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REVIEW ARTICLE

Lennox-Gastaut syndrome: a comprehensive review

Ali A. Asadi-Pooya [1,2]

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Abstract Lennox-Gastaut syndrome (LGS) is considered an epileptic encephalopathy and is defined by a triad of multiple drug-resistant seizure types, a specific EEG pattern showing bursts of slow spike-wave complexes or generalized paroxysmal fast activity, and intellectual disability. The prevalence of LGS is estimated between 1 and 2% of all patients with epilepsy. The etiology of LGS is often divided into two groups: identifiable (genetic-structural-metabolic) in 65 to 75% of the patients and LGS of unknown cause in others. Lennox-Gastaut syndrome may be considered as secondary network epilepsy. The seizures in LGS are usually drug-resistant, and complete seizure control with resolution of intellectual and psychosocial dysfunction is often not achievable. Reduction in frequency of the most incapacitating seizures (e.g., drop attacks and tonic-clonic seizures) should be the major objective. Valproate, lamotrigine, and topiramate are considered to be the first-line drugs by many experts. Other effective antiepileptic drugs include levetiracetam, clobazam, rufinamide, and zonisamide. The ketogenic diet is an effective and well-tolerated treatment option. For patients with drug resistance, a further therapeutic option is surgical intervention. Corpus callosotomy is a palliative surgical procedure that aims at controlling the most injurious seizures. Finally, vagus nerve stimulation offers reasonable seizure improvement. The long-term outcome for patients with LGS is generally poor. This syndrome is often associated with long-term adverse effects on intellectual development, social functioning, and independent living.

Keywords Definition · Epidemiology · EEG · Lennox-Gastaut syndrome · Epilepsy · Treatment

Introduction

Lennox-Gastaut Syndrome (LGS) was first described by Lennox as "Petit mal variant." Later and in 1966, this syndrome was described by Marseille School in France, where Gastaut et al. proposed the term Lennox syndrome to describe a specific childhood-onset epilepsy syndrome characterized by frequent tonic and absence seizures [1]. The definition of LGS subsequently was clarified by the International League Against Epilepsy (ILAE) in 1989 [2]. Lennox-Gastaut syndrome is considered an epileptic encephalopathy, which implies that the epileptic activity contributes to mental problems and behavioral disorders [3]. In this article, I have provided a comprehensive review of all aspects of this syndrome.

Definition

Lennox-Gastaut syndrome is a severe form of epilepsy with onset in childhood. This syndrome is defined by a triad of multiple drug-resistant seizure types, a specific interictal electroencephalographic (EEG) pattern showing bursts of slow spike-wave (SSW) complexes or generalized paroxysmal fast activity (GPFA) and intellectual disability (ID) [3]. However, not all patients have all of the core seizure types (i.e., tonic, atonic, and atypical absences), especially at the onset [4]. In addition, the interictal EEG pattern of SSW, that is associated with LGS, is not pathognomonic to the disorder [4]. Some

✉ Ali A. Asadi-Pooya
aliasadipooya@yahoo.com

[1] Neurosciences Research Center, Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran

[2] Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA

experts consider the presence of GPFA that may or may not be associated with tonic seizures, an essential criterion [4]. Finally, it has been thought that ID is seen in all patients and it was suggested that it should be a part of the diagnostic criteria [3], but there are reports on patients with LGS and without ID [5, 6]. Therefore, not all patients have all the three criteria at the onset of the disease and diagnosis may be established after several years of follow-up.

Epidemiology

The prevalence of LGS is estimated between 1 and 2% of all patients with epilepsy [7] and between 1 and 10% of childhood epilepsies [6–10]. This wide range is probably the result of the different diagnostic criteria and research settings in various studies. In a previous study from the USA [8], the authors conducted a population-based study of LGS. Children were defined as having LGS if they had onset of multiple seizure types before age 11 years, with at least one seizure type resulting in falls, and an EEG demonstrating SSW complexes (< 2.5 Hz). Intellectual disability was not used as a diagnostic criterion. The lifetime prevalence of LGS at age 10 years was 0.26/1000. Ninety-one percent of those with LGS had ID. Seventeen percent of all children with profound ID (IQ < 20) had LGS. Lennox-Gastaut syndrome accounted for about 4% of all childhood epilepsies [8]. In one study from Iran, 5.4% of all patients with epilepsy (children and adults) had LGS [6]. Because LGS rarely remits, prevalence studies should find a higher frequency of LGS than incidence studies [3]. In a population-based study of children with new-onset epilepsy (incidence cases) [11], 12% had symptomatic generalized epilepsies. However, only 4% of those with symptomatic generalized epilepsies had LGS. Of all new-onset epilepsies, the incidence of LGS was only 0.6% [3, 11].

Age at the onset of LGS usually occurs before 8 years [3, 6]. However, late-onset LGS has been reported in the literature. In about 10% of the patients, in one study, the syndrome started after 8 years of age [6]. In another study, 16% of the patients with LGS had late-onset disease (i.e., age at onset > 8 years) [10]. Males often outnumber females in LGS. Male to female ratio in one study was 1.6 [6], and in another study, this ratio was 1.49 [10]. The reason for this male predominance is not clear yet.

Etiology

The etiology of LGS is often divided into two groups: identifiable (genetic-structural-metabolic) or unknown [3]. Approximately, 65 to 75% of patients have an identifiable cause. The list of the identifiable etiologies may include brain damage (e.g., birth asphyxia or head injuries), tuberous sclerosis complex, congenital central nervous system (CNS) infections, brain malformations, and hereditary metabolic disorders, among other etiologies. In one previous study [6], epilepsy risk factors were reported to be as follows: perinatal complications in 25% (including hypoxic-ischemic insults, sepsis, low birth weight, and hyperbilirubinemia), CNS infections in 3.7%, and history of significant head trauma in less than 1%. Identifiable causes are usually the result of a static brain disorder; progressive or metabolic disorders are rare [3]. Brain magnetic resonance imaging (MRI) is probably the most important diagnostic tool to help identify the etiology of LGS [6]. Modern 3-T MRI scanners and sequences can be used to identify subtle abnormalities in patients with LGS and previously unremarkable or inconclusive brain MRI scans [12]. The LGS of unknown cause group (i.e., no apparent cause) account for approximately 25 to 35% of patients [3, 13]. However, the attribution of unknown is highly dependent on the sophistication of the investigations [3]. In one previous study [14], 70% of the adult patients had LGS of unknown cause (cryptogenic). One previous study [15] tried to characterize LGS of unknown cause by phenotypic analysis of patients and their parents. One hundred thirty-five patients with LGS with no known etiology and their parents were enrolled from 19 centers in the USA and Australia. The authors concluded that LGS of unknown cause has distinctive characteristics including a broad age range of onset, male predominance, and often normal development prior to the onset of seizures. The authors suggested that the phenotypic description of LGS of unknown cause coupled with future genetic studies will advance our understanding of this epilepsy syndrome [15]. When LGS has no apparent cause, a genetic predisposition or etiology is probable. Copy number variants [16], SCN1A mutations [17], CHD2 mutations [18], de novo missense mutation in the forkhead box G1 (FOXG1) gene [19], and mutations in dynamin 1 (DNM1), encoding the presynaptic protein DNM1 [20], have been reported in association with LGS in different studies. One study underlined the genetic heterogeneity of LGS and introduced rare copy number variants as important risk factors for LGS [16]. The gene CHD2 is situated on 15q26.1, a region associated with various human developmental disorders. Mutations of this gene are probably important in the etiological spectrum of LGS [18]. As various epileptic encephalopathies share overlapping features and may evolve from one to another, it is important to investigate whether the identification of genetic etiology may aid clinicians in predicting the prognosis of such patients [21]. For example, LGS may evolve from West syndrome/infantile spasms in about 20% of patients [4, 9]. Results from such genetic studies may have major implications for therapeutic choices,

prognosis, and genetic counseling for children and their families [21].

Network studies

Lennox-Gastaut syndrome may be considered as a "secondary network epilepsy." The usual epileptic manifestations, including tonic seizures, SSW complexes, and GPFA, reflect network dysfunction rather than the specific initiating process, such as a focal lesion [22]. In one study [23], simultaneous with fMRI, GPFA was recorded in six patients and SSW complexes in nine patients with LGS. Generalized paroxysmal fast activity events showed almost uniform increases in blood oxygen level-dependent (BOLD) signal in "association" cortical areas, as well as brainstem, basal ganglia, and thalamus. Slow spike-wave complexes showed a different pattern of BOLD signal change with many areas of decreased BOLD signal, mostly in primary cortical areas. The authors concluded that GPFA is associated with activity in a diffuse network that includes association cortices as well as an unusual pattern of simultaneous activation of subcortical structures. However, SSW complexes are quite different, with cortical and subcortical activations and deactivations [23]. In another EEG-fMRI study of patients with LGS [24], cognitive networks showed reduced within-network integration, including weaker connectivity within the default mode network, and also impaired between-network segregation, including stronger connectivity between the default mode and dorsal attention networks. Abnormal interactions were present during fMRI periods with and without epileptiform discharges on scalp EEG [24]. The authors concluded that, in patients with LGS, cognitive network interactions are persistently abnormal. These findings suggest that the epileptic process in LGS may initiate and perhaps sustain an abnormal network behavior [24].

Clinical characteristics

Intellectual and psychosocial dysfunction

Lennox-Gastaut syndrome has deleterious effects on intellectual function of the affected patients. Cognitive impairments are clinically apparent in many patients (20 to 60%) at the time of diagnosis. The cognitive impairment usually becomes more apparent over time, and within 5 years of onset, serious intellectual problems have been noted in most patients (75 to 99%) [3, 4, 25]. A minority (10–20%) of the affected children are within the accepted limits of normality but usually have difficulties in everyday life that seem to be caused by a slowing of the mental processing [4]. It is suggested that favorable cognitive outcomes are more likely in patients with a later age at onset [10].

Along with cognitive problems, many patients with LGS have behavioral and psychiatric problems. Attention problems, aggression, and autistic behaviors can be very prominent in patients with LGS and represent enormous challenges for their family and caregivers [3, 26]. The behavioral problems may arise from a combination of factors, including the epilepsy itself, abnormal network characteristics (see above), and the effects of medication(s).

Seizure types

Tonic seizures are the most characteristic type of seizures in LGS, and their presence is considered as a prerequisite for the diagnosis of this syndrome by some experts (is seen in all patients, although they may not always be present at the onset of LGS) [4]. However, the reported occurrence of tonic seizures varies among different studies. The frequency of tonic seizures, especially if they are subtle, is easily underestimated because they occur most often during nonrapid eye movement (non-REM) sleep [3]. A higher incidence of this seizure type has been found in published series of patients in whom EEG recordings of sleep were obtained. A periictal single-photon emission computed tomography (SPECT) study [27] suggested that tonic seizures of LGS result from activity in a network, containing bilateral frontal and parietal association areas and the pons. The authors of that study postulate that tonic seizures recruit the cortico-reticular system, which connects frontal attention areas to the pontine reticular formation and is normally responsible for postural tone and orienting behavior [27].

Atypical absences are the second most common type of seizures in LGS. These seizures are often difficult to recognize; therefore, an accurate estimate of their frequency is not possible. They have gradual onset and termination in patients whose diminished cognitive abilities may already limit their responsiveness [3, 4]. Reliable diagnosis and counting of atypical absence seizures in patients with LGS cannot be made on the basis of observation or history alone. Video-EEG monitoring is recommended in patients with LGS with suspected atypical absence seizures [28].

Epileptic drop attacks are particularly hazardous and occur in more than half of the patients with LGS. These could be the result of tonic, atonic, or even myoclonic seizures. However, drop attacks are also observed in other epilepsy syndromes (e.g., in myoclonic-atonic seizures) that do not necessarily evolve to LGS. Therefore, the presence of drop attacks is not diagnostic for LGS [3, 4].

About two thirds of patients with LGS have episodes of nonconvulsive status epilepticus (NCSE). These usually consist of prolonged atypical absences with varying degrees of altered consciousness that are periodically interrupted by recurring brief tonic seizures [3, 4]. Nonconvulsive status epilepticus may last from hours to weeks. This 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 NCSE is a major contributor to the intellectual impairment [3]. In one study [29], the authors identified four independent risk factors for severe ID in patients with LGS. These were NCSE [odds ratio (OR) 25.2], a previous diagnosis of West syndrome (OR 11.6), a symptomatic etiology of epilepsy (OR 9.5), and an early age at onset of epilepsy (OR 4.7).

In addition to the core seizures of LGS mentioned above, other types of seizures (e.g., myoclonic seizures, focal seizures, generalized tonic-clonic seizures, and unilateral clonic seizures) are also common. These types of seizures usually occur in the later stages of LGS but may sometimes precede the core seizures, which further complicates the diagnosis [3, 4].

Electroencephalographic features

The EEG background activity is probably never normal in LGS and shows a diffuse increase in slow waves (e.g., theta and delta) with a slow or absent posterior dominant rhythm. The characteristic EEG feature in LGS is slow (< 2.5 Hz) spike-and-wave complexes with an abnormally slow background activity (Fig. 1) [3, 4, 30]. Not every slow wave is preceded by a spike or sharp wave, and the bursts may be remarkably irregular without a clear onset and offset. Bursts of SSW complexes may "come and go." The distinction between ictal and interictal discharges may be difficult. However, clinically apparent atypical absence seizures always have an associated SSW burst [3, 4]. In one study [23], simultaneous with fMRI, SSW complexes were recorded in nine patients with LGS. The authors concluded that SSW complexes differed from typical generalized spike and wave complexes (seen in genetic generalized epilepsies) in several ways, including deactivation in the primary cortical areas, variability of the pattern, inconsistency of thalamic activation, and the occasional positive activation in caudate and basal ganglia [23]. It should be mentioned that not all patients with LGS have SSWs in their EEGs. In one study, about 13% of patients did not have SSWs in their EEGs [6]. Bursts of GPFA also define the EEG profile of LGS [3].

Bursts of diffuse or bilateral fast (10–25 Hz) rhythm patterns, also called GPFA, are usually recorded during slow wave sleep (Fig. 2). These bursts may last for a few seconds but tend to recur at brief intervals and are almost identical, but shorter, to the bursts commonly seen in tonic seizures that have a recruiting rhythm [i.e., an initial lowering of amplitude followed by a gradual increase in amplitude (recruitment)] (Fig. 3) [3, 4, 30]. In one study [23], simultaneous with fMRI, GPFA was recorded in six patients with LGS. Generalized paroxysmal fast activity showed activation across broad areas of cortex but appeared to spare the primary cortices. Generalized paroxysmal fast activity showed increased BOLD signal in a number of subcortical structures including the thalamus, basal ganglia, and brainstem, all known to have broad connections to the association cortices [23].

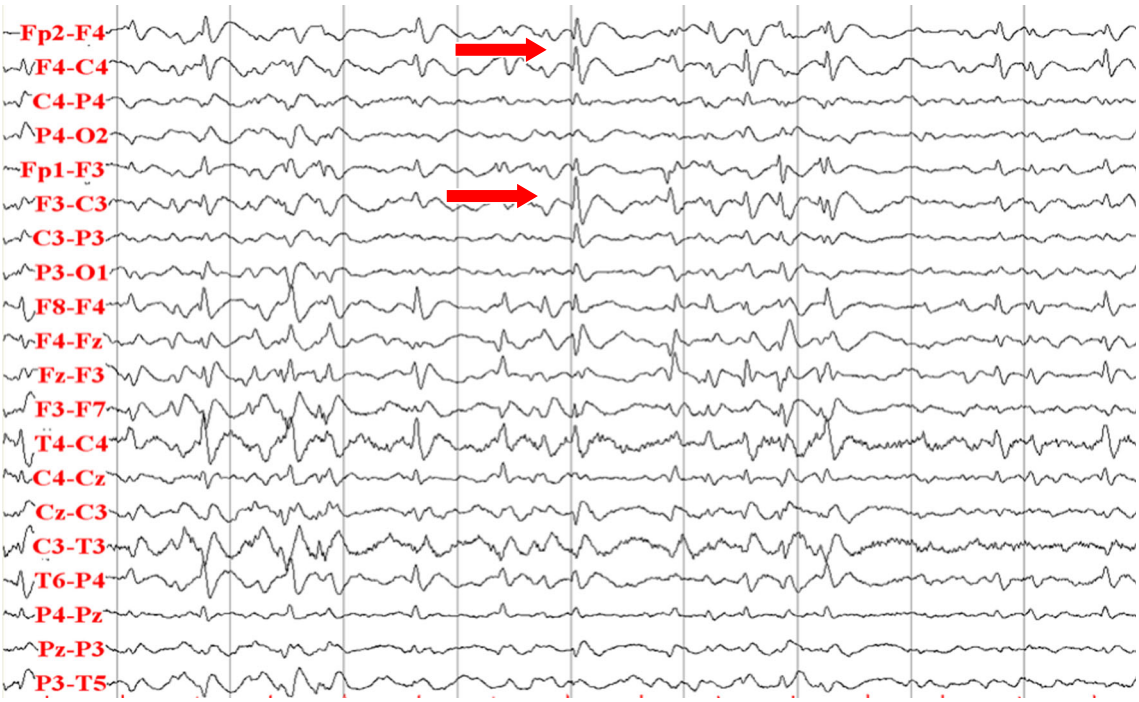

Fig. 1 Slow spike-waves (arrows) and diffusely slow background in Lennox-Gastaut syndrome. Adapted from Asadi-Pooya et al. [30]

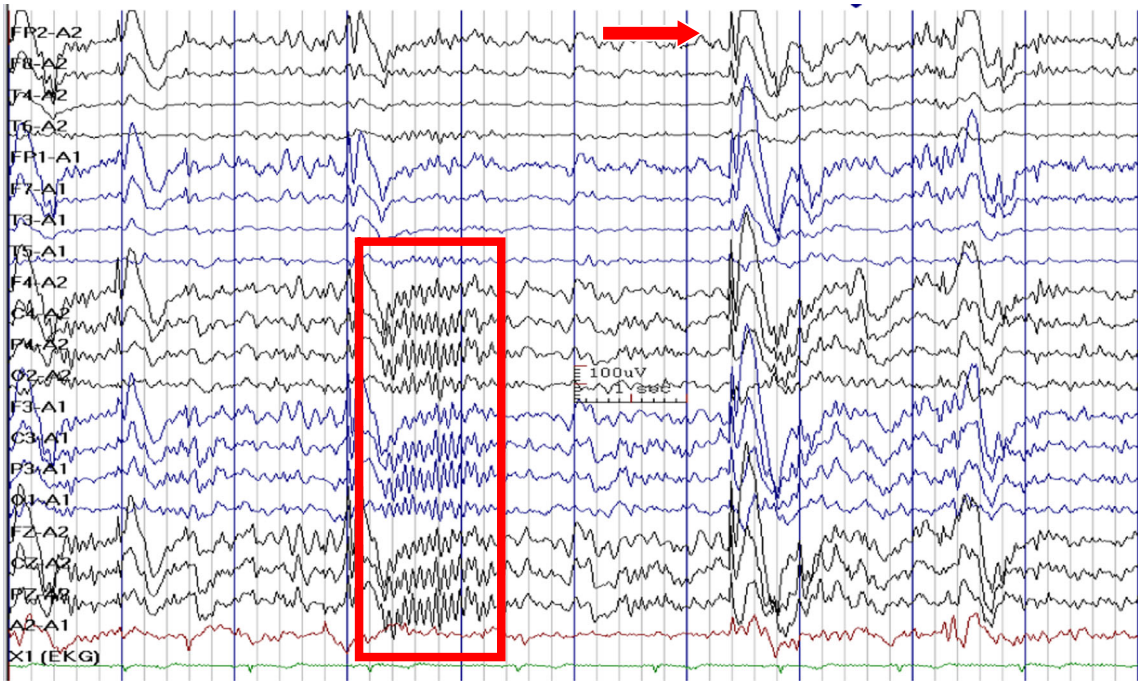

Fig. 2 Generalized paroxysmal fast activity (box) and slow spike-waves (arrow) in Lennox-Gastaut syndrome. Adapted from Asadi-Pooya et al. [30]

Differential diagnosis

The diagnosis of LGS depends on the combination of the electroclinical criteria as defined above. The predominance of tonic seizures and the specific EEG patterns are probably the most indicative features of the syndrome. However, these features are not necessarily present at the onset [4]. In addition, many other epilepsy syndromes may have one or more criteria of LGS [3]. These include Dravet syndrome, myoclonic-atonic epilepsy (Doose syndrome), atypical benign focal epilepsy of childhood, and West syndrome, among other diagnoses (Table 1) [31]. Because LGS may evolve from other syndromes, particularly West syndrome, the diagnosis may emerge only after several years of follow-up [3, 32].

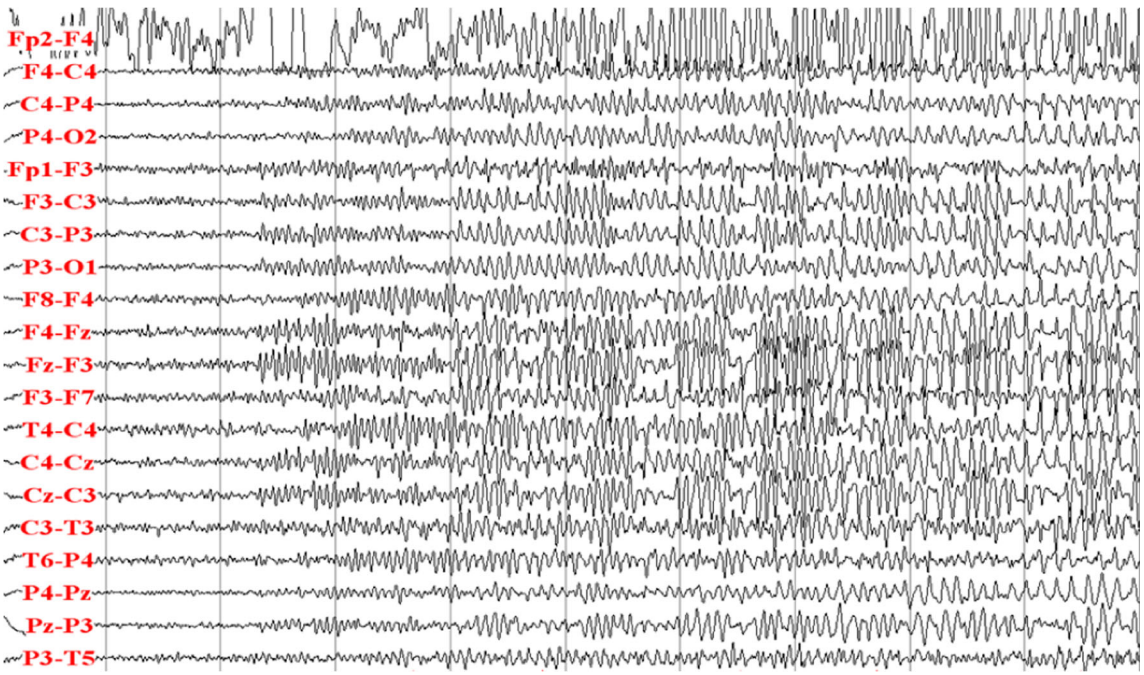

Fig. 3 Tonic seizure with a recruiting rhythm in Lennox-Gastaut syndrome. Adapted from Asadi-Pooya et al. [30]

Table 1 Differential diagnoses of Lennox-Gastaut syndrome

Syndrome	Age at onset	Seizure types	EEG features
West syndrome	Peak at 4–6 months	Epileptic spasms	Hypsarrhythmia
Dravet syndrome [severe myoclonic epilepsy in infancy]	First year	Often prolonged seizures (focal or secondarily generalized) with fever, myoclonus after 1 year of age	Often normal at onset; generalized spikes and polyspikes activated with photic stimulation after onset of myoclonus
Pseudo-Lennox-Gastaut syndrome (atypical benign partial epilepsy)	Early childhood	Atypical absence, myoclonus, atonic, and focal seizures	Rolandic sharp waves, multifocal sharp waves, electrical status epilepticus in sleep
Doose syndrome (myoclonic-atonic epilepsy)	Early childhood	Myoclonic-atonic, myoclonus, and atypical absence	2–3 Hz generalized spike-waves, photoparoxysmal response, parietal 4–7 Hz rhythms

Longitudinal studies have shown that typical features of LGS that are expected during childhood may evolve and change over time; in adulthood, it might be difficult to recognize LGS in a previously undiagnosed patient [33]. By adulthood, more than half of the patients diagnosed with LGS during their childhood no longer have all of the clinical and EEG characteristics used to diagnose the syndrome. The frequency, severity, and variety of seizure types usually decrease over time, although tonic seizures tend to persist. Only a minority of patients have SSW complexes in their EEG in adulthood. However, the presence of GPFA during sleep appears to be relatively consistent among adults with LGS. Finally, more than 90% of the patients have moderate to severe cognitive impairment by adulthood, often associated with behavioral problems, which affects their social life [33].

The diagnosis of LGS must be based on a detailed clinical history (past and present) and physical examination and, at a minimum, an awake and sleep EEG. An overnight video-EEG monitoring may be helpful in making the correct diagnosis.

Treatment

The seizures in LGS are usually resistant and intractable to antiepileptic drugs (AEDs) and complete seizure control with resolution of intellectual and psychosocial dysfunction is often not achievable. Reduction in frequency of the most incapacitating and injurious seizures (e.g., drop attacks and tonic-clonic seizures) should be the major objective in the management of patients with LGS [34].

Antiepileptic drugs

Clobazam, felbamate, lamotrigine, rufinamide, and topiramate are reported to be effective in LGS in randomized controlled trials [35–39]. Felbamate is reasonably effective, although it has much greater risk of significant adverse effects (e.g., fatal aplastic anemia or liver failure) that limit the use of felbamate. Rufinamide is approved for adjunctive treatment of seizures associated with LGS in children 4 years of age and older. It might be preferred to other drugs as a second-line treatment when drop attacks are frequent [40]. Expert consensus suggests valproate, lamotrigine, and topiramate as effective AEDs in treating LGS [34]. Other AEDs including levetiracetam, clobazam, nitrazepam, and zonisamide have also been reported to be effective [34]. Valproate, lamotrigine, and topiramate are considered to be the first-line drugs by many experts [34]. Lamotrigine may exacerbate myoclonic seizures in some patients. Generally speaking, for the generalized epilepsies, valproate may have the greatest efficacy. Valproate has superior efficacy with regard to seizure control in comparison to topiramate, and topiramate is better than lamotrigine. In respect to side effects and tolerability, lamotrigine is better than valproate and valproate is better than topiramate. In regard to time to treatment failure (considering both efficacy and tolerability), valproate is the most effective drug and lamotrigine is better than topiramate [41]. Evidence suggests that adjunctive clobazam is effective and well tolerated in both pediatric and adult patients with LGS [39].

Importantly, some AEDs are ill-advised in generalized epilepsies. These include phenytoin, carbamazepine, oxcarbazepine, gabapentin, vigabatrin (also associated with significant visual field defects), and tiagabine [40, 42]. These drugs may aggravate myoclonus or absence seizures [40]. Lacosamide can exacerbate tonic seizures and drop attacks and the encephalopathy associated with LGS. However, it may be helpful in generalized tonic-clonic and focal seizures [43]. Although phenobarbital may be effective against tonic and tonic-clonic seizures, sedation is a common adverse effect and this drug may exacerbate seizures in patients with LGS [34]. Similarly, clonazepam and nitrazepam often result in sedation and may exacerbate seizures. Moreover, benzodiazepines used in the treatment of absence status may induce tonic status epilepticus [34].

Valproate

Valproate is considered to be the first treatment of choice in patients with LGS by many experts [34]. Myoclonic, atypical absence, and atonic seizures are the seizure types most effectively controlled by valproate in LGS [34]. Gastrointestinal upset and weight gain are common adverse effects. Valproate hepatotoxicity and pancreatitis are rare but serious adverse effects. Valproate hepatotoxicity occurs more often in children below 3 years of age, particularly in those receiving polytherapy [34]. There are many drug interactions that can occur with valproate [40]. The starting dose is 7–10 mg/kg/day PO, 3–4 times daily for nonenteric-coated capsules or syrup, and twice daily is recommended for delayed-release tablets and once daily for the extended release preparation. A typical adult starting dose is 500 mg daily. Increase the dose by 5 mg/kg/day at weekly intervals as tolerated and necessary. The maximum dose limit is 60 mg/kg/day or 3000 mg/day. For patients who do not respond, measure plasma concentrations to determine whether they are within the usual accepted range (50–100 μg/mL). Younger children, especially those receiving concomitant enzyme-inducing AEDs, may need larger (sometimes > 100 mg/kg/ day) maintenance doses to attain target total and unbound serum valproic acid concentrations compared to adults [40].

Topiramate

Topiramate has multiple mechanisms of action and is a broad spectrum AED [40]. Anorexia and weight loss are commonly reported adverse effects. Cognitive slowing can be a problem, particularly at high doses. The incidence of renal stones due to the use of topiramate has been reported to be 2–4 times that in the general population [34]. Starting dose in adults, adolescents, and children > 10 years is 25 mg nightly for 1 week and in children 2–10 years of age is 0.5–1 mg/kg/day for 1–2 weeks. In adults, adolescents, and children > 10 years, during weeks 2–4 increase gradually (weekly) by 25 mg/day, administered in two daily divided doses, up to 100 mg daily. Initial maintenance dose is 50 mg twice daily. If further increases are needed, increase the daily dose in 50 mg increments on a weekly basis, and dose twice daily. If urgent seizure control is needed, more rapid titration of drug can be performed, starting at 50 mg twice daily. In children 2–10 years of age, increase gradually by 0.5–1 mg/kg/day every 1–2 weeks. Recommended maintenance dose is 3–6 mg/kg/day. Maximum dosage limit in adolescents > 16 years, adults, and elderly is 600 mg/day and may increase up to 1600 mg/day. Maximum dosage limit in patients < 16 years is up to 18 mg/kg/day. Relative contraindications to topiramate use are hypersensitivity to topiramate and metabolic acidosis [40].

Lamotrigine

Lamotrigine is particularly effective in reducing the frequency of tonic-clonic seizures and drop attacks [34]. Lamotrigine is generally well tolerated. Skin reactions, drowsiness, nausea, anorexia, headache, and ataxia are the most common adverse effects [34]. Lamotrigine should be initiated at a low dose, with gradual increase. This may minimize the occurrence of skin rash [40]. In patients not receiving valproic acid or enzyme-inducing AEDs, the starting dose is 25 mg daily for the first 2 weeks in adults and adolescents > 12 years of age and 0.3 mg/kg/day in 1 or 2 divided doses given for the first 2 weeks (rounded down to the nearest whole tablet) in children. For adults and adolescents > 12 years of age give 25 mg twice daily (50 mg/day) for weeks 3–4; then, the dose may be increased by up to 50 mg daily every 1–2 weeks until the maintenance dosage is achieved. The usual maintenance dose is 200–400 mg/day, given in 1–2 divided doses. For children, give 0.6 mg/kg/day in 2 divided doses for weeks 3–4. Thereafter, the dose should be increased every 1–2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose. The usual maintenance dose is 4.5–7.5 mg/kg/day (maximum 300 mg/day in 2 divided doses). Maintenance dose in patients less than 30 kg may need to be increased by as much as 50%, based on clinical response. In patients currently receiving treatment with an enzyme- inducing AED, the above doses are often doubled, and in patients currently receiving valproate, the doses are often halved. Hypersensitivity to lamotrigine is a contraindication to its use [40].

Clobazam

Clobazam was recently approved by the US Food and Drug Administration (FDA) for the treatment of LGS in patients at least 2 years of age. Though classified as a benzodiazepine, the drug differs structurally from other drugs in the class [44]. Clobazam is particularly helpful in decreasing drop attacks [45, 46]. Adverse events associated with clobazam are generally mild to moderate. The incidence of sedative effects compared to other benzodiazepines is less with clobazam. Tolerance to the drug's antiepileptic effects does not seem to be a common occurrence. The drug has proven to be a cost-effective option for therapy, particularly due to its ability to decrease the number of seizures that require medical treatment [44]. Starting dose in adults and adolescents is 5–10 mg/day, in 1–2 doses. Starting dose in children and infants (weight < 30 kg) is 0.25 mg/kg/day in 2 divided doses. In adults and adolescents, dosage may be increased by 5–15 mg every 5 days until seizures are controlled or adverse reactions limit further increase. The typical maintenance dose ranges 20–

40 mg/day. In elderly and debilitated adult patients, slower dosage titration is recommended. In children and infants, increase dosage gradually every 5 days, until seizures are controlled or adverse reactions limit further increase. Maximum dosage limit in adults and adolescents (weight > 30 kg) is 80 mg/day and in children and infants (weight < 30 kg) 1 mg/kg/day [40].

Rufinamide

Rufinamide is often well tolerated and is effective in reducing the frequency of generalized tonic-clonic, tonic, atonic, and focal seizures in both children and adults with LGS [47]. The most common adverse effects include somnolence, vomiting, and weight loss [47]. Starting dose in children > 4 years is 10 mg/kg/day administered in two equally divided doses and in adults 400–800 mg/day administered in two equally divided doses. Patients on valproate should begin rufinamide at a dose lower than 10 mg/kg/day (children) or 400 mg/day (adults). In children > 4 years, titrate by 10 mg/kg increments every other day to a target dose of 45 mg/kg/day or 3200 mg/day, whichever is less. In adults, the dose should be increased by 400–800 mg every other day until a maximum dose of 3200 mg/day. Maximum dosage limit in children > 4 years is 45 mg/kg/day or 3200 mg/day, whichever is less, and in adults 3200 mg/day. Rufinamide is contraindicated in patients with familial short QT syndrome [40].

Alternative agents

If a patient with drug-resistant LGS is not a candidate for surgical treatment, alternative therapies may be considered.

Cannabidiol Cannabidiol may reduce seizure frequency in patients with LGS [48]. More studies are needed to characterize the efficacy and safety profile of this compound.

Steroids Corticosteroid therapy may reduce seizure frequency in patients with LGS [49]. However, large randomized clinical trials are lacking to support its efficacy in LGS.

Intravenous immunoglobulin Intravenous immunoglobulin (IVIG) may reduce seizure frequency in patients with LGS [50]. However, large randomized clinical trials are lacking to support its efficacy in LGS.

The following key points may help when prescribing AEDs in patients with LGS [40]:

1. Because there are several good options, choose the specific agent based on the patient's profile (i.e., gender, age, etc.), comorbidity, potential adverse effects, and drug interactions.
2. Titrate doses gradually when initiating therapy to improve drug tolerability and reduce adverse effects. If needed for immediate seizure control, levetiracetam, rufinamide, topiramate, valproate, and zonisamide can be rapidly titrated.
3. It is preferable to prescribe medications that can be taken once or twice daily. Patient adherence to a medication regimen may be higher with once- or twice-daily dosing regimens.
4. Observe closely for adverse effects. Because patients are often unaware of cognitive or behavioral side effects, question family members and close friends about adverse effects as well.
5. The goal of treatment is to prevent the most disabling seizures and avoid adverse effects. Assess whether these goals have been met. If not, adjust therapy accordingly. If the first drug fails, convert the patient to monotherapy on a new agent. If a second drug fails, consider adding a second drug to the existing agent [40].

Ketogenic diet

The ketogenic diet is an effective and well-tolerated treatment option for patients with LGS, not only for those with unknown cause but also for those with structural disease. The diet should be considered early in the course of this syndrome [51]. In one study, over half of the children showed a > 50% reduction in seizures, and 20% achieved seizure freedom. Patients who responded well to the diet did not further mentally deteriorate. Interictal epileptiform abnormalities improved in most of the patients who had a seizure reduction of more than 75% [51]. Ketogenic diet has potential adverse effects, but the risk of serious adverse events is low. Common adverse effects of the ketogenic diet include constipation, vomiting, abdominal pain, lack of energy, hunger, hypercholesterolemia, mineral deficiencies, acidosis, and effects on growth. The rigidity of the ketogenic diet and difficulties with altering lifestyles may pose challenges in maintaining the diet [52]. There is some evidence showing the efficacy and tolerability of the modified Atkins diet and low glycemic index diet in patients with LGS [53, 54].

Surgery

In spite of ongoing investigation into drug treatments for LGS, outcomes for chronic administration of AEDs remain disappointing. Generally, LGS is drug-resistant, resulting in poor prognoses. For patients with drug resistance, a further therapeutic option is surgical intervention [55]. Several presurgical investigations are required, including video-EEG with a natural sleep recording, magnetic resonance imaging (MRI) with a specific epilepsy protocol, and age-appropriate

neuropsychological assessment. Resective brain surgery, where and when seizure foci are removable, may successfully control seizures [56]. In patients with LGS, there are some considerations to keep in mind. Patients with LGS do not necessarily have to have all their epileptiform discharges coming from one brain area; there are reports of successful surgical outcomes in patients with a predominantly focal MRI abnormality [55–57]. In order to have a successful resective surgery, one should be able to localize the epileptogenic region for resection (using clinical history, video-EEG monitoring, MRI, positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetoencephalogram (MEG), and electrocorticography) and also its relation to the eloquent cortex (using Wada, functional MRI, and electrocorticography with brain stimulation) [55]. However, resective brain surgery is rarely an option in patients with LGS, who often have a diffuse or multifocal brain abnormality. In addition, the effect of surgical resection may wane, similar to what happens with medical therapies [58]. Corpus callosotomy is a palliative surgical procedure that aims at controlling the most injurious seizures (e.g., drop attacks and tonic-clonic seizures). Finally, vagus nerve stimulation (VNS), another palliative procedure, offers reasonable seizure improvement [54]. If one surgery option (either corpus callosotomy or VNS) fails to help the patient the other may follow with potentially beneficial effects in reducing the seizures [59, 60].

Corpus callosotomy The rationale underlying the amelioration of the epileptic seizures by corpus callosotomy is based on the hypothesis that the corpus callosum is the most important pathway for interhemispheric spread of the epileptic activity. Severing connections between the hemispheres hampers the spread of the ictal activity [61, 62]. According to topographic knowledge of the interhemispheric connections of corpus callosum, it is sufficient to perform an anterior one half to four fifths callosotomy. Sparing of splenium may preserve sufficient fibers for interhemispheric transfer of some perceptual information and diminish the complications of a disconnection syndrome [63]. This procedure has been accepted as a palliative surgical option for some patients with drug-resistant seizures, particularly those with tonic, atonic, and tonic-clonic seizures, who are not amenable to resective focal brain surgery [63]. In one study [64], corpus callosotomy dramatically helped patients with LGS and devastating seizures. One year after surgery, 38.8% of the patients were free of their disabling seizures (i.e., generalized tonic-clonic seizures or drop attacks); this figure was 33.3% at 2 years. The rate of significant and satisfactory seizure reduction (> 85% reduction in seizure frequency) was much higher (about two thirds of the patients) [64]. Permanent serious complications are rare after callosotomy; most adverse effects are temporary (e.g., disconnection syndrome) [63]. Total corpus callosum section in adults generally shows an approximately 10% higher response rate for all of the seizure types compared with that in anterior corpus callosotomy; however, the chance of experiencing adverse effects is also higher [63].

Vagus nerve stimulation VNS therapy is considered a palliative treatment in patients with drug-resistant epilepsy, who are not candidates of resective brain surgery, for all types of seizures in adults and children [65]. Despite many studies, the exact mechanism by which VNS helps patients with epilepsy and reduces seizure frequency is unknown. VNS may interrupt the synchronous electrical activity characteristic of the epileptic seizures [65]. In addition, a number of studies using functional imaging techniques have demonstrated widespread changes in blood flow and metabolism in several cortical and subcortical regions during VNS use [66, 67]. In one study including 347 children at 6, 12, and 24 months after VNS implantation, 32.5, 37.6, and 43.8% of patients had ≥ 50% reduction in baseline seizure frequency of the predominant seizure type. Just 5.5% of the patients were rendered seizure-free at 12 months postimplantation [68]. In another study including 43 adults with drug-resistant epilepsy, 63% of patients had ≥ 50% reduction in their seizure frequency at 18 months postimplantation of VNS [68]. In various published series, ≥ 50% reduction in baseline seizure frequency was achieved in about 50% of patients (18.4–67%), and the mean reduction in the frequency of seizures was 42.8% (range 28–66%) [69]. Adverse effects are relatively minimal with VNS compared with corpus callosotomy. The more common adverse effects include voice alteration, increased drooling, dyspnea, and coughing [55].

Corpus callosotomy might be preferred as the primary surgical option in children with LGS if atonic seizures predominate in the patient's clinical picture; when myoclonic seizures prevail, VNS might be preferred as the primary surgical option. When atypical absence or tonic-clonic seizures are the main concern, both procedures carry similar effectiveness, but VNS might be considered as the preferred option, taking into account the adverse event profile [70]. A meta-analysis comparing the outcomes of VNS vs. corpus callosotomy in patients with LGS concluded that corpus callosotomy had a significantly better outcome than VNS for > 50% atonic seizure reduction (80.0 vs. 54.1%, $p < 0.05$) and for > 75% atonic seizure reduction (70.0 vs. 26.3%, $p < 0.05$). For all other seizure types, VNS offered comparable rates to corpus callosotomy (49.3 vs. 63.0%) [71].

Prognosis

The long-term outcome for patients with LGS is generally poor and complete seizure freedom is unusual [3]. Overall, the evidence indicates that epileptic encephalopathies in childhood (especially, LGS) are usually associated with long-term

adverse effects on intellectual development, social functioning, and independent living. These unfavorable outcomes have a significant impact on family members and caregivers [3]. In one retrospective study of 68 patients with LGS with a mean follow-up duration of 19.3 years [72], the authors concluded that patients experience changes to their seizure types and EEG characteristics with the passage of age. Although the frequency and intensity of seizures was found to decrease, many patients sustained seizures; these were predominantly tonic or tonic-clonic seizures. With regard to cognitive function, 94.7% of the patients had moderate to profound intellectual disability [72]. Lennox-Gastaut syndrome is a costly disease. In one study, compared with non-LGS patients, those with probable LGS had substantially higher (2–4 times higher) total healthcare costs and medical costs were the main cost drivers [73]. Timely diagnosis and appropriate treatment of LGS are likely to result in improved outcomes and less costly management in patients affected [73].

Conclusions

Lennox-Gastaut syndrome is considered an epileptic encephalopathy. The encephalopathy is the result of epileptic activity (epileptic encephalopathy) with or without developmental problems (developmental encephalopathy) [74]. This syndrome is defined by a triad of multiple drug-resistant seizure types, a specific EEG pattern, and intellectual disability. The prevalence of LGS is estimated between 1 and 2% of all patients with epilepsy. The etiology of LGS is often divided into two groups: identifiable (genetic-structural-metabolic) in 65 to 75% of the patients and LGS of unknown cause in others.

The seizures in LGS are usually drug-resistant. Reduction in the frequency of the most incapacitating seizures should be the major objective. Valproate, lamotrigine, and topiramate are considered to be the first-line drugs by many experts. Other effective AEDs include levetiracetam, clobazam, rufinamide, and zonisamide. The ketogenic diet is an effective and well-tolerated treatment option. For patients with drug resistance, a further therapeutic option is surgical intervention. Corpus callosotomy is a palliative surgical procedure that aims at controlling the most injurious seizures. VNS also offers reasonable seizure improvement. If a patient with drug-resistant LGS is not a candidate for surgical treatment, alternative therapies may be considered [75, 76]. The long-term outcome for patients with LGS is generally poor.

Compliance with ethical standards

Conflict of interest The author has the following disclosures: consultant: Cerebral Therapeutics, LLC and UCB Pharma; honorarium: Hospital Physician Board Review Manual and Cobel Daru; and royalty: Oxford University Press (book publication).

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