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Epilepsy Syndromes in Neonates and Infants

Updated classifications and clinical management guidelines

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

Neonatal and infantile epilepsy

Children with epilepsy who experience seizure onset prior to 2 years of age suffer from:

- Cognitive and behavioural comorbidities—especially among children with drug-resistant epilepsy—and frequent seizures
- Higher rates of drug-resistance
- Higher mortality rates
- Delayed development

Syndromes have conventionally been categorised by their electroclinical features but with development of genetic research in epilepsy:

Certain electroclinical phenotypes have emerged

Structural, metabolic, immune, and infectious aetiologies have been linked with specific electroclinical phenotypes

This necessitates an update to the current 2017 ILAE classification of epileptic syndromes, and the guidelines to manage them

Epilepsy syndromes

These are a characteristic cluster of clinical and EEG features, often supported by specific aetiological findings (structural, genetic, metabolic, immune, and infectious)

The diagnosis of such syndromes in people with epilepsy affects their prognosis and treatment

These syndromes have:

- A range of specific associated comorbidities
- Age-dependent presentations

The ILAE also introduces the concept of aetiology-specific epilepsy syndromes which have:

- A distinct clinical presentation
- Consistent EEG findings
- Neuroimaging and/or genetic correlations

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Epilepsy syndromes with onset in neonates and infants

Self-limited epilepsy syndromes

- Likely to spontaneously resolve as the child grows older

Developmental and epileptic encephalopathies (DEEs)

- Severe, early-onset syndromes with associated neurodevelopmental comorbidities
- Most neonatal-onset epileptic syndromes are DEEs

Aetiology-specific epilepsy syndromes are associated with a clearly-defined, relatively uniform, and distinct clinical phenotype (which may include a genetic disorder)

Most of these syndromes are DEEs

Self-limited epilepsy syndromes

- Self-limited neonatal epilepsy
- Self-limited familial neonatal-infantile epilepsy
- Self-limited infantile epilepsy
- Genetic epilepsy with febrile seizures plus
- Myoclonic epilepsy in infancy

Developmental and epileptic encephalopathies (DEEs)

- Early infantile DEE
- Epilepsy of infancy with migrating focal seizures
- Infantile epileptic spasms syndrome
- Dravet syndrome

Aetiology-specific syndromes

- *KCNQ2*-DEE
- Pyrodoxine-dependent (*ALDH7A1*)-DEE
- Pyridox(am)ine 5'-phosphate deficiency
- *CDLK5*-DEE
- *PCDH19* clustering epilepsy
- Glucose transporter 1 deficiency syndrome
- Sturge Weber syndrome
- Gelastic seizures with hypothalamic hamartoma

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Features of self-limited syndromes

	Seizure and EEG pattern	Imaging/other studies
Self-limited (familial) neonatal epilepsy	• Seizures have focal tonic features at onset • Affect mainly the head, face, and limbs • Focal tonic and clonic seizures may alternate sides • May evolve to bilateral tonic or clonic seizures	• A non-lesional MRI is required for diagnosis • Positive family history
Self-limited familial neonatal-infantile epilepsy	• Focal tonic seizures with head and eye deviation followed by other tonic and clonic features • May evolve to bilateral tonic-clonic seizures	• A non-lesional MRI is required for diagnosis • Positive family history
Self-limited (familial) infantile epilepsy	• Usually brief (<3 minutes) focal seizures accompanied by behavioural arrest, impaired awareness, automatisms, head/eye version, and clonic movements • Seizures often alternate sides • Progression to a hemiclonic or focal and then bilateral tonic-clonic seizure	• A non-lesional MRI is required for diagnosis • Positive family history
Febrile seizures plus spectrum	• Febrile seizures, either generalised or focal, continuing beyond 6 years of age • Additionally, other generalised or focal afebrile seizures may be seen • Normal background in EEG	• No causal lesion seen on brain MRI
Myoclonic epilepsy in infancy	• Myoclonic seizures, usually occurring multiple times in a day (independent of wakefulness) • Can occur in clusters and lead to falls • Reflex-induced myoclonic seizures (triggered by sudden noise, touch, or startling) and febrile seizures are seen in about one-third of cases • Normal background in EEG (while awake) • A sleep EEG showing generalised spike–and–wave, polyspike, and polyspike–and–wave at approximately 3 Hz during myoclonus patterns	• A non-lesional MRI is required for diagnosis • Clinical presentation of seizures is mandatory for diagnosis

Diagnostic criteria for self-limited syndromes in resource-limited regions

Syndrome	Minimum diagnostic criteria
Self-limited (familial) neonatal epilepsy	Suggestive family history in a patient who meets all other mandatory and exclusionary clinical criteria
Self-limited (familial) infantile epilepsy	
Self-limited familial neonatal-infantile epilepsy	
Febrile seizures plus spectrum	Patient meets all other mandatory and exclusionary clinical criteria
Myoclonic epilepsy in infancy	A sleep EEG showing generalised spike-wave

Features of developmental and epileptic encephalopathies (DEEs)

	Seizure and EEG pattern	Imaging/other studies
Early infantile DEE	• Tonic and/or myoclonic seizures • Onset between birth to 3 months • Interictal EEG shows burst suppression and multi-focal discharges with diffuse slowing • Developmental impairment and abnormal neurodevelopment (including intellectual disability) seen	
Epilepsy of infancy with migrating focal seizures	• Focal/multifocal tonic or clonic seizures, with or without subtle behavioural arrest, and prominent autonomic features • Seizures migrate from one hemisphere or lobe to another • Seizure frequency rapidly increases in the first weeks and months, often progressing to status epilepticus • Age of onset <12 months • Ictal EEG shows a migrating pattern; interictal EEG shows multifocal discharges • Neurodevelopmental delay and developmental plateauing or regression with frequent seizures	• MRI required for diagnosis
Infantile epileptic spasms syndrome	• Flexor, extensor, or mixed epileptic spasms occurring in clusters • Onset between 1-24 months • Developmental slowing may be absent during initial disease course but presents after onset of spasms • Interictal EEG shows either hypsarrhythmia, multifocal, or focal epileptiform discharges, seen quickly after onset of spasms	• Infants with brain injury, malformations, or specific genetic conditions should be monitored carefully for epileptic spasms
Dravet syndrome	• Recurrent focal clonic (hemiclonic) febrile and afebrile seizures (which often alternate sides from seizure to seizure), or focal to bilateral tonic-clonic and/or generalised clonic seizures • Onset from 1-20 months of age • May progress to drug-resistant epilepsy or intellectual disability	• A pathogenic *SCN1A* variant to further support diagnosis

Diagnostic criteria for DEEs in resource-limited regions

Syndrome	Minimum diagnostic criteria
Early infantile DEE	Cannot be diagnosed without an interictal EEG
Epilepsy of infancy with migrating focal seizures	Clinical observation of seizure migration without EEG or MRI
Infantile epileptic spasms syndrome	Interictal EEG
Dravet syndrome	By meeting all other clinical criteria, without EEG, MRI, or genetic testing

Reference:

Zuberi, S. M., Wirrell, E., Yozawitz, E., Wilmshurst, J. M., Specchio, N., ...& Nabbout, R. (2022). ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia*, 1–49, https://doi.org/10.1111/epi.17239.

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