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SPECIAL REPORT

Methodology for classification and definition of epilepsy syndromes with list of syndromes: Report of the ILAE Task Force on Nosology and Definitions

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Abstract

Epilepsy syndromes have been recognized for >50 years, as distinct electroclinical phenotypes with therapeutic and prognostic implications. Nonetheless, no formally accepted International League Against Epilepsy (ILAE) classification of epilepsy syndromes has existed. The ILAE Task Force on Nosology and Definitions was established to reach consensus regarding which entities fulfilled criteria for an epilepsy syndrome and to provide definitions for each syndrome. We defined an epilepsy syndrome as "a characteristic cluster of clinical and electroencephalographic features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious)." The diagnosis of a syndrome in an individual with epilepsy frequently carries prognostic and treatment implications. Syndromes often have age-dependent presentations and a range of specific comorbidities. This paper describes the guiding principles and process for syndrome identification in both children and adults, and the template of clinical data included for each syndrome. We divided syndromes into typical age at onset, and further characterized them based on seizure and epilepsy types and association with developmental and/or epileptic encephalopathy or progressive neurological deterioration. Definitions for each specific syndrome are contained within the corresponding position papers.

KEYWORDS

developmental and epileptic encephalopathy, electroencephalogram, focal epilepsy, idiopathic generalized epilepsy, semiology

1 | HISTORICAL OVERVIEW OF THE CONCEPT OF AN EPILEPSY SYNDROME

Epilepsy syndromes were recognized as distinctive conditions long before the first International League Against Epilepsy (ILAE) Classification of Epilepsies and Epilepsy Syndromes was proposed in 1985. These syndromes had distinctive electroclinical phenotypes. For example, the first clinical description of West syndrome dates back to 1841, when Dr W. J. West described the clinical semiology of spasms in his son,[1] followed by Gibbs and Gibbs' description of the characteristic electroencephalographic (EEG) pattern of hypsarrhythmia in 1952.[2] Lennox recognized the characteristic EEG pattern of Lennox–Gastaut

Key Points

- An epilepsy syndrome is a characteristic cluster of clinical and EEG features, often supported by specific etiological findings
- The diagnosis of a syndrome in an individual with epilepsy frequently carries prognostic and treatment implications
- Syndromes can be subdivided into those with (1) generalized onset seizures, (2) focal onset seizures, (3) generalized and focal onset seizures, and (4) developmental and/or epileptic encephalopathy or progressive neurological deterioration
- Syndromes are also divided based on age at onset

syndrome in 1950, which was followed by Gastaut and colleagues publishing the first electroclinical description in 1966.[3,4] Childhood absence epilepsy (CAE) was first described by Tissot in 1770.[5] The term "pyknolepsy" was introduced by Sauer in 1916,[6] translated into English by Adie in 1924[7] and further defined in 1955.[8] However, the key criteria and boundaries of these syndromes were not well delineated. Other syndromes were also described by one or two groups without a consensus on their existence by the epilepsy community.

In July 1983, a historic meeting was organized by the Centre Saint Paul in Marseille, with participation of 30 international epilepsy experts representing 13 countries and including members of the ILAE Commission on Classification and Terminology. A definition of an epilepsy syndrome was agreed upon, which was later adapted by the ILAE, and criteria for the diagnosis of each syndrome, utilizing clinical and EEG features, as well as etiology, where known, and evolution were documented. The meeting minutes, known as the "Blue Guide," were published in 1984.[9]

The Proposal for Revised Clinical and Electroencephalographic Classification of Seizures, published by the ILAE in 1981, provided a basic schema for epileptic seizures and noted that classification of epileptic syndromes should be the next logical area to address.[10] The Proposal for Classification of Epilepsies and Epileptic Syndromes, published by the ILAE in 1985, defined an epilepsy syndrome as "an epileptic disorder characterized by a cluster of signs and symptoms, customarily occurring together. These signs and symptoms may be clinical (e.g. history, seizure type, modes of seizure recurrence, and neurological and psychological findings) or findings detected by ancillary studies (e.g. EEG, x-ray, CT and MRI)."[11] Syndromes were not thought to necessarily have a single etiology and prognosis. Some syndromes were considered to represent broad concepts (e.g., "sleep-related grand mal"), whereas others were much more specific (e.g., juvenile myoclonic epilepsy [JME]).

The Revised Classification, published in 1989, defined an epilepsy syndrome similarly, and noted that defining features could include seizure type, etiology, anatomy, precipitating factors, age at onset, severity, chronicity, diurnal or circadian cycling, and sometimes prognosis.[12] Again, it was noted that some syndromes may evolve from one to another, such as infantile spasms evolving to Lennox–Gastaut syndrome.[12]

The ILAE Commission for Classification and Terminology published updated position papers on both the Classification of the Epilepsies and an Operational Classification of Seizure Types in 2017.[13–15] The revised framework for classification of the epilepsies uses a multilevel approach, with the third level being Epilepsy Syndrome, which was defined as "a cluster of features that tend to occur together including seizure types, EEG and imaging findings."[13] It was noted that syndromes often have age-dependent features such as age at onset and remission (where applicable), seizure triggers, diurnal variation, and sometimes prognosis. They also can have distinctive comorbidities such as intellectual and psychiatric dysfunction, together with specific findings on EEG and neuroimaging studies. The framework noted that although an epilepsy syndrome may have associated etiologic implications, there was no clear one-to-one correlation with an underlying etiologic diagnosis. Thus, both etiology and epilepsy syndrome diagnosis are useful and complementary pieces of the diagnostic puzzle, informing optimal management and prognosis.

Although many well-recognized syndromes were included in both the 1985 and 1989 proposals,[11,12] there have never been formally accepted ILAE definitions of these epilepsy syndromes. Following the 2017 publications by the ILAE Commission of Classification and Terminology, the new Nosology and Definitions Task Force created in 2017 was charged with providing a means to classify and define epilepsy syndromes. The goal of this paper is to summarize the methodology that we employed in this endeavor.

2 | METHODS

2.1 | What is an epilepsy syndrome?

The newly established Nosology and Definitions Task Force first met in 2017 and agreed on a definition of an epilepsy syndrome as "a characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious)." The diagnosis of a syndrome in an individual with epilepsy frequently carries prognostic and treatment implications. Syndromes often have age-dependent presentations and a range of specific comorbidities.

The Task Force considered whether disorders that result in seizures with characteristic clinical and EEG features implicating specific focal brain networks should be considered epilepsy syndromes. Although such epilepsies involving specific networks and reflex epilepsies may have a consistent constellation of symptoms and EEG findings, they lack other features that are often seen in syndromes, including specific etiologies, prognoses, and range of comorbidities. Thus, we have not included these epilepsies as syndromes. However, we acknowledge that certain focal epilepsies (e.g., insular, anterior cingulate, occipital) may meet the agreed definition of an epilepsy syndrome, although more work is required to characterize these further.

Epilepsy syndromes have traditionally been grouped according to age at onset, and we established working groups with the following divisions: (1) neonatal and infantile onset, (2) childhood onset, and (3) variable age at onset, as well as (4) idiopathic generalized epilepsies (IGEs). A syndrome has a "variable age" of onset if it can begin both in those aged ≤18 years and in those aged ≥19 years (i.e., in both pediatric and adult patients). In keeping with the 2017 Epilepsy Classification, we further subdivided syndromes in each age group into generalized, focal, or generalized and focal, based on seizure type(s), and established a separate category for syndromes with developmental and/or epileptic encephalopathy (DEE) and syndromes with progressive neurological deterioration.

The term DEE was proposed in the 2017 Classification of the Epilepsies to denote an epilepsy associated with developmental impairment that may be due to either the underlying etiology or the superimposed epileptic activity, or both.[13] In most cases of DEE, epilepsy onset and developmental impairment are seen very early in life. Brain development is ongoing through adolescence, and early normal development does not necessarily exclude a developmental problem. However, the term DEE is more challenging to apply when epilepsy begins later in life, following a prolonged period of normal development. Examples of the latter include onset of Rasmussen syndrome or progressive myoclonus epilepsy in a previously developmentally normal adolescent or adult. In other cases, there may be subtle developmental problems, which gradually become more apparent with seizure onset or worsening. Thus, we propose to combine epilepsy syndromes with DEE and epilepsy syndromes with progressive neurological deterioration to encompass the group of syndromes associated with cognitive impairment with or without other neurological deterioration, and recognize that this impairment may be due to the underlying etiology, superimposed epileptic activity, or both.

Our group then established guiding principles, as well as a template outlining which clinical data should be included for each syndrome. Each member of the Task Force was invited to propose new syndromes that should be included. Each newly proposed syndrome was discussed at a large, in-person meeting of our Task Force, and a decision to include it as a new syndrome was reached by a majority vote.

2.1.1 | Guiding principles

1. The main goal of our Task Force was to define epilepsy syndromes using terminology consistent with the 2017 Classification of the Epilepsies and Seizure types[13,14] and to delineate "typical" features of each syndrome to facilitate recognition by clinicians as well as a "range" of accepted findings. We also delineated "alerts"—features that were rarely seen in a syndrome but were not exclusionary.
2. This resource should be available worldwide and applicable to both resource-limited and resource-equipped regions.
3. A clear lexicon employing descriptive syndromic names should be used, where possible. "Named" syndromes should be avoided, with few exceptions.
4. Groups of related syndromes should be identified.

2.1.2 | Template of clinical data

A brief overview, summarizing key concepts, preceded each template. The template for each syndrome included:

- Epidemiology.
- Clinical context, including age at onset (typical and range), sex ratio, significant antecedent history (antenatal and perinatal factors, preceding febrile seizures), cognition, development, and neurologic examination at presentation.
- Natural history, including evolution from or to other syndromes, overall response to antiseizure medications (ASMs) and other therapies, likelihood of remission, and risk of specific comorbidities.
- Seizure type(s), characterized as mandatory, typical, occasional, and exclusionary.
- EEG findings, including background, interictal epileptiform discharges, ictal patterns, and provoking factors. It is noted that incidental focal or generalized discharges are seen in a small proportion of the population. For example, .7%–2% of children without epilepsy have centrotemporal spikes, consistent with a self-limited focal epilepsy,[16,17] and generalized spike-wave discharge can be seen in up to 3.6% of persons without epilepsy.[18] Thus, the presence of such discharges must be interpreted in the context of the entire electroclinical picture.
- Neuroimaging findings.
- Genetic findings: The term "pathogenic" gene variant, when used, is meant to indicate either a "pathogenic" or "likely pathogenic" variant that can cause specific syndromes.
- Other laboratory studies that provide relevant information.
- Differential diagnosis.

We did not provide recommendations for syndrome-specific antiseizure therapies, as this was not the primary focus of the Task Force and given the variable levels of scientific evidence available and differential access to therapies around the world. However, we did identify

particular ASMs that could exacerbate seizures in specific syndromes, and addressed some iron-clad associations, such as ketogenic diet treatment for glucose transporter 1 deficiency syndrome.

2.1.3 | Process of defining each syndrome

The ILAE website, EpilepsyDiagnosis.org, which had recently been developed as an educational resource, contained detailed information on well-established epilepsy syndromes, and provided an excellent starting point for our work. EpilepsyDiagnosis.org was proposed in 2010 by the ILAE Commission on Classification and Terminology with a goal of providing a resource with a global reach to health care workers in primary and secondary health care settings. This website's content is accessible to the public using a simple registration process.

In the process of creating EpilepsyDiagnosis.org, the Commission agreed on a proposed template for data collection, seizure nomenclature, features, and EEG data. Two members of the 2010–2013 Diagnostic Manual Task Force were then assigned to develop text for each syndrome, which was reviewed and revised by both the Commission on Classification and Terminology and the EEG Commission in 2013. Videos were uploaded, with patient consent. The entire website was then reviewed by the 2010–2013 Diagnostic Manual Taskforce and by the ILAE Executive and Chairs of Commissions in 2014 and was officially released by the ILAE on August 29, 2014. An expanded version was released in February 2016 to include more videos and a structural etiology section. It was further revised in 2018 to align with the 2017 ILAE Classification of Epilepsy publication, and in 2019 to align with the 2017 ILAE Classification of Seizures publication. Members of the 2010–2013 ILAE Commission on Classification and Terminology and the Diagnostic Manual Taskforce, and of the 2013–2017 ILAE Syndromes and EpilepsyDiagnosis.org Task Force, are listed in Table S1.

Each of the working groups in our first Task Force reviewed the syndromes listed under EpilepsyDiagnosis.org for their defined age group, to determine whether each met the proposed definition of a syndrome, and also considered other potential syndromes for inclusion. To establish clinical criteria for each syndrome, we relied on:

- Literature review through July 2019 (including how studies defined each syndrome, as the definition impacted on the frequency of specific clinical features in the population studied).
- The most recent edition (2019) of the Blue Guide, "Epileptic Syndromes of Infancy, Childhood and Adolescence."[19]
- Current criteria listed on EpilepsyDiagnosis.org.
- Expert opinion from original Task Force members.

One member of each working group from the first Task Force drafted the template of each syndrome, using the above data, and reviewed the literature for cohort or case series studies pertaining to the specific syndrome name (along with any former names or synonyms). For syndromes not contained in "Epileptic Syndromes of Infancy, Childhood and Adolescence," case series and cohort studies of that entity were reviewed. The draft was circulated to all members of that specific working group for review. Where appropriate, working group members identified additional studies that provided clinical data (including seizure type(s), age at onset, development, EEG, imaging, and/or genetic findings, where relevant) to support statements or proposed revisions, and the initial drafts were amended to include these relevant references. Case reports were generally not considered.

All drafts were discussed in detail, with the majority discussed at virtual meetings. Members who were unable to attend meetings were requested to forward any questions or concerns, and these were addressed at the time of the meeting. A smaller number of in-person meetings of Task Force members were held in conjunction with the American Epilepsy Society 2018 and 2019, the European Congress of Epileptology 2018, or the International Epilepsy Congress 2019. The number of Task Force group participants who provided comments was variable but exceeded four experts for each syndrome. Any areas of disagreement were discussed in further detail, and where necessary, additional review of the literature was performed. Based on this feedback, amendments to each syndrome template were made, and the final proposal was again submitted electronically to all Task Force members for their final comments. Each syndrome template was then finalized by the appropriate working group. Discussion of each template was based on literature review, and when literature was not fully available or was contradictory, the description was based on clinical expertise.

2.1.4 | Consensus: Modified Delphi process

Using the template described above, core criteria for each syndrome were proposed, subdivided into the following groups:

Mandatory: Criteria that must be present to diagnose the syndrome. If a mandatory criterion is absent, the syndrome cannot be diagnosed.

Exclusionary: Criteria that must be absent to diagnose the syndrome. If an exclusionary criterion is present, the syndrome cannot be diagnosed.

Alerts: Criteria that are absent in the vast majority of patients who have a syndrome, but rarely can be seen. Alerts alone would not exclude the syndrome but should cause the clinician to rethink the diagnosis and undertake further investigations to rule out other conditions. The more alerts that are present, the less confident one can be about diagnosis of a specific syndrome.

We used a modified Delphi process[20] to achieve consensus on the criteria for each syndrome. The panel participants were comprised of all Nosology and Definitions Task Force members (see author list), and additionally, we enriched the panel with recognized external experts in pediatric and adult epilepsy syndromology, nominated and voted on by Nosology and Definitions Task Force members. We included additional members from each of the six ILAE regions (four each from Europe and Oceania/Asia, three each from North America and Latin America, one or two from Africa, and one from the Eastern Mediterranean region), including both pediatric epilepsy experts (those seeing mostly children younger than 16 years) and adult epilepsy experts (those seeing mostly persons age 16 years and older). To enhance diversity, no more than one panelist from each center was included, and experts represented different countries in each region. The initial two Delphi rounds included a total of 54 panelists.

Pediatric epilepsy panelists or those who saw both children and adults ($n = 36$) were asked to rate criteria for all epilepsy syndromes, whereas syndromes that typically remitted in infancy or childhood were not rated by panelists who saw only adults ($n = 18$).

Panelists were provided the finalized templates with references for each syndrome. The Delphi process was performed by electronic survey. Links to each survey were sent electronically to each panelist, and panelists were provided two email reminders to complete the surveys. Responses were anonymous. Panelists rated all criteria proposed as mandatory, exclusionary, or alert on a 9-point Likert scale (where 1 is "strongly disagree" and 9 is "strongly agree," with a no judgment option to reflect "no opinion"). Panelists were given space for additional comments and asked to provide comments for any criterion rated as <7, citing references when available. On the first round of the Delphi, panelists were also invited to propose other specific criteria, which were included on the subsequent round.

The responses were aggregated and shared with the relevant working group after each round. Criteria with median ratings of 3 or less, without discordance (discordance being defined as >25% of panelists rating the item as 7 or higher), were excluded. Those with median ratings of 7 or higher, without discordance (discordance being defined as >25% of panelists rating the item as 3 or lower), were included. Criteria with median ratings of 4–7, or showing discordance, were reviewed by the appropriate working group, with careful consideration of the panelist comments. As needed, amendments were made based on these comments, and these were included in the second round of the Delphi survey. In that iteration, panelists were provided the median rating of each item from the first round, a summary of the comments of the panelists, and the rationale of the working group for any changes in the wording. They were then invited to rescore the item, based on their opinion and their interpretation of the group response provided to them. Items that did not achieve consensus following the second round were adjudicated by a core group of the Nosology and Definitions Task Force, including the cochairs, and the core members of the small working group for that syndrome.

Additionally, for selected syndromes, we proposed two further definitions:

1. *Syndrome-in-evolution*: This term should be used early in the epilepsy course for syndromes that lack all mandatory diagnostic features at onset but take time to evolve. An example would be Rasmussen syndrome early in the course, prior to appreciation of imaging findings. Syndrome-in-evolution is not pertinent to all syndromes.
2. *Syndrome without laboratory confirmation*: This term should be utilized only in resource-limited regions, with limited or no access to EEG, magnetic resonance imaging (MRI), or other investigations that would be considered mandatory in resource-equipped regions. It may not be possible to diagnose some syndromes with reasonable certainty in the absence of these further investigations.

The proposed position papers were widely disseminated via the ILAE website for public comments for a 3-month period and submitted for review by *Epilepsia*. Subsequently, the ILAE assembled a second Task Force to ensure that comments from both the journal reviewers and the public were appropriately addressed and incorporated in the final position papers. This Task Force had 19 members, nine from the original Task Force and 10 additional external reviewers representing all six geographic regions

of the ILAE. The position papers were then revised, and a final Delphi survey addressing the revised points was sent to all members of both Task Forces, as well as to the additional non-Task Force members representing the six ILAE regions.

We sought to use clear terminology that could be readily translated into different languages, for ease of use by the international community, and requested translations of these documents by the local ILAE affiliates into Spanish, French, Italian, Mandarin, Korean, German, Portuguese, Arabic, Russian, Japanese, and Hindi, which will be posted on the ILAE website.

3 | RESULTS

The proposed syndrome organization is shown in Figure 1 and Table 1. Syndrome abbreviations are noted in Table 2. The proposed syndrome organization is shown in Figure 1. Syndromes are divided based on age at onset and on syndrome type (generalized epilepsy syndromes, focal epilepsy syndromes, focal and generalized epilepsy syndromes, and syndromes associated with DEE or progressive neurological deterioration). Position papers that arose from each working group include:

- IGEs.[21]
- Epilepsy syndromes with onset in neonates and infants (for the purpose of the proposed classification, infancy was defined as the period up to age 24 months).[22]
- Epilepsy syndromes with onset in childhood.[23]
- Epilepsy syndromes with onset at a variable age.[24]

In person, Task Force discussions also focused on two additional important questions.

3.1 | Do we include the increasing number of etiology-specific epilepsies with a distinct phenotypic spectrum as syndromes?

We propose including etiology-specific syndromes as syndromes, where there is a specific etiology for the epilepsy that is associated with a clearly defined, relatively uniform, and distinct clinical phenotype in most affected individuals (clinical presentation, seizure types, comorbidities, course of illness, and/or response to specific therapies), as well as consistent EEG, neuroimaging, and/or genetic correlates. The etiology may be a gene mutation, specific structural lesion, defined metabolic disturbance, specific neuronal autoantibody, or infectious agent. In some of these, the phenotype is dependent on age at presentation, often with more severe presentations at younger age.

Specifically, we propose that the electroclinical entities designated in 2010 as "constellations,"[25] namely, mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), Rasmussen syndrome, gelastic seizures with hypothalamic hamartoma, and hemiconvulsion–hemiplegia–epilepsy (HHE) syndrome, should now be considered as etiology-specific syndromes. Recognition of these syndromes is important, as it guides optimal treatment. MTLE-HS and Rasmussen syndrome are included in the epilepsy syndromes with onset at a variable age,[24] HHE is included in the epilepsy syndromes with onset in childhood,[23] and gelastic seizures with hypothalamic hamartoma are included in the epilepsy syndromes with onset in neonates and infants.[22]

Furthermore, there are gene-specific epilepsy syndromes, characterized by distinct electroclinical phenotypes due to a pathogenic variant in a single gene. Examples include *CDKL5*-DEE, *PCDH19* clustering epilepsy, glucose transporter 1 deficiency syndrome–DEE, and *KCNQ2*-DEE. These are included in the paper on epilepsy syndromes with onset in neonates and infants.[22] This group of etiology-based syndromes is a work in progress, and decisions on which entities should be included, as well as specific definitions, will be the task of a subsequent working group.

Finally, although autoimmune epilepsies other than Rasmussen syndrome were not included in this paper, some (including LGI1-antibody encephalitis) may meet the definition of an epilepsy syndrome. However, their specific clinical presentations are covered elsewhere.[26] These conditions further illustrate the importance of a focus on etiology, as their prompt recognition allows earlier, appropriate treatments to optimize outcome.

3.2 | How can we ensure the four IGEs are retained as a distinct subgroup of the broader group of genetic generalized epilepsies in our classification?

In the 1989 Proposal for Revised Classification of the Epilepsies and Epilepsy Syndromes, the IGEs were "defined by age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic etiology." The term "idiopathic" was defined as "no known or suspected etiology other than possible hereditary predisposition."[12] The 2017 Classification of the Epilepsies replaced the terms "idiopathic," "cryptogenic," and "symptomatic" with more straightforward language, defining six etiological categories: genetic, structural, metabolic, immune, infectious, and unknown.[13] It was acknowledged that the

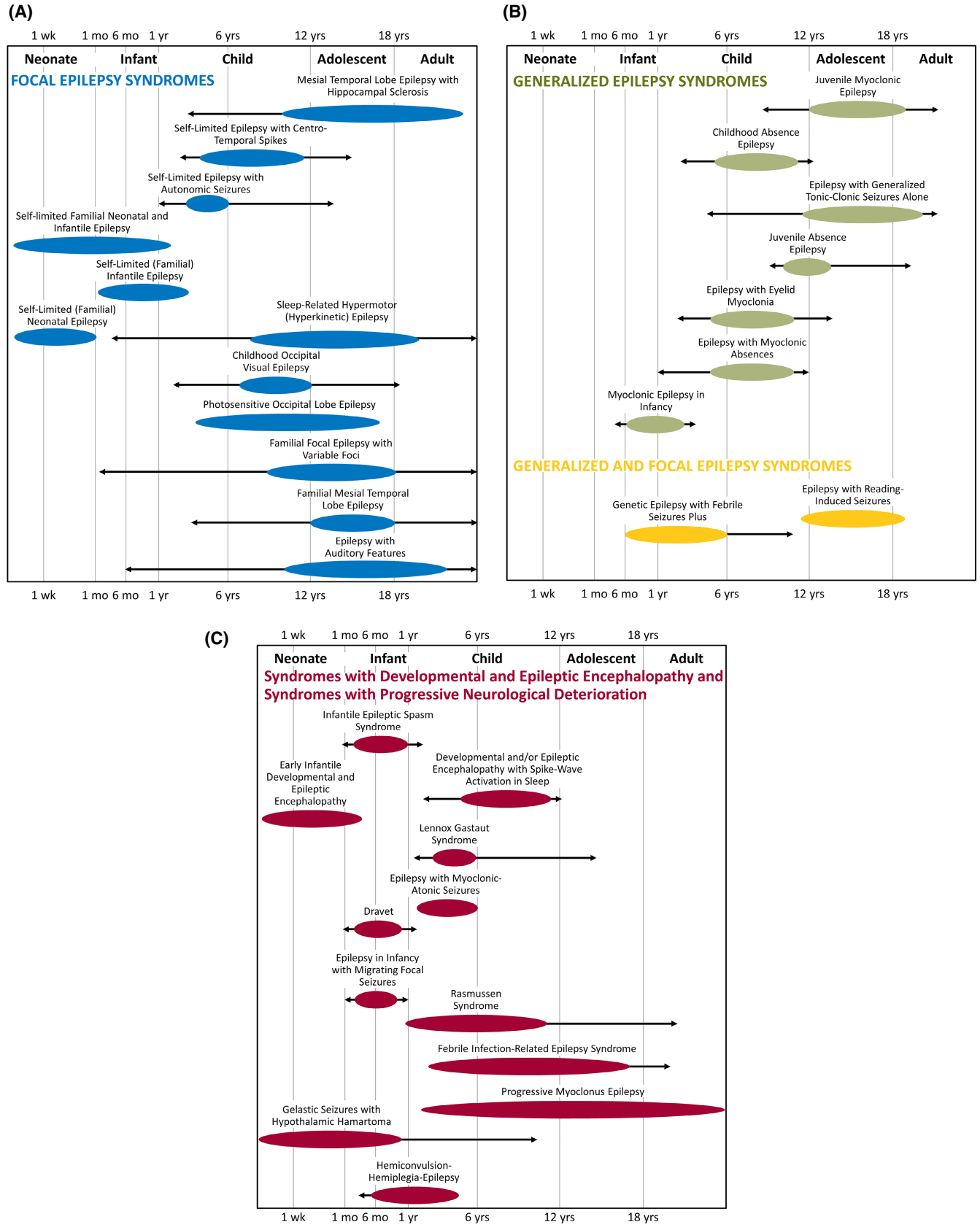

FIGURE 1 Classification of epilepsy syndromes, based on age at presentation. Shown are the typical ages of presentation, with ranges indicated by arrows. Focal epilepsy syndromes are indicated in blue, generalized epilepsy syndromes in green, focal and generalized syndromes in yellow, and syndromes with developmental and/or epileptic encephalopathy or with progressive neurological deterioration in red

TABLE 1 Epilepsy syndromes included in specific position papers

Position paper	Type of epilepsy			
	Focal	**Focal and/or generalized**	**Generalized**	**Syndromes with DEE or with progressive neurological deterioration**

Epilepsy syndromes with onset in neonates and infants[22]	• Self-limited (familial) neonatal epilepsy
	• Self-limited (familial) infantile epilepsy
	• Self-limited familial neonatal-infantile epilepsy
		• Genetic epilepsy with febrile seizures plus	• Myoclonic epilepsy in infancy	• Early infantile DEE
				• Epilepsy of infancy with migrating focal seizures
				• Infantile epileptic spasms syndrome
				• Dravet syndrome
				• Etiology-specific DEEs
				  • *KCNQ2*-DEE
				  • Pyridoxine-dependent and pyridox(am)ine 5′ phosphate deficiency DEE
				  • *CDKL5*-DEE
				  • *PCDH19* clustering epilepsy
				  • GLUT1DS-DEE
				  • Sturge–Weber syndrome
				  • Gelastic seizures with HH

Epilepsy Syndromes with onset in childhood[23]	Self-limited focal epilepsies • Self-limited epilepsy with centrotemporal spikes • Self-limited epilepsy with autonomic seizures • Childhood occipital visual epilepsy • Photosensitive occipital lobe epilepsy		• Epilepsy with myoclonic absences • Epilepsy with eyelid myoclonia	• Epilepsy with myoclonic–atonic seizures • Lennox–Gastaut syndrome • DEE or EE with spike-and-wave activation in sleep • Febrile infection-related epilepsy syndrome • Hemiconvulsion–hemiplegia–epilepsy
Epilepsy syndromes with onset at a variable age[24]	• Mesial temporal lobe epilepsy with hippocampal sclerosis • Familial mesial temporal lobe epilepsy • Sleep-related hypermotor (hyperkinetic) epilepsy • Familial focal epilepsy with variable foci • Epilepsy with auditory features	Epilepsy with reading-induced seizures		Rasmussen syndrome Progressive myoclonus epilepsies
Idiopathic generalized epilepsies[21]			• Childhood absence epilepsy • Juvenile absence epilepsy • Juvenile myoclonic epilepsy • Epilepsy with generalized tonic–clonic seizures alone	

Abbreviations: DEE, developmental and/or epileptic encephalopathy; EE, epileptic encephalopathy; GLUT1DS, glucose transporter 1 deficiency syndrome; HH, hypothalamic hamartoma.

TABLE 2 Epilepsy syndrome abbreviations

Syndrome group	Syndrome name	Abbreviation
Neonatal–infant	*CDKL5*-developmental and epileptic encephalopathy	*CDKL5*-DEE
	Dravet syndrome	DS
	Early infantile developmental and epileptic encephalopathy	EIDEE
	Epilepsy of infancy with migrating focal seizures	EIMFS
	Genetic epilepsy with febrile seizures plus	GEFS+
	Gelastic seizures with hypothalamic hamartoma	GS-HH
	Glucose transporter 1 deficiency syndrome	GLUT1DS
	Infantile epileptic spasm syndrome	IESS
	KCNQ2-developmental and epileptic encephalopathy	*KCNQ2*-DEE
	Myoclonic epilepsy in infancy	MEI
	Protocadherin 19 clustering epilepsy	*PCDH19* clustering epilepsy
	Pyridoxine-dependent (*ALDH7A1*) developmental and epileptic encephalopathy	PD-DEE
	Pyridox(am)ine 5′-phosphate deficiency (*PNPO*) developmental and epileptic encephalopathy	P5PD-DEE
	Self-limited familial neonatal–infantile epilepsy	SeLFNIE
	Self-limited infantile epilepsy	SeLIE
	Self-limited neonatal epilepsy	SeLNE
	Sturge–Weber syndrome	SWS
Child	Childhood occipital visual epilepsy	COVE
	Developmental and epileptic encephalopathy with spike-and-wave activation in sleep	DEE-SWAS
	Epileptic encephalopathy with spike-and-wave activation in sleep	EE-SWAS
	Epilepsy with eyelid myoclonia	EEM
	Epilepsy with myoclonic absences	EMA
	Epilepsy with myoclonic–atonic seizures	EMAtS
	Febrile infection-related epilepsy syndrome	FIRES
	Hemiconvulsion–hemiplegia epilepsy syndrome	HHE
	Lennox–Gastaut syndrome	LGS
	Photosensitive occipital lobe epilepsy	POLE
	Self-limited epilepsy with autonomic seizures	SeLEAS
	Self-limited epilepsy with centrotemporal spikes	SeLECTS
Idiopathic generalized epilepsies	Childhood absence epilepsy	CAE
	Epilepsy with generalized tonic–clonic seizures alone	GTCA
	Juvenile absence epilepsy	JAE
	Juvenile myoclonic epilepsy	JME
Variable age	Epilepsy with auditory features	EAF
	Epilepsy with reading-induced seizures	EwRIS
	Familial focal epilepsy with variable foci	FFEVF
	Familial mesial temporal lobe epilepsy	FMTLE
	Mesial temporal lobe epilepsy with hippocampal sclerosis	MTLE-HS
	Progressive myoclonus epilepsies	PME
	Rasmussen syndrome	RS
	Sleep-related hypermotor (hyperkinetic) epilepsy	SHE

well-recognized and common subgroup of the IGEs existed within the genetic generalized epilepsies. Evidence for a genetic basis is drawn from clinical research of family and twin studies and does not require that specific pathogenic variant(s) be identified. The 2017 Commission retained the term IGE specifically for the four epilepsy syndromes CAE, juvenile absence epilepsy (JAE), JME, and epilepsy with generalized tonic–clonic seizures alone (GTCA),[13] and proposed that either IGE or genetic generalized epilepsy could be used to describe these four syndromes.

Our Task Force noted that the majority of if not all epilepsy syndromes with only generalized seizures have a genetic or presumed genetic etiology, and thus would fall under the term genetic generalized epilepsy. We concurred with the 2017 report that IGE is not a syndrome on its own, but is a distinct subgroup of the genetic generalized epilepsies comprised solely of the syndromes CAE, JAE, JME, and GTCA. The IGEs are considered a specific group for the following reasons:

- They are the most common syndromes within the genetic generalized epilepsies.
- They generally have a favorable prognosis for seizure control.
- They do not evolve to a developmental and/or epileptic encephalopathy.
- There is clinical overlap between CAE, JAE, and JME. They may evolve with age to another syndrome in the IGE group (e.g., CAE evolving to JME).
- They have similar EEG findings, including a normal background activity with 2.5–6-Hz generalized spike-wave and/or polyspike-wave discharges that may activate with hyperventilation or photic stimulation.

It is recognized that there is genetic overlap between the IGEs and other genetic generalized epilepsy syndromes.[27–31] Furthermore, genetic epilepsy with febrile seizures plus (GEFS+) also has genetic overlap in families with IGE,[32] but is more phenotypically diverse, including focal seizures. Figure 2 illustrates the relationship between syndromes in the genetic generalized epilepsy group.

We recognize that many persons with genetic generalized epilepsy do not have a clearly defined epilepsy syndrome. They may have typical EEG features of normal background activity with 2.5–6-Hz generalized spike-wave or polyspike-wave discharges, which may activate with hyperventilation or photic stimulation, drug-responsive epilepsy, and no evolution to DEE. These individuals should be classified as having a genetic generalized epilepsy if they do not meet criteria for one of the four syndromes within the IGE group.

The syndromes in the IGE group are discussed in a separate paper,[21] which focuses on important distinguishing features of each, as well as addressing the areas of overlap.

3.2.1 | Modified Delphi process

Response rates (number of respondents who completed the survey divided by number of respondents who were sent the survey) for each syndrome from the first and second rounds of the Delphi ranged from 59%–69% and 57%–64%, respectively (Table S2).

Following both rounds of the Delphi process, consensus was achieved on nearly all proposed syndrome criteria, with the exception of one criterion for CAE, one criterion for MTLE-HS, and three criteria for self-limited familial neonatal–infantile epilepsy (SeLFNIE). Following discussion with the cochairs and working group members, and review of additional literature suggested by panelists, consensus for these items was achieved as follows:

- For CAE, “consistently unilateral focal spikes” was moved from the exclusionary to the alert category, as some children with CAE have been reported to also have centrotemporal spikes or sharp waves.
- For MLTE-HS, “complete and enduring seizure control achieved with ASMs” was removed from the alert category, as seizure control may be achieved for many years, and thus it was not deemed useful for diagnosis.
- For SeLFNIE, “sequential seizures” was moved from the exclusionary to the alert category, as there is inadequate information in the literature to confirm it is truly exclusionary; “a history of other acute symptomatic cause of seizures including intracranial infection, ischemic or hemorrhagic stroke, hypoxic–ischemic brain injury, significant metabolic disturbances” was moved to the alert category, as rare patients could have acute symptomatic seizures preceding onset of SeLFNIE; and in resource-limited regions, we have indicated that "SeLFNIE can be diagnosed without EEG and MRI in a neonate or infant with a family history suggestive of SeLFNIE who meets all other mandatory and exclusionary clinical criteria and has no alerts." However, we added a caution that the clinical history of affected family members should be consistent with the expected course for this syndrome, and furthermore, careful follow-up of the patient is required to ensure their course is also consistent with this syndrome. We have added similar statements to both self-limited neonatal and self-limited infantile epilepsy.

Based on the comments received by the *Epilepsia* reviewers and the public comments, the second Task Force included the description of one additional syndrome,

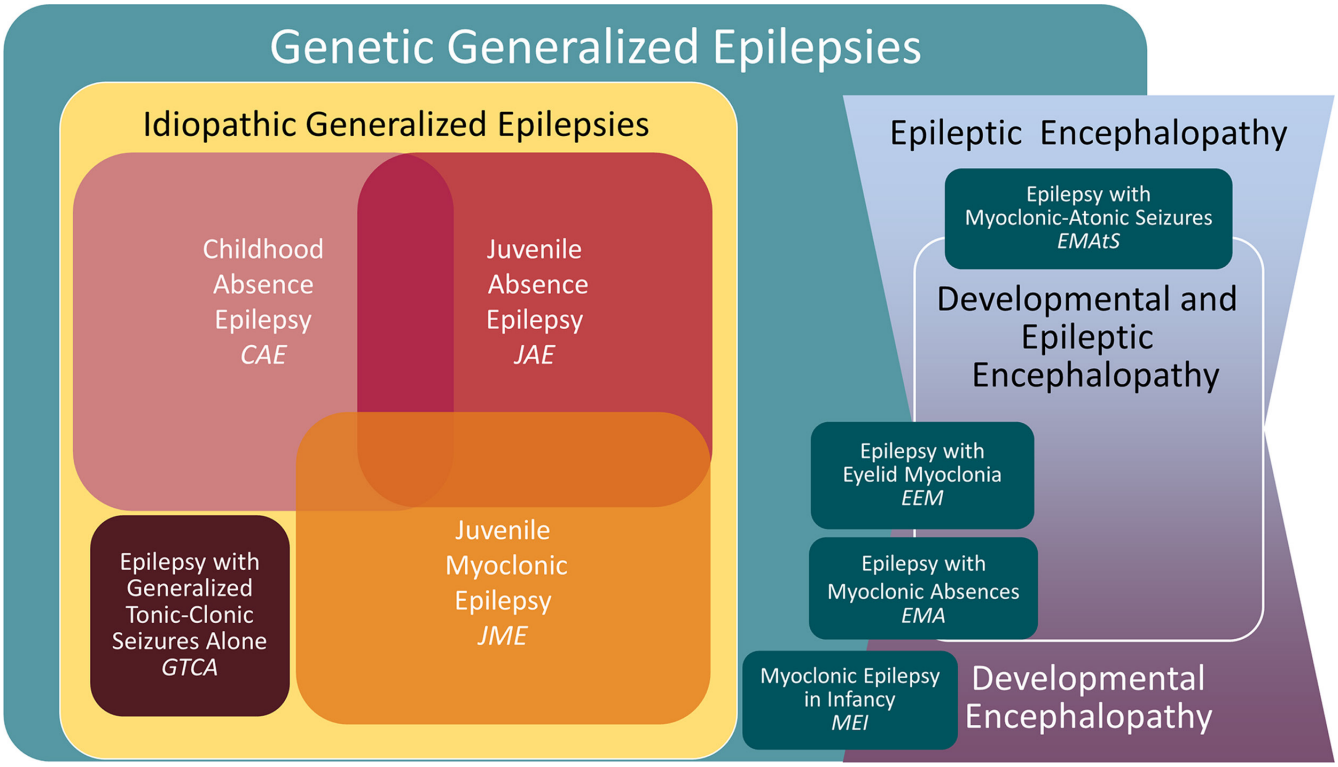

FIGURE 2 Concept of genetic generalized epilepsy (GGE) versus idiopathic generalized epilepsy (IGE). The IGEs are a subgroup of GGEs, comprised of the following four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone. These four syndromes may show some degree of overlap. In addition to the IGEs, GGEs include (1) individuals with generalized seizure types who do not meet criteria for a specific syndrome, and (2) less common generalized epilepsy syndromes. These latter syndromes also have a genetic basis and may occur in the setting of normal intellect or intellectual disability. Some present with an epileptic encephalopathy such as epilepsy with myoclonic–atonic seizures, whereas other syndromes, such as epilepsy with myoclonic absences and epilepsy with eyelid myoclonia, may be associated with a developmental and epileptic encephalopathy, an epileptic encephalopathy, or a developmental encephalopathy. Other syndromes such as myoclonic epilepsy in infancy may present as a generalized epilepsy in a child with a developmental encephalopathy (i.e., intellectual disability) or normal intellect

familial mesial temporal lobe epilepsy. The latter description and 27 other points added/modified in the revision process were included in the final (third) Delphi survey, which had a response rate of 58/67 (87%), and consensus was reached on all points. The diagnostic criteria and detailed summaries of each syndrome are discussed in the respective position papers.[21–24]

4 | DISCUSSION

Epilepsy syndromes have been recognized for >50 years, and their identification is critical in guiding investigations, selecting optimal therapy, and assisting with prognostic counseling on seizure outcome and comorbidities. Although both the 1985 and 1989 Classifications of the Epilepsies refer to the existence of syndromes, syndrome-specific diagnostic criteria have not been defined and subjected to a formal consensus process.[11,12] The major goal of our Task Force was to reach consensus regarding which entities met epilepsy syndrome criteria and then define each one, using a rigorous consensus-gathering process.

Our main goal was to identify criteria to assist with clinical diagnosis. For each epilepsy syndrome diagnosis, we describe the electroclinical picture, drawing together seizure type(s), typical age at onset, developmental course, comorbidities, possible antecedents, examination findings, EEG findings, and other investigations (imaging, genetic, metabolic, infectious, and immunological results). Based on these, we identified mandatory and exclusionary criteria. Additionally, we identified alerts for each syndrome, as we recognize that some individuals may have atypical features, which require careful clinical correlation prior to making a syndrome diagnosis. These mandatory and exclusionary criteria, as well as alerts, were carefully validated using a rigorous modified Delphi process. This process is a systematic method for compiling experience-based opinion from a group of experts, arriving at a high level of consensus that minimizes bias. We obtained input from all ILAE regions, as all members of our Task Force were included as panelists. Furthermore,

we identified recognized external experts in epilepsy syndromology, again representing all ILAE regions, and invited them to act as panelists. Finally, we sought public comment from the international epilepsy community on our proposal, and then created a second Task Force to critically address these comments and revise the position papers accordingly.

One of our guiding principles was to use descriptive names of syndromes as opposed to eponyms. We were successful in most cases; however, we elected to retain the terms "Dravet syndrome" and "Lennox–Gastaut syndrome" for several reasons. Most importantly, these terms are crucial in allowing patients to acquire the multiple supportive therapies that they require on a daily basis. Replacing this term would lead to a lapse in services that these patients critically require. Additionally, both of these syndromes comprise multiple seizure types, and Lennox–Gastaut syndrome comprises several etiologies that would be challenging to capture in a succinct name. We also retained the term "Rasmussen syndrome," because the Task Force was unable to propose a unifying alternative to this well-established term that could explain the nature of this multifaceted condition, that is, the epilepsy, the neurological deficits, the cognitive/language impact, the imaging, and the unknown etiology of the hemispheric atrophy.

We recognized that some syndromes may have specific clinical features that are required for diagnosis but can take time to evolve. Many of these are associated with drug-resistant epilepsy and other comorbidities, such as Rasmussen syndrome or Lennox–Gastaut syndrome. As we see the increased development of precision-based therapies, identifying these syndromes early in their course will be crucial. Thus, we propose the term "syndrome-in-evolution" for cases early on in their epilepsy course, who show clear evidence that they are evolving to one of these syndromes but lack all mandatory criteria.

Additionally, we recognize that access to many investigations may be limited in certain regions of the world. Some syndromes can be diagnosed with reasonable accuracy using clinical criteria alone; however, for most, combining the EEG and clinical findings will refine diagnostic precision. For each syndrome, we identified the minimum criteria for diagnosis in resource-limited regions, which have little or no access to EEG, advanced neuroimaging, or genetic studies, and designated these as "syndrome without laboratory confirmation." This term should be utilized solely in resource-limited regions, and as much as possible, confirmation of the syndrome with appropriate studies should be strongly encouraged.

Although the diagnosis of a specific epilepsy syndrome may have therapeutic implications, we have not included specific treatment recommendations. Evidence-based, comparative trials of ASMs for most syndromes are lacking, and the availability of therapies varies significantly across regions. However, we did specify when exacerbation of seizures by certain ASMs can provide a clue to diagnosis of a specific syndrome. Furthermore, we identified those syndromes with high likelihood of drug resistance but favorable response to epilepsy surgery, to prompt early referral to a comprehensive epilepsy center. Importantly, with increased identification of the underlying etiology of specific epilepsy syndromes, precision medical or genetic therapies will be developed. Early recognition may be critical to optimize long-term outcomes.

Syndromes have been divided based on age at onset. However, many syndromes that begin in infancy or childhood are lifelong; thus, they should not be thought of solely as pediatric syndromes.

We propose the term “etiology-specific epilepsy syndromes” to describe syndromes in which there is a specific etiology for the epilepsy that is associated with a clearly defined, relatively uniform, and distinct clinical phenotype in most affected individuals (clinical presentation, seizure types, comorbidities, and natural history, and at times, response to specific therapies), as well as consistent EEG, neuroimaging, and/or genetic results. Conversely, other specific etiologies cause a diverse range of syndromes or epilepsy types, such as tuberous sclerosis complex (which can present in early life with infantile spasms syndrome and Lennox–Gastaut syndrome, or at any time with multifocal or focal epilepsy) or epilepsies due to *SCN1A* pathogenic variants (febrile seizures, GEFS+, Dravet syndrome), and thus would not be considered in this group. Given the significant advances in the genetics, neuroimaging, and immunological fields, we will continue to identify new etiologies with distinct phenotypes. The etiology-specific epilepsy syndromes should be considered a work in progress. As we progress into the era of precision medicine, we must ensure our classification system can encompass this complexity to facilitate prompt access to the most effective therapies to minimize or eliminate seizures as well as attenuate or prevent comorbidities.

In conclusion, we hope that this work will allow clearer recognition of epilepsy syndromes across all ages, in both resource-equipped and resource-limited regions, to improve understanding of the expected natural history, and choice of optimal investigations and therapies. The definitions for epilepsy syndromes provided in these position papers will require validation in longitudinal studies and may be further refined as new data are published.

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CONFLICT OF INTEREST

E.C.W. has served as a paid consultant for Encoded Therapeutics and BioMarin. She is the Editor-in-Chief of Epilepsy.com. R.N. has served as principal investigator in clinical trials for Novartis, Nutricia, Eisai, UCB, GW Pharma, and LivaNova. She has received consulting fees from Biogene, BioMarin, GW Pharma, Zogenix, Novartis, Nutricia, Stoke, Ionis, Targeon, and Takeda and honoraria from Nutricia, Biocodex, Zogenix, GW Pharma, Advicennes, and Eisai. She received unrestricted research grants from Eisai, UCB, LivaNova, and GW Pharma and academic research grants from EJP-RD (Horizons 2020) and IDEAL-EPISTOP. I.E.S. has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, Chiesi, Encoded Therapeutics, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, BioMarin, and Eisai; has served as an investigator for Zogenix, Zynerba, Ultragenyx, GW Pharma, UCB, Eisai, Anavex Life Sciences, Ovid Therapeutics, Epigenyx, Encoded Therapeutics, and Marinus; and has consulted for Zynerba Pharmaceuticals, Atheneum Partners, Ovid Therapeutics, Care Beyond Diagnosis, Epilepsy Consortium, and UCB. T.A. has received consultation fees from Ely Lilly, Lundbeck, Merck, Hikma, Novartis, and Sanofi, and research support from Novartis and Biogen. J.A.F. receives NYU salary support from the Epilepsy Foundation and for consulting work and/or attending scientific advisory boards on behalf of the Epilepsy Study Consortium for Adamas, Aeonian/Aeovian, Anavex, Arkin Holdings, Arvelle Therapeutics, Athenen Therapeutics/Carnot Pharma, Baergic Bio, Biogen, BioXcel Therapeutics, Cavion, Cerebral Therapeutics, Cerevel, Crossject, CuroNZ, Eisai, Eliem Therapeutics, Encoded Therapeutics, Engage Therapeutics, Engrail, Epiminder, Equilibre BioPharmaceuticals, Fortress Biotech, Greenwich Biosciences, GW Pharma, Janssen Pharmaceutica, Knopp Biosciences, Lundbeck, Marinus, Mend Neuroscience, Merck, NeuCyte, Neurocrine, Otsuka Pharmaceutical Development, Ovid Therapeutics, Passage Bio, Praxis, Redpin, Sage, SK Life Sciences, Sofinnova, Stoke, Supernus, Synergia Medical, Takeda, UCB, West Therapeutic Development, Xenon, Xeris, Zogenix, and Zynerba. J.A.F. has also received research support from the Epilepsy Research Foundation, Epilepsy Study Consortium (funded by Andrews Foundation, Eisai, Engage, Lundbeck, Pfizer, SK Life Science, Sunovion, UCB, Vogelstein Foundation), Epilepsy Study Consortium/Epilepsy Foundation (funded by UCB, Engage, Neurelis, SK Life Science), GW/One8 Foundation/FACES, and NINDS. She is on the editorial board of *Lancet Neurology* and *Neurology Today*. She is Chief Medical/Innovation Officer for the Epilepsy Foundation, for which NYU receives salary support. She has received travel reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Arvelle Therapeutics, Biogen, Cerevel, Engage, Lundbeck, NeuCyte, Otsuka, Sage, UCB, Xenon, and Zogenix. E.H. has received honoraria from UCB, Eisai, LivaNova, Novartis, and GW Pharmaceuticals. S.K. has served as principal investigator in clinical trials for UCB, Eisai, and SK. He has served on scientific advisory boards for Kyowa Hakko and Eisai. K.R. has received speaker honoraria, advisory board payments, and/or research funding from UCB, Eisai, Novartis, Zogenix, SK Lifesciences, AFT Pharmaceuticals, LivaNova, Queensland Genomic Health Alliance, Department of Health (Australia), Medicure International, Novartis, and Janssen-Cilag. E.S. reports research support from Eisai, UCB, Zynerba, Marinus, SK Life Sciences, Upsher-Smith, Cerevel, National Health and Medical Research Council of Australia, and Australian Research Council. He received support for educational activities from Sanofi, UCB, and ILAE. He reports speaker's fees from Eisai and the Epilepsy Consortium and consulting fees from Eisai, UCB, and Seqirus. N.S. has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Eisai, BioMarin, LivaNova, and Sanofi; and has served as an investigator for Zogenix, Marinus, BioMarin, UCB, and Roche. E.T. reports personal fees from EVER Pharma, Marinus, Argenix, Arvelle, Medtronic, Bial–Portela & C[a], NewBridge, GL Pharma, GlaxoSmithKline, Hikma, Boehringer Ingelheim, LivaNova, Eisai, UCB, Biogen, Genzyme Sanofi, GW Pharmaceuticals, and Actavis; his institution received grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Österreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank outside the submitted work. S.M.Z. has received

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SUPPORTING INFORMATION

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

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