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Received: 5 May 2026 | Revised: 27 August 2026 | Accepted: 28 August 2026

DOI: 10.1002/epi.70489

Epilepsia®

RESEARCH ARTICLE

Diagnosing Lennox–Gastaut syndrome in adulthood: A scoping review of diagnostic challenges and age-related electroclinical evolution

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Abstract

Objective: Lennox–Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy typically diagnosed in childhood. The 2022 International League Against Epilepsy (ILAE) criteria provide a diagnostic framework built on pediatric data, but their applicability in adulthood is challenged by disease evolution, treatment effects, and missing pediatric records. This scoping review aimed to identify adult LGS features and to evaluate the adaptability of current criteria in adults.

Methods: We conducted a systematic search on MEDLINE (PubMed) following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. Studies involving individuals 16 years of age and older with LGS or suspected LGS were included. Data were extracted on seizure semiology, electroencephalography (EEG) patterns, comorbidities, and etiological factors across the lifespan.

Results: Forty-five sources (78% case reports/series) encompassing 421 patients were included, with substantial heterogeneity in reporting. The analysis suggests a longitudinal attenuation or under-documentation of several classical LGS features: studies with fulfillment of the ILAE seizure-type criteria decreased from 73% in childhood to 41% in adulthood; tonic seizures often persisted (frequently during sleep), whereas atonic and atypical absence seizures significantly declined. The mandatory EEG hallmarks (generalized paroxysmal fast activity and slow spike-and-wave complexes) were documented in less than half of adult patients, possibly due to the reduced frequency of sleep EEG monitoring. Comorbidities were reported inconsistently, representing a major knowledge gap, as sleep and behavioral disorders may further mask diagnostic markers.

Significance: Given the heterogeneity and predominantly low-level evidence of the included literature, these findings warrant cautious interpretation; nonetheless, strict adherence to pediatric-centric criteria in adults may plausibly

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contribute to underdiagnosis or false negatives. Transitioning from a "snapshot" to a "longitudinal" diagnostic mindset is essential. Clinicians should prioritize life-spanning anamnesis and recognize that the clinical and EEG core criteria of LGS may evolve or diminish over time. Age-adapted diagnostic frameworks are needed to ensure that adult patients receive appropriate diagnosis and therapeutic pathways.

KEYWORDS

adult, developmental and epileptic encephalopathy, ILAE 2022 criteria, Lennox–Gastaut syndrome, LGS

1 | INTRODUCTION

Lennox–Gastaut syndrome (LGS) is a developmental and epileptic encephalopathy (DEE) associated with multiple etiologies.[1] LGS is caused by synchronized, high-frequency activity in bilaterally distributed brain networks, which develop during childhood.[2] The long-lasting lack of clear, consistent diagnostic criteria, the clinical overlap with other DEEs, and the evolution of LGS signs and symptoms during aging determine serious diagnostic challenges,[3–5] despite LGS being first described in 1966.[6] These difficulties are also highlighted by the latest epidemiological data: incidence and prevalence estimates are 14.5–28 and 5.8–60.8 per 100 000 individuals, respectively. Furthermore, diagnostic delays are frequently reported, with patients' ages ranging from 2 to 15 years at diagnosis.[7]

According to the current classification and definition of DEEs by the International League Against Epilepsy (ILAE), LGS is characterized by a diagnostic triad: (1) multiple types of drug-resistant seizures with onset prior to 18 years of age (one of which must be a tonic seizure); (2) cognitive and often behavioral impairments, which may not be present at seizure onset; and (3) generalized slow spike-and-wave (SSW) and generalized paroxysmal fast activity (GPFA) in sleep, on electroencephalography (EEG) (see Table 1 for the full diagnostic criteria).[1] However, not all patients present with all of the core seizure types (i.e., atonic, tonic, and atypical absences), especially at the onset.

The diagnostic boundaries of LGS are inherently imprecise, as none of its defining features is either universal or pathognomonic. The interictal EEG pattern of SSW is not pathognomonic to the disorder, and some consider the presence of GPFA (which may or may not be associated with tonic seizures) an essential criterion.[3,8] Similarly, although intellectual disability (ID) was long considered invariably present and was proposed as a formal diagnostic criterion, reports of patients with LGS without ID challenge this assumption.[3,9–11] Furthermore, because not all patients present with the three cardinal criteria at disease onset, diagnosis may only be established after many years of follow-up.[1,5] Conversely, several patients with ID and drug-resistant seizures causing falls may have been loosely diagnosed with LGS in the absence of a rigorous diagnostic workup.[5]

Key points

- Lennox–Gastaut syndrome (LGS) is defined by criteria built on pediatric data, yet many patients are first assessed as adults, when that picture no longer fits.
- Seizure types and electroencephalography (EEG) hallmarks of LGS may fade, be suppressed by treatment, or simply go unrecorded as patients move into adulthood.
- Nocturnal tonic seizures, sleep-related fast rhythms, and intellectual disability are the features most likely to persist into adulthood.
- Diagnosis in adulthood calls for a longitudinal mindset, weighing old records, prior EEG studies, and treatment history alongside current findings.
- Age-adapted criteria, grounded in prospective adult-focused studies, are needed so that adults are not denied a diagnosis and proper care.

The evolution of LGS clinical manifestations during the course of life increases difficulty in diagnosis. Adult patients may display very different clinical and EEG features not consistent with the typical ones of early-onset LGS, due to treatment and/or the longitudinal progression of the syndrome. The number and variety of seizure types and the presence of SSW complexes on EEG usually decrease over time, whereas the presence of diffuse fast rhythms and tonic seizures during sleep tend to persist.[12,13] Moreover, patients who present at a later stage may fail to provide details of medical history and care

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TABLE 1 The 2022 Lennox-Gastaut syndrome (LGS) diagnostic criteria according to the International League Against Epilepsy (ILAE) Task Force on Nosology and Definitions.

	Mandatory	Alerts	Exclusionary
Seizures	Tonic seizures In addition to tonic seizures, at least one additional seizure type must be present, which may include any of the following: • Atypical absences • Atonic • Myoclonic • Focal impaired awareness • Generalized tonic–clonic • Nonconvulsive status epilepticus • Epileptic spasms		
EEG	Generalized slow spike-and-wave complexes of <2.5 Hz (or history of this finding on prior EEG) Generalized paroxysmal fast activity in sleep (or history of this finding on prior EEG)	Photoparoxysmal response at low frequencies (consider CLN2 disease)	Persistent focal abnormalities without generalized spike-and-wave pattern
Age at onset	<18 years	>8 years	
Long-term outcome	Drug-resistant epilepsy Mild to profound intellectual disability		

Note: An MRI is not required for diagnosis but is usually performed to evaluate for underlying etiology. An ictal EEG is not required for diagnosis. However, it should be strongly considered in a child with alerts or with clinical features that may suggest epilepsy with myoclonic atonic seizures syndrome. Syndrome-in-evolution: approximately 50% of infants with a severe DEE, e.g., IESS or early infantile DEE, evolve over time to LGS. Syndrome without laboratory confirmation: in resource-limited regions, at a minimum, an interictal EEG showing characteristic generalized SSW pattern during wakefulness is required for diagnosis. Reproduced from Specchio et al.[1] under the Creative Commons license CC-BY 4.0.

Abbreviations: CLN2, neuronal ceroid lipofuscinosis type 2; DEE, developmental and epileptic encephalopathy; EEG, electroencephalography; IESS, infantile epileptic spasms syndrome; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; MRI, magnetic resonance imaging; SSW, slow spike-and-wave.

during childhood; investigation may be compromised by complex behavioral problems associated with ID, thereby leading clinicians to overlook LGS as a diagnostic option in the adult population.[12,13] The LGS diagnostic criteria were established on a pediatric cohort and may not be adequate to diagnose older patients; although a diagnostic algorithm for adults has been proposed (see Montouris et al. (2020)[13]), a broad clinical consensus has yet to be reached. Thus, the identification and diagnosis of LGS in adults—whether it be due to a late-onset or due to a missing pediatric diagnosis—proves to be more challenging than in children[13] and likely contributes to the underdiagnosis of LGS in this population.[7,13]

In light of these observations, we carried out a scoping review with the aim of identifying LGS indicators in adulthood, to contribute to and facilitate diagnosis. The decision to use a scoping review approach was based on the expected heterogeneity of study designs, outcomes, and populations, as well as the exploratory objective of our study. Compared to systematic reviews, scoping reviews pose broader questions and employ less restrictive inclusion criteria. They serve the purpose of identifying and mapping the available evidence, establishing knowledge gaps, scoping bodies of literature, and clarifying concepts.[14] The present study aims to address the following questions:

- How can LGS in adulthood be identified when the LGS diagnosis was either overlooked or misdiagnosed during childhood?
  - How does the LGS adult clinical picture differ from the childhood one?
    - What are the differences in EEG?
    - What are the differences in seizure types and frequency?
    - How do (adult) comorbidities affect the clinical presentation?
    - How do ongoing and previous treatment affect clinical presentation?
  - What genetic mutations are more often associated with LGS, and can they be of use for the diagnosis?

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- Can pediatric diagnostic criteria be applied to an adult population? If not, why? And how can they be adapted?
- What are the best diagnostic tools in this context?

2 | METHODS

The review methods were specified a priori in a written protocol (Supplementary Materials, Appendix S1), which guided all subsequent steps of the review. The protocol was for internal use and was not registered prospectively. The results are reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.[15]

2.1 | Study protocol

2.1.1 | Population–Concept–Context (PCC) framework

The present study was guided by a PCC framework.

The population comprised older adolescents, defined as individuals ≥16 years of age, and adults with LGS or suspected LGS.

The central objective was the identification and characterization of LGS in adulthood, particularly with regard to missed, delayed, or uncertain pediatric diagnosis. We included any study that provided information relevant to the diagnosis or clinical reasoning for LGS in adults, including at least one of the following domains: (1) adult clinical phenotype (seizure types, seizure frequency, seizure-related falls, evolution of seizures from childhood to adulthood); (2) adult EEG features (interictal and/or ictal patterns, evolution of EEG from childhood to adulthood); (3) comorbidities (e.g., intellectual disability, psychiatric, behavioral, motor, sleep, systemic comorbidities) and their impact on clinical manifestation or recognition of LGS; (4) ongoing and previous treatments (anti-seizure medications (ASMs) and non-pharmacological therapies) and their impact on seizure/EEG phenotype or diagnostic recognition; (5) genetic etiology and other etiological factors (including structural, metabolic, or infectious causes) relevant to adult diagnosis; (6) diagnostic criteria, diagnostic algorithms, and diagnostic tools (e.g., video-EEG, magnetic resonance imaging [MRI], genetic testing) suggested or applied in adult patients.

The review considered evidence from all clinical settings (tertiary epilepsy centers, general neurology clinics, inpatient and outpatient services, community settings) and all geographical regions.

2.1.2 | Eligibility criteria

Eligible studies included original clinical sources of evidence such as cohort studies (prospective or retrospective), case–control and cross-sectional studies, case series and single case reports, as well as qualitative or mixed-methods studies (e.g., interviews, clinician surveys) that provided clinical-level information on adult LGS. We excluded narrative reviews, books and manuals, expert opinion pieces without primary clinical data, editorials without original data, and studies that did not provide extractable data on adult clinical presentation or diagnostic aspects. Moreover, randomized controlled trials and interventional studies enrolling only patients with an already-established diagnosis of LGS were excluded, because their reliance on pre-applied diagnostic criteria would have introduced a selection bias incompatible with our aim of characterizing the features of LGS and their evolution across the lifespan, independently of current diagnostic thresholds. Conversely, given the rarity of the syndrome, case reports and small case series were deliberately retained, as they represent the principal source of granular clinical data when large cohorts are lacking. We considered only peer-reviewed full-text articles and abstract-only reports. Only English-language articles were eligible. No restrictions were placed on year of publication.

2.2 | Information sources and search strategy

The search strategy was developed and refined iteratively, based on the PCC framework and the research questions, using a combination of controlled vocabulary (e.g., Medical Subject Headings [MeSH] terms) and free-text keywords. Search terms covered three main concepts, that is, (1) LGS and related developmental and epileptic encephalopathies; (2) adolescence and adulthood (including transitional age); and (3) diagnosis, clinical presentation, EEG, seizures, comorbidities, and genetics.

The search was conducted from October to November 2024. To identify additional relevant sources, we screened the reference lists of included articles. Due to time and resource constraints, we only searched within one electronic database, namely MEDLINE via PubMed.

The complete, final electronic search strategy is provided in the protocol in the Supplementary Materials (Appendix S1).

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2.3 | Selection of sources of evidence

2.3.1 | Literature screening

All identified records were imported into Microsoft Excel. Screening was conducted in two stages, a preliminary title and abstract screening and subsequently a full-text screening.

Two reviewers (F.P. and C.L.) independently screened titles and abstracts against the eligibility criteria. Articles not meeting the inclusion criteria were excluded at this stage. Any discrepancies during the first screening were resolved by submitting the study to further full-text screening.

The full texts of potentially relevant articles were selected and equally distributed among four reviewers (S.C., E.C.I., C.L., and M.P.) to be independently assessed for eligibility. Disagreements at any stage were resolved via collegial consensus.

Included studies for every step of the literature screening are reported in the Supplementary Materials (Appendix S2).

2.3.2 | Data charting process

Data extracted from the included sources was charted using a standardized data-charting form developed a priori in Microsoft Excel, based on the protocol and on research questions. The form was piloted on a sample of five studies and refined iteratively to ensure clarity and consistency. The data-charting form is available in Supplementary Materials (Appendix S3).

Four reviewers (S.C., E.C.I., C.L., and M.P.) charted data from the same studies included during the full-text screening process. Subsequently, these studies were redistributed to another reviewer for further independent data extraction. Any discrepancies were resolved via collegial deliberation and, where necessary, through consultation of the original article.

2.4 | Synthesis of results

In compliance with the current guidelines for scoping reviews, the primary objective was to map the breadth and nature of the evidence, rather than to estimate effect sizes. Therefore, meta-analysis or other quantitative pooling methods were not conducted, due to anticipated heterogeneity in study designs, outcomes, and reporting; furthermore, no formal critical appraisal or risk-of-bias assessment of individual sources of evidence was performed. Using Microsoft Excel, simple descriptive statistics were provided where relevant (e.g., counts, percentages, medians), to summarize the distribution of key variables across studies.

Findings are interpreted in compliance with the ILAE 2022 diagnostic criteria for LGS and in alignment with established consensus definitions,[1] particularly focusing on how adult data can support the adaptation of pediatric criteria and the development of pragmatic diagnostic approaches for adults with suspected LGS.

3 | RESULTS

3.1 | Selection of sources of evidence

The electronic search of MEDLINE (PubMed) yielded 1283 records for title and abstract screening. No duplicates were found.

Following title and abstract screening, 930 records (72.5%) were excluded, and 353 (27.5%) full-text articles were assessed for eligibility. Through backward citation chasing of the reference lists and relevant reviews, 10 additional records were identified; these were assessed directly at full-text level, resulting in a total of 363 records.

Of these, 313 (86.2%) were excluded after full-text screening, and 50 (13.8%) underwent data charting. After charting, five additional studies were further excluded because, although their patients had been described originally as having LGS, on closer review they did not fulfill the diagnostic criteria adopted for this review. The final analytic set, therefore, comprised 45 studies,[11,16–59] which are presented in Table S1 and discussed in the present review.

A PRISMA-ScR flow diagram summarizing the study selection process is presented in Figure 1.

3.2 | Characteristics of included sources

The evidence base consisted predominantly of case reports/series (~78%), with a smaller contribution from observational studies (~18%), and publication dates covering from 1976 to 2023. Most sources enrolled older adolescents (≥16 years) and adults, whereas adult-only cohorts were infrequent. Sample sizes were typically small (median 1 patient per source), with a minority of larger observational datasets (up to 135 patients). Sex was inconsistently reported: only 60% of sources provided a complete male/female breakdown, showing a male predominance among those with complete reporting (60.3% male). Age at LGS diagnosis was variably documented; among sources with extractable

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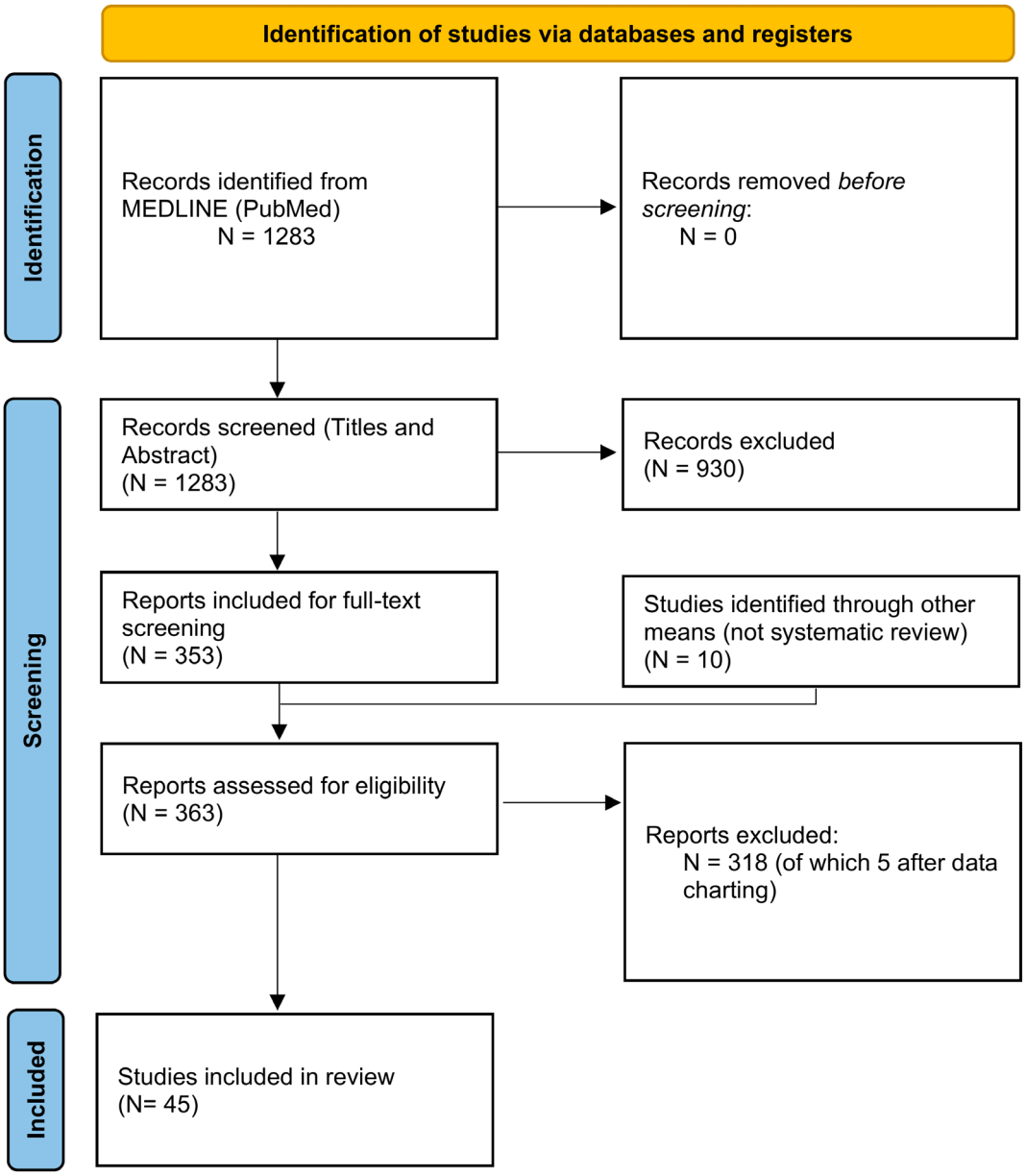

FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram illustrating the scoping review process.

numeric values, diagnosis occurred across a broad range (0–24 years of age), whereas several sources provided only qualitative or unclear timing (Table S2).

3.3 | Seizure phenotypes

Across 45 included sources, seizure semiology was variably reported for childhood (32/45 sources) and adulthood (33/45 sources). Tonic seizures were the most consistently documented seizure type in both childhood (25/32 sources) and adulthood (23/33 sources), when reported. By comparison, atonic/drop seizures and absence seizures were reported less frequently in adulthood than in childhood, and explicit mention of "atypical" absences also decreased (17/32 in childhood vs 8/33 in adulthood) (Table 2).

In the subset of sources reporting seizure types for both childhood and adulthood ($n = 22$), approximately one-third no longer explicitly reported tonic seizures in adulthood despite having described tonic seizures in childhood. Similarly, loss of other "classic" LGS seizure types (atonic/drop and absences) was frequent, and among sources reporting the classic triad in childhood, most did not continue to report the full triad in adulthood. Using the ILAE minimum seizure-type requirement (tonic plus ≥1 additional seizure type) as a reporting-based proxy, fewer sources of adulthood

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TABLE 2 Reported seizure phenotypes across childhood and adulthood: Source-level and patient-level synthesis (45 sources, 421 patients).

	Childhood		Adulthood	
Seizure type	**Sources, *n* (%)**	**Patients, *n* (%)**	**Sources, *n* (%)**	**Patients, *n* (%)**
Tonic	25/32 (78.1%)	197/265 (74.3%)	23/33 (69.7%)	164/213 (77.0%)
Atypical absence	23/32 (71.9%)	183/265 (69.1%)	13/33 (39.4%)	83/213 (39.0%)
Atonic/drop (incl. astatic)	18/32 (56.2%)	149/265 (56.2%)	13/33 (39.4%)	60/213 (28.2%)
Generalized tonic–clonic	16/32 (50.0%)	126/265 (47.5%)	9/33 (27.3%)	74/213 (34.7%)
Myoclonic	8/32 (25.0%)	128/265 (48.3%)	4/33 (12.1%)	19/213 (8.9%)
Focal	13/32 (40.6%)	50/265 (18.9%)	6/33 (18.2%)	24/213 (11.3%)
Epileptic spasms	4/32 (12.5%)	42/265 (15.8%)	2/33 (6.1%)	12/213 (5.6%)
Other/unclassifiable	–	9/265 (3.4%)	–	0/213 (0%)
Denominators	32/45 sources	265 patients with per-patient data	33/45 sources	213 patients with per-patient data

Note: Sources, *n* (%): sources documenting the type in that life stage (non-exclusive), among the 32 (childhood)/33 (adulthood) sources reporting seizure semiology for that stage. Patients, *n* (%): patients documented with the type among those with per-patient seizure data in that stage (denominators 265 childhood; 213 adulthood; Appendix S4). Categories are non-exclusive. Status epilepticus/non-convulsive status epilepticus (source-level 5/32 childhood, 2/33 adulthood) and explicitly seizure-free patients (2/33 adulthood) were recorded narratively and are not coded as patient-level types.

seizure descriptions met this minimum than childhood seizure descriptions (Table 3). The same cross-sectional pattern was confirmed at the individual-patient level across all 421 patients, with source- and patient-level estimates reported together in Table 2 (full dataset in Appendix S4); patient-level childhood estimates were dominated by two large cohorts,[47,59] which is why both levels are shown side by side.

Combined, these data suggest that the adult clinical seizure repertoire described in literature often appears narrower than that reported in childhood. This may contribute to diagnostic uncertainty when clinicians evaluate adults without complete pediatric documentation. This pattern is consistent with the longitudinal clinical development of LGS, suggesting that some features may become less overt over time, whereas some elements (notably tonic seizures, often sleep-related) may persist.

3.3.1 | Seizure-related diagnostic features across childhood and adulthood

Within the 45 included sources, age at LGS diagnosis was inconsistently reported and was often missing; among the 14 sources with extractable numeric data, the median age at diagnosis was 8.5 years (range 2.4–24). Seizure semiology was reported in 32 of 45 sources for childhood and in 32 of 45 sources for adulthood, although within-source longitudinal reporting was limited (only 22/45 sources described seizure types in both pediatric and adult stages) (Table 3).

When compared to the 2022 ILAE LGS seizure-type diagnostic requirements (mandatory tonic seizures plus at least one additional seizure type), tonic seizures were still the most reported seizure type in both life stages, whereas absences and atonic/drop seizures were less documented in adulthood than in childhood. In the subset of sources reporting both childhood and adulthood semiology, the proportion fulfilling the strict ILAE seizure-type pattern fell from 73% (16/22) in childhood to 41% (9/22) in adulthood. This decline was attributed primarily to a reduction in documented "additional" seizure types and/or lack of adult documentation of tonic seizures, rather than an explicitly reported absence (Table 3).

Overall, these findings suggest that adult LGS characterizations may present fewer seizure types over time and that tonic seizures, often occurring during sleep, may be among the most persistent features. A strict application of pediatric seizure-type criteria in adulthood, when semiology is incompletely reported or when seizure types have evolved due to treatment and aging, may determine false negatives, thus highlighting a methodological issue for adult diagnosis.

3.4 | EEG features relevant to ILAE LGS diagnostic criteria

EEG was consistently documented across the 45 sources (95.6%); nevertheless, key ILAE-relevant EEG details were frequently under-specified, with unclear entries common in GPFA and background activity. In sources explicitly

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TABLE 3 Seizure-related diagnostic features across childhood and adulthood (mapped to ILAE 2022 LGS criteria).

Item	Childhood	Adulthood	Notes/interpretation (strict ILAE focus)
Age at LGS diagnosis (sources of evidence, $N=45$)	—	—	Reported in any form: 27/45. Numeric extractable: 14/45, median 8.5 years, range 2.4–24. Not reported: 18/45. Reported as ranges: 2/45. Uncertain/multiple and not usable for numeric summary: 3/45
Seizure types reported	32/45	32/45	Seizure semiology was frequently incompletely described, especially when focusing on adulthood
Tonic seizures	25/32 (78%)	22/32 (69%)	Mandatory seizure type per ILAE criteria
Absence/absences (incl. atypical when specified)	23/32 (72%)	13/32 (41%)	Commonly reported in childhood; less often reported in adulthood
Atonic/drop attacks	18/32 (56%)	12/32 (38%)	Drop attacks are a key "classic" LGS feature but appear less frequently described in adulthood
Generalized tonic–clonic	16/32 (50%)	9/32 (28%)	Considered an admissible "additional seizure type" in ILAE criteria
Focal (incl. focal impaired awareness/partial terminology)	14/32 (44%)	6/32 (19%)	Focal impaired awareness is included among admissible additional types in ILAE criteria
Myoclonic	9/32 (28%)	4/32 (12%)	Admissible additional type in ILAE criteria
Clonic (reported separately from GTCS in extraction text)	7/32 (22%)	5/32 (16%)	Not specifically listed by ILAE as an "additional seizure type" category, but often appears in clinical descriptions
NCSE	5/32 (16%)	2/32 (6%)	NCSE is explicitly listed by ILAE as an admissible additional type
Epileptic spasms	4/32 (12%)	2/32 (6%)	Explicitly listed by ILAE as an admissible additional type
Strict ILAE seizure-type criterion met (tonic + ≥1 additional type)	24/32 (75%)	17/32 (53%)	*Operationalized from reported semiology only; "not specified" treated as missing, not absence*
Childhood vs adulthood comparison (22/45 sources reporting both periods, used for within-source evolution/comparison)			
Met strict ILAE criterion (within these 22)	16/22 (73%)	9/22 (41%)	Reduction in the number of sources reporting strict ILAE criterion from childhood to adulthood. Most often due to fewer "additional" seizure types being described in adulthood and/or tonic seizures no longer being reported
Loss of specific seizure types from childhood → adulthood (among 22 reporting both)	Counts represent "present in childhood" AND "not reported in adulthood": tonic 7, absence 8, atonic/drop 8, GTCS 8, focal 8, myoclonic 7. (Interpret cautiously: could reflect true evolution, treatment response, or under-reporting.)		
Seizure evolution described narratively	Reported in 17/45 sources; where described, trajectories included stable patterns, improvement/seizure control, occasional worsening, and occasional statements of disappearance with age; nocturnal tonic seizures were sometimes highlighted as persisting		

Abbreviations: GTCS, generalized tonic–clonic seizures; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; NCSE, non-convulsive status epilepticus.

stating adult EEG was recorded ($n=21$), approximately half (47.6%) presented with the two mandatory ILAE EEG features (GPFA, plus generalized SSW). However, incomplete reporting was frequent, thereby limiting interpretation, and missing data cannot be assumed to indicate absence (Table 4). At the individual-patient level (Table 4; Appendix S4), atypical SSW was the most consistently documented feature in both life stages, whereas GPFA was documented in only a minority of adults when referred to all adults with an available EEG, consistent with the source-level estimate.

In the longitudinal subset ($n=9$) describing EEG in both childhood and adulthood, GPFA and SSW were found consistently when documented, although loss of SSW by adulthood was observed in a minority of cases, and slow background activity exhibited the most variability (Table 5). Notably, this pattern is consistent with ILAE-oriented educational resources, emphasizing that SSW may no longer be evident by adulthood and may require confirmation from previous EEG studies, potentially complicating adult reassessment when pediatric records are unavailable.

Among the seven sources providing a detailed characterization of EEG evolution, reported trajectories included: (1) stability of EEG patterns from childhood into adulthood; (2) persistence of GPFA/SSW;

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TABLE 4 EEG features relevant to ILAE LGS diagnostic criteria: Source-level and patient-level synthesis (45 sources, 421 patients).

	Childhood		Adulthood	
EEG feature	**Sources, *n***	**Patients, *n* (%)**	**Sources, *n***	**Patients, *n* (%)**
GPFA	10	42/145 (29.0%)	15	57/86 (66.3%)
SSW	20	203/225 (90.2%)	28	122/157 (77.7%)
Slow background activity	10	114/178 (64.0%)	10	58/82 (70.7%)
Patients with EEG assessed in the stage	290/421		157/421	

Note: Pooled across timepoints (source-level, 45 sources): EEG reported 43/45; GPFA 14/45; atypical SSW 26/45; slow background 16/45. Sources: sources reporting the feature as present in that life stage (non-exclusive; derived from the patient-level re-extraction, Appendix S4). Patients: patients with the feature among those in whom that feature was assessed in that stage (feature-specific denominators—childhood: GPFA 145, SSW 225, slow background 178; adulthood: GPFA 86, SSW 157, slow background 82). Denominators differ because EEG features are reported selectively; e.g., in the study by Widdess-Walsh et al.[59] GPFA/SSW are scored over its 71-patient digital-EEG subset and its background over 135; in the study by Ferlazzo et al.,[31] GPFA is scored over the 24 patients with sleep EEG.

Abbreviations: EEG, electroencephalography; GPFA, generalized paroxysmal fast activity; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; SSW, slow spike-and-wave.

TABLE 5 Within-source EEG evolution of EEG features relevant to ILAE LGS diagnostic criteria (subset with both childhood and adult EEG recorded; $n = 9$ sources).

Feature (timing-coded)	Persisted into adulthood	Lost by adulthood	Emerged in adulthood	Not reported/unclear
GPFA	5	0	0	4 (2 not reported; 1 unclear; 1 absent)
Atypical SSW	5	1	0	3 (1 not reported; 1 unclear; 1 timing unclear/partial)
Slow background activity	2	1	1	5 (2 not reported; 2 unclear; 1 absent)
ILAE mandatory EEG features (GPFA + SSW)	4 retained	1 lost	0 emerged	4 not demonstrable (insufficient reporting/unclear/absent)

Abbreviations: EEG, electroencephalography; GPFA, generalized paroxysmal fast activity; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; SSW, slow spike–and–wave.

(3) treatment-associated normalization or reduction in slow activity; (4) emergence of more focal epileptiform abnormalities (e.g., post-surgical, due to ASMs, or with aging); and (5) occasional disappearance of classic features in adulthood.

3.5 | Etiology and diagnostic workup: Genetic testing, MRI, and ID

Etiology was addressed, to varying degrees of detail, across the 45 included sources. Using the nomenclature adopted by each original study (not remapped to current ILAE etiological categories), the underlying cause was classified as genetic in 13 sources (19/421 patients, 4.5%), genetic-structural in 2 sources (5 patients, 1.2%), structural in 10 sources (20 patients, 4.8%), symptomatic in 4 sources (86 patients, 20.4%, of whom a structural cause was further specified for 6 patients in a single source), and cryptogenic/unknown in 23 sources (269 patients, 63.9%); etiology was not reported at all in 4 sources (22 patients, 5.2%) (Table 6). "Cryptogenic" and "unknown" labels were merged, whereas "not reported" indicates the absence of any etiological statement in the source.

Genetic testing was addressed with varying granularity across sources. A causative variant was identified in 19 of 421 patients (4.5%, 13 sources); testing was performed but negative or non-diagnostic in 116 of 421 patients (27.6%, 9 sources); and in the remaining 286 of 421 patients (67.9%, 26 sources) testing was either not performed or not reported. This distinction could not be established with confidence from the original full texts, particularly in older sources predating routine molecular testing. Identified genes and copy-number variants, reported across 14 sources, included: *GABRB1*, *MBD5* (with a co-occurring 22q13.3 deletion and *MECP2* duplication in one patient), *ABAT*, *COL18A1*, *DCX*, *TCF4*, *ATP6V1B2*, 15q11-13 duplication (two independent sources), *GABRB3*, *DNM1*, *SCN2A*, and an inverted duplication of chromosome 15.

Brain MRI status was reported, in some form, for 279 of 421 patients (66.3%). Abnormal findings were documented in 77 of 421 patients (18.3%, 23 sources), and normal or unremarkable in 189 of 421 patients (44.9%, 14 sources); such a proportion is driven substantially by a

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TABLE 6 Etiology, genetic testing, brain MRI, and intellectual disability among 421 patients across 45 included sources.

Domain	Category	Sources, *n*[a]	Patients, *n* (%)
Etiology	Genetic	13	19 (4.5)
	Genetic—structural	2	5 (1.2)
	Structural	10	20 (4.8)
	Symptomatic	4	86 (20.4)
	Cryptogenic/unknown	23	269 (63.9)
	Not reported	4	22 (5.2)
Genetic testing	Performed—causative variant identified	13	19 (4.5)
	Performed—negative/non-diagnostic	9	116 (27.6)
	Not performed/not reported	26	286 (67.9)
Brain MRI	Normal/unremarkable	14	189 (44.9)
	Abnormal findings	23	77 (18.3)
	Not performed	6	13 (3.1)
	Not reported	15	142 (33.7)
Intellectual disability (ID)	Present	37	253 (60.1)
	Borderline	1	1 (.2)
	Absent	5	9 (2.1)
	Not specified	9	158 (37.5)

Abbreviations: ID, intellectual disability; MRI, magnetic resonance imaging.

[a]Sources, *n* is non-exclusive: a source is counted in more than one row within a domain if it includes patients belonging to more than one category (e.g., a cohort with both genetic-testing-positive and genetic-testing-negative patients). Patients, *n* and % are of the 421-patient analytic set and are mutually exclusive within each domain; percentages may not sum to exactly 100% due to rounding.

single large cohort in which a normal MRI was itself part of the inclusion criteria. MRI was explicitly not performed in 13 of 421 patients (3.1%, 6 sources, including patients who underwent computed tomography [CT] only), and imaging status was not reported for 142 of 421 patients (33.7%, 15 sources).

ID was the most consistently reported comorbid feature. Among the 421 patients, ID was present in 253 (60.1%, 37 sources) and borderline in 1 (.2%, 1 source); ID was explicitly absent in 9 patients (2.1%, 5 sources). ID status was not specified for 158 patients (37.5%, 9 sources), again largely attributable to the single large cohort noted. Among sources that reported ID status, presence markedly outweighed absence (253 vs 9 patients), consistent with ID being among the more constant features of LGS across the lifespan, while underscoring that a substantial share of the literature does not address it at all (Table 6).

4 | DISCUSSION

The present scoping review assessed the literature supporting the 2022 ILAE diagnostic criteria for LGS,[1] addressing the significant challenges of applying these frameworks to older adolescent and adult populations. Although the 2022 criteria provide a robust foundation for pediatric diagnosis, our findings highlight a gap in their adaptability for patients who transition to adult epilepsy centers or are re-evaluated later in life.

The first concern emerging from the literature is the high degree of data heterogeneity; many studies omit essential demographic details, such as biological sex and exact age at diagnosis, and fail to characterize EEG features, seizure types, comorbidities, ID severity, etiology, and ASM regimens beyond a generic label of "drug resistance." This lack of granular data complicates the clinical picture.

4.1 | Seizure semiology

A pivotal observation of this review addresses the longitudinal evolution of seizure semiology. Although tonic seizures are traditionally considered a hallmark of LGS, their clinical expression often diminishes or alters during the transition to adulthood. Evidence from both longitudinal and cross-sectional studies indicates that although tonic seizures persist into adulthood, their clinical prominence often diminishes, or their semiology undergoes age-related modifications.[31] Indeed, our source-level analysis (Table 3) reveals a sharp decline

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in the studies fulfilling ILAE seizure criteria, which decrease from a 73% positivity rate in pediatric cohorts to 41% in adult cohorts. The patient-level analysis (Table 2) complements this cross-sectional narrowing, where tonic seizures were the only type whose documented prevalence did not decline into adulthood. This phenomenon may be attributed to neurodevelopmental maturation or, more likely, to the cumulative effect of polytherapy; certain seizure types, such as atonic or drop attacks, may be successfully suppressed by medications, whereas tonic seizures often persist as a refractory core. The current consensus in the medical literature is that the transition to adulthood is associated with changes in both frequency and semiology of tonic seizures, which can complicate diagnosis and management in adult patients affected by LGS.[13] Consequently, clinicians must prioritize lifespan-oriented anamnesis, actively seeking longitudinal records from caregivers and pediatric records to reconstruct the early clinical phenotype.

4.2 | EEG features

The neurophysiological profile undergoes a similar transformation. Although nearly all studies incorporate EEG data, the defining EEG patterns included in the ILAE criteria (specifically GPFA and atypical SSW) are documented in fewer than half of studies with adult patients. At the patient level (Table 4), atypical SSW remained the most frequently documented EEG feature into adulthood, whereas GPFA, although present in most patients in whom it was specifically sought, was documented in only a minority of adults overall; this dependence of apparent prevalence on whether a feature was actively looked for reinforces that a missing EEG finding cannot be equated with true absence. EEG features also evolve in LGS, as documented previously; diffuse fast rhythms during sleep remain characteristic, whereas SSW discharges during wakefulness may diminish or even normalize in some adults.[31] The scarcity of sleep EEG recordings in adults, often due to challenges in patient compliance and the logistical difficulties of telemetry in populations with cognitive disabilities, further hinders the identification of these diagnostic markers. Such findings suggest that the absence of typical EEG features in an adult patient should not automatically preclude an LGS diagnosis, as these patterns may be masked by aging, prior epilepsy surgery, or pharmacological modulation. Clinical consensus highlights that defining EEG abnormalities in LGS are frequently modulated by ASMs, prior surgical interventions, and the natural evolution of the syndrome, often resulting in atypical or absent interictal patterns in adult cohorts.[8,13,60] Consequently, adult diagnostic algorithms advocate for an integrated approach that prioritizes clinical history, longitudinal seizure semiology, and extended sleep or video-EEG monitoring, over a strict reliance on classic electrographic hallmarks.[13] Given the recognized nosological heterogeneity of LGS, the diagnosis must be contingent upon the comprehensive electroclinical profile rather than the presence of canonical EEG findings alone.[8] A normal or atypical EEG in adulthood does not preclude an LGS diagnosis; a multi-dimensional assessment incorporating sleep-state recordings and a detailed lifespan-oriented history remains essential for diagnostic accuracy in this population.

4.3 | Etiology and diagnostic workup

As for seizure semiology and EEG features, etiological and diagnostic workup data were frequently incomplete, and the absence of a stated finding cannot be assumed to indicate a true negative. Cryptogenic/unknown etiology and unperformed or unreported genetic testing dominated the dataset, reflecting both the historical use of clinical (pre-molecular) diagnostic approaches in older sources and inconsistent adoption of etiology-oriented workup across settings. By contrast, ID emerged as the most robustly documented feature, reinforcing its role as a comparatively stable diagnostic anchor across childhood and adulthood. Although recent advances in high-resolution neuroimaging and next-generation sequencing have identified specific genetic and structural etiologies in a subset of patients, 25% to 49% of LGS cases remain idiopathic even after exhaustive evaluation.[3,61] This idiopathic subgroup is defined by the absence of detectable genetic, structural, or metabolic markers, remaining refractory to sophisticated diagnostic protocols.[62,63] The etiological landscape of LGS is further complicated by its extreme heterogeneity; most identified genetic variants account for only a minute fraction of cases, whereas sporadic and de novo presentations continue to predominate despite the use of expanded genetic panels.[64,65] Phenotypic analyses indicate that LGS of unknown etiology shares the pathognomonic electroclinical core of secondary forms, yet it is frequently characterized by normal neurodevelopment prior to seizure onset and an absence of familial or environmental risk factors.[8] This persistent "idiopathic fraction" reinforces the notion of LGS as a complex, network-based disorder and emphasizes the necessity for continued research into its multifactorial pathogenesis.

4.4 | Comorbidities

Regrettably, the review point regarding comorbidities could not be addressed due to frequent underreporting within the

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reviewed literature. Furthermore, when documented, the data exhibited such significant heterogeneity that a conclusive analysis was precluded. This represents a substantial knowledge gap that demands further investigation. The discussion that follows on sleep, behavioral, and cognitive comorbidities is therefore drawn from the broader external literature rather than from findings of the present review, and is included to provide clinical context rather than as a synthesis of reviewed evidence. Comorbidities well recognized in LGS such as sleep disorders, behavioral disturbances, and cognitive impairment must be integrated into the global clinical assessment, as they often require targeted therapeutic interventions and must be carefully considered when establishing an ASM regimen. Current evidence indicates that cognitive impairment and behavioral disturbances could be considered defining features of LGS. Up to 95% of patients manifest moderate-to-severe ID, often compounded by a complex spectrum of neuropsychiatric comorbidities including hyperactivity, irritability, anxiety, and autism spectrum disorder. Moreover, the interplay between sleep disorders and systemic comorbidities significantly exacerbates the overall disease burden and functional decline in these individuals.[66,67] Evidence suggests that comorbidities in LGS frequently exert a more profound impact on quality of life and daily functioning than the seizures themselves, necessitating a robust, multidisciplinary management strategy. The pharmacological profile of ASMs must be carefully weighed against their potential to either exacerbate or ameliorate neurobehavioral symptoms. For instance, agents such as topiramate, zonisamide, levetiracetam, and perampanel are frequently associated with cognitive slowing or behavioral adverse effects. Conversely, treatments like cannabidiol, fenfluramine, lamotrigine, and rufinamide tend to support cognitive stability and behavioral modulation.[68–73] In addition, sleep disturbances—which significantly influence the electroclinical phenotype—must be addressed through individualized therapy, as specific medications can either disrupt or improve sleep architecture.[72,74] Expert consensus thus advocates for a holistic assessment that includes longitudinal monitoring of cognitive, behavioral, and sleep domains, ensuring that ASM selection optimizes both seizure control and neuropsychiatric resilience. This may contribute to the "devolution" of diagnostic criteria; for instance, sleep disorders can significantly alter sleep EEG patterns, and severe behavioral issues may hinder the compliance necessary for essential neurophysiological examinations.

4.5 | Limitations

A number of limitations of this scoping review should be acknowledged. First, the electronic search was restricted to a single database, MEDLINE via PubMed; although reference lists of included articles were screened to identify additional sources, the exclusion of databases such as Embase, Scopus, or Web of Science may have reduced the comprehensiveness of the search and could have led to missed eligible sources, especially if not indexed in MEDLINE. Second, the evidence base was dominated by case reports and case series (~78% of included sources), with only a minority of observational cohort studies; this predominance of low-level evidence should be borne in mind when interpreting patterns of diagnostic-criteria fulfillment or when considering the generalizability of proposed diagnostic approaches for adult patients, and likely reflects, at least in part, publication bias toward atypical or diagnostically challenging presentations. Third, across most charted variables, it was frequently not possible to determine with confidence whether a given diagnostic feature was genuinely absent in adulthood or simply not reported in the original publication. We have therefore consistently distinguished, wherever the data allowed, between features explicitly reported as absent and those not addressed by the source, but this distinction could not always be verified from the published full texts, especially in older or narratively written case reports. These limitations, taken together, support a cautious interpretation of our findings, and particularly of the observation that strict application of pediatric-centric diagnostic criteria may contribute to underdiagnosis in adulthood, which should be regarded as a hypothesis-generating observation warranting confirmation in prospective, adequately powered studies rather than a definitive causal claim.

5 | CONCLUSIONS

Given the clinical necessity of ensuring an accurate diagnosis of LGS at any age, this scoping review highlights the urgent need for a "longitudinal diagnostic mindset" in adult epileptology, considering diagnostic criteria that account for patient aging, symptoms and signs evolution, and the impact of long-term ASMs and other therapeutic interventions. The available evidence suggests that both clinical semiology (seizure types) and EEG patterns may undergo substantial modifications throughout the patient's life, with classical seizure types and EEG patterns becoming less evident, less consistently documented, or more difficult to capture in adulthood. Consequently, evaluating LGS in adulthood requires a broader perspective that moves beyond pediatric features and integrates historical seizure semiology, previous EEG documentation, treatment history, sleep EEG recordings, comorbidities, and caregiver-derived information. Of note, adult LGS features remain poorly and inconsistently documented in the literature, probably because they have rarely been

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investigated through systematic, adult-focused protocols. Future prospective studies are therefore needed to characterize seizure evolution, sleep-related EEG abnormalities, comorbidities, and treatment effects across adulthood, with the aim of developing age-adapted diagnostic frameworks. Such frameworks are essential to ensure access to appropriate therapeutic and care pathways, particularly in a population characterized by drug-resistant epilepsy, ID, substantial caregiver burden, and high psychosocial impact. See Box 1 for actionable points that can help move research and clinical practice on LGS forward.

BOX 1 Action points for clinical practice and research

In the clinic

- Think longitudinally: reconstruct the childhood picture from old records, previous EEG studies, treatment history, and caregiver accounts before diagnosing.
- "Not seen" is different from "absent": features may have evolved, been suppressed by treatment, or simply not been recorded.
- Chase the persistent markers: nocturnal tonic seizures and sleep diffuse fast rhythms; add sleep or video-EEG when a routine adult EEG is unrevealing.
- Diagnose on the whole electroclinical profile plus history, not on canonical EEG hallmarks alone.
- Use intellectual disability as the stable anchor across the lifespan.
- Fold comorbidities (sleep, behavior, cognition) into the assessment and into ASM choice.

For the field

- Expect the dissipation of classic seizure and EEG features with age: criteria built on pediatric data may miss adults.
- Move toward age-adapted diagnostic criteria, supported by prospective, adult-focused, longitudinal studies.

Designing and reporting future studies

- Run prospective, adult-focused studies, moving beyond single case reports toward large, multicenter cohorts.
- Follow the same patients longitudinally from childhood into adulthood, to capture how seizures and EEG actually evolve.
- Include sleep and video-EEG and track ASM and other treatments over time.
- State explicitly, for every feature, whether it was "absent" or "not sought/reported."
- Report seizure types and EEG features stratified by life stage (childhood vs adulthood) and by wake vs sleep state.
- Cover the full picture consistently: seizure semiology, EEG, diagnostic workup, comorbidities, and treatment.

AUTHOR CONTRIBUTIONS

Study conception and design: Fabio Perversi, Claudio Liguori, and Nicola Specchio. Literature search, title and abstract screening: Fabio Perversi and Claudio Liguori. Full-text screening and data extraction/charting: Sara Casciato, Emanuele Cerulli Irelli, Claudio Liguori, and Marco Perulli. Interpretation of results: all authors. Drafting of the manuscript: Fabio Perversi and Claudio Liguori. Critical revision of the manuscript for important intellectual content: all authors. Supervision: Claudio Liguori and Nicola Specchio. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

The authors thank Formedica srl for editorial and project management support.

FUNDING INFORMATION

Nicola Specchio was funded by the Italian Ministry of Health with Current Research Funds.

CONFLICT OF INTEREST STATEMENT

Claudio Liguori served as consultant or received research support from Takeda, Lundbeck, UCB, and Jazz Pharmaceuticals. No other conflicts of interest are present related to this work. Sara Casciato received speaker fees from Angelini Pharma and travel support from UCB Pharma, Angelini Pharma, Lusofarmaco, and Eisai outside the submitted work. Emanuele Cerulli Irelli received speaker fees from Angelini Pharma and travel support from UCB Pharma, Jazz Pharmaceuticals, Angelini Pharma, and Eisai outside the submitted work. Marco Perulli received travel support from Jazz Pharmaceuticals outside the submitted work. Fabio Perversi is a professional medical writer whose work on this manuscript was funded by Formedica srl; he met the authorship criteria and is therefore listed as an author rather than acknowledged, in accordance with Good Publication Practice (GPP 2022). Nicola Specchio has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Eisai, BioMarin, Livanova, and Sanofi; has served as an investigator for Zogenix, Marinus, BioMarin, UCB, and Roche. None of the authors has any conflict of interest to disclose that is directly related to the content of this manuscript.

DATA AVAILABILITY STATEMENT

All data extracted and analyzed during this scoping review are included in the present article and in the Supporting

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Information files (Appendices S2 and S3). The complete patient-level analysis dataset (seizure semiology, EEG, etiology, and diagnostic workup) is provided in Appendix S4, and the study list and source characteristics in Tables S1 and S2. Further information can be obtained from the corresponding author upon reasonable request.

ETHICS APPROVAL

Ethics committee approval was not required for this study, as it consists exclusively of a review of previously published, peer-reviewed literature and does not involve any new data collection from human subjects.

PATIENT CONSENT

Not applicable. This work is a scoping review of published literature and does not involve patients or new individual-level data.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

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CLINICAL TRIAL REGISTRATION

Not applicable. This is a scoping review of published literature and does not constitute a clinical trial.

EPILEPSIA ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The work described is original, has not been published previously (in whole or in part, except in abstract form), is not under consideration for publication elsewhere, and all authors have read and approved the final version of the manuscript.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE MANUSCRIPT PREPARATION PROCESS

During the preparation of this work, the authors used ChatGPT (OpenAI) to support the development of the database search strings and to assist with the organization of extracted data; ChatGPT and Claude (Anthropic) were used for language editing, manuscript editing, and submission preparation. During peer review, Claude was used to support the extraction of individual patient data and to address minor comments. Generative AI was not used to interpret data, generate scientific content, or draw conclusions. After using these tools, the authors reviewed and edited the content as needed and they take full responsibility for the content of the publication.

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How to cite this article: Liguori C, Casciato S, Cerulli Irelli E, Perulli M, Perversi F, Specchio N. Diagnosing Lennox–Gastaut syndrome in adulthood: A scoping review of diagnostic challenges and age-related electroclinical evolution. Epilepsia. 2026;00:1–17. https://doi.org/10.1002/epi.70489

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