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Diagnosis of Lennox-Gastaut syndrome and strategies for early recognition

Suresh Pujar[a,b] and J Helen Cross[a,b]

[a]Paediatric Neurosciences Department, Great Ormond Street Hospital for Children, London, UK; [b]Developmental Neurosciences Research & Teaching Department, University College London NIHR BRC Great Ormond Street Institute of Child Health, London, UK

ABSTRACT

Introduction: Lennox Gastaut syndrome (LGS) as an electroclinical diagnosis has been utilized as a clinical entity for more than 70 years. However, with the recognition of other distinct electroclinical epilepsy syndromes, no consistent single etiology, and the variability of criteria used in clinical trials, the clinical utility of such a diagnosis has been questioned. Recently, the International League Against Epilepsy for the first time defined diagnostic criteria for epilepsy syndromes, thereby allowing consistent language and inclusion criteria to be utilized.

Areas covered: Recent diagnostic criteria for syndrome diagnosis are explored as defined by the International League Against Epilepsy, with further literature reviewed to highlight relevant features, and differential diagnosis explored.

Expert Opinion: Developmental and Epileptic Encephalopathy (DEE) is an overall term that may be descriptive of many different epilepsies, most of early onset, whether electroclinically or etiologically defined, of which LGS is one. Although we have moved forward in defining an increasing number of etiologically specific syndromes, this to date remains a minority of the DEEs. Although there is progress with precision medicine targeted at specific causes, the term LGS still remains useful as a diagnosis in defining treatment options, as well as overall prognosis.

1. Introduction

Lennox-Gastaut Syndrome (LGS) is a severe form of childhood-onset epilepsy characterized by multiple seizure types, cognitive and behavioral impairment, and distinctive electroencephalogram (EEG) abnormalities. It is classified by the International League Against Epilepsy (ILAE) as a 'developmental and epileptic encephalopathy (DEE)', implying that it is an epilepsy syndrome associated with developmental impairment that may be due to either the underlying etiology or the superimposed epileptic activity, or both [1,2]. Because of the variable presentation and delay in evolution of the characteristic clinical and EEG features, early diagnosis can be difficult and misdiagnosis is not uncommon [3–8]. Early recognition and diagnosis is important not only to determine prognosis but also to provide access to newer therapies now licensed for use in LGS as well as participation in clinical trials for novel therapies. This paper reviews the challenges in making an early diagnosis of LGS, explores current diagnostic criteria, and discusses strategies for early diagnosis, drawing upon relevant literature and research studies.

1.1. Definition and diagnostic criteria

Since the first description in 1950 by Lennox and Davis, and Gastaut et al. in 1966, the definition of LGS has evolved over the years [9,10]. The clinical picture of LGS is the triad of a pharmacoresistant seizure disorder, characteristic abnormalities on electroencephalogram (EEG), and cognitive dysfunction. However, given the variability in presentation and the absence of characteristic clinical and EEG features early in the course of the disease, the diagnosis has been loosely applied to describe any severe, early onset epilepsy with intractable seizures leading to falls. In the 1989 classification, the ILAE described LGS as 'an epilepsy manifesting in children from ages 1–8 years with the most common seizure types reported as tonic-axial, atonic, and absence seizures, though other types such as myoclonic, GTC, or focal seizures were also described' [11].

In a recent ILAE position paper, a clearer definition of LGS and diagnostic criteria are provided [12]. In this paper, LGS is described as 'a syndrome characterized by the presence of (1) multiple types of drug-resistant seizures with onset prior to 18 years (one of which must include tonic); (2) cognitive and often behavioral impairments, which may not be present at seizure onset; and (3) diffuse slow spike-and-wave and generalized paroxysmal fast activity on EEG.' Age at epilepsy onset <18 years, presence of tonic seizures and at least one other seizure type, and EEG features of generalized slow spike-and-wave complexes of <2.5 Hz and generalized paroxysmal fast activity (10 Hz or more) in sleep (or history of these findings on prior EEG) are mandatory for diagnosis of LGS.

1.2. Epidemiology

LGS is relatively rare, with population-based studies estimating a prevalence of 2.9–28 per 100,000 [13]. It is estimated that LGS comprises between 1% and 2% of all patients with epilepsy and between 1% and 10% of childhood epilepsies [4,14–16]. Approximately 10% of the children with epilepsy onset before the age of 5 years and 19% of the children with epilepsy onset in infancy will be subsequently diagnosed with LGS [15,17]. Between 10% and 25% of the patients with LGS have a previous diagnosis of infantile epileptic spasm syndrome (IESS) (previously known as West syndrome) [15,17,18].

While the typical age of LGS onset is before 8 years (peak age at onset of 3–5 years), late-onset LGS has been reported in 10–16% [6,14,19,20]. For reasons not yet clear, the prevalence of LGS is up to five times higher in males [6,15].

1.3. Aetiology of LGS

About 65% to 75% of the patients with LGS have an identifiable cause. The most common is a nonprogressive brain disorder resulting from either a brain malformation (e.g. lissencephaly, other malformation of cortical development, tuberous sclerosis) or acquired perinatal brain damage (e.g. hypoxic ischemic encephalopathy, hypoglycemia, kernicterus, infections). Reported genetic causes of LGS include copy number variants in 3–19% and mutations of other genes involved in human brain development (e.g. the forkhead box G1 (FOXG1), chromodomain-helicase-DNA-binding protein 2 (CHD2) genes) and the gene for presynaptic protein dynamin 1 (DNM1) [4,21,22]. In addition, various gene mutations causing cortical malformations (i.e. LIS1, DCX, or GPR56) or neurocutaneous syndromes (TSC1 and TSC2) have been frequently associated with LGS [22].

In 25% to 35% of reported LGS patients, an identifiable cause has not been found [4,21]. With the increasing use of next-generation whole-genome sequencing and advancements in neuroimaging techniques, it is likely that more genetic and subtle structural causes of LGS will be identified in the future.

2. Clinical characteristics

2.1. Seizure types

Tonic seizures, atypical absences, and epileptic drop attacks (tonic or atonic) are the most characteristic seizure types described in LGS.

'Tonic seizures, consisting of a sustained increase in axial and limb muscle contraction lasting from 3 sec to 2 min, are mandatory for diagnosis and are most prominent in sleep.' [12] While they may not always be present at the onset of LGS, all patients will develop tonic seizures during the course of the disease and persist into adulthood [23]. The tonic seizures can be quite obvious and result in tonic drops, or be subtle and seen only during sleep and therefore often under-reported.

'In addition to tonic seizures, a second seizure type is mandatory for the diagnosis of LGS and may include any of the following seizure types' [12]:

(1) Atypical absence seizures: second most common type of seizures in LGS. However, they are often difficult to recognize due to their gradual onset and offset in a patient with underlying cognitive impairment.
(2) Atonic seizures: manifest with an abrupt loss of axial tone, with head nods or a sudden fall (drop attacks), often causing injury.
(3) Myoclonic seizures: Myoclonic seizures are very brief (<100 ms) and may lead to falls (drop attacks).
(4) Focal impaired awareness seizures: These may remain focal or evolve to bilateral tonic – clonic seizures.
(5) Generalized tonic – clonic seizures.
(6) Nonconvulsive status epilepticus: approximately 50% to 75% of the patients with LGS have one or more episodes of nonconvulsive status epilepticus. This presents as subcontinuous atypical absence seizures with variable degrees of awareness, with erratic, generalized, or multifocal myoclonic, and atonic components, and interspersed clusters of brief tonic seizures.
(7) Epileptic spasms

While drop attacks occur in more than 50% of the patients with LGS, especially in younger children, it is not a pathognomonic clinical manifestation. Drop attacks could be the result of tonic, atonic, or myoclonic seizures [3,4,6]. Focal impaired awareness seizures and generalized tonic-clonic seizures are more common in the later stages of LGS, in early adolescence and adulthood [22,23].

2.2. Cognition and behaviour

About a third of patients report normal cognitive development prior to seizure onset in LGS [19,24]. However, cognitive impairment usually becomes apparent over time, and moderate-to-severe intellectual difficulties are reported in the majority within 5 years of onset [6,25]. While cognition in 10–20% of the children with LGS is reported to be within the accepted normal ranges, they usually have slow mental processing, resulting in difficulties in performing day-to-day activities. Presence of nonconvulsive status epilepticus (NCSE),

a previous diagnosis of IESS/West syndrome, a determined etiology of epilepsy, and an early age at the onset of epilepsy are recognized as independent risk factors for severe cognitive impairment in patients with LGS [22].

In addition to cognitive difficulties, many patients with LGS have behavioral and psychiatric problems, such as autism spectrum disorder, ADHD, oppositional behavior, physical aggression, and sleep disturbances. Often the management of these behavioral difficulties is quite challenging for their caregivers and impacts on their quality of life [4,6,25].

2.3. EEG features

While the background EEG activity is usually abnormal, with diffuse theta-delta slowing, the following "two interictal EEG patterns are mandatory for the diagnosis of LGS [12]:

(1) Generalized slow spike-and-wave: slow spike-and-wave pattern characterized by spikes (<70 ms) or sharp waves (70–200 ms), followed by negative high-voltage slow waves (350–400 ms), which are bilaterally synchronous, often anterior predominant, and occur at a frequency of ≤2.5 Hz. It can be associated with atypical absence seizures, but the distinction between ictal and interictal discharges is difficult, particularly in children with cognitive impairment and due to lack of clear onset and offset. This pattern is more frequently present in young children. After the age of 16 years, the majority of patients no longer exhibit the typical slow spike-and-wave pattern [23,26].

(2) Generalized paroxysmal fast activity (GPFA): GPFA consists of bursts of diffuse or bilateral fast (10 Hz or more) activity often seen during slow wave sleep. These typically are brief, lasting a few seconds or less." They are almost identical, but shorter, to the bursts commonly seen in tonic seizures that have a recruiting rhythm (an initial diffuse lowering of amplitude followed by a gradual increase in amplitude). Unlike the generalized slow spike-wave pattern, recording of GPFA during slow wave sleep is more constant in adolescents and adults [23,26].

The EEG patterns may change over time and may show focal epileptiform discharges, diffuse and focal slow waves, and disappearance of the characteristic slow spike-and-wave pattern [3,23,26]. Indeed, EEGs from earlier during the disease course can be more beneficial when reviewing diagnosis in adolescents and adults. The ILAE task force therefore has specifically mentioned in the mandatory EEG criteria for LGS that a history of generalized slow spike-and-wave complexes of <2.5 Hz and GPFA finding on prior EEG is sufficient to make a diagnosis [12].

The photoparoxysmal response is unusual in LGS and a photoparoxysmal response at low frequencies should alert the clinician to consider other diagnosis such as CLN2 disease [12]. In addition, persistent focal abnormalities without generalized spike and wave patterns exclude LGS diagnosis and should consider possibility of a brain malformation such as a focal cortical dysplasia or a genetic focal epilepsy.

2.4. Differential diagnoses

LGS can be differentiated from other childhood epilepsy syndromes based on the characteristic seizure types, EEG findings, and presence of cognitive impairment. However, as the syndrome evolves over time, there can be significant overlap between LGS and other early onset DEEs. One retrospective study reported misdiagnosis in nearly 30% of the patients referred with a diagnosis of LGS [8].

Infantile Epileptic Spasm syndrome (IESS, previously known as West syndrome): Up to 30% of infants with IESS may progress to LGS [17,27]. The distinction between epileptic spasms and brief tonic seizures can be difficult and therefore establishing a diagnosis can be challenging during the transition. Sleep EEG with polygraphic recording can help distinguish between epileptic spasms and brief tonic seizures and characteristic interictal EEG patterns may provide diagnostic clues.

Epilepsy with myoclonic atonic seizures (EMAtS, previously known as Doose syndrome): children present with explosive onset generalized tonic clonic seizures and drop attacks and can be difficult to distinguish from LGS at disease onset. However, distinction is important, not least because of the marked difference in prognosis. Presence of myoclonic-atonic seizures is mandatory for the diagnosis of EMAtS. Children typically have normal development prior to seizure onset and the typical EEG pattern is of faster (>3 Hz) generalized spike-and-wave discharges. Despite the explosive onset and initial pharmacoresistance, up to two-thirds of children achieve seizure remission within 3 years of onset [28,29].

Dravet syndrome: children typically present with prolonged, hemiclonic seizures in the context of a febrile illness in the first year of life. Tonic seizures are not typical, and a pathogenic variant in SCN1A gene is found in over 80% of the cases of Dravet syndrome [30].

DEE-SWAS or EE-SWAS (developmental/epileptic encephalopathy with spike-and-wave activation in sleep): This term replaces syndromes previously named epileptic encephalopathy with continuous spike-and-wave complexes during sleep (CSWS) and atypical benign partial epilepsy (pseudo-Lennox syndrome) [12]. The key characteristics are developmental (cognitive, behavioral, and/or motor) regression or plateauing associated with marked spike-and-wave activation in sleep, with nearly continuous diffuse spike-and-wave complexes. Regression is seen within weeks from the EEG pattern. Landau – Kleffner syndrome (LKS) is a specific subtype of EE-SWAS, where regression affects mainly language, with an acquired auditory agnosia. The EEG pattern associated with EE-SWAS and DEE-SWAS was known as electrical status epilepticus in sleep (ESES). Drop attacks, often negative myoclonus, may herald the onset of the syndrome.

Other early onset DEEs with multiple seizures types and associated with cognitive impairment.

Ring (20) syndrome: This can present with a clinical phenotype that may be interpreted as LGS; pharmacoresistant epilepsy, intellectual disability, and behavioral abnormalities.

Similar to LGS, tonic seizures usually appear during sleep, and nonconvulsive status epilepticus is frequent [31]. It is diagnosed by means of conventional cytogenetics (karyotyping). Since karyotype testing is not a routine investigation when epilepsy first presents, the diagnosis of r(20) syndrome may be delayed or go unrecognized.

Pharmacoresistant focal epilepsies (such as frontal lobe epilepsy): while patients with frontal lobe epilepsy have frequent brief tonic seizures from sleep, they often have asymmetrical features. EEG may show persistent focal slowing/epileptiform discharges and the characteristic LGS EEG features of slow spike-and-wave and GPFA are not seen. High-resolution neuroimaging may identify subtle cortical malformation, if not seen on conventional brain imaging.

Progressive neurodegenerative disorders (such as CLN2 disease): Late-onset LGS can initially be confused with rare progressive myoclonus epilepsies (PMEs) that present with seizures and cognitive decline. Unlike in LGS, patients with PMEs have progressive motor and cognitive decline, and ataxia. The EEG may show some characteristic features (such as a photoparoxysmal response at 1–3 Hz in CLN2 disease). The diagnosis is usually confirmed on genetic testing.

3. Challenges in early diagnosis of LGS

Accurate early diagnosis of LGS is challenging due to several reasons and is discussed below:

3.1. LGS is a syndrome-in-evolution

Children with early-onset LGS often experience an evolution through several related conditions or syndromes. Approximately 20% of children, with seizures starting in infancy and about 50% of the infants with a severe DEE evolve over time to LGS [17]. A typical example of age-dependent presentation is a newborn with a significant brain injury or a brain malformation who may present with early infantile developmental and epileptic encephalopathy (previously described as Ohtahara syndrome) in the newborn period and at 3 months evolve into infantile epileptic spasm syndrome (previously called West syndrome). About 30% children with IESS will go on to develop LGS [17,27,32]. Accurate characterization of seizure types and updating the diagnosis in someone with a previously diagnosed epilepsy syndrome can be challenging during the transition.

3.2. Heterogeneity of clinical presentation and time for evolution of characteristic features

As LGS can result from a wide range of etiologies, the clinical presentation may vary according to the cause. As discussed above, the presentation in a child whose LGS evolves from a previously diagnosed DEE may be different from a child with no obvious cause. The age at seizure onset, the seizure types, severity of epilepsy at onset, and EEG features may vary accordingly. The typical gap from initial seizure presentation and the emergence of LGS diagnostic features is between 1 and 2 years. Thus, the characteristic seizure types such as tonic seizures and atypical absences may not be present at the onset [6,7,19]. This said the appearance of diffuse slow spike wave at 2–2.5 Hz, although nonspecific for LGS may lead the clinician to be alert to the possibility of the diagnosis and search for further seizure types.

3.3. Delay in recognition of characteristic seizure types

Tonic seizures, the mandatory seizure type for LGS diagnosis, can be subtle and occur most often during non-REM sleep and therefore may not be recognized by caregivers. Therefore, this seizure type may not be reported until they are captured on a sleep EEG. Similarly, atypical absences, the second most common seizure type in LGS, are often difficult to recognize due to gradual onset and offset in patients with diminished cognitive abilities in whom it is difficult to assess responsiveness. A video EEG may be necessary to confirm this seizure type and establish LGS diagnosis. Nonconvulsive status epilepticus, which is seen in up to 75% patients with LGS is particularly difficult to recognize in patients with severe cognitive impairment.

3.4. Overlap with other severe epilepsy syndromes

As discussed in differential diagnoses section, LGS shares some features with several early-childhood onset epilepsy syndromes associated with multiple seizure types and cognitive impairment. For example, drop attacks, seen in over 50% of the children with LGS are not pathognomonic and also seen in epilepsy with myoclonic atonic seizures. Similarly, while slow spike-and-wave is considered a characteristic EEG pattern in patients with LGS, it is not pathognomonic, and may also be seen in focal epilepsy with secondary bilateral synchrony [33].

3.5. Lack of characteristic LGS features in adolescence and adulthood

Due to evolution of symptoms and EEG features, it might be difficult to recognize LGS in adulthood, in a previously undiagnosed patient [23,34]. More than half of LGS patients diagnosed during childhood no longer have all diagnostic clinical and EEG features by adulthood. Atypical absences and generalized slow spike-and-wave complexes are seen in a minority of adults although tonic seizures and GPFA during sleep tend to persist [23,26]. Therefore, in a previously undiagnosed patient, a diagnosis of LGS may be missed if a detailed history is not taken and EEGs from early childhood not carefully reviewed.

3.6. Other confounding factors include:

Given the poor prognosis, some caregivers may not accept the diagnosis of LGS until the evolution of all characteristic clinical and EEG features.

Lack of familiarity with LGS diagnosis among pediatricians and child neurologists and therefore delaying diagnosis and labeling it generically as 'drug-resistant epilepsy' or 'mixed seizure disorder.'

In some countries and communities, there may be lack of access to specialists and/or resources for diagnostic tests, and therefore a diagnosis may not be established.

4. Strategies for early recognition of LGS

4.1. High degree of suspicion and pattern recognition

As the characteristic clinical and EEG features of LGS evolve over time, awareness about the diagnosis and a high degree of suspicion is key for early recognition. This is particularly important in those children with a previously diagnosed DEE and epilepsy syndromes such as IESS. Tonic seizures may be subtle and only seen in sleep and atypical absences difficult to recognize in a child with impaired cognition. Therefore, video EEG with sleep is important to identify these features early and establish a diagnosis.

4.2. Appropriate diagnostic work-up

In addition to a thorough clinical assessment, judicious use of diagnostic modalities can help establish a LGS diagnosis, identify etiology, and rule out LGS mimics.

Video EEG can demonstrate characteristic interictal EEG patterns such as generalized slow spike-and-wave complexes and GPFA in sleep. It can also help confirm the presence of atypical absences and brief tonic seizures from sleep.

High-resolution neuroimaging can be useful in the identification of an etiology, namely congenital malformations of cortical development, acquired brain injuries, and features characteristic of neurometabolic disorders. It is important that the neuroimaging scanning protocols include appropriate sequences to increase the identification of subtle abnormalities. As incomplete myelination during infancy may make it difficult to identify some lesions, MR imaging should be repeated after 24–30 months if normal in the first 2 years of life. Recently developed automated surface-based machine-learning algorithms for the identification of subtle MRI lesions show promising results and may have clinical application in the near future [35]. Other imaging modalities such as MR spectroscopy and positron emission tomography (PET) may be useful in identifying metabolic disorders when conventional MR imaging is normal or show subtle abnormalities.

Genetic investigations including microarray to identify copy-number variants, karyotype to diagnose conditions such as ring chromosome 20 syndrome, and next-generation whole-genome sequencing should be considered, particularly in those with a family history and clinical features suggestive of a genetic condition and in whom a diagnosis is not apparent on brain imaging. Genetic testing is also important to support diagnoses of conditions such as Dravet syndrome and tuberous sclerosis, to ensure appropriate screening and access to targeted therapies.

Appropriate metabolic and genetic testing should be undertaken to exclude neurometabolic disorders, including progressive conditions such as CLN2 disease.

4.3. Periodic review of diagnosis

As the diagnostic features of LGS may not be present at onset and evolve over time, it is important to review the diagnosis periodically and look for clinical and EEG features to establish a diagnosis of LGS.

5. Expert opinion

LGS is a severe pharmacoresistant DEE, which may be caused by a variety of different etiologies with a heterogeneous initial presentation. The diagnostic clinical and EEG characteristics evolve over time, and therefore may pose a challenge to diagnosis. This may result in delays in access to specialist discussion and access to appropriate therapies. Overall, however, the long-term prognosis for neurocognitive and seizure outcomes in LGS is poor – important when considering expectations of seizure response to medication and educational achievement. It is important to characterize the correct electroclinical syndrome to delineate the appropriate treatment course and the likely prognosis.

Previous diagnostic criteria have been broad, specifically when defined for inclusion criteria in clinical trials, and have led to a high rate of misdiagnosis and heterogeneity of inclusion to the trials of specific antiseizure medications. LGS diagnosis is based on electro-clinical criteria. There is no single specific etiology; LGS appears to be an age-dependent pattern seen with a variety of different causes. The ILAE has recently defined criteria for a diagnosis of LGS, which should allow consistency and a common language in research. Awareness of these diagnostic criteria, a high degree of clinical suspicion, judicious use of investigations and periodic review of diagnosis are key for making an early accurate diagnosis. Use of these criteria in future research should also allow insights into possible successful therapies and address the question as to whether early treatment could potentially alter the course of the disease and improve the overall long-term quality of life in patients.

As the definition of other electroclinical syndromes has evolved, the question arises as to whether the entity described as Lennox Gastaut syndrome, remains useful. Although a recognized electroclinical syndrome, LGS is heterogeneous with regard to underlying etiology. Genetic studies have not determined predominant genetic variants as a cause; it is unlikely a single genetic cause will be found although genetic predisposition may be a reason for the ultimate clinical expression seen with the range of etiologies. One could therefore question whether the term adds further to a diagnosis of a Developmental and Epileptic Encephalopathy (DEE)? The latter is an overall term that may be descriptive of many different epilepsies, most of early onset, whether electroclinically, or etiologically defined, where the ongoing neurodevelopmental impairment is believed to be the result of both the underlying cause and ongoing electrical activity, whether overt seizures or ongoing epileptiform activity. Designing antiseizure medication trials restricted to specific syndromes has allowed orphan designation from a regulatory perspective, but in certain circumstances ultimately has restricted availability through reimbursement. Utilizing the term DEE, with later stratification into more well-defined electroclinical syndromes, as diagnosed using the ILAE diagnostic criteria may be a way forward in the future.

As we enter the era of precision medicine, underlying etiology may also lead to use of alternative targeted treatments. Although we have moved forward in defining an increasing number of etiologically specific epilepsy syndromes, this to date remains a minority of the DEEs, and requires further delineation. Currently, there is a role for making both an etiological and an electroclinical diagnosis in the same individual. The term LGS still remains useful with its definition as outlined in recent diagnostic criteria in giving a diagnosis for those where such etiology is not clear, in defining treatment options, as well as overall prognosis.

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Declaration of interest

Reviewer disclosures

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