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ORIGINAL ARTICLE

Facilitating the timely diagnosis of Lennox–Gastaut syndrome: A checklist to support clinical practice

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Abstract

Objective: To develop and evaluate a simple-to-use checklist to support physicians with the timely diagnosis of Lennox–Gastaut syndrome (LGS).

Methods: A panel of 10 pediatric and adult epileptologists used the International League Against Epilepsy (ILAE) criteria for LGS classification and definition to develop seven questions for the checklist, through an iterative process. A scoring system formulated for the checklist yielded four distinct outcomes: likely LGS, possible LGS, unlikely LGS, and insufficient data. The checklist was then tested for reliability. Firstly, each expert selected LGS and non-LGS cases from their patient medical records and, for each case, provided the original diagnosis and answers to the checklist questions to an independent third party, who subsequently compared the outcome with the original diagnosis. The checklist questions were then refined based on the initial assessment. All cases were re-evaluated by the panel, and the results were collected as previously. Correct outcomes were defined as a perfect level of agreement with the original diagnosis provided by the expert (both LGS and non-LGS cases) or "possible LGS" outcome matching an original LGS diagnosis.

Results: Of the 120 cases evaluated (LGS, $n = 64$; non-LGS, $n = 56$), the outcome was correct for 95% ($n = 114$): 66.7% ($n = 80$) had a perfect level of agreement with the original diagnosis, and 28.3% ($n = 34$) were "possible LGS" matching an original LGS diagnosis. Incorrect matches, where the checklist outcome did not match the original LGS diagnosis, were due to the absence of documented characteristic EEG features and, related to young age, lack of cognitive/behavioral impairment.

Significance: The checklist offers a simple-to-use resource for treating physicians to support earlier LGS diagnosis, using the ILAE criteria as the framework. The findings also highlight the importance of EEG data for LGS diagnosis, that

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For affiliations refer to page 12.

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mandatory ILAE diagnostic features are not always initially present and may evolve over time, and the need to re-evaluate patients during follow-up.

KEYWORDS

checklist, developmental and epileptic encephalopathies, diagnosis, Lennox–Gastaut syndrome

1 | INTRODUCTION

Developmental and epileptic encephalopathies (DEEs) are a heterogeneous group of neurodevelopmental disorders in which both the underlying pathology and epileptic activity itself result in developmental impairment.[1,2] DEEs encompass conditions arising from a range of etiologies, which are characterized by early-onset and often drug-resistant seizures.[3]

Lennox–Gastaut syndrome (LGS) is a severe DEE,[4] with an estimated incidence of 14.5–28 per 100 000, and prevalence of 5.8–60.8 per 100 000.[5] Onset is most frequent between the ages of 3 and 5 years, although later onset is also possible,[4,6] and it persists through adolescence and into adulthood.[4] LGS is caused by a wide range of different etiologies, including structural brain abnormalities, genetic, and metabolic disorders, and can evolve from other epilepsy syndromes.[4,7,8] Etiology is unknown in 25%–33% of cases.[9,10] Additionally, there is no single biological marker that identifies this syndrome.[9] Patients with LGS have a substantial symptom burden because of frequent, severe drug-resistant seizures,[11,12] and a number of comorbidities,[4,11] including moderate to severe cognitive impairment, behavioral problems, physical and motor disabilities, and sleep disorders, which affect daily functioning and quality of life.[4,11,12] Moreover, LGS has been shown to be associated with increased mortality compared with both the general epilepsy and control populations,[12,13] with mortality rates being reported up to seven times higher than the general epilepsy population.[12,14,15] Due to the severe nature of the condition, parents and caregivers also experience physical, social, psychological, and financial difficulties associated with caring for a patient with LGS.[12,16,17]

In 2022, the International League Against Epilepsy (ILAE) defined LGS based on a "triad" of key features: (a) multiple and drug-resistant seizure types, of which tonic seizures are the hallmark; (b) abnormal EEG, with both diffuse, slow spike-and-wave (SSW) complexes, and generalized paroxysmal fast activity during sleep; and (c) mild to severe cognitive and behavioral impairments, which may develop after seizure onset.[4,10] Based on this triad of symptoms, the ILAE identified mandatory criteria, which must be present for a diagnosis of LGS, exclusionary criteria, which must be absent, and alerts, which are generally absent in the vast majority of cases, but can rarely be seen[4] (see Figure 1).

Key points

- Lennox–Gastaut syndrome (LGS) can be challenging to diagnose due to its clinical variability and evolution of symptoms over time.
- A group of epilepsy experts formulated an easy-to-use checklist to help physicians with their diagnosis when LGS is suspected.
- The checklist, based on the ILAE criteria for LGS, has four possible outcomes: likely LGS, possible LGS, unlikely LGS, and insufficient data.
- The reliability of the checklist was 95%, offering a simple-to-use resource for physicians to support LGS diagnosis.
- The study highlights the importance of collecting information on mandatory ILAE features and re-evaluating patients for accurate LGS diagnosis.

Diagnosing LGS can be challenging because it is characterized by a broad and variable clinical presentation and evolution of symptoms.[9] Indeed, taken separately, the characteristic EEG features and seizure types are not uniquely indicative of LGS, and they evolve and change over time,[9] with clinical and EEG features typically presenting 1–2 years following seizure onset.[18] Moreover, cognitive impairment, another core feature of LGS, might not always be present at onset and becomes evident over time, presenting with variable severity ranging from mild to severe.[9,19] The irregularity of these mandatory features for LGS diagnosis may hinder the diagnostic process for treating physicians. Additionally, other electroclinical syndromes often evolve into LGS,[9] including infantile epileptic spasm syndromes (IESS) or etiology-related syndromes such as tuberous sclerosis complex (TSC).[4,20] As a consequence, features of LGS may overlap with those of other DEEs, leading to a delay in diagnosis and sometimes to misdiagnosis.[6,9] The diagnosis of LGS is further complicated by the fact that, in some countries, there

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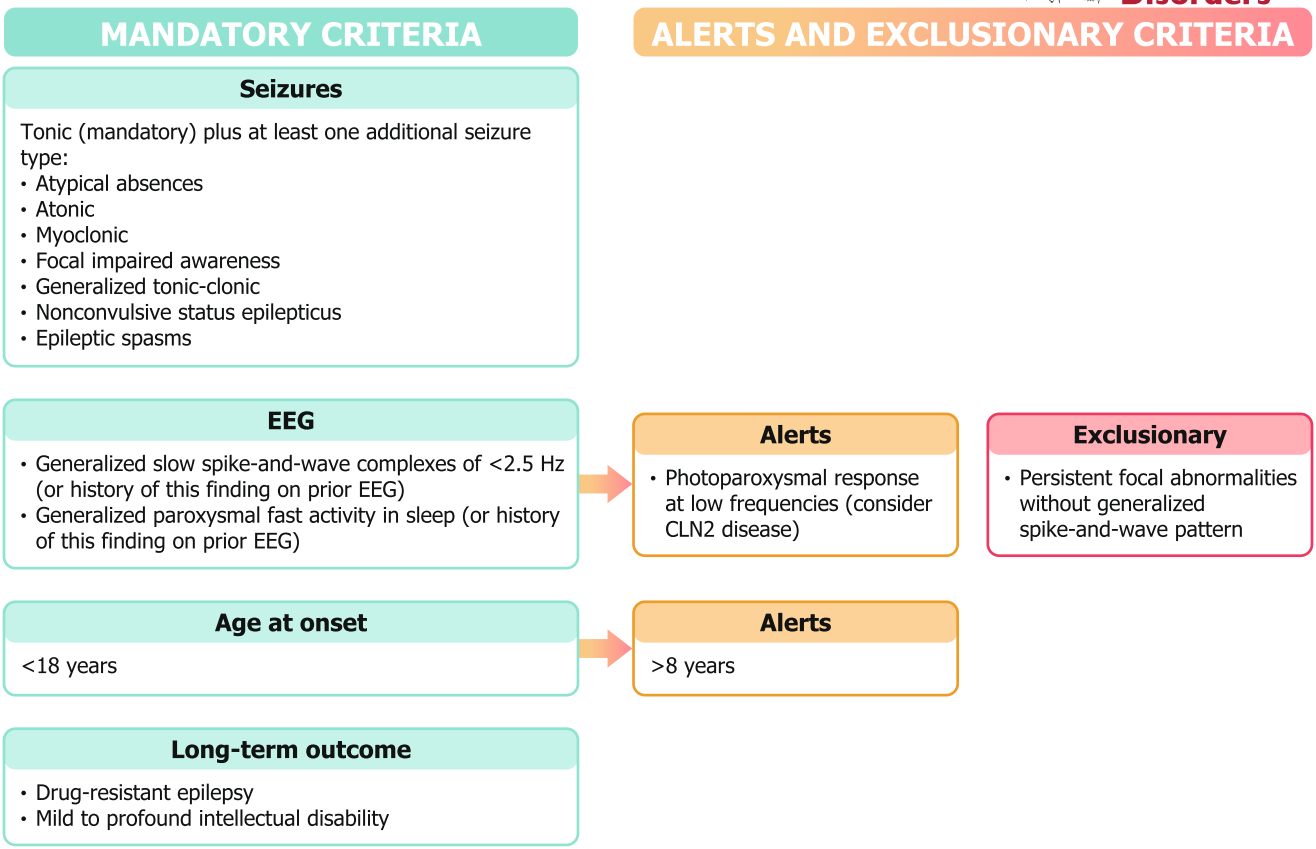

FIGURE 1 Mandatory criteria, exclusion criteria and alerts defined by the ILAE for the diagnosis of LGS. CLN2, ceroid lipofuscinosis type 2; EEG, electroencephalogram; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; MRI, magnetic resonance imaging; IESS, infantile epileptic spasms syndrome.

may be limited access to resources or specialists to conduct diagnostic tests, particularly prolonged video EEG monitoring during sleep or genetic screening when indicated.[16]

An early and accurate diagnosis is essential to ensure timely intervention and potentially improve the prognosis,[7,9,21] by ensuring selection of the most appropriate treatment options, avoiding treatments that may aggravate seizures or worsen comorbidities, and providing an opportunity to arrange specific rehabilitation. It also provides clarity to families, reducing uncertainty and facilitating informed care planning and long-term decision-making.[22] Despite the guidance provided by the ILAE, treating physicians may struggle with recognition of LGS, resulting in delayed diagnosis, misdiagnosis, or overdiagnosis.[18] To address this challenge, a group of international epilepsy experts collaborated to develop a simple-to-use checklist for physicians, based on the ILAE diagnostic criteria, with the aim of supporting the timely diagnosis of LGS in both pediatric and adult patients.

2 | METHODS

A panel of 10 pediatric and adult epileptologists from seven European countries was convened to develop a structured checklist that could be used by clinicians when suspecting a diagnosis of LGS. The group was selected based on their long-standing expertise in the field of epilepsy and with specific clinical experience in DEEs. Most of the experts are members of the European Reference Network for Rare and Complex Epilepsies (ERN EpiCARE)[23] and some were part of the ILAE epilepsy syndrome definition taskforce.

The questions were formulated in line with the ILAE criteria for LGS diagnosis, using an iterative process through a series of meetings. A total of seven questions were developed, and a scoring system was defined wherein each question was assigned a score of 1 point (for a total of 7 points). Each point was then allocated a color based on the alignment with the ILAE criteria: green, if the answer was in line with the mandatory criteria of the ILAE for an LGS diagnosis; amber, if the answer was unknown or not available; red, if it was not in line with the mandatory criteria determined by the ILAE. The total number of green, amber, and red points was then calculated and one of four possible outcomes determined based on the total score: "likely diagnosis of LGS"; "possible diagnosis of LGS"; "unlikely diagnosis of LGS"; or "insufficient data". The full checklist and possible scenarios are reported in Figure 2.

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The checklist was tested for reliability in a two-step process. During the first step, each expert assessed the checklist by re-evaluating some of their previous LGS and non-LGS clinical cases, selected from their patient records. For each case, each expert answered the questions in the checklist and provided these to an independent party, along with the original diagnosis: only anonymized data were provided by the experts. The independent party calculated the total score for each case and compared the outcome of the checklist with the original diagnosis. The panel re-convened to assess the findings of the first step and to refine the questions and outcomes into a final checklist. In the second step, all clinical cases were re-evaluated by each expert using the final updated checklist, and the results were collected and analyzed as previously described.

Correct cases were defined as those that either had a perfect level of agreement with the original clinical diagnosis (both LGS and non-LGS cases) or those determined as "possible diagnosis of LGS" with a matching original LGS diagnosis. Incorrect cases were those that had an outcome different from the original diagnosis provided by the expert, such as an original diagnosis of LGS matching a checklist outcome of "unlikely diagnosis of LGS" or an original non-LGS diagnosis matching a checklist outcome of "likely diagnosis of LGS". "Possibly (other)" were those cases matching a checklist outcome of "possible diagnosis of LGS" with an original diagnosis of non-LGS.

3 | RESULTS

A total of 120 patient cases were included and assessed with the checklist. Of these, 64 were LGS cases and 56 non-LGS cases. Non-LGS diagnoses included: frontal lobe epilepsy, IESS, Dravet syndrome, epilepsy with myoclonic-atonic seizures (EMAtS), developmental and epileptic encephalopathy with spike-and-wave activation in sleep, epilepsy of infancy with migrating focal seizures, and early infantile developmental and epileptic encephalopathy. The outcome of the checklist was correct for 95% ($n = 114$) of cases: 66.7% ($n = 80$) had a perfect level of agreement with the initial diagnosis provided by the expert (LGS or non-LGS), and 28.3% ($n = 34$) were "possible diagnosis of LGS" with a matching original diagnosis of LGS (Figure 3). Of the 80 cases that had a perfect level of agreement, 27 were a likely diagnosis of LGS matching an original diagnosis of LGS, and the remaining 53 were an unlikely diagnosis of LGS matching a non-LGS diagnosis.

Only 2.5% of cases ($n = 3$) were classified as "possibly (other)". For these cases, key information on the EEG was unknown or had insufficient data, making a diagnosis of LGS still possible based on the amount and type of information available at diagnosis. In the remaining 2.5% of cases ($n = 3$), the outcome of the checklist was incorrect as it did not match the original LGS diagnosis provided by the expert (Tables 1 and 2).

Below we discuss some selected cases which were assessed using the checklist.

3.1 | Patient case #1: Perfect level of agreement on checklist (Likely diagnosis of LGS vs. original LGS diagnosis)

This case describes an ideal scenario, where a clinician is able to definitively identify all the key diagnostic criteria associated with LGS. The patient details are reported in Table 1. The patient was a 22-year-old male with seizure onset at 7 years. This case displays all the typical features of LGS, in line with the ILAE criteria, with the patient experiencing multiple seizure types, including tonic seizures, and the characteristic EEG features (Figure 4). In addition to the mandatory cognitive delay, the patient experienced mood disorder and migraine as comorbidities.

3.2 | Patient case #2: Possibly (other) on checklist (Possible diagnosis of LGS vs. original non-LGS diagnosis)

This case illustrates that there are overlapping features between LGS and other epilepsy syndromes. The patient was a 3-year-old male with seizure onset at 6 months (Table 1). The original diagnosis provided by the expert was EMAtS. The patient showed several of the typical LGS features, sometimes displaying frontal slowing with spike–wave complexes on EEG and moderate delayed development. Initially, the patient experienced myoclonic seizures. Later, he began to experience typical myoclonic-atonic seizures and sometimes longer tonic seizures during the day, followed by a fall. Most of the criteria for LGS were met, but there was no documented confirmation of the presence of generalized paroxysmal fast activity in sleep (Question 7), making the diagnosis of LGS still a possibility when using the checklist; however, the patient ultimately did not develop the full spectrum of characteristic LGS features.

3.3 | Patient case #3: Correct match on checklist (Possible diagnosis of LGS vs. original LGS diagnosis)

This case illustrates how LGS can evolve from other syndromes. The original diagnosis provided by the expert was

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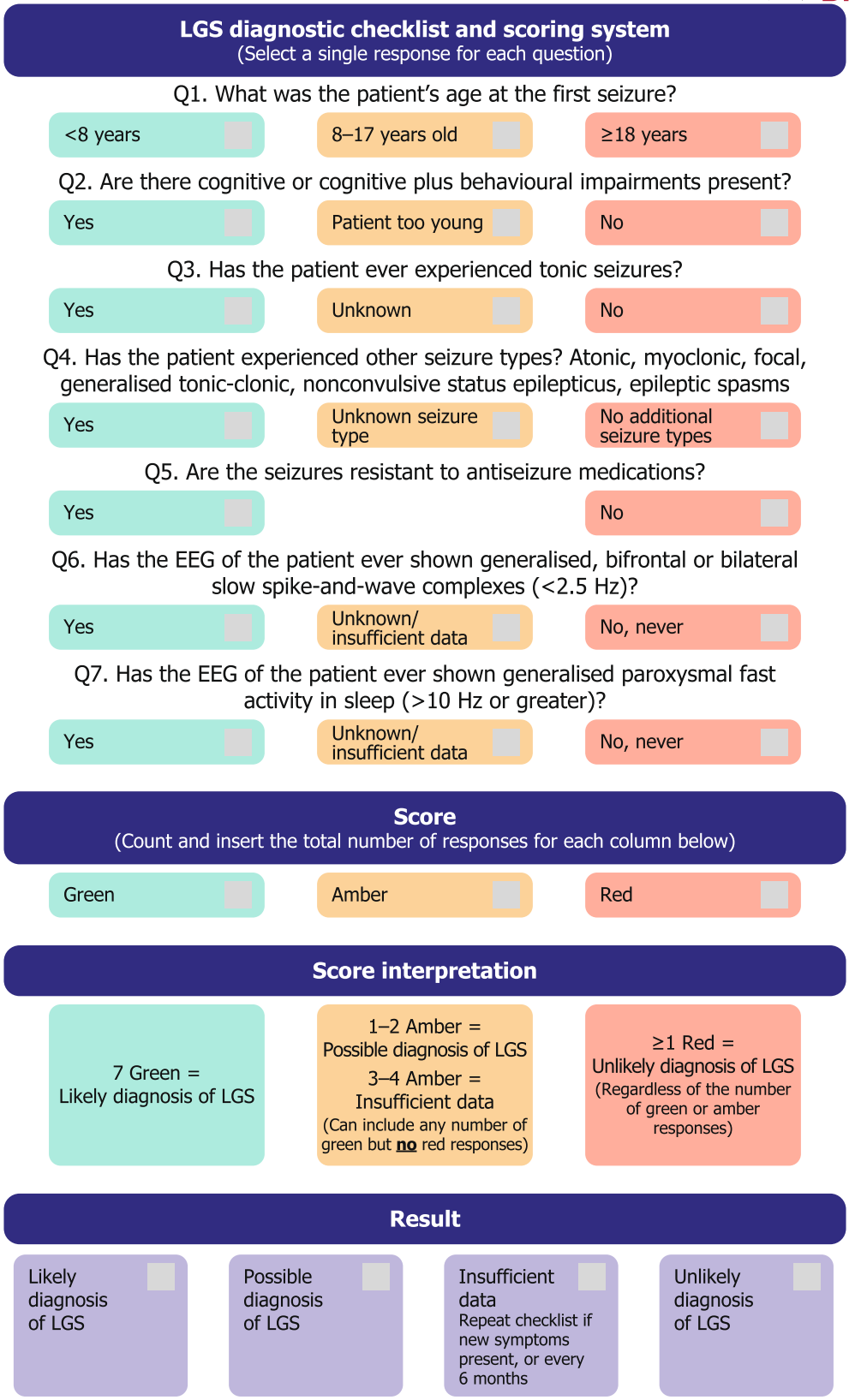

FIGURE 2 LGS diagnostic checklist and scoring system. Likely diagnosis of LGS: This patient meets the mandatory criteria for the diagnosis of LGS; Possible diagnosis of LGS: Particularly in cases where the only missing criteria is age of onset (8–17; Q1) or presence of cognitive/behavioral impairments (Q2) because the patient is too young. Re-evaluation is recommended if the patient is <8 years of age, or new information is made available; Insufficient data: Information is insufficient to draw a conclusion and/or more data are needed. Re-evaluation is recommended if the patient is <8 years of age, or new information is made available; Unlikely diagnosis of LGS: This patient does NOT present at least one mandatory characteristic criterion for the diagnosis of LGS. EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome; Q, question.

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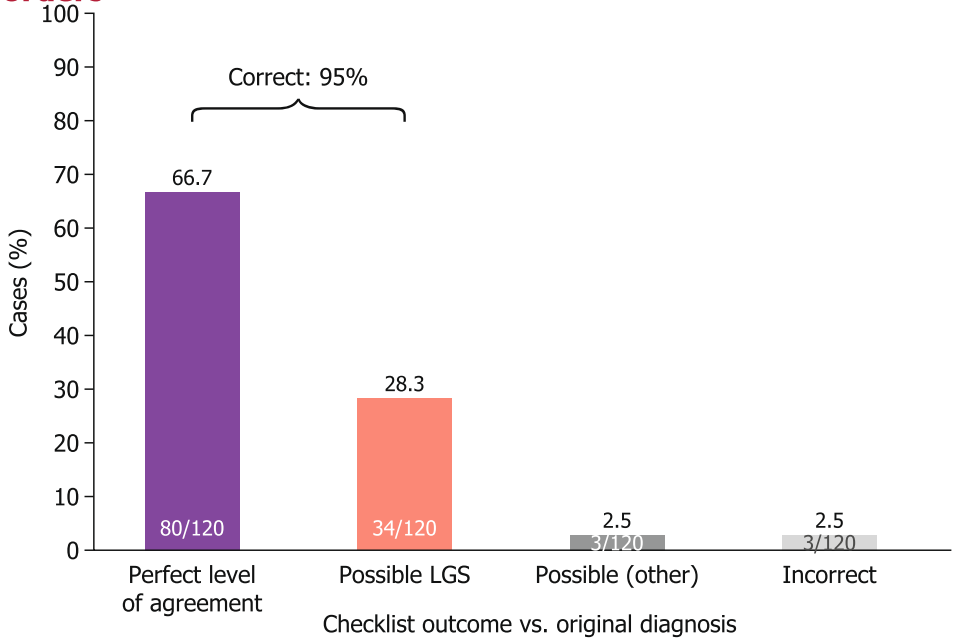

FIGURE 3 Evaluation of checklist outcome versus original diagnosis provided by the expert. Perfect level of agreement: Checklist outcome matched the original diagnosis by the expert (both LGS and non-LGS); Possible LGS: Checklist outcome of 'possible diagnosis of LGS' matched the original diagnosis of LGS; Possible (other): Checklist outcome of 'possible diagnosis of LGS' matched with an original diagnosis of non-LGS; Incorrect: Checklist outcome did not match the original diagnosis by the expert (i.e. expert diagnosed LGS and checklist outcome was 'unlikely diagnosis of LGS', or expert diagnosed another condition, and the checklist outcome was 'likely diagnosis of LGS'). LGS, Lennox–Gastaut syndrome.

focal epilepsy evolving to LGS due to structural etiology (Table 1). The patient, a 19-year-old male, started to experience seizures at 6 months of age and was diagnosed with focal epilepsy at 3 years of age. As EEG information was limited, and seizure semiology was not clear, with tonic seizures only being reported in adolescence, the LGS diagnosis was delayed until the patient was 18 years old, during the transition to adult care. Comprehensive re-evaluation eventually led to the diagnosis of LGS, once the triad of symptoms characterizing LGS became clear.

3.4 | Patient case #4: Perfect level of agreement on checklist (Likely diagnosis of LGS vs. original LGS diagnosis)

This patient presented with focal seizures at 10 months, initially occurring in clusters. A gain-of-function variant in the *SCN2A* gene was determined at an early age, and a targeted treatment approach was pursued accordingly. Unfortunately, seizures continued, with evolution to include atonic seizures and stiffening episodes from sleep and developmental delay from 4 years of age (Table 1). The diagnosis of LGS resulted from a full clinical evaluation showing all the manifestations of LGS, including typical EEG abnormalities, cognitive delay, and multiple and intractable seizure types.

3.5 | Patient cases #5, #6 and #7: Incorrect matches on checklist (Unlikely diagnosis of LGS vs. original probable or confirmed LGS diagnosis)

For these patients, not all the typical EEG abnormalities characterizing LGS were ever recorded, making the diagnosis of LGS unlikely using the checklist. Cases #5 and #7 never showed generalized, bifrontal or bilateral slow spike-and-wave complexes, while generalized paroxysmal fast activity in sleep was never reported for Case #6 (Tables 1 and 2). In addition, case #6 did not show cognitive impairment, but, as the patient was still very young, it may have been too early to detect any signals of this during diagnosis. As at least one of the key features of LGS was never recorded, a diagnosis of LGS was therefore unlikely using the checklist, even though the patients displayed all the other key features of LGS.

4 | DISCUSSION

The aim of this study was to develop a checklist to help physicians evaluate the possibility that a patient has LGS when such a diagnosis is suspected, and, critically, to initiate appropriate further validation steps that can facilitate an earlier and accurate diagnosis. The checklist may also support

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TABLE 1 Details of selected cases evaluated using the checklist.

	Gender	Age	Age at seizure onset	Etiology	Examination (imaging, EEGs, other testing)	Comorbidities	Seizure types, frequency and duration
Case #1	Male	22 years	7.8 years	Idiopathic	**EEG**: • Abnormal brain activity with poor spatial organization and differentiation • Frequent epileptiform abnormalities, characterized by SSW complexes, isolated or in generalized sequences at 2–2.5 Hz, predominantly involving the bilateral frontal or occipital regions, lasting up to 10 s; on one occasion associated with motor arrest and possible alteration of awareness (not tested) • During sleep, epileptiform abnormalities organize into diffuse paroxysmal discharges, without apparent clinical correlate, alternating with phases of voltage attenuation lasting 2–3 s **Brain MRI**: Negative **NGS epilepsy panel**: Negative	• Mild–moderate intellectual disability[a] • Mixed anxiety-depressive disorder • Migraine	**Seizure types**: • Atypical absence seizures, tonic seizures; previous atonic seizures **Seizure frequency**: • Atypical absence seizures: 3–4 per day • Tonic seizures: 1–2 per week
Case #2	Male	9 years	6 years 6 months	Unknown (EMAtS)	**EEG:** • Background normal • Sometimes frontal slowing with spike–wave complexes **MRI:** Normal **Trio WES:** Negative	• Developmental delay: needs considerable support in normal primary school[a]	**Seizure types:** • Initially: myoclonic seizures • Later: typical myoclonic-atonic seizures • Sometimes longer tonic seizures (daytime) followed by a fall
Case #3	Male	19 years	6 months	Focal epilepsy (3 years) evolving to LGS (18 years)	**EEG:** • SSW and GPFA **MRI:** Structural abnormalities reported at 10 years	• Hypoplastic left heart syndrome with hypoplastic pulmonary arteries, multiple surgeries since birth • Hypothyroidism • Combined immunoglobulin deficiency • Microcytic iron deficiency anemia • Cognitive impairment[a]	**Seizure types:** • Tonic: in adolescence, 10–20 s (reported on presentation) • Dyscognitive (FIAS): 10–30 min (reported via video and EEG) • Generalized tonic–clonic: 1–2 min (reported via video and EEG) **Seizure frequency:** • Dyscognitive (FIAS): 2–3 per month • Generalized tonic–clonic: 1–2 per year

(Continues)

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TABLE 1 (Continued)

	Gender	Age	Age at seizure onset	Etiology	Examination (imaging, EEGs, other testing)	Comorbidities	Seizure types, frequency and duration
Case #4	Male	11 years	10 months	Genetic: *SCN2A* mutation [c2850>A;p(Cys950Ter)]	**MRI:** Normal **EEG** • Bifrontal SSW • Fast rhythms in sleep **Genetics test:** *SCN2A* mutation	Slowed neurodevelopment from 4 years of age[a] Currently: • Significant intellectual disability • Social communication difficulties • Non-verbal	• Focal seizures – up to 8-9/day • Tonic seizures in sleep and causing drop by day • Myoclonic jerks • Currently, clusters requiring emergency rescue every 2 weeks
Case #5[b]	Male	15 years 3 months	4 years	Unknown	**EEG:** • Paroxysmal fast, with or without tonic seizure **MRI:** Normal	• Poor coordination • Moderate learning difficulty[a]	• GTCS from sleep • Tonic seizures 3–30 s as goes to sleep • Atypical absence, 15–20 s 3-4/day
Case #6[b]	Male	3 years	6 months	Structural (pachygyria frontal bilateral)	**EEG:** • Multifocal spikes, sometimes frontal SSW **MRI:** Frontal pachygyria	• Delayed development (no quantitative assessments)[a] • Language delay Normal in kindergarten	**Seizure types**: • Initially: epileptic spasms • Later: short myoclonic/tonic seizures, rare convulsive seizures
Case #7[b]	Male	14 years 6 months	3 years	Unknown	**EEG** • Paroxysmal fast in slow sleep • Generalized slow; no slow spike and wave **Genetic:** *SCN1B* variant – pathogenic **MRI:** Normal	• Moderate learning difficulty[a] • Challenging behavior	• Tonic seizures, from sleep, night 2–12 × 3/week • Atonic seizures (drops) 2-40/day • GTCS • Atypical absence seizures 3-15/day

Abbreviations: EEG, electroencephalogram; EMAtS, epilepsy with myoclonic-atonic seizures; FIAS, focal impaired awareness seizure; GPFA, generalized paroxysmal fast activity; GTCS, generalized tonic–clonic seizure; LGS, Lennox–Gastaut syndrome; MRI, magnetic resonance imaging; NGS, next-generation sequencing; s, seconds; *SCN2A*, *sodium channel protein type 2 subunit alpha*; SSW, slow spike-and-wave; WES, whole exome sequencing.

[a]Comorbidities that are also mandatory criteria which must be present for a diagnosis of LGS.

[b]This was an incorrect case.

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TABLE 2 Clinical cases where the checklist outcome did not match the original diagnosis.

	What was the patient's age at the first seizure?	Are there cognitive or cognitive plus behavioral impairments present?	Has the patient ever experienced tonic seizures?	Has the patient experienced other seizure types?	Are the seizures resistant to antiseizure medications?	Has the EEG of the patient ever shown generalized, bifrontal or bilateral slow spike-and-wave complexes (< 2.5 Hz)?	Has the EEG of the patient ever shown generalized paroxysmal fast activity in sleep (> 10 Hz or greater)?	Checklist outcome	What was the patient's diagnosis?	Does diagnosis match checklist outcome?
Case #5	<8 years old	Yes	Yes	Yes	Yes	No, Never	Yes	Unlikely diagnosis of LGS	Probable LGS	No
Case #6	<8 years old	Patient too young	Yes	Yes	Yes	Yes	No, Never	Unlikely diagnosis of LGS	LGS	No
Case #7	<8 years old	Yes	Yes	Yes	Yes	No, Never	Yes	Unlikely diagnosis of LGS	LGS	No

Abbreviations: EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome.

the re-evaluation of patients in whom an LGS diagnosis was previously ruled out but who continue to experience uncontrolled seizures. Considering that LGS is a complex syndrome, that only a limited number of questions based on the key ILAE criteria were included in the checklist, and that the cases evaluated are likely to represent complex cases being provided by experts from tertiary referral centers, an overall reliability of 95% is promising and indicates the potential for wider use in clinical practice.

There are currently limited readily available and accessible resources to help clinicians with the diagnosis of LGS. The Refractory Epilepsy Screening Tool for LGS (REST-LGS) was designed to aid the identification and differentiation of adult patients with LGS from other refractory epilepsies, accounting for the challenges of prolonged EEG and limited historical records in adult patients with epilepsy and intellectual disability.[24] Despite its ease of use and consequent role in clinical settings, the tool is limited to the adult population, and does not require updating EEG findings and does not specify tonic seizures or sleep EEG as diagnostic criteria, which are considered mandatory in the recent ILAE syndrome description.[24,25]

The patient cases discussed illustrate the complexities of accurately diagnosing LGS and provide some key learnings. In all three incorrect cases, the reason for the mismatch was related to the lack of information on EEG, highlighting the importance of EEG features for an accurate LGS diagnosis. A very young patient may not present with the mandatory EEG characteristics at the time of seizure onset, thus re-evaluation of the patient is critical if aged <8 years or if new data become available, as the key clinical features might not be present at onset, but may manifest over time. Sleep EEG is also crucial, and should be performed whenever possible. Missing EEG information increases the risk of misdiagnosis, particularly in settings where there may be limited resources or specialists able to conduct an EEG.[18] However, in some patients and/or clinical settings, performing EEG and obtaining sufficient data is not feasible, thereby limiting both the applicability and the full scope of the checklist (as this would result in an amber point) and the accurate diagnosis of LGS.

The correct identification of seizure types is also key for diagnosis, but this can be challenging because seizure types can be nonspecific in the early stages and may change and evolve later in life.[4,11,26] Tonic seizures are mandatory for diagnosis and occur most often during sleep.[6] They can be subtle and may therefore be under-reported by parents or caregivers, only detected by sleep EEG recording.

In most cases of LGS, seizure onset may cause or coincide with developmental decline or plateauing, culminating in mild to profound intellectual disability over the course of the disease.[6] While this is a mandatory diagnostic criterion, it may impact the diagnostic process

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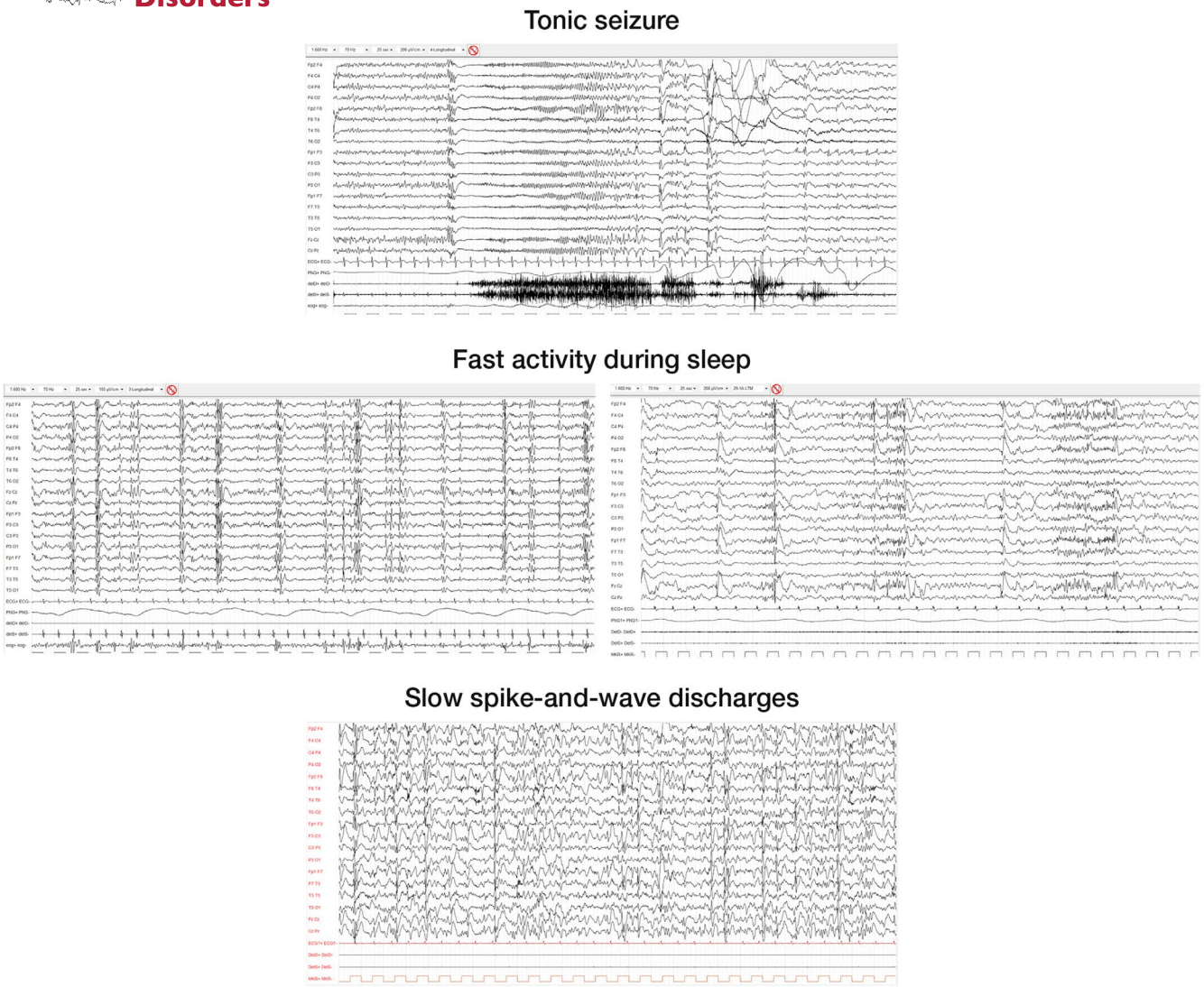

FIGURE 4 Electroencephalographic features during sleep in LGS. Representative EEG recordings obtained during NREM sleep in a patient with LGS demonstrate typical electroclinical patterns of the disorder. A tonic seizure is shown, characterized by the abrupt onset of diffuse, low-voltage fast activity (10–20 Hz), predominantly frontal, associated clinically with axial tonic stiffening. Interictal abnormalities include bursts of paroxysmal fast activity during sleep, consisting of generalized or frontally predominant rhythmic fast activity, a hallmark feature of LGS. In addition, generalized slow spike-and-wave discharges (< 2.5 Hz) are present, consisting of high-amplitude slow spike–wave complexes, representing the characteristic interictal pattern of the syndrome. These findings illustrate the electrographic signature of LGS, with the co-existence of tonic seizures, paroxysmal fast activity during sleep, and generalized slow spike-and-wave discharges, particularly activated during NREM sleep. EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome; NREM, non–rapid eye movement.

in situations where this feature has not yet developed or where quantitative assessments have not been performed, or in patients who have shown previous intellectual disability. This demonstrates the importance of re-evaluation when characteristic EEG features, seizure types, or cognitive and behavioral issues are not initially present, and to ensure that all available patient information is collected and analyzed, as some features may have been documented in the past but may have since faded.

Another diagnostic challenge for physicians is the overlapping features between LGS and other syndromes, which may result from LGS evolving from these conditions,[18] thereby increasing the risk of misdiagnosis. This was illustrated in one case where the original diagnosis was EMAtS (formerly named Doose syndrome) and the outcome using the checklist was a "possible diagnosis of LGS" due to missing EEG data. EEG data for differentiating LGS and re-evaluation of those patients who meet some of the requirements for LGS are crucial, in order to check for evolution to LGS.[4,9] Multiple rounds of re-evaluation should be undertaken, generally at intervals of every 4–6 months, with the exact timing determined by the age of the patient and the frequency of seizures, as evolution to LGS may take up to 2 years.[27]

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Nevertheless, differential diagnosis is essential to ensure correct and timely management, improve the prognosis, and to provide a clear definition of the syndrome to patients and families. Of note, the transition from IESS to LGS has a consistent "electroclinical overlap period," where features of both syndromes can be present simultaneously.

Regular re-evaluation and reassessment of clinical diagnoses is particularly important in adult and adolescent patients with treatment-resistant seizures and cognitive impairment. Adult patients with LGS may be misdiagnosed if some of the LGS characteristic features are missing or if prior medical history is incomplete.[28] Additionally, seizure types may also evolve over time during maturation and in response to treatment.[26] All aspects of a patient's encephalopathy should be assessed during re-evaluation, as illustrated in one of the cases discussed, where the comprehensive re-evaluation performed during the transition to adult care allowed for the triad of symptoms to be eventually identified, facilitating an LGS diagnosis. Transition from pediatric to adult care provides an important opportunity to assess all aspects of patient care.

It is also important to remember that LGS is an electroclinical syndrome with a variety of etiologies. Despite the usefulness of genetic and other testing (e.g., metabolic, MRI), the diagnosis should not be based on this evidence, but rather on the electroclinical features as highlighted by the ILAE. However, identification of the etiology is important with the possibility of personalized treatments.[29,30]

This study has several limitations. Firstly, the high level of agreement observed (95%) should be interpreted with caution. The checklist was developed and evaluated by the same group of experts, and both the checklist and reference diagnoses were based on the same ILAE framework, which likely increased concordance. In addition, the retrospective selection of cases from expert centers may have introduced selection and spectrum bias, potentially inflating agreement. Selection and spectrum bias may arise because cases seen in specialist centers might not always be representative of the broader clinical population, but they are often referred due to diagnostic uncertainty, severity, or atypical features, leading to an overrepresentation of complex cases. Future prospective validation steps in real-world clinical practice will better assess its usability and variability. Therefore, these findings are best interpreted as concordance with expert diagnosis rather than formal validation or inter-rater reliability, and external validation in independent and non-expert settings is warranted. Although the checklist did not undergo a formal validation process as a medical tool, over 100 cases were evaluated, comprising both LGS and non-LGS cases collected across multiple centers across Europe, which represent a considerable number given that these cases are rare epilepsies. Secondly, the checklist is limited to the key ILAE diagnostic criteria and represents a single snapshot at a specific point in a patient's clinical course; therefore, it should be repeated over time to capture clinical changes and disease evolution. A key consideration is the age-dependent and evolving nature of LGS, as the full electroclinical phenotype may not be present at onset, particularly in young children. The checklist is therefore intended as a longitudinal support tool, rather than a static or age-specific diagnostic instrument. The category "possible diagnosis of LGS" is especially relevant in early stages, prompting structured follow-up and repeated evaluation. Accordingly, the checklist should be applied iteratively over time to capture the emergence of defining features and support timely diagnosis. Lastly, the checklist was tested based on the assumption that the original diagnosis of the expert was correct, and the cases used to test the checklist were those selected by the experts who developed it, and were not subject to external scrutiny.

The checklist has been developed as a supportive aid to assist physicians in organizing clinical information and guiding diagnostic decision-making and to facilitate longitudinal monitoring of patients showing some of the characteristic features of LGS, but in whom the syndrome is still evolving. Importantly, the checklist does not replace a full clinical evaluation: clinicians are advised to conduct a full evaluation of their patients when LGS is suspected and seek expert advice when needed to ensure an accurate and timely diagnosis. The checklist can support the initial suspicion of an LGS diagnosis by identification of clinical features that are suggestive of the syndrome, but that may be incomplete, evolving, or not yet specific (e.g., seizure types). Establishing a diagnosis of LGS requires the certain identification of the characteristic clinical and electroclinical features as per the LGS definition.

Future steps include prospective validation of the checklist in real-world settings, alongside evaluation of its performance, usability, and reliability when utilized by non-experts.

5 | CONCLUSIONS

The diagnosis of LGS can be challenging due to its heterogeneity of clinical presentation and evolution of characteristic features over time. However, an early and accurate diagnosis is crucial to allow for timely intervention and ultimately improve outcomes for both patients and families. There is an unmet need for additional guidance and tools to aid LGS diagnosis in clinical practice. This checklist provides clinicians with a simple-to-use resource, based

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on the ILAE criteria, when an LGS diagnosis is suspected and can help facilitate earlier referral to a specialist and accelerate the diagnostic pathway. The study also highlights the need to re-evaluate patients during follow-up, using tools such as the checklist, given the evolving and complex nature of LGS.

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CONFLICT OF INTEREST STATEMENT

Nicola Specchio: Scientific advisory boards: GW Pharmaceuticals (now Jazz Pharmaceuticals), BioMarin, Arvelle, Marinus, Takeda; speaker's honoraria: Eisai, BioMarin, Livanova, Sanofi; Investigator: Zogenix (now a part of UCB), Marinus, BioMarin, UCB, Roche. Alexis Arzimanoglou: Co-director of the European Consortium for Epilepsy Trials (ECET). Scientific advisory boards: Jazz Pharmaceuticals, Arvelle, Neuraxpharma, Stoke, Takeda, UCB; speaker's honoraria: Biocodex, Eisai, Jazz Pharmaceuticals, UCB. Stéphane Auvin: Deputy Editor, Epilepsia; personal fees, lectures/advice: Acadia, Angelini, Biocodex, Eisai, Encoded Therapeutics, Grintherapeutics, Jazz Pharmaceuticals, Longboard, Lunbeck, Mosaica, Neuraxpharm, Nutricia, Orion, Proveca, Servier, Stoke, Stream Neuroscience UCB, Xenon; Investigator: Eisai, Marinus, Proveca, Servier, Takeda, UCB. Antonio Gil-Nagel: Speakers bureau, advisory boards, or committees: Angelini Pharma, Bial, Biocodex, Eisai, Esteve, GW Pharmaceuticals (now Jazz Pharmaceuticals), Oils4Cure, Pharvaris, PTC Therapeutics, Rapport Therapeutics, Stoke, UCB, and Zogenix (now a part of UCB); research support: Biogen, Jazz Pharmaceuticals, PTC Therapeutics, and UCB. Lieven Lagae: Received grants and consultant and/or speaker: Eisai, Epihunter, LivaNova, NEL, Novartis, Shire, Takeda/Ovid, UCB, Zogenix (now a part of UCB). Rima Nabbout: Research funding: Eisai, GW Pharmaceuticals (now Jazz Pharmaceuticals), Novartis, Shire, UCB, Zogenix (now a part of UCB); consultant/advisor: Eisai, Biogen, GW Pharmaceuticals (now Jazz Pharmaceuticals), Novartis, Shire, Zogenix (now a part of UCB); speaker: Advicenne, Eisai, BioMarin, GW Pharmaceuticals (now Jazz Pharmaceuticals), Novartis, Zogenix (now a part of UCB).

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DATA AVAILABILITY STATEMENT

Data from non-interventional studies are outside of UCB's data sharing policy and are unavailable for sharing.

CONSENT

Informed consent for the use of anonymized clinical data for research and publication purposes was obtained from patients and/or patients' legal guardians.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. The typical age of onset for LGS is?
   A. Neonatal period (0–1 month).
   B. 3–5 years of age.
   C. 9–15 years of age.
   D. Adulthood.
2. Which seizure type is most characteristic of LGS?
   A. Focal impaired-awareness seizures.
   B. Atypical absence seizures.
   C. Myoclonic seizures.
   D. Tonic seizures, particularly during sleep.
3. Which of the following represents the classic triad of key features suggestive of Lennox–Gastaut syndrome (LGS)?
   A. Focal seizures, normal EEG, and normal cognition.
   B. Multiple seizure types, slow spike-and-wave EEG pattern, and cognitive impairment.
   C. Absence seizures only, photoparoxysmal response, and normal development.
   D. Infantile spasms, hypsarrhythmia, and developmental regression.

Answers may be found in the Supporting Information.

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