An overview of International League Against Epilepsy(ILAE) definitions of Epilepsy and Epilepsy Syndromes

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Disclosure

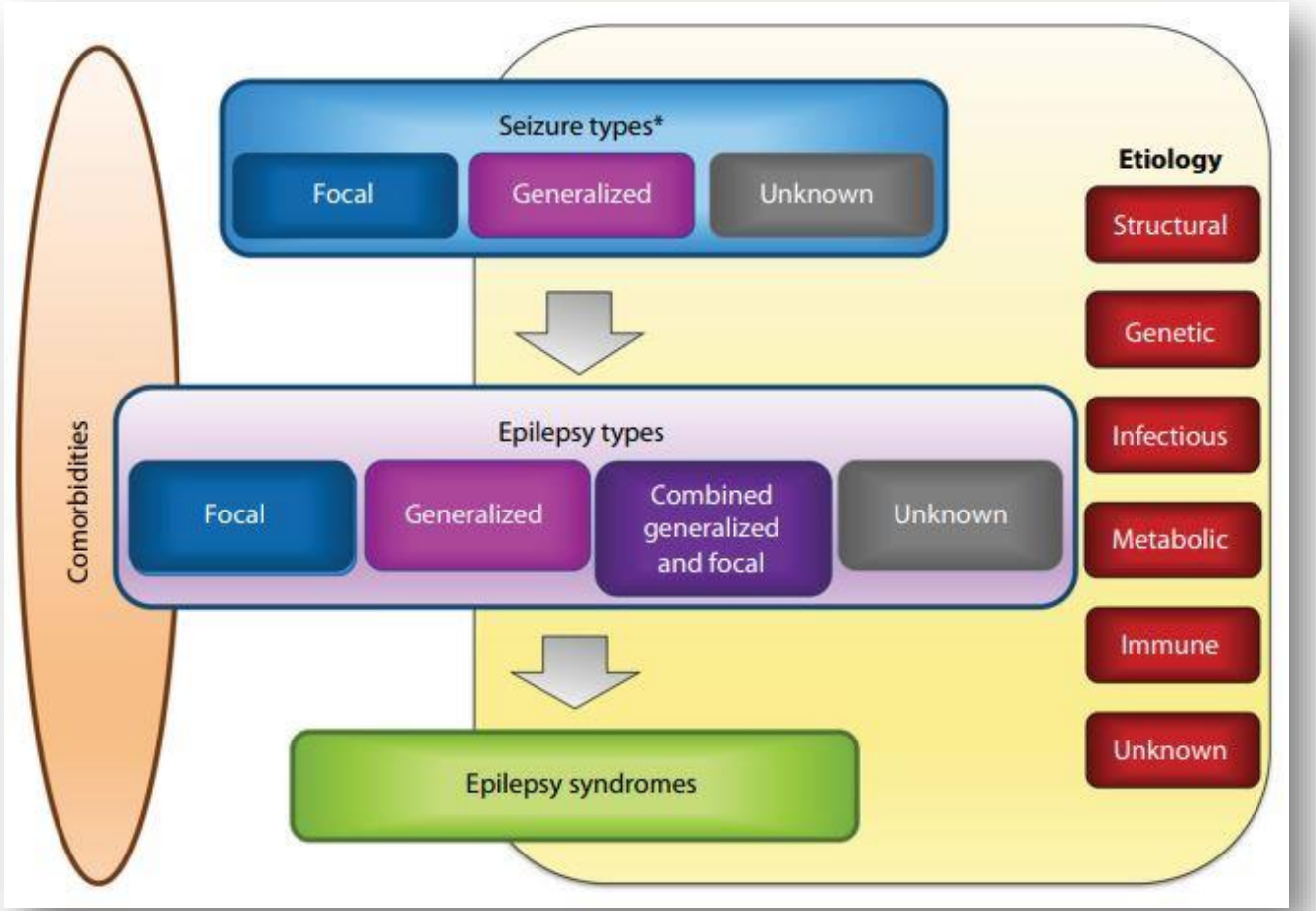
- Honoraria from **Cobel daru**

Table 2. Operational (practical) clinical definition of epilepsy

Epilepsy is a disease of the brain defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be *resolved* for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.


Seizure types*
Focal
Generalized
Unknown
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown
Comorbidities
Epilepsy types
Focal
Generalized
Combined generalized and focal
Unknown
Epilepsy syndromes

Changes in New Classification

- 1) “Partial” becomes **“focal”**
- 2) **Awareness** is used as a classifier of focal seizures
- 3) The terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized **are eliminated**
- 4) **New focal seizure types** include automatisms, behavior arrest, hyperkinetic, autonomic, cognitive, and emotional
- 5) Atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of **either focal or generalized onset**

- 6) **focal to bilateral tonic–clonic** seizure replaces secondarily generalized seizure
- 7) **new generalized seizure types** are absence with eyelid myoclonia, myoclonic absence, myoclonic–atonic, myoclonic–tonic–clonic
- 8) **seizures of unknown onset** may have features that can still be classified
- **Note**: the new classification does not represent a fundamental change, but allows **greater flexibility and transparency** in terminology of seizure types, which is welcome (Fisher et al., 2017)

Rules for classifying seizures help to avoid confusion about what is meant by certain terms

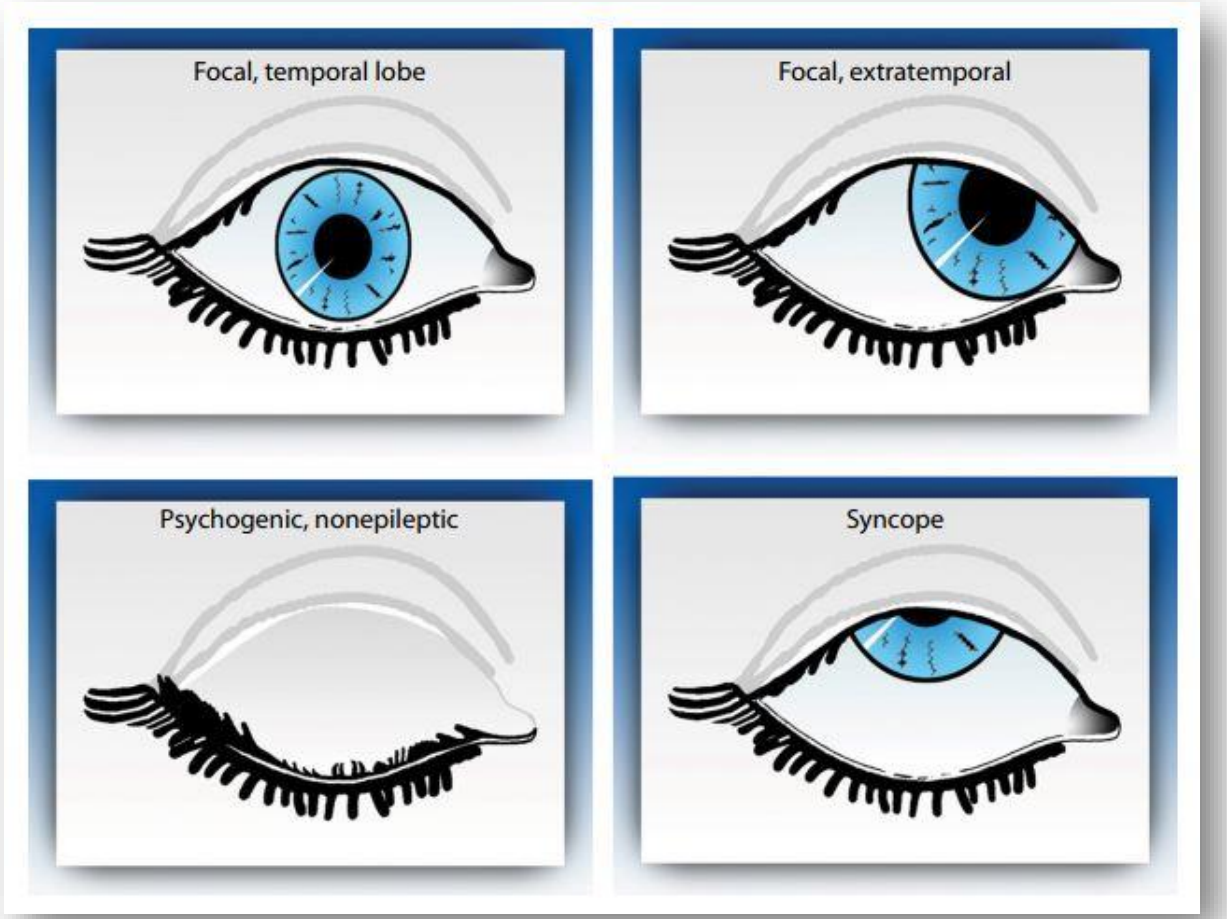
- **1-Onset:** Decide whether seizure onset is focal or generalized, using an 80% confidence level. Otherwise, onset is unknown.
- **2-Impaired awareness at any point:** A focal seizure is *a focal impaired awareness seizure* if awareness is impaired at any point during the seizure.
- **3-Onset predominates:** Classify a focal seizure by its first prominent sign or symptom.

- **4-Behavior arrest:** A *focal behavior arrest seizure* shows arrest of behavior as the prominent feature of the entire seizure.
- **5-Motor/non-motor:** A *focal aware or impaired awareness seizure* may be further sub-classified by motor or non-motor characteristics. Alternatively, a focal seizure can be characterized by motor or non-motor characteristics, without specifying level of awareness. Example, a *focal tonic seizure*.

- **6-Bilateral versus generalized:** Use the term “bilateral” for tonic–clonic seizures that propagate to both hemispheres and “generalized” for seizures that apparently originate simultaneously in both hemispheres.
- **7-Atypical absence:** Absence is atypical if it has slow onset or offset, marked changes in tone or EEG spike-waves at less than 3 per second.

- **8-Clonic versus myoclonic:** Clonic refers to sustain rhythmical jerking and myoclonic to a regular un-sustained jerk.
- **9-Eyelid myoclonia:** *Absence with eyelid myoclonia* refers to forced upward jerking of the eyelids during an absence seizure.

For differential diagnosis among epileptic seizures, one strategic question is whether the eyes are open or closed at the onset



The predominant site of focal cerebral dysfunction determines the clinical manifestations of focal seizures

- **Chewing movements or smacking of lips** (anterior temporal lobe dysfunction),
- **Complex automatic behavior** (anteromedial temporal lobe)
- **Visual hallucinations with formed images** (posterior temporal lobe)
- **Bilateral tonic posture** (supplementary motor cortex, frontal lobe)
- **Localized twitching of muscles without impaired awareness in a Jacksonian seizure** (motor cortex, frontal lobe)
- **Localized numbness or tingling** (sensory cortex, parietal lobe)
- **Visual hallucinations with flashes of light** (occipital lobe)

Localizing semiologic findings pointing to the contralateral location

Semiology	Lateralizing value (PPV)	Symptomatogenic zone	Mechanism
Homonymous hemifield visual aura or defect	100%	Brodmann areas 17-19	Activation
Unilateral ictal paresis or immobile limb	100%	Negative motor areas	Activation
Forced head version less than 10 second before secondary generalization	> 90%	Brodmann areas 6 & 8 (frontal eye and motor areas)	Activation
Unilateral ictal dystonia	> 90%	Spread from seizure onset zone to ipsilateral basal ganglia	Activation
Postictal (Todd's) palsy	> 90%	Brodmann areas 4 & 6 (primary motor area)	Exhaustion/ Inhibition
Fencing posture	90%	SMA	Activation
Figure-of-4 sign (Asymmetric tonic limb posturing)	~ 90%	SMA/ Prefrontal area	Activation
Unilateral tonic activity	~ 90%	SMA/Brodmann area 6	Activation
Unilateral sensory or painful aura	~ 90%	Brodmann areas 1, 2, 3 (primary SSA)	Activation
Unilateral clonic activity	> 80%	Brodmann areas 4 & 6 (primary motor area)	Activation
Emotional facial asymmetry	> 80%	Unknown	Unknown
Epileptic nystagmus	N/A	Posterior head regions	Unknown

Localizing semiologic findings pointing to the ipsilateral location

Semiology	Lateralizing value (PPV)	Symptomatogenic zone	Mechanism
Unilateral automatisms with contralateral dystonic posturing*	> 95%	N/A	Release phenomenon / Activation
Postictal nose wiping	> 90%*	Unknown	Unknown
Unilateral ictal eye blinking	> 80%	Unknown	Unknown
Ictal piloerection (goose bumps)*	> 80%	Unknown	Unknown
Last clonic jerk	> 80%	Brodmann areas 4 & 6 (primary motor area)	? Exhaustion of the hemisphere of onset

Lateralizing semiologic findings pointing to the non-dominant hemisphere

Semiology	Lateralizing value (PPV)	Symptomatogenic zone	Mechanism
Preserved consciousness and automatisms*	100%	Unknown	Unknown
Ictal speech preservation*	> 80%	N/A	Impairment of non-language areas
Ictal vomiting*	> 80%	Temporal lobe and Papez circuit	Activation
Ictal spitting*	75%	Unknown	Unknown
Ictal urinary urge	N/A	Mesial frontal region/ Medial temporal gyrus	Activation
Orgasmic auras	N/A	Mesiotemporal / frontal / amygdala	Activation
Peri-ictal water drinking*	N/A	Lateral hypothalamus	Activation

Lateralizing semiologic findings pointing to the dominant hemisphere

Semiology	Lateralizing value (PPV)	Symptomatogenic zone	Mechanism
Ictal speech arrest*	67%	language areas	Impairment of language areas
Postictal dysphasia	> 80%	language areas	Impairment of language areas

Non-lateralizing semiologic findings in focal epilepsies

Semiology	Symptomatogenic zone	Mechanism
Auditory auras	Superior temporal gyrus	Activation
Ictal vocalization	Broca's area	Activation
Postictal Cough	N/A	N/A
Gelastic Seizure	Hypothalamus	N/A
Olfactory and Gustatory auras	Temporal lobe structures	Activation

Definition for an epilepsy syndrome

- **“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 **principal aim** of this classification, consistent with the 2017 ILAE Classification of the Epilepsies, is to support epilepsy diagnosis and emphasize the importance of classifying epilepsy in an individual both by **syndrome and etiology**.

Framework for classification

- **Mandatory:** Criteria that must be present in order to diagnose the syndrome.
- **Alerts:** Criteria that are absent in the vast majority of cases within a syndrome, but rarely can be seen.
- **Exclusionary**: Criteria that must be absent in order to diagnose the syndrome.

TABLE 4 Childhood onset visual epilepsy

	Mandatory	Alerts	Exclusionary
Seizures	Focal sensory visual seizures with elementary visual phenomena (multicolored circles), with or without impaired awareness, and with or without motor signs (deviation of the eyes or turning of the head) Seizures arise predominantly or exclusively from wakefulness	Prolonged seizure lasting >15 min GTCS during wakefulness	Drop (tonic or atonic) seizures Atypical absences Progressive myoclonus
EEG	Occipital spikes or spikes-and-wave abnormalities (awake or sleep)	Sustained focal slowing not limited to the postictal phase	
Age at onset		<6 years >14 years	<1 year or >19 years
Development at onset		Intellectual disability	Neurocognitive regression
Neurological exam		Any significant neurological examination abnormality	Persistent visual field deficit
Imaging			Causal lesion on brain MRI Cerebral occipital lobe calcifications
Course of illness			Neurocognitive regression Development of myoclonic seizures, ataxia, spasticity
An MRI is required for diagnosis to exclude a causal lesion. An ictal EEG is not required for diagnosis.			
Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an interictal EEG and MRI are required to confidently diagnose this syndrome.			

- For each syndrome, **epidemiology, clinical course, seizure types, EEG, neuroimaging, genetics** were reported.
- Syndromes are separated into **self-limited syndromes**, and **developmental and epileptic encephalopathies**

- The **emerging class of etiology-specific epilepsy 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 as well as consistent EEG, neuroimaging, and/or genetic correlates, is presented.
- The number of etiology-defined syndromes will continue to **increase**

Epilepsy syndromes with onset in neonates and infants(17)

Self-limited epilepsies

- Self-limited neonatal epilepsy (SeLNE)
- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
- Self-limited infantile epilepsy (SeLIE)
- Genetic epilepsy with febrile seizures plus (GEFS+)
- Myoclonic epilepsy in infancy (MEI)

Developmental and epileptic encephalopathies (DEE)

- Ealy infantile developmental and epileptic encephalopathy (EIDEE)
- Epilepsy in infancy with migrating focal seizures (EIMFS)
- Infantile epileptic spasms syndrome (IESS)
- Dravet syndrome (DS)

Etiology-specific syndromes

- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5'-Phosphate Deficiency (PNPO)-DEE (P5PD-DEE)
- *CDKL5*-DEE
- *PCDH19* clustering epilepsy
- Glucose Transporter 1 Deficiency Syndrome (GLUT1DS)
- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

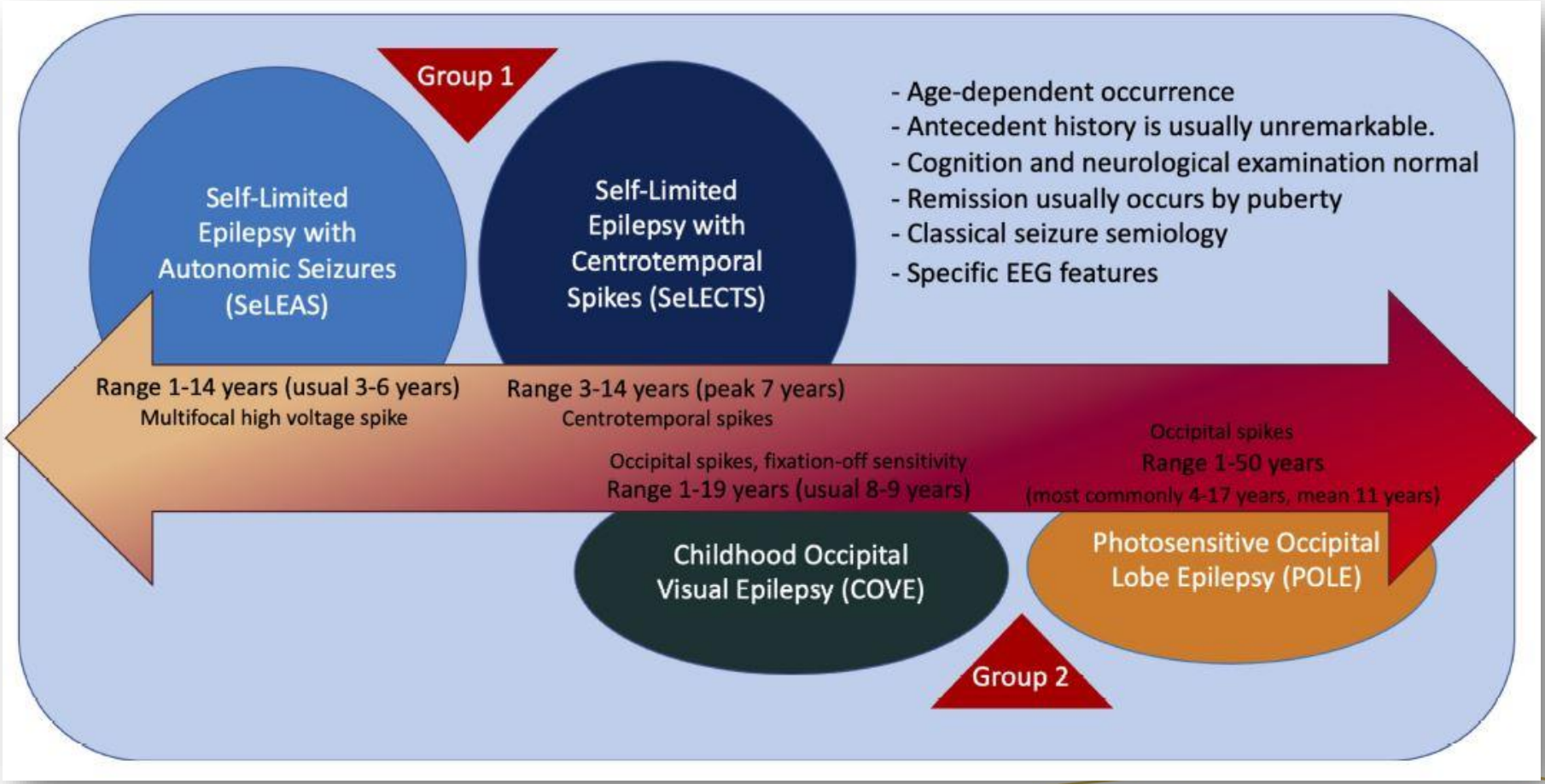
Key Points

- **No eponymous names**, with some exceptions, such as **IESS** (Infantile Epileptic Spasm Syndrome) . Many infants **do not fulfill the full triad of West syndrome**
- **EIDEE** (Early Infantile Developmental and Epileptic Syndrome) instead of **Ohtahara syndrome** and **Early Myoclonic Encephalopathy** (both syndromes sharing genetic and structural etiologies and many infants do not meet criteria for either syndrome)
- Many **Specific-Etiology** Syndrome

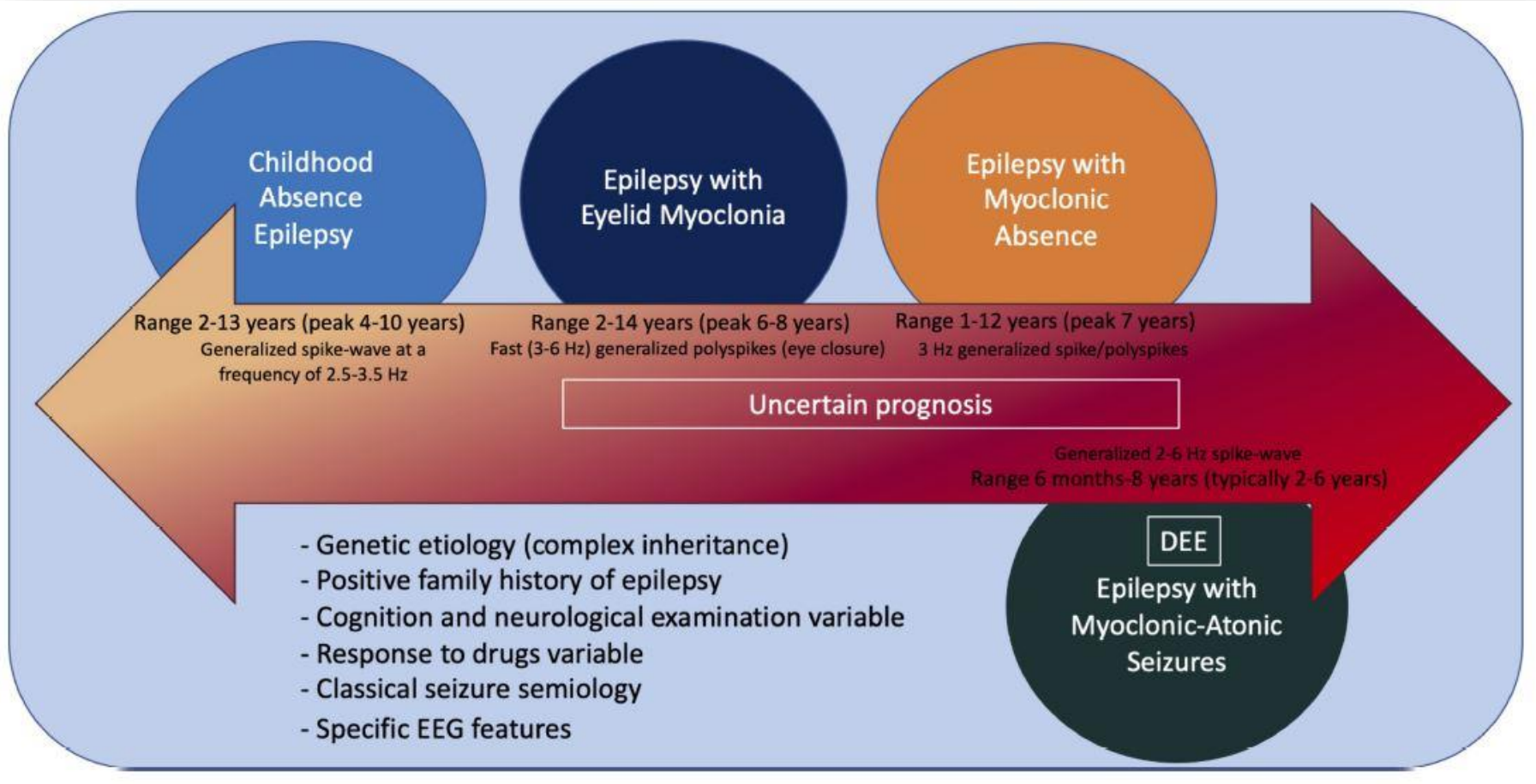
Epilepsy syndromes with onset in childhood(12)

- **Three categories**:
- (1) **self-limite focal epilepsies**, comprising four syndromes
- (2) **generalized epilepsies**, comprising three syndromes
- (3) **developmental and/or epileptic encephalopathies**, comprising five syndromes: epilepsy with myoclonic–atonic seizures, Lennox–Gastaut syndrome, developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep, hemiconvulsion–hemiplegia–epilepsy syndrome, and febrile infection related epilepsy syndrome.

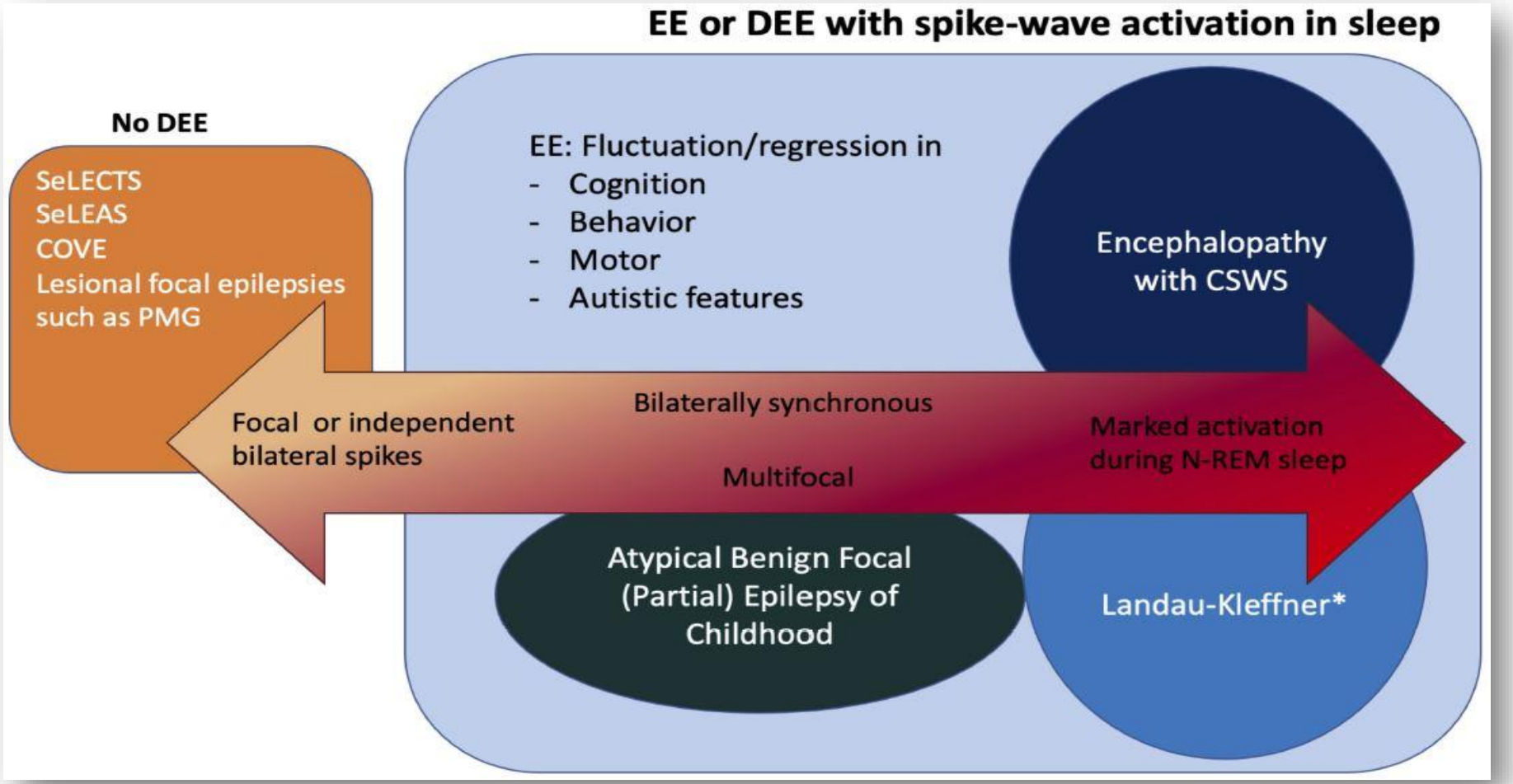
Self-limited focal epilepsies of childhood (SeLFE) syndromes



Genetic generalized epilepsies of childhood



Developmental and/or epileptic encephalopathy (DEE) and epileptic encephalopathy (EE) with spike-and-wave activation in sleep (SWAS)



Key Points

- A **sleep EEG** is required to identify mandatory EEG patterns in some syndromes, such as LGS, DEE-SWAS, and EE-SWAS.
- However, for seizure types in certain syndromes, an **ictal EEG** recording is required for diagnosis. For example, it is not easy to determine a specific seizure type for a **“drop attack”** based on history alone.

- Whereas some syndromes are highly correlated with **specific etiologies**, others are associated with a **diverse group of etiologies**.
- **specific ASMs may exacerbate** certain conditions, such as **sodium channel agents for many of the IGEs.**
- Thus, early syndrome identification will allow for selection of the optimal therapy, which is most likely to lead to early seizure control and to prevention of other seizure types **that may evolve** into a specific syndrome.

- **Accurate syndrome definition** will often inform natural history and likelihood of remission. Some syndromes are **self-limited over time**. Conversely, other syndromes have a much **poorer outcome**, such as **LGS, HHE, or FIRES**

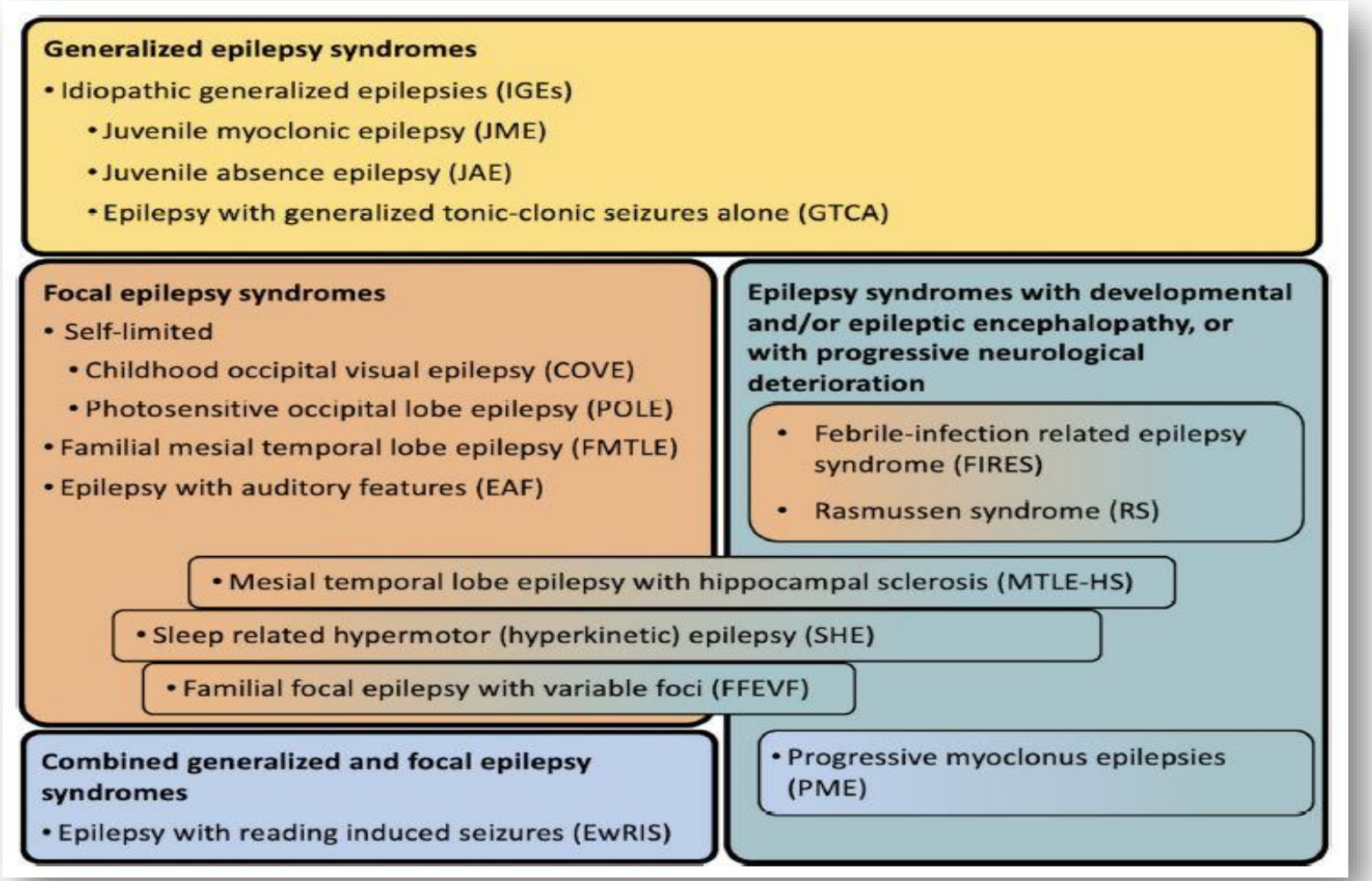
- As described before, some syndromes may **evolve to another syndrome over time**, such as **SeLEAS to SeLECTS**, and **SeLECTS to EE-SWAS**. This raises the question of the possible **neurobiological links** between these syndromes.

- The **most significant nosological changes** in the childhood syndromes are in the **SeLFEs**, which were formerly known as **“benign” or “idiopathic”** focal epilepsies, and **DEE-SWAS or EE-SWAS**, which was formerly known by the terms **LKS, ESES, and EE with CSWS**.

- The term **“benign” is inappropriate**, as many children have associated **cognitive and psychiatric comorbidities**.
- For each syndrome, the nomenclature used reflects the **major phenotypic features**, such as **centrotemporal spikes** in SeLECTs, **autonomic** seizures in SeLEAS, **occipital semiology and EEG findings** in COVE, and **photic-induced focal sensory visual seizures** and genetic predisposition in POLE.

- The **term LGS is crucial** in allowing patients to **acquire the multiple supports** including medical and disability support therapies that they require on a daily basis. Replacing this term would lead to a **lapse in services** that these patients critically require. Additionally, the syndrome comprises **multiple seizure type and etiologies**, which would be **challenging** to capture in a succinct name.

Epilepsy syndromes with onset at a variable age



Key Points

- A patient with **JME** can have aggravation of their epilepsy, **to mimic PME**, when treated with sodium channel blockers (such as carbamazepine).
- Seizures in PME can be **aggravated significantly by sodium channel blockers** (such as phenytoin).

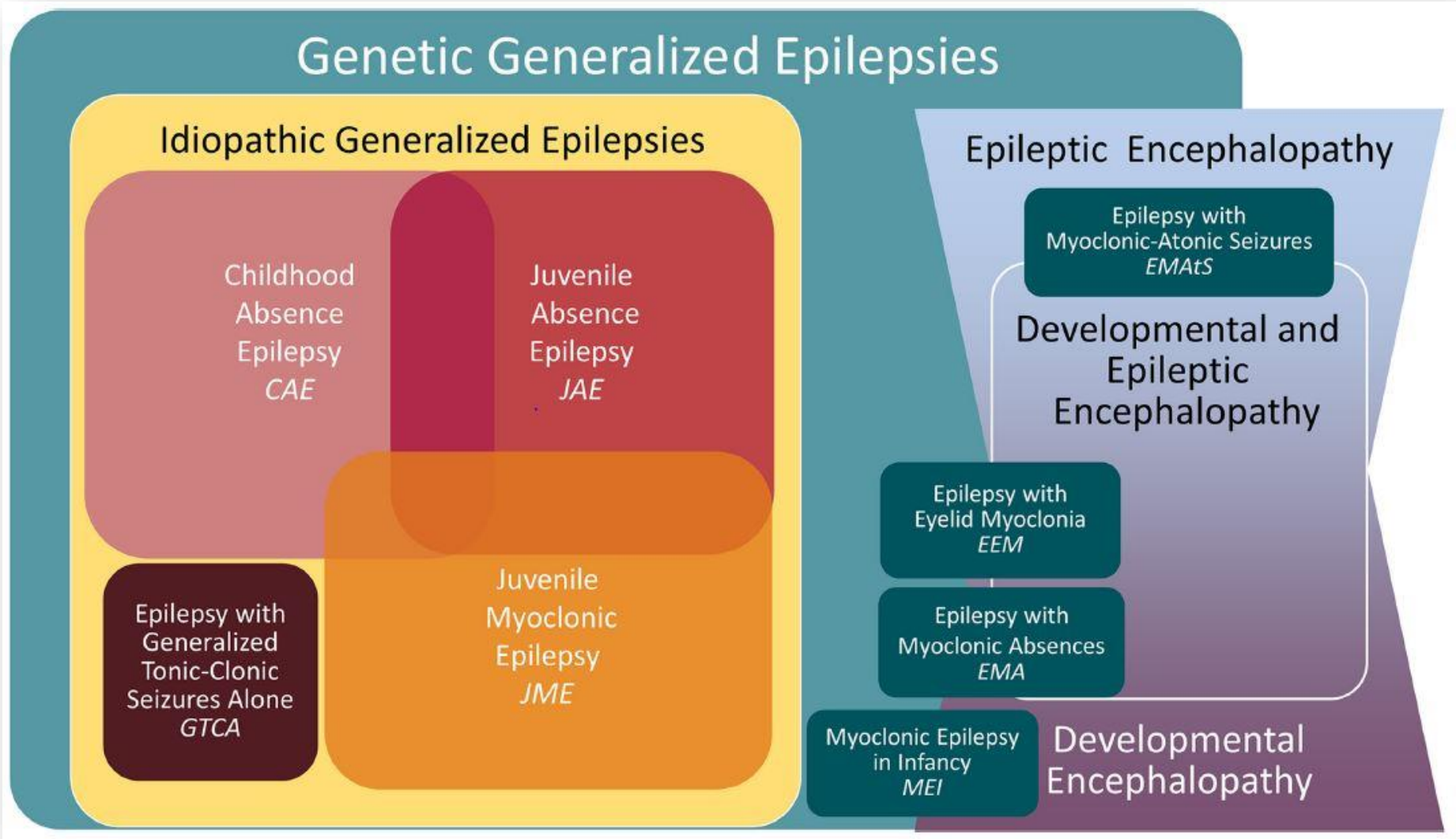
- As time passed, and with contributions from **genetic research**, the **phenotypic spectrum** for some syndromes has expanded and etiology-specific epilepsy syndromes are **increasingly being characterized.**
- This is likely to continue, and **etiology-specific epilepsy syndromes will become increasingly important.**

- Although recognition of **autoimmune-associated epilepsies** other than RS is important, as their prompt identification allows earlier treatment and improved cognitive outcomes, the literature on these epilepsies **is still emerging**.

Idiopathic Generalized Epilepsy Syndromes

- ILAE propose that the term IGE should pertain to a distinct subgroup of the GGEs, 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 an epileptic encephalopathy**.
- There is **clinical overlap** between CAE, JAE, and JME.
- They may **evolve with age to another IGE syndrome** (e.g., CAE evolving to JME).

- Development is typically normal; however, **mood disorders, ADHD, and learning disabilities** are common comorbidities
- Seizure types include **one or a combination of the following**: absence, myoclonic, tonic–clonic, and myoclonic–tonic– clonic seizures
- The EEG shows **generalized 2.5–5.5 Hz spike-wave**, which may be **activated** by hyperventilation or photic stimulation



Key Points

- **Recognition of the IGEs is important** for clinical care, as it informs diagnosis, prevents unnecessary investigation, allows optimal selection of ASMs, and provides prognostic guidance.
- It also enables identification of a relatively **homogeneous group** of patients for clinical research and **antiseizure therapy trials**.

Thanks For Your Attention

COBEL DAROU