

Lennox–Gastaut Syndrome: A Narrative Review of Etiology, Pathophysiology, Clinical Features, Diagnosis, and Management

Achsah Achu Benoy*, Anjali S and Philip Jacob

Department of Pharmacy Practice, Nazareth College of Pharmacy, Othara, Thiruvalla, Kerala.

World Journal of Biology Pharmacy and Health Sciences, 2026, 27(01), 186–193

Publication history: Received on 20 June 2026; revised on 25 July 2026; accepted on 28 July 2026

Article DOI: <https://doi.org/10.30574/wjbphs.2026.27.1.0406>

Abstract

Lennox-Gastaut syndrome (LGS) represents a serious form of developmental and epileptic encephalopathy, which is defined by drug-resistant seizures of various types, cognitive problems and typical EEG slow spike wave discharges. LGS starts in childhood and is usually associated with a high neurologic, developmental, and psychosocial burden. The cause of LGS is different and can be represented by structural, genetic, metabolic problems, infections and idiopathic forms of LGS. Even with all progress in diagnostic and therapeutic approaches, a complete cure of seizures is difficult to attain for most of the LGS patients; thus, many individuals remain affected with seizures throughout their lifetime. The diagnosis is made based on clinical history, semiology of seizures, specific EEG pattern, neuroimaging and genetic testing. Treatment is complex and involves the use of anti-seizure medications, dietary management, neuroimaging, surgery, rehabilitation, and psychosocial support. New therapeutic approaches approved in recent years and precision medicine have changed the treatment and improved prognosis in some LGS cases.

Keywords: Lennox-Gastaut Syndrome; Developmental and epileptic encephalopathy; Drug-resistant epilepsy; Electroencephalopathy; Anti-seizure medications

1. Introduction

Lennox-Gastaut syndrome (LGS) is among the severest of all developmental and epileptic encephalopathies occurring in children, comprising approximately 1-4% of all childhood epilepsies and almost 10% of drug-resistant epilepsies in children [1,2,26]. Lennox-Gastaut syndrome is defined by the presence of the triad of multiple seizures, mental and behavioural impairments, and distinctive electroencephalogram (EEG) features, featuring generalised slow spike-and-wave complexes accompanied by bursts of fast activity during sleep [2,11].

LGS usually develop itself at 3 to 5 years of age. Nevertheless, the symptoms are different depending on the specific cause. While tonic seizures can be described as the most distinctive type of seizure, patients suffer from other types of seizures, such as atonic, atypical absence, myoclonic, generalised tonic-clonic, and focal seizures, which result in high morbidity and the risk of sudden falls leading to injuries. In general, intellectual disability, behaviour problems, and reduced quality of life are observed among people with LGS, causing significant difficulties for patients and their families [2,6,11].

Although there has been much improvement in research on epilepsy, LGS is still one of the most difficult epilepsy syndromes to manage due to the resistance of seizures to traditional drugs used in the treatment of epilepsy. In the past decade, many new pharmacological substances, ketogenic diet therapy, vagus nerve stimulation, corpus callosotomy, and other neuromodulation methods have been developed. [19,13,29]

* Corresponding author: Achsah Achu Benoy

This review provides a complete description of available literature on the pathophysiology, aetiology, epidemiology, clinical manifestations, diagnostics and modern management of Lennox-Gastaut Syndrome.

2. History

The history of LGS starts with the work of William G. Lennox and Henri Gastaut in the middle of the twentieth century, who discovered a distinct epilepsy syndrome with its own characteristics and specific electroencephalographic findings. [5] At first, the syndrome was described in patients who had difficult-to-treat epilepsy and developmental delay along with EEG changes (diffuse slow spike-and-wave discharges). Further studies were conducted by Gastaut, who highlighted the distinctive characteristics of LGS seizures and EEG findings. [11]

In the 1960s and 1970s, with increasing clinical experience, the syndrome was defined as an epilepsy syndrome rather than a seizure type. The syndrome was found to involve tonic seizures, atypical absence seizures, atonic seizures and intellectual disabilities, with many patients not responding well to the traditional antiseizure drugs. [22]

Modern progress in imaging, molecular genetics and neurophysiology made the scientists get deeper understanding of the syndrome. They have found structural brain malformations, genetic abnormalities and metabolic diseases that can cause LGS. As a result, it became clear that LGS is a heterogeneous developmental and epileptic encephalopathy and not a disease of only one aetiology. [10,11,6]

3. Epidemiology

Lennox-Gastaut Syndrome (LGS) is a rare yet serious disorder of developmental and epileptic encephalopathy that makes up around 1-4% of childhood epilepsies and 1-2% of all epilepsies throughout the world. [18,24] Although the syndrome is not widespread, it contributes heavily to the problem of drug-resistant epilepsy due to the high prevalence of seizures in affected patients who continue having such symptoms through childhood and even into adulthood. [2,26]

The prevalence of Lennox-Gastaut Syndrome is estimated at between 15 and 30 cases per 100,000 people, but these figures may vary significantly based on the methodology of the study. The incidence is estimated at 0.1-0.3 per 100,000 people per year. [18,24]

The disease often affects children within their first decade of life. Seizures usually start between ages 3 to 5. About 90% of the cases have symptoms by the age of 8, while very few cases appear in adolescence and adulthood. There is an incidence of slight male predominance, but the cause is yet unknown. However, according to the long-term follow-up studies, over 70% of the patients experience drug-resistant epilepsy, while only few of them can be free from seizures. Recurrent seizures have been found to correlate with progressive cognitive impairment, behavioral problems, poor socialization, and decreased quality of life. The risk of mortality is significantly higher compared to the general population and mainly due to status epilepticus, injury due to seizures, aspiration pneumonia, and sudden unexplained death in epilepsy (SUDEP).

4. Etiology

Etiology of Lennox-Gastaut Syndrome is very heterogeneous, including structural, genetic, infectious, metabolic, and idiopathic origins. About 70-80% of patients have a defined aetiology, while others are described as cryptogenic or idiopathic. [10,16]

The most common etiologic factors include the presence of structural abnormalities, including cortical dysplasia, hypoxic-ischemic encephalopathy, brain injury, intracranial bleeding, congenital brain malformations, tuberous sclerosis complex, and brain tumours. All these factors affect the normal brain structure, leading to the disruption of proper neuronal connectivity and facilitation of the epileptogenic network formation, causing seizures. [11,22]

Genetic factors are becoming more apparent due to the increased application of next-generation sequencing. Mutations in genes encoding such proteins as SCN1A, SCN2A, SCN8A, STXBP1, GABRB3, CHD2, DNMT1, and ALG13 have been linked with LGS. Such mutations affect ion channel functioning, neurotransmission, neuronal migration, and cortical development, resulting in generalised hyperexcitability and developmental delay. [10,14,25]

Acquired etiologies include prenatal infections, meningitis, encephalitis, perinatal asphyxia, metabolic conditions, serious brain injury, and other neurological problems occurring at the stage of brain development. In addition, some

children with infantile spasms progress and develop LGS later in life. However, about 20-30% of patients do not have an identifiable cause. [11]

5. Pathophysiology

Lennox-Gastaut Syndrome is described by multiple alterations in broad neuronal network consisting of cortical and subcortical areas. Several causes combine to cause sustained neuronal hyperexcitability, disturbed inhibitory neurotransmission and disrupted neurodevelopment, leading to seizures, cognitive deficits and behavioural disorders. [2,10]

5.1. Alterations in Thalamo-cortical Network Function

Impaired synchronisation of the cerebral cortex and thalamus is the key pathophysiology responsible for seizures development in LGS patients. Alteration of thalamocortical circuits leads to appearance of characteristic generalized slow spike-and-wave discharges (≤ 2.5 Hz) during wakefulness, and generalized paroxysmal fast activity in non-rapid eye movement sleep periods. Abnormal oscillating networks cause seizures onset and maintenance and participate in neurological dysfunction development. [2,10,11]

5.2. Neurotransmitter Dysbalance

Dysfunction of the balance between excitatory neurotransmission through glutamate receptors and inhibitory neurotransmission via γ -aminobutyric acid (GABA) mediators is a significant pathophysiology of LGS. Low levels of GABA-induced inhibition and elevated glutamate-induced excitation increase neuronal excitability and result in seizures development. Dysbalance is also responsible for the drug resistance of this syndrome. [3,8,10]

5.3. Mechanisms of Structural Abnormalities and Genetic Pathology

Pathogenic structural brain defects and gene mutations work through shared pathways via the dysfunction of neuronal migration, synaptogenesis, ion channels, and cortical connections. Such genes as SCN1A, SCN2A, SCN8A, STXBP1, GABRB3, CHD2, DNM1, and ALG13 were identified to be involved in disease pathogenesis. These factors negatively impact neuronal transmission and cause epileptic encephalopathy. [10,14,25]

5.4. Neuroinflammation

Current research shows that neuroinflammation plays a role in the persistence of seizures and the progression of the condition. Microglial and astroglial activation promotes the release of pro-inflammatory substances, such as interleukin-1 β , interleukin-6, and tumour necrosis factor- α , which increase neuronal excitability and stimulate recurring epileptic events. Chronic inflammation can also result in cognitive disorders and progressive neurological deficits. [1,10]

5.5. Mechanisms of Cognitive Deficits

The presence of numerous seizures and epileptic discharges leads to the disturbance of synaptic plasticity, maturation of neurons, as well as learning and memorising processes. The result is usually the development of progressive intellectual and behavioural deficits along with poor quality of life for the patient. Early detection and treatment are important for preventing neurological complications. [2,16,26]

6. Clinical features

The Lennox-Gastaut syndrome (LGS) is a complex developmental and epileptic encephalopathy that is marked by wide variation in seizure types, intellectual deficits, behavioural disorders, and EEG changes. The presentation of the disorder is highly variable and determined by various factors, including the aetiology of LGS, age at onset, and disease progression. Even though all the three features of LGS do not appear in the early stages of the disorder, the majority of the patients exhibit all three features. [2,6,11]

6.1. Types of Seizures

The combination of several types of seizures is typical for LGS. The tonic seizures are the characteristic type of seizures, and they usually develop while a patient sleep. This type of seizure involves sudden bilateral muscle stiffening of the neck, trunk, and extremities. It lasts for a few seconds up to one minute and occurs several times a day. The atonic seizures, which are also called drop attacks, develop due to a sudden loss of muscle tone and cause falls, facial trauma

and bone fractures requiring special helmet protection. Atypical absence seizures are accompanied by impairment of consciousness and have a gradual start and finish and also slow spike-and-wave discharge on EEG. Many patients suffer from myoclonic seizures, generalized tonic-clonic seizures, focal seizures and even from non-convulsive or convulsive status epilepticus. The patients have drug-resistant seizures in spite of taking many antiepileptic drugs. [11,22,3]

6.2. Cognitive Dysfunction and Developmental Delays

Cognitive problems are characteristic of LGS and are seen in most people suffering from LGS. The severity of intellectual problems is determined by the cause of the condition, the patient's age at the beginning of seizures, seizure frequency, and length of epilepsy period. Some children suffer from developmental delays prior to seizures, while others develop developmental regressions after seizures. Cognitive disorders include language development problems, memory issues, attention problems, executive functions, learning problems, and adaptive behavioural deficits. Epilepsy in the early years of life affects brain development negatively. [10,6]

6.3. Behavioural and Psychiatric Symptoms

It is not unusual for LGS patients to have behavioural problems that add to the stress of caregivers and diminish the quality of life. Examples of symptoms that have been observed among such patients include hyperactivity, aggression, impulsiveness, irritability, autism-like behaviour, attention deficit-hyperactivity disorder (ADHD), anxiety, depression, emotional lability, and insomnia. These behavioural problems are frequently seen in association with intellectual impairment and can get worse as the number of seizures increases. [16]

6.4. Electroencephalographic Abnormalities

Electroencephalography continues to be an important part of the diagnostic workup for LGS. The typical electroencephalogram shows generalised slow spike-and-wave discharges at a frequency of ≤ 2.5 Hz in the waking state and generalised paroxysms of fast activity during non-rapid eye movement sleep. This abnormality indicates the disruption of thalamocortical circuits and helps to distinguish LGS from other forms of developmental and epileptic encephalopathies. As the EEG changes can develop over time, repeat or prolonged video-EEG recordings are often needed to establish the diagnosis. [11,2,22]

6.5. Neurological and Systemic Manifestations

The results of neurological examination depend on the aetiology of LGS. If a patient has any structural brain abnormalities, there may be spasticity, hypotonia, ataxia, hemiparesis, or some other neurological deficits. Seizures and chronic anticonvulsant therapy can also cause gait problems, poor coordination, malnutrition, and physical disability. Moreover, recurrent injuries due to drop attacks add to the morbidity of the disorder. [16,26,10]

7. Diagnosis

The diagnosis of Lennox–Gastaut syndrome (LGS) is clinical and is based on seizure semiology, characteristic electroencephalographic (EEG) findings, cognitive or developmental impairment, and exclusion of other developmental and epileptic encephalopathies. In addition, because the full clinical picture may not be evident at presentation, the diagnosis of LGS is frequently established after more than one clinical assessment. The need for an early diagnosis should be emphasised since it can improve the patient's outcome by ensuring timely therapeutic intervention. [2,11,22]

7.1. Clinical Assessment

The clinical history should include the age at seizure onset, the types and frequency of seizures, developmental profile, history of neurological problems, family history of epilepsy, and response to anti-epileptic drugs (AEDs). Patients typically present with multiple seizure types, often including tonic seizures, and the majority of them are usually diagnosed before the age of eight. Developmental delays or any form of intellectual disability may precede or follow the onset of seizures depending on the cause of the condition. [6,11]

7.2. Electroencephalography

The hallmark of LGS is the slow spike-and-wave pattern (≤ 2.5 Hz) associated with generalised paroxysmal fast potentials that are seen during wakefulness and non-rapid eye movement (NREM) sleep during video-telemetry. EEG should always be performed when diagnosing LGS, while prolonged video-EEG monitoring is recommended if the diagnosis is uncertain. [2,11]

7.3. Neuroimaging

An extensive neuroimaging work-up using magnetic resonance imaging (MRI) is an essential part of the diagnostic evaluation. MRI should be performed in all patients to determine whether there are any cortical malformations, hypoxic-ischemic injury, tuberous sclerosis, vascular problems, tumours, or other structural anomalies. The outcome of the procedure is often critical in identifying the cause of the condition, which determines the patient's prognosis and treatment options, including epileptic surgery. [6,10]

7.4. Genetic and Metabolic Screening

Genetic and metabolic screening has greatly improved in recent years due to the emergence of chromosomal microarray hybridisation, epilepsy gene panels, and exome sequencing technologies. These procedures are critical in diagnosing developmental and epileptic encephalopathy by identifying various genetic causes that could benefit from specific treatments. The metabolic work-up is indicated in cases of early-onset epilepsy, regression of development, and suspicion of inherited metabolic diseases. Similar findings can also be detected in patients with developmental epileptic encephalopathies. [10,14]

7.5. Epileptic Encephalopathy with Differential Diagnosis

LGS is a catastrophic epileptic encephalopathy that often overlaps with other conditions that present with similar symptoms. Other differential diagnoses include West syndrome, Dravet syndrome, epilepsy with myoclonic-atonic seizures (Doose syndrome), and other developmental epileptic encephalopathies that have genetic causes. All these conditions can present with tonic seizures alongside other seizure types, developmental regression, or intellectual disabilities. As a result, the final diagnosis should be made after a thorough evaluation of the patient's symptoms and physical examination, including EEG results, clinical assessment, age at onset, and genetic and neuroimaging studies. [10,25]

8. Management

The management of Lennox-Gastaut syndrome (LGS) entails a holistic, interdisciplinary, and customised strategy because it is hard to achieve full seizure control. [2,26,29] The main objectives in the management of this condition are to lower the seizure rates and severity, limit injuries from the seizures, especially drop attacks, promote good cognitive and behavioural development, and improve the quality of life in general. Early diagnosis and timely treatment are critical to avoid neurological impairment. The current treatment involves the use of ASMs, dietary therapy, neuromodulators, epilepsy surgery, rehabilitation, and precision treatments.

8.1. Anti-epileptic Drugs

Antiepileptics continue to be the mainstay of LGS treatment. Nonetheless, owing to pharmacoresistance characterising the syndrome, polytherapy is needed in many patients rather than monotherapy. Selection of drugs depends on seizure type, patient's age, associated conditions, side effects, and previous experience. [3]

Valproic acid is usually seen as a first-line therapy drug owing to its anticonvulsive effect on several types of seizures, including tonic, atonic, atypical absence, and generalised tonic-clonic ones. This drug is often chosen as monotherapy unless there are contraindications. However, regular monitoring of the patient's condition during therapy is required because of possible development of liver toxicity, thrombocytopenia, hyperammonemia, pancreatitis, and weight gain [8,29].

Lamotrigine is quite often used as an additional drug and has proven efficacy in reducing seizure attacks and increasing the patient's awareness and cognitive abilities. Owing to a considerable increase in concentration caused by concurrent use of valproate, special attention should be paid to gradual dosage increase.

Clobazam, which belongs to the class of drugs called 1,5-benzodiazepines, is quite effective in treating drop seizures and therefore is suggested as one of the preferred treatments in LGS. Clobazam can lead to sedation, behavioural change, and development of tolerance with long-term use.

Rufinamide is an approved drug for adjunctive therapy in LGS and is known for providing considerable relief from tonic-atonic seizures, especially drop attacks. Rufinamide increases the inactive phase of voltage-gated sodium channels, resulting in reduced neuronal hyperexcitability. Common side effects are dizziness, nausea, somnolence, and shortening of the QT interval. [3,8]

Topiramate is another broad-spectrum ASM and has been proven to be efficient in controlling many types of seizures in LGS. The limitations in the use of topiramate are cognitive slowing, anorexia, nephrolithiasis, paresthesia, and metabolic acidosis.

The emergence of cannabidiol (CBD) as an important add-on treatment was made after the success of randomised clinical trials that proved to provide a clinically relevant reduction in drop seizures. [4,20,21] The administration of cannabidiol usually goes along with clobazam, but their combined use can lead to increased sedation as a result of pharmacokinetic interactions that require dose adjustments and liver monitoring.

Fenfluramine has recently been prescribed for LGS, as clinical trials revealed a clinically relevant reduction in the incidence of seizures, mainly drop attacks. Unlike its previous prescription for weight loss purposes, today the drug is taken in lower doses under cardiovascular monitoring as a consequence of possible valvulopathy and pulmonary hypertension; however, these side effects are rare enough in clinical practice. [17,29]

Levetiracetam, zonisamide, felbamate, and perampanel can be prescribed for specific patients who suffer from refractory epilepsy. Felbamate is only prescribed for cases when there are serious complications with other anticonvulsive drugs, as it is associated with aplastic anaemia and hepatic failure.

8.2. Dietary Therapy

Dietary therapy constitutes an essential non-medication alternative, especially in drug-resistant LGS in children. The ketogenic diet (KD), which is comprised of a high-fat, low-carbohydrate intake, leads to ketosis and changes in brain metabolic processes, hence effective seizure control. Studies have repeatedly shown that about half of patients treated have shown over 50% seizure reduction, while some patients have attained nearly complete seizure cessation.

Other types of diets, such as the modified Atkins diet (MAD) and low glycemic index treatment (LGIT), can be adopted by adolescents and adults who cannot adhere to the classical KD regime. These diets provide more freedom regarding food intake but still possess seizure control effects. Possible side effects include gastrointestinal problems, dyslipidemia, renal stone formation, nutritional deficiency, and poor growth; thus, dietary therapy should be done under expert guidance. [13,26]

8.3. Surgical and Neuromodulation Treatment Options

Surgery is recommended for patients with medically refractory LGS who experience disabling seizures even after optimised medication treatment. The effect of corpus callosotomy is especially pronounced among those with atonic and drop attack seizures, since the procedure helps stop the spread of seizures between hemispheres and thus reduces the number of falls and associated injuries. Though seizure freedom is rarely attained, significant improvement in quality of life is usually noted. [7,26]

Vagus nerve stimulation (VNS) represents one of the approved methods for treatment of LGS. Stimulation of the left vagus nerve leads to changes in widespread brain networks that are involved in the initiation of seizures. Numerous clinical trials have proved a sustained decrease in seizure frequency along with improvements in consciousness, mood and quality of life. Adverse events include hoarseness, discomfort in the throat, cough and changes in voice due to stimulation.

Resective epilepsy surgery may help some patients with generalised seizures due to a defined epileptogenic focus. A detailed presurgical assessment is required to make the decision about surgery. It should involve prolonged video electroencephalography, high-resolution MRI and functional imaging.

Deep brain stimulation (DBS), especially aimed at the centromedian nucleus of the thalamus, is now considered a novel treatment for very difficult cases of LGS. Even though there is a lack of sufficient research at this point, there are already some clinical reports pointing to benefits in terms of seizure load and severity. [19,7]

8.4. Precision Medicine and New Treatment Options

The recent developments in molecular genetics have revolutionized the knowledge of LGS and provided possibilities for precision medicine. Discovery of pathogenic changes in genes like SCN1A, SCN2A, SCN8A, STXBP1, CHD2, DNM1, and GABRB3 allows developing personalized treatments depending on the particular genetic mutation. Gene therapies, antisense oligonucleotides, gene therapy using viruses as vectors, and RNA therapies are currently being studied and may drastically change the treatment of developmental and epileptic encephalopathies in the future.

There is an ongoing study of new anticonvulsant drugs, improved methods of neuromodulation, targeted molecular therapies, and other treatments that may prevent the development of epilepsy instead of treating seizures only. These advancements constitute the prospective ways of improving the prognosis in patients with LGS.

8.5. Supportive and Multidisciplinary Treatment

Effective treatment goes beyond seizure control, and requires multidisciplinary team effort by pediatric neurologists, epileptologists, rehabilitation professionals, psychologists, psychiatrists, dietitians, physical therapists, occupational therapists, speech therapists, teachers, and social workers. Cognitive deficits, behavioral problems, autism spectrum disorder, attention-deficit hyperactivity disorder, sleep disorders, problems with feeding, and developmental delay must be evaluated and properly managed.

Parents need ongoing education concerning seizure first aid, antiepileptic drugs, protection from injuries, psychosocial assistance, and transitional care during adulthood. Individualized education plans and regular neurodevelopmental assessments ensure maximum independence and overall quality of life in the future. Even though seizure remission is rarely possible in these children, advancements in multidisciplinary treatment, novel pharmaceutical drugs, diets, neuromodulation techniques, and precision medicine have positively impacted the prognosis of Lennox-Gastaut syndrome. [26,29]

9. Conclusion

Lennox-Gastaut syndrome (LGS) represents a very serious form of developmental and epileptic encephalopathy defined by the presence of many drug resistant seizures, cognitive dysfunction, behavior alterations and specific EEG changes. Due to the fact that the heterogeneous structure of LGS involves a great number of structural, genetic, metabolic, infectious and unknown causes, diagnosing and treatment represent rather complicated tasks which require careful clinical investigation, electrophysiological testing, imaging studies and genetical examinations aimed at defining the nature of the disease.

Although the advances in the field of anti-seizure drugs allowed making significant steps in improving the state of patients suffering from LGS, full seizure control cannot be achieved by medication treatment alone. Thus, complex treatment of LGS should include various measures, including dietary treatment, neuromodulation techniques, surgical interventions, rehabilitation and psycho-social help. The latest developments in molecular genetics, precision medicine, the appearance of new pharmacological products, like cannabidiol and fenfluramine, made it possible to increase the number of treatment alternatives and improve the results of therapy for some particular patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

- [1] Samanta D, Karakas C, Fine AL, Pong AW, Koh HY, Keator C, et al. Biomarker discovery in Lennox-Gastaut syndrome: Advances and challenges in electrophysiological, genetic, neuroimaging, and neuroinflammatory approaches. *Epilepsy Behav.* 2026;176:110834.
- [2] Warren AEL, Patel AD, Cross JH, Clarke DF, Dalic LJ, Grinspan ZM, et al. Mobilizing a new era in Lennox-Gastaut syndrome treatment and prevention. *Epilepsy Curr.* 2025;25(3):236-243.
- [3] Samanta D, Nath M. Current and emerging pharmacotherapies in Lennox-Gastaut syndrome. *Expert Opin Pharmacother.* 2025;26(10):1133-1147.
- [4] Borowicz-Reutt K, Czernia J, Krawczyk M. CBD in the treatment of epilepsy. *Molecules.* 2024;29(9):1981.
- [5] Gélisse P, Crespel A, Genton P, Dravet C. History of Lennox-Gastaut syndrome: Sixty years of advancements in therapeutic practices. *Seizure.* 2026;134:165-172.
- [6] Zhou Z, Jiao X, Gong P, Niu Y, Xu Z, Zhang G, et al. Clinical features and underlying etiology of children with Lennox-Gastaut syndrome. *J Neurol.* 2024;271(8):5392-5401.

- [7] Shields LBE, Oluigbo CO, Karakas C. Neuromodulation in Lennox-Gastaut syndrome: Emerging therapies and future directions. *Semin Pediatr Neurol.* 2025;56:101237.
- [8] Besag F, Vasey MJ, Chin R. Current and emerging pharmacotherapy for the treatment of Lennox-Gastaut syndrome. *Expert Opin Pharmacother.* 2023;24(11):1249-1268.
- [9] Verrotti A, Striano P. Novel therapeutic options for Dravet and Lennox-Gastaut syndrome. *Expert Rev Neurother.* 2021;21(11):1191-1194.
- [10] Na JH, Lee YM. Unraveling Lennox-Gastaut syndrome: From molecular pathogenesis to precision diagnosis and targeted therapy evolving therapeutic strategies. *Int J Mol Sci.* 2026;27(3):1382.
- [11] Pujar S, Cross JH. Diagnosis of Lennox-Gastaut syndrome and strategies for early recognition. *Expert Rev Neurother.* 2024;24(4):383-389.
- [12] Knowles JK, Warren AEL, Mohamed IS, Stafstrom CE, Koh HY, Samanta D, et al. Clinical trials for Lennox-Gastaut syndrome: Challenges and priorities. *Ann Clin Transl Neurol.* 2024;11(11):2818-2835.
- [13] Vasquez A, Fine AL. Dietary therapies in Lennox-Gastaut syndrome. *Semin Pediatr Neurol.* 2025;56:101238.
- [14] Miller IO, Sotero de Menezes MA. SCN1A seizure disorders. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, et al., editors. *GeneReviews®*. Seattle (WA): University of Washington; 1993-2026.
- [15] Hisamoto Y. Late onset Lennox-Gastaut syndrome. *Semin Pediatr Neurol.* 2025;56:101240.
- [16] Pino AF, Naik S, Erdemir G. Lennox-Gastaut syndrome: Comorbidities and clinical implications. *Semin Pediatr Neurol.* 2025;56:101239.
- [17] Knupp KG, Scheffer IE, Ceulemans B, Sullivan JE, Nickels KC, Lagae L, et al. Efficacy and safety of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome: A randomized clinical trial. *JAMA Neurol.* 2022;79 (6):554-564.
- [18] Sullivan J, Benítez A, Roth J, Andrews JS, Shah D, Butcher E, et al. A systematic literature review on the global epidemiology of Dravet syndrome and Lennox-Gastaut syndrome: Prevalence, incidence, diagnosis, and mortality. *Epilepsia.* 2024;65(5):1194-1208.
- [19] Dalic LJ, Bulluss KJ, Thevathasan W, Roten A, Churilov L, et al. DBS of thalamic centromedian nucleus for Lennox-Gastaut syndrome (ESTEL trial). *Ann Neurol.* 2022;91(2):253-267.
- [20] Wechsler RT, Burdette DE, Gidal BE, Hyslop A, McGoldrick PE, Thiele EA, et al. Consensus panel recommendations for the optimization of EPIDIOLEX® treatment for seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex. *Epilepsia Open.* 2024;9(5):1632-1642.
- [21] Talwar A, Estes E, Aparasu R, Reddy DS. Clinical efficacy and safety of cannabidiol for pediatric refractory epilepsy indications: A systematic review and meta-analysis. *Exp Neurol.* 2023;359:114238.
- [22] Amrutkar C, Riel-Romero RM. Lennox-Gastaut syndrome. *StatPearls.* Treasure Island (FL): StatPearls Publishing; 2022-2026.
- [23] Samanta D, Bhalla S, Bhatia S, Fine AL, Haridas B, Karakas C, et al. Antiseizure medications for Lennox-Gastaut syndrome: Comprehensive review and proposed consensus treatment algorithm. *Epilepsy Behav.* 2025;164:110261.
- [24] Poke G, Stanley J, Scheffer IE, Sadleir LG. Epidemiology of developmental and epileptic encephalopathy and of intellectual disability and epilepsy in children. *Neurology.* 2023;100(13).
- [25] Paprocka J, Coppola A, Cuccurullo C, Stawicka E, Striano P. Epilepsy, EEG and chromosomal rearrangements. *Epilepsia Open.* 2024;9(4):1192-1232.
- [26] Nelson JA, Knupp KG. Lennox-Gastaut syndrome: Current treatments, novel therapeutics, and future directions. *Neurotherapeutics.* 2023;20(5):1255-1262.
- [27] Katayana A, Diaz-Medina G. Epilepsy. *Neurol Clin.* 2021;39(3):779-795.
- [28] Pong AW, Xu KJ, Klein P. Recent advances in pharmacotherapy for epilepsy. *Curr Opin Neurol.* 2023;36(2):77-85.
- [29] Auvin S, Arzimanoglou A, Falip M, Striano P, Cross JH. Refining management strategies for Lennox-Gastaut syndrome: Updated algorithms and practical approaches. *Epilepsia Open.* 2025;10(1):85-106.
- [30] Menon RN, Cross JH. Childhood epilepsy. *Lancet.* 2025;406(10503):636-649.