Lennox–Gastaut Syndrome: A State of the Art Review

Mario Mastrangelo

1 Division of Pediatric Neurology, Department of Pediatrics, Child Neurology and Psychiatry, Sapienza-University of Rome, Rome, Italy

Abstract

Lennox–Gastaut syndrome (LGS) is a severe age-dependent epileptic encephalopathy usually with onset between 1 and 8 years of age. Functional neuroimaging studies recently introduced the concept of Lennox–Gastaut as “secondary network epilepsy” resulting from dysfunctions of a complex system involving both cortical and subcortical structures (default-mode network, corticoreticular connections, and thalamus). These dysfunctions are produced by different disorders including hypoxic–ischemic encephalopathies, meningoencephalitis, cortical malformations, neurocutaneous disorders, or tumors. The list of etiologies was expanded to pathogenic copy number variants at whole-genome array comparative genomic hybridization associated with late-onset cases or pathogenic mutations involving genes, such as GABRB3, ALG13, SCN8A, STXBP1, DNM1, FOXP1, or CHD2. Various clinical trials demonstrated the usefulness of different drugs (including rufinamide, clobazam, lamotrigine, topiramate, or felbamate), ketogenic diet, resective surgery, corpus callosotomy, and vagus nerve stimulation in the treatment of epileptic manifestations. The outcome of LGS often remains disappointing regarding seizure control or cognitive functioning. The realization of animal models, which are still lacking, and the full comprehension of molecular mechanisms involved in epileptogenesis and cognitive impairment would give a relevant support to further improvements in therapeutic strategies for LGS patients.

Keywords

► epileptic encephalopathies
► intellectual disability
► epilepsy

Introduction

Lennox–Gastaut syndrome (LGS) is an electroclinical syndrome, with onset in the prescholar or scholar ages, including three distinct hallmarks: (1) multiple seizure types (mainly tonic, atonic, and atypical absences); (2) interictal diffuse 1.5 to 2.5 Hz slow spike-and-wave discharges during the wake state, and paroxysmal fast activity during the sleep state at the electroencephalogram (EEG); and (3) intellectual disability and/or behavior disorders.1,2 The onset of seizures is usually between 1 and 8 years of age.1–3 Males to females ratio is approximately 5 to 1 (prevalence 10 per 100,000 versus 2 per 100,000).2,3 A prior West syndrome can be assessed in 10 to 25% of patients with LGS.2,3 Different studies evidenced a similar prevalence of LGS in Europe and United States (0.1–0.28 per 1,000 live births) with an incidence of approximately 2 per 100,000 children per year (0.6% of all new-onset epilepsies).2,3

Epidemiology

LGS accounts for 3 to 5% of childhood epilepsies and involves 7% of the children with intellectual disability (55% of patients with LGS have an intellectual quotient under 50).2,3

Etiology

An identifiable cause of LGS can be defined in about 70% of the cases, and it is usually represented by a static brain disorder while progressive metabolic diseases are very...
rare. Several etiologies including hypoxic-ischemic encephalopathies, meningoencephalitis, tuberous sclerosis complex, cerebral malformations, monogenic disorders, chromosomal abnormalities, tumors (such as hypothalamic hamartomas) or idiopathic intracranial hypertension can be involved. Despite their rare occurrence some inborn errors of metabolism, such as biotinidase defects or disorders of creatine metabolism, have a relevant importance because of the availability of specific effective treatments.

Recent data demonstrated that LGS children with history of birth hypoxia or other perinatal events have more severe epilepsy with an earlier onset and a higher incidence of delayed milestones. No significant difference in number of antiepileptic drugs consumed, motor deficits or magnetic resonance imaging (MRI) abnormalities were detected in the comparison with LGS patients without evidences of perinatal events.

Whole-genome array comparative genomic hybridization identified pathogenic or potentially pathogenic copy number variants in 8 out of 21 adult patients with LGS of unknown etiology. Cases of late-onset LGS were described in adult patients with 15q11.1q13.3 or 15q11.2-q13.1 duplication.

Various gene mutations causing cortical malformations (i.e., LIS1, DCX or GPR56) or neurocutaneous syndromes (TSC1 and TSC2) have been frequently associated with LGS. The causative role of mutations in other genes (such as GABRB3, ALG13, SCN8A, STXBP1, DNM1, FOXG1 or CHD2) have been elucidated in recent exome studies or in case reports in patients with LGS without a history of infantile spasms. A heteroplasmic variant in the mitochondrial MT-ND1 gene, resulting in a reduced stability of the protein, was recently demonstrated in a patient with a LGS evolving from a West syndrome. A pathogenic mutation in SCN1A gene was reported in 1 out of 22 Norwegian adult patients with LGS. In this patient epileptic pattern mainly included myoclonic seizures.

**Pathophysiological Hypothesis**

The comprehension of the pathophysiology of LGS has always been limited because of the lack of an animal model, a very slow progression of the studies on the genetic basis of the syndrome and the existence of multiple etiologies. LGS is an epileptic encephalopathy in which epileptic seizures are directly responsible for a severe impairment of cognitive, motor, and sensorial functions. It shares with Ohtahara syndrome and West syndrome, that occur earlier, the condition of “age-dependent epileptic encephalopathy” in which common electroclinical pathways are activated by an insult acting in a specific period of brain development. The promoting insult can be realized by different etiologies that can impair a wide range of molecular and neuronal mechanisms. Transition between West syndrome and LGS after the first year of life denote that the related epileptic manifestations and the involved neuronal networks can be activated by similar epileptogenic processes. These processes result in distinct phenotypes according to the different period of brain maturation in which the promoting insult occur. Specific molecular mechanisms that regulate the transition between phenotypes of West syndrome and LGS are still unknown.

The impairment or the instability of complex networks involving different cortical and subcortical structures seems the first common step toward the LGS electroclinical phenotype. In this context, LGS can be conceptualized as a “secondary network epilepsy,” in which epileptic activity (including both seizures and epileptic discharges) is amplified through intrinsic cognitive cerebral networks. The EEG hallmarks of LGS suggest a widespread cortical activation during ictal and interictal epileptic activity and different functional neuroimaging studies confirmed the involvement of diffuse zones of association cortex and spares primary cortical regions in the epileptogenesis. Generalized paroxysmal fast activity and 1.5 to 2.5 Hz diffuse slow spike and waves were interpreted as the electroencephalographic expression of the activation of distinct neuronal networks in a simultaneous functional MRI (fMRI)-EEG study on 13 patients. Generalized paroxysmal fast activity was associated with a diffuse recruitment of association cortices, brainstem, thalamus, and basal ganglia while diffuse 1.5 to 2.5 Hz slow spike and waves-related fMRI pattern included combined cortical/subcortical activations and deactivations.

Some authors proposed that an abnormal recruitment of intrinsic attention and default-mode networks could contribute to a rapid amplification of epileptic activity within a cascade including corticoreticular and reticulospinal connections. Focal lesions causing LGS, such as cortical malformations, probably produce chronic interference with these networks. The association of different types of cortical lesions with LGS and the control of epileptic manifestations after their surgical ablation support the prominent importance of cortical networks and, subsequently, the secondary role of subcortical structures in the epileptogenesis. Thalamus probably plays a role of synchronizer and amplifier rather than a seizure focus. This hypothesis was consistent with the demonstration of a thalamic activation in only 4 out of 13 patients with diffuse slow spike and waves who recently underwent simultaneous EEG-3 Tesla fMRI. An ictal–interictal single-photon emission computed tomography study during video-EEG recording in seven patients with LGS demonstrated that pons is involved in the pathogenesis of tonic seizures within a corticoreticular network including bilateral frontal and parietal association areas.

Transcranial magnetic stimulation data detected a lower interictal cortical excitability in 18 adult LGS patients than in control groups including 40 patients with other refractory epilepsies and 20 healthy nonepileptic subjects. Lower interictal cortical excitability could contribute to the cognitive, sensorimotor, and behavioral regression that is usually observed in LGS even if no similar studies are available for other epileptic encephalopathies. Different recent studies suggested other mechanisms involved in cognitive impairment induced by epileptic manifestations.
Concurrent EEG-fMRI data on 15 LGS adult patients demonstrated an abnormal interaction between cognitive networks (default-mode, dorsal attention, executive control, and anterior salience) both in ictal phases and in periods in which no scalp-detectable epileptic activity was present. These results evidenced that the impaired functioning of neuronal networks involved in cognitive processes may endure after the acute phases of epileptic seizures. Task-free fMRI evidenced an increased connectivity in critical areas of association cortex and a decreased connectivity in primary cortex of nine adult LGS patients with severe epileptic phenotypes. In the same study abnormal network connectivity was also demonstrated in other structures involved in cognitive mechanisms, such as brainstem, limbic system, and striatum.

**Clinical Presentation**

The association of characteristic multiple seizure types, the specific EEG pattern and intellectual disability represents the classic hallmark of LGS and remains the basis for the diagnosis. This diagnostic triad is not necessarily completely present at the onset of seizures and a precise diagnosis of LGS often requires time to be formulated.

**Seizure Types**

Tonic seizures (Fig. 1, parental informed consent was obtained), atypical absences, and atonic seizures (Fig. 2) are the most common seizure types in LGS. Drop attacks (tonic or atonic falls) often result in frequent traumatic injuries (Fig. 2). Nonconvulsive status epilepticus can be observed in 50 to 75% of LGS patients and it is often represented by subcontinuous atypical absences with variable degrees of consciousness impairment with or without recurring brief tonic seizures. Other seizure types, including focal seizures with or without secondary generalization or tonic-clonic generalized seizures, are more common in the later stages of LGS in early adolescence and adulthood.

**Intellectual Disability**

Most of patients with LGS presents with intellectual disability and behavioral problems (aggression, hyperactivity, or autistic spectrum) including different degrees of severity. Cognitive impairment worsens in cases with a high recurrence of seizures and interictal epileptic activity, according to the actually accepted concept of “epileptic encephalopathy,” even if it can also be secondary to the underlying causes of LGS and not only to epileptic activity itself. A cognitive impairment involves up to 95% of patients within 5 years from the onset of epilepsy. Up to 10 to 20% of patients with LGS reaches acceptable ranges of intellectual functioning despite variable limitations in daily activities and cases of lacking cognitive impairment have been recently reported. Main risk factors for intellectual delay in LGS include earlier age of onset, a previous West syndrome, a symptomatic etiology, and episodes of nonconvulsive status epilepticus.

**Electroencephalogram Patterns**

The two typical EEG features of LGS are represented by 1.5 to 2.5 Hz diffuse slow spike and waves and generalized paroxysmal fast activity (Fig. 3).
In adulthood sleep, EEG remains the most important diagnostic tool for LGS because the recording of a diffuse paroxysmal fast activity during slow sleep is more constant than diffuse slow spike-wave discharges during wakefulness. In a recent retrospective study of 27 adults between 40 and 59 years of age, EEG showed persistence of generalized paroxysmal fast activity in all subjects while diffuse slow spike-wave discharges persisted in only 7 of them.

**Diagnostic Investigations**

The detailed clinical evaluation and the realization of both awake and sleep EEG represents the minimum required for the diagnosis. Physical examination should identify neurological deficits, hypomelanotic macules, fibromas, or heart murmur. Retinal abnormalities or visual impairment should be excluded. In addition to the developmental history, neuropsychological assessments at the time of diagnosis and during the follow-up reveal the degree of intellectual disability and the eventual cognitive deterioration.

Sleep EEG with video and overnight video-EEG with electromyogram electrodes are recommended if available in the resource setting. Neuroimaging is useful for the characterization of morphologic brain abnormalities (cortical malformations, such as lissencephaly or polymicrogyria, tuberous sclerosis complex, neoplasia, hypoxic-ischemic encephalopathy) (Fig. 4). Recent data outlined that all LGS patients, independently by the etiology, have a minor whole brain volume than healthy subjects with a prominent involvement of mesial frontal region, bilateral anterior temporal poles, and reticular formation. Functional neuroimaging including fMRI, positron emission tomography, and single-photon emission computed tomography offers a contribution in the presurgical evaluation of well localized epileptogenic areas.

Genetic workup should include array comparative genomic hybridization or selected genes sequencing should be guided by clinical suspect.

**Pharmacological Treatment**

No international guidelines exist for the pharmacological treatment of LGS because of the paucity of available clinical...
trials. The choice of antiepileptic drugs at the onset is tailored to seizures types, clinical presentation, and EEG patterns and its principles are the same that are currently used for all epilepsies. In the common clinical practice, valproate is used as a first-line treatment because of its efficacy in both focal and generalized seizures while lamotrigine and topiramate are possible alternatives in the following steps. Other drugs, including rufinamide, felbamate, clobazam and zonisamide are used in add-on as second-line treatment.

Rufinamide
Rufinamide resulted in a median reduction in total seizures of 32.7% (vs. a decrease of 11.7% in placebo group) in a double-blinded, randomized, placebo-control study in 138 patients (age range: 4–30 years). A subsequent open label extension study, enrolling 124 out of 138 original patients, demonstrated a reduction of more than 50% of both total seizures and tonic–atonic seizures frequency in 45.1% of patients. Similar data were obtained in a randomized, double-blind placebo-controlled trial in 59 Japanese patients aged between 4 and 30 years. In this study, a higher decrease of tonic–atonic and total seizures frequency was reported in patients receiving rufinamide than in placebo group (−24.2% and −32.9 vs. −3.3% and −3.1%, respectively). A following open-label extension of this study on 41 out of the original 59 patients demonstrated comparable benefits in the long-term period in both tonic–atonic and total seizure control with the use of rufinamide.

An efficacy of rufinamide was also suggested for 40 children under age 4 with drug-resistant epilepsies, including only 4 LGS patients. This aspect represents a relevant methodological limit because data from other epileptic syndromes cannot be applied to LGS (LGS patients have a higher retention rate for rufinamide). A recent interim analysis of an in progress multicenter, randomized, active-controlled, open-label study evidenced a similar profile of safety and pharmacokinetic features of rufinamide in LGS children between 1 and 4 years and in children older than 4 years. A responder rate of 33.3% for total seizures (57.1% for drop attacks) was also demonstrated in a sample of 31 LGS adults aged between 18 and 37 years.

Some clinically relevant drug interactions of rufinamide should always be considered in LGS patients with polytherapy (rufinamide increases phenytoin serum concentrations, while valproate increases rufinamide serum concentrations).

Clobazam
Two randomized controlled studies (a phase II and a phase III) and a related multicentre, open-label extension study, in which clobazam was used as adjunctive therapy, recently demonstrated more than 50% of seizure reduction in more than 50% of the enrolled LGS patients. None of the other drugs with the approval of U.S. Food and Drugs Administration for LGS treatment produced similar results. Reported reduction of drop attacks frequency in the two randomized controlled studies was approximately 12% for patients treated with a low dosage of clobazam (0.25 mg/kg/d) while it ranged between 68.3 and 85% in patients treated with high dosages (1 mg/kg/d). Responder rate ranged between 77.6 and 83% in patients who received 1 mg/kg/d of clobazam. The subsequent open-label extension study reported a median decrease in weekly drop seizures of 91.6 and 79.5% of the enrolled subjects experienced a reduction in weekly drop seizures more than 50% from baseline at 24 months. The introduction of clobazam resulted in an improvement of global functioning in the concomitant use of other antiepileptic drugs. No differences between different age groups were defined regarding efficacy and safety.

Lamotrigine
No recent data on the use of lamotrigine in LGS are available. A reduction of 32% of generalized seizures frequency was observed in an old double-blind placebo-controlled trial in 169 LGS patients (79 treated with lamotrigine as an add-on therapy and 90 with placebo). In this trial, no significant differences were observed in the main side effects (especially severe skin reactions) between patients treated with lamotrigine and patients who received placebo.

Topiramate
A reduction ranging from 14.8 to 58% of drop attacks was assessed in two main studies in which topiramate was
administered in the add-on. In one of these studies a median reduction of 25.8% in major motor seizures was recorded in patients who received topiramate at a target dose of 6 mg/kg/d (vs. an increase of 5.1% in the placebo group).

**Felbamate**
Felbamate is indicated as an add-on therapy in selected LGS patients in whom previous antiepileptic drugs did not obtain an adequate seizure control. The best results with felbamate were obtained in the treatment of drop attacks (reduction of seizures frequency ranging from 34 to 50%) with a significant improvement of the quality of life. The most severe side effect and limiting factor of felbamate is aplastic anemia notwithstanding its rare occurrence (34 cases in the United States in the period 1994–2006). Patients with high risk for aplastic anemia (history of cytopenia, autoimmune disorder or positive antinuclear antibody titer) should not receive felbamate.

**Other Antiepileptic Drugs**
The spectrum of antiepileptic drugs that have been used in the clinical practice in LGS patients also includes clonazepam, zonisamide, and lacosamide. The weak evidences for efficacy in LGS for these drugs were collected in uncontrolled studies on small samples. Recent risks of exacerbation of tonic and atonic seizures were recently reported in LGS adults treated with lacosamide.

A recent open-label uncontrolled trial including 30 patients with LGS treated with cannabidiol evidenced a median reduction of 36.8% of motor seizures over a period of 12 weeks of treatment with a prominent efficacy in atomic (68.8%) and tonic seizures (44%). An online parental survey including 24 patients with LGS and 53 patients with LGS following infantile spasms evidenced a relevant perceived efficacy of cannabidiol on seizure frequency (79% of parents reported fewer seizures while seizures freedom was observed in 13% of cases). Additional benefits were observed on sleep, alertness, and mood while the main reported side effects included somnolence, abnormal appetite, diarrhea, fatigue, and convulsions.

**Other Therapeutic Options**

**Ketogenic Diet**
Data on the use of ketogenic diet in patients with LGS were reported by a limited number of studies with several methodological limitations (short duration, prominently retrospective nature, samples including both LGS patients and other epilepsies).

A recent retrospective analysis of 71 patients with LGS who underwent ketogenic diet at Johns Hopkins Hospital between 1994 and 2012 evidenced a seizure reduction higher than 50% in 44% of patients after 12 months. Similar data (more than 50% of seizure reduction in 47% of patients) were identified in a meta-analysis in 189 subjects from 18 published studies in the period 1989 to 2010. A low incidence of side effects was reported (including recurring vomiting, hypoglycemia, constipation, weight loss, kidney stones, hyperlipidemia, and poor linear growth). In the most recent published series ketogenic diet was started after a median number of six previous antiepileptic drugs while no experiences in the early stages of treatment have been reported for LGS.

**Surgery**
Two main different groups of diagnostic investigations should be performed before the surgery: tests for the localization of epileptogenic focus for resection (single-photon emission computed tomography, positron emission tomography, intracranial EEG, and magnetoencephalogram) and tests for the definition of eloquent cortex to minimize the risk of neurological deficits related to surgery (electrocorticography and fMRI or Wada test if fMRI fails to show a clear lateralization). Most of the abovementioned diagnostic tools are available in a few specialized centers. For this reason, early referral to specialized pediatric neurosurgical centers is recommended if a clear surgical indication is defined.

Two main surgical approaches can be indicated for children with LGS: (1) resection of the epileptic focus (lesionectomies, lobar, multilobar, or hemispheric resections); (2) corpus callosotomy to avoid the interhemispheric propagation of seizure activity. Resective surgery is usually curative, and it should be preferred if it is possible while corpus callosotomy and vagus nerve stimulation are palliative approaches. The best outcome for resective surgery in LGS was reported for children younger than 5 years. Corpus callosotomy often has a higher efficacy in resolving drop attacks while vagus nerve stimulation offers comparable results for the other typical seizure types of LGS. Corpus callosotomy can also precede resective surgery resulting in a more lateralized epileptic network.

**Vagus Nerve Stimulation**
In an old retrospective analysis on a large series of 483 LGS subjects, without prior surgical treatments, vagus nerve stimulation resulted in more than 50% of seizure reduction in 55% of the patients after 18 months. In more recent published studies on different series enrolling between 9 and 50 patients, the efficacy of vagus nerve stimulation was evaluated over a whole treatment length lasting between 3 and 52 months. The percentage of patients in which more than 50% of seizures reduction was obtained ranged between 25 and 78%. Improvements were also achieved for other parameters including quality of life, behavior, and cognitive abilities.

**Differential Diagnosis**
The adherence to the abovementioned electroclinical diagnostic criteria helps physicians in the differential diagnosis between LGS and other epileptic syndromes, such as infantile spasms (discrimination between spasms and tonic seizures), atypical benign partial epilepsy, partial epilepsies or
secondarily generalized epilepsies with origin in the frontal lobe, Doose syndrome (discrimination between myoclonic-astatic seizures and drop attacks).\textsuperscript{1,2,17}

The differentiation between prolonged spasms and short tonic seizures can be hard also with video-polygraphy even if spasms usually present in clusters.\textsuperscript{2,17} In atypical benign partial epilepsies discriminating diagnostic criteria are the prolonged periods of seizure freedom, the lack of tonic seizures and the sleep EEG features (recurring episodes of continuous spike-waves of slow sleep and generalized paroxysmal fast activity).\textsuperscript{1,2,17} Partial epilepsies or secondarily generalized epilepsies with origin in the frontal lobe are characterized by bilateral asymmetrical tonic seizures with secondary bilateral synchrony at the EEG.\textsuperscript{2,17} The diagnosis of Doose syndrome is suggested by the prominence of myoclonic or myoclonic-astatic seizures and the combination of fast spike-wave complexes and slow spike-wave complexes at the EEG.\textsuperscript{2,17}

### Outcome

A minority of patients with LGS reaches satisfying levels of autonomy while up to 76\% of them have severe lifelong limitations because of the intellectual disability and drug-resistant epilepsy.\textsuperscript{68,69}

Tonic seizures are commonly the most drug-resistant seizure type while atypical absences and myoclonic seizures are easier to control with pharmacologic therapy.\textsuperscript{69} Seizure freedom achieves 82\% in children younger than 5 years with etiologies treatable with neurosurgery.\textsuperscript{34,70}

The typical diffuse slow spike-waves pattern of LGS is often replaced with age by focal or multifocal epileptic discharges while up to 11.8\% of recently reported patients achieved a normalization of the EEG.\textsuperscript{69}

Long-term outcome of a patient with LGS is often disappointing regarding seizure control and cognitive functioning in patients with earlier onset and higher frequency of seizures, in subjects with constant slower background activity at the EEG and in cases with a prior West syndrome.\textsuperscript{1,2,17,29} This statement was not confirmed in a recent study in which no correlations were found between seizure onset, etiology, brain abnormalities on MRI, history of infantile spasms, and intellectual quotient and the importance of appropriate treatments on seizures and cognitive outcome was stressed.\textsuperscript{69}

The mortality rate has been reported up to 13.92 per 1,000 person-years in patients with LGS.\textsuperscript{71} In these subjects death often results from an accident during seizures or complications of status epilepticus.\textsuperscript{4,5}

### Conclusions

A large body of literature has been published about LGS since its original characterization, and several pieces of knowledge on etiology, pathophysiology, clinical presentation, therapeutic management, and outcome have been obtained in the past years. Despite these contributions, LGS remained one of the most severe age-dependent epileptic encephalopathies, and a multidisciplinary approach is always mandatory to support clinical, social, and economic needs of patients and their families.

### References


Acknowledgment

The author has no conflict of interest to declare
Lennox–Gastaut Syndrome

26 Pedersen M, Curwood EK, Archer JS, Abbott DF, Jackson GD. Brain regions with abnormal network properties in severe epilepsy of Lennox-Gastaut phenotype: Multivariate analysis of task-free fMRI. Epilepsia 2015;56(11):1767–1773
33 Siniatchkin M, Capovilla G. Functional neuroimaging in epileptic encephalopathies. Epilepsia 2013;54(Suppl 8):27–33
41 Kessler SK, McCarthy A, Cnaan A, Dlugos DJ. Retention rates of rufinamide in pediatric epilepsy patients with and without Lennox-Gastaut Syndrome. Epilepsy Res 2015;112:18–26


Karceski S. Vagus nerve stimulation and Lennox-Gastaut syndrome: a review of the literature and data from the VNS patient registry. CNS Spectr 2001;6(9):766–770


Ng YT, Pati S, Fesler JR. Lennox-Gastaut syndrome may be a curable, reversible epileptic encephalopathy. Epilepsia 2015;56(3):499–500