

Lennox-Gastaut syndrome (LGS)

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Abstract

Lennox-Gastaut syndrome (LGS) belongs to the group of severe childhood epileptic encephalopathies. This disorder is defined as a cryptogenic or symptomatic generalized epilepsy, which is characterized by the following symptomatic triad: several epileptic seizures (atypical absences, axial tonic seizures and sudden atonic or myoclonic falls); diffuse slow interictal spike wave in the waking electroencephalogram (EEG) (< 3 Hz) and fast rhythmic bursts (10 Hz) during sleep; slow mental development associated with personality disturbances. Incidence is estimated to 1:1,000,000 inhabitants per year, and the prevalence to 5-10% of epileptic patients, representing 1-2% of all childhood epilepsies. The onset occurs between 2 and 7 years. The most characteristic clinical manifestations in LGS consist of tonic seizures (17-92%), atonic seizures (26-56%) and atypical absences (20-65%). Diagnosis is based on the presence of specific EEG recordings. Treatment is difficult as LGS is usually refractory to conventional therapy. Some of the new antiepileptic drugs (AED) (Felbamate, Lamotrigine, Topiramate) have proven efficient in the control of seizures in LGS. The symptoms in cryptogenic LGS forms (20-30%) appear without antecedent history or evidence of brain pathology, whereas symptomatic LGS cases (30-75%) are associated with pre-existent brain damage.

Keywords

Lennox-Gastaut syndrome (LGS), childhood epileptic encephalopathies, tonic seizures, EEG recordings, new antiepileptic drugs (AED)

Disease name and synonyms

Lennox-Gastaut syndrome (LGS)

Historical overview

In 1938, Gibbs *et al.* described the characteristic EEG pattern of spikes and slow frequency waves and proposed the term of "petit mal"

variant" to differentiate it from the petit mal absence seizures associated with rhythmic spike-and-waves (1). In 1950, Lennox and Davis found clinical correlation between this type of EEG and patients with multiple epileptic crisis (2). Based upon the contributions of Lennox and colleagues, Gastaut (3) and Dravet and colleagues of the Marseille school, the term "Lennox-Gastaut Syndrome" (LGS) was adopted.

Diagnosis criteria / definition

LGS belongs to the group of severe infantile epileptic syndromes (epileptic neonatal encephalopathy with suppression-burst, West syndrome, severe myoclonic epilepsy of infancy), which represent the most distressing epileptic encephalopathies of infancy. LGS is characterized by the following symptomatic triad: several epileptic seizures (atypical absences, axial tonic seizures and sudden atonic or myoclonic falls); diffuse slow interictal spike wave in the waking EEG (<3 Hz) and fast rhythmic bursts (10 Hz) during sleep; slow mental development associated with personality disturbances.

Although this last element is not indispensable for the diagnosis, it is manifested in a high percentage of cases (4).

LGS is a controversial entity due to the difficulty of establishing its semiological electroclinical features and some authors have considered that severe cases of myoclonic astatic epilepsy represent myoclonic variants of LGS (4; 5). However the myoclonic phenomenon is not predominant in LGS, and this review focuses only on Lennox-Gastaut syndrome, as strictly defined above.

LGS is defined by the International Classification of Epilepsies, Epileptic Syndromes, and Related Seizure Disorders as a cryptogenic or symptomatic generalized epilepsy (6).

Differential diagnosis

All the epilepsies with frequent and brief seizures occurring in childhood should be eliminated from differential diagnosis:

Myoclonic epilepsies

- Benign atypical partial epilepsy of the childhood
- Partial post-traumatic epilepsy with slow spike-wave

- ESES syndrome
- [Rett syndrome](#)
- [Angelman syndrome](#)

Epilepsy absence with tonic or atonic component.

- [Landau-Kleffner syndrome](#)
- Multifocal severe epilepsy
- [Ceroid-lipofuscinosis](#)
- Gobbi syndrome (epilepsy, celiac disease and occipital calcifications)

Epidemiology

Although the incidence is estimated to 0.1 in 100.000 inhabitants per year, the prevalence is high (5-10% of epileptic patients), representing 1-2% of all childhood epilepsies. The onset occurs between 2 and 7 years. Cryptogenic cases have a later onset (7). Males seem to be more frequently affected. No family cases of LGS have been reported.

Clinical description

The most characteristic clinical manifestations in LGS (4, 8) consist of:

- *Tonic seizures*, the most frequent finding (17–92%), occurring especially during the slow sleep and never in the rapid eye movement (REM) phase. Duration is from a few seconds to a minute. Seizures can be tonic-axial, proximal appendicular or global. They are accompanied with apnoea and facial flushing, and they may lead to sudden falling if they appear when patient is awake.
- *Atonic seizures* (26–56%) are characterized by sudden loss of tone that either involve the head or the whole body. They can be very brief and may be associated with myoclonic seizures at the beginning of the crisis.
- *Atypical absences* (20–65%) are associated with decrease or loss of consciousness. The onset and termination are less abrupt than in typical absence. Duration is from 5 to 30 seconds. These seizures are neither induced by hyperventilation, nor by photic stimulation.
- *Nonconvulsive status epilepticus* has been reported in two-thirds of the patients, with duration ranging from hours to weeks. The episodes may be subtle and hardly noticeable. *Tonic status epilepticus* appears frequently following intravenous administration of benzodiazepines.
- Other seizure types, such as *tonic-clonic seizures*, *clonic seizures*, *partial seizures* and spasms can sometimes be observed, although they are not typical of LGS.

Evolution

LGS, one of the most severe epileptic syndromes in childhood, is refractory to treatment and tends to become chronic. Mental retardation, which is frequently associated with the condition (9), especially in symptomatic cases (10), tends to worsen as disease progresses, although it is not the absolute rule.

Psychosis may manifest during disease evolution (8).

Patients with symptomatic LGS, especially with pre-existent West syndrome, frequent seizures and repeated episodes of status epilepticus, have the worse prognosis.

The mortality rate is around 5%, but is rarely bound to the evolution of the epilepsy itself, as death is often related to accidents or episodes of tonic status epilepticus.

Treatment

LGS is essentially characterized by a lack of responsiveness to treatment, especially the classic anti-epileptic drugs (AED) (11). Barbiturates must be avoided as they exacerbate seizures and also worsen the behaviour of many patients. Bitherapy should be preferred over polytherapy.

The association of valproic acid (VPA) and benzodiazepines (specifically clobazam, in our experience) is usually the first-line therapy for most authors. The recommended doses are 20–40 mg/kg/day for valproic acid, and 0.5–1 mg/kg/day for clobazam.

Among the classic AED, phenytoin and carbamazepine are effective on tonic and tonic-clonic seizures, but they can increase the other types of seizures. Ethosuximide is useful in some cases to control absences.

Some of the new AED have proven efficiency in the control of LGS in clinical “add-on” trials. Felbamate has been reported to control 8% of seizures and to reduce 50% of all seizures type in 50% of patients treated. However, as this drug is associated with severe adverse side effects, it is important to weigh benefits versus risks. Lamotrigine has also shown a significant effect in multicentric studies (12), with at least a 50% reduction in seizure frequency in 32% of the cases. When associated with VPA, this drug should be introduced slowly at low initial dose to prevent serious rash. Topiramate has also been shown effective (13, 14, 15), with a responder rate of 55-85%, its effects on atonic seizures (suppression rate of 15%) being of special interest. Preliminary studies suggest that levetiracetam as add-on therapy appeared effective in reducing atonic and tonic-clonic seizures in Lennox-Gastaut syndrome seizures (16, 17) ACTH (adrenocorticotrophic hormone) or corticosteroids treatment (for up to four months) may be helpful in LGS not responding to therapy, although it may induce a Cushing’s syndrome.

Ketogenic diet has been used in intractable infantile epilepsies (18) and we have had positive results in LGS patients (19, 20). Control of all seizure types improved the first days after the beginning of this therapy, but this diet requires very strict compliance.

Barbiturate anesthesia is generally used in the treatment of status epilepticus; a 5-day treatment under these conditions proved a significant improvement of seizures, but long term results indicated that seizures recurred, and the number of AEDs was significantly greater after than before the anesthesia (21).

Clinical trials of intravenous immunoglobulins in high doses have shown effectiveness in reduced series.

Surgical treatment is an exceptional option in cases of well-located lesions. Callosotomy has been shown effective in intractable atonic seizures, but it does not improve other seizure types and the focal crises can even increase.

Presurgical study with PET allows to differentiate four forms of SLG: cortical resections located in cases of focal hypometabolism, hemisferectomy and callosotomy in cases of unilateral diffuse hypometabolism, callosotomy in bilateral diffuse hypometabolism and abstention in cases without demonstrable alteration.

Results of vagal stimulation in children with LGS are difficult to evaluate because of the methodology used in the published cases. A serie showed an effectiveness limited in epileptic encephalopathy (22). Another study reported effective long-term results (over 5 years) with 50% reduction of seizures and with restricted adverse side effects (23).

In any event, treatment of LGS should minimise seizures and maximise quality of life, since the last studies on the syndrome outcome maintain bad prognosis in LGS (24), even when using stringent criteria in defining the cryptogenic LGS subgroups (25).

Etiology

In the cryptogenic forms (20–30%), symptoms appear without antecedent history or evidence of brain pathology, but dendrites alterations have been described in some of them (26). The symptomatic cases (30–75%) are associated with perinatal asphyxia, tuberous sclerosis, meningoencephalitis sequelae, cortical dysplasia, cranial trauma and more rarely, tumours and metabolic dysfunction. Some idiopathic cases have been described (5%) to be not associated with mental retardation or neurological signs, normal neuroimaging, family antecedents of epilepsy and genetic features in the EEG studies.

Diagnostic methods

The hallmark of the awake interictal EEG in patients with LGS is the diffuse slow spike wave pattern (equal or inferior tp 2.5 Hz) (8,). The epileptiform discharges last from several minutes to a near continuous state, they are prevalent in frontal regions, and asymmetric in 25% of cases.

Spike discharges at 10 Hz lasting 1 to 10 seconds are common during non-REM sleep. The ictal EEG depends on the seizure type. In tonic seizures, the activity pattern consists of diffuse, rapid (10–25 Hz), and bilateral discharges in the anterior or vertex areas. During atonic seizures, the EEG shows slow spike waves and fast-recruiting discharges. Myoclonic seizures are characterized by synchronous and symmetrical spike and sharp waves of brief duration, followed by one or several slow waves.

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