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The refractory epilepsy screening tool for Lennox–Gastaut syndrome (REST-LGS)☆

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ABSTRACT

Background: The complex clinical presentation and progression of Lennox–Gastaut syndrome (LGS) can complicate the accurate diagnosis of this severe, lifelong, childhood-onset epilepsy, often resulting in suboptimal treatment. The Refractory Epilepsy Screening Tool for LGS (REST-LGS) was developed to improve the identification of patients with LGS.
Methods: Using the Modified Delphi Consensus, a group of experts developed and tested the REST-LGS Case Report Form (CRF) comprising 8 criteria (4 major, 4 minor) considered potentially indicative of LGS. Diagnosis-blinded specialist and nonspecialist raters at 2 epilepsy centers applied the CRF to deidentified patient records, including 1:1 records of patients with drug-resistant epilepsy or confirmed LGS. Interrater reliability was measured by Cohen's κ. Diagnosis was then unblinded to reveal common criteria for LGS or drug-resistant epilepsy. Cronbach's α was used to measure internal consistency between raters for all criteria combined.
Results: Of 200 patients, 81% to 85% met 1 to 3 major criteria. At both sites, moderate (κ, 0.41–0.60) to good (κ, 0.61–0.80) agreement on most criteria was reached between expert and nonexpert raters. Unblinding revealed that most patients with LGS met 3 major and 2 to 3 minor criteria, while patients with drug-resistant epilepsy met ≤1 major and only 1 to 2 minor criteria. Cronbach's α of raters at both sites was 0.64.
Conclusions: The combined number of major/minor criteria on the CRF may be particularly indicative of LGS. Therefore, the REST-LGS may be a valuable clinical tool in identifying patients requiring further diagnostic evaluation for LGS.

1. Introduction

Lennox–Gastaut syndrome (LGS) is a severe childhood-onset epileptic encephalopathy typically characterized by multiple intractable seizure types, cognitive impairment, and an abnormal electroencephalogram (EEG) with generalized slow spike-and-wave (SSW) discharges (1.5–2.5 Hz) [1–7]. Accounting for ≤10% of childhood epilepsies [6], LGS most often develops secondary to an underlying brain pathology (e.g., injury, infection, tumor, congenital abnormality); however, approximately 25% of cases have no clear etiology [6,8,9]. Though onset typically occurs by 12 years of age, with peak onset occurring between 3 and 5 years [9], the syndrome emerges over many years and persists into adulthood, at which time, 1 or more of the classic symptoms may no longer be evident [7,10,11]. Such varied clinical presentation and progression makes LGS one of the most challenging epileptic disorders to identify [12,13], and misdiagnosis can result in suboptimal treatment selections that could paradoxically worsen seizures and increase the likelihood of medication-related adverse events [5,14,15]. Early diagnosis of LGS can also aid patients and caregivers in setting appropriate expectations regarding prognosis and long-term management as well as provide access to LGS-specific services [9,16].

Diagnosing LGS in adolescents and adults is particularly problematic as details of medical history may be lost during transfer from pediatric

Abbreviations: AED, antiepileptic drug; CRF, case report form; DRE, drug-resistant epilepsy; EEG, electroencephalogram; HIPAA, Health Insurance Portability and Accountability Act; IRR, interrater reliability; LGS, Lennox–Gastaut Syndrome; REST-LGS, Refractory Epilepsy Screening Tool for Lennox–Gastaut syndrome; SPSS, Statistical Package for the Social Sciences; SSW, slow spike-and-wave discharge; VNS, vagus nerve stimulation.

☆ Statistical Analysis conducted by Danielle Boyce, Neurology Parent Professionals.

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to adult care, patients may no longer tolerate an EEG, or comorbid conditions may develop [5,7]. Thus, LGS may only be suspected in adolescent and adult patients with complete medical histories, including a previously confirmed diagnosis. Often, if the patient is not identified as having LGS in childhood, the healthcare practitioner seeing the patient as an adult may not consider an LGS diagnosis for patients with refractory epilepsy. Conversely, with the increased education regarding the diagnosis of LGS, there is a greater likelihood of overdiagnosis, resulting in misdiagnosis of patients without the past history of distinct EEG abnormality. With these challenges in mind, a group of experts who care for patients with refractory epilepsy and intellectual and developmental disabilities created the Refractory Epilepsy Screening Tool for LGS (REST-LGS) to improve both the identification and treatment of patients with LGS. In addition to the major symptoms associated with LGS, the REST-LGS was designed to take into account identification of further "minor" features suggestive of LGS, which may help to diagnose LGS in clinical settings. The REST-LGS may, therefore, be a guide for clinicians to help assure that the correct questions are asked to increase the detection of LGS. The methodology and the initial steps to validate the tool for use in a clinical setting are described here.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

Approval from ethical standards committees to conduct this study was received at Mount Sinai Health System and University of Pennsylvania. All data from this chart review were deidentified, and none of the 18 Health Insurance Portability and Accountability Act (HIPAA) [17] identifiers were revealed.

2.2. Modified Delphi technique

The REST-LGS was conceptualized and designed using the Modified Delphi Consensus [18], by which the available scientific evidence and collective judgment of a group of experts were combined to yield the screening tool in its current form (Fig. 1). To be selected as a panelist, clinicians were required to be long-tenure experts in the field of epilepsy (including epileptologists, advanced practice nurses trained in epilepsy, neurology residents, and scientists) and affiliated with clinical centers with high volume management of epilepsy in general and including LGS specifically. The steps taken in the development of the REST-LGS are as follows: 1) formation of a monitoring team, 2) selection of panel(s) and panelists, 3) development of the first-round Delphi questionnaire, 4) testing the questionnaire for proper wording, 5) transmission of the first questionnaires to the panelists, 6) analysis of the first-round responses, 7) preparation of the second-round questionnaires (and possible testing), 8) transmission of the second-round questionnaires to the panelists, 9) analysis of the second-round responses (steps 7–9 were reiterated as long as desired or necessary to achieve stability in the results), and 10) preparation of a report by the analysis team to present the conclusions of the exercise.

2.3. Questionnaire development

Questionnaire development proceeded in 2 rounds. First, aiming to develop a reliable, reproducible, clinically applicable, and flexible instrument, the panel discussed whether the instrument should be a diagnostic tool with a numeric scoring system or a screening tool. Following majority agreement to pursue the development of a screening tool, the following clinical criteria were identified: cognitive impairment; multiple seizure types; seizure onset at <12 years of age; history of ketogenic diet; history of multiple seizure types; frequent seizures; inpatient and outpatient encounter frequency; history of helmet use, corpus callosotomy, vagus nerve stimulation (VNS), or focal cortical resection; and identifiable etiology consistent with LGS diagnosis (brain damage, tuberous sclerosis, Dravet syndrome, acquired destructive lesions, metabolic diseases, or other). Second, panelists rated the importance (low, medium, or high) of each item on the questionnaire. Panelists used their clinical experience to rate the importance of an item based on the likelihood of the presence of that item in a patient's chart being associated specifically with LGS. A panel rating was afforded to an item if agreement was reached by all but 1 panelist, i.e., if 1 panelist rated an item as "medium" and all remaining panelists rated the item as "high," the item was afforded "high" importance.

Please fill out demographic information and determine whether the patient meets the following criteria:

Patient ID #		Gender : ☐ Male ☐ Female		
Patient's age at last visit:		Date of chart review:		*Please Check YES if True*
1. Persistent seizures despite trial of 2 or more antiseizure medications				☐ *YES* ☐ *NO* ☐ *Unavailable*
2. Two or more seizure types				☐ *YES* ☐ *NO* ☐ *Unavailable*
3. Seizure onset before age of 12 years				☐ *YES* ☐ *NO* ☐ *Unavailable*
4. Evidence of seizure-related helmet use, or head or face injuries				☐ *YES* ☐ *NO* ☐ *Unavailable*
5. Cognitive impairment since childhood (may include past or current learning difficulties, history of special education, autism, intellectual disabilities or developmental delays)				☐ *YES* ☐ *NO* ☐ *Unavailable*
6. History of vagal nerve stimulator (VNS), ketogenic diet, or epilepsy surgery				☐ *YES* ☐ *NO* ☐ *Unavailable*
7. History of EEG with generalized slow spike-and-wave (SSW) discharges (<2.5Hz)				☐ *YES* ☐ *NO* ☐ *Unavailable*
8. One of the following EEG abnormalities: multifocal spikes, symptomatic generalized discharges, generalized polyspikes, generalized periods of attenuation of background/electrodecrement, or paroxysmal fast activity				☐ *YES* ☐ *NO* ☐ *Unavailable*
Rater feedback, comments, and/or questions:				

Fig. 1. Refractory epilepsy screening tool CRF. CRF, case report form.

2.4. Case report form

The iterative process described above culminated in the development of the REST-LGS Case Report Form (CRF; Fig. 1) to be administered at 2 large, diverse epilepsy centers (Site 1, Mount Sinai Health System; Site 2, University of Pennsylvania) for the identification of clinically important criteria related to LGS that potentially require clarification. The 8 criteria listed on the CRF were considered by the group to be potentially indicative of LGS beyond the current diagnostic standards [4,19,20] and were decided upon based on the clinical experience of the working group. These criteria were divided into 2 groups: major and minor (4 each), though the designation of each criterion as major or minor is not indicated on the CRF during chart review; this designation was only used in the analysis after data collection was complete.

2.5. Study conduct

2.5.1. Manual of operations

Spreadsheet templates and CRFs were provided in a manual of operations and distributed to participating members of the working group in advance of study implementation. All key terms used in the screener were operationalized, and instructions for data collection, data entry, and submission were outlined.

2.5.2. Patients, blinding, and rater qualifications

Patient records were chosen by a certified registered nurse practitioner epilepsy expert at each site. Records from patients aged >12 years with refractory epilepsy (defined as epilepsy that has failed to respond to ≥2 appropriate antiepileptic drugs [AEDs] with adequate dosing) who had ≥2 clinic notes within the previous 2 years were used in this study. Patient records were assigned a unique study identification number, and no individual HIPAA identifiers were revealed [17]. Full patient records were not made available for assessment by raters because it was determined that only recent records are commonly available in typical clinic appointments and group home settings. Two diagnosis-blinded raters at each center completed a CRF for each deidentified patient record; rater 1 was a specialist (i.e., epileptologist/epilepsy nurse practitioner), and rater 2 was a non-specialist (i.e., registered nurse, social worker, neurology resident, or medical student). Raters were blinded to each other's responses.

2.5.3. Sampling method

A sample size of 100 patients per site (50 patients with LGS and 50 patients with drug-resistant epilepsy [DRE]) was selected based on previously described methodology [21]. The group with LGS included patients who had slow SSW discharges on an EEG, multiple seizure types, and intellectual disability. The group with DRE included all patients who met the International League Against Epilepsy definition of DRE: failure of adequate trials of 2 tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [22]. If data were missing from a medical record, abstractors were asked to take notes explaining the extent and nature of missing data. During data preparation, missing data were assessed to determine if it was a result of the screener item, electronic medical error, abstractor training, or other. If raters described conflicting data, the method to resolve differences was to accept the first recorded observation.

2.5.4. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 22 (IBM SPSS Statistics). Variables were described with absolute and relative frequencies, mean and standard deviation, or median and interquartile range, where appropriate. Pearson's chi-square test for linear trend or Fisher exact test was used to assess possible associations; the level of significance was set at $P \leq 0.05$. The extent of interrater reliability (IRR) on each criterion of the CRF was analyzed via Cohen's kappa (κ) statistic [23], which ranges from 0 to 1.0, with larger numbers corresponding to better reliability. A value above 0.70 is conventionally considered to be adequate, and values near or <0 suggest that agreement is attributable to chance alone [24,25]. If, during chart review, a patient met all 4 major criteria, they were assigned a designation of "Definite LGS." The IRR, combined with expert consensus achieved by the LGS Screening Tool Working Group, allowed for assessment of the feasibility of the screener, determination of the adequacy of the instrument, and identification of any methodological pitfalls.

2.6. Unblinding

After initial validation, data collected from CRFs were unblinded to reveal the true LGS or non-LGS (e.g., DRE) diagnosis for each patient. Cronbach's alpha (α) statistic was applied to measure the degree of internal consistency across sites for all 8 criteria combined or among criteria-grouped functionally [26]. The upper limit for the Cronbach's α measure is 1.0, with higher α values indicating greater internal consistency [27].

3. Results

3.1. Reliability

Eight criteria were abstracted during chart review (Table 1). Of 200 patient records evaluated (100 at each site), most patients (81% and 85% at Sites 1 and 2, respectively) met 1 to 3 major criteria. Gender distribution at each site was comparable, but patients from Site 1 were significantly younger than those from Site 2 (mean age at last visit ± SD: 24 ± 12 vs. 41 ± 12 years; $P < 0.0001$). At Site 1, moderate agreement ($\kappa = 0.41–0.60$) was reached between the 2 raters' judgments on whether patient records reflected persistent seizures despite trial of ≥2 AEDs; at Site 2, both raters agreed that all patients had persistent seizures (Table 1). Moderate agreement ($\kappa = 0.41–0.60$) to good agreement ($\kappa = 0.61–0.80$) was reached between raters at both sites for the following variables: ≥2 seizure types, seizure onset <12 years, history of EEG with generalized SSW discharges <2.5 Hz, and other EEG abnormalities. At both sites, good to very good agreement ($\kappa = 0.81–1.00$) was reached on the variables of cognitive impairment since childhood and history of VNS, ketogenic diet, or epilepsy surgery. Poor agreement ($\kappa < 0.20$) at Site 1 and fair agreement ($\kappa = 0.21–0.40$) at Site 2 were found on evidence of seizure-related helmet use or head or face injuries. At Site 1, raters reached very good agreement on the classification of "Definite LGS" (i.e., 4 major

Table 1
Demographics and interrater reliability at separate epilepsy centers.

	Site 1 (N = 100)[a]	Site 2 (N = 100)[a]
Patient characteristics		
Female, n (%)	46 (46)	50 (50)
Age at last visit, mean (SD), y	24 (12)[b]	41 (12)[b]
Major diagnostic criteria, κ (95% CI)[c,d]		
≥2 seizure types	0.430 (0.299 to 0.561)	0.698 (0.433 to 0.963)
Seizure onset <12 years	0.654 (0.523 to 0.785)	0.759 (0.647 to 0.871)
History of EEG with generalized SSW discharges <2.5 Hz	0.602 (0.428 to 0.776)	0.602 (0.687 to 0.915)
Cognitive impairment since childhood	0.884 (0.776 to 0.992)	0.814 (0.710 to 0.918)
Minor diagnostic criteria, κ (95% CI)[c,d]		
Persistent seizures despite trial of ≥2 AEDs	0.595 (0.425 to 0.762)	N/A[e]
History of VNS, ketogenic diet, or epilepsy surgery	0.909 (0.823 to 0.995)	0.801 (0.687 to 0.915)
Evidence of seizure-related helmet use/head or face injuries	0.138 (−0.062 to 0.338)	0.367 (0.228 to 0.506)
History of other EEG abnormalities	0.705 (0.584 to 0.827)	0.624 (0.457 to 0.747)
Definite LGS, κ (95% CI)[c]		
4 major criteria met	0.823 (0.584 to 1.062)	0.764 (0.487 to 0.761)

AED, antiepileptic drug; CRF, case report form; EEG, electroencephalogram; κ, Cohen's statistic; LGS, Lennox–Gastaut Syndrome; N/A, not applicable; SSW, slow spike-and-wave discharge; VNS, vagus nerve stimulation.

[a] 50 patients with drug-resistant localization-related epilepsy, 50 patients with LGS.

[b] $P < 0.0001$ (Site 1 vs. Site 2).

[c] $P < 0.0005$ (between-rater difference at individual site).

[d] Raters were blinded to which criteria were "major" vs. "minor," as those designations were not included on the CRF.

[e] Both raters fully agreed that all patients had persistent seizures; the field is a constant.

criteria met), while raters at Site 2 reached moderate agreement on this criterion.

3.2. Validation

Unblinding of patient diagnoses revealed that a greater percentage of patients with LGS at each site met the major criteria versus patients with DRE, though the overall percentage of patients with a history of EEG with SSW (<2.5 Hz) was low compared with the other 3 major criteria (Fig. 2a). Most patients with LGS and patients with DRE were identified as having persistent seizures despite trial of ≥2 AEDs (Fig. 2b). Of the patients with LGS at Site 1 who met 3 major criteria, 73.7% (as scored by rater 1) and 77% (as scored by rater 2) also met ≥2 minor criteria. Of the patients with LGS at Site 2 who met 3 major criteria, 90% (as scored by rater 1) and 81.8% (as scored by rater 2) also met ≥2 minor criteria. Overall, a majority of patients with LGS met 3 major criteria and 2 to 3 minor criteria (Fig. 3a), while most patients with DRE met only 1 major and 1 to 2 minor criteria (Fig. 3b).

Because a history of EEG with SSW discharges was not available in all charts, a subanalysis was conducted to include only the 3 non-SSW major criteria. When the SSW criterion was removed from patients evaluated at Site 1, over one-third of patients with LGS (46%, rater 1; 36%, rater 2) met the 3 remaining major criteria, while fewer than 1 in 6 patients with DRE met the 3 non-SSW criteria (16%, rater 1; 4%, rater 2). Removing the SSW criterion from the patients evaluated at Site 2 resulted in most patients with LGS (68%, rater 1; 60%, rater 2) meeting the 3 non-SSW major criteria; conversely, <10% of patients with DRE met 3 non-SSW major criteria (4%, rater 1; 8%, rater 2). Among the patients with LGS at Site 1 who met the 3 non-SSW major criteria, ≥99.9% of patients with LGS also met ≥1 minor criteria, and 69.5% (rater 1) and 77.8% (rater 2) had ≥2 minor criteria. At Site 2, all of the patients with LGS meeting 3 non-SSW major criteria had ≥1 minor criteria, and 88.3% (rater 1) and 86.7% (rater 2) had ≥2 minor criteria.

A Cronbach's α analysis was conducted to determine the internal consistency of the REST-LGS. When the expert rater at each site was considered separately with all 8 criteria as 1 construct, the analysis yielded an α of 0.55 for Site 1 and an α of 0.72 for Site 2. Combining the expert raters from both sites with all criteria as 1 construct, the analysis yielded an α of 0.64. When the 2 EEG criteria were combined into 1 itemized construct, they yielded an α of 0.24 for Site 1 and an α of 0.60 for Site 2; combining the sites yielded an α of 0.42.

4. Discussion

The REST-LGS was developed to improve the identification of patients who may potentially have LGS by specialists and nonspecialists alike. The CRF contains 4 major (≥2 seizure types, seizure onset <12 years, history of EEG with generalized SSW discharges <2.5 Hz, cognitive impairment since childhood) and 4 minor (persistent seizures despite trial of ≥2 AEDs; history of VNS, ketogenic diet, or epilepsy surgery; evidence of seizure-related helmet use or head or face injury;

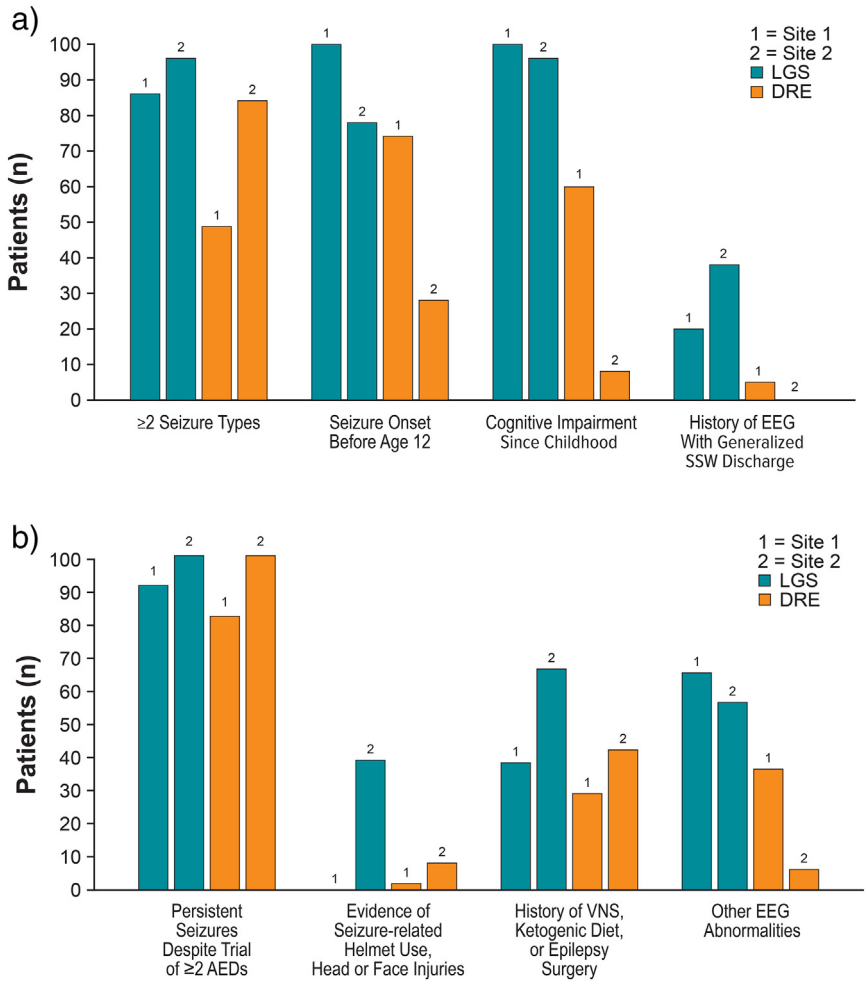

Fig. 2. Patients meeting major criteria (a) or minor criteria (b) for LGS per the CRF. AED, antiepileptic drug; CRF, case report form; DRE, drug-resistant epilepsy; EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome; SSW, slow spike-and-wave; VNS, vagus nerve stimulation.

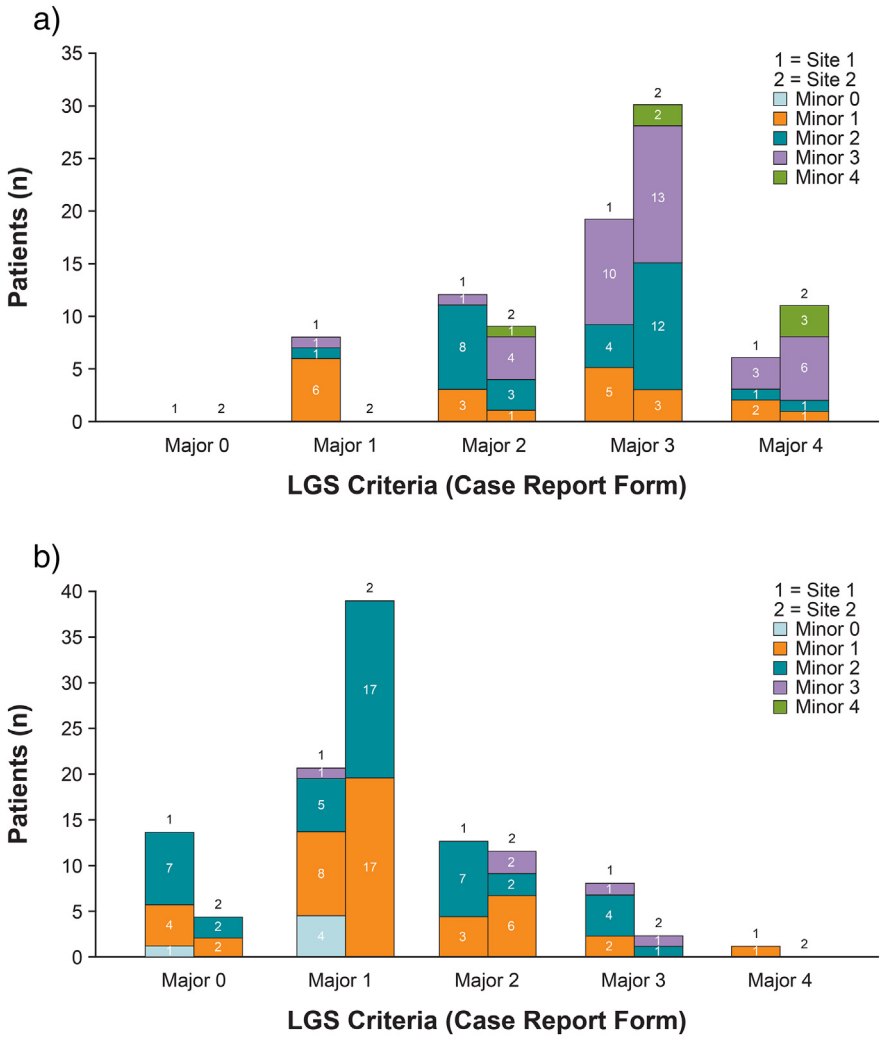

Fig. 3. Patients with diagnoses of LGS (a) or DRE (b) who met LGS criteria per the CRF. Major criteria: ≥2 seizure types; seizure onset <12 years of age; history of EEG with generalized SSW discharges <2.5 Hz; cognitive impairment since childhood. Minor criteria: persistent seizures despite use of ≥2 AEDs; history of VNS, ketogenic diet, or epilepsy surgery; evidence of seizure-related helmet use or head or face injuries; other EEG abnormalities (e.g., multifocal spikes, generalized discharges, paroxysmal fast activity). AED, antiepileptic drug; CRF, case report form; DRE, drug-resistant epilepsy; EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome; SSW, slow spike-and-wave; VNS, vagus nerve stimulation.

history of other EEG abnormalities) criteria that were considered by a panel of experts to be specific to LGS. Application of the CRF during a diagnosis-blinded retrospective chart review revealed that a majority of patients with confirmed LGS diagnosis met 3 major criteria and 2 to 3 minor criteria. Application of the REST-LGS in clinical practice and group home settings could lead to more timely diagnosis of LGS and could have important implications for treatment options, prognosis, and possible inclusion on managed care formulary coverage and access to services in the United States [9,16,28].

Reliability testing of the REST-LGS revealed moderate to very good agreement on a majority of criteria between raters at 2 epilepsy centers, indicating that experts and nonexperts could use the screening tool effectively. Poor to fair agreement was reached on only 1 criterion: evidence of seizure-related helmet use or head or face injuries. This result was likely driven by incomplete patient records and different interpretations of the "unavailable" response between raters on the CRF. Unblinding after chart review allowed for validation of the instrument through comparison of CRF-identified criteria and physician-based diagnosis. This analysis revealed that the combined number of major and minor criteria on the CRF was particularly indicative of a patient with LGS. This study had moderate intracohort variance when all 8 criteria were combined across both centers, indicating that diverse centers identified screening criteria comparably.

Of the 4 major criteria, cognitive impairment was identified by raters at both sites in more patients with LGS than in patients with DRE. Because most patients in this study were adults, this finding is consistent with reports that patients with LGS experience more prevalent and severe cognitive impairment over time [7]. For the major criterion history of EEG with generalized SSW discharges <2.5 Hz, detailed EEG information, including SSWs, were not available on all charts. In a subanalysis that removed SSW as a major criterion, many patients with LGS still met the other 3 major criteria. This finding is consistent with observations that SSW complexes may not be durable. For example, in a study that followed patients with LGS for over 40 years, SSW complexes were present for a mean duration of only 8.2 years [29].

The potential benefits of early treatment, including decreased risk of injury from falls, decreased seizure frequency, and maintenance of quality of life [5,7,30,31] underscore the importance of identifying patients with LGS. Early diagnosis and treatment may improve clinical outcomes and help reduce the risk of psychomotor regression and intractability associated with LGS [12,32]. The REST-LGS screening tool allows practitioners to cast a wider net for patients who may have LGS, supplementing current diagnostic standards. For example, use of this screening tool indicates that LGS diagnosis should not be ruled out when characteristic clinical encephalopathies present in the absence of generalized SSW discharges, particularly in an adult patient

with intractable seizures and a history of frequent falls with injury. This screening tool likely has wide applicability, especially for patients who are transitioning from family-based to group-home care or from pediatric to adult care, and can be applied by primary care providers and general neurologists at outpatient practices, because documented diagnosis may be required to obtain insurance coverage for medications that are only indicated for LGS.

This study is limited by its retrospective design, such that lack of certain patient details (i.e., a designation of helmet use not available on all charts) could lead to nonresponder bias. Also, the Cronbach's α analysis was not specified a priori, but was undertaken after unblinding to determine the tool's internal consistency. The validity and reliability of the REST-LGS could be extended in the future by including more epilepsy centers, assessing responses from raters in alternative settings (i.e., outpatient facilities or group homes), or using the tool with patients in a clinic.

Overall, the REST-LGS screening tool is simple, is easy to administer in a clinical setting, and can detect features of LGS in patients and across medical record formats. The preliminary validation presented here suggests that REST-LGS is a promising instrument for aiding clinicians in differentiating between LGS and other refractory epilepsies. The REST-LGS may prove to be a valuable instrument for both experts and nonexperts to identify patients with potential LGS who require further diagnostic evaluation, thus reducing the risk of underdiagnosis of this chronic disease.

Declaration of interests

JEPG has served as a consultant and/or speaker for Eisai Co., Ltd, Lundbeck, Sunovion Pharmaceuticals, Inc., Supernus Pharmaceuticals, and UCB. DB, KAD, HG, GL, PEM, BT, and SMW have participated in advisory boards and have received consulting fees from Lundbeck. KAD has also served as a consultant for UCB, Liva Nova, and Supernus. PEM has also served as a consultant or speaker for Supernus, Eisai, Neuropace, Greenwich Pharma, and Sunovion. SMW has served as a speaker or consultant for Supernus, Eisai, Neuropace, Sunovion, Greenwich Pharma, UCB, and Aquestive. DMT was an employee of Lundbeck at the time this analysis was conducted.

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Author contributions

All authors contributed to the study concept, design, and interpretation of data. DB analyzed the data.

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