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Epilepsy with Variable Age of Onset

Redefining diagnostic criteria and epilepsy syndromes

Epilepsy is a neurological disorder associated with abnormal electrical activity in the brain and marked by recurrent paroxysmal episodes of sensory disturbance, loss of consciousness, or convulsions

Most epilepsy syndromes typically present in neonates, infants, and children

However, some could manifest later in life or at a variable age (i.e., in children and adults)

Prompt and accurate recognition of these syndromes could improve disease outcomes

Using newly emerging knowledge from advances in:

Genetics | EEG | Imaging

The ILAE's 2017 Epilepsy and Seizure Classification for syndromes presenting at a variable age was updated

Here, specific phenotypes of these epilepsy syndromes have been defined

The updated nomenclature for each syndrome aims to reflect:

Key features of the electroclinical phenotypes

The aetiology, if important for syndrome diagnosis

Epilepsy syndromes with onset at variable age

Focal epilepsy syndromes with genetic, structural, or genetic-structural aetiologies

- Sleep-related hypermotor (hyperkinetic) epilepsy (SHE)
- Familial focal epilepsy with variable foci (FFEVF)
- Epilepsy with auditory features (EAF)
- Familial mesial temporal lobe epilepsy (FMTLE)

Generalised epilepsy syndromes with polygenic aetiologies

- Idiopathic generalised epilepsies (IGE)
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalised tonic-clonic seizures alone (GTCA)

Combined generalised and focal epilepsy syndrome with polygenic aetiology

- Epilepsy with reading-induced seizures (EwRIS)

Self-limited focal epilepsy syndromes with presumed complex inheritance

- Childhood occipital visual epilepsy (COVE)
- Photosensitive occipital lobe epilepsy (POLE)

Epilepsy syndromes with developmental and/or epileptic encephalopathy (DE, EE, or DEEs) and epilepsy syndromes with progressive neurological deterioration

- Progressive myoclonus epilepsies (PMEs)
- Febrile infection-related epilepsy syndrome (FIRES)

Focal aetiology-specific epilepsy syndromes

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS)
- Rasmussen syndrome (RS)

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Focal epilepsy syndromes with genetic, structural, or genetic-structural aetiologies

Clinical, diagnostic, and genetic features

	Familial focal epilepsy with variable foci	Sleep-related hypermotor (hyperkinetic) epilepsy	Epilepsy with auditory features	Familial mesial temporal lobe epilepsy
Age of onset	First or second decade of life	Second decade of life	Second or third decade of life	Adolescence or adulthood
Clinical presentation	• Focal seizures: - Presentation dependent on the cortical brain area involved	• Brief hyperkinetic or asymmetric tonic/dystonic focal motor seizures during sleep	• Focal: - Sensory auditory seizures - Cognitive seizures with receptive aphasia	• Typically, focal aware seizures with intense déjà vu and associated features like dreaming, panic, slow motion, visual or auditory illusions, and autonomic manifestations
Interictal EEG	• Focal epileptiform abnormalities: - Generally in the frontal, temporal, or centroparietal regions, with the focal area remaining constant over time - Enhanced by sleep deprivation and sleep	• Normal background • Focal sharp waves or spikes may be seen most commonly in frontal regions	• Mostly normal but may show focal sharp waves, usually temporal, and often activated by sleep	• Background is usually normal or may show mild temporal slowing • Temporal epileptiform abnormality may be seen
Magnetic resonance and other imaging	• Normal or focal cortical dysplasia	• Usually normal but may show focal cortical dysplasia or, less commonly, an acquired structural abnormality	• Usually normal	• Usually normal • Rarely, hippocampal atrophy or increased T2 signal is seen
Related genes	*DEPDC5, NPRL2, NPRL3*	*CHRNA4, CHRNA2, CHRNB2, DEPDC5, KCNT1, NPRL2, NPRL3, PRIMA1*	*LGI1, RELN, MICAL1*	*DEPDC* Mendelian inheritance is rare; FMTLE typically displays complex inheritance

Generalised epilepsy syndromes with polygenic aetiologies

General characteristics of idiopathic generalised epilepsies (IGEs)

Genetic generalised epilepsies

The most frequent epilepsies that present during adolescence and adulthood

IGEs are seen in about 15%–20% of all persons with epilepsy

Combined generalised and focal epilepsy syndromes with polygenic aetiology, and epilepsy syndromes with developmental and/or epileptic encephalopathy and epilepsy syndromes with progressive neurological deterioration

	Epilepsy with reading-induced seizures	Progressive myoclonus epilepsies
 Age of onset	Typically in the late teens, with a male predominance	2–50 years
 Seizures	Reflex myoclonic seizures, affecting orofacial muscles; triggered by reading/language related tasks	Myoclonic seizures (at times with other seizure types)
 EEG	• Interictal epileptiform abnormalities may be absent • Myoclonic seizures are accompanied by brief, sharp spike or spike–and–wave	• Generalised spike/polyspike–and–wave • Progressive background slowing
 Neurological exam	Normal	Normal at onset, but progressive worsening of myoclonic seizures and neurological and cognitive function seen
 Minimum requirements for diagnosis	Clinical features	Clinical and electrographic features with progressive course

Focal aetiology-specific epilepsy syndromes

General characteristics

These syndromes have a specific aetiology, with:

- A clearly defined, uniform, and distinct clinical phenotype
- Consistently correlating EEG, neuroimaging, and genetic features

	Mesial temporal lobe epilepsy with hippocampal sclerosis	Rasmussen syndrome
Aetiology	Hippocampal sclerosis, which may have many contributing causes	Hemispheric atrophy, which may have many contributing causes
Age of onset	Most commonly, seizure onset is in adolescence and young adult years	Most commonly, age at onset is 1–10 years (median 6 years)
Neurological, cognitive, and other features	• Seizures are often drug resistant • Memory concerns • Higher risk of mood disorders	• Progressive neurological impairment with hemiparesis, hemianopsia, and language and cognitive concerns, with frequent drug-resistant seizures
Seizures	Focal aware or impaired awareness seizures with initial semiology referable to medial temporal lobe networks	Focal/hemispheric seizures that often increase in frequency over weeks to months
EEG	• Background is normal; may show focal slowing over the temporal region(s) • Characteristic anterior or mid-temporal spikes and sharp waves - Often increased during sleep	• Hemispheric slowing and epileptiform abnormality
Minimum requirements for diagnosis	• MRI showing hippocampal sclerosis is required for confirmation of diagnosis	• Presence of focal/hemispheric onset seizures with typical progression • MRI showing progressive hemispheric atrophy

Reference:
Riney, K., Bogacz, A., Somerville, E., Hirsch, E., Nabbout, R., ... & Tinuper, P. (2022). International League Against Epilepsy classification and definition of epilepsy syndromes with onset at a variable age: position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia*, 1–32, https://doi.org/10.1111/epi.17240.

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