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A Comprehensive Review on Clinical Characteristics and Management of Lennox-Gastaut Syndrome

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ABSTRACT

Lennox-Gastaut Syndrome (LGS) is a severe and rare form of epilepsy that typically begins in childhood, although it may continue well into adulthood. It is a complex developmental disorder characterised by multiple seizure types, cognitive impairment, and abnormal electrical activity of the brain. LGS is thought to be caused by abnormal brain development or brain damage. Children with LGS typically have intellectual disabilities, behavioural problems, and developmental delays. Tonic seizures, which involve sudden contractions of the muscles in the body and loss of consciousness, are the most common type of seizure associated with LGS. Other common types of seizures occurring in LGS that are necessary to make a clinical diagnosis are atypical absence seizures, myoclonic seizures, and atonic seizures. Despite advances in medical treatments, LGS remains a difficult condition to treat, with many patients experiencing seizures and cognitive dysfunction regardless of the treatment. Early diagnosis and treatment, on the other hand, can help improve outcomes and reduce long life dependency of LGS patients

Keywords: Lennox-Gastaut Syndrome; Development Epileptic Encephalopathy; Epilepsy; Cognitive Impairment

I. BACKGROUND

Treatment of LGS is very complex; in order to reduce unexpected deaths due to seizures, reduce years spent with disabilities, and improve patients' cognitive functions, it is critical to correctly diagnose and follow up on childhood patients until adulthood for clinical characteristics of LGS. As LGS persists into adulthood and associated seizures remain drug resistant, repeated evaluation of the LGS triad and protocol may be required in nearly all cases. [15]

II. INTRODUCTION

Lennox-Gastaut Syndrome (LGS) is a severe form of childhood 'Development Epileptic Encephalopathy' (DEE) resulting from high-frequency, synchronised activity in bilaterally distributed brain networks that develops in a susceptible age period in childhood and affects patients well into adulthood.[3,4] The International League Against Epileptic Encephalopathies (ILAE) Task Force defined epileptic encephalopathies as diseases in which epileptic activity contributes to severe cognitive and behavioural impairments above and beyond that would be expected from the underlying aetiology alone.[3] LGS usually appears between the ages of 18 months and 8 years, with peak occurrence rates occurring between the ages of 3 and 5 years often persisting into adulthood.[1-4,7] The symptoms most commonly associated with LGS are motor symptoms such as, Clonic - rhythmic jerking; Atonic - muscles losing tonicity temporarily and Tonic - muscle rigidity or stiffening. Non motor symptoms include staring spells; changes in emotions, cognition; lack of movement (behaviour arrest), tachy/bradycardia, dyspnoea, cyanosis, diaphoresis, irregular temperature regulation. [11,22] The true incidence of Lennox-Gastaut syndrome is unknown due to the various criteria used by neuro physicians to diagnose the syndrome. Trevathan et al (1997) conducted a retrospective population-based, cross-sectional study and found that the prevalence of LGS among Atlanta children was 0.26/1,000, accounting for only 4% of all childhood epilepsy.[12] Similarly, prospective epidemiology studies had observed that LGS is a rare syndrome with prevalence varied from 4.2 to 60.8 per

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100,000 people across studies for probable LGS and 2.9 to 28 per 100,000 people for confirmed with narrow definition of LGS.[13,14] According to many prevalence studies the incidence of LGS is predominant in males than in females.[3,9,13]

OBJECTIVES

The primary goal of this review is to educate physicians on potential aspects that can be focused on to provide better treatment for patients with LGS, as well as to emphasise the importance of identifying clinical characteristics and ruling out differential diagnoses in LGS patients.

METHODOLOGY

We conducted a literature search using databases such as PubMed, Mendeley, Medline, and Google Scholar. The search terms used for surveying were "Lennox-Gastaut Syndrome," "Clinical Characteristics," "Management," and "Treatment of LGS," and our search yielded _ of articles. Our search period was from 2005 to 2023 and was limited to only the English language.

III. DISCUSSION

CLASSIFICATION

To provide better treatment options and perform a detailed differential diagnosis of the patient, it is necessary to have a clear description of the classification of childhood epilepsies. The International League Against Epilepsy classification (ILAE) of 2020 established a three-tiered system, with epilepsy syndrome at the third level. Epilepsy syndromes beginning in childhood have been divided into three categories:

1. Self-limited Focal Epilepsies
2. Generalised Epilepsies
3. Developmental and/or Epileptic Encephalopathies, comprising of five other syndromes with Lennox–Gastaut syndrome

ETIOLOGY

According to the National Organization for Rare Diseases (NORD) report, LGS can be either cryptogenic or symptomatic. The cause of cryptogenic LGS is unknown or cannot be determined even after evaluation, and there is no associated underlying condition. Individuals with cryptogenic LGS do not have a history of seizure activity, neurological problems, or cognitive impairment prior to the onset of the disorder. While symptomatic LGS occurs either due to structural, genetic or metabolic causes. Symptomatic LGS develops secondarily as a result of brain injury suffered during the prenatal, perinatal, or neonatal periods. [6,7] Prenatal causes include conditions like tuberous sclerosis, cortical dysplasias, congenital central nervous system (CNS) infections, brain malformations, and hereditary metabolic disorders, among others. Hypoxia, birth injuries, sepsis, low birth weight, and hyperbilirubinemia, meningitis, and encephalitis are all perinatal and postnatal causes. [2,9,51]

EPIDEMIOLOGY

Around 2-5% of all childhood epilepsies are caused by LGS. [61,62] But only around 10% of these instances occur before the age of five. [9,62-65] An approximately 0.10 – 0.28 cases of LGS occur for every 100,000 people. Children are estimated to be affected at a rate of 2 per 100,000. The prevalence is roughly 26 per 100,000 individuals overall compared to women, men are more likely to have LGS. [63, 64]

CLINICAL CHARACTERISTICS

Lennox-Gastaut syndrome (LGS) is characterised primarily by the presence of a tonic seizure with a triad of multiple seizure types that are often multidrug resistance, electroencephalogram (EEG) findings inferring diffuse slow spike-and-wave (≤ 2.5 Hz) and generalised paroxysmal fast activity (>10Hz), and lastly cognitive and intellectual disability. These specific characteristics of LGS are known as classic LGS triad or as core LGS features.

ELECTROENCEPHALOGRAM (EEG)

The following interictal patterns are mandatory for the diagnosis of LGS:

Generalised slow spike-and-wave (GSSW): This interictal slow spike-and-wave (SSW) pattern is characterised by spikes or sharp waves (70–200 ms), followed by negative high-voltage slow waves (350–400 ms), that are bilaterally synchronous, often anterior predominant, and occur at a frequency of ≤2.5 Hz. GSSW complexes are more frequent in children, whereas in adolescence and adulthood there is a decrease in the frequency of the spike-and-wave pattern. The majority of patients no longer exhibit the typical slow SSW pattern, after the age of 16 years. [16,17]

Generalised paroxysmal fast activity (GPFA): GPFA pattern consists of bursts of diffuse or bilateral fast (>10 Hz) activity often seen during sleep. These are typically brief, lasting a few seconds or less. [3]

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COGNITIVE DYSFUNCTION

Many studies have found that LGS has a profound deleterious impact on cognitive and psychosocial function. Cognitive impairments are clinically evident in around 20-60% of LGS patients at the time of diagnosis. It usually worsens over time, and serious intellectual problems have been observed in 75-95% of patients within 5 years of onset. [4,7] Blume et al (2004) presented a clear hypothesis and experimental evidence that excessive neocortical excitability observed during LGS is due to immature CNS. The epileptogenic processes associated with the LGS can result in abnormal patterns of CNS activity that competes with normal developmental mechanisms leading to cognitive impairment. [22] Recurrent or prolonged seizures impair brain growth and damage the neocortex and hippocampus. In addition to cognitive dysfunction, many patients also develop behavioural and psychiatric disorders. Attentional problems, aggression, hyperactivity and autistic features can be common in LGS and may be associated to many factors such as use of AEDS and epileptogenic mechanisms. [23,51,52]

SEIZURE TYPES

Tonic seizures are the most common and mandatory type of seizure in LGS, and a second seizure type, which may include any of the following seizure types, is required for the diagnosis of LGS.

Tonic seizures

Tonic seizures vary in severity consisting of a sustained increase in axial and limb muscle contraction lasting from 3 second to 2 min. Tonic seizures may be subtle and limited to eye movements (slow upward eye rolling or deviation), alterations in respiration, facial tightening or grimace, and a brief vocalisation. [3,7] They may present, at times with flexor movements of the head or trunk, apnea and bilateral fist clenching. Flexion of the lower limbs and axis can sometimes lead to a forceful fall, further complicating differential diagnosis with atonic seizures. Transient truncal and proximal limb stiffening can also be present. In such cases, the use of polygraphy, including surface electromyography recording, is particularly useful. [10] More dramatic tonic seizures may involve axial muscles with a vibratory component (tonic vibratory). The frequency of tonic seizures is underestimated as they are more prominent during sleep (NREM sleep). The associated EEG shows a sudden onset of generalised, diffuse, rapid (10–13 Hz), low-amplitude spikes.

Atypical absence

The second leading seizure type occurring in LGS is atypical absence. Atypical absence seizures are difficult to detect as they are very subtle. The main clinical manifestation is a brief lapse in consciousness, though some awareness may be preserved. Atypical absence seizures do not have a clear onset and offset; patients may appear to fade in and out of consciousness. The accompanying EEG shows slow and irregular spike waves (<2.5 Hz), which may be difficult to differentiate from interictal bursts. [3,10]

Sudden tonic or atonic seizures

Nearly 50% of LGS patients experience "drop attacks." Drop attacks, unlike tonic and atypical absence seizures, are not subtle and are common cause of fall resulting in severe injuries to the nose or teeth. Atonic seizures consist of sudden, brief (1–4 s) and severe loss of postural tone. [10] They are preceded by a single generalised myoclonic jerk, followed by a tonic contraction of axial muscles or axial atony, or a combination of the two, resulting in sudden fall. They are frequent and involve the whole body or only the head. Longer atonic seizures lasting for 30 s up to 1–2 min arerare. [7,10]

Nonconvulsive status epilepticus

Nonconvulsive status epilepticus occurs in about two thirds of LGS patients and consists of continuous atypical absences that cause varying levels of diminished consciousness. Nonconvulsive status may also feature occasional superimposed brief tonic seizures. The EEG shows a nearly continuous slow spike-and-wave pattern occasionally interrupted by brief bursts of generalised polyspikes. Nonconvulsive status may last from hours to weeks and is particularly difficult to recognize in patients with severe cognitive impairment. It is not easy to assess the effect of these prolonged episodes; however, there is a strong suspicion that nonconvulsive status is a major contributor to intellectual impairment. [3,10]

Myoclonic seizures

Most patients with LGS have myoclonic seizures that may be subtle or severe enough to cause falls. Myoclonia are not required for the diagnosis of LGS and occur in many other epilepsy syndromes. These seizures seem to occur most

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frequently in the later stages of LGS. However, the diagnosis of LGS may be obscured if they are very frequent. [7]

DIFFERENTIAL DIAGNOSIS

LGS symptoms evolve over time, making a diagnosis difficult to make immediately and necessitating years of follow-up. [15,66] Atypical benign focal epilepsy of childhood, Dravet syndrome, myoclonic-atonic epilepsy (Doose syndrome), Pseudo-Lennox syndrome, and West syndrome are among the alternative diagnosis that can be ruled out while considering LGS. [67] Although not all children with epilepsy can be diagnosed with a specific syndrome, identifying one can help with management and prognosis. [3]

MANAGEMENT

The prime focus of LGS treatment is to reduce the frequency and severity of seizures to the greatest extent possible in order to improve quality of life and reduce years spent with disability, while acknowledging that complete seizure freedom is unlikely for most patients. However, multiple factors complicate the successful treatment of LGS. Management of LGS consists of both pharmacological treatment and non-pharmacological treatment. Anti-Epileptic Drugs (AEDs) are frequently used in pharmacological treatment and are prescribed based on knowledge gained from clinical research studies.

PHARMACOLOGIC TREATMENT

Although, AEDs are generally accepted as the primary treatment option for LGS, no single AED has proven to be effective in patients with the syndrome, as well as continued polytherapy increases the risk of adverse effects. [7,18,19] Due to the various types of seizures that can occur in LGS and the use of drug combinations, primarily based on retrospective data, choosing the best AED can be challenging. The fact that an AED may be helpful in controlling one type of seizure while aggravating another further complicates views on treatment. Furthermore, Loscher et al. (2006) conducted a review of experimental and clinical evidence on the loss of AED effects on long-term treatment and concluded that tolerance to effect can occur in a minority of patients with epilepsy initially responding to AEDs. Dose increments are not able to overcome effect tolerance and, in this case, the epilepsy can be drug resistant. Additionally, they provided evidence that once tolerance to one AED develops, it may extend to other AEDs. Such cross-tolerance was a key factor in patients with medically intractable epilepsy developing "multidrug resistance". The review also duly noted that despite these factors, the extent of tolerance to AEDs in patients with epilepsy has never been comprehensively studied. [19]

First line therapy

According to the recent National Institute for Health and Care Excellence (NICE) guidelines, first line treatment for LGS consists of prescribing sodium valproate to boys, men and women who are not of childbearing potential. Sodium valproate should be avoided in women and girls of childbearing potential, unless other options are ineffective. In children and adults, adjunctive treatment with lamotrigine is considered when sodium valproate is ineffective. If the adjunctive treatment is also ineffective or not tolerated, rufinamide and topiramate can be prescribed. Note that topiramate can impair the effectiveness of hormonal contraceptives. Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, or vigabatrin should not be given. Only the use of felbamate is recommended when all of the AEDs listed above have proven ineffective. The International League Against Epilepsy guidelines also concur the notion of NICE guidelines that valproic acid should be avoided wherever possible in women of childbearing age and recommends valproic acid as first line treatment wherever necessary while discussing the risk benefit ratio. [3]

Wheless et al (2005) surveyed a group of 41 US epilepsy physicians the experts were asked to recommend overall treatment approaches for specific syndromes including LGS. Many of the experts recommended valproate as initial therapy for LGS and should be considered as a treatment of choice, with topiramate and lamotrigine also as first line therapy. Second-line agents were zonisamide, levetiracetam, felbamate, and the ketogenic diet. [20] Through our literature search we came to conclude that valproic acid should be given as first line therapy for patients suffering from LGS.

Valproic, lamotrigine, topiramate, rufinamide, and clobazam, as well as other antiepileptic drugs such as cinromide, felbamate, levetiracetam, zonisamide, and benzodiazepines, are frequently used to treat LGS. [9]

Kelly Knupp et al (yr of the study) conducted a PHASE-3 RCT in patients with treatment-

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refractory LGS which demonstrated a reduction in the drop seizure frequency in patients who used 0.7 mg/kg/day fenfluramine. Fenfluramine also significantly reduced GTC seizures, indicating that it may be a beneficial option for patients with this seizure subtype.

NON-PHARMACOLOGICAL TREATMENT

Nonpharmacologic therapies are crucial in the management of LGS in many patients, particularly in patients presenting with psychiatric comorbidities, refractory or drug resistant epilepsy. [26] Ketogenic Diet, Vagus Nerve Stimulation, and Corpus Callosotomy surgery are some additional therapy options for people not responding to antiepileptic medications. Moreover, new novel stimulation techniques that excite the centromedian thalamic nucleus are currently being tested in clinical studies. [25]

KETOGENIC DIET (KD)

Ketogenic diet (KD) is a restricted-calorie diet that is high in fat, low in carbs, and moderately high in protein.[27] The beta-hydroxybutyrate, acetoacetate, and acetone concentrations in the KD are elevated, simulating the systemic ketosis of the fasting state.[28] The KD and comparable diets have been demonstrated to be effective in treating a number of pharmacoresistant paediatric epilepsies, including LGS.[27] Although the exact mechanism of action for the KD's anticonvulsant effects is unknown, theories suggest that the ketone bodies alters the metabolism of glutamatergic and GABAergic neurotransmitters, restrict or divert glycolysis, improve cellular bioenergetics, mitochondrial function, and reduce oxidative stress, as well as have direct inhibitory effects on fatty acids and the tricarboxylic acid cycle.[27,28,32] In youngsters with drug-resistant epilepsy, KD lowers seizure frequency while children with refractory epilepsy can benefit from KD as a therapy option. A 20-year Cochrane Database Systematic Review was uncovered by Kirsty J. Martin-McGill, who was investigating 11 Randomised controlled trials for KD in drug-resistant epilepsy. Patients in the KD groups had a range of 35% to 56% seizure independence rates against 0% to 18% in the control groups, who were more likely to achieve a 50% reduction in seizure frequency. [29] In addition to seizure management, the KD may also aid patients with refractory epilepsy by enhancing their subjective levels of alertness, attentiveness, and general cognition. [30]

VAGUS NERVE STIMULATION

A well-known treatment for drug-resistant epilepsy is vagus nerve stimulation (VNS) which involves intermittent electrical stimulation of the left cervical vagus nerve using an implanted helical electrode connected to a pulse generator. There is some evidence that VNS is effective in treating LGS. Based on four studies, the American Academy of Neurology (AAN) updated its evidence-based guidelines for the use of VNS to treat epilepsy and found that it may be able to reduce seizures by more than 50% in individuals with LGS who have the condition. [33,34,35] It has been demonstrated that both animal and human seizure frequency can be reduced by routine VNS. Yet, the exact mechanisms and pathways by which this phenomenon occurs is not fully understood. There is no single and consistent method of action. Vast autonomic, reticular, and brainstem tissues are said to be affected when the left vagus nerve is stimulated. And according to the mounting data Noradrenaline may also be involved in the mechanism. The brain structures stated are stimulated, and the noradrenaline and GABA levels may be released contributing to the reduction in seizure frequency. [25] The early incorporation of VNS therapy should be taken into consideration as it may reduce the adverse effects of both seizures and epileptic abnormalities in patients with LGS who receive treatment very early in their disease process. This has shown to result in overall favourable outcomes in patients with LGS. Patients with LGS should be thoroughly assessed for VNS therapy implantation before more invasive palliative surgical operations in order to improve seizure control in the individuals. [36-38]

CORPUS CALLOSOTOMY

For individuals with refractory epilepsy, the corpus callosotomy surgery includes severing the corpus callosum, the bundle of nerve fibres that connects the two cerebral hemispheres, to stop the spread of epileptic discharges and seizure patterns to both hemispheres. Patients who have drop attacks are given extra attention. [39] During a corpus callosotomy, the corpus callosum is either completely severed or severed anteriorly by two-thirds. In general, corpus callosotomy is performed either through an open approach using a standard craniotomy and an operating microscope, or alternatively using a mini-craniotomy with endoscope assistance. The latter has the advantages of a smaller incision, minimal brain retraction, and reduced postoperative pain.[40-42] Recent case

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reports have demonstrated the effectiveness of a minimally invasive technique called Stereotactic Laser Interstitial Thermal Treatment (LITT) guided by and MRI.[43-50] In the largest study carried out to date by Tao et al (2020), investigating MRI-guided stereotactic laser anterior corpus callosotomy (SLACC) in 10 adult patients with LGS, eight (80%) patients had more than 80% reduction in drop attacks, of which five (50%) patients became free of drop attacks, and six (60%) patients had more than 80% reduction in seizures, with two (20%) patients becoming seizure free.[50]

RESECTIVE EPILEPSY SURGERY

Individuals suffering from treatment resistant epilepsy surgical management remains the most successful approach for long-term seizure control. LGS has historically been described as an incurable epileptic encephalopathy due to the often diffuse or generalised EEG findings and intractable seizures despite aggressive medical management.[54,57] However, major developments in neurophysiology and neuroimaging have made it possible to more accurately identify and treat epileptogenic zones.[55,56] In most cases, LGS patients with structural aetiology and lesions that are primarily in one hemisphere or Tuberous sclerosis complex(TSC) are the only ones for whom resective surgery is often advised.[39][59] A prospective study from Korea examined the long-term effects of resective epilepsy surgery in 90 individuals with LGS who had focal epileptic pathology. With an average postoperative follow-up of 6.1 2.2 years, 45 patients (50%) had no seizures, and 15 (16.7%) reported seizures that occurred alone. Notably, at the second and third follow-ups (2–3 years after surgery) and at the fourth follow-up (4-6 years after surgery), seizure-free patients had improved adaptive behaviour and social competence compared to patients with persistent seizures, and a shorter latent period between the onset of the seizures and the surgery was associated with better adaptive behavioural functioning. The authors came to the conclusion that it's crucial to conduct thorough, early tests to identify patients with focal aetiologies who are eligible in order to improve behavioural functioning. [60] A controlled trial has not been reported, and the evidence for resective epilepsy surgery in LGS patients is generally thin. [32,60]

IV. CONCLUSION

The ILAE guidelines should be followed to classify the epileptic manifestations in the LGS patients in India. This can help in diagnosis and provide better holistic treatment to the patient while minimising the years spent with disability. The following recommended general guidelines such as NICE, AAN and ILAE for the treatment of LGS can help to reduce the global burden of the disease and the risk of Sudden Unexpected Death in Epilepsy (SUDEP) patients, thereby lowering the overall mortality rate associated with LGS. Most epilepsy cases are treated by either neurologists or paediatricians; improving their knowledge and keeping them up to date on guidelines and clinical studies may aid in providing patients with a more holistic approach. Additionally, more clinical trials on AEDs and increased knowledge of patients and attendees for non-pharmacological management are required for better management of LGS.

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