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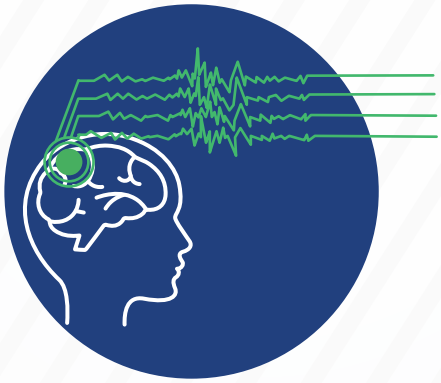
Lennox-Gastaut Syndrome: Aetiology, Clinical Presentations, Diagnosis, and Treatment Challenges

A guide for health professionals



Epilepsy syndromes are characterised by a cluster of symptoms, and clinical and electroencephalographic (EEG) features with distinct underlying aetiologies[1]

Structural | Genetic | Metabolic | Immune | Infectious

They are classified on the basis of:[1]

Age at onset

- Neonatal and infantile onset
- Childhood onset
- Variable age at onset
- Idiopathic generalised epilepsies

Epilepsy and seizure type

- Generalised
- Focal
- Generalised and focal

Association with developmental and/or epileptic encephalopathy (DEE/EE) or progressive neurological deterioration

Lennox-Gastaut Syndrome (LGS) is a complex and severe DEE which begins in childhood and has a wide range of aetiologies[2,3]

It is a rare condition, accounting for 2–5% of all childhood epilepsies[2]

LGS has an estimated prevalence of:[2]

- 0.1–0.28 per 100,000 people
- 2 per 100,000 children

- Slightly more common in males
- Usually begins before 18 years of age with a peak onset between 3 to 5 years[3]

The clinical presentation of LGS is diverse and evolves over time[3]

Severe infantile epilepsy syndromes often evolve to LGS[1,3]

3.6% of all children with epilepsy

19% of children with infantile seizures

30% of children with infantile epileptic spasms syndrome

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Characteristics and distinguishing features[1,3]

- Multiple types of drug-resistant seizures with onset prior to 18 years
- Persistent focal abnormalities with diffuse slow spike-and-wave complexes of <2.5 Hz
- Generalised paroxysmal fast activity (GPFA) in sleep ≥10 Hz

- Atypical absences with rhythmic jerking or loss of tone
- Tonic seizures along with at least one additional seizure type: atypical absences, atonic, myoclonic, focal impaired awareness, generalised tonic-clonic, nonconvulsive status epilepticus, and epileptic spasms
- Cognitive and behavioural impairments, which may not be present at seizure onset

Aetiology[3,4]

Results from high-frequency, synchronised activity in bilaterally distributed brain networks that develops during a susceptible period in childhood

- **Identifiable factors – 65% to 75% of patients**
  - Acquired brain injury or insult
  - Tuberous sclerosis complex
  - Congenital central nervous system infections
  - Brain malformations
  - Hereditary metabolic disorders
- **LGS from unknown causes**

Clinical course[3]

- Developmental impairment preceding onset of seizures or normal behaviour and development at the time of onset
- Developmental stagnation or decline following frequent seizures
- Drug-resistant seizures which persist into adulthood
- Atypical absence and tonic seizures remain frequent in adults, while atonic seizures settle over time
- Developmental regression or plateauing is associated with significant intellectual disability in >90% of patients
- Can co-exist with other childhood behavioural disorders including hyperactivity, aggression, autism spectrum disorder, and sleep disturbances

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Diagnosis[3]

Neurophysiology – EEG

- Tonic seizure recorded in sleep + one additional seizure type, brief apnoea with electromyographic axial muscle contraction

Structural aetiologies – magnetic resonance imaging

- Focal or diffuse cortical malformations
- Tuberous sclerosis complex
- Tumours
- Acquired brain injury such as hypoxic–ischemic encephalopathy

Pathogenic genetic variants – molecular and genetic testing

- Chromosomal microarray
- Next-generation sequencing techniques – whole genome/exome sequencing, or an epilepsy gene panel

Assessment of neuro-metabolites

Challenges in the diagnosis of LGS[1,3]

LGS and other epilepsy syndromes share clinical and imaging features

Typical features of LGS during childhood onset can evolve over time and may be missed in previously undiagnosed adults

Differential diagnosis of LGS[3]

Ruling out other epilepsy syndromes

Epilepsy syndrome	Distinguishing features compared to LGS
Epilepsy with myoclonic-atonic seizures	• Normal development prior to seizure onset • Myoclonic-atonic seizures • Faster generalised spike-and-wave pattern, typically >3 Hz
Prolonged, hemiclonic seizure in infancy, often during a febrile illness	• Prolonged, hemiclonic seizures • Tonic seizures occur later
DEE spike-and-wave activation in sleep (SWAS) and EE-SWAS	• Regression and marked activation of epileptiform abnormalities in sleep • SWAS – 'nearly continuous diffuse SW complexes in slow-wave sleep'
Ring chromosome 20 syndrome	• Refractory epilepsy • Intellectual disability • Behavioural abnormalities • Tonic seizures usually appear during sleep • Awake patients frequently experience nonconvulsive status epilepticus
Frontal lobe epilepsy	• Bilateral tonic seizures, often with asymmetrical features • Slow spike-and-wave and generalised paroxysmal fast activity characteristic of LGS are not noted
Rare metabolic disorders	• Features similar to LGS • Neuronal ceroid lipofuscinosis type 2 disease has a childhood onset with normal development or isolated speech delay • Progressive motor and cognitive decline and ataxia following onset of seizures • Characteristic photoparoxysmal response at 1–3 Hz on EEG

Challenges in the treatment of LGS[3,4]

- Drug-resistant and refractory seizures
- Multiple seizure types can lead to poor prognosis and long-term outcomes
- Unfavourable evolution and life-long neurodevelopmental sequelae
- Conventional biochemical and molecular biomarkers have limited applicability
- Seizure aggravation requires polytherapy, which can increase the risk of adverse effects

Complete control of seizures along with resolution of developmental and psychosocial dysfunction is nearly unachievable[4]

Treatment goals[3,4]

Seizure control

- Medical treatment
- Dietary modifications
- Surgical management

Reducing the frequency of incapacitating seizures like drop attacks and tonic-clonic seizures

Improving cognition, mood, alertness, and overall quality of life

Considerations for improving the diagnosis and treatment of LGS[1,3,4,5]

Defining epilepsy syndromes based on their specific aetiology and electroclinical phenotype can aid their accurate diagnosis

Understanding the evolution of seizures and periodic assessments can help reduce misdiagnosis

Assessment of specific biomarkers such as paroxysmal fast activity in the brain tissue, which are associated with the generation of seizures, can aid the diagnosis and treatment of LGS

GPFA, a key EEG feature of LGS, is strongly associated with seizure changes and may serve as a valuable prognostic biomarker

Periodic assessments of LGS criteria during the evolution of seizures can help clinicians include appropriate anti-seizure medications in the therapeutic regimen

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