ORIGINAL ARTICLE

International consensus definitions for infection-triggered encephalopathy syndromes

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Abstract

Aim: To develop standardized diagnostic criteria for 'infection-triggered encephalopathy syndrome (ITES)' and five specific clinical syndromes of ITES.

Method: The draft definitions were based on existing criteria, standardized, and discussed by a panel of international experts using nominal group technique over 18 months to achieve consensus. All criteria use the same format: (1) presence of infection/fever; (2) clinical features including encephalopathy; (3) neuroradiological features on magnetic resonance imaging; (4) exclusion of other causes.

Results: We first highlighted differences between ITES and infectious and autoimmune encephalitis, which is the most important differential diagnosis. Consensus was achieved to define five specific ITESs: acute encephalopathy with biphasic seizures and late reduced diffusion; acute necrotizing encephalopathy; mild encephalopathy with a reversible splenial lesion; acute fulminant cerebral oedema; and acute shock with encephalopathy and multiorgan failure. Two further conditions that are currently classified as epilepsy syndromes but have similar features to ITES, namely febrile infection-related epilepsy syndrome and hemiconvulsion–hemiplegia–epilepsy syndrome, are also discussed.

Interpretation: The consensus definition is expected to improve awareness of this disease concept, provide diagnostic framework, and facilitate future international research and clinical trials.

Acute encephalopathy is generally defined as a pathobiological brain process that develops acutely and is characterized by impaired consciousness and/or altered mental status.[1] This term refers to a clinical state rather than a disease, and includes a variety of causes, including metabolic, hypoxic–ischaemic, and autoimmune/immune-mediated encephalopathies, and drug intoxication.[2] In paediatrics, acute encephalopathy is often secondary to infection.[3]

An important acute neurological syndrome associated with viral infections is primary encephalitis, which is caused by the invasion of a neurotropic virus into the brain. Various viral infections can also induce autoimmune/immune-mediated

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Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AFCE, acute fulminant cerebral oedema; ANE, acute necrotizing encephalopathy; ASEM, acute shock with encephalopathy and multiorgan failure; FIRES, febrile infection-related epilepsy syndrome; HSES, haemorrhagic shock and encephalopathy syndrome; ITES, infection-triggered encephalopathy syndrome; MERS, mild encephalopathy with a reversible splenial lesion.

For affiliations refer to page 11.

reactions against the central nervous system (CNS). The most common is acute disseminated encephalomyelitis, and in children autoimmune encephalitis is often triggered by infection. Typically, the mode of onset of autoimmune neurological diseases is 'postinfectious' and the infection is resolved at the time of neurological onset. In contrast, some patients can present with infection and fever which is rapidly followed by encephalopathy; that is, the temporal association is para-infectious (the infection is still present) rather than postinfectious. When features of encephalitis are absent these can be termed 'infection-triggered encephalopathy syndromes (ITES)'. ITES frequently presents with encephalopathy and seizures reflecting widespread brain dysfunction, and less frequently with focal symptoms such as hemiplegia, although there may be clinical overlap of neurological symptoms with infectious and autoimmune encephalitis.

Advances in imaging techniques have identified several groups of acute encephalopathies that present with characteristic neuroradiological findings. These imaging findings are not only unique and highly uniform in distribution, but also correlate with specific clinical course patterns, each with a particular age at onset and prognosis. Thus, they can be considered syndromes characterized by a specific clinico-radiological phenotype. An observation that these encephalopathy syndromes can be triggered by many different viruses, yet present with common clinical and imaging features, leads us to speculate that the condition arises from the host's cellular response to the virus rather than the virus itself.

These include the following syndromes: (1) acute encephalopathy with biphasic seizures and late reduced diffusion (AESD);[4] (2) acute necrotizing encephalopathy (ANE);[5,6] (3) mild encephalopathy with a reversible splenial lesion (MERS);[7] (4) acute fulminant cerebral oedema (AFCE);[8] (5) acute shock with encephalopathy and multi-organ failure (ASEM) (previously known as 'haemorrhagic shock and encephalopathy syndrome [HSES]').[9] Most of these syndromes were first observed in Japan and seem to have significantly higher prevalence in East Asia than elsewhere in the world. However, these entities do occur in all regions of the world[10,11] (often with East and South Asian ethnic vulnerability), yet these syndromes are not widely recognized internationally, which has hindered the progress of disease research. To further accelerate prognostic studies and therapeutic trials, we need to create consensus definitions for these syndromes and establish a platform for future research. We herein designate ITES to encompass the above syndromes and propose their definitions according to their clinical and neuroimaging features. Previously, the individual definitions lacked structure and consistent format.[1,8,9] We thus aimed to generate a standardized format common to the general ITES term, and the individual terms. It should be noted, however, that there is overlap between the syndromes, and that there are many 'unclassifiable' encephalopathies whose clinical course is consistent with ITES but which do not fall into any specific syndromic category.

What this paper adds

- Infection-triggered encephalopathy syndrome (ITES) is defined following international expert opinion.
- Five specific ITESs were defined.
- Each syndrome is characterized by specific clinical and radiological phenotypes.
- Core ITES criteria include the presence of a febrile illness followed by neurological symptoms including encephalopathy.
- The diagnosis of ITES requires the exclusion of encephalitis and other causes of encephalopathy.

METHOD

First, we formed the international ITES study group of clinical researchers from Asia, Europe, and Oceania who have expertise in these syndromes. The primary task of this study group was to conduct a systematic meta-analysis of the literature on ITES. However, it was recognized that there are inconsistent terminologies and definitions in the literature, although there is a recent definition for febrile infection-related epilepsy syndrome (FIRES),[12] and some previous proposed definitions for AESD, ANE, MERS, AFCE, and HSES (later replaced by the revised nomenclature ASEM).[1,8,13,14] We thought it important to standardize the definitions and thus developed them using the following methods.

First, a standardized format was determined for all definitions. (1) The mode of onset: the presence of a febrile illness which is within a week of the neurological onset (often 1–2 days), and fever is typically still present at neurological onset. (2) Clinical features: the obligatory presence of encephalopathy, and other neurological symptoms (when present). (3) Neuroradiological and other investigation criteria. (4) The exclusion of other causes (within reason).

For all features, we provide features that are essential for diagnosis, and features that are commonly seen but not essential (common). A nominal group technique with a facilitator was used to reach consensus on the ITES definitions: the criteria were reviewed by the whole group, discussed in structured correspondence and regular meetings over 18 months, and revised accordingly six times until agreement was reached (see Appendix S1 for method). An initial set of criteria were based on existing diagnostic criteria: Japanese diagnostic criteria were used for AESD, ANE, and MERS,[1] and the criteria from the original report for HSES.[13] All of these were structured and modified to conform to the above format.

RESULTS

It is recognized that the primary differential diagnosis involves separating ITES from encephalitis, which is important

for therapeutic and prognostic reasons. To aid in this separation, Table 1 provides clinical, biological, and investigation features of ITES, infectious encephalitis, and inflammatory/autoimmune encephalitis.

For the diagnosis of ITES, our consensus definition recommends a two-step approach. Patients are first evaluated to determine whether they meet the general diagnostic criteria for ITES, and then whether they meet the individual ITES criteria (see below for specific criteria for AESD, ANE, MERS, AFCE, and ASEM).

Core ITES criteria (Table 2) include the presence of a febrile illness followed by neurological symptoms including encephalopathy (decreased or altered level of consciousness, altered mental status, lethargy, or personality change). Seizures are another commonly observed symptom. Additional symptoms including dyskinesia or cerebellar ataxia may be seen. Neurological symptoms, by definition, appear within 7 days of previous infection, but typically within 2 days when the previous infection is still active, and fever is still present. The diagnosis of ITES also requires the exclusion of encephalitis (infection in the CNS or autoimmune process) and other causes of encephalopathy (Table 2), while acknowledging that the hyperacute course of ITES may preclude full availability of virological, metabolic, immunological, and genetic investigations.

Some patients do not have a radiological phenotype but have all other features of ITES: if these patients have supportive electroencephalography (EEG) or biomarker findings and other aetiologies are carefully excluded, they are diagnosed with 'possible ITES' (Table 2). Importantly, 'possible ITES' is presumed to be a heterogeneous group that may include undiagnosed or unknown diseases, and new syndromes may

TABLE 1 Clinical, biological, and investigation features distinguishing ITES from infectious and autoimmune/inflammatory encephalitis.

Feature	ITES	Infectious encephalitis	Inflammatory or autoimmune encephalitis
Examples	ANE, MERS	Herpes simplex encephalitis	Anti-NMDAR encephalitis, acute disseminated encephalomyelitis
Pathophysiology	Infection-triggered cytotoxicity and cytokine storm of CNS, without parenchymal cellular infiltration of CNS	Direct CNS invasion of microorganism with secondary CNS parenchymal cellular infiltration	Infection or tumour triggered CNS parenchymal cellular (with or without autoantibody) infiltration without microorganism CNS invasion
Preceding fever/systemic infection	Essential, para-infectious (present at neurological onset)	Common, infectious	Variable, if present usually postinfectious
Encephalopathy[a]	Essential	Essential	Essential
Serum or CSF antineuronal autoantibodies	Not present	Not present (except complicating post-HSV autoimmune encephalitis)	Present in seropositive autoimmune encephalitis
CSF pleocytosis	Uncommon (mild in FIRES and MERS[b])	Common	Common
CSF oligoclonal bands	Not present	Unmatched bands may be present	Unmatched or mirrored bands may be present
Evidence of microorganism in CNS (CSF)	Rare (occasional in MERS)	Common	Rare
EEG	Typically abnormal (slow and/or epileptiform)	Typically abnormal (slow and/or epileptiform)	Typically abnormal (slow and/or epileptiform)
MRI: localization of lesions	Syndrome specific (corpus callosum in MERS, bithalamic in ANE, subcortical white matter in AESD)	Varied in degree and pattern. Diffuse cortical grey, white matter, and deep grey matter involvement	Varied in degree and pattern. Diffuse cortical grey, white matter, and deep grey matter involvement. MRI may also be normal or non-specific in autoimmune encephalitis.
MRI: symmetry of lesions	Typically symmetrical (except HHE)	Typically asymmetrical	Typically asymmetrical
MRI: diffusion restriction on DWI/ADC sequences	Typical[c]	May be present (e.g. HSV encephalitis)	Rare

Abbreviations: ADC, apparent diffusion coefficient; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AFCE, acute fulminant cerebral oedema; ANE, acute necrotizing encephalopathy; CNS, central nervous system; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EEG, electroencephalography; FIRES, febrile infection-related epilepsy syndrome; HHE, hemiconvulsion–hemiplegia–epilepsy; HSV, herpes simplex virus; ITES, infection-triggered encephalopathy syndrome; MERS, mild encephalopathy with a reversible splenial lesion; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor.

[a]Encephalopathy: altered level of consciousness, lethargy, cognitive deficits, or personality change lasting longer than 24 hours.

[b]Mild pleocytosis in FIRES and MERS is sometimes seen, up to 20 cells/mm^3.

[c]Although diffusion restriction on MRI is essential for the diagnosis of many ITES syndromes (see below), it is acknowledged that some probable ITES syndromes have normal imaging and future biomarkers are required to improve diagnostics for these syndromes.

TABLE 2 Core definition for definite ITES.

1. The mode of onset Essential: a previous febrile illness starting within a week before the onset of the first neurological manifestation. Common: fever is typically still present at neurological onset. **2. Clinical** Essential: a clinical presentation of decreased or altered level of consciousness, altered mental status, lethargy, or personality change, lasting for >24 hours. Common: these symptoms may not last for >24 hours in rapidly progressive fatal cases or mild encephalopathy with a reversible splenial lesion. **3. Neuroradiological and other investigation** Essential: neuroradiological abnormalities specific to each syndrome. **4. Diseases to be excluded** Essential: encephalitis (both infectious and autoimmune) and other inflammatory (including systemic), neurological (epilepsy, stroke), metabolic (inborn error of metabolism, mitochondrial, Reye syndrome), traumatic, and toxic causes of acute encephalopathy.
Possible ITES: criteria 1–4 with modifications as follows Criterion 3. In the absence of neuroradiology for definite ITES, at least one of the following is required for possible ITES: (a) EEG findings suggestive of encephalopathy, such as slowing of background activity; (b) elevated ITES-related inflammatory biomarkers (neopterin, pro-inflammatory cytokines, etc.) in cerebrospinal fluid (but typically lacking pleocytosis). Criterion 4. In the absence of neuroradiology features of ITES, the following needs to be additionally excluded: non-convulsive status epilepticus, transient delirium associated with fever.

All four features are essential for definite ITES.

Abbreviations: EEG, electroencephalography; ITES, infection-triggered encephalopathy syndrome.

emerge in the future. Overuse of the term 'possible ITES' needs to be avoided, and a thorough differential diagnosis is crucial.

ITES occur in all age groups, but children are more susceptible than adults except for MERS.[15,16] Each syndrome has an age of predilection, which can be helpful in diagnosis. Most ITES-triggering pathogens are viruses, including influenza virus, human herpesvirus-6 (HHV-6), respiratory-syncytial virus, rotavirus, dengue virus, and SARS coronavirus-2;[15–18] however, bacterial infections (pathogenic *Escherichia coli* infection, acute focal bacterial nephritis, etc.) can also cause ITES.[19,20]

In ITES, brain pathology does not demonstrate the presence of virus in the brain, and viral polymerase chain reaction in the cerebrospinal fluid (CSF) is typically negative.[21] CSF cell counts may be mildly increased, particularly in FIRES and sometimes in MERS, but are typically normal in ANE and AESD. Significant CSF pleocytosis suggests primary encephalitis or meningitis. However, there is some evidence to support the involvement of neuroinflammation in ITES. CSF neopterin and quinolinic acid are biomarkers of neuroinflammation and can discriminate ITES and encephalitis from other causes of new-onset seizures or status epilepticus.[22] Pro-inflammatory cytokines including interleukin-6 have been reported to been elevated in ITES.[23] EEG is helpful in diagnosing ITES. Although there are no known EEG findings specific for ITES, abnormalities in background activities including diffuse slowing support the diagnosis of encephalopathy.[24] EEG may be useful in discriminating

ITES from other brain syndromes where behavioural change may occur such as paediatric acute-onset neuropsychiatric syndrome, in which EEG does not show encephalopathic changes.

Outcome depends on the syndrome: severe forms of ITES, such as ANE, AFCE, and ASEM, are associated with significant risk of death and severe neurological disability, while MERS is typically self-limiting and patients recover to baseline within a month.[15,18]

ITES

AESD

AESD (Table 3) is the most common type of acute encephalopathy in Japan and is described globally.[16] It mainly occurs in infants, with an average age at onset of 1 years 8 months.[25]

AESD typically presents with an early and prolonged seizure on the day of, or the day after, the onset of fever associated with infection. Symptoms often improve over the next 2 to 4 days but are commonly aggravated again over the next 3 to 7 days with a cluster of seizures (late seizure) and encephalopathy.[4]

AESD presents with characteristic imaging findings over time: normal computed tomography or magnetic resonance imaging (MRI) on days 1 and 2, progressing later to diffusion restriction in the subcortical white matter (bright tree appearance) and high signal along the subcortical U-fibres on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images on days 3 to 9 (Figure 1a–c).[4,26]

In some cases, the early and late seizures may merge into a long single phase. Acute leukoencephalopathy with restricted diffusion is proposed as a subgroup of AESD that includes all cases that exhibit restricted diffusion predominantly in the subcortical white matter, regardless of the temporal progression pattern of seizures.[27,28] It is reasonable to consider AESD and acute leukoencephalopathy with restricted diffusion to be part of the same spectrum, although further study is needed in their pathophysiology and outcomes.

ANE

ANE (Table 4) is a syndrome characterized by acute neurological deterioration, with bilateral and multiple brain lesions primarily involving the thalamus.[5,6] It can be divided into sporadic and familial/recurrent (genetic) forms.

ANE generally presents with decreased level of consciousness and seizures associated with febrile illness, and often rapidly leads to coma.

The most striking feature of ANE is the neuroimaging findings. Bilaterally symmetrical thalamic lesions are essential, and crucial for the diagnosis of ANE (Figure 1d–f). By days 3 to 5, the thalamic lesions show a trilaminar appearance

TABLE 3 Diagnostic criteria of definite AESD.

1. The mode of onset
Essential: febrile illness preceding or concurrent to the onset of neurological manifestation.
2. Clinical
Essential: a clinical presentation of decreased or altered level of consciousness, altered mental status, lethargy, or personality change, lasting for >24 hours.
Common:
- Early seizure(s) associated with the fever on days 1–2, usually lasting longer than 30 minutes.
- Late seizures on day 3–7, most often in a cluster of focal seizures, with interictal encephalopathy (deterioration of consciousness level).
- In severe cases, transient recovery after early seizures is not evident, and therefore early and late seizures may not be distinguished. Late seizures may also be masked by aggressive antiseizure therapy.
3. Neuroradiological and other investigation
Essential: restricted diffusion on MRI in the subcortical white matter (BTA) at day 3–14 after onset of neurological symptoms.
Common:
- Restricted diffusion on MRI in the cortex.
- Spared (unaffected) pre- and postcentral gyrus (central sparing).
4. Diseases to be excluded
Essential: to exclude AESD mimics in which patients may have an acute (and often febrile) encephalopathy with seizures and a BTA on MRI: accidental and non-accidental head trauma, hypoxic–ischaemic encephalopathy, hypoperfusion injury, meningitis.

Possible AESD
Criterion 3. If BTA is not determined in the acute phase (or if MRI is not performed in the acute phase owing to the patient's critical condition), either of the following convalescent findings are supportive of possible AESD: (1) subcortical hyperintensity on T2/FLAIR within the distribution typically observed in BTA; (2) decreased blood flow on SPECT or arterial spin labelling in the frontal or fronto-parietal region, often with central sparing.

AESD variants and related disorders
AIEF
AIEF is characterized by status epilepticus and encephalopathy suggestive of frontal lobe dysfunction, manifesting with features such as lack of spontaneity, speech regression, and occasional bizarre stereotypical behaviours. MRI shows selective involvement of the frontal lobes, and SPECT highlights decreased blood flow in the affected areas during the recovery period. AIEF is now included in AESD, which is recognized as a subgroup with prominent frontal lobe involvement.
Hemispheric AESD
AESD may present with obvious laterality, with clinico-radiological features similar to those of hemiconvulsion–hemiplegia–epilepsy syndrome. AESD associated with exanthema subitum in infants often results in unilateral status epilepticus. The diagnosis of 'hemispheric AESD' may be preferred if the clinical course is consistent with that of AESD.
AESD associated with neurological comorbidities
AESD sometimes occurs in association with neurological comorbidities; Dravet syndrome is susceptible to acute febrile encephalopathy with clinico-radiological features that are consistent with AESD. Missense mutations in the *SCN1A* and *SCN2A* genes have also been shown to be predisposing factors for AESD. In addition, AESD associated with various congenital brain diseases has been reported. If a patient with these underlying diseases develops encephalopathy following a febrile infection and meets the neuroradiological criteria for AESD, then it is included in AESD. However, if other triggers are involved, such as traumatic brain injury, they are excluded from AESD.
Other neurological disorders presenting with BTA
BTA may be seen in accidental and non-accidental head trauma, hypoxic–ischaemic encephalopathy, and hypoperfusion injury. These cases may resemble AESD when associated with seizures but are excluded from AESD because they are not induced by infection. Such AESD mimics may exhibit the following features that are atypical for AESD, which are useful in differentiating them from AESD: (1) lack of a biphasic pattern to seizures; (2) absence of a central-sparing pattern in the BTA distribution; (3) bilateral BTA lesions in a multifocal pattern, occasionally distributed in the vascular watershed locations; (4) presence of subdural haematoma in the acute stage.

All four criteria are essential for definite AESD.

Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AIEF, acute infantile encephalopathy predominantly affecting the frontal lobe; BTA, bright tree appearance; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography.

on MRI. In addition to the thalamus, symmetrical lesions are often seen in the brainstem tegmentum, cerebral white matter around the lateral ventricles, and cerebellar dentate nuclei.[29]

Prognosis is generally poor, with high rates of death (28%) and sequelae (56%).[15]

Familial/recurrent ANE

Missense mutations in the nuclear pore-associated protein RanBP2/Nup358 were identified in familial and recurrent ANEs and designated ANE1.[30] Mutations in the *RANBP2* gene show incomplete penetrance, with considerable symptomatic diversity among patients.[31] Typical cases develop encephalopathies that are consistent with ANE, whereas others lack characteristic thalamic lesions. ANE1 is commonly a relapsing disease. Neuroimaging in ANE1 shows lesions confined to the bilateral thalami and pons rather than diffuse lesions, and in addition to the areas mentioned above, lesions may be seen in the external capsules, claustra, medial temporal lobes, amygdalae, and hippocampi.[31]

Recently, biallelic variants in *RNH1* have been reported to be associated with a clinico-radiological syndrome reminiscent of ANE (ANE2).[32]

MERS

MERS (Table 5) is a clinico-radiological syndrome characterized by transient delirium and other neurological symptoms
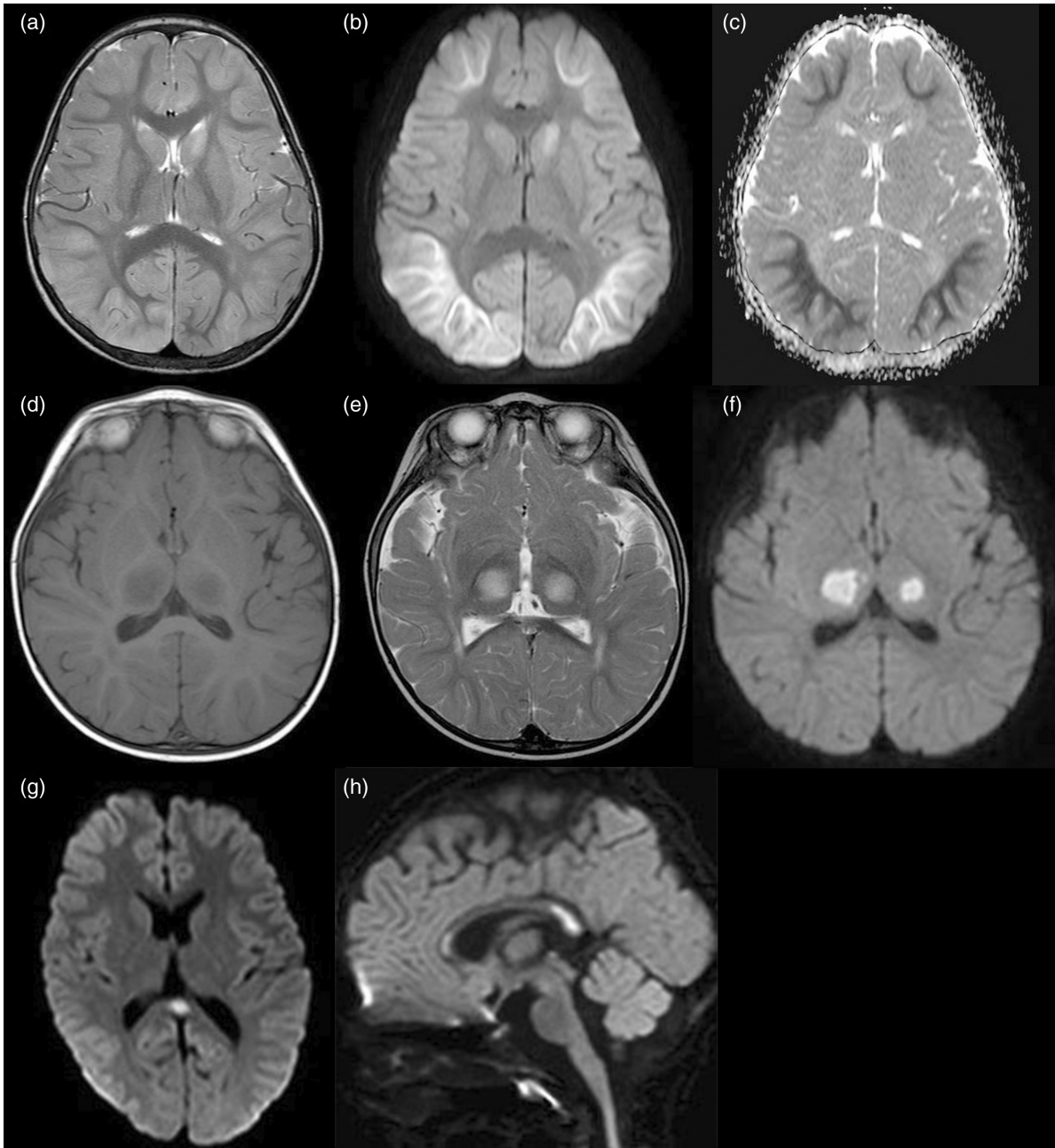
FIGURE 1 Typical magnetic resonance imaging (MRI) findings in infection-triggered encephalopathy syndromes. (a–c) MRI on day 4 in acute encephalopathy with biphasic seizures and late reduced diffusion (from Figure 2 in Takanashi and Uetani[26]). T2-weighted image shows (a) cortical swelling and T2 prolongation. Diffusion-weighted image shows symmetrical high-signal lesions in the bilateral frontoparietal subcortical white matter with (b) sparing around the central sulci with (c) reduced apparent diffusion coefficient. (d–f) MRI on day 4 in acute necrotizing encephalopathy (from Figure 7.6 in Yamanouchi et al.,[2] with permission). Bilateral symmetrical thalamic lesion shows (d) low intensity on T1-weighted image, (e) high intensity on T2-weighted image, with (f) restricted diffusion. (g,h) MRI in mild encephalopathy with reversible splenial lesion (from Figure 3 in Takanashi and Uetani[26]). Diffusion-weighted image shows restricted diffusion in the (g,h) splenium and (h) genu of the corpus callosum.

occurring simultaneously within a week of infection, especially viral infection, with reversible corpus callosum lesions on diffusion-weighted MRI.[7]

MERS is generally self-limiting: in most cases, these neurological symptoms promptly resolve and disappear within a month (often 10 days).[7] MRI is essential for the diagnosis of MERS. In the acute phase, lesions in the splenium of corpus callosum usually show hyperintensity on T2-weighted images and less commonly show hypointensity on T1-weighted images. Diffusion-weighted images show marked diffusion restriction, typically appearing as an oval lesion with a decreased apparent diffusion coefficient (Figure 1g,h).[26] The lesions are transient and disappear within 2 months (often within a week).[7]

TABLE 4 Diagnostic criteria of ANE.

1. The mode of onset
Essential: febrile illness preceding or concurrent to the onset of neurological manifestations.
2. Clinical
Essential: a clinical presentation of decreased or altered level of consciousness, altered mental status, lethargy, or personality change, lasting for >24 hours.
Common: rapid (hours) reduction of consciousness with or without seizures and/or focal neurological signs (pyramidal or extrapyramidal motor signs).
3. Neuroradiological and other investigation
Essential: symmetrical thalamic lesions on head computed tomography and/or MRI
Common:
- Thalamic lesions are typically not homogeneous and often show concentric structures, suggesting necrosis and/or haemorrhage in the centre.
- Symmetrical and multiple brain lesions in the periventricular white matter, internal capsules, putamina, temporal lobes, upper brainstem tegmentum, or cerebellum.
- Cerebrospinal fluid examination typically shows normal cell counts and increased protein concentration.
- Elevated serum transaminase levels with no elevation in serum ammonia levels.
4. Diseases to be excluded[a]
Essential: acute disseminated encephalomyelitis with deep grey matter involvement, mitochondrial disorders such as Leigh encephalopathy, Reye syndrome, glutaric acidaemia, methylmalonic acidaemia, infantile bilateral striatal necrosis, Wernicke encephalopathy, carbon monoxide poisoning, acute haemorrhagic leukoencephalopathy, angiitis, arterial and venous infarction, hypoxia, and traumatic head injury, flavivirus encephalitis (e.g. Japanese encephalitis virus or dengue virus), enterohaemorrhagic *Escherichia coli*-related encephalopathy, cerebrovenous sinus thrombosis with thalamic infarction.
[a]If cases with ANE also meet ASEM criteria, the diagnosis of ANE is preferred.

Familial/recurrent ANE
Familial/recurrent ANE is diagnosed if any of the following criteria are met: (1) familial clustering of encephalopathy following fever including at least one episode of ANE; (2) recurrent encephalopathy following fever including at least one episode of ANE. Familial cases without these genetic abnormalities may also exist. Sporadic ANE cases do not have these mutations, highlighting that these genetic encephalopathies are distinct from sporadic ANE.

All four criteria are essential for definite ANE.

Abbreviations: ANE, acute necrotizing encephalopathy; ASEM, acute shock with encephalopathy and multiorgan failure.

TABLE 5 Diagnostic criteria of MERS.

1. The mode of onset
Essential: febrile illness preceding or concurrent to the onset of neurological manifestations.
2. Clinical
Essential: a clinical presentation of decreased or altered level of consciousness, altered mental status, lethargy, or personality change, lasting for >24 hours.
Common:
- Other clinical features include seizures or hallucinations.
- Self-limiting clinical course with spontaneous recovery.
- Alteration in consciousness and change in personality/behaviour may be intermittent and may occasionally not persist past 24 hours.
3. Neuroradiological and other investigation
Essential: a splenial corpus callosum lesion with homogeneously restricted diffusion on MRI.
Common:
- Lesion involving at least the splenium. It may expand to the entire corpus callosum or involve the cerebral white matter symmetrically.
- The corpus callosum lesion usually shows hyperintensity on T2-weighted images/FLAIR, and less commonly hypointensity on T1-weighted images.
- If interval imaging is performed, the lesion is typically resolved within 1–2 months.
4. Diseases to be excluded
Essential: acquired demyelinating syndromes (acute disseminated encephalomyelitis, etc.), AESD, RESLES with non-infectious causes (antiseizure medication withdrawal, high-altitude cerebral oedema, metabolic disorders [hypoglycaemia and hypernatraemia], X-linked Charcot–Marie–Tooth disease, Kawasaki disease).

MERS variants and related disorders
Rotavirus cerebellitis
Reversible splenial lesions associated with rotavirus infection often later develop into cerebellar white matter and deep nuclei lesions along with cerebellar mutism, which does not always have a favourable prognosis.
Other disorders presenting with reversible splenial lesions
Reversible splenial lesions can also result from environmental factors or diseases other than viral infections, such as altitude sickness (also known as high-altitude cerebral oedema), Kawasaki disease, X-linked Charcot–Marie–Tooth disease, electrolyte abnormalities (hyponatraemia), hypoglycaemia, and withdrawal from antiseizure medication. Several neurometabolic diseases and genetic encephalopathies including ATP1A3-related diseases and GNAO1 encephalopathy may also show reversible splenial lesions. These are collectively referred to as RESLES but are not included in MERS.

All four criteria are essential for definite MERS.

Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; FLAIR, fluid-attenuated inversion recovery; MERS, mild encephalopathy with a reversible splenial lesion; MRI, magnetic resonance imaging; RESLES, reversible splenial lesion syndrome.

TABLE 6 Diagnostic criteria of AFCE and ASEM.

1. The mode of onset Essential: febrile illness preceding or concurrent to the onset of neurological manifestations. **2. Clinical** Essential: acute encephalopathy: rapid reduction of consciousness and/or seizures. Essential (for ASEM): shock[a] not due to massive haemorrhage or cardiac disease. **3. Neuroradiological and other investigation** Essential: progression to diffuse cerebral oedema evident on neuroimaging and/or autopsy. Common: appearing within 48 hours of onset if imaged, although rapidly progressive fatal cases may not fulfil these criteria before reaching an irreversible state. Essential (for ASEM): signs of multiple organ failure (at least three of the following): (1) anaemia; (2) thrombocytopaenia; (3) disseminated intravascular coagulation; (4) acidosis; (5) raised hepatocellular enzymes; (6) renal dysfunction. **4. Diseases to be excluded** Essential: metabolic encephalopathies (organic aciduria, urea cycle disorders, septicaemic shock, etc.), hypoxic–ischaemic encephalopathy. [a]Organ and tissue hypoperfusion despite preserved intravascular volume, typically manifesting as hypotension with vasopressor requirement and lactic acidosis.
HSES/ASEM variants *Overlapping syndrome* Cases of other types of ITES, including ANE, may occasionally meet the diagnostic criteria for ASEM. However, they differ significantly in terms of neuroimaging findings: ASEM typically shows diffuse cerebral oedema, whereas ANE with ASEM typically has ANE features on MRI.

All four criteria are essential for AFCE or ASEM.

Abbreviations: AFCE, acute fulminant cerebral oedema; ANE, acute necrotizing encephalopathy; ASEM, acute shock with encephalopathy and multiorgan failure; HSES, haemorrhagic shock and encephalopathy syndrome; ITES, infection-triggered encephalopathy syndrome; MRI, magnetic resonance imaging.

AFCE and ASEM

This section describes a subtype of ITES characterized by rapid deterioration of consciousness and fatal cerebral oedema (Table 6).

ASEM, previously known as HSES

HSES was described in 1983 as a syndrome of high-grade fever as well as shock, encephalopathy, haemorrhage associated with disseminated intravascular coagulation, and multiorgan failure, which most frequently affects children under 1 year of age.[13,14] The term 'haemorrhagic shock' was reminiscent of hypovolemic shock due to haemorrhage; however, haemorrhage was not evident in all cases, even in those with coagulopathy. To address these problems, ASEM was proposed as a revised nomenclature applicable to all ages.[9]

ASEM is generally a hyperacute state in which the patient rapidly falls into a coma and critical illness over a period of hours. Within 48 hours of onset, liver and kidney function rapidly deteriorate, often with diarrhoea.[33]

Neuroradiologically, marked brain oedema of the whole cerebrum progresses rapidly, occasionally associated with haemorrhage. The prognosis is extremely poor, with most patients dying or being left with severe neurological disability.[34]

AFCE

While shock and multiorgan failure are core features of ASEM, some cases present with rapidly progressive encephalopathy and cerebral oedema, yet signs of multiple organ failure, coagulopathy, haemorrhage, and shock are not evident. Recently, a new clinical entity called AFCE was proposed.[8] AFCE is a syndrome characterized by symptoms of encephalopathy and acute, fulminant, and often fatal cerebral oedema in both children and adults. Prognosis is extremely poor, with a mortality of 80%.[8]

AFCE overlaps with ASEM in its clinical and neuroradiological features. Here we define AFCE and ASEM to be of the same continuum of a fulminant brain inflammation/oedema distinguished by shock and end organ failure. However, AFCE should not be recognized as a milder form of ASEM. Future studies are needed to clarify the relationship between ASEM and AFCE.

ITES-related conditions

There are other syndromes that have clinical and biological similarities to ITES syndromes, but their classification is still under review.

FIRES

FIRES, a subcategory of new-onset refractory status epilepticus, is a syndrome of acute onset in individuals with no apparent underlying neurological abnormality, presenting with extremely refractory seizures associated with fever.[12,35] FIRES is defined as an epileptic syndrome by the International League Against Epilepsy; however, for reasons discussed below, it is described here as an ITES-associated syndrome.

FIRES is extremely rare, occurring in fewer than 1 per million, and is most common in young and school-aged children.[36] After a latent period of about 5 days after previous fever, seizures develop, which gradually increase to a clustering status epilepticus within about 1 week.[37] Seizures are extremely intractable and persistent, and highly refractory to conventional antiseizure medication, often requiring the use of intravenous anaesthetics. Neuroradiological findings are not essential for the diagnosis of FIRES.

Hemiconvulsion–hemiplegia–epilepsy syndrome

Hemiconvulsion–hemiplegia–epilepsy syndrome is another epilepsy syndrome occurring in the context of febrile illness. It is typically seen in infancy and early childhood.[36,38] Most cases begin with a unilateral convulsive status epilepticus associated with fever, followed by appearance of focal seizures and permanent motor deficit on the affected side.

TABLE 7 Core features of ITES syndromes and ITES-related conditions.

	Age	Common pathogens[15,16]	Genetic susceptibility[40]	Neurological manifestations	Systemic involvement
ITES					
AESD	0–3 years	HHV-6, influenza virus	*SCN1A*, *SCN2A* variants, *ADORA2A*, *IL1B*, *STK39* polymorphisms	First phase: prolonged seizure; second phase: a cluster of seizures and encephalopathy	Not typically described
ANE	6 months – 5 years	Influenza virus, HHV-6, SARS-CoV-2 virus[51]	Pathogenic variants in *RANBP2* (ANE1),[30] *RNH1* (ANE2),[32] or *DBR1*,[41] *IL-10*, HLA-DR, and -DQ polymorphisms	Decreased level of consciousness (coma), seizures	Shock, vomiting, diarrhoea, elevated transaminase and lactate dehydrogenase, thrombocytopenia, coagulopathy
MERS	Young child to adults	Multiple viruses and bacteria	*MYRF* mutation[52] (in rare genetic form)	Delirium, abnormal speech and behaviour, seizures, visual hallucination	Hyponatraemia
ASEM	Infants to school-aged children	Unknown	Unknown	Decreased level of consciousness (coma), seizures	Shock, multiple organ failure (liver and kidney dysfunction), thrombocytopenia, coagulopathy, acidosis, diarrhoea
AFCE	Infants to school-aged children	Unknown (SARS-CoV-2)	Unknown	Decreased level of consciousness (coma), seizures	Unknown
ITES-related conditions					
FIRES	Young children to adults	Unknown	Pathogenic variants in *FADD*,[53] *IL-1RN* polymorphism	Refractory status epilepticus (focal-onset, highly refractory)	Drug-induced hypersensitivity syndrome
HHES	Infants and young children	Multiple viruses	Unknown	Unilateral convulsive status epilepticus followed by focal seizures and hemiplegia on the affected side	Not typically described

Abbreviations: AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AFCE, acute fulminant cerebral oedema; ANE, acute necrotizing encephalopathy; ASEM, acute shock with encephalopathy and multiorgan failure; FIRES, febrile infection-related epilepsy syndrome, HHES, hemiconvulsion–hemiplegia–epilepsy syndrome; HHV-6, human herpesvirus-6; ITES, infection-triggered encephalopathy syndrome; MERS, mild encephalopathy with a reversible splenial lesion.

Neuroradiological studies show hemispheric brain swelling with restricted diffusion in the acute phase.[39] In the recovery period, there remains marked atrophy of the affected hemisphere.

DISCUSSION

In the present consensus document, we propose ITES as a CNS syndrome induced by infection or fever, and distinct from either infectious or autoimmune encephalitis. ITES is still underrecognized globally and may be misdiagnosed as viral encephalitis, acute disseminated encephalomyelitis, or seronegative autoimmune encephalitis. In addition, two ITES-related conditions were also discussed. Core features of these syndromes are summarized in Tables 7 and 8.

Although ITES syndromes are described as distinct entities, the relationship between them needs to be further clarified. For example, AESD and acute leukoencephalopathy with restricted diffusion share characteristic MRI features, but it is uncertain whether they are diseases of the same spectrum. We joined AFCE with ASEM as a related entity, but whether the two are distinguishable requires future discussion based on pathological considerations. Furthermore, there are some cases that meet criteria for both ANE and ASEM, and such overlap syndromes need to be further investigated. It remains to be determined to what extent these syndromes share common pathomechanisms despite their different clinico-radiological manifestations.

FIRES is classified as an epilepsy syndrome because it is characterized by refractory seizures. However, the acute onset with fever, the clinical or EEG-proven encephalopathy, and the inflammatory change in CSF separates FIRES from most other epilepsies and is more akin to ITES. Therefore, it may be necessary to discuss whether FIRES can be considered within the spectrum of ITES.

In ITES, infection is the trigger but not the direct aetiological agent; therefore it is important to understand the mechanism of ITES pathogenesis. Genetic vulnerability

TABLE 8   Neuroimaging features and outcome of the individual syndromes.

	Neuroimaging	Prognosis
AESD	MRI: normal at onset; bright tree appearance = diffusion restriction in the subcortical white matter (frontally predominant and usually symmetrical), high signal along the subcortical U-fibres on T2/FLAIR images on days 3–9; bright tree appearance disappears, cortical diffusion restriction, persistent T2/FLAIR hyperintensity in the subcortical white matter on days 9–25. Magnetic resonance spectroscopy: elevated glutamate (1–4 days) and glutamine (4–12 days) peaks.	Variable from normal or mild intellectual disability to severe psychomotor impairment, residual epilepsy.
ANE	Bilaterally symmetrical thalamic lesions: may be absent in the early stage but typically show hypointensity on T1 and hyperintensity on T2, a tri-laminar appearance = an outer ring of facilitated diffusion representing vasogenic oedema, a middle ring of restricted diffusion due to cytotoxic oedema, and a central area of T1-hyperintensity representing necrosis (best seen on DWI, ADC map, and T1 MRI), haemorrhage within a lesion (best seen on susceptibility-weighted imaging), computed tomography can also show early features such as thalamic hypodensity and swelling. Extrathalamic lesions: brainstem tegmentum, cerebral white matter around the lateral ventricles, and cerebellar dentate nuclei (symmetrical).	Generally poor, with high rates of death (28%) and sequelae (56%).
MERS	Reversible lesions in the splenium of corpus callosum: high intensity on T2 and less commonly show iso- or slightly low intensity on T1. DWI shows marked diffusion restriction, typically appearing as an oval lesion with a decreased apparent diffusion coefficient. Symmetrical cerebral white matter lesions may be seen (MERS type 2).	Full recovery in most cases.
AFCE, ASEM	Marked cerebral oedema, MRI may show T2 or FLAIR hyperintensity in the watershed region in the early stages, cortical laminar necrosis may be present during recovery.	The poorest, with most patients dying or surviving with severe neurological disability.
FIRES	No specific findings. Swelling of the hippocampi with T2-hyperintensity followed by atrophy, bilateral periinsular, and/or claustral lesions.	Refractory epilepsy, intellectual disability.
HHES	Hemispheric brain swelling with restricted diffusion, followed by hemispheric cerebral atrophy.	Hemiplegia, epilepsy.

Abbreviations: ADC, apparent diffusion coefficient; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AFCE, acute fulminant cerebral oedema; ANE, acute necrotizing encephalopathy; ASEM, acute shock with encephalopathy and multiorgan failure; DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery; FIRES, febrile infection-related epilepsy syndrome, HHES, hemiconvulsion–hemiplegia–epilepsy syndrome; MERS, mild encephalopathy with a reversible splenial lesion; MRI, magnetic resonance imaging.

underlies some causes of ITES.[40] For example, some familial ANE is caused by the pathogenic variants in the *RANBP2*, *RNH1*, or *DBR1* genes.[30,32,41] Specific human leukocyte antigen genotypes confer susceptibility to the aberrant immune responses in ANE.[42]

CSF biomarkers such as the inflammatory metabolite neopterin are useful in differentiating ITES and encephalitis from other causes of seizures. This is consistent with the enhanced inflammatory response represented by the hypercytokine state seen in ANE, ASEM, and FIRES. Although clinico-radiological features are the best diagnostic basis for ITES currently, they may be replaced by biomarkers including genetic and metabolite analysis in the future.[22]

Given the hyperacute progression of ITES, early diagnosis is essential. Neuroimaging abnormalities are key to diagnosis and may be evident on cranial computed tomography early in the course of the illness in ASEM, AFCE, and ANE. Brain MRI is usually necessary for a diagnosis of AESD or MERS.

To date, no evidence-based therapy for ITES is known. Many reports describe neuroprotective strategies to maintain cerebral perfusion pressure, aggressive treatment of seizures, and the use of normothermia or hypothermia.[1,43] The presence of hyperinflammation provides a rationale for immune-directed therapies.[23,44] Although the quality of evidence that immune therapy changes the natural history in ITES is limited, there is anecdotal evidence that early institution of intravenous methylprednisolone can improve outcomes in the severe ITES syndromes such as ANE.[45] Likewise, early use of anti-cytokine therapies such as tocilizumab and anakinra are gaining interest, although more research is required to demonstrate their efficacy.[46–48] Many of these reports discuss the possibility that earlier initiation of therapy may improve prognosis, emphasizing the importance of suspecting and diagnosing ITES as early as possible. There is no evidence of efficacy of antiviral therapy for ITES, while rituximab (which is used in autoimmune encephalitis) is unlikely to be effective in ITES where the adaptive immune system is not thought to be involved in pathophysiology.

Our proposed definitions have several limitations. First, the definitions are expert opinion-based, were not generated from a systematic review, and need to be validated in

a real-world cohort. Second, there are many cases that meet the criteria for ITES but do not fit any of the syndromes; these unclassified ITES cases need further study. Indeed, we recognize that there are some ITES-like syndromes that are currently hard to categorize: some forms of rotavirus[49] and influenza encephalopathy[17] have features of ITES and yet have normal MRI. Likewise, some infections such as parechovirus cause white matter diffusion restriction on MRI reminiscent of ITES, and yet parechovirus is found in the CSF so whether this is best categorized as ITES or encephalitis is currently unclear.[50] Third, the diagnosis of ITES is entirely based on clinical and imaging features, and exclusion of other diseases. Therefore, the concept of ITES may evolve over time as pathobiological studies unravel mechanisms leading to new understanding, which will necessitate modification of these diagnostic criteria.

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CONFLICT OF INTEREST STATEMENT

ME is supported by Action Medical Research and the British Paediatric Neurology Association. ML has received consultation fees from CSL Behring, Novartis, Octapharma, and Roche; grants from Boston Children's Hospital Research Funds, Great Ormond Street Hospital, and Great Ormond Street Hospital/Guy's and St Thomas' Trust/St Mary's Hospital Charity; has received travel grants from Merck Serono; and was awarded educational grants to organize meetings by Novartis, Biogen Idec, Merck Serono, and Bayer.

DATA AVAILABILITY STATEMENT

All data underlying the results are available as part of the article and no additional source data are required.

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SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1: Nominal group technique.