, mean age 8.5 (range 4–15) years	Febrile illness	Unknown
Fox et al., 2017	Case report	[a]Female, 6 years	Fever	Unknown
Fukuyama et al., 2011	Case report	[d]Male, 6 years		Unknown
Gall et al., 2013 [26]	Case series	Male, 26 years Male, 34 years Male, 30 years Female, 23 years Female, 22 years	Headache, vomiting Fever, myalgia Headache, acute confusion Headache, fever, vomiting Fever, acute confusion	Unknown (anti-TPO antibodies; history of hyperthyroidism) Unknown Unknown Unknown Unknown
Gaspard et al., 2015 [20]	Case series	*N* = 130, male:female = 47:83, age range 18–81		Unknown (67/130) Non-paraneoplastic autoimmune (25/130) (anti-NMDAR, anti-VGKC complex, steroid-responsive encephalopathy associated with autoimmune thyroiditis, cerebral lupus, anti-GAD, anti-striational) Paraneoplastic (23/130) (anti-NMDAR, anti-VGKC complex, anti-Hu, anti-VGCC, anti-CRMP5, anti-Ro, seronegative) Infection-related (10/130) (EBV, VZV, CMV, WNV, mycoplasma pneumoniae, syphilis, toxoplasma gondii) Subacute encephalopathy with seizures in alcoholic patients (2/130) Leptomeningeal carcinomatosis (2/130) Creutzfeldt–Jakob disease (1/130)
Geva-Dayan et al., 2012	Case series	[a]*N* = 9, age range 2.5–15	Febrile illness	Unknown
Gofshteyn et al., 2017	Case series	[a]*N* = 7, male:female = 5:2, average age 7 (range 3–8) years	Fever	Unknown
Gonzalez-Martinez et al., 2020	Case report	Female, 82 years	Altered consciousness, aphasia	Creutzfeldt–Jakob disease
Goyal et al., 2020	Case report	[a]Male, 13 months	Fever	Unknown
Gugger et al., 2019	Case series	*N* = 20, male:female = 10:10, median age 50.5 (IQR 29–69.5) years; remote history/recurrence of cancer (4/20)	Fever or infectious symptoms (9/20) Headache (5/20) Encephalopathy (12/20)	Autoimmune encephalitis (18/20) (anti-PCA-2, voltage-gated potassium channel, CASPR2 antibodies) Unknown (1/20) *CACNA1A* mutation (1/20)
Hainsworth et al., 2014	Case report	Male, 24 years		Encephalitis associated with anti-$GABA_BR$
Hamano et al., 2003	Case report	[d]Female, 5 years		Unknown
Hau Man et al., 2017	Case report	Male, 27 years		Possible autoimmune encephalitis

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Helbig et al., 2020	Case series	[a]*N* = 50, male:female = 33:17, median age 6 (range 2–15) years	Febrile illness	Unknown
Hirayama et al., 2016	Case series	[d]*N* = 2, male:female = 1:1, median age 128 (range 105–151) months		Unknown
Horino et al., 2021	Case control	[a]*N* = 6, male:female = 5:1, mean age 6 (range 4–8) years	Febrile illness	Unknown; increased CSF concentrations of CXCL10, CXCL9, IFN-γ, neopterin, IL-1β, IL-6 and IL-8
Houk et al., 2019	Case report	Male, 19 years	Fever, malaise	Unknown
Howell et al., 2012	Case series	[a]*N* = 7, male:female = 7:0, median age 10.8 (range 6.7–14) years	Fever, headache, confusion and lethargy (7/7); upper respiratory tract symptoms and myalgias variably noted	Unknown
Hsieh et al., 2020 [40]	Case control	[a]*N* = 5, male:female = 4:1, age range (2–13) years	Febrile illness	Unknown; adenovirus and enterovirus in throat cultures (2/5) Serum IgM of mycoplasma pneumoniae and HSV (2/5) Impaired TLR3, TLR4, TLR7/8 and TLR9 responses in peripheral blood mononuclear cells and monocyte-derived dendritic cells
Hsu et al., 2020	Case control	[a]*N* = 7, male:female = 5:2, age range 4–13 years	Fever	Unknown
Hurth et al., 2019	Case report	Female, 51 years		Possible autoimmune encephalitis
Husari et al., 2020 [21]	Case series	*N* = 40, male:female = 21:19, median age 6.6 (IQR 3.0–10.4) years	Fever either at home or upon admission (30/40) Fever only upon admission (12/40) Fever prior to admission (27/40) Upper respiratory tract infection (15/40) Gastroenteritis (9/40) Headache (3/40) Cutaneous rash (1/40) Psychiatric and behavioural symptoms (1/40)	Unknown (23/40) Viral infection (8/40) (EBV, HSV, enterovirus, influenza virus) ADEM (3/40) Autoimmune encephalitis (2/40) Steroid-responsive encephalopathy with autoimmune thyroiditis (1/40) Genetic (3/40) (*DNM1L* mutation, *KCNT1* mutation, compound heterozygous POLG and cathepsin D mutations)
Husari et al., 2021	Case series	Male, 75 years	Confusion, cognitive decline	Possible autoimmune encephalitis
Ibrahim et al., 2014	Case report	Male, 21 years		Influenza A (H1N1 infection)
Iizuka et al., 2017 [31]	Case series	*N* = 11, male:female = 4:7, median age 27 (range 17–59) years	Fever (10/11), headache (6/11)	Unknown
Iizuka et al., 2019	Case series	*N* = 24		Unknown
Iizuka et al., 2020	Case control	*N* = 30, male:female = 13:17, median age 25 years		Unknown

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Illingworth et al., 2011	Case report	[d]Male, 4 years	Febrile illness	Anti-VGKC complex antibodies
Ishikura et al., 2015	Case report	Male, 23 years	Antecedent infection	Unknown; serum antibodies reacting against cytoplasm and nucleus in hippocampal neurons of rat brain section
Ismail et al., 2011	Case report	[a]Female, 14 years	Fever, diarrhoea	Unknown
Ito et al., 2005	Case report	[d]Male, 11 years	Fever	Serum and CSF anti-Gluε2 antibodies
Jafarpour et al., 2017	Case series	Age 3 months Age 5 months Age 3 years Age 12 years	Gastroenteritis Otitis media Fever	Unknown De novo mutation of *SCN10A* Unknown Unknown
Jang et al., 2021 [27]	Case series	Male, 24 years	Fever, headache	Anti-myelin oligodendrocyte glycoprotein-associated disorder
Jayalakshmi et al., 2016	Case series	*N* = 36		Unknown (33/36) HSV encephalitis (3/36)
Jose et al., 2021	Case series	*N* = 13	Fever (5/13)	Autoimmune encephalitis (10/13) Viral encephalitis (3/13)
Juhász et al., 2013	Case report	Male, 56 years	Headache	Unknown
Jun et al., 2018 [44]	Case series	Male, 58 years Female, 61 years Female, 24 years Male, 22 years Male, 47 years Female, 19 years Female, 25 years	Behaviour change, headache Fever Fever Fever, headache Fever, behaviour change Fever, behaviour change	Unknown Encephalitis associated with anti-NMDAR antibodies Unknown Unknown Unknown Unknown Unknown
Kaplan et al., 2017	Case report	Female, 29 years	Focal sensory-motor deficits, cognitive decline, emotional lability, intermittent confusion	Encephalitis associated with anti-NMDAR antibodies
Katz et al., 2021	Case report	Female, 29 years	Fever, headache, emesis, fatigue	Unknown
Kaufman et al., 2017	Case report	[c]Female, 6 years	Fever, strep throat	Moyamoya angiopathy
Kenney-Jung et al., 2016 [42]	Case report	[a]Female, 32 months	Febrile respiratory infection	Unknown
Kern Smith et al., 2020	Case report	Male, 5 years		*Bartonella henselae* infection
Khawaja et al., 2015 [84]	Case series	*N* = 11, male:female = 2:9, mean age 48 (range 21–90) years		Autoimmune encephalitis (7/11) (anti-GAD, anti-NMDAR, anti-VGCC, anti-VGKC antibodies) Unknown (3/11) PRES (1/11)
Kikuchi et al., 2007	Case report	[d]Male, 9 years	Gastrointestinal infection	Unknown
Kim et al., 2020 [90]	Case series	*N* = 39, male:female = 24:15, median age 33 (IQR 22.0–42.0) years		Unknown (35/39) Encephalitis associated with anti-NMDAR antibodies (1/39) EBV encephalitis (1/39) Polymicrogyria (1/39) History of traumatic subarachnoid haemorrhage (1/39)
Kobayashi et al., 2010 [61]	Case series	[d]*N* = 7, male:female = 5:2, age range 5–8 years	Common cold (4/7), fever (2/7), acute enterocolitis (1/7)	Unknown; *SCN1A*-R1575C mutation (1/7)

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Kobayashi et al., 2012 [62]	Case series	[d]*N* = 8	Fever and cold-like symptoms	Unknown; missense mutation c.3383T>C (Met1128Thr) in *SCN2A* (1/8)
Kodama et al., 2018	Case report	Male, 31 years	Fever	Unknown
Kothur et al., 2019 [37]	Case control	[a]*N* = 4	Febrile illness	Unknown; increased CSF levels of Th1-associated cytokines/chemokines (TNF-α, CXCL9, CXCL10, CXCL11), IL-6, CCL2, CCL19 and CXCL1
Kramer et al., 2005 [14]	Case series	*N* = 8, age range 2.5–15 years	Fever (7/8), erythematous rash (1/8)	Unknown
Kramer et al., 2011	Case series	*N* = 77, male:female = 4:3, median age 8 (range 2–17) years	Fever (74/77), upper respiratory tract infection (30/77), gastroenteritis (15/77), otitis media (2/77), mastoiditis (1/77), pneumonia (1/77), herpes labialis (1/77), rash (1/77)	Unknown; anti-GAD antibodies in two of five tested patients, and anti-GluR3 antibodies in one of four tested patients
Kumari et al., 2015	Case report	Male, 31 years	Generally feeling unwell and weight loss	Neurosyphilis
Kurukumbi et al., 2019	Case report	Male, 25 years	Upper respiratory tract infection	Unknown
Kwan et al., 2020	Case report	Male, 67 years		Encephalitis associated with $GABA_BR$ antibodies (in small cell prostate cancer)
Lai et al., 2020	Case series	[a]*N* = 25, male:female = 16:9, median age 8 (range 5–16) years	Febrile illness	Unknown; increased CSF cytokines (3/10) Increased CSF neopterin (3/10) Increased serum cytokines (8/9) Increased serum neopterin (3/9)
Lam et al., 2019	Case series	[a]*N* = 20, male:female = 12:8, mean age 9.6 ± 4.4 (range 1.6–17.2) years	Upper respiratory tract infection (14/20), fever with unknown focus (4/20), gastrointestinal tract symptoms (2/20)	Unknown
Laswell et al., 2015	Case report	Female, 28 years		*Bartonella henselae* infection
Lee et al., 2018	Case series	[a]*N* = 29, male:female = 12:17, median age 8.9 (range 1.2–17.8) years	Fever (27/29), upper respiratory tract infection (21/29), nausea/vomiting/diarrhoea (10/29)	Unknown
Li et al., 2013	Case series	Female, 43 years Male, 51 years Female, 39 years	Flu-like illness Febrile illness Flu-like illness	Autoimmune encephalitis Autoimmune encephalitis Autoimmune encephalitis
Lin et al., 2009	Case series	[d]*N* = 9, male:female = 7:2, age range 5–15 years	Fever (9/9), upper respiratory tract infection (6/9), headache (4/9), vomiting (3/9), altered consciousness (2/9), sore throat (1/9)	Unknown
Lin et al., 2012	Case series	[a]Male, 10 years [a]Female, 4 years	Fever, flu-like symptoms Febrile illness	Unknown
Maegaki et al., 2006	Case series	[d]Male, 8 years [d]Female, 12 years	Fever, nausea Fever	Unknown Unknown
Maloney et al., 2020	Case report	Male, 19 years		Anti-GAD antibodies

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Manganotti et al., 2021 [50]	Case series	Male, 37 years Male, 71 years	Respiratory failure symptoms	Post SARS-CoV-2 autoimmune encephalitis Post SARS-CoV-2 autoimmune encephalitis
Marashly et al., 2017 [91]	Case report	Female, 3 years		Focal cortical dysplasia type II
Matar et al., 2017 [85]	Case report	Male, 46 years	Headache, wide-based gait, unsteadiness	Primary angiitis of the central nervous system
Matsuzono et al., 2014	Case report	[d]Male, 22 years	Fever, headache	Unknown
Matthews et al., 2020 [28]	Case series	*N* = 26, male:female = 8:18, age peaks at 27 and 63 years	Fever (13/26), fatigue/malaise (17/26), headache (11/26), myalgias (3/26), upper respiratory infection (6/26), diarrhoea (2/26), nausea/vomiting (8/26), rash (5/26), agitation (2/26), paranoia (3/26), hallucinations (4/26), insomnia (2/26), mutism (1/26), uncontrollable laughter (1/26)	Unknown (19/26) Encephalitis associated with anti-NMDAR antibodies (4/26) HSV encephalitis (1/26) Candida encephalitis (1/26) ADEM (1/26)
Mazzuca et al. 2011	Case series	[a]*N* = 8, male:female = 5:3, age range 4.3–8.6 years	Febrile illness	Unknown
Meenakshi-Sundaram et al., 2021	Case report	[a]Male, 14 years	Fever, throat pain, rhinorrhoea, headache, vomiting	Hemophagocytic lymphocytic histiocytosis
Meletti et al., 2017	Case series	*N* = 31, male:female = 14:17, mean age 24.6 ± 12.4 years	Fever with flu/cold symptoms/general malaise (28/28) Altered mental status (22/31)	Unknown
Mikaeloff et al., 2006 [15]	Case series	[e]*N* = 14, male:female = 7:7, median age 7.5 (range 4–11) years	Febrile illness (mainly upper respiratory tract infection, with or without rash)	Unknown
Milh et al., 2011	Case report	[a]Male, 5 years	Fever, upper respiratory tract infection	Serum and CSF anti-neuropil antibodies
Miràs Veiga et al., 2017	Case report	[a]Male, 4 years	Fever, pharyngitis	Unknown
Mizutani et al., 2019	Case report	Male, 30 years	Fever, diarrhoea, headache	Unknown
Moise et al., 2019	Case series	*N* = 12		Encephalitis associated with anti-NMDAR antibodies (*N* = 4) Encephalitis associated with anti-VGKC antibodies (*N* = 1) Encephalitis associated with anti-GAD antibodies (*N* = 3) Probable autoimmune encephalitis (*N* = 4)
Monti et al., 2020 [51]	Case report	Male, 50 years	Fever, psychiatric symptoms (confabulations and delirious ideas)	Encephalitis associated with anti-NMDAR antibodies; asymptomatic SARS-CoV-2 infection
Morrison et al., 2020 [57]	Case report	Female, 23 years		Mutation in *POLG*
Myers et al., 2017	Case report	Male, 23 months	Fever	Unknown
Nair et al., 2014	Case report	Female, 24 years	Headache, fever	Unknown
Nardetto et al., 2017	Case report	Female, 19 years	Fever, laterocervical lymphadenopathy	Unknown

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Neuwirth et al., 2008	Case series	[d]*N* = 5, median age 11.5 (8–14) years		Unknown
Newey et al., 2019	Case series	Male, 28 years	Upper respiratory viral illness	Unknown; serum anti-thyroid peroxidase and anti-thyroglobulin antibodies
Nolan et al., 2014	Case report	Male, 20 years		Encephalitis associated with anti-NMDAR antibodies
Nozaki et al., 2013	Case report	[c]Male, 7 years	Fever associated with tonsillitis	Unknown
Ogawa et al., 2016	Case report	[d]Male, 11 years	Fever	Unknown
Okanishi et al., 2007	Case report	[d]Male, 14 years	Fever, headache, vomiting, eruption	Serum anti-Gluε2 antibodies
Patel et al., 2017 [82]	Case report	Male, 19 years	History of synthetic cannabinoid-associated seizures	Abuse of synthetic cannabinoids
Patil et al., 2016	Case series	[c]*N* = 15, male:female = 12/3, median age 6.3 (range 3–15) years	Non-specific respiratory infection (12/15), acute diarrhoeal disease (2/15), fever with non-specific lymphadenopathy (1/15)	Unknown
Peng et al., 2019	Case series	[a]*N* = 7, male:female = 4:3, median age 8 (range 1.5–13) years	Fever of unknown origin (3/7), upper respiratory tract infection (3/7), gastroenteritis (1/7)	Unknown
Petit-Pedrol et al., 2014 [23]	Case control	*N* = 6, male:female = 5:1, median age 22 (range 3–63) years	Memory, cognitive and affective problems, behavioural changes, choreoathetoid movements	Encephalitis associated with $GABA_AR$ antibodies
Puoti et al., 2013	Case report	Male, 41 years	Fever, vomiting	Unknown
Rivas-Coppola et al., 2016	Case series	[a]*N* = 7, male:female = 6:1, median age 4.7 years (range 3 months to 9 years)	Non-specific febrile illness (upper respiratory tract infection, gastroenteritis)	Unknown
Rochtus et al., 2020	Case series	[c]*N* = 5, male:female = 3:2, age range 7–14 years	Fever	Unknown
Sa et al., 2019	Case series	[a]Male, 9 years [a]Male, 5 years	Fever, vomiting, headache Fever, abdominal pain, coryza	Unknown (increased CSF neopterin levels) Unknown
Saito et al., 2007	Case series	[d]Male, 10 years [d]Female, 7 years [d]Female, 9 years	Fever, bronchopneumonia, headache, consciousness fluctuation Fever Fever	Unknown Late positivity of serum GluRε2 antibodies Unknown
Saitoh et al., 2016 [65]	Case control	[c]*N* = 19	Fever	Unknown; association with *IL1RN* haplotype containing RN2; possible association of *IL1RN* rs4251981G>A and *SCN2A* rs1864885A>G
Sakuma et al., 2001	Case series	[d]*N* = 22		Unknown
Sakuma et al., 2010 [16]	Case series	[d]*N* = 29, male:female = 19:10, mean age 6.8 ± 4.0 (range 1–14) years	Febrile illness (29/29)	Unknown; serum (6/9) and CSF (5/9) anti-GluRε2 antibodies; increased CSF neopterin (4/4)

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Sakuma et al., 2015 [36]	Case control	[d]*N* = 14	Fever	Unknown Increased serum and CSF levels of proinflammatory cytokines (such as IL-6, macrophage migration inhibitory factor) and chemokines (such as CXCL10, IL-8); T-cell-associated cytokines (such as IL-2, IL-17A) and homeostatic chemokines (such as CCL21, CXCL12) unchanged or downregulated
Sarria-Estrada et al., 2014	Case series	Female, 55 years Male, 77 years Male, 49 years Male, 60 years Male, 57 years	Progressive memory, language and writing impairment, auditive illusions Subacute confusional state, behaviour disorder, auditive illusions Memory impairment, fatigue, weight loss, confusion Headache, visual illusions, language impairment Apathy, anorexia, weight loss, aphasia, hypersomnolence	Paraneoplastic autoimmune encephalitis associated with anti-Hu antibodies (in small cell lung carcinoma) Seronegative autoimmune encephalitis (in mixed small cell lung carcinoma and adenocarcinoma) Paraneoplastic autoimmune encephalitis associated with anti-Hu antibodies (in small cell lung carcinoma) Seronegative autoimmune encephalitis (in colorectal adenocarcinoma) Seronegative autoimmune encephalitis (in lung adenocarcinoma)
Sato et al., 2016	Case report	[d]Male, 11 years	Fever	CSF anti-GluRε2 antibodies; increased CSF cytokine levels (TNF-α), IL-6, IL-10, IFN-γ
Savard et al., 2018	Case report	Male, 31 years	Headache, fever, myalgia	Encephalitis associated with Jamestown Canyon virus infection
Schoeler et al., 2021	Case series	[a]*N* = 8, male:female = 6:2, mean age 7.9 ± 1.7 (range 5.8–10.8) years	Febrile illness	Unknown
Seniaray et al., 2020	Case report	Male, 14 years	Fever	Unknown
Serrano-Castro et al., 2013	Case report	[c]Female, 19 years	Fever, myalgia, malaise	Unknown
Sharma et al., 2013	Case report	Male, 30 years	Fever	Unknown
Shibata et al., 2019	Case control	[d]*N* = 18, male:female = 15:3, mean age 81.4 ± 35.4	Febrile illness	Unknown
Shiraga et al., 2010	Case report	[d]Male, 5 years	Fever	Unknown
Shrivastava et al., 2017	Case report	Female, 24 years		Unknown
Shukla et al., 2018	Case series	[a]*N* = 5, male:female = 4:1, median age 7 (range 4–15) years	Febrile illness	Unknown

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Shyu et al., 2008	Case series	[d]*N* = 14, male:female = 7:7, age range 1–15 years	Fever (13/14), upper respiratory tract infection symptoms (12/14), gastrointestinal tract discomfort (6/14)	Unknown
Singh et al., 2014	Case series	[a]Male, 7 years [a]Female, 10 years	Fever, headache, malaise, papular rash, erythematous oropharynx Fever, myalgias, abdominal pain and nausea	Unknown Unknown
Singhal et al., 2003	Case series	Female, 27 years Female, 66 years	Confusion	*Bartonella henselae* infection *Bartonella henselae* infection
Specchio et al., 2010	Case series	[c]*N* = 8, mean age 7.4 ± 5.9 years	Fever	Unknown; positivity of anti-GAD antibodies (2/8)
Specchio et al., 2011	Case report	[c]Female, 8 months	Febrile gastroenteritis	Missense mutation (c.1129G>C; p.Asp377His) in *PCDH19*
Steriade et al., 2018	Case control	*N* = 5, male:female = 1:4, mean age 57 (range 26–83) years		Encephalitis associated with anti-VGKC and LGI1 antibodies (3/5), encephalitis associated with $GABA_BR$ antibodies (1/5), seronegative autoimmune encephalitis (1/5)
Stredny et al., 2020	Case report	[a]Male, 6 years	Febrile illness	Unknown
Strohm et al., 2019	Case series	*N* = 12, male:female = 10:2, mean age 40 (range 14–78) years	Viral prodrome (7/12)	Encephalitis associated with anti-NMDAR antibodies (4/12), anti-GAD antibodies (3/12), anti-LGI1 antibodies (1/12), anti-$GABA_BR$ receptor antibodies (1/3), anti-VGKC complex antibodies (1/12)
Suleiman et al, 2013	Case series	[c]Male, 3 years [c]Female, 8 years	Fever, blanching rash, irritability Fever, headache, lethargy	Unknown Unknown
Tan et al., 2018	Case report	[a]Female, 8 years	Fever, headache	Unknown
Theroux et al., 2020	Case report	[a]Male, 11 years	Fever	HHV-6 encephalitis; a single variant of uncertain significance in *PLCB1*
Trandafir et al., 2020	Case report	Female, 21 years	Fever	Unknown
Tsubouchi et al., 2017	Case series	[d]Female, 101 months		Unknown
Uchida et al., 2016	Case report	[d]Male, 9 years	Vomiting, diarrhoea, drowsiness	CSF anti-GluRε2-NT and anti-GluRε2-CT1 antibodies Increased CSF neopterin levels
Ueda et al., 2015	Case series	[d]*N* = 6, male:female = 4:2, age range 7–10 years	Febrile illness	Unknown
Ungureanu et al., 2018	Case report	Male, 62 years	Fever	Unknown
Vaccarezza et al., 2012	Case series	[a]*N* = 3	Fever	Unknown
Vallecoccia et al, 2020	Case report	Male, 34 years	Fever, headache	Unknown
van Baalen et al., 2010 [17]	Case series	[c]*N* = 22, male:female = 16:6, median age 6.5 (range 3–15) years	Respiratory tract infection (11/22), non-specific febrile infection (6/22), headache (2/22), otitis media (1/22), mastoiditis (1/22), herpes labialis (1/22)	Unknown; serum anti-GluR-3 antibodies (1/22)

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
van Baalen et al., 2012	Case series	[c]*N* = 12, male:female = 6:6; median age 6 (range 2–12) years	Respiratory tract infection (8/12), parvovirus B19 infection (1/12), lethargy (1/12), enteritis (1/12), vomiting and headache (1/12)	Unknown
Van Lierde et al., 2003	Case series	*N* = 6, male:female = 2:4, median age 23 (range 18–30) years	Febrile illness	Unknown
Varrasi et al., 2017 [29]	Case report	Male, 48 years		Hashimoto's encephalopathy
Verma et al., 2013	Case report	Female, 35 years	Fever, cough	HSV encephalitis
Villamar et al., 2020	Case report	Female, 15 years	Listlessness and decline in academic performance	Rabies encephalitis
Visser et al., 2011 [59]	Case series	Female, 19 years Female, 17 years		*POLG-1* mutation *POLG-1* mutation
von Spiczak et al., 2017 [60]	Case series	[a]Female, 4.5 years	Febrile illness	*DNM1* mutation (c.1117G>A; p.Glu373Lys)
Waheed et al., 2014 [80]	Case report	Female, 27 years	Drowsiness; bradycardia, bronchorrhoea, drooling of saliva, pinpoint pupils	Organophosphate poisoning
Wakamoto et al., 2012	Case report	[d]Male, 7 years	Fever and cough	Unknown Serum and CSF antibodies against GluRε2, ζ1 and δ2 subunits Increased serum levels of IL-2, IL-6, IL-10, TNF-α and IFN-γ; increased CSF levels of IL-6 Decreased natural killer cell activity in peripheral blood mononuclear cells
Wang D et al., 2020	Case series	*N* = 18, male:female = 6:12, median age 23.5 (range 17–76) years		Unknown (8/18 with positive serum immunostaining and 4/18 with positive serum and CSF immunostaining of rat hippocampus section were considered to have antibodies against hippocampus neuropils)
Wang X et al., 2020	Case series	[a]*N* = 10, male:female = 4:6, median age 9 (range 5–13) years	Fever	Unknown
Watanabe et al., 2014	Case report	[d]Male, 8 years		Unknown
Westbrook et al., 2019 [43]	Case report	[a]Female, 21 years	Intermittent fever, headache	Unknown; serum positivity for CASPR2 antibodies and weak positivity for anti-GAD antibodies after 5 days of intravenous immunoglobulin administration
Wilder-Smith et al., 2005	Case series	*N* = 7	Fever (2/7), fever and headache (2/7), fever and diarrhoea (1/7)	Unknown
Wu et al., 2020 [87]	Case report	Female, 46 years		Unknown (history of multiple blood transfusions)
Yamamoto et al., 2014	Case report	Male, 35 years	Febrile upper respiratory illness	Unknown
Yamashita et al., 2001	Case report	Male, 29 years	Flu-like symptoms	Unknown

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Prodromes	Aetiology
Yamazoe et al., 2017	Case report	Male, 24 years	Fever, upper respiratory infection, delirium, shouting of meaningless words	Encephalitis associated with anti-GluR antibodies
Yanagida et al., 2020 [30]	Case series	$N = 33$		Unknown
Zhang et al., 2016	Case report	[d]Male, 46 years	Fever, headache	Unknown

Note: Studies ($n = 197$) are sorted in alphabetical order.

Patients presented with [a]febrile infection-related epilepsy syndrome, [b]idiopathic catastrophic epileptic encephalopathy presenting with acute onset intractable status, [c]fever induced refractory epileptic encephalopathy in school-aged children, [d]acute encephalitis with refractory, repetitive partial seizures and [e]devastating epileptic encephalopathy in school-aged children.

Farias-Moeller et al. (2018) included patients previously described in Farias-Moeller et al. (2017). Kramer et al. (2011) included patients previously described in Baxter et al. (2003), Kramer et al. (2005), Mikaeloff et al. (2006), Shyu et al. (2008), Specchio et al. (2010) and van Baalen et al. (2010). Lee et al. (2018) included patients previously published in Saito et al. (2007). Peng et al. (2019) included patients previously published in Howell et al. (2012) and Kramer et al. (2011). Yanagida et al. (2020) included patients previously described in Iizuka et al. (2019).

Abbreviations: ADEM, acute disseminated encephalomyelitis; CACNA1A, calcium voltage-gated channel subunit alpha 1A; CASPR2, contactin-associated protein-like 2; CMV, cytomegalovirus; CRMP5, collapsing response mediator protein 5; CSF, cerebrospinal fluid; DNM1L, dynamin 1-like protein; EBV, Epstein–Barr virus; $GABA_AR$, γ-aminobutyric acid A receptor; $GABA_BR$, γ-aminobutyric acid B receptor; GAD, glutamate decarboxylase; GluR, glutamate receptor; HHV-6, human herpesvirus 6; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IL-1RA, IL-1 receptor antagonist; IQR, interquartile range; KCNT1, potassium sodium-activated channel subfamily T member 1; LGI1, leucine-rich glioma-inactivated 1; NMDAR, *N*-methyl-D-aspartate receptor; PCA-2, Purkinje cell cytoplasmic antibody type 2; PCDH19, protocadherin 19; PLCB1, phospholipase C β1 gene; POLG, DNA polymerase subunit G; PRES, posterior reversible encephalopathy syndrome; RELN, reelin; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2; SCN2A, sodium voltage-gated channel alpha subunit 2; SCN10A, sodium voltage-gated channel alpha subunit 10; SMC3, structural maintenance of chromosomes 3; SOX1, SRY-box transcription factor 1; TLR, toll-like receptor; TNF-α, tumour necrosis factor α; TPO, tireoperoxidase; VGCC, voltage-gated calcium channel; VGKC, voltage-gated potassium channel; VZV, varicella zoster virus; WNV, West Nile virus.

the mechanisms of seizure generation are not fully understood, anti-NMDAR antibodies can induce the internalization of the receptors, antibodies anti-LGI1 can promote the disruption of synaptic protein localization, and antibodies against $GABA_BR$ can act as neurotransmitter antagonists [22]. The $GABA_AR$ has been identified more recently as a target of autoimmune, usually non-paraneoplastic, encephalitis and associated with NORSE both in children and in adults [23,24]. Interestingly, $GABA_AR$ antibodies cause a selective decrease of the clusters of $GABA_AR$ at synaptic sites, without altering other post-synaptic proteins such as the NMDAR or gephyrin; further, the total density of $GABA_ARs$ including synaptic and extra-synaptic receptors is not affected, suggesting a relocation of receptors from synaptic to extra-synaptic sites [23]. Antibodies against glutamate decarboxylase and classic onconeural antibodies targeting intracellular neural antigens, including antibodies against collapsing response mediator protein 5, Hu, Yo, Ri, Ma2, SRY-box transcription factor 1 (SOX1) and amphiphysin, are variably associated with different types of tumours.

In contrast to antibodies directed against neuronal cell surface antigens, onconeural antibodies are thought to mainly represent the epiphenomenon of the underlying immune cascade in which cellular immunity can play the dominant role, mainly through cytotoxic T cell infiltration and granzyme B-mediated damage [22,25].

Cases of NORSE have also been reported in association with other autoimmune disorders, including autoimmune encephalopathy with elevated anti-thyroid antibodies, for example anti-thyroid peroxidase, myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease, acute disseminated encephalomyelitis, and encephalitis associated with systemic lupus erythematosus [20,21,26–30].

Distinguishing NORSE secondary to autoimmune encephalitis from c-NORSE is important as treatment and prognosis may differ [31]. In clinical practice, however, excluding the possibility of c-NORSE may be challenging, mainly at the early stage of SE before the results of antibody testing become available [30]. In this regard, the c-NORSE score is a clinically based scoring system that has been developed to early predict c-NORSE and includes the following features: presence of prodromal high fever of unknown origin before the onset of SE, absence of prodromal psycho-behavioural or memory alterations before SE onset, absence of sustained orofacial-limb dyskinesias despite a profoundly decreased level of consciousness, and symmetric brain magnetic resonance imaging abnormalities [30]. Patients with a high score are more likely to be negative for neuronal antibodies, have c-NORSE, be less responsive to first-line immunotherapy and have poor outcome [30].

Interestingly, the presence of neuronal antibodies is rare in cases of FIRES, but testing in this population is often incomplete [21,22], and the underlying aetiology cannot be identified in most patients. Cases of FIRES also appear to have less inflammatory cellular infiltrate and be less responsive to first-line immunotherapies than NORSE associated with autoimmune encephalitis [22]. Autoantibodies may not have a relevant contribution to c-NORSE and FIRES, and innate immune pathways may play a more important role than adaptive immunity [31]. Inflammation-mediated epileptogenesis has been proposed [32], and a vicious cycle involving inflammation and seizure activity is assumed to promote cell death and

network reorganization, ultimately leading to refractory seizures. An imbalance between pro- and anti-inflammatory mediators, possibly following a febrile or infectious illness, can activate innate immune pathways in glial cells, neurons, astrocytes and cellular components of the blood–brain barrier resulting in an uncontrolled neuroinflammatory cascade [33]. The release of cytokines, chemokines and adhesion molecules promotes infiltration of peripheral immune effectors. The inflammatory milieu contributes to developing a hyperexcitable state via phosphorylation of NMDAR, change in ion channels, altering glutamate and GABA release and reuptake, modification of GABA receptor trafficking and deficient buffering of astrocytes [33]. Concerning chemokines, CCL2 has an important role in promoting the production of interleukin-1β (IL-1β), causing neuronal cell death and altering calcium signalling, whilst CX3CL1 negatively influences GABA-ergic activity [34]. Prolonged exposure to neuroinflammation induces long-term transcriptional changes leading to changes in neurogenesis, sprouting and angiogenesis, and contributing to increased epileptogenesis [35]. In turn, seizure activity triggers neuroinflammation perpetuating a cycle of innate immune activation. Of note, the presence of brain inflammation in c-NORSE and FIRES is strongly suggested by either the antecedent febrile infectious diseases or laboratory findings. Proinflammatory cytokines such as IL-1β and IL-6 have received attention as potential key molecules in c-NORSE, and high levels of IL-6 and chemokines like CXCL10 and IL-8 have been found in serum and cerebrospinal fluid (CSF) in paediatric cases of FIRES with an immune signature markedly different from that associated with encephalitis [36,37]. The higher levels of inflammatory cytokines and interleukins found in FIRES compared to afebrile SE or refractory epilepsies with high frequency of seizures support the presence of neuroinflammation and its relationship with disease pathogenesis rather than simply being the effect of seizure activity [37,38]. The reported co-occurrence of FIRES and secondary hemophagocytic lymphocytic histiocytosis, a rare hyperinflammatory haematological syndrome characterized by cytokine storm [39], further reinforces the possibility of an immune dysregulation phenotype serving as one mechanism underlying acute epileptogenesis. It is noteworthy that around one-fifth of patients with c-NORSE had a past medical history of febrile convulsions, a family history of febrile convulsion or both [30]: it is arguable that a genomic susceptibility may exist, and a genetic predisposition may contribute to the development of these conditions following fever illness in a small group of subjects. Impairment of toll-like receptor pathways with weakened phagosome-associated responses and decreased T naïve and regulatory cells have been observed in children with FIRES [40]. As well as the lower number of naïve T cells can increase susceptibility to viral infections, weakened phagocytosis cannot allow the timely eradication of pathogens, mainly viruses, and result in the accumulation of damaged debris. By mimicry mechanisms, damaged debris can behave as epitopes cross-reactive with neural components and induce autoimmunity. The reduction in T regulatory cells can further result in inadequate suppression to counteract unwanted autoimmune and inflammation responses [40]. The potential pathogenetic role of immune mechanisms is further sustained by the evidence, despite limited to a few case reports, of successful response to anti-cytokine therapies like anakinra [41–43], an IL-1 receptor antagonist, and tocilizumab, an IL-6 receptor antagonist [44], in patients refractory to steroids, intravenous immunoglobulins, plasma exchange and second-line therapies such as rituximab.

The limits to using antibodies as biomarkers of autoimmune processes need to be acknowledged. Indeed, not all autoimmune diseases are mediated by antibodies, not all antibodies are known, and detecting antibodies, mainly in serum, does not necessarily prove a causative relationship. As antibodies represent the downstream products of the immune activation, biomarkers of upstream immune alterations may be more reliable to detect and monitor autoimmune-related conditions [17]. Cytokine and inflammatory molecular panels in serum and CSF are being considered and may represent promising candidates for diagnosis and prognosis in NORSE and FIRES [22].

Infectious-related encephalitis can cause NORSE. A variety of pathogenic organisms can be responsible, viruses being the most implicated, and may depend on the agents that are endemic in each region. Infections are the prevalent aetiology of paediatric NORSE and represent around 20% of cases [21], whereas they are the causes in only around 10% of adult patients [45]. Infectious causes should be sought early as delays in starting treatment may worsen prognosis, as in encephalitis due to herpes simplex virus (HSV), and the identification of the responsible agent can guide targeted therapies [45]. In this regard, clinical metagenomic next-generation sequencing of CSF or brain tissue represents a promising tool to investigate the various aetiologies of central nervous system (CNS) infections [46]. It allows for identification and genomic characterization of a comprehensive spectrum of potential causes including bacteria, fungi, parasites and viruses in a single test and without need for prior knowledge of a specific pathogen [47]. This technique may be helpful in identifying the pathogen, especially when other more directed assays such as polymerase chain reaction fail [48], or excluding an infectious aetiology.

Recently, cases of NORSE have been reported in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, either asymptomatic or symptomatic [49–51]. Therapeutic approaches included the administration of intravenous immunoglobulin and plasma exchange, which resulted in the complete resolution of seizures; anti-NMDAR antibody positivity and raised levels of IL-6 and IL-8 in CSF were found in one patient [51]. Although a definite pathogenetic role cannot be proved, the reported cases suggest that SARS-CoV-2 infection could trigger autoimmune responses with CNS involvement. Some patients with autoimmune encephalitis associated with coronavirus disease 2019 (COVID-19) have been reported, in which behavioural disturbances, confusion, drowsiness and new-onset epilepsy represented the main symptoms at onset [52,53]. Furthermore, anti-NMDAR encephalitis can be triggered by viral infection, as reported after the infection by HSV [54]. The secondary hyper-inflammation syndrome and 'cytokine storm' associated with COVID-19 may also play a role in promoting and sustaining refractory or super-refractory SE [55]. Of note, IL-6 is raised during the inflammatory phase of COVID-19, and increased CSF levels of

IL-6 have been shown to facilitate intrathecal synthesis of autoantibodies in anti-NMDAR encephalitis [56].

Genetic and congenital disorders can also have a causative role in NORSE. Mitochondrial disorders associated with mutations of the genes encoding the presynaptic dynamin 1-like protein (DNM1L) and the catalytic subunit of mitochondrial DNA polymerase gamma (POLG1) have been diagnosed in patients presenting NORSE [21,57–60]. Of note, valproic acid should preferentially be avoided in these cases due to the risk of inducing hepatic failure, and propofol and thiopental have also been suggested to potentially lead to the development of hepatocellular dysfunction [58]. Importantly, the absence of the typical abnormalities observed in mitochondrial diseases does not exclude the diagnosis. Indeed, normal serum and CSF lactate, normal very long chain fatty acids, and muscle biopsy revealing normal histology and normal mitochondrial respiratory chain enzyme analysis have been found within the spectrum of *DNM1L* variants [58].

Mutations of genes encoding neuronal channels, including different types of voltage-gated sodium channel alpha subunits (SCN1A, SCN2A, SCN10A) [61–63], potassium sodium-activated channel subfamily T member 1 (KCNT1) [21], calcium voltage-gated channel subunit alpha1 (CACNA1A) [64] and mutation in cathepsin D [21] have been detected in cases of NORSE. In addition, FIRES in female patients during infancy and early childhood can be one of the possible phenotypes of mutations in *protocadherin 19* gene.

Cytokine-related polymorphism, namely the IL-1 receptor antagonist (*IL1RN*) haplotype containing RN2 allele, has been associated with FIRES in Japanese patients [65]. The *IL1RN* encodes the IL-1 receptor antagonist (IL-1RA), a member of the IL-1 cytokine family that binds non-productively to the cell surface interleukin-1 receptor (IL-1R) preventing IL-1 from sending the signal to the cell. The IL-1RA inhibits the activities of IL-1α and IL-1β and modulates a variety of IL-1-related immune and inflammatory responses during the acute phase of infection and inflammation. The presence of RN2 results in reduced *IL1RN* expression and enhanced IL-1β production [66,67] and may confer susceptibility to excessive inflammatory response. This evidence is further support for the growing evidence of the implication of neuroinflammation in NORSE and NORSE-related conditions. Although the association between *IL1RN* polymorphism and the susceptibility to specific infections with a predilection to CNS complications cannot be excluded, it is worth noticing that symptoms of febrile illnesses preceding FIRES are non-specific and pathogens remain unidentified in most cases [65]. An inherited heterozygous single nucleotide variant in the structural maintenance of chromosomes protein 3 (*SMC3*) gene was identified in a patient with NORSE [68]. Whilst mutations in the *SMC3* have been associated with the Cornelia de Lange syndrome type 3, the patient did not have the typical expressive phenotype, and the clinical significance remains unknown. A case of prolonged NORSE with no evidence of autoimmune activation and a good neurological recovery was described in a patient with a mild form of Axenfeld–Rieger syndrome [69]. This is a rare genetic disorder characterized by dysgenesis of the anterior segment of the eye, craniofacial dysmorphism, dental, cardiac and umbilical anomalies, and generally associated with mutations and deletions in the *FOXC1* and *PITX2* genes [70]. Genetic analysis in this patient was declined, however, and a causal association could not be proved. Recently, a heterozygous variant in *RELN* was found in a case of FIRES responsive to plasmapheresis and tocilizumab [71]. The gene encodes reelin, a secreted glycoprotein that is produced by specific cell types within the developing brain and activates a signalling pathway in post-mitotic migrating neurons required for proper positioning of neurons within nervous system parenchyma [72]. Mutations in *RELN* have already been associated with lissencephaly and familial temporal lobe epilepsy 7 [73,74]; the causative significance in FIRES remains to be further explored.

Genetic technologies have the potential to enhance our understanding of the causes and mechanisms of NORSE. So far, genetic testing is still underperformed, and its role is worth improving. Furthermore, rapid whole exome sequencing may be advantageous over a stepwise approach based on epilepsy panels and the relevance of this technique in the critical care setting will certainly improve as it becomes more readily available and affordable [75]. Alcohol has been associated with the development of NORSE within the context of subacute encephalopathy with seizures in alcoholic patients (SESA) [20]. First described in 1981 [76,77], SESA syndrome occurs in chronic alcoholism, is quite distinct from patients presenting with typical alcohol withdrawal seizures, and is characterized by focal nonconvulsive SE, lateralized periodic discharges on the electroencephalogram, encephalopathy, chronic microvascular ischaemia on neuroimaging studies, and possible recurrence when chronic antiseizure treatment is stopped [78]. Cases of NORSE have also been reported after exposure to toxic substances, including organophosphate compounds that are pesticides extensively used in agriculture [79,80] and synthetic cannabinoids [81,82]. Delta-9-tetrahydrocannabinol (THC) is the major constituent of marijuana and decreases GABA synaptic transmission by acting at the cannabinoid receptor type 1 (CB-1). As most of the synthetic cannabinoids are full agonists at CB-1, they can produce a more profound GABA inhibition and be associated with an increased risk of epileptic activity compared with natural compounds, as THC is only a partial CB-1 agonist [83].

Less commonly reported causes of NORSE include disorders of vascular origin, such as posterior reversible leukoencephalopathy [84] and primary angiitis of the CNS [85]; carotid artery stenting has also been hypothesized to be associated with NORSE through cerebral hyper-perfusion syndrome [86].

New-onset refractory status epilepticus following multiple blood transfusions in a patient with severe anaemia secondary to menorrhagia was recently reported [87]; speculative mechanisms may include the rise in blood viscosity and sudden reversal of compensatory vasodilation, which result in endothelial damage, vasogenic oedema and parenchymal irritation [88]. Paradoxical worsening of oxygen delivery secondary to red blood cell storage lesions could also occur [89], although the effects on the CNS have not been described. Structural defects, like polymicrogyria [90] and focal cortical dysplasia [91], and rare conditions such as primary leptomeningeal melanomatosis, an exceedingly uncommon manifestation of

melanoma [92], and Creutzfeldt–Jakob disease have also been described in association with NORSE presentation [20,93]. This review summarizes the available evidence about the aetiologies of NORSE and NORSE-related conditions, provides critical insights into the underlying pathophysiology and suggests implications for clinical practice and future research. Nonetheless, there are some shortcomings to acknowledge. First, only one electronic database was extensively examined to identify relevant literature. In this regard, however, it is worth noticing that the search strategy was comprehensive, including several terms to consider the similarities with FIRES reported under different diagnoses over decades, and additional data were sought at the NORSE institute website, which is a dedicated source for medical professionals providing references to both published studies and non-peer-reviewed conference abstracts and updated reading lists on NORSE and FIRES curated by experts in the field. A further major limitation is that the characteristics of available data such as retrospective observational studies, case series and case reports with a high risk of bias were included. Because NORSE can be defined in the absence of a clear acute or active structural, toxic or metabolic cause within the related time window, the risk of failing to appropriately apply the diagnostic criteria due to the retrospective study design should be considered. Importantly, there was great heterogeneity in the diagnostic work-up used both between and within the studies. Further, included studies were performed in both high- and middle- or low-income countries, and over a time frame of more than four decades. The lack of standardized diagnostic protocols and differences in healthcare resources and scientific knowledge at the time each study was performed may have been a source of bias and heterogeneity in the diagnostic yield of studies. Missing the identification of a specific aetiology leading a case of NORSE to be labelled as 'cryptogenic' may, hence, rely on the nature and extent of the diagnostic investigations carried out in individual cases. At the same time, the publication bias in favour of those cases where a cause underlying the clinical presentation was detected needs to be considered. In addition, only a few large case series of adult and paediatric patients presenting with NORSE were included and used to estimate the actual frequency of the different aetiologies. As not every case series provided individual patient data, it was not possible to perform a quantitative synthesis on demographics, aetiologies and treatments pooling together results from the different studies.

CONCLUSION

Far from being a unitary condition or entity, NORSE is a heterogeneous and clinically challenging presentation with varied causes, which remain unidentified in many cases.

It is noteworthy that, despite the high prevalence of autoimmune or paraneoplastic aetiologies, one survey involving 107 neurocritical care practitioners in the USA about the diagnostic and therapeutic approach to NORSE revealed that about two-thirds of institutions did not employ a protocol to evaluate patients, one-quarter of respondents would not perform an autoimmune or paraneoplastic assessment in the absence of a suggestive history or physical examination, and most sent antineuronal antibody studies only as part of an extended work-up; in addition, 29% of respondents reported they would never use intravenous immunoglobulin and 24% would not use plasma exchange [94].

Finally, although outside the scope of this review, it is worth mentioning that there are preliminary findings about the effectiveness of new candidates as treatments throughout the SE continuum, including anti-cytokine therapies and neuroactive steroids, and additional more solid evidence is necessary [41–44,71,95–97].

The issues highlighted in this comprehensive systematic review underlie the need for better and consistent research on the topic. The following are suggested.

1. Further research is warranted to recognize clinical characteristics that may point early to a specific aetiology and suggest what treatment strategy will be most effective.
2. Analyses of larger case series where individual patient data are available may allow any associations between individual aetiologies, response to treatment and outcome to be explored.
3. Prospective studies based on standardized eligibility and diagnostic criteria, adopting a standardized diagnostic work-up, and recruiting a larger population would allow the actual frequency of aetiologies of NORSE to be estimated and possible associations with clinical presentation to be identified.
4. Multicentre registries could offer the opportunity to speed up the prospective collection of data to analyse and interpret in a timely fashion.
5. Retrospective analyses may be useful to identify still unappreciated causes for NORSE and generate testable hypotheses for further scrutiny. Hospitals should be encouraged to store first obtained CSF, urine and serum for at least a month at −20°C or at −80°C, and in those cases with prolonged RSE (>7 days) for 5–10 years to allow for retrospective analysis when new data become available.
6. Protocols to standardize diagnostic work-up should be developed to increase the diagnostic yield and guarantee the prompt recognition of NORSE.
7. Protocols to guide therapeutic approaches according to the aetiology underlying NORSE should be implemented to allow the reliable care of patients.
8. Diagnostic and therapeutic guidelines should be shared across scientific communities and working groups, and dissemination of clinical decision support tools may decrease the time to diagnosis and treatment.
9. Planning and advancing strategies to identify barriers, facilitators and resources to make sustainable diagnostic interventions possible across healthcare settings should accompany advancing scientific knowledge.
10. Global cooperation and multicentre research represent priorities of the road map to improve the understanding and management of NORSE.

CONFLICT OF INTEREST

Simona Lattanzi has received speaker's or consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals and UCB Pharma and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, BIAL and GW Pharmaceuticals. Markus Leitinger reports a travel grant from UCB Pharma and a speaker's honorarium from Eisai. Francesco Brigo acted as consultant for Eisai. Stefano Meletti received research grant support from the Ministry of Health (MOH), from the non-profit organization Foundation 'Fondazione Cassa di Risparmio di Modena—FCRM'; has received personal compensation as scientific advisory board member for UCB and EISAI. Eugen Trinka received speaker's honoraria from Arvelle, Abbott, Angelini Pharma, UCB, Biogen, Gerot-Lannacher, Bial, Eisai, Epilog, Takeda, Newbridge, Hikma, GW Pharmaceuticals, Sunovion Pharmaceuticals Inc., LivaNova and Novartis; consultancy funds from Angelini Pharma, Argenix, Arvelle, Epilog, UCB, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, GW Pharmaceuticals, Sunovion Pharmaceuticals Inc., Marinus and Novartis; directorship funds from Neuroconsult GmbH. E. Trinka's Institution received grants from Biogen, Red Bull, Merck, UCB, European Union, FWF Österreichischer Fond zur Wissenschaftsförderung and Bundesministerium für Wissenschaft und Forschung. All are not related to the present publication. The remaining authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Simona Lattanzi: Conceptualization (lead); data curation (lead); formal analysis (lead); supervision (lead); writing—original draft (lead); writing—review and editing (equal). Markus Leitinger: Writing—review and editing (equal). Chiara Rocchi: Data curation (equal); formal analysis (equal). Sergio Salvemini: Data curation (equal); formal analysis (equal). Sara Matricardi: Writing—review and editing (equal). Francesco Brigo: Writing—review and editing (equal). Stefano Meletti: Writing—review and editing (equal). Eugen Trinka: Conceptualization (equal); supervision (equal); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—report of the ILAE task force on classification of status epilepticus. *Epilepsia*. 2015;56:1515-1523.
2. Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. *Neurocrit Care*. 2014;20:476-483.
3. Brigo F, Del Giovane C, Nardone R, Trinka E, Lattanzi S. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: a systematic review and network meta-analysis. *Epilepsy Behav*. 2019;101:106466.
4. Lattanzi S, Giovannini G, Brigo F, Orlandi N, Trinka E, Meletti S. Status epilepticus with prominent motor symptoms clusters into distinct electroclinical phenotypes. *Eur J Neurol*. 2021;28:2694-2699.
5. Lattanzi S, Giovannini G, Brigo F, Orlandi N, Trinka E, Meletti S. Clinical phenotypes within nonconvulsive status epilepticus. *Epilepsia*. 2021;62:e129-e134.
6. Ferlisi M, Hocker S, Trinka E, Shorvon S, International Steering Committee of the StEp Audit. Etiologies and characteristics of refractory status epilepticus cases in different areas of the world: results from a global audit. *Epilepsia*. 2018;59(Suppl 2):100-107.
7. Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. *Epilepsia*. 2012;53(Suppl 4):127-138.
8. Leitinger M, Trinka E, Giovannini G, et al. Epidemiology of status epilepticus in adults: a population-based study on incidence, causes, and outcomes. *Epilepsia*. 2019;60:53-62.
9. Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. *Epilepsia*. 2018;59:739-744.
10. Moher D, Liberati A, Tetzlaff J, Altman D, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*. 2009;6:e1000097.
11. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ*. 2020;368:l6890.
12. Kessi M, Liu F, Zhan Y, et al. Efficacy of different treatment modalities for acute and chronic phases of the febrile infection-related epilepsy syndrome: a systematic review. *Seizure*. 2020;79:61-68.
13. Baxter P, Clarke A, Cross H, et al. Idiopathic catastrophic epileptic encephalopathy presenting with acute onset intractable status. *Seizure*. 2003;12:379-387.
14. Kramer U, Shorer Z, Ben-Zeev B, Lerman-Sagie T, Goldberg-Stern H, Lahat E. Severe refractory status epilepticus owing to presumed encephalitis. *J Child Neurol*. 2005;20:184-187.
15. Mikaeloff Y, Jambaque I, Hertz-Pannier L, et al. Devastating epileptic encephalopathy in school-aged children (DESC): a pseudo encephalitis. *Epilepsy Res*. 2006;69:67-79.
16. Sakuma H, Awaya Y, Shiomi M, et al. Acute encephalitis with refractory, repetitive partial seizures (AERRPS): a peculiar form of childhood encephalitis. *Acta Neurol Scand*. 2010;121:251-256.
17. van Baalen A, Häusler M, Boor R, et al. Febrile infection-related epilepsy syndrome (FIRES): a nonencephalitic encephalopathy in childhood. *Epilepsia*. 2010;51:1323-1328.
18. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
19. Trinka E, Lattanzi S, Carpenter K, et al. Exploring the evidence for broad-spectrum effectiveness of perampanel: a systematic review of clinical data in generalised seizures. *CNS Drugs*. 2021;35(8):821-837. 10.1007/s40263-021-00831-y
20. Gaspard N, Foreman BP, Alvarez V, et al. Critical Care EEG Monitoring Research Consortium (CCEMRC). New-onset refractory status epilepticus: etiology, clinical features, and outcome. *Neurology*. 2015;85:1604-1613.
21. Husari KS, Labiner K, Huang R, Said RR. New-onset refractory status epilepticus in children: etiologies, treatments, and outcomes. *Pediatr Crit Care Med*. 2020;21:59-66.
22. Tan TH, Perucca P, O'Brien TJ, Kwan P, Monif M. Inflammation, ictogenesis, and epileptogenesis: an exploration through human disease. *Epilepsia*. 2021;62:303-324.
23. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the $GABA_A$ receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol*. 2014;13:276-286.

24. Caputo D, Iorio R, Vigevano F, Fusco L. Febrile infection-related epilepsy syndrome (FIRES) with super-refractory status epilepticus revealing autoimmune encephalitis due to $GABA_AR$ antibodies. *Eur J Paediatr Neurol*. 2018;22:182-185.
25. Bien CG, Vincent A, Barnett MH, et al. Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. *Brain*. 2012;135:1622-1638.
26. Gall CR, Jumma O, Mohanraj R. Five cases of new onset refractory status epilepticus (NORSE) syndrome: outcomes with early immunotherapy. *Seizure*. 2013;22:217-220.
27. Jang Y, Lee WJ, Lee HS, Chu K, Lee SK, Lee ST. Tofacitinib treatment for refractory autoimmune encephalitis. *Epilepsia*. 2021;62:e53-e59.
28. Matthews E, Alkhachroum A, Massad N, et al. New-onset super-refractory status epilepticus: a case series of 26 patients. *Neurology*. 2020;95:e2280-e2285.
29. Varrasi C, Vecchio D, Magistrelli L, Strigaro G, Tassi L, Cantello R. Auditory seizures in autoimmune epilepsy: a case with anti-thyroid antibodies. *Epileptic Disord*. 2017;19:99-103.
30. Yanagida A, Kanazawa N, Kaneko J, et al. Clinically based score predicting cryptogenic NORSE at the early stage of status epilepticus. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:e849.
31. Iizuka T, Kanazawa N, Kaneko J, et al. Cryptogenic NORSE: its distinctive clinical features and response to immunotherapy. *Neurol Neuroimmunol Neuroinflamm*. 2017;4(6):e396.
32. Nabbout R, Vezzani A, Dulac O, Chiron C. Acute encephalopathy with inflammation mediated status epilepticus. *Lancet Neurol*. 2011;10:99-108.
33. Farias-Moeller R, LaFrance-Corey R, Bartolini L, et al. Fueling the FIRES: hemophagocytic lymphohistiocytosis in febrile infection-related epilepsy syndrome. *Epilepsia*. 2018;59:1753-1763.
34. Orsini A, Foiadelli T, Costagliola G, et al. The role of inflammatory mediators in epilepsy: focus on developmental and epileptic encephalopathies and therapeutic implications. *Epilepsy Res*. 2021;172:106588.
35. Matin N, Tabatabaie O, Falsaperla R, et al. Epilepsy and innate immune system: a possible immunogenic predisposition and related therapeutic implications. *Hum Vaccin Immunother*. 2015;11:2021-2029.
36. Sakuma H, Tanuma N, Kuki I, Takahashi Y, Shiomi M, Hayashi M. Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection related refractory status epilepticus. *J Neurol Neurosurg Psychiatry*. 2015;86:820-822.
37. Kothur K, Bandodkar S, Wienholt L, et al. Etiology is the key determinant of neuroinflammation in epilepsy: elevation of cerebrospinal fluid cytokines and chemokines in febrile infection-related epilepsy syndrome and febrile status epilepticus. *Epilepsia*. 2019;60:1678-1688.
38. Appenzeller S, Helbig I, Stephani U, et al. Febrile infection-related epilepsy syndrome (FIRES) is not caused by SCN1A, POLG, PCDH19 mutations or rare copy number variations. *Dev Med Child Neurol*. 2012;54:1144-1148.
39. Henter J-I, AnnaCarin H, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124-131.
40. Hsieh MY, Lin JJ, Hsia SH, et al. Diminished toll-like receptor response in febrile infection-related epilepsy syndrome (FIRES). *Biomed J*. 2020;43:293-304.
41. Dilena R, Mauri E, Aronica E, et al. Therapeutic effect of anakinra in the relapsing chronic phase of febrile infection-related epilepsy syndrome. *Epilepsia Open*. 2019;4:344-350.
42. Kenney-Jung DL, Vezzani A, Kahoud RJ, et al. Febrile infection-related epilepsy syndrome treated with anakinra. *Ann Neurol*. 2016;80:939-945.
43. Westbrook C, Subramaniam T, Seagren RM, et al. Febrile infection-related epilepsy syndrome treated successfully with anakinra in a 21-year-old woman. *WMJ*. 2019;118:135-139.
44. Jun JS, Lee ST, Kim R, Chu K, Lee SK. Tocilizumab treatment for new onset refractory status epilepticus. *Ann Neurol*. 2018;84:940-945.
45. Gofton TE, Gaspard N, Hocker SE, Loddenkemper T, Hirsch LJ. New onset refractory status epilepticus research: what is on the horizon? *Neurology*. 2019;92:802-810.
46. Wilson MR, Sample HA, Zorn KC, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. *N Engl J Med*. 2019;380:2327-2340.
47. Chiu CY, Miller SA. Clinical metagenomics. *Nat Rev Genet*. 2019;20:341-355.
48. Simner PJ, Miller S, Carroll KC. Understanding the promises and hurdles of metagenomic next-generation sequencing as a diagnostic tool for infectious diseases. *Clin Infect Dis*. 2018;66:778-788.
49. Dono F, Carrarini C, Russo M, et al. New-onset refractory status epilepticus (NORSE) in post SARS-CoV-2 autoimmune encephalitis: a case report. *Neurol Sci*. 2021;42:35-38.
50. Manganotti P, Furlanis G, Ajčević M, et al. Intravenous immunoglobulin response in new-onset refractory status epilepticus (NORSE) COVID-19 adult patients. *J Neurol*. 2021;268(10):3569-3573.
51. Monti G, Giovannini G, Marudi A, et al. Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19. *Seizure*. 2020;81:18-20.
52. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. 2020;143:3104-3120.
53. Panariello A, Bassetti R, Radice A, et al. Anti-NMDA receptor encephalitis in a psychiatric COVID-19 patient: a case report. *Brain Behav Immnunity*. 2020;87:179-181.
54. Armangue T, Spatola M, Vlagea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol*. 2018;17:760-772.
55. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033-1034.
56. Byun J-I, Lee S-T, Moon J, et al. Distinct intrathecal interleukin-17/interleukin-6 activation in anti-*N*-methyl-D-aspartate receptor encephalitis. *J Neuroimmunol*. 2016;297:141-147.
57. Morrison HD, Morgan C, Urankar K, et al. New-onset refractory status epilepticus (NORSE) in a 23-year-old female. *J Clin Neurosci*. 2020;82(Pt B):247-248.
58. Ryan CS, Fine AL, Cohen AL, et al. De novo *DNM1L* variant in a teenager with progressive paroxysmal dystonia and lethal super-refractory myoclonic status epilepticus. *J Child Neurol*. 2018;33:651-658.
59. Visser NA, Braun KP, Leijten FS, van Nieuwenhuizen O, Wokke JH, van den Bergh WM. Magnesium treatment for patients with refractory status epilepticus due to POLG1-mutations. *J Neurol*. 2011;258:218-222.
60. von Spiczak S, Helbig KL, Shinde DN, et al. DNM1 encephalopathy: a new disease of vesicle fission. *Neurology*. 2017;89:385-394.
61. Kobayashi K, Ouchida M, Okumura A, et al. Genetic seizure susceptibility underlying acute encephalopathies in childhood. *Epilepsy Res*. 2010;91:143-152.
62. Kobayashi K, Ohzono H, Shinohara M, et al. Acute encephalopathy with a novel point mutation in the *SCN2A* gene. *Epilepsy Res*. 2012;102:109-112.
63. Jafarpour S, Hodgeman RM, De Marchi Capeletto C, et al. New-onset status epilepticus in pediatric patients: causes, characteristics, and outcomes. *Pediatr Neurol*. 2018;80:61-69.
64. Gugger JJ, Husari K, Probasco JC, Cervenka MC. New-onset refractory status epilepticus: a retrospective cohort study. *Seizure*. 2020;74:41-48.
65. Saitoh M, Kobayashi K, Ohmori I, et al. Cytokine-related and sodium channel polymorphism as candidate predisposing factors for childhood encephalopathy FIRES/AERRPS. *J Neurol Sci*. 2016;368:272-276.

66. Korthagen NM, van Moorsel CHM, Kazemier KM, Ruven HJT, Grutters JC. IL1RN genetic variations and risk of IPF: a meta-analysis and mRNA expression study. *Immunogenetics*. 2012;64:371-377.
67. Santtila S, Savinainen K, Hurme M. Presence of the IL-1RA allele 2 (IL1RN*2) is associated with enhanced IL-1beta production in vitro. *Scand J Immunol*. 1998;47:195-198.
68. Dillien P, Ferrao Santos S, van Pesch V, Suin V, Lamoral S, Hantson P. New-onset refractory status epilepticus: more investigations, more questions. *Case Rep Neurol*. 2016;8:127-133.
69. Ferlisi M, Greco E, Zanoni T, Zamagni M, Liviero MC, Zanatta P. A case of very prolonged new onset refractory status epilepticus (NORSE) with no evidence of autoimmune activation and a good neurological recovery. *Neurol Sci*. 2020;41:3003-3006.
70. Seifi M, Walter MA. Axenfeld–Rieger syndrome. *Clin Genet*. 2018;93:1123-1130.
71. Cantarín-Extremera V, Jiménez-Legido M, Duat-Rodríguez A, et al. Tocilizumab in pediatric refractory status epilepticus and acute epilepsy: experience in two patients. *J Neuroimmunol*. 2020;340:577142.
72. Zaki M, Shehab M, El-Aleem AA, et al. Identification of a novel recessive RELN mutation using a homozygous balanced reciprocal translocation. *Am J Med Genet*. 2007;143A:939-944.
73. Hong SE, Shugart YY, Huang DT, et al. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human *RELN* mutations. *Nat Genet*. 2000;26(1):93-96.
74. Dazzo E, Fanciulli M, Serioli E, et al. Heterozygous *reelin* mutations cause autosomal-dominant lateral temporal epilepsy. *Am J Hum Genet*. 2015;96:992-1000.
75. Scala M, Bianchi A, Bisulli F, et al. Advances in genetic testing and optimization of clinical management in children and adults with epilepsy. *Expert Rev Neurother*. 2020;20:251-269.
76. Niedermeyer E, Freund G, Krumholz A. Subacute encephalopathy with seizures in alcoholics: a clinical-electroencephalographic study. *Clin Electroencephalogr*. 1981;12:113-129.
77. Freund G, Niedermeyer E. Subacute encephalopathy with seizures in alcoholics. *Electroencephalogr Clin Neurophysiol*. 1981;51:53P-54P; Abstract.
78. Fernández-Torre JL, Kaplan PW. Subacute encephalopathy with seizures in alcoholics syndrome: a subtype of nonconvulsive status epilepticus. *Epilepsy Curr*. 2019;19:77-82.
79. Acharya S, Shukla S, Malpani V. An unusual case of triazophos poisoning presenting with new-onset refractory status epilepticus. *Toxicol Int*. 2015;22:172-173.
80. Waheed S, Sabeen A, Ullah KN. New onset refractory status epilepticus as an unusual presentation of a suspected organophosphate poisoning. *Case Rep Emerg Med*. 2014;2014:676358.
81. Babi MA, Robinson CP, Maciel CB. A spicy status: synthetic cannabinoid (spice) use and new-onset refractory status epilepticus—a case report and review of the literature. *SAGE Open Med Case Rep*. 2017;5:2050313X1774520.
82. Patel NA, Jerry JM, Jimenez XF, Hantus ST. New-onset refractory status epilepticus associated with the use of synthetic cannabinoids. *Psychosomatics*. 2017;58:180-186.
83. Harris CR, Brown A. Synthetic cannabinoid intoxication: a case series and review. *J Emerg Med*. 2013;44:360-366.
84. Khawaja AM, DeWolfe JL, Miller DW, Szaflarski JP. New-onset refractory status epilepticus (NORSE)—the potential role for immunotherapy. *Epilepsy Behav*. 2015;47:17-23.
85. Matar RK, Alshamsan B, Alsaleh S, et al. New onset refractory status epilepticus due to primary angiitis of the central nervous system. *Epilepsy Behav Case Rep*. 2017;8:100-104.
86. Deshmukh ND, Singh RK, Lalla RS, Karapurkar AP, Khadilkar SV. Rare complication of carotid stenting: new-onset refractory status epilepticus: a study of five patients. *Ann Indian Acad Neurol*. 2019;22:210-212.
87. Wu C, Von Stein E, Culbertson C, Walia S, Krishnamohan P, Threlkeld Z. Cryptogenic new-onset refractory status epilepticus (NORSE) following blood transfusion in a patient with severe anemia (3932). *Neurology*. 2020;94(15 Supplement).
88. Pawloski JR, Stamler JS. Nitric oxide in RBCs. *Transfusion*. 2002;42:1603-1609.
89. Yoshida T, Prudent M, D'alessandro A. Red blood cell storage lesion: causes and potential clinical consequences. *J Blood Transfus*. 2019;17:27-52.
90. Kim HJ, Lee SA, Kim HW, Kim SJ, Jeon SB, Koo YS. The timelines of MRI findings related to outcomes in adult patients with new-onset refractory status epilepticus. *Epilepsia*. 2020;61:1735-1748.
91. Marashly A, Lew S, Koop J. Successful surgical management of new onset refractory status epilepticus (NORSE) presenting with gelastic seizures in a 3 year old girl. *Epilepsy Behav Case Rep*. 2017;8:18-26.
92. Eaton J, Lee S, Kerrigan DLG. Primary leptomeningeal melanomatosis manifesting as new-onset refractory status epilepticus a case report—where do you get the best cerebrospinal fluid sample? *Seizure*. 2021;86:77-79.
93. Gonzalez-Martinez A, Quintas S, Redondo N, Casado-Fernández L, Vivancos J. Sporadic Creutzfeldt–Jakob disease with tau pathology mimicking new-onset refractory non-convulsive status epilepticus: case report and review of the literature. *Eur J Neurol*. 2021;28:1385-1391.
94. Cabrera Kang CM, Gaspard N, LaRoche SM, Foreman B. Survey of the diagnostic and therapeutic approach to new-onset refractory status epilepticus. *Seizure*. 2017;46:24-30.
95. Zolkowska D, Wu CY, Rogawski MA. Intramuscular allopregnanolone and ganaxolone in a mouse model of treatment-resistant status epilepticus. *Epilepsia*. 2018;59(Suppl 2):220-227.
96. Meletti S, Lucchi C, Monti G, et al. Low levels of progesterone and derivatives in cerebrospinal fluid of patients affected by status epilepticus. *J Neurochem*. 2018;147:275-284.
97. Lattanzi S, Riva A, Striano P. Ganaxolone treatment for epilepsy patients: from pharmacology to place in therapy. *Expert Rev Neurother*. 2021;1-16.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Supplementary Material

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