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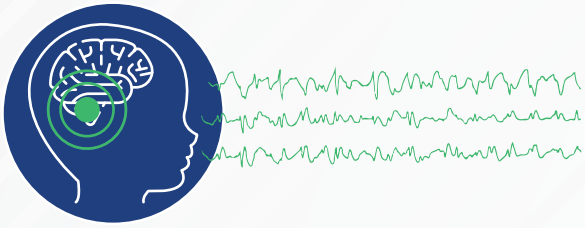
Understanding Challenges and Treatment Strategies in the Management of Patients with Lennox-Gastaut Syndrome

Insights on recent approaches in therapeutics and care coordination



Lennox-Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy characterised by multiple treatment-resistant seizures and intellectual disability[1]

It typically begins in childhood and persists through adolescence and adulthood[1]

Distinguishing electroclinical features[1]

- Tonic seizures occurring predominantly during sleep with other seizure types
- Abnormal electroencephalographic (EEG) patterns
  - Interictal pattern of diffuse, slow spike-wave complexes at <2.5 Hz during wakeful periods
  - Paroxysmal fast rhythms (10–20 Hz) during sleep[1]

Defined by the association of seizure types and EEG features[2,4]

Delay between initial symptoms and emergence of LGS diagnostic features[3]

Therefore, there is a need for repeated assessments and monitoring

Seizures are often severe and incapacitating

They can worsen intellect and impair quality of life (QoL)

Complete remission with anti-seizure medications (ASMs) is difficult to achieve

Treatments should be focused on:[2,4]

Seizure control and freedom from disabling seizures

Rationalising anti-seizure therapy and considering non-drug therapies like ketogenic diet (KD) or vagus nerve stimulation (VNS)

Improving QoL and independence in daily activities

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Early and aggressive interventions may help improve outcomes[3]

Pharmacological treatments – ASMs[5]

- Cannabidiol
- Clobazam
- Felbamate
- Fenfluramine
- Lacosamide
- Lamotrigine
- Levetiracetam
- Perampanel
- Rufinamide
- Topiramate
- Valproate
- Zonisamide

*in alphabetical order

Non-pharmacological approaches

KD therapy[1,5]

- Mimics the metabolic effects of fasting
- A specific diet is recommended by a specialist
- Requires medical and dietitian follow-up

Resective/disconnective surgery – focal, lobar, or multilobar[1,5]

- Identification of suitable candidates through pre-surgical evaluation with video-EEGs, structural high-resolution epilepsy protocol magnetic resonance imaging (MRI), and other advanced neuroimaging techniques
- In selected individuals, early surgical intervention could improve seizure control and long-term outcomes
- Surgery may be considered for patients with LGS experiencing disabling seizures as palliative treatment in rare instances and for patients with focal lesions

VNS[1,5]

- >50% reduction in seizures in more than half of the patients
- Well tolerated and can be used in conjunction with other therapies
- Does not interact with ASMs

Corpus callosotomy[1,5]

- Effective in drop attacks
- Suitable for patients experiencing debilitating drop attacks

Deep brain stimulation (DBS)

- Potential non-pharmacological treatment
- Limited evidence in adult patients

Paediatric-to-adult care transition of patients with LGS[1,5,6]

Just like children, adults may experience tonic seizures during sleep

Evolution of clinical and EEG features may lead to the underdiagnosis of LGS in adults

LGS in adults

Typical slow generalised spike-wave discharges are rarely noted

Persistent paroxysmal fast-frequency discharges

Changes in seizure type and frequency

A few EEG features might disappear in adulthood

Background activity during wakefulness may appear normal or show multiple independent spike foci

Treatment challenges

- Evolution of clinical and EEG features
- Continued treatment-resistance
- Diagnosis of seizures with non-epileptic causes
- Difficult paediatric-to-adult transition; needs beyond seizures related to comorbidities add to the complexity of the transition
- Autism-related behavioural and special healthcare needs
- Disabled social life and poor QoL

General factors leading to poor transition

- Lesser knowledge of the adult teams of paediatric epilepsy syndromes
- Less access to newer therapies
- Poor management of comorbidities
- Difficulties in communication during seizure diagnosis
- Changes of age-related adverse events

Contributing clinician- and patient-related factors

- Positive long-term attachments may discourage patients and families from transferring to adult care
- Cultural differences between paediatric care being family-centred and adult care being patient-centred
- Lack of multidisciplinarity and holistic care in epilepsy care for paediatrics compared to adults
- Whole-person care management is particularly difficult for patients aged 16–18 years who fall between paediatric and adult groups

Considerations for a smooth transition to adult care[1,5]

- Measurement of baseline EEG following transfer
- Re-assessment of ASMs and polytherapy use
- Re-consideration of non-pharmacological therapies
- Seeking the opinion of an epilepsy expert familiar with the patient with the syndrome
- Annual review by a neurologist

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Proposed diagnostic algorithm for adults with LGS[7]

Adult patients with refractory seizures

Medical history assessment
- Types of seizure during childhood and age at onset
- Developmental delays and cognitive impairment

Physical examination
- Normal or non-specific neurological deficits
- Elucidate aetiology based on physical findings
  - Neurocutaneous, hemiparesis, and cognitive impairment

Obtain additional records
- Genetic testing
- MRI
- Recent and previous EEG reports

Slow spike and wave activity while awake

Diffuse fast rhythms while asleep

LGS diagnosis

Probable LGS (not all criteria and examination results available at presentation) – retrieve previous examination reports and/or repeat testing and monitoring

Proposed treatment algorithm for adults with LGS[7]

Mono- or poly-ASM therapy

Tier 1:
ASMs approved for use in treating LGS-associated seizures
Cannabidiol, clobazam, fenfluramine, lamotrigine, levetiracetam, perampanel, rufinamide, topiramate, valproate, zonisamide

Tier 2:
ASMs used less frequently
Brivaracetam, cenobamate, felbamate, lacosamide

Tier 3:
ASMs which may exacerbate certain seizure types
Carbamazepine, eslicarbazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, vigabatrin

*ASMs listed in alphabetical order

Non-pharmacological interventions

KD therapy, physical therapy, resective/ disconnective surgery, VNS, DBS, callosotomy

Community services

Transportation, education, occupational skills training, recreation, equipment/ protective gear

Psychosocial measures

Psychiatrist/psychologist, family therapy, social worker, home service/ health aid

Recommendations for improved care management in adult patients with LGS

Frequent re-assessment and follow-up every 3/6/12 months based on[7]:
- Seizure frequency
- Cognitive and behavioural status
- Medication needs
- VNS implant assessment

Total seizure burden, seizure-free days, and QoL can help assess the effectiveness of treatments more reliably than drop seizure counts[8,9]

A multimodal and individualised treatment approach is needed which caters to patients' medical, educational, psychological, and social needs[1]

Patients' QoL and impact on their family and caregivers should be reassessed annually[1]

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