Methodology for Classification and Definition of Epilepsy Syndromes: Report of the ILAE Task Force on Nosology and Definitions

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Summary

Epilepsy syndromes have been recognized for more than 50 years, as distinct electroclinical phenotypes with therapeutic and prognostic implications. Yet, no formally accepted 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 provide definitions for each syndrome. We defined an epilepsy syndrome as *"a characteristic cluster of clinical and EEG features, often supported by specific etiological findings"*, noting that syndromes often have age-dependent presentations and a range of specific comorbidities. This paper describes the guiding principles and process for syndrome identification, and the template of clinical data included for each syndrome. We divided syndromes into typical age at presentation, and further characterized them based on seizure and epilepsy types and association with developmental and epileptic encephalopathy.

Historical overview of the concept of an epilepsy syndrome

Epilepsy syndromes were recognized as distinctive conditions long before the first ILAE Classification of Epilepsies and Epilepsy Syndromes was proposed in 1985. 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 EEG pattern of hypsarrhythmia in 1952[2]. Lennox recognized the characteristic EEG pattern of Lennox-Gastaut syndrome in 1950, which was followed by Gastaut and colleagues publishing the first electroclinical description in 1966[3, 4]. Childhood absence epilepsy was first described by Tissot in 1770[5]. The term "pyknolepsy" was first 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 were known as the "Guide Bleu", published in 1984[9].

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[10]. These signs and symptoms may be clinical (ie history, seizure type, modes of seizure recurrence, and neurological and psychological findings) or findings detected by ancillary studies (eg EEG, x-ray, CT and MRI)." Syndromes were not thought to necessarily have a single etiology and prognosis. Some syndromes were considered to

represent broad concepts (ie "sleep-related grand mal"), whereas others were much more specific (e.g. Juvenile Myoclonic Epilepsy).

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[11]. Again, it was noted that some syndromes may evolve from one to another, such as Infantile Spasms evolving to Lennox-Gastaut syndrome[11].

The ILAE Commission for Classification and Terminology published updated position papers on both the Classification of the Epilepsies as well as an Operational Classification of Seizure Types in 2017[12-14]. The revised framework for classification of the epilepsies uses a multilevel approach (Figure 1) 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"[12]. 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 while an epilepsy syndrome may have associated etiologic implications, there was no clear one-to-one correlation with an underlying etiologic diagnosis. Both etiology and epilepsy syndrome diagnosis are useful and complementary pieces of the diagnostic puzzle, informing optimal management and prognosis.

While many well-recognized syndromes were included in both the 1985 and 1989 proposals[10, 11], 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.

Methods:

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, carries prognostic and treatment implications. Syndromes often have age-dependent presentations and a range of specific co-morbidities.

The ILAE website, epilepsydiagnosis.org, which had been recently developed as an educational resource, contained detailed information on well-established epilepsy syndromes, and provided an excellent starting point for our work. Epilepsy syndromes have traditionally been grouped according to age at onset, and we established small working groups with the following divisions: (1) Neonatal and Infantile onset, (2) Childhood onset, and (3) Adolescent/ Adult and Variable age at onset, as well as (4) Idiopathic Generalized Epilepsies. Our group then established guiding principles, as well as a template outlining which clinical data should be included for each syndrome. Discussion of each template was based on literature review and when literature was not fully available or contradictory, the description was based on clinical expertise.

a. Guiding Principles:

1. The main goal was to define epilepsy syndromes using terminology consistent with the 2017 Classification of the Epilepsies and Seizure types[12, 13] 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" to alert the clinician to features that were rarely seen in a syndrome but were not exclusionary.
2. This resource should be available world-wide 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.

b. 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 including antenatal and perinatal factors as well as preceding febrile seizures, cognition and development at presentation and neurologic examination at presentation
- Natural history including evolution from or to other syndromes, overall response to antiseizure medications 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, 0.7-2% of children without epilepsy have centrotemporal spikes, consistent with a self-limited focal epilepsy[15 16] and generalized spike-

wave discharge can be seen in up to 3.6% of persons without epilepsy[17]. Thus, the presence of such discharges must be interpreted in the context of the entire electroclinical picture.

- Neuroimaging findings
- Genetic findings
- 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.

Process of Defining Each Syndrome

Each of the working groups reviewed the current syndromes listed under epilepsydiagnosis.org for their defined age-group, to determine if 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 of "Epileptic Syndromes of Infancy, Childhood and Adolescence"[18]
- Current criteria listed on epilepsydiagnosis.org
- Expert opinion from current Task Force members

One member of the working group drafted the template of each syndrome. The draft was circulated to all members of that specific working group for comments, and each component discussed in detail, either at an on-line meeting, or an in-person meeting of Task Force members, which was held in conjunction with either the American Epilepsy Society 2018 and 2019, the European Congress of Epileptology 2018 or the International Epilepsy Congress 2019. 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. The number of Task Force group participants who provided comments was variable but exceeded 4 experts for each syndrome. Any areas of disagreement were discussed in further detail, and where necessary, additional literature searches were performed. Based on this feedback, amendments to each syndrome template were made, and the final proposal again submitted electronically to all Task Force members for their final comments. Each syndrome template was then finalized by the appropriate Working group.

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 in order to diagnose the syndrome. If a mandatory criterion is absent, the syndrome cannot be diagnosed.
> ***Alerts***: Criteria that are absent in the vast majority of cases within 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.
> ***Exclusionary***: Criteria that must be absent in order to diagnose the syndrome. If an exclusionary criterion is present, the syndrome cannot be diagnosed.

We used a modified Delphi process[19] to achieve consensus on the criteria for each syndrome. The panel participants were comprised of all Nosology 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 Task Force members. We included additional members from each of the six ILAE regions (4 each from Europe and Oceania/Asia, 3 each from North America and Latin America, 2 from Africa and 1 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 Delphi panel included a total of 54 panelists.

Pediatric epilepsy panelists were asked to rate criteria for all epilepsy syndromes, whereas syndromes that typically remitted in infancy or childhood were not rated by adult epilepsy panelists.

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, alert or exclusionary on a 9-point Likert scale (where 1 is “strongly disagree”, and 9 is “strongly agree”, with a no judgement option to reflect “no opinion”). Panelists were given space for additional comments and asked to provide comments for any criterion rated as lower than 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 those showing discordance were reviewed by the appropriate working group, with careful consideration of the panelist comments. If needed, amendments were made based on these comments, and these were included in the next iteration 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 re-score the item, based on their opinion and how they interpret 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 Task Force, including the Co-Chairs, 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 Encephalitis 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, 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.

We sought to use clear terminology that could be readily translated into different languages, for ease of use by the international community.

Results:

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 developmental and epileptic encephalopathy syndromes). Position papers that arose from each working group include:

- Idiopathic Generalized Epilepsies[20]
- Epilepsy Syndromes with Onset in Neonates and Infants[21]
- Epilepsy syndromes with Onset in Childhood[22]
- Epilepsy Syndromes with Onset in Adolescents, Adults or at Variable Ages[23]

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

1. <u>Do we include the increasing number of etiology-specific epilepsies, with a distinct phenotypic spectrum as syndromes?</u>

We propose including Etiology-specific Syndromes as syndromes, if they have, in the majority of patients, a distinctive phenotypic spectrum that is caused by a single etiology, which 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"[24], namely mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS), Rasmussen Encephalitis, 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 with HS and Rasmussen Encephalitis are included in the Epilepsy Syndromes with Onset in Adolescents, Adults and at Variable Ages[23], HHE is included in the Epilepsy Syndromes with onset in Childhood[22] and Gelastic Seizures with Hypothalamic Hamartoma are included in the Epilepsy Syndromes with onset in Neonates and Infants[21].

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, GLUT1DS-DEE and *KCNQ2*-DEE. These are included in the paper on Epilepsy Syndromes with onset in Neonates and Infants[21]. 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.

We excluded autoimmune epilepsies apart from Rasmussen Encephalitis, as these are considered acute symptomatic seizures[25].

2. <u>How can we ensure the group of the four *Idiopathic Generalized Epilepsies (IGEs)* are retained as a distinct subgroup of the broader group of *Genetic Generalized Epilepsies (GGEs)* in our classification?</u>

In the 1989 Proposal for Revised Classification of the Epilepsies and Epilepsy Syndromes, the idiopathic generalized epilepsies 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"[11]. 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[12]. It was acknowledged that the well-recognized and common subgroup of the *IGEs* existed within the GGEs. Evidence for a genetic basis is drawn from clinical research of family and twin studies and does not require that specific genetic mutation(s) be identified. The 2017 Commission retained the term *IGE* specifically for the four epilepsy syndromes of Childhood Absence Epilepsy, Juvenile Absence Epilepsy,

Juvenile Myoclonic Epilepsy and Epilepsy with Generalized Tonic Clonic Seizures Alone[12] and proposed that either *IGE* or GGE could be used to describe these four syndromes.

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

- They are the most common syndromes within the GGEs.
- They generally have a good prognosis for seizure control.
- They do not evolve to a developmental and epileptic encephalopathy.
- There is clinical overlap between CAE, JAE and JME. They may evolve with age to another syndrome in the IGE group, i.e. Childhood Absence Epilepsy evolving to Juvenile Myoclonic Epilepsy.
- They have similar EEG findings, including a normal background activity with 3-6 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 GGE syndromes[26-30]. Furthermore, genetic epilepsy with febrile seizures plus also has genetic overlap in families with *IGE* [31], but is more phenotypically diverse, including focal seizures. Figure 2 illustrates the relationship between syndromes in the GGE group.

We recognize that many persons with GGE do not have a clearly defined epilepsy syndrome. They may have typical EEG features of normal background activity with 3-6 Hz generalized spike-wave or polyspike-wave discharges, which may activate with hyperventilation or photic stimulation, drug-responsive epilepsy and no evolution to developmental or epileptic encephalopathy. These individuals should be classified as having a GGE 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[20], which focuses on important distinguishing features of each, as well as addressing the areas of overlap.

3. 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 (Supplementary Table 1).

Following both rounds of the Delphi process, consensus was achieved on nearly all proposed syndrome criteria, with the exception of one criterion for childhood absence epilepsy, one criterion for mesial temporal lobe epilepsy with hippocampal sclerosis and three criteria for self-

limited neonatal-infantile epilepsy (familial and non-familial). Following discussion with the Co-Chairs and working group members, and review of additional literature suggested by panelists, consensus for these items was achieved as follows:

- For childhood absence epilepsy, "consistently unilateral focal spikes" was moved from Exclusionary to Alert, as some children with childhood absence epilepsy have been reported to also have centrotemporal spikes or sharp waves.
- For mesial temporal lobe epilepsy with hippocampal sclerosis, "complete and enduring seizure control achieved with antiseizure medicine" 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 self-limited neonatal-infantile epilepsy (SeLNIE):
    - "sequential seizures" was moved from Exclusionary to Alert, 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 Alert, as rare patients could have acute symptomatic seizures preceding onset of SeLNIE.
    - In resource limited regions, we have indicated that "Self-limited neonatal-infantile epilepsy can be diagnosed without EEG and MRI in a neonate or infant with a family history suggestive of familial self-limited neonatal-infantile epilepsy 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 epilepy.

The diagnostic criteria and detailed summaries of each syndrome are discussed in the respective papers from our Task Force[20-23].

Discussion:

Epilepsy syndromes have been recognized for over 50 years and their identification is critical in guiding investigations, selecting optimal therapy, and assisting with prognostic counselling on seizure outcome and comorbidities. While 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[10, 11]. 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, exam findings, EEG findings and other investigations (imaging, genetic, metabolic, infectious and immunological results). Based on that, we identified mandatory and exclusionary criteria. Additionally, we identified Alerts for each syndrome, as we recognize that many 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.

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 pharmaco-resistant epilepsy and other comorbidities, such as Rasmussen Encephalitis 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.

While the diagnosis of a specific epilepsy syndrome may have therapeutic implications, we have not included specific treatment recommendations. Evidence-based, comparative trials of antiseizure medications for most syndromes are lacking and the availability of therapies varies significantly across regions. However, we did specify when exacerbation of seizures by certain antiseizure medications 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 surgical 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.

Our Task Force proposed the term "*Etiology-Specific Epilepsy Syndromes*" to describe syndromes in which there is a specific etiology, which have 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 genetic results. Conversely, other specific etiologies cause a varied range of syndromes or epilepsy types, such as tuberous sclerosis complex (infantile spasms syndrome, Lennox-Gastaut syndrome, 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 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 ensure patients with epilepsy have prompt access to the most effective therapies to minimize or eliminate seizures as well as attenuate or prevent comorbidities.

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Table 1: Epilepsy Syndromes Included in Specific Position Papers

	Type of Epilepsy			
Position Paper	**Focal**	**Focal and/or Generalized**	**Generalized**	**Developmental and Epileptic Encephalopathy Syndromes (DEEs)**

Epilepsy Syndromes with Onset in Neonates and Infants[21]	• 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 Spasms Syndrome
				• Dravet Syndrome
				• Etiology-specific DEEs
				  • KCNQ2-DEE
				  • Pyridoxine/P5P dependent-DEE
				  • *CDKL5*-DEE
				  • *PCDH19* Clustering Epilepsy
				  • GLUT1DS-DEE
				  • Sturge-Weber syndrome
				  • Gelastic seizures with HH

Epilepsy Syndromes with Onset in Childhood[22]	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	• Myoclonic-Atonic Epilepsy • Lennox-Gastaut Syndrome • DEE with spike-wave activation in sleep • Febrile infection related epilepsy syndrome (FIRES) • Hemiconvulsion-Hemiplegia-Epilepsy (HHE)
Epilepsy Syndromes with Onset in Adolescents, Adults and at Variable Ages[23]	• Mesial Temporal Lobe Epilepsy with HS • Sleep-Related Hypermotor Epilepsy • Familial Focal Epilepsy with Variable Foci • Epilepsy with Auditory Features	Epilepsy with Reading induced seizures		• Rasmussen Encephalitis • Progressive Myoclonic Epilepsies
Idiopathic Generalized Epilepsies[20]			• Childhood Absence Epilepsy • Juvenile Absence Epilepsy • Juvenile Myoclonic Epilepsy • Generalized Tonic Clonic Seizures Alone	

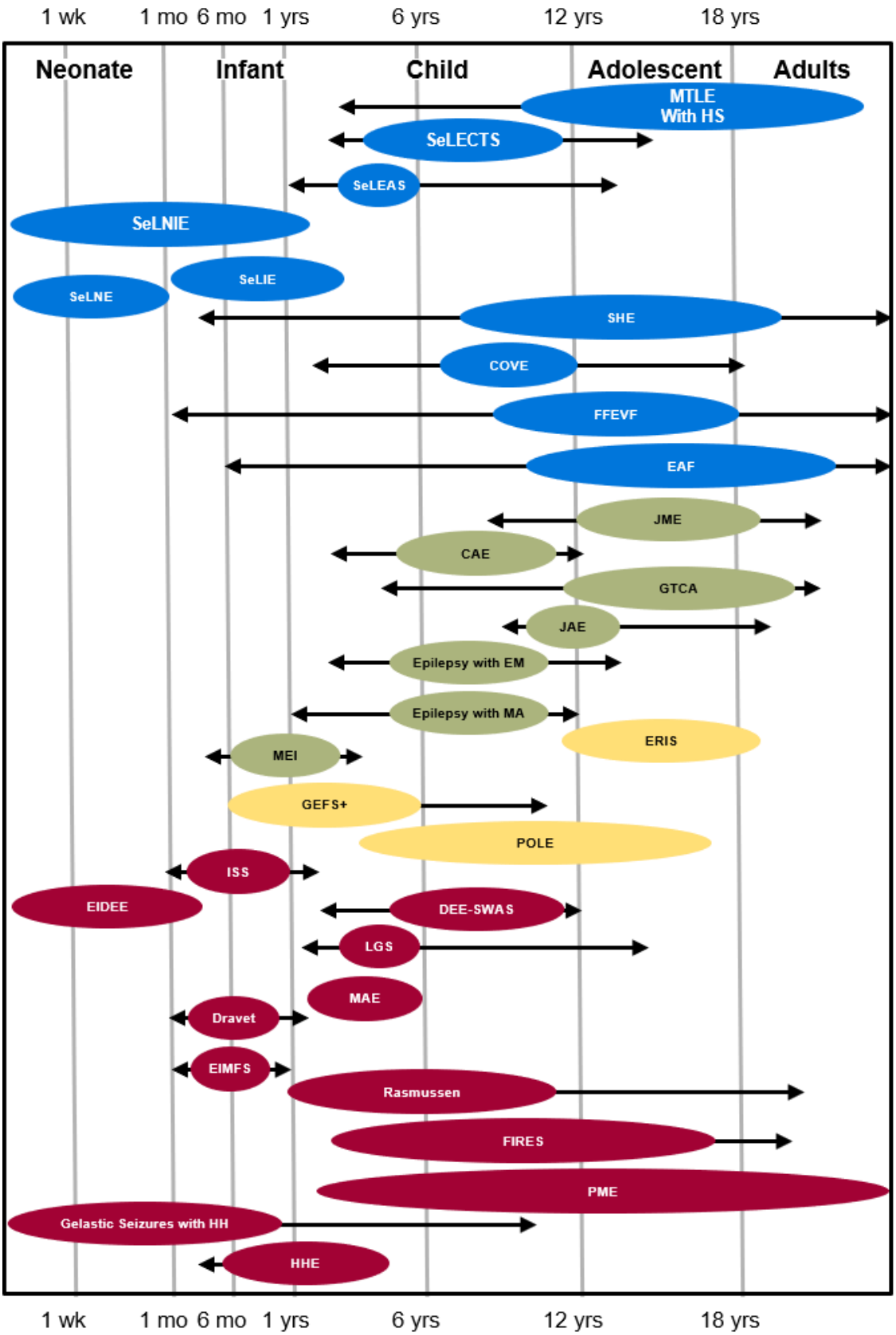
Supplemental Table 1: Response rates for Delphi Surveys, for each syndrome

Syndrome	Response rate Survey #1 (%)	Response rate Survey #2
Neonatal/Infantile onset		
• Self-limited Neonatal Epilepsy (Familial and Non-familial)	24/36 (67)	23/36 (64)
• Self-limited Infantile Epilepsy (Familial and Non-familial)	24/36 (67)	NA
• Self-limited Neonatal Infantile Epilepsy (Familial and Non-familial)	NA	23/36 (64)
• Genetic epilepsy with Febrile Seizures Plus	35/54 (65)	31/54 (57)
• Myoclonic epilepsy in infancy	24/36 (67)	NA
• Early infantile DEE	23/36 (64)	23/36 (64)
• Epilepsy in Infancy with Migrating Focal Seizures	23/36 (64)	23/36 (64)
• Infantile Spasms Syndrome	23/36 (64)	23/36 (64)
• Dravet Syndrome	23/36 (64)	NA
• KCNQ2 DEE	23/36 (64)	23/36 (64)
• Pyridoxine/P5P dependent DEE	23/36 (64)	NA
• CDKL5 DEE	23/36 (64)	NA
• PCDH19 Clustering Epilepsy	23/36 (64)	NA
• GLUT1 DEE	23/36 (64)	NA
• Sturge-Weber syndrome	23/36 (64)	NA
• Gelastic seizures with hypothalamic hamartoma	23/36 (64)	23/36 (64)
	23/36 (64)	NA
Childhood-onset		
• Self-limited Epilepsy with Centrotemporal Spikes	24/36 (67)	23/36 (64)
• Self-limited Epilepsy with Autonomic Seizures	24/36 (67)	23/36 (64)
• Childhood Occipital Visual Epilepsy	35/54 (65)	NA
• Photosensitive Occipital Lobe Epilepsy	35/54 (65)	NA
• Epilepsy with Myoclonic Absences	35/54 (65)	31/54 (57)
• Epilepsy with Eyelid Myoclonia	35/54 (65)	31/54 (57)
• Myoclonic-Atonic Epilepsy	22/36 (61)	23/36 (64)
• Lennox-Gastaut Syndrome	32/54 (59)	31/54 (57)
• DEE with spike-wave activation in sleep	22/36 (61)	23/36 (64)
• Febrile infection related epilepsy syndrome (FIRES)	32/54 (59)	31/54 (57)
• Hemiconvulsion-Hemiplegia-Epilepsy (HHE)	22/36 (61)	23/36 (64)
Adolescent/Adult/Variable age		
• Mesial Temporal Lobe Epilepsy with HS	37/54 (69)	31/54 (57)
• Sleep-Related Hypermotor Epilepsy	37/54 (69)	31/54 (57)
• Familial Focal Epilepsy with Variable Foci	37/54 (69)	31/54 (57)
• Epilepsy with Auditory Features	37/54 (69)	31/54 (57)
• Epilepsy with Reading-Induced Seizures	37/54 (69)	31/54 (57)
• Rasmussen Encephalitis	37/54 (69)	31/54 (57)
• Progressive Myoclonic Epilepsies	37/54 (69)	NA

Idiopathic Generalized Epilepsies • Childhood Absence Epilepsy • Juvenile Absence Epilepsy • Juvenile Myoclonic Epilepsy • Generalized Tonic Clonic Seizures Alone	 35/54 (65) 35/54 (65) 35/54 (65) 35/54 (65)	 31/54 (57) 31/54 (57) 31/54 (57) 31/54 (57)

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 **Developmental and Epileptic Encephalopathy Syndromes** in red.


1 wk
1 mo
6 mo
1 yrs
6 yrs
12 yrs
18 yrs
Neonate
Infant
Child
Adolescent
Adults
MTLE With HS
SeLECTS
SeLEAS
SeLNIE
SeLIE
SeLNE
SHE
COVE
FFEVF
EAF
JME
CAE
GTCA
JAE
Epilepsy with EM
Epilepsy with MA
ERIS
MEI
GEFS+
POLE
ISS
EIDEE
DEE-SWAS
LGS
MAE
Dravet
EIMFS
Rasmussen
FIRES
PME
Gelastic Seizures with HH
HHE
1 wk
1 mo
6 mo
1 yrs
6 yrs
12 yrs
18 yrs

CAE - Childhood Absence Epilepsy

COVE - Childhood Occipital Visual Epilepsy

DEE-SWAS – Developmental Epileptic Encephalopathy with Spike-Wave Activation in Sleep

GTCA - Generalized Tonic-Clonic Seizures Alone

EIDEE - Early Infantile Developmental and Epileptic Encephalopathy

EIMFS - Epilepsy of Infancy with Migrating Focal Seizures

Epilepsy with EM - Epilepsy with Eyelid Myoclonia

Epilepsy with MA - Epilepsy with Myoclonic Absences

ERIS – Epilepsy with Reading-Induced Seizures

FFEVF - Familial Focal Epilepsy with Variable Foci

FIRES - Febrile Infection Related Epilepsy Syndrome

GEFS+ - Genetic Epilepsy with Febrile Seizures Plus

Gelastic Seizures with HH - Gelastic Seizures with Hypothalamic Hamartoma

HHE – Hemiconvulsion-Hemiplegia-Epilepsy syndrome

POLE - Photosensitive Occipital Lobe Epilepsy

ISS - Infantile Spasm Syndrome

JAE - Juvenile Absence Epilepsy

JME - Juvenile Myoclonic Epilepsy

LGS - Lennox Gastaut Syndrome

MAE – Myoclonic-Atonic Epilepsy

MEI - Myoclonic Epilepsy in Infancy

MTLE with HS- Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis

PME - Progressive Myoclonic Epilepsy

SeLEAS - Self-Limited Epilepsy with Autonomic Seizures

SeLECTS - Self-Limited Epilepsy with Centro-Temporal Spikes

SHE - Sleep Related Hypermotor Epilepsy

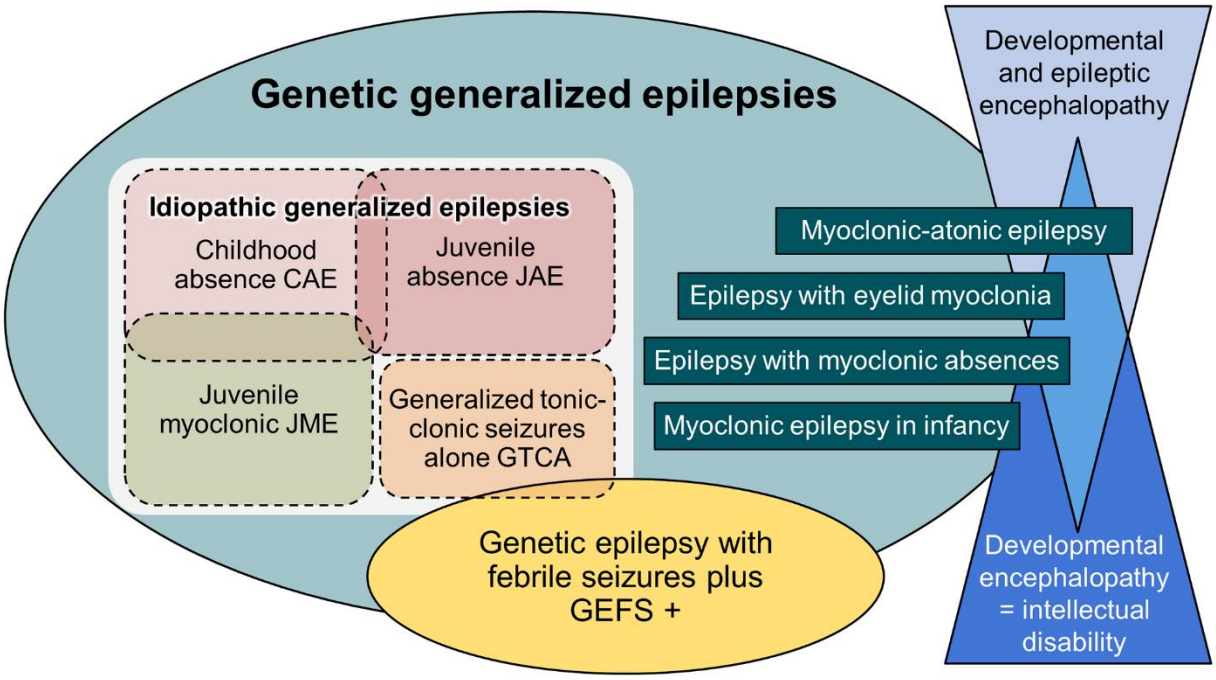
SeLIE - Self-Limited (Familial) Infantile Epilepsy

SeLNE - Self-Limited (Familial) Neonatal Epilepsy

SeLNIE – Self-limited (Familial) Neonatal and Infantile Epilepsy

Figure 2: Concept of Genetic Generalized Epilepsy versus Idiopathic Generalized Epilepsy

The IGEs are a specific subgroup of Genetic Generalized Epilepsies, comprised solely of CAE, JAE, JME and GTCA. In addition to the IGEs, Genetic Generalized Epilepsies include (1) individuals with generalized seizure types and generalized 2.5-5.5 spike-wave discharge on EEG who do not meet criteria for a specific syndrome, and (2) syndromes which have genetic overlap with the IGE syndromes but may also, at times, be associated with DEEs, such as Myoclonic-Atonic Epilepsy, Epilepsy with Myoclonic Absences and Epilepsy with Eyelid Myoclonia; other syndromes such as Myoclonic Epilepsy in Infancy are more consistent with a generalized epilepsy which may have a developmental encephalopathy (ie. intellectual disability). Additionally, certain cases of GEFS+, with only generalized seizure types could be classified as GGEs, but individuals with GEFS+ and focal seizures would not be included. The triangles denote individuals with generalized epilepsies and developmental delay/intellectual disability (dark blue) and those with DEEs (light blue). The distinction between these two groups is that patients with DEEs have developmental slowing or regression with frequent epileptiform activity on EEG and/or frequent seizures.



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