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.

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$_B$R) [22]. Although
| Study                                      | Study design | Population | Prodromes                                      | Aetiology                                                                 |
|-------------------------------------------|--------------|------------|------------------------------------------------|---------------------------------------------------------------------------|
| Acharya et al., 2015 [79]                | Case report  | Male, 45 years | Sinus infection, fever                         | Triazophos poisoning                                                      |
| Agarwal et al., 2015                     | Case report  | Male, 4 years | Sinus infection, fever                         | Infection by simian virus 40                                              |
| Agarwal et al., 2018                     | Case report  | Male, 23 years | Fever, painless complete vision loss           | Unknown                                                                  |
| Akbik et al., 2020                       | Case series  | Male, 76 years | Headache, encephalopathy                      | Posterior reversible encephalopathy syndrome                              |
|                                           |              | Female, 63 years |                                              | HSV encephalitis                                                         |
|                                           |              | Male, 71 years |                                              | Checkpoint inhibitor-induced autoimmune encephalitis                    |
|                                           |              | Male, 61 years |                                              |                                                                          |
| Akiyama et al., 2020                     | Case report  | Male, 84 years |                                              | Encephalitis associated with anti-GABA<sub>g</sub> 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      |                                               |                                                                          |
| Alparslan et al., 2017                    | Case report  | Male, 8 years | Fever, upper respiratory infection             | Unknown                                                                  |
| Appavu et al., 2016                      | Case series  | N = 1       | Fever                                         | Unknown                                                                  |
| Appenzeller et al., 2012                 | Case series  | 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 (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                                      | 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 | Flu-like symptoms, headache, abdominal discomfort, diarrhea |
|                                           |              | Female, 18 years | Fever, headache, nausea, sores on lips       | Unknown                                                                  |
|                                           |              | Female, 31 years | Fever, abdominal pain, vomiting               | Unknown                                                                  |
|                                           |              | Male, 75 years | Feeling drowsy                                 | Unknown                                                                  |
|                                           |              | Male, 39 years | Vomiting, fever                                | Unkown (Continues)                                                       |
|                                           |              | Female, 27 years | Fever, myalgia, headache, neckache, confusion | Unkown                                                                   |
|                                           |              | Male, 71 years | Subacute cognitive deterioration                | Unkown                                                                   |
| Baba et al., 2021                        | Case report  | Female, 8 years | Fever, diarrhoea, anorexia                    | Unknown                                                                  |
| Study | Study design | Population | Prodromes | Aetiology |
|-------|--------------|------------|-----------|-----------|
| Babi et al., 2017 [81] | Case report | Male, 40 years | Non-specific symptoms suggestive of infection (4/6), fever (2/6) | Exposure to synthetic cannabinoids |
| Baxter et al., 2003 [13] | Case series | bN = 6, male:female = 4:2, age range 5 months to 6 years | | 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 | aMale, 5 years | Fever, coryza, diarrhoea | Unknown |
| Cantarín Extremera et al., 2020 [71] | Case report | aMale, 9 years | Fever | Increased serum and CSF IL-6 levels; heterozygous variant of uncertain significance in RELN |
| Capizzi et al., 2015 | Case report | aFemale, 15 years | Fever, asthenia, upper respiratory tract infection | Unknown |
| Caputo et al., 2017 | Case report | aFemale, 13 years | Fever | Encephalitis associated with GABA_R antibodies |
| Carballo et al., 2013 | Case series | aN = 12, male:female = 8:4, mean age 8.5 (range 2–13.5) years | Fever and upper respiratory tract infection (9/12) | Unknown |
| Carranza Rojo et al., 2012 | Case series | aN = 10, age range 3–14 years | Fever (10/10) | Unknown |
| | | | Confusion (8/10) | | |
| | | | Upper respiratory tract infection (1/10) | | |
| | | | Vomiting (4/10) | | |
| | | | Rash (1/10) | | |
| Chahub 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) | Unknown |
| | | | Fever (8/13) | | |
| | | | Headache (5/13) | | |
| | | | Upper respiratory tract infection symptoms (4/13) | | |
| | | | Nausea/vomiting (3/13) | | |
| | | | Acute memory impairment or confusion (12/13) | | |
| Chou et al., 2016 | Case report | aFemale, 12 years | Fever and upper respiratory tract infection | Unknown |
| Clarkson et al., 2019 | Case control | aN = 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 | | |
### Table 1 (Continued)

| Study | Study design | Population | Prodromes | Aetiology |
|-------|--------------|------------|-----------|-----------|
| Collaborative Group for Fever-induced Refractory Epileptic Encephalopathy in School-aged Children, 2012 | Case series | \(N = 13\), 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 | 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 | 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 | \(N = 7\), 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 | \(N = 5\), 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 | Female, 29 years | Febrile episode | Unknown |
| Ferlisi et al., 2020 [69] | Case report | Female, 28 years; mild form of Axenfeld-Rieger syndrome | | Unknown |

(Continues)
| Study                         | Study design | Population               | Prodromes                                      | Aetiology                                                                 |
|------------------------------|--------------|--------------------------|------------------------------------------------|---------------------------------------------------------------------------|
| Fisher et al., 2020          | Case series  | 4N = 8, mean age 8.5 (range 4–15) years | Febrile illness                                | Unknown                                                                   |
| Fox et al., 2017             | Case report  | Female, 6 years          | Fever                                          | Unknown                                                                   |
| Fukuyama et al., 2011        | Case report  | Male, 6 years            | Unknown                                        | Unknown                                                                   |
| Gall et al., 2013 [26]       | Case series  | Male, 26 years           | Headache, vomiting                              | Unknown (anti-TPO antibodies; history of hyperthyroidism)                 |
|                              |              | Male, 34 years           | Fever, myalgia                                 | Unknown                                                                   |
|                              |              | Male, 30 years           | Headache, acute confusion                      | Unknown                                                                   |
|                              |              | Female, 23 years         | Headache, fever, vomiting                      | Unknown                                                                   |
|                              |              | Female, 22 years         | Fever, acute confusion                         | 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  | 4N = 9, age range 2.5–15 | Febrile illness                                | Unknown                                                                   |
| Gofshetyn et al., 2017       | Case series  | 4N = 7, male:female = 5:2, average age 7 (range 3–8) years | Fever                                          | Unknown                                                                   |
| Gonzalez-Martinez et al.,    | Case report  | Female, 82 years         | Altered consciousness, aphasia                 | Creutzfeldt-Jakob disease                                                |
| 2020                         |              |                          |                                                |                                                                           |
| Goyal et al., 2020           | Case report  | 4Male, 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<sub>A</sub>R                     |
| Hamano et al., 2003          | Case report  | Female, 5 years          |                                                | Unknown                                                                   |
| Hau Man et al., 2017         | Case report  | Male, 27 years           |                                                | Possible autoimmune encephalitis                                         |
| Study                  | Study design | Population | Prodromes                                   | Aetiology                                                                 |
|-----------------------|--------------|------------|---------------------------------------------|---------------------------------------------------------------------------|
| Helbig et al., 2020   | Case series  | $N = 50$,  | Febrile illness                              | Unknown                                                                   |
|                       |              | male:female |                                             |                             | 33:17, median age 6 (range 2-15) years                                    |
| Hirayama et al., 2016 | Case series  | $N = 2$,   |                                             | Unknown                     |
|                       |              | male:female |                                             |                             | 1:1, median age 128 (range 105-151) months                               |
| Horino et al., 2021   | Case control | $N = 6$,   | Febrile illness                              | Unknown; increased CSF concentrations of CXCL10, CXCL9, IFN-γ, neopterin, IL-1β, IL-6 and IL-8 |
|                       |              | male:female |                                             |                             | 5:1, mean age 6 (range 4-8) years                                        |
| Houk et al., 2019     | Case report  | Male, 19   | Fever, malaise                               | Unknown                     |
| Howell et al., 2012   | Case series  | $N = 7$,   | Fever, headache, confusion and lethargy (7/7); upper respiratory tract symptoms and myalgias | Unknown                     |
|                       |              | male:female |                                             |                             | 7:0, median age 10.8 (range 6.7-14) years                                |
| Hsieh et al., 2020    | Case control | $N = 5$,   | Febrile illness                              | Unknown; adenovirus and enterovirus in throat cultures (2/5)              |
|                       |              | male:female |                                             |                             | 4:1, age range (2-13) years                                              |
| Hsu et al., 2020      | Case control | $N = 7$,   | Fever                                       | Unknown                     |
|                       |              | male:female |                                             |                             | 5:2, age range 4-13 years                                                |
| Hurth et al., 2019    | Case report  | Female, 51 | Fever either at home or upon admission (30/40) | Possible autoimmune encephalitis   |
| Husari et al., 2020   | Case series  | $N = 40$,  | Fever only upon admission (12/40)            | Unknown (23/40)                                                          |
|                       |              | male:female |                                             |                             | 21:19, median age 6.6 (IQR 3.0-10.4) years                               |
| Iizuka et al., 2017   | Case series  | $N = 11$,  | Upper respiratory tract infection (15/40)    | Unknown (8/40) (EBV, HSV, enterovirus, influenza virus)                   |
|                       |              | male:female |                                             |                             | 4.7, median age 27 (range 17-59) years                                   |
| Iizuka et al., 2019   | Case series  | $N = 24$,  | Gastroenteritis (9/40)                       | ADEM (3/40)                                                              |
|                       |              | male:female |                                             |                             | 13:17, median age 25 years                                               |
| Iizuka et al., 2020   | Case control | $N = 30$,  | Cutaneous rash (1/40)                        | Steroid-responsive encephalopathy with autoimmune thyroiditis (1/40)      |
|                       |              | male:female |                                             |                             | 13:17, median age 25 years                                               |

(Continues)
| Study                     | Study design | Population | Prodromes                        | Aetiology                                                                 |
|--------------------------|--------------|------------|----------------------------------|---------------------------------------------------------------------------|
| Illingworth et al., 2011 | Case report  | 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  | Female, 14 years | Fever, diarrhoea                 | Unknown                                                                   |
| Ito et al., 2005         | Case report  | Male, 11 years | Fever                            | Serum and CSF anti-Glu2 antibodies                                        |
| Jafarpour et al., 2017   | Case report  | Age 3 months | Gastroenteritis                  | Unknown                                                                   |
| Jang et al., 2021 [27]   | Case report  | Male, 24 years | Fever, headache                  | Anti-myelin oligodendrocyte glycoprotein-associated disorder               |
| Jayalakshmi et al., 2016 | Case series  | N = 36      |                                  | Unknown (33/36)                                                            |
| Jose et al., 2021        | Case series  | N = 13      | Fever (5/13)                     | Autoimmune encephalitis (10/13)                                          |
| Juhász et al., 2013      | Case report  | Male, 56 years | Headache                         | Viral encephalitis (3/13)                                                |
| Jun et al., 2018 [44]    | Case series  | Male, 58 years | Behaviour change, headache       | Unknown                                                                   |
| Jun et al., 2018 [44]    | Case series  | Female, 61 years | Fever                            | Encephalitis associated with anti-NMDAR antibodies                         |
| Jun et al., 2018 [44]    | Case series  | Female, 24 years | Fever                            | Unknown                                                                   |
| Jun et al., 2018 [44]    | Case series  | Male, 22 years | Fever, headache                  | Unknown                                                                   |
| Jun et al., 2018 [44]    | Case series  | Male, 47 years | Fever, behaviour change          | Unknown                                                                   |
| Jun et al., 2018 [44]    | Case series  | Female, 19 years | Fever, behaviour change          | Unknown                                                                   |
| Jun et al., 2018 [44]    | Case series  | Female, 25 years | Fever, behaviour change          | Unknown                                                                   |
| Kaplan et al., 2017      | Case report  | Female, 29 years | Focal sensory-motor deficits,    | Encephalitis associated with anti-NMDAR antibodies                         |
| Katz et al., 2021        | Case report  | Female, 29 years | cognitive decline, emotional     | Unknown                                                                   |
| Kaufman et al., 2017     | Case report  | Female, 6 years | Fever, headache, emesis, fatigue | Unknown                                                                   |
| Kenney-Jung et al., 2016 [42] | Case report | Female, 32 months | Fever                            | Bartonella henselae infection                                              |
| 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 | Fever, strep throat            | Autoimmune encephalitis (7/11)                                           |
| Khawaja et al., 2015 [84]| Case series  | N = 11, male:female = 2-9, mean age 48 (range 21-90) years | Fever, strep throat            | (anti-GAD, anti-NMDAR, anti-VGCC, anti-VGKC antibodies)                    |
| Kikuchi et al., 2007     | Case report  | 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 | Common cold (4/7), fever (2/7), acute enterocolitis (1/7) | Unknown; SCN1A-R1575C mutation (1/7)                                      |
| Kobayashi et al., 2010 [61]| Case series   | N = 7, male:female = 5:2, age range 5-8 years |                          | Unknown                                                                   |
| Study                      | Study design | Population | Prodromes                              | Aetiology                                                                 |
|---------------------------|--------------|------------|----------------------------------------|---------------------------------------------------------------------------|
| Kobayashi et al., 2012   | Case series  | $N = 8$    | 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       | Case control | $N = 4$    | 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       | 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 | Upper respiratory tract infection       | Encephalitis associated with GABA<sub>B</sub>R antibodies (in small cell prostate cancer) |
| Lai et al., 2020          | Case series  | $N = 25$, 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  | $N = 20$, 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 | Fever (27/29), upper respiratory tract infection (21/29), nausea/vomiting/diarrhoea (10/29) | Bartonella henselae infection                                             |
| Lee et al., 2018          | Case series  | $N = 29$, male:female = 12:17, median age 8.9 (range 1.2–17.8) years | Flu-like illness | Unknown                                                                   |
| Li et al., 2013           | Case series  | Female, 43 years Male, 51 years Female, 39 years | Flu-like illness | Autoimmune encephalitis Autoimmune encephalitis Autoimmune encephalitis |
| Lin et al., 2009          | Case series  | $N = 9$, 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  | Male, 10 years Female, 4 years | Fever, flu-like symptoms Febrile illness | Unknown                                                                   |
| Maegaki et al., 2006      | Case series  | Male, 8 years Female, 12 years | Fever, nausea Febrile illness | Unknown; Anti-GAD antibodies                                               |
| Maloney et al., 2020      | Case report  | Male, 19 years | Fever | Anti-GAD antibodies                                                        |

(Continues)
| 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                          |                                                                          |                                                                          |
| Matar et al., 2017 [85]       | Case report  | Male, 46 years                            | Headache, wide-based gait, unsteadiness                                  | Focal cortical dysplasia type II                                         |
| Matsuzono et al., 2014        | Case report  | 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/maisale (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) | 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  | N = 8, male:female = 5:3, age range 4.3–8.6 years | Febrile illness                                                          | Unknown                                                                  |
| Meenakshi-Sundaram et al., 2021| Case report  | 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  | 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  | Male, 5 years                             | Fever, upper respiratory tract infection                                  | Serum and CSF anti-neuropil antibodies                                    |
| Miràs Veiga et al., 2017      | Case report  | 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                                                                  |

TABLE 1 (Continued)
### Table 1 (Continued)

| Study                  | Study design | Population | Prodromes                                      | Aetiology                                                                 |
|------------------------|--------------|------------|------------------------------------------------|---------------------------------------------------------------------------|
| Neuwirth et al., 2008  | Case series  | N = 5, median age 11.5 (8-14) years | Unknown                                      | 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 | Unknown                                                                  |
| Nozaki et al., 2013    | Case report  | Male, 7 years | Fever associated with tonsillitis             | Unknown                                                                  |
| Ogawa et al., 2016     | Case report  | Male, 11 years | Fever                                        | Unknown                                                                  |
| Okanishi et al., 2007  | Case report  | Male, 14 years | Fever, headache, vomiting, eruption          | Serum anti-Glu2 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  | 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  | 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 GABAAR antibodies                             |
| Puoti et al., 2013     | Case report  | Male, 41 years | Fever, vomiting                               | Unknown                                                                  |
| Rivas-Coppola et al., 2016 | Case series  | 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  | N = 5, male:female = 3:2, age range 7-14 years | Fever                                        | Unknown                                                                  |
| Sa et al., 2019        | Case series  | Male, 9 years | Fever, vomiting, headache                     | Unknown (increased CSF neopterin levels)                                  |
| Saito et al., 2007     | Case series  | Male, 10 years | Fever, bronchopneumonia, headache, consciousness fluctuation | Unknown                                                                  |
| Saitoh et al., 2016 [65]| Case control | 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  | N = 22 | Febrile illness (29/29)                       | Unknown                                                                  |
| Sakuma et al., 2010 [16]| Case series  | N = 29, male:female = 19:10, mean age 6.8 ± 4.0 (range 1-14) years | Unknown; serum (6/9) and CSF (5/9) anti-GluR2 antibodies; increased CSF neopterin (4/4) | Unknown                                                                  |
TABLE 1 (Continued)

| Study                          | Study design | Population               | Prodromes                                                                 | Aetiology                                                                 |
|-------------------------------|--------------|---------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Sakuma et al., 2015 [36]      | Case control | 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          | Progressive memory, language and writing impairment, auditory illusions    | Paraneoplastic autoimmune encephalitis associated with anti-Hu antibodies (in small cell lung carcinoma) |
|                               |              | Male, 77 years            | Subacute confusional state, behaviour disorder, auditory illusions         | Seronegative autoimmune encephalitis (in mixed small cell lung carcinoma and adenocarcinoma) |
|                               |              | Male, 49 years            | Memory impairment, fatigue, weight loss, confusion                         | Paraneoplastic autoimmune encephalitis associated with anti-Hu antibodies (in small cell lung carcinoma) |
|                               |              | Male, 60 years            | Headache, visual illusions, language impairment                            | Seronegative autoimmune encephalitis (in colorectal adenocarcinoma) |
|                               |              | Male, 57 years            | Apathy, anorexia, weight loss, aphasia, hypersomnolence                    | Seronegative autoimmune encephalitis (in lung adenocarcinoma) |
| Sato et al., 2016              | Case report  | Male, 11 years            | Fever                                                                     | CSF anti-GluR2 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  | 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  | Female, 19 years          | Fever, myalgia, malaise                                                   | Unknown                                                                   |
| Sharma et al., 2013            | Case report  | Male, 30 years            | Fever                                                                     | Unknown                                                                   |
| Shibata et al., 2019           | Case control | N = 18, male:female = 15:3, mean age 81.4 ± 35.4 | Febrile illness                                                            | Unknown                                                                   |
| Shiraga et al., 2010           | Case report  | Male, 5 years             | Fever                                                                     | Unknown                                                                   |
| Shrivastava et al., 2017       | Case report  | Female, 24 years          |                                                                            | Unknown                                                                   |
| Shukla et al., 2018            | Case series  | N = 5, male:female = 4:1, median age 7 (range 4–15) years | Febrile illness                                                            | Unknown                                                                   |
| Study                           | Study design | Population | Prodromes                                                                 | Aetiology                                                                 |
|--------------------------------|--------------|------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Shyu et al., 2008              | Case series  | a\(N = 14,\)  |
|                                |              | 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\(\text{Male, 7 years}\)           | Fever, headache, malaise, papular rash, erythematous oropharynx            | Unknown                                                                   |
|                                |              | a\(\text{Female, 10 years}\)         | Fever, myalgias, abdominal pain and nausea                                 | Unknown                                                                   |
| Singhal et al., 2003           | Case series  | Female, 27 years | Confusion                                                                | Bartonella henselae infection                                              |
| Specchio et al., 2010          | Case series  | a\(N = 8,\) mean age 7.4 ± 5.9 years  | Fever                                                                    | Unknown; positivity of anti-GAD antibodies (2/8)                         |
| Specchio et al., 2011          | Case report  | c\(\text{Female, 8 months}\)          | 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\(_B\)R antibodies (1/5), seronegative autoimmune encephalitis (1/5) | Unknown                                                                   |
| Stredny et al., 2020           | Case report  | a\(\text{Male, 6 years}\)           | 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\(_B\)R receptor antibodies (1/3), anti-VGKC complex antibodies (1/12) |
| Suleiman et al, 2013           | Case series  | c\(\text{Male, 3 years}\)           | Fever, blanching rash, irritability                                      | Unknown                                                                   |
|                                |              | c\(\text{Female, 8 years}\)          | Fever, headache, lethargy                                                | Unknown                                                                   |
| Tan et al., 2018               | Case report  | a\(\text{Female, 8 years}\)          | Fever                                                                    | Unknown                                                                   |
| Theroux et al., 2020           | Case report  | a\(\text{Male, 11 years}\)           | 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  | c\(\text{Female, 101 months}\)       |                                                                          | Unknown                                                                   |
| Uchida et al., 2016            | Case report  | c\(\text{Male, 9 years}\)           | Vomiting, diarrhoea, drowsiness                                           | CSF anti-GluR\(_{\text{2}}\)-NT and anti-GluR\(_{\text{2}}\)-CT1 antibodies increased CSF neopterin levels |
| Ueda et al., 2015              | Case series  | c\(N = 6,\) 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                                                                    | 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)
| Study                          | Study design | Population | Prodromes                                                                 | Aetiology                                                                 |
|-------------------------------|--------------|------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| van Baalen et al., 2012       | Case series  | N = 12,    | Respiratory tract infection (8/12), parvovirus B19 infection (1/12),      | Unknown                                                                   |
|                               |              | male:female= 6:6, median age 6 (range 2-12) years | lethargy (1/12), enteritis (1/12), vomiting and headache (1/12)            |                                                                           |
| Van Lierde et al., 2003       | Case series  | N = 6,     | Febrile illness                                                           | Unknown                                                                   |
|                               |              | male:female= 2:4, median age 23 (range 18-30) years |                                                                           |                                                                           |
| 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 | POLG-1 mutation                                                          |                                                                           |
|                               |              | Female, 17 years | POLG-1 mutation                                                          |                                                                           |
| von Spiczak et al., 2017 [60] | Case series  | 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  | Male, 7 years | Fever and cough                                                           | Unknown                                                                   |
|                               |              |                                                                        | Serum and CSF antibodies against GluR2, 1 and 62 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,    | 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) |                                                                           |
|                               |              | male:female = 6:12, median age 23.5 (range 17-76) years |                                                                           |                                                                           |
| Wang X et al., 2020           | Case series  | N = 10,    | Fever                                                                      | Unknown                                                                   |
|                               |              | male:female = 4:6, median age 9 (range 5-13) years |                                                                           |                                                                           |
| Watanabe et al., 2014         | Case report  | Male, 8 years | Intermittent fever, headache                                              | Unknown                                                                   |
| Westbrook et al., 2019 [43]   | Case report  | 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                                                                   |
### 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  | Case series  | N = 33      |                                                                             |                                                                           |
| Zhang et al., 2016     | Case report  | Male, 46 years | Fever, headache                                                             | Unknown                                                                   |

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

Patients with 

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_{R, γ}aminobutyric acid A receptor; GABA_{R, α}aminobutyric acid B receptor; GAD, glutamate decarboxylase; GluR, glutamate receptor; HHV-6, human herpesvirus 6; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IL-1R, 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; PLCB1, phospholipase Cβ1 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, thyreoperoxidase; 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_{R, α} can act as neurotransmitter antagonists [22]. The GABA_{R, α} 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_{R, α} antibodies cause a selective decrease of the clusters of GABA_{R, α} at synaptic sites, without altering other post-synaptic proteins such as the NMDAR or gephyrin; further, the total density of GABA_{R, α} 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 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 granyme 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 lymphohistiocytosis, 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 hepatice failure, and propol and thio- pental 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 (KCN1T1) [21], calcim 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, laterized 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 leptome- ningeal 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.
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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

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