ИНФОРМАЦИЯ ЗА:
Наименование на заболяването
Синдром на Lennox-Gastaut (LGS)
Определение на заболяването
Рядка, тежка ранна епилептична енцефалопатия, характеризираща се с триада от интелектуално увреждане, множество видове пристъпи и типични електроенцефалографски (ЕЕГ) аномалии. При 70-80% от децата е симптоматичен, а при 30-50% от децата със синдром на West преминават в LGS.
Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)
G40.4
Код на заболяването по Orpha code
ORPHA:2382
Епидемиологични данни за заболяването в Република България
Разпространението на LGS е 5% от пациентите с епилепсия от всички възрасти и около 10% от пациентите с епилепсия под 15 годишна възраст. Най-често се среща при деца на възраст 2-7 г. (диапазон 1 – 14 г.). Прогнозата е неблагоприятна – заболяването се характеризира с висока смъртност (5%), интелектуален дефицит при 85 - 95% и персистиране на припадъците при 78% до 96%, най-чести след пубертета са нощните тонични пристъпи.
В т.ч. научни публикации от последните пет години и приложена
НСЦРЛП (2023). Фармакотерапевтично ръководство за лечение на неврологични заболявания. Достъпно на: https://ncpr.bg/images/Naredbi/2023/%D0%9F%D1%80%D0%B8%D1%82%D1%83%D1%80
Епидемиологични данни за заболяването в Европейския съюз

Епидемиологичните данни за разпространението на заболяването в Европейския съюз са оскъдни. Болестността варира от 4,2-60,8 на 100 000 при вероятен LGS, и между 2,9-28 на 100 000 при потвърдена диагноза.
Резултати от големи епидемиологични проучвания показват, че разпространението на вероятен LGS от 39,2 на 100 000 в Германия до 6,5 на 100 000 за потвърдена диагноза. Докладвано е разпространение от 10 на 100 000 в Естония, 2,1 -28 на 100 000 във Финландия и 20 на 100 000 в Швеция.
Ретроспективен анализ на застрахователни искове от Германия отчита смъртност (процентът на починалите пациенти, разделен на общия брой пациенти в проучването) за 10-годишния период на проучването от 10,01% за пациентите според широката дефиниция на LGS и 2,88% за тясната дефиниция спрямо 0,01% за контролната популация, съответстваща на възрастта и пола ($p < 0,001$).

В т.ч. научни публикации от последните пет години и приложена

1. Strzelczyk A, Zuberi SM, Striano P, Rosenow F, Schubert-Bast S. The burden of illness in Lennox-Gastaut syndrome: a systematic literature review. Orphanet J Rare Dis. 2023 Mar 1;18(1):42. doi: 10.1186/s13023-023-02626-4. PMID: 36859290; PMCID: PMC9979426.
2. Strzelczyk A, Schubert-Bast S, Simon A, et al. Epidemiology, healthcare resource use, and mortality in patients with probable Lennox–Gastaut syndrome: a population-based study on German health insurance data. Epilepsy Behav. 2021;115: 107647

Оценка на съответствието на заболяването с дефиницията за рядко заболяване съгласно § 1, т. 42 от допълнителните разпоредби на Закона за здравето

LGS отговаря на критериите за рядко заболяване, съгласно изискванията на Закона за здравето (разпространение не повече от 5 на 10 000 от населението на Европейския съюз).

Критерии за диагностициране на заболяването

Критерии за типичния LGS са:

1. Полиморфни, терапевтично резистентни пристъпи - тонични, атонични, атипични абсанси (2 от 3 типа). Възможни са и ГТКП, прости фокални и миоклонични пристъпи.
2. ЕЕГ с генерализирани разряди от бавни комплекси острие-бавна вълна (< 3 Hz) в будност и генерализирани бързи ритми (≥ 10 Hz) по време на сън.
3. Увредени интелектуални функции - когнитивни, поведение.

Най-подходящите диференциални диагнози включват миоклонична атонична епилепсия, синдром на Драве и фокални епилепсии с вторична двустранна синхронизация.

Етиологията е хетерогенна и включва органични мозъчни увреждания при пренатални или перинатални инфаркти, инфекции на централната нервна система, травматични лезии и кортикални малформации; метаболитни нарушения; идентифицирани генетични de-novo мутации има при около 18-20% от случаите, като например в GABRB3 (15q12), CHD2 (15q26.1) DNM1 (9q34.11), SCN1A (2q24.3), MAPK10 (4q21.3), CUX2 (12q24.11-q24.12) и CACNA1A (19p13.13).

В т.ч. научни публикации от последните пет години и приложена

1. НСЦРЛПП (2023). Фармакотерапевтично ръководство за лечение на неврологични заболявания. Достъпно на: https://ncpr.bg/images/Naredbi/2023/%D0%9F%D1%80%D0%B8%D1%82%D1%83%D1%80%D0%BA%D0%B0.pdf
2. Божинова В. Диагностика и нови възможности за лечение на детските епилептични енцефалопатии- синдром на Dravet и синдром на Lennox-Gastaut. GP MEDIC, 2023, 5(5);10-16.
3. Montouris G, Aboumatar S, Burdette D, Kothare S, Kuzniecky R, Rosenfeld W, Chung S. Expert opinion: Proposed diagnostic and treatment algorithms for Lennox-Gastaut syndrome in adult patients. Epilepsy Behav. 2020 Sep;110:107146. doi: 10.1016/j.yebeh.2020.107146. Epub 2020 Jun 18. PMID: 32563898.
4. Nelson JA, Knupp KG. Lennox-Gastaut Syndrome: Current Treatments, Novel Therapeutics, and Future Directions. Neurotherapeutics. 2023 Sep;20(5):1255-1262. doi: 10.1007/s13311-023-01397-x. Epub 2023 Jun 23. PMID: 37353676; PMCID:

Алгоритми за диагностициране на заболяването

Наличието на типични клинични характеристики и ЕЕГ отклонения потвърждава диагнозата. Магнитно-резонансната томография установява структурни аномалии при повече от две трети от пациентите.

Генетичните изследвания помагат за разграничаване на LGS от други болестни единици и трябва да се извършват в избрани случаи (напр. съмнение за туберозна склероза комплекс, късна детска невронална цероидна липофусциноза, синдром на пръстеновидната хромозома 20).

В т.ч. научни публикации от последните пет години и приложена

1. Божинова В. Диагностика и нови възможности за лечение на детските епилептични енцефалопатии- синдром на Dravet и синдром на Lennox-Gastaut. GP MEDIC, 2023, 5(5);10-16.
2. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, Guerreiro M, Gwer S, Zuberi SM, Wilmshurst JM, Yozawitz E, Pressler R, Hirsch E, Wiebe S, Cross HJ, Perucca E, Moshé SL, Tinuper P, Auvin S. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022 Jun;63(6):1398-1442. doi: 10.1111/epi.17241. Epub 2022 May 3. PMID: 35503717.
3. Montouris G, Aboumatar S, Burdette D, Kothare S, Kuzniecky R, Rosenfeld W, Chung S. Expert opinion: Proposed diagnostic and treatment algorithms for Lennox-Gastaut syndrome in adult patients. Epilepsy Behav. 2020 Sep;110:107146. doi: 10.1016/j.yebeh.2020.107146. Epub 2020 Jun 18. PMID: 32563898.
4. НСЦРЛПП (2023). Фармакотерапевтично ръководство за лечение на неврологични заболявания. Достъпно на: https://ncpr.bg/images/Naredbi/2023/%D0%9F%D1%80%D0%B8%D1%82%D1%83%D1%80%D0%BA%D0%B0.pdf

Алгоритми за лечение на заболяването

Пристъпите при LGS се лекуват трудно и лечението трябва да има за цел да подобри качеството на живот и да намали тежестта на дроп-атаките. Антиепилептични лекарства на първи избор са натриевият валпроат lamotrigine (LTG), topiramate (TPM). Като алтернативи се прилагат ethosuximide (ESM), levetiracetam (LEV), carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), clonazepam, rufinamide, zonisamide (ZNZ), felbamate. Cannabidiol в комбинация с Clobazam според преобладаващите пристъпи в дадения момент; курсове с АСТН /кортикостероиди. При LGS се прилага и хирургия с резекция на лезии и калозотомия при чести и травматизиращи дроп-атаки.

В т.ч. научни публикации от последните пет години и приложена

1. Александрова И, Божинова В. Терапия при синдром на Lennox-Gastraux. 2017, 19(2):24-30.
2. НСЦРЛП (2023). Фармакотерапевтично ръководство за лечение на неврологични заболявания. Достъпно на: https://ncpr.bg/images/Naredbi/2023/%D0%9F%D1%80%D0%B8%D1%82%D1%83%D1%80%D0%BA%D0%B0.pdf
3. Nelson JA, Knupp KG. Lennox-Gastaut Syndrome: Current Treatments, Novel Therapeutics, and Future Directions. Neurotherapeutics. 2023 Sep;20(5):1255-1262. doi: 10.1007/s13311-023-01397-x. Epub 2023 Jun 23. PMID: 37353676; PMCID: PMC10480363.
4. Samanta D. Management of Lennox-Gastaut syndrome beyond childhood: A comprehensive review. Epilepsy Behav. 2021 Jan;114(Pt A):107612. doi: 10.1016/j.yebeh.2020.107612. Epub 2020 Nov 24. PMID: 33243685.

Алгоритми за проследяване на заболяването

- Неврологично изследване – периодично
- ЕЕГ и периодичен ЕЕГ контрол в зависимост от терапевтичния ефект, при терапевтично овладени пристъпи - през 6 месеца. ЕЕГ е необходима за установяване вида на епилептичните пристъпи и за доказване на фотопароксизмален отговор. ЕЕГ по време на сън се извършва при индикации при деца и млади хора след сънна депривация или употреба на melatonin. Видео-ЕЕГ е необходима при пациенти с диагностични затруднения.

В т.ч. научни публикации от последните пет години и приложена

1. НСЦРЛП (2023). Фармакотерапевтично ръководство за лечение на неврологични заболявания. Достъпно на: https://ncpr.bg/images/Naredbi/2023/%D0%9F%D1%80%D0%B8%D1%82%D1%83%D1%80%D0%BA%D0%B0.pdf
2. Nelson JA, Knupp KG. Lennox-Gastaut Syndrome: Current Treatments, Novel Therapeutics, and Future Directions. Neurotherapeutics. 2023 Sep;20(5):1255-1262. doi: 10.1007/s13311-023-01397-x. Epub 2023 Jun 23. PMID: 37353676; PMCID: PMC10480363.

Алгоритми за рехабилитация на заболяването

С течение на времето се наблюдава забавяне на развитието, плато или регресия, които завършват с умерена до тежка интелектуална недостатъчност при > 90 % от пациентите. Поведенчески разстройства като хиперактивност, агресия, аутистичен спектър и разстройства на съня са често срещани в детството и юношеството.
Рехабилитационните терапии за съпътстващи заболявания и дългосрочни резултати включват физическа, професионална, речева и когнитивна терапия, поведенческа терапия, както и специално образование и подкрепа от психолог.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, Guerreiro M, Gwer S, Zuberi SM, Wilmshurst JM, Yozawitz E, Pressler R, Hirsch E, Wiebe S, Cross HJ, Perucca E, Moshé SL, Tinuper P, Auvin S. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022 Jun;63(6):1398-1442. doi: 10.1111/epi.17241. Epub 2022 May 3. PMID: 35503717.
2. Samanta D. Management of Lennox-Gastaut syndrome beyond childhood: A comprehensive review. Epilepsy Behav. 2021 Jan;114(Pt A):107612. doi: 10.1016/j.yebeh.2020.107612. Epub 2020 Nov 24. PMID: 33243685.

Необходими дейности за профилактика на заболяването (ако такива са приложими)

Не е приложимо.

В т.ч. научни публикации от последните пет години и приложена

Не е приложимо.

Предложения за организация на медицинското обслужване на пациентите и за финансиране на съответните дейности, съобразени с действащата в страната нормативна уредба

В България диагностиката и проследяването на болните със синдром на Lennox-Gastaut се извършва в рамките на клинична пътека №62. „Епилепсия и епилептични пристъпи“, а в извънболничната помощ от невролози и детски невролози.

Клинична пътека №62. „Епилепсия и епилептични пристъпи“ включва диагнозите по МКБ-10 „G40.6. Grand mal припадъци (с малки припадъци [petit mal] или без тях), неуточнени“ и „G40.7. Малки припадъци [petit mal], без припадъци grand mal, неуточнени“, като отделните видове епилептични пристъпи, участващи като комбинации

Пациентът със синдром на Lennox-Gastaut се диагностицира на базата на неврологично изследване, ЕЕГ при характерна за синдрома находка и невропсихологично изследване и се прилага антиепилептично лечение според актуалния Консенсус за диагностика и лечение на епилепсиите и антиепилептичните сидроми, 2023 г и Фармакотерапевтичното ръководство за лечение на неврологичните заболявания, 2023 г.

- Критерии за типичния LGS, според които той се диагностицира са: 1. Полиморфни, терапевтично резистентни пристъпи - тонични, атонични, атипични абсанси (2 от 3 типа). Възможни са и епилептични спазми след синдром на West, ГТКП, прости фокални и миоклонични пристъпи. 2. ЕЕГ с генерализирани разряди от бавни комплекси острие - бавна вълна (< 3 Hz) в будност и генерализирани бързи ритми (≥ 10 Hz) по време на сън. 3. Увредени интелектуални функции - когнитивни, поведение.
- Лечение. Не е възможен пълен контрол на пристъпите. Антигърчови лекарства (АГЛ) на първи избор са Валпроат (VPA), Ламотрижин (LTG), Топирамат (TPM), алтернативни – Етосукцимид (ESM), Леветирацетам (LEV), Карбамазепин (CBZ), Фенобарбитал (PB), Phenytoin (PHT), Clonazepam, Rufinamide, Зонизамид (ZNS), Cannabidiol в комбинация с Clobazam, Fenfluramine според преобладаващите пристъпи в дадения момент; курсове с АСТН /кортикостероиди. При LGS се прилага и хирургия с резекция на лезии, калозотомия и вагус-нерв-стимулация при чести и травматизиращи дроп атаки.

1. НСЦРЛП (2023). Фармакотерапевтично ръководство за лечение на неврологични заболявания. Достъпно на: https://ncpr.bg/images/Naredbi/2023/%D0%9F%D1%80%D0%B8%D1%82%D1%83%D1%80%D0%BA%D0%B0.pdf
2. Божинова В. Диагностика и нови възможности за лечение на детските епилептични енцефалопатии- синдром на Dravet и синдром на Lennox-Gastaut. GP MEDIC, 2023, 5(5);10-16.
3. Александрова И, Божинова В. Терапия при синдром на Lennox-Gastraux. 2017, 19(2):24-30.

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CURRENT PERSPECTIVES

Lennox-Gastaut Syndrome: Current Treatments, Novel Therapeutics, and Future Directions

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Abstract

Lennox-Gastaut syndrome is a severe drug-resistant developmental and epileptic encephalopathy with slow spike and wave on EEG (DEE-SSW) composing about 1–2% of epilepsy patients. Seizures in DEE-SSW are caused by a variety of etiologies, and there is a large unmet treatment need as seizures are usually treatment-resistant and individuals are often unable to function independently. The updated definition by the International League Against Epilepsy has established formal diagnostic criteria allowing for more uniform diagnosis. This article provides a review of typical medication management and treatment strategies, including new and developing surgical approaches. Future directions in treatment include expanding genetic testing with the potential for gene therapy and continuously improving surgical options with the goal to prevent progression to DEE-SSW.

Keywords Lennox-Gastaut syndrome · Developmental and epileptic encephalopathy · Anti-seizure medication · Novel therapeutics · Review

Introduction

Lennox-Gastaut syndrome is a severe drug-resistant developmental and epileptic encephalopathy (DEE-SSW), consisting of numerous underlying etiologies and as such has a large unmet treatment need. About 1–10% of children with epilepsy have transitioned to DEE-SSW, and it represents around 1–2% of all epilepsy patients [1]. This epilepsy syndrome was first described in 1966 by Gastaut as a severe type of childhood epilepsy, intractable to treatment, and characterized by frequent tonic seizures, atypical absence seizures, intellectual disability, and slow spike-and-wave discharges [2]. He termed the syndrome "childhood epileptic encephalopathy with diffuse slow spike-waves" or "Lennox syndrome" [2]. The ILAE first recognized this syndrome in 1989, further describing the condition, though has only recently established formal diagnostic criteria [3, 4]. The goal of this review is to provide an update regarding the new diagnostic criteria and new and developing treatments of this syndrome.

Definition

The ILAE has recently published updated criteria to define DEE-SSW as a syndrome characterized by (1) multiple types of drug-resistant seizures with onset prior to 18 years (one of which must include tonic seizures); (2) cognitive and potentially behavioral impairments, not necessarily present at seizure onset; and (3) diffuse slow spike-and-wave (SSW) and generalized paroxysmal fast activity (PFA) on EEG [3]. There has been evolution in the definition for DEE-SSW compared to the prior definition from the ILAE in 1989, in which DEE-SSW was described as an epilepsy manifesting in children from ages 1–8 years with the most common seizure types reported as tonic-axial, atonic, and absence seizures, though other types such as myoclonic, GTC, or focal seizures were also described [4]. Tonic seizures were not considered mandatory. EEG criteria are now more specific, with the prior definition described as usually having slow spike and wave (< 3 Hz), now updated to ≤ 2.5 Hz in the 2022 definition. In addition, the EEG was previously described as having bursts of fast rhythms nearing 10 Hz and is now defined as diffuse or bilateral fast activity (≥ 10 Hz)

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in sleep. Both SSW and PFA are now requirements in the current definition, while SSW was mentioned as a usual characteristic in the prior definition. In addition, the prior definition reported that there was intellectual disability (previously defined as mental retardation) and mostly unfavorable development, though this was not a clear criterion. The updated definition has also expanded to include individuals with seizure onset prior to 18 years of age, allowing more individuals to meet diagnostic criteria, rather than the prior definition's description of seizure onset between 1 and 8 years of age [3, 4].

Existing ASMs and Current Treatment Strategies

There are currently seven anti-seizure medications (ASMs) with an FDA approval to treat DEE-SSW as adjunctive treatment: felbamate, lamotrigine, topiramate, rufinamide, clobazam, and the more newly approved ASMs fenfluramine and cannabidiol.

The American Academy of Neurology (AAN), in conjunction with the American Epilepsy Society, previously reported that felbamate is effective for adjunctive treatment in DEE-SSW in 1999, though caution was needed regarding its use given the possible side effects of aplastic anemia and liver failure [5]. In an updated practice guideline in 2004, the group reported that lamotrigine and topiramate were found to be effective in treating drop attacks in DEE-SSW based on level A evidence [6]. It has most recently revised its recommendations for treatment-resistant epilepsy in 2018, with the recommendation that rufinamide was an effective add-on treatment for DEE-SSW based on 2 class 1 studies [7, 8] with level A evidence [9]. It also reports that clobazam is probably effective as add-on therapy for DEE-SSW based on 2 class II studies [10, 11] with level B evidence [9].

Both clobazam and rufinamide have been found to be protective against additional seizure types in addition to motor seizures associated with a drop. The trials for clobazam did find that at the high (1 mg/kg/day) dose, there was a significant reduction in both drop and non-drop seizures [10, 11]. Rufinamide was found to significantly reduce all seizure types ($p=0.0015$), have a greater reduction in absence and atypical absence seizures ($p=0.0222$), reduce atonic seizures ($p=0.0125$) in a double-blind, randomized, placebo-controlled trial in patients with DEE-SSW [7]. In addition, rufinamide was found to significantly reduce the frequency of tonic seizures ($p=0.031$), myoclonic seizures ($p=0.021$), and partial seizures ($p=0.025$) compared with placebo in another multi-center placebo-controlled trial [8].

Anti-seizure medications (ASMs) which may also be commonly used may include valproate, levetiracetam, zonisamide, ethosuximide, perampanel, and brivaracetam, though they do not currently have an FDA approval [12, 13]. In fact, recent clinical trials for DEE-SSW found levetiracetam, valproate, topiramate, clobazam, lamotrigine, and rufinamide [14, 15] as the most frequent concomitant medications for enrolled patients reflecting real-world evidence for use of these ASMs.

According to the DEE-SSW Transition of Care advisory board meeting in 2017, ASMs recommended for the treatment of DEE-SSW were divided into tiers. Tier 1 included the FDA approved ASMs for DEE-SSW, included clobazam, lamotrigine, rufinamide, topiramate, and cannabidiol [12]. Tier 2 was composed of ASMs commonly used, including levetiracetam, perampanel, and zonisamide. Tier 3 represents the ASMs which are less frequently used in DEE-SSW treatment and with limited data to support efficacy or potential for side effects, including felbamate, lacosamide, brivaracetam, and cenobamate [12].

An expert panel on management of DEE-SSW in 2017 reports that upon new diagnosis of DEE-SSW, the first ASM should be valproate [13]. If seizures persist, lamotrigine should be added. If seizures are still occurring, then rufinamide should be added, followed by attempts to wean the valproate or the lamotrigine as there is no evidence of the effectiveness of more than 2 ASMs in combination, other than unnecessarily exposing the patient to possible side effects [13] (Table 1).

Epidiolex, a highly purified form of cannabidiol, was FDA approved for treatment of DEE-SSW in 2018 after the results of two double-blind, placebo-controlled trials [14, 15]. In the first study, 225 patients aged 2–55 years with DEE-SSW with 2 or more drop seizures (defined as seizures associated with a fall) per week were given doses of 20 mg/kg/day, 10 mg/kg/day, and placebo. After 14 weeks of treatment, the 20 mg/kg/day group had a 41.9% reduction in drop seizures ($p=0.005$ compared to placebo), 10 mg/kg/day group had a 37.2% reduction ($p=0.002$ compared to placebo), and placebo had 17.2% [14]. The median percent reduction of frequency of all seizures was 38.4% in the 20 mg/kg/day cannabidiol group ($p=0.009$), 36.4% in the 10-mg cannabidiol group ($p=0.002$), and 18.5% in the placebo group. Fourteen patients developed elevated liver aminotransferase concentrations [14]. In the second phase III trial, 171 patients with the same seizure frequency criteria experienced a median percentage reduction in drop seizure frequency of 43.9% in the 20 mg/kg/day group compared to 21.8% in the placebo group ($p=0.0135$). The most common side effects were diarrhea, decreased appetite, somnolence, vomiting, and pyrexia [15].

Fenfluramine was recently approved in 2022 for treatment of DEE-SSW after approval for treatment of Dravet syndrome in 2020 based on two clinical trials [16, 17]. The multi-center, double-blind, placebo-controlled, parallel group phase 3 trial for DEE-SSW consisted of 263 patients [18]. Patients must have experienced 2 or more seizures associated with a fall (termed "drop seizures" in the

Table 1 Anti-seizure medications

ASM	FDA approval for DEE-SSW	Common adverse reactions	Contra-indications	Lab monitoring	Special considerations	Notable interactions
Brivaracetam	No	Psychiatric disturbance Sedation Dizziness	Hypersensitivity to brivaracetam or component of formulation	Baseline CBC with differential Liver function Renal function Assessment for depression and suicidality	Consider if LEV was effective but had to discontinue due to behavioral side effects	None
Cenobamate	No	Maculopapular rash DRESS (drug reaction with eosinophilia and systemic symptoms) Shortened QTc interval Fatigue Dizziness	Familial short QT syndrome Hypersensitivity to cenobamate or component of formulation	Liver function Potassium as indicated Assessment for depression and suicidality	None	Caution with additional sodium channel blockers due to additive side effects and arrhythmia risk Moderately inhibits CYP2C19 (clobazam levels increased)
Clobazam	Yes	Drowsiness Drooling Aggressive behavior Irritability	Hypersensitivity to clobazam or component of formulation	CBC Liver function Renal function Assessment for depression and suicidality	Metabolized by CYP2C19 and CYP3A4	Levels may be increased with concomitant epidiolex, felbamate, cenobamate
Epidiolex	Yes	Weight loss Decreased appetite Diarrhea Vomiting	Hypersensitivity to epidiolex or component of formulation	Liver function testing at baseline, 1 month, 3 months, 6 months of initiation. Baseline CBC Assessment for depression/suicidality	Risk of transaminitis Inhibits CYP2C19	May increase clobazam levels
Felbamate	Yes	Drowsiness Weight loss	Hypersensitivity to felbamate, carbamates, history of blood dyscrasia or hepatic dysfunction	CBC with diff Reticulocyte count Liver function At baseline then every 2 weeks for the first month, once monthly for 3 months, then can gradually decrease frequency	Black box warning for aplastic anemia and liver failure Inhibits 2C19 (weak)	May increase clobazam levels
Fenfluramine	Yes	Elevated blood pressure Pulmonary hypertension Serotonin syndrome Valvular heart disease Weight loss CNS depression	Hypersensitivity to fenfluramine or component of formulation Concomitant use within 14 days of a monoamine oxidase inhibitor	None	REMs program, baseline echocardiogram and every 6 months required	Clobazam may increase levels; limit dose when used in conjunction with stiripentol and clobazam
Lamotrigine	Yes	Aseptic meningitis Blood dyscrasias Hypersensitivity reactions	Hypersensitivity to lamotrigine or component of formulation	EKG in patients with known cardiac disease or major risk factors Consider CBC and renal and hepatic function testing	Slow initial titration due to Stevens Johnson risk	Valproate inhibits metabolism, decrease dose by ½ when adding concomitant VPA

Table 1 (continued)

ASM	FDA approval for DEE-SSW	Common adverse reactions	Contra-indications	Lab monitoring	Special considerations	Notable interactions
Levetiracetam	No	Behavioral problems and psychotic symptoms Drowsiness Delayed Hypersensitivity reactions Elevated blood pressure	Hypersensitivity to levetiracetam or component of formulation	Psychiatric and behavioral disturbance Renal function CBC Diastolic blood pressure in children < 4 years	None	None
Perampanel	No	Dizziness Aggression Vertigo Drowsiness	Hypersensitivity to perampanel or component of formulation	Renal function Hepatic function Assess for psychiatric disturbance	Boxed warning for worsening of aggression, anger, homicidal ideation, within the first 6 weeks with or without prior psychiatric history	None
Rufinamide	Yes	Shortened QT interval Nausea Dizziness Drowsiness Headache	Familial short QT syndrome Hypersensitivity to rufinamide or component of formulation	CBC Signs and symptoms of suicidality Consider EKG with concurrent medications which can shorten QT interval	None	None
Topiramate	Yes	Cognitive dysfunction Metabolic acidosis Nephrolithiasis Ocular effects Oligohidrosis Weight loss	Hypersensitivity to topiramate or component of formulation	Electrolytes Ammonia in patients with unexplained lethargy Intraocular pressure Kidney stones	None	None
Valproate	No	Alopecia Abdominal pain Thrombocytopenia Dizziness	Hypersensitivity to valproate or component of formulation Hepatic disease or impairment Urea cycle disorders Blood dyscrasias	Liver enzymes Ammonia with mental status change CBC Lipase with persistent vomiting	Avoid use in women of childbearing age if possible	Inhibits metabolism of lamotrigine
Zonisamide	No	Anorexia Dizziness Drowsiness	Hypersensitivity to zonisamide, sulfonamides, or component of formulation	Electrolytes Ammonia in patients with unexplained lethargy	None	

study) per week during a baseline period and were treated for 12 weeks with a 2-week dose titration with groups randomized to placebo, 0.7 mg/kg/day dose, or 0.2 mg/kg/day. Patients in the 0.7 mg/kg/day group achieved a 19.9 percentage point drop in seizures ($p=0.001$) compared to placebo, the primary endpoint. Patients in the 0.2 mg/kg/day group experienced a 10.5 percentage point reduction in seizures ($p=0.09$). Generalized tonic clonic seizures (GTC) were the seizure type most reduced with fenfluramine treatment, with a 45.7% reduction in the 0.7 mg/kg/day group ($p=0.001$) and a 58.2% reduction in the 0.2 mg/kg/day group ($p<0.001$) [18].

Perampanel had been studied in a small case study ($n=13$) of DEE-SSW patients treated with adjunctive therapy, and at a 10-month follow-up, 69% were found to have a $\geq 50\%$ reduction in total seizure frequency [19]. In addition, it had briefly been studied as a potential adjunctive therapy, though the trial was discontinued due to lack of recruitment [20].

Novel Therapeutics

There are several new anti-seizure medications that are currently undergoing clinical trials. While there may be further treatment options for the DEE-SSW patient population, this is further evidence of the unmet treatment need.

There was a recent case series in 2022 describing four patients with DEE-SSW who were treated with the newer anti-seizure medication cenobamate, which was FDA-approved for focal seizures in 2019 [21]. Focal seizures may be a predominant seizure type in some patients with DEE-SSW. The case series followed 4 patients with DEE-SSW who are treated with cenobamate, a drug with a novel mechanism consisting of inhibiting persistent currents of voltage-gated sodium channels and acting as a positive allosteric modulator of $GABA_A$ receptor-binding sites. Four adults with a diagnosis of DEE-SSW and history of focal seizures and drug resistance were included, and after treatment with cenobamate for 12 months, they experienced between a 25 and 74% reduction in seizures, two of which experienced a greater than 50% reduction in seizures [21].

The drug soticlestat is a promising first-in-class selective inhibitor of cholesterol 24-hydroxylase (CH24H). CH24H functions to catalyze the conversion from cholesterol to 24S-hydroxycholesterol and is mainly expressed in neurons [22]. 24S-hydroxycholesterol is thought to be toxic, leading to oxidative stress and inflammation. In animal models, soticlestat has been shown to decrease glutamate levels and lead to reduced hyperexcitability [22]. A phase 2, randomized, double-bind, placebo-controlled study evaluated soticlestat in children 2–17 years with either Dravet syndrome (DS) or DEE-SSW [23]. Children with DEE-SSW were required to have at least 4 or more seizures associated with a fall (drop seizure) per month to enroll. One hundred and thirty-nine children were recruited into study (51 DS, 88 DEE-SSW). After an 8-week dose titration period and 12-week maintenance period, median reductions in convulsive and drop seizures approached significance 17.08% ($p=0.116$) in children with DEE-SSW. The most common side effects were lethargy and constipation [23]. As the phase 2 trial was potentially underpowered in DEE-SSW patients, soticlestat is currently undergoing a phase 3 international, double-blind, placebo-controlled phase 3 trial in DEE-SSW with results expected in 2023/2024.

Carisbamate is currently being studied for treatment of DEE-SSW, and in the recruitment stage of a phase 3 clinical trial. This medication has been shown to inhibit voltage-gated sodium channels expressed in rat hippocampal neurons [24] in addition to reducing pre-synaptic glutamate levels in rat dentate gyrus [25]. This drug had previously been trialed in patients over 16 years of age with intractable focal epilepsy though results were of mixed significance [26–28]. Carisbamate is currently undergoing in a phase I trial in children and adults with DEE-SSW [29].

Lorcaserin is a novel therapeutic drug with a similar mechanism of action to fenfluramine, working as a selective serotonin receptor (5-HT2C) agonist for receptors located in the central nervous system. It has been shown to decrease the frequency of non-convulsive seizures in a rat model [30]. There is a retrospective case series without a control group in a small multi-center cohort of children and young adults with drug-resistant focal epilepsy ($n=3$), intractable generalized epilepsies ($n=3$) including Dravet syndrome ($n=20$) and DEE-SSW ($n=9$) [31]. Lorcaserin was associated with a reduction of motor seizures in all groups: 50% in DEE-SSW, 43% in Dravet syndrome, and 23% in drug-resistant/generalized epilepsies. Major side effects (reported by > 10 patients) were decreased appetite, decreased attentiveness, and weight loss [31]. It is currently in phase 3 clinical trials for Dravet syndrome.

Surgical Approaches

In addition to anti-seizure medications, there are also promising surgical approaches to offer other than the existing treatments of VNS and corpus callosotomy. Deep brain simulation (DBS) of the anterior nucleus of the thalamus for treatment of focal onset seizures was approved in 2018 after the results of the SANTE trial [32]. However, there is a growing body of evidence that chronic stimulation of the centromedian (CM) nucleus of the thalamus may be efficacious in reducing seizures in DEE-SSW. The CM represents a main source of input to the striatum, in addition to having connections to the brainstem and cortex, and plays a role in attention, arousal, and coordination [33]. In addition, the

centromedian parafascicular nucleus has been shown to be involved early on the generation of generalized spike wave discharges, preceding involvement of anterior nucleus of the thalamus, which is thought to have a role in propagation of generalized-onset seizures [34]. Given that the centromedian parafascicular nucleus has projections to the bilateral frontocentral cortices, the area of maximal prominence where generalized discharges are noted on scalp EEG, and is activated early on in generalized spike wave discharges, this nucleus is thought to either drive, or have an important early role, in the propagation of generalized onset seizures [34].

A case series from 2006 evaluated 13 patients with DEE-SSW from 4 to 22 years of age who underwent bilateral CM implantation and found that overall seizure reduction was 80% at 18 months of follow-up [35].

The ESTEL trial, a prospective, double-blind, randomized trial of deep brain stimulation (DBS) in the bilateral centromedian (CM) nuclei of the thalamus in patients with DEE-SSW was recently completed [36]. From years 2017–2019, 19 young adults with DEE-SSW underwent implantation of DBS device to bilateral CM nuclei, 10 in the treatment and 9 in the control group.

Three months after implantation, half of patients received 3 months of stimulation as part of the blinded phase, and then all received 3 months of stimulation. The DBS stimulation settings were slightly slower than the SANTE trial (goal voltage of 2.5 V, while SANTE trial voltage began at 5 V and could increase to 7.5 V). The remaining parameters of pulse width of 90 μs, 145 Hz frequency (though in SANTE could increase to 185 Hz), and cycling "on" at 1 min and "off" at 5 min were the same as the SANTE trial [32]. The primary outcome was the proportion of participants with ≥ 50% reduction in diary-recorded seizures in the last month of the blinded period, which was achieved by 50% of the stimulation group ($n=5$) compared with 22% ($n=2$) of controls ($p=0.25$). The secondary outcome was the proportion of patients with a ≥ 50% reduction in electrographic seizures on 24-h ambulatory EEG recording done at the end of the third month of the blinded period, which was 89% ($n=8$) in the stimulation group compared with none of the controls ($p=0.05$). In addition, after all patients entered the treatment group, subjective reports from parents/caregivers of increased alertness occurred in 95% (18/19) and feelings overall benefit were reported by 79% (15/19) [36]. This study was only powered to find a large difference (at least 70% seizure reduction with stimulation) and given the relatively low number of subjects ($n=19$), it is possible that a repeat study with larger numbers of patients, there may be statistically significant results [36].

While limited, there is growing evidence for the use of responsive neurostimulation (RNS) in DEE-SSW with promising results. One case series describes two patients with clear benefit from RNS implanted into the bilateral centromedian nuclei, with a 70–95% seizure reduction 8–12 months after implantation [37].

There is currently a phase II study in recruitment to evaluate RNS in DEE-SSW patients with the plan to implant two neurostimulators with depth leads in the bilateral CM in addition to cortical or strip leads targeting the prefrontal cortex [38].

Future Directions

In addition to newly developing ASMs and expanding surgical options, the importance of continuing the pursuit of identifying the underlying etiology for the patient's epilepsy cannot be understated. With the continued development and widespread use of genetic testing such as whole exome and whole genome sequencing, there may be more targeted treatments in the future, such as gene therapy [39].

In summary, there are promising new treatments of DEE-SSW in both pharmacologic realm and with the advancement of neurostimulation, including both DBS and RNS devices. As future developments in novel therapeutics and surgical techniques may lead to the increasing use of tailored treatments for a patient's epilepsy, the progression to DEE-SSW may be able to be avoided in some patients. However, the underlying heterogeneity and poorly understood pathophysiology of DEE-SSW do remain significant challenges, and more research is needed in this area.

Declarations

Conflict of Interest None.

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Epidemiology, healthcare resource use, and mortality in patients with probable Lennox-Gastaut syndrome: A population-based study on German health insurance data

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ABSTRACT

Objective: This retrospective study examined patients with probable Lennox-Gastaut syndrome (LGS) identified from German healthcare data.
Methods: This 10-year study (2007–2016) assessed healthcare insurance claims information from the Vilua Healthcare research database. A selection algorithm considering diagnoses and drug prescriptions identified patients with probable LGS. To increase the sensitivity of the identification algorithm, two populations were defined: all patients with probable LGS (broadly defined) and only those with a documented epilepsy diagnosis before 6 years of age (narrowly defined). This specific criterion was used as LGS typically has a peak seizure onset between age 3 and 5 years. Primary analyses were prevalence and demographics; secondary analyses included healthcare costs, hospitalization rate and length of stay (LOS), medication use, and mortality.
Results: In the final year of the study, 545 patients with broadly defined probable LGS (mean [range] age: 31.4 [2–89] years; male: 53%) were identified. Using the narrowly defined probable LGS definition, the number of patients was reduced to 102 (mean [range] age: 7.4 [2–14] years; male: 52%). Prevalence of broadly defined and narrowly defined probable LGS was 39.2 and 6.5 per 100,000 people. During the 10-year study, 208 patients with narrowly defined probable LGS were identified and followed up for 1379 patient-years. The mean annual cost of healthcare was €22,787 per patient-year (PPY); greatest costs were attributable to inpatient care (33%), home nursing care (13%), and medication (10%). Mean annual healthcare costs were significantly greater for those with prescribed rescue medication (45% of patient-years) versus those without (€33,872 vs. €13,785 PPY, $p < 0.001$). Mean (standard deviation [SD]) annual hospitalization rate was 1.6 (2.0) PPY with mean (SD) annual LOS of 22.7 (46.0) days. Annual hospitalization rate was significantly greater in those who were prescribed rescue medication versus those who were not (2.2 [2.3] vs. 1.1 [1.6] PPY, $p < 0.001$). The mean (SD) number of different medications prescribed was 11.3 (7.3) PPY and 33.8 (17.0) over the entire observable time per patient (OET); antiepileptic drugs only accounted for 2.1 (1.1) of the medications prescribed PPY and 3.8 (2.0) OET. Over the 10-year study period, mortality in patients with narrowly defined probable LGS was significantly

Abbreviations: AED, antiepileptic drug; AHR, annual hospitalization rate; ATC, Anatomical Therapeutic Chemical Classification System; CI, confidence interval; DS, Dravet syndrome; GKV, Gesetzliche Krankenversicherung (statutory health insurance); ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome; LOS, length of stay; OET, over the entire observable time per patient; PPY, per patient-year; Q, quarter; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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higher than the matched control population (six events [2.88%] vs. one event [0.01%], $p < 0.001$).
Conclusion: Annual healthcare costs incurred by patients with probable LGS in Germany were substantial, and mostly attributable to inpatient care, home nursing care, and medication. Patients prescribed with rescue medication incurred significantly greater costs than those who were not. Patients with narrowly defined probable LGS had a higher mortality rate versus control populations.
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1. Introduction

Lennox-Gastaut syndrome (LGS) is a polyetiological, predominantly childhood-onset, severe developmental epileptic encephalopathy associated with high morbidity and mortality, with an estimated prevalence rate of 1–10% of all childhood epilepsies [1–5]. Treatment options for LGS are limited and long-term prognosis is poor [5]. No single treatment approach has been shown to be highly efficacious and many patients receive polypharmacy without adequate seizure control [5,6]. The management of LGS is further complicated by its associated comorbidities, especially cognitive impairment and behavioral problems, and the variety of different seizure types that characterize the syndrome [3,4]. Such complexity can make it difficult to tailor therapeutic approaches to those without a clearly defined and treatable etiology.

The burden of LGS is multifaceted and extends beyond the availability of adequate treatment; seizure burden is typically quantified using seizure frequency but this gives limited scope for understanding the breadth of impact [7]. The implications of the syndrome can be wide-ranging: patients often experience mobility or behavioral impacts, while families/caregivers can experience limited career opportunities [8]. Furthermore, patients and their families/caregivers can be exposed to decreased social participation [8,9]. The high cost of treatment and necessity for long-term care can exacerbate these negative effects and create further stress for those living with the burden of LGS [8–10].

Healthcare cost and utilization data offer an opportunity to quantify some of the burden associated with medical conditions and may provide insight that can change treatment approaches and improve patient care [11]. Currently, there is a lack of such analyses for LGS and other epileptic encephalopathies, particularly for pediatric patients [12].

The general lack of healthcare cost and utilization data for LGS is most likely due to its low prevalence and different underlying etiologies, and a lack of appropriately captured healthcare information in medical records/databases. Furthermore, the International Classification of Diseases, 10th Revision (ICD-10) did not include a specific code for LGS. The future release of ICD-11 (scheduled for 2022) will include a code for LGS (8A62.1 Lennox-Gastaut syndrome), although it is believed that widespread adoption and implementation of the code could take at least another decade, and perhaps even longer, to yield data for research. In the meantime, the need for healthcare utilization and cost analyses in LGS is beginning to be addressed using patient selection algorithms to identify patients with probable LGS using ICD-10 data.

The few published healthcare utilization studies in patients with LGS have all reviewed healthcare data from patients based in the USA (Medicaid and MarketScan® databases) [6,11,13,14]. Since all previous studies have used an algorithm to detect the patients most likely to have been diagnosed with LGS, all studies refer to patients with 'probable LGS'. The algorithm used was highly consistent between these studies [6,11,13,14]. As noted previously, LGS is a predominantly childhood-onset syndrome, most commonly manifesting itself between ages 3–5 years [4], yet no previous study has included a maximum age cut-off for the first diagnosis of epilepsy as an indicator for probable LGS.

The objective of this retrospective study was to examine epidemiology, healthcare cost and utilization, medication use, comorbidities, injuries, and mortality for patients with LGS. Using information from a German healthcare insurance claims database, this study is the first to present these analyses for patients with LGS based in Europe.

2. Materials and methods

2.1. Data source

This study utilized healthcare insurance claims data obtained from the Vilua Healthcare research database, which contains entries for >4 million individuals, and represents approximately 5% of the German population covered by statutory health insurance (Gesetzliche Krankenversicherung; GKV). The database is continuously evaluated to ensure that it is comparable to the German population by comparison to the annual publications of the German Federal Office for Social Security (Bundesamt für Soziale Sicherung) and has been used previously for epidemiological studies in epilepsy, status epilepticus, and multiple sclerosis [15–18]. All data obtained from this database were de-identified; entries were routinely inspected for outliers, data errors, and longitudinal changes. Analyses of these data were approved by the ethics committee of the University of Frankfurt and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [19].

2.2. Identification of patients with probable Lennox-Gastaut syndrome

In the Vilua Healthcare research database, there was no option to select specifically for those diagnosed with LGS due to the absence of an LGS-specific diagnosis code in the ICD-10 classification system. All ICD codes used for this study are listed in Appendix Table S1.

To account for the lack of an ICD code for LGS, and to retrieve those patients most likely to have a diagnosis of LGS, while also excluding those with other neurological disorders, an identification algorithm considering diagnoses and drug prescriptions was defined (Fig. 1). This selected patients with ≥1 ICD-10 diagnosis of G40 (epilepsy)/G41 (status epilepticus) and ≥1 claim of either rufinamide or felbamate (during the year of identification). If there was no claim of rufinamide or felbamate, ≥2 different antiepileptic drugs (AEDs) in combination with ≥1 developmental delay diagnosis and no diagnosis code for competing etiologies were required (also during the year of identification; ICD codes are listed in Appendix Table S1). For example, those with an ICD-10 code for malignant neoplasms were excluded on the basis of competing etiology. Patients with probable Dravet syndrome (DS) were excluded from the present study population using a DS-specific algorithm based on diagnosis of epilepsy and prescription of certain AEDs that was defined for a separate analysis. Patients with tuberous

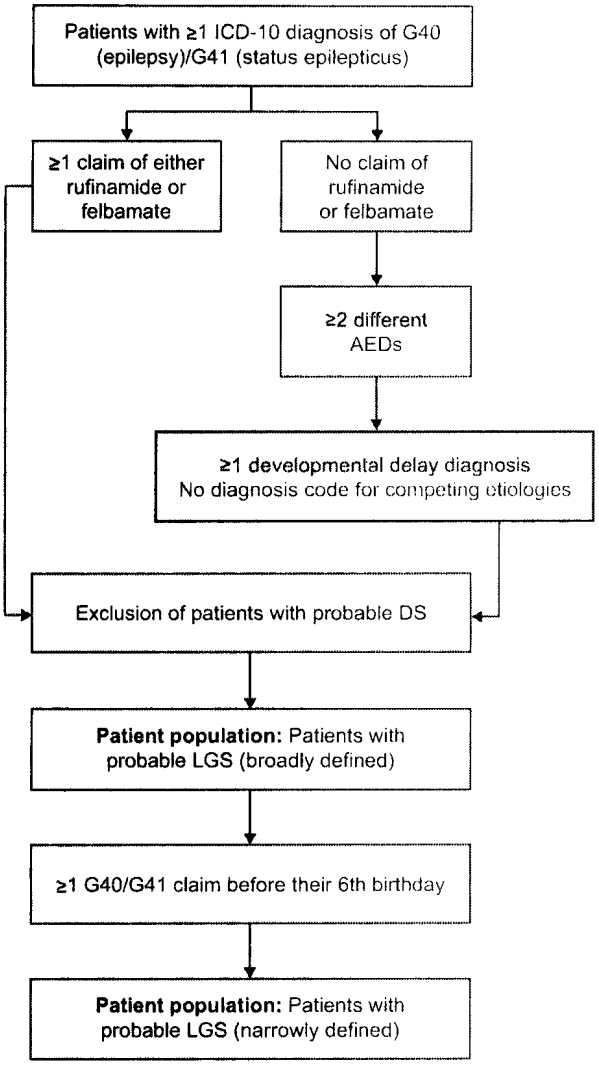


Fig. 1. Patient selection process for probable LGS. AED, antiepileptic drug; ICD-10, International Classification of Diseases, 10th Revision; LGS, Lennox-Gastaut syndrome.

sclerosis complex (TSC) were also excluded and are part of a separate analysis.

To increase the sensitivity of the identification algorithm, two populations were defined: all patients with probable LGS (broadly defined probable LGS) and only those with ≥1 documented G40/G41 claim before their 6th birthday (narrowly defined probable LGS). Patients aged 6 years or older on the first day of the study could not be included in the narrowly defined LGS population. The selection of those with ≥1 G40/G41 claim prior to age 6 was informed by previous literature; LGS typically presents before age 8, with peak seizure onset between age 3 and 5 [4]. The stratification of patients with probable LGS based on this additional criterion increased the sensitivity (true-positive rate) of the study.

2.3. Outcomes

Data from a 10-year period between January 1, 2007 and December 31, 2016 were assessed. The primary analyses were prevalence, and age and sex distribution in the two populations: broadly defined and narrowly defined probable LGS. These analyses were calculated using the number of patients identified in the final year of the study (2016); the final year was chosen because coding quality improved from study onset (2007) through to completion (2016) and so presenting the final year data ensured the highest possible reporting accuracy. Furthermore, with 2016 being the final year, it also allowed the study to present the most recent epidemiological data available. Secondary analyses were annual healthcare costs, annual hospitalization rate and length of stay (LOS, measured in days; all patients, patients hospitalized due to primary probable LGS diagnosis, and patients hospitalized with mechanical ventilation), medication use, comorbidities, injuries, and mortality. Secondary analyses were assessed using the number of patients identified across the entire study (2007–2016) and were only conducted in the narrowly defined probable LGS population. All analyses, apart from prevalence, were based on fully observable patients, defined as those whose data were available for the complete observation year in question. Annual healthcare costs were stratified by age group (0–1, 2–9, and 10–19 years); given that most AEDs are only approved for use in patients with LGS ≥1 year of age, it was of interest to evaluate costs in younger patients.

Previous analyses have suggested a lower age of seizure onset, increased frequency of seizures, and an increased number of prescribed AEDs in patients with rescue medication use versus those with no rescue medication use [20]. To explore this further, subgroup analyses of cost, hospitalization rate, LOS, and mortality data were conducted based on prescription of rescue medication, defined as at least one prescription of midazolam, diazepam (rectal formulation), or chloral hydrate in at least 1 year during the study period.

The cost of illness associated with probable LGS was assessed using a top-down approach, from the perspective of the statutory health insurer. This approach was applied to all hospitalization admissions within the specified analysis period. Cost data by age were evaluated over a 10-year period; within this, costs were recorded annually according to age at the time of assessment. All costs were calculated in Euros (€) and were adjusted to the 2015 price year using the German Health Consumer Price Index [21]. LOS at discharge was calculated using the database. The number of different medications was determined from the number of different Anatomical Therapeutic Chemical Classification System (ATC) codes noted throughout the study for a particular patient. The most commonly prescribed AEDs (ATC code N03A + clobazam) were assessed using the data for each patient in their last observation year; this was either the final year of the study or the year in which the patient left the database (for example, the patient may have switched to another insurance company, left the country, or died). Injury and mortality were compared to age- and sex-matched (standardized) controls over an equal observation time. To generate these controls, the database was searched for as many patients as possible who did not have a diagnosis of probable LGS, probable DS, or TSC and were of the same age and sex, and with at least an equal observation time, as the patient with probable LGS.

2.4. Statistical analysis

All data were analyzed with SQL Server 2016 SP2, R 3.5.0 and Microsoft Excel. *P*-values were derived from a *t*-test hypothesizing that the mean costs (per setting) of the patients with prescribed rescue medication were equal to the mean costs (per setting) of the patients with no prescribed rescue medication. *P*-values were also derived from a log rank test (using chi-squared distribution) to assess the significance of mortality data versus standardized controls.

3. Results

3.1. Patient demographics and characteristics

Using data from the final year of this 10-year study (2016), the classification algorithm identified 545 patients with broadly defined probable LGS, of whom 102 (19%) fulfilled the criteria for narrowly defined probable LGS (Table 1). During the 10-year study, 1571 patients with broadly defined probable LGS were identified and followed up for 12,090 patient-years; 208 patients with narrowly defined probable LGS were identified and followed up for 1379 patient-years.

Using data from 2016, the prevalence (age and sex standardized to German GKV population) of broadly defined and narrowly defined probable LGS was 39.2 and 6.5 per 100,000 people. The mean (range) age was 31.4 (2–89) years in the broadly defined and 7.4 (2–14) years in the narrowly defined population. The narrowly defined population included only those patients for whom the initial epilepsy diagnosis took place within the overall study period (2007–2016); thus, the oldest patient in this population was 14 years old on the final day of study (<6 years of age on the first day of study). Sex distribution (% male) was similar in the broadly defined (53%) and narrowly defined (52%) populations and was consistent across all age groups in both populations.

During the 10-year study period, almost all (178/208, 86%) patients in the narrowly defined probable LGS population were prescribed rescue medication at some point during the follow-up period.

3.2. Healthcare costs

All cost analyses were conducted using the narrowly defined probable LGS population (n = 208; 1379 patient-years).

3.2.1. All patients

During the 10-year study period, the mean annual cost of healthcare was €22,787 per patient-year (Table 2). The greatest contributors to healthcare costs were inpatient care (33%), home intensive nursing care/nursing care (13%), and medication (10%). Inpatient costs resulting from hospital stays related to epilepsy were high (€5636 per patient-year). However, AEDs alone accounted for a small proportion (14%) of the medication costs. High non-AED medication costs were influenced by several expensive medications that were prescribed to a small number of patients over the study period, for example anterior pituitary lobe hormones and analogs to one patient (total of three prescriptions at a mean cost of €3642 per prescription), systemic antimycotics to two patients (four prescriptions, €1823), and immunoglobulins to seven patients (31 prescriptions, €1215).

3.2.2. Patients with prescribed rescue medication

During the 10-year study period, the mean annual cost of healthcare was significantly greater for those prescribed with rescue medication (patient-years in which patients received rescue medication: 618/1379, 45%) versus those not (€33,872 vs. €13,785 per patient-year, $p < 0.001$; Table 2). Similar to the overall population, inpatient care was the largest component of the total costs and was significantly greater for patients with prescribed rescue medication than those without. Costs for home nursing, special equipment, and other physical therapies were markedly and significantly greater in patients with prescribed rescue medication than those without. Medication costs comprised 10% of overall costs in the prescribed rescue medication subgroup and 9% in the subgroup not prescribed rescue medication; the proportions of these costs associated with AEDs were equivalent in both subgroups (14%). In those prescribed rescue medication, mean annual cost per patient-year was greatest in the 0- to1-year age category (€53,073 per patient-year); costs were similar between the 2- to 9-year and 10- to 19-year age categories (€31,614 and €33,030 per patient-year). Higher costs in the 0- to 1-year age category were mostly attributable to inpatient care (€26,369 vs. €7976 and €7817 per patient-year in the 2- to 9-year and 10- to 19-year categories, respectively).

Table 1
Epidemiology of patients with probable LGS (broadly and narrowly defined) in 2016.

	Patients identified with probable LGS			
	Broadly defined		Narrowly defined	
No. of patients, n (%)	545 (100)		102 (19)	
Mean age, years	31.4		7.4	
Prevalence (per 100,000 people)				
Unstandardized to the German GKV population	41.1		7.7	
Standardized to the German GKV population	39.2		6.5	
Sex distribution per age group, n (%)				
Age range (years)	Male	Female	Male	Female
0–1	0 (0)	0 (0)	0 (0)	0 (0)
2–9	40 (14)	37 (15)	39 (74)	34 (69)
10–19	56 (19)	71 (28)	14 (26)	15 (31)
20–29	53 (18)	36 (14)	0 (0)	0 (0)
30–39	38 (13)	31 (12)	0 (0)	0 (0)
40–49	38 (13)	18 (7)	0 (0)	0 (0)
50–59	35 (12)	31 (12)	0 (0)	0 (0)
60–69	22 (8)	17 (7)	0 (0)	0 (0)
70–79	7 (2)	10 (4)	0 (0)	0 (0)
80+	2 (1)	3 (1)	0 (0)	0 (0)

GKV, Gesetzliche Krankenversicherung (statutory health insurance); LGS, Lennox-Gastaut syndrome.
[a] Prevalence calculations are based on all patients, including those who changed insurance company or died during an observation year (patients identified with probable LGS [broadly defined], n = 553; patients identified with probable LGS [narrowly defined], n = 104); all other analyses are based on fully observable patients only i.e. those whose medical data were available across the entire observation year in question (patients identified with probable LGS [broadly defined], n = 545; patients identified with probable LGS [narrowly defined], n = 102).

Table 2
Summary of cost data, including stratification into patient groups with/without prescription of rescue medication[a] for patients with narrowly defined probable LGS during the 10-year study period.

	All patients	Years where patients prescribed with rescue medication	Years where patients not prescribed with rescue medication[a]	p-value[b]
Annual cost per patient-year, €				
Patient-years	1379	618	761	
Total				
Mean	22,787	33,872	13,785	<0.001
Median (Q1–Q3)	4439 (0–18,489)	11,897 (0–30,500)	2058 (0–9120)	
Inpatient				
Mean	7422	9776	5511	0.001
Median (Q1–Q3)	0 (0–5394)	1427 (0–10,628)	0 (0–1947)	
Epilepsy-related				
Mean	5636	8336	3288	<0.001
Median (Q1–Q3)	0 (0–5243)	2580 (0–8814)	0 (0–2008)	
Outpatient				
Mean	1390	1826	1036	<0.001
Median (Q1–Q3)	708 (0–1681)	1122 (0–2005)	388 (0–1336)	
Medication				
Mean	2243	3479	1240	<0.001
Median (Q1–Q3)	427 (0–1991)	1126 (0–3797)	146 (0–971)	
AEDs				
Mean	309	483	169	<0.001
Median (Q1–Q3)	100 (0–354)	225 (17–576)	0 (0–196)	
Services and devices				
Mean	11,731	18,791	5997	<0.001
Median (Q1–Q3)	703 (0–5282)	2310 (0–11,327)	27 (0–2256)	
Intensive home nursing care				
Mean	1971	3479	746	0.018
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Special equipment				
Mean	1309	2316	490	<0.001
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Home nursing care				
Mean	985	1761	354	0.027
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Other physical therapies				
Mean	573	1014	215	0.013
Median (Q1–Q3)	0 (0–0)	0 (0–49)	0 (0–0)	
Physiotherapy				
Mean	187	311	86	<0.001
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Transport for medical needs				
Mean	65	112	27	<0.001
Median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	
Other costs				
Mean	6643	9799	4080	0.020
Median (Q1–Q3)	0 (0–2853)	354 (0–5632)	0 (0–1439)	
Mean annual cost per age group per patient-year, €				
0–1 year				
No. of patients, *n*	113	49	99	
Patient-years	210	61	149	
Cost (SD), €	24,434 (82,453)	53,073 (138,514)	12,709 (36,686)	<0.001
2–9 years				
No. of patients, n	204	166	167	
Patient-years	1038	496	542	
Cost (SD), €	22,996 (63,199)	31,614 (73,093)	15,110 (51,356)	<0.001
10–19 years				
No. of patients, *n*	59	38	34	
Patient-years	131	61	70	
Cost (SD), €	18,487 (45,263)	33,030 (61,799)	5813 (13,748)	<0.001

AED, antiepileptic drug; LGS, Lennox-Gastaut syndrome; Q1–Q3, interquartile range; SD, standard deviation.
[a] Rescue medication use is defined by having ≥1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate.
[b] *t*-test for patients with versus without rescue medication prescription.

3.3. Hospitalization rates and LOS

All hospitalization and LOS analyses were conducted using the narrowly defined probable LGS population ($n = 208$; 1379 patient-years).

3.3.1. All patients

During the 10-year study period, patients were admitted to hospital a mean (SD; median) of 1.6 (2.0; 1) times annually and reported a mean (SD; median) annual LOS of 22.7 (46.0; 3) days per patient-year (Table 3). The range was wide for these data;

Table 3
Summary of hospitalization rates and LOS, including stratification into patient groups with/without prescription of rescue medication[a] for patients with narrowly defined probable LGS during the 10-year study period.

	All patients		Years where patients prescribed with rescue medication		Years where patients not prescribed with rescue medication[a]		*p*-value[b]	
No. of patients, *n* (%)	208 (100)		178 (86)		188 (90)			
	AHR	LOS (days)	AHR	LOS (days)	AHR	LOS (days)	AHR	LOS (days)
All patients								
Patient-years	1379	1379	618	618	761	761		
Mean (SD)	1.6 (2.0)	22.7 (46.0)	2.2 (2.3)	30.1 (55.4)	1.1 (1.6)	16.7 (35.6)	<0.001	<0.001
Median (range)	1 (0–13)	3 (0–804)	2 (0–13)	10 (0–804)	1 (0–13)	1 (0–309)		
95% CI	1.5–1.7	20.3–25.1	2.0–2.4	25.7–34.5	1.0–1.2	14.2–19.2		
All patients (due to primary probable LGS diagnosis)								
Patient-years	1379	1379	618	618	761	761		
Mean (SD)	0.7 (1.3)	10.3 (26.9)	1.1 (1.6)	15.4 (32.3)	0.4 (1.0)	6.2 (20.8)	<0.001	<0.001
Median (range)	0 (0–10)	0 (0–294)	1 (0–10)	0 (0–294)	0 (0–10)	0 (0–208)		
95% CI	0.7–0.8	8.9–11.8	1.0–1.3	12.9–18.0	0.3–0.5	4.7–7.7		
Patients hospitalized with mechanical ventilation								
Patient-years	32	32	17	17	15	15		
Mean (SD)	1.3 (0.6)	40.5 (44.6)	1.5 (0.8)	21.5 (17.3)	1.0 (0.0)	61.9 (56.0)	0.015	0.016
Median (range)	1 (1–3)	27.5 (3–181)	1 (1–3)	20 (3–66)	1 (1–1)	40 (11–181)		
95% CI	1.1–1.5	25.0–55.9	1.2–1.9	13.3–29.7	1.0–1.0	33.6–90.3		

AHR, annual hospitalization rate; CI, confidence interval; LGS, Lennox-Gastaut syndrome; LOS, length of stay; SD, standard deviation.
[a] Rescue medication use is defined by having ≥1 prescription of midazolam, diazepam (rectal formulation), or chloral hydrate.
[b] *t*-test for patients with versus without rescue medication prescription.

hospitalizations ranged from 0 to 13 and LOS from 0 to 804 days per patient-year. The main reason for hospitalization was epilepsy and recurrent seizures (G40 ICD-10 code), occurring in 87% of patients during the study; pneumonia (J18, 23%) and acute bronchitis (J20, 19%) were the next most common reasons. Patients hospitalized with mechanical ventilation had a mean (SD; median) LOS of 40.5 (44.6; 27.5) days, almost double that of the overall population.

3.3.2. Patients with prescribed rescue medication

The mean (SD) annual hospitalization rate was significantly greater in those who were prescribed with rescue medication ($n = 178$; 618 patient-years) versus those who were not ($n = 188$; 761 patient-years) (2.2 [2.3] vs. 1.1 [1.6] per patient-year, $p < 0.001$; Table 3). This trend was also observed with LOS, with a significantly longer LOS recorded in those who were prescribed rescue medication versus those who were not. Among patients who received mechanical ventilation, those prescribed with rescue medication had a much shorter mean (SD) LOS than those who were not (21.5 [17.3] vs. 61.9 [56.0] days).

3.4. Medication use

All analyses of medication use were conducted using the narrowly defined probable LGS population ($n = 208$; 1379 patient-years). During the 10-year study period, the mean (SD; median) number of different medications prescribed was 11.3 (7.3; 10) per patient-year and 33.8 (17.0; 29.5) over the entire observable time for each patient. In this same population, AEDs alone accounted for a mean (SD; median) of 2.1 (1.1; 2) of the medications prescribed per patient-year and 3.8 (2.0; 3) over the entire observable time. Patients typically received between one and three different AED combinations in each year (range: 1–9) and most patients received either two, three, or four different AEDs (29%, 24%, and 16%) [range: 1–12] over the entire observable time. During the last year of observation for each patient, the top six prescribed AEDs/AED combinations (number of patients, %) were valproate (62, 37%), lamotrigine (25, 15%), lamotrigine and valproate (16, 10%), oxcarbazepine (15, 9%), oxcarbazepine and valproate (8, 5%), and clobazam (8, 5%). Over the entire study period, the top five prescribed medications (number of patient-years, %) were ibuprofen (782, 57%), xylometazoline (744, 54%), paracetamol (609, 44%), diazepam (582, 42%), and valproate (571, 41%). Three AEDs (valproate, levetiracetam, and lamotrigine) featured within the top 20 most commonly prescribed medications.

3.5. Comorbidities

Comorbidities were common in the narrowly defined probable LGS population; comorbidity and aggregated comorbidity data are shown in Fig. 2A and B.

3.6. Injuries

During the 10-year study period, the frequency of reported injuries was concordant between the narrowly defined probable LGS population and the control group. At least one injury was reported by 67% of patients (control: 69%); injuries to the trunk (46%; vs. control: 50%) and head (41%; vs. control: 36%) were the most common injuries observed. 'Epilepsy and recurrent seizures' (G40) was the most commonly reported secondary diagnosis in all patients hospitalized due to a fracture (probable fall) during the study.

3.7. Mortality

Over the 10-year study period, the mortality rate in patients with narrowly defined probable LGS was higher than that observed in the control population (2.88% [six events] vs. 0.01% [one event], $p < 0.001$; Fig. 3A). The mortality rate was greater in the broadly defined probable LGS population versus the narrowly defined population (10.01% [157 events] vs. 2.88% [six events], $p < 0.001$; Fig. 3B).

In the narrowly defined probable LGS population, the mortality rate was 3.39% (four events) in those prescribed with rescue medication versus 2.22% (two events) in those with no prescribed rescue medication (Fig. 3C).

4. Discussion

This retrospective study provides healthcare cost and utilization data in patients with LGS in Germany. This is the first study to

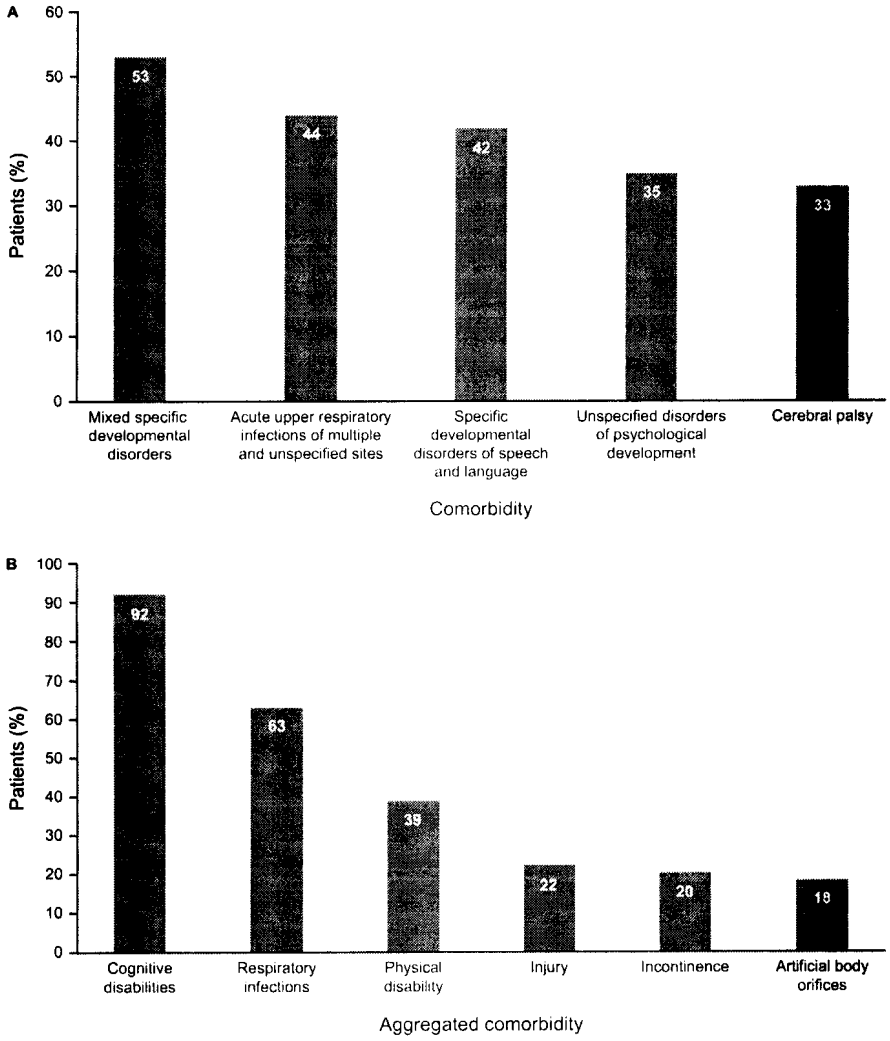


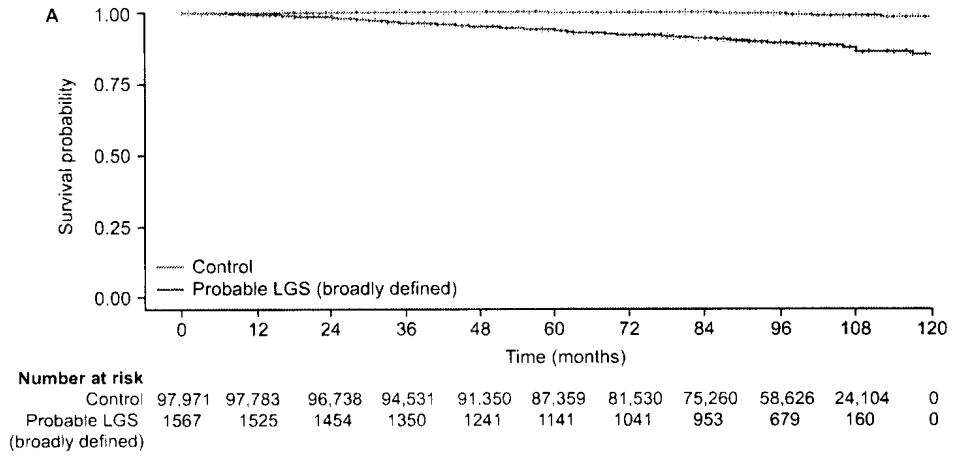
Fig. 2. Comorbidity (A) and aggregated comorbidity (B) data for patients with narrowly defined probable LGS during the 10-year study period. LGS, Lennox-Gastaut syndrome.

report direct cost analyses for patients with LGS within Europe. Furthermore, few studies have reported the prevalence of LGS, with some published over 20 years ago [22,24]. The present study adds important recent epidemiological data to a small field and provides a foundation for further research. These data from the Vilua Healthcare research database cover a 10-year period up to 2016 and are representative of the German population covering 5% of the total population. Within this, the study provides a good representation of the two probable LGS patient groups (broadly defined and narrowly defined probable LGS).

In the final year of our study (2016), the selection algorithm identified 545 patients with probable LGS (broadly defined); an additional criterion was applied (≥1 epilepsy diagnosis <6 years of age) to increase the specificity of the patient selection algorithm and strengthen the likelihood of selecting patients with LGS. The application of this further stratification selected 102 patients from the previous 545 (narrowly defined probable LGS). It should be noted that patients were not excluded because they definitely did not have LGS, but rather because there was less certainty around their diagnosis as the age criterion with onset <6 years of age could only be applied to a subset of patients (those born after January 1, 2001). The lack of a specific code for LGS is a limitation of all retrospective analyses that use healthcare database data. The introduction of ICD-11 in the healthcare community will in future yield data from which patients with LGS will be easier to identify, providing that recommended data entry protocols are followed and an ICD code for LGS is adopted.

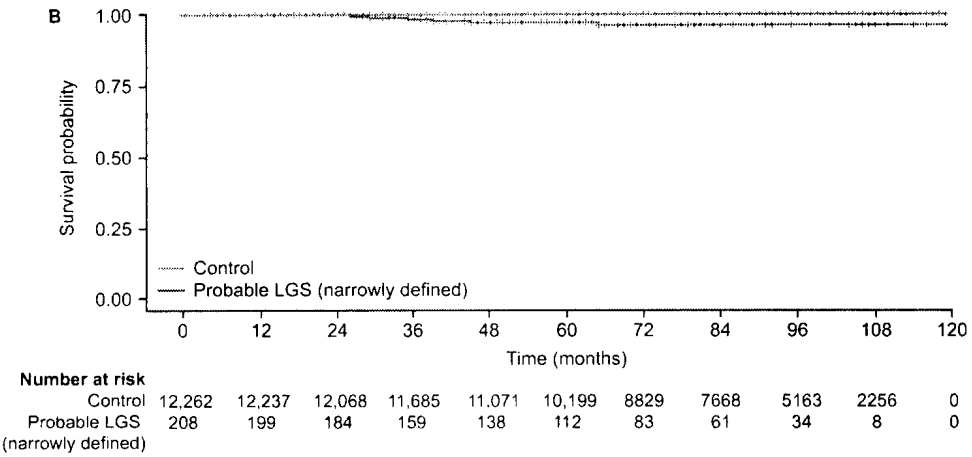
In 2016, for the broadly and narrowly defined probable LGS populations, the standardized prevalence was 39.2 and 6.5 per 100,000 people. A previous study of children in the USA aged 10 and born between 1985 and 1987 noted a prevalence rate of 26 per 100,000 for probable LGS [23]. The inclusion criteria used in the previous study classified all patients with mixed types of generalized seizures and intellectual disability as having probable LGS [23]. In comparison, the present study employed selection criteria that were based on previous analyses [6,11,13], but attempted to increase algorithm accuracy by stratifying patients with probable LGS based on age at diagnosis.

Our findings agree with previously published analyses that the healthcare costs associated with LGS are significant [6,11,13]. All previous studies note that the mean annual costs associated with probable LGS are very high; where the comparison has been shown, these costs exceed those of patients without LGS (Appendix [illegible]), and also exceed those of other encephalopathies such as DS and TSC [34]. In the present study, the largest component of direct healthcare costs was inpatient care (33%). This trend is



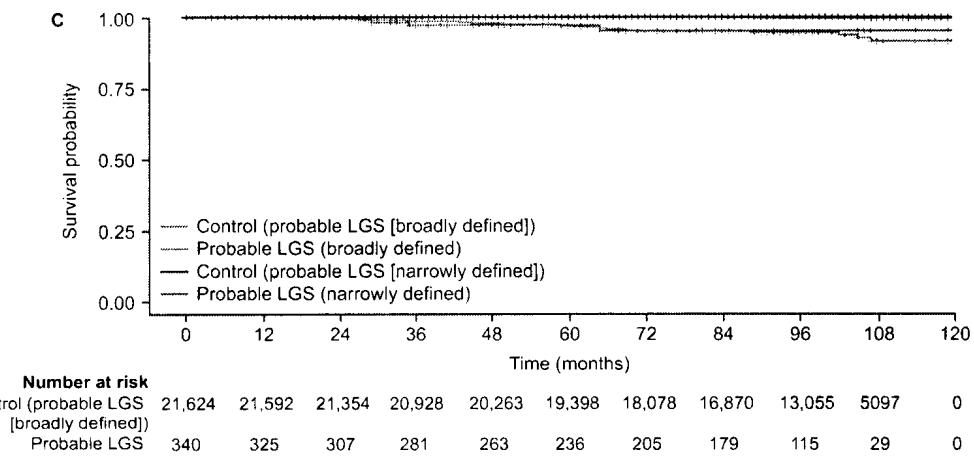
Number at risk

Control	97,971	97,783	96,738	94,531	91,350	87,359	81,530	75,260	58,626	24,104	0
Probable LGS (broadly defined)	1567	1525	1454	1350	1241	1141	1041	953	679	160	0



Number at risk

Control	12,262	12,237	12,068	11,685	11,071	10,199	8829	7668	5163	2256	0
Probable LGS (narrowly defined)	208	199	184	159	138	112	83	61	34	8	0



Number at risk

Control (probable LGS [broadly defined])	21,624	21,592	21,354	20,928	20,263	19,398	18,078	16,870	13,055	5097	0
Probable LGS (broadly defined)	340	325	307	281	263	236	205	179	115	29	0
Control (probable LGS [narrowly defined])	5852	5838	5763	5545	5221	4787	4106	3550	2355	796	0
Probable LGS (narrowly defined)	118	110	100	83	73	57	39	26	13	2	0

Fig. 3. Survival rate of patients with probable LGS and the control group[a] during the 10-year study period (A – broadly defined; B – narrowly defined; C – probable LGS with ≥1 recorded instance of rescue medication prescription[b] during the study period [broadly and narrowly defined]). LGS, Lennox-Gastaut syndrome. [a] The control group consists of individuals of the same age and sex distribution over an equal observation time. [b] 'Rescue medication prescription' is defined by having at least one prescription of midazolam, diazepam (rectal formulation), or chloral hydrate.

reflected by previous analyses of probable LGS, which showed that hospitalization and inpatient-related expenses represented the bulk of mean annual costs. It should be noted that the current study only presents data from the child and adolescent population (maximum age included: 14 years) due to the stratification algorithm employed; direct comparisons with other studies in patients with probable LGS with wider age ranges are therefore limited. The substantial cost of home nursing care (13% of total costs) is also noteworthy and highlights that children with LGS have complex medical and physical needs and often require continuous care.

In the present study, the rate of hospital admissions was considerable (mean: 1.6 per patient-year) and annual LOS was long (mean: 22.7 days) for those within the narrowly defined probable LGS population. Most hospitalizations were the result of epilepsy and/or recurrent seizures, indicating that there is still a high unmet treatment need in this population. It should be noted that there was at least one instance of very long hospitalization (>804 days). This trend was reflected in annual cost data: there was again at least one instance of very high inpatient-related costs (range: €0–€524,838).

Our findings are broadly consistent with previous studies that have observed frequent inpatient admissions among populations with LGS and other epilepsies. Two studies conducted in the USA reported lower hospitalization rates for patients with probable LGS (0.3–0.7 per patient-year), although direct comparisons between studies are limited by methodological differences [11,13]. In line with our analysis, one of these studies reported that seizure-related inpatient visits represented roughly two-thirds of all inpatient visits for patients with probable LGS [13]. A survey conducted in Germany found that 15.7% of children and adolescents with epilepsy were admitted to hospital at least once over a 3-month period with a mean LOS of 9.3 days [12]. It is interesting to note that our findings regarding high hospitalizations in patients with probable LGS are also in line with those reported in two similar recent bottom-up analyses of healthcare data from patients with DS, another epileptic encephalopathy [24,25]. In particular, both studies observed considerable inpatient LOS in patients with DS. In the first study, mean LOS due to DS was 25.6 days over the previous 12 months [24]. The second study compared patients with DS to age- and sex-matched patients either with drug-resistant epilepsy (without encephalopathy) or in seizure remission. LOS in the DS group was comparable with that in patients with drug-resistant epilepsy (2.5 and 2.9 days over 3 months) and significantly longer than for those in seizure remission (0.3 days over 3 months) [25].

Patients with prescribed rescue medication incurred costs significantly greater than those of patients without (€33,872 vs. €13,785 per patient-year, $p < 0.001$). Those patients with prescribed rescue medication also had a significantly higher annual hospitalization rate and longer LOS. Interestingly, mortality was similar between those prescribed with rescue medication and those who were not (3.39% vs. 2.22%). Several clinical or social factors may have influenced costs and hospitalizations in patients who were prescribed rescue medication, but it is beyond the scope of this analysis to evaluate such factors. It should be noted that all comparisons of those prescribed versus not prescribed rescue medication are limited by the difference in size of these populations; few patients did not receive rescue medication at least once during the study.

As expected in this population, patients were prescribed multiple medications including AEDs. However, the number of different AEDs prescribed for each patient was generally low, suggesting that AED treatment remained relatively stable throughout the study period. This is supported by the fact that most patients received either two, three, or four different AEDs (29%, 24%, and 16%) over the entire observable time. The most commonly prescribed AEDs in this study were valproate and lamotrigine; this is in keeping with current expert opinion for the treatment of LGS [4]. This trend was also observed in previous studies of patients with probable LGS: patients generally used more non-AED versus AED medications, and the number of different AEDs prescribed was low [11,13]. The present study also shows that a few patients were prescribed very expensive non-AED medications which influenced mean treatment costs.

Over two-thirds of the narrowly defined probable LGS population reported at least one injury. This may be partly explained by the high incidence of drop seizures in patients with LGS. Drop seizures tend to occur suddenly and with the potential to cause significant injury [3]. Interestingly, however, there was no marked difference between the frequency of injuries in patients with narrowly defined probable LGS and matched controls. Each probable LGS patient was matched to at least 100 Vilua Healthcare database entries of the same age, sex, and observation time. Consequently, the matched control population would be aged ≤15 years and it is likely that a large proportion of this pediatric population would have experienced at least one injury across a 10-year period.

In line with other published data in patients with LGS, most patients in this study had other comorbidities besides epilepsy [1,26–28], emphasizing the need for the impact of this additional burden to be considered when contemplating both the costs associated with LGS and the treatment plans that should be offered in its management. In the present study, the most common aggregated comorbidities were cognitive disabilities, although this is unsurprising as cognitive disabilities formed part of the possible patient selection criteria. The next most common comorbidities were respiratory infections, physical disabilities, and injuries. It is unclear if these comorbidities influenced the costs reported in this study and this could form the basis for future analyses.

This study reports a mortality rate of 2.88% for patients with narrowly defined probable LGS, which is comparable with other published data for patients with LGS, which report mortality as between 3% and 7% [26–28]. Six patients aged ≤14 years died over the 120 months of the present study. Since death in LGS can often be attributed to status epilepticus, the result of an accident during a seizure or sudden unexpected death in epilepsy [29–31], these findings underline the unmet need in LGS as improved seizure control may reduce mortality [2].

5. Limitations

Although our selection algorithm was informed by the methodology of previous studies in LGS and other encephalopathies [11,13,15], it is possible that misclassification of LGS patients may have occurred. In addition, the analyses were based on healthcare insurance data; there may have been inaccuracies such as under- or over-reporting within the Vilua Healthcare research database. Although the requirement for ≥1 epilepsy diagnosis <6 years of age for inclusion in the narrowly defined population may have increased the sensitivity of the study, this excluded older patients with LGS from the study population. This was unavoidable due to the study duration (2007–2016) and the retrospective nature of the analysis i.e. the need to verify a diagnosis before age 6 within the 10-year study period. A prospective study that enrolls patients following diagnosis would remove this exclusion, although data would take many years to acquire. The present study was 10 years in length and enrolled patients at different ages; individual patients within the study may not have been longitudinally present across all of the age categories they were captured within at study conclusion. Patients with prescribed rescue medication were identified in our analysis as those who were prescribed midazolam, diazepam (rectal formulation), or chloral hydrate. However, recent

data have indicated that unsuitable benzodiazepines with slow absorption rate or off-label products are frequently used as emergency medication for adults with epilepsy in Germany [20]. Thus, our definition may have been too narrow to identify all prescriptions that were intended for use as rescue medication. Also, patient data reviewed within this study were exclusively obtained from the German Vilua Healthcare database. The hospitalization rate may be high in Germany compared with other countries, with 12% of the general population reporting inpatient treatment over 6 months [32]. Hospitalizations in patients with active epilepsy, however, have remained stable in Germany over the past decade [33]. Further research is necessary to validate the outcomes of this study and ensure that findings are applicable to patients with LGS across Europe and the rest of the world.

6. Conclusions

This study presents a German healthcare database analysis that provides a welcome assessment of the epidemiology and characteristics of LGS within Europe. Annual healthcare costs incurred by those with probable LGS were substantial; inpatient care, home nursing care, and medication were the greatest contributors to these costs. Patients prescribed with rescue medication incurred significantly greater costs than those who were not. Patients with probable LGS with epilepsy diagnosis before 6 years of age had a higher mortality rate versus control populations.

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All authors met the International Committee of Medical Journal Editors authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship.

Author contributions

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

Data-sharing statement

The sponsor adheres to current requirements of the USA and the European Union and so will not make individual de-identified participant data available; however, the protocol and statistical analysis plan will be made available upon request to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107647.

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Review

Management of Lennox-Gastaut syndrome beyond childhood: A comprehensive review

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ABSTRACT

Lennox-Gastaut syndrome (LGS) is a childhood-onset epileptic encephalopathy characterized by multiple types of medically intractable seizures, cognitive impairment, and generalized slow spike-wave discharges in electroencephalography (EEG). Although the onset of this epileptic syndrome occurs typically before eight years of age with a peak age between 3 and 5 years, lifelong persistence of the syndrome is usual. The evolution of clinical features, EEG findings, and paucity of knowledge about LGS among adult health care providers can make LGS significantly underdiagnosed in the adult population. Management of LGS remains problematic beyond childhood due to intractable seizures, the difficult transition from pediatric to adult neurologists, challenging behaviors, impaired cognition, poor quality of life, and disabled social life. In focusing on the management of LGS beyond childhood, this narrative review describes medical and surgical management of epilepsy, the transition from pediatric to adult care, and management of other common comorbidities associated with LGS. Several antiepileptic drugs (AEDs) such as lamotrigine, topiramate, felbamate, rufinamide, clobazam, and Epidiolex (pure pharmaceutical grade cannabidiol (CBD) oil) have been noted to be effective in well-designed, randomized controlled trials. Other nonpharmacological therapies, such as vagus nerve stimulation, ketogenic diet, and epilepsy surgery, have been frequently utilized in the management of intractable seizures associated with LGS. However, effective management of LGS requires a broader perspective to not only control seizures but improve the quality of life by addressing cognitive and behavioral problems, sleep disturbances, physical disability, social disability, and educational and employment challenges.

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1. Introduction

Lennox-Gastaut syndrome(LGS) is a childhood-onset epileptic encephalopathy [1]. Many comprehensive reviews highlighted diagnostic criteria of LGS: multiple types of medically intractable seizures (tonic, atypical absence, myoclonic, tonic/atonic drop seizures, generalized tonic–clonic, and focal seizures), cognitive impairment, and generalized slow (≤2.5 Hz) spike-wave discharges in electroencephalography(EEG) [2,3]. Although the onset of this epileptic syndrome is typically before eight years of age with a peak between 3 and 5 years, lifelong persistence of the syndrome is usual. However, LGS is significantly underdiagnosed in the adult population due to evolution of clinical features, EEG findings, and paucity of knowledge about LGS among adult health care providers.

Although late-onset LGS has been reported with seizure-onset in the 2nd decade of life, vast majority of adult patients have childhood onset typical LGS [4]. Roger et al. followed 338 LGS patients from the pediatric age group to adulthood and noted that 46.5% of adult patients continued to have all the classic features of LGS [5]. An additional 15.6% of patients had persistent multifocal epilepsy. The patients (37% of patients) with relatively better outcome had later onset LGS (between 7 and 11 years of age) with a brief duration (2–6 years) of active epilepsy. Even in this relatively good outcome group, 20% of the total patients continued to have focal seizures with persistent neurological and psychiatric abnormalities. Although adult LGS patients may not experience frequent drop seizures, nocturnal tonic seizures during sleep may continue and remain undiagnosed without a high level of suspicion. Besides the change in the seizure type and frequency, remarkable change occurs in the EEG features of LGS during adulthood. Classically described slow generalized spike-wave discharges are rarely seen in adult patients with LGS. Background activity during wakefulness may show slowing with multiple independent spike foci or may

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look apparently normal. However, paroxysmal fast frequency discharges may be persistent during sleep.

Besides evolution of clinical and EEG changes, many adult LGS patients are undiagnosed due to misclassification. Due to only recent explosion of genetic testing in pediatric patients with epileptic encephalopathy, most adult LGS patients without known etiology have not undergone genetic evaluation and categorized as epilepsy of 'unknown etiology'. There is profound difference in perception and use of genetic testing between pediatric and adult epileptologists. However, approximately 25–30% of LGS patients may have underlying genetic causes. Limited research has been done to understand genetic causes in adult LGS patients. Lund et al. identified rare copy number variants (CNVs) in 8 (4 of the highly probable as the causative agent) among 21 adult LGS patients [6]. Pathogenic CNVs are also associated with particular seizure types (atypical absence and tonic) in adult patients with intellectual impairment and epilepsy to suggest potential usefulness of genetic testing in adult LGS patients, especially in patients without obvious structural brain abnormality [7].

Due to significant underdiagnoses and misclassification, adult LGS patients may not receive appropriate treatment with potentially efficacious AEDs. Besides difficulty in managing continuing intractable seizures, management of LGS remains problematic beyond childhood due to difficult transition from pediatric to adult neurologists, and presence of challenging behaviors, impaired cognition, poor quality of life, and disabled social life in these patients. Additionally, adult neurologists may not feel completely comfortable treating LGS patients with various cognitive and behavioral issues, especially with coexisting severe intellectual disability or autism. In focusing on the management of LGS in adolescents and adults, this narrative review describes medical and surgical management of epilepsy, the transition from pediatric to adult care, and management of other common comorbidities associated with LGS (Fig. 1).

2. Medical treatment

2.1. Antiepileptic drugs (AEDs)

Most clinical studies and reviews concerning the treatment of LGS have been focused on the pediatric population. Rigorous clinical data or management guidelines have not been published to guide treatment for adult LGS patients. The prescribing practice is based on clinical experience, adverse effect profile, concomitant medication effects, and the presence of other comorbidities. There are some AEDs such as valproate that are commonly used, but there are other AEDs-specifically approved for LGS– that are underutilized. Commonly used AEDs with efficacy and safety data from clinical studies are summarized in Table 1.

2.1.1. Valproate

Valproic acid has never been specifically approved for LGS, but many physicians use this as first-line medicine. Valproate is broadly active against many different seizure types and does not worsen generalized seizures as compared with some other AEDs. Vassella et al. reported that adjunctive valproate therapy with phenobarbital was more effective in controlling seizures compared with phenobarbital monotherapy in 17 LGS patients [8]. Covanis et al. reported that more than half of the patients had greater than 50% reduction of seizures when treated with valproic acid as a monotherapy or in combination with other agents [9]. About 21% of patients became seizure-free out of 38 LGS patients in this study. The higher response rate was observed in drop, atypical absence, and myoclonic seizures compared with tonic and tonic-clonic seizures. Adult neurologists are extremely familiar with prescribing valproate due to its prevalent use against several seizure types in all age groups. However, valproic acid should not be used in females of childbearing potential: due to the risk of neural tube defects and adverse neurodevelopmental outcomes in the exposed fetus during pregnancy. Some countries regulate valproate use in women of childbearing potential by following an annual risk assessment protocol: assessing pregnancy risk regularly, educating negative neurodevelopmental outcome and teratogenicity risk, performing regular pregnancy tests, and providing information about highly effective contraception. Female LGS patients with no plan of becoming pregnant and good seizure control on valproate therapy can continue this with strict contraception. However, continuous scrutiny for adverse effects such as weight gains, alopecia, hyperammonemia, low platelet count, coagulopathy, pancreatitis, and the polycystic ovarian syndrome is necessary. But, the most feared adverse effect in children- acute hepatic failure- is rarely encountered in adults.

2.1.2. Lamotrigine

The Food and Drug Administration (FDA) approved lamotrigine as an adjunctive treatment for LGS patients ≥2 years old. A double-blind placebo-controlled trial demonstrated that 33% of patients on lamotrigine had >50% reduction of seizures compared with 16% in the placebo group ($P = 0.01$) over the 16 weeks of the study period, with the most benefit in tonic-clonic and drop seizures [10]. Atypical absence seizures did not improve in this cohort, but accurately counting these seizures might be challenging. Additionally, lamotrigine can worsen myoclonic seizures in some patients. As an adjunctive treatment, lamotrigine does not alter the concentration of most other AEDs, and it has a synergistic pharmacodynamic effect with valproic acid. A single-center, open-label, prospective study in 14 adult patients (21–51 years) showed that add-on lamotrigine therapy decreased >50% of every types of seizures (drop, focal seizures, and secondarily generalized seizures) in 12 patients [11]. Most improvement was noted in drop seizures with 6 patients becoming completely free of this type of seizures. However, the metabolism of lamotrigine is affected by enzyme inducers (phenytoin, phenobarbital, carbamazepine, etc.) and inhibitors (valproic acid), and higher lamotrigine dose is necessary with enzyme inducers, and a lower dose and a slower titration are required when co-medicated with valproate. Clinical and laboratory monitoring is needed as valproate effectively double the serum concentration of lamotrigine, and the sudden introduction of valproic acid in a patient with stable lamotrigine dose can induce lamotrigine toxicity. If lamotrigine needs to be replaced with valproate, careful consideration should be given to this complex interaction. In spite of probable higher efficacy of lamotrigine in combination with valproic acid, risk of skin rash, including Steven-Johnson syndrome and toxic epidermal necrolysis, makes physicians apprehensive selecting this combination. However, it is unclear if the risk of serious cutaneous reaction is significantly higher than some first-generation AEDs, such as carbamazepine, phenytoin, or phenobarbital. A bidirectional relationship exists between hormonal contraceptives and lamotrigine: Lamotrigine modestly decreases levonorgestrel level, and combined systemic contraceptives also accelerate lamotrigine clearance to decrease its serum concentration. However, a significant advantage of its use in women of childbearing potential is that the prevalence of major congenital malformation from lamotrigine is significantly lower than valproate, phenobarbital, phenytoin, and carbamazepine.

2.1.3. Topiramate

Topiramate, a broad-spectrum AED, was approved by the FDA in 2001 as an adjunctive treatment for LGS patients. A double-blind RCT demonstrated a significant decrease in the monthly seizure

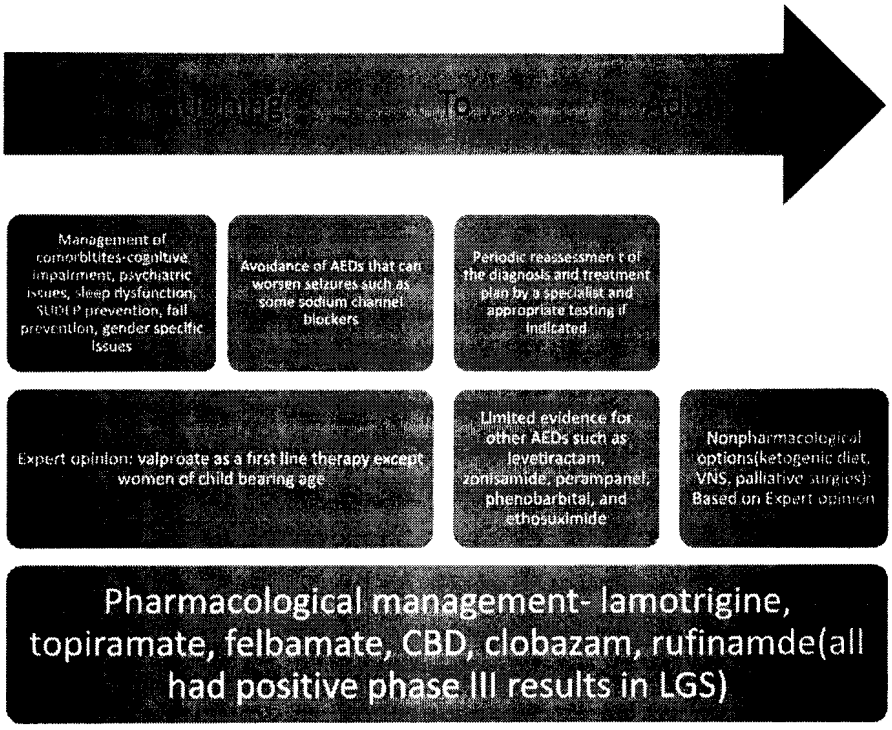


Fig. 1. Schematic illustration of the management plan for LGS patients beyond childhood.

rate and seizure severity in the topiramate group. Additionally, a significantly higher seizure responder rate (≥50% seizure reduction rate) was noted in the topiramate group (33% in the topiramate group versus 8% in the placebo group) [12]. However, this study only enrolled patients up to 30 years of age, and it is unclear if the older population would experience significantly higher cognitive adverse effects with a higher dose of topiramate. Other adverse effects to consider are loss of appetite, weight loss, paresthesia, kidney stone, hypohidrosis, and open-angle glaucoma. An open-label extension of this study, lasting 6 months, showed that more than 50% of patients had >50% reduction in drop seizures and, more interestingly, approximately 15% of the patients ceased to have drop seizures completely [13]. Topiramate is categorized as a Pregnancy Category D medicine as its exposure during pregnancy increases the risk of cleft lip and cleft palate in infants. Additionally, a higher dose of topiramate (>200 mg/day) may cause contractive failure and unintended pregnancy in women of childbearing age.

2.1.4. Felbamate

Felbamate is rarely used for any epilepsy indication currently due to black box warnings of aplastic anemia and acute liver injury [14]. However, felbamate has an approved indication for LGS if seizures fail to control with 1st and 2nd line therapies. An RCT demonstrated that felbamate could significantly reduce all seizure types associated with LGS ($P = 0.002$) [15]. During treatment and maintenance periods, a substantial reduction of atonic seizures was observed; 10% of patients stopped having atonic seizures during the treatment period, and approximately 18% were free of atonic seizures during the maintenance phase. After the randomized trial, an open-label 12-month follow-up study showed continued benefit with >50% reduction of total seizures and a 67% reduction in the drop seizures [16].

2.1.5. Zonisamide

Zonisamide has noted to be effective for the management of seizures associated with LGS by retrospective evaluation. You et al. showed that approximately 50% of LGS patients had >50% reduction of seizures over a 12-month period after the addition of zonisamide in the existing treatment regimen [17]. Sedation and loss of appetite can be problematic as with topiramate; however, due to the long half-life, zonisamide can be used once daily as a night time dose to alleviate some of these adverse effects.

2.1.6. Clobazam

The FDA approved clobazam as an adjunctive treatment for LGS patients two years and older in 2011. However, it continued to be underutilized in the adult population. A phase II study in LGS showed that high dose clobazam was more effective than the low dose to reduce all types of seizures, including drop seizures [18]. A placebo-controlled phase III trial in 238 LGS patients (2–60 years) reported similar findings [19]. A dose-dependent response was observed in the trial with an incrementally higher chance of ≥50% of reduction of drop seizures across the low (43.4%), medium (58.6%), and high-dose clobazam (77.6%) groups; the placebo rate was 31.6%. Approximately one-quarter of patients had complete cessation of drop seizures in the high dose clobazam group. Patients, after completion of the previous two trials, enrolled in another study that demonstrated long term efficacy of clobazam [20]. However, clobazam is still not widely used as an AED in adult LGS patients. Though the exact reason for this is unclear, concern about tolerance may be responsible for its underuse. However, a post-hoc analysis in 200 LGS patients demonstrated that tolerance to clobazam– defined as clobazam dose increase of >40% in the setting of an increase in seizure frequency–only rarely develops over two years [21]. Moreover, further improvement in the seizure control may occur after the increase of the clobazam dose if only a low or medium dose of clobazam

Table 1
Clinical data for commonly used medications in Lennox-Gastaut syndrome.

AED	Trial design	Efficacy	Reported common side effects	Other considerations
Valproate	Uncontrolled, observational ($N = 336$ epileptic patients, 38 LGS)[5]	↓ >50% in all-seizure frequency in 55% patients	Gastrointestinal effects, weight increase, drowsiness, hair loss, thrombocytopenia, and abnormal liver function tests	Should not be used in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of high teratogenic potential and risk of developmental disorders in infants exposed *in utero*. An additional benefit of mood control is present.
Lamotrigine	Double-blind, placebo-controlled trial ($N = 169$)[6]	↓32% in frequency of major seizures versus ↓9% in the placebo group ($p = 0.002$)	Pharyngitis, fever, infection, skin rash	Counseling should be given regarding Stevens-Johnson syndrome and hemophagocytic lymphohistiocytosis. An additional benefit of mood control is present. Lower dose and the slower titration is required when used concomitantly with valproate
Topiramate	Multicenter, randomized, double-blind, placebo-controlled, 11-week trial ($N = 98$)[7] Open-label extension ($N = 97$)[8]	↓14.8% in frequency of drop attacks versus ↑5.1% in the placebo group ($p = 0.041$) ↓56–58% median reduction in drop attacks	Expressive language disorder, confusional state, disorientation, disturbance in attention, memory impairment, amnesia	Close surveillance is necessary to detect cognitive impairment in older people It increases the risk of cleft lip and/or cleft palate in infants exposed *in utero*. A higher dose (>200 mg/day) may cause contractive failure
Felbamate	Randomized, placebo-controlled ($N = 73$)[10] Open-label extension ($N = 70$)[11]	↓34% in frequency of atonic seizures versus ↓9% in the placebo group ($p = 0.01$) ↓≥50% in frequency of astatic seizures in ~66% of patients	Anorexia, insomnia, somnolence	Black box warning over risk of aplastic anemia and acute liver failure
Zonisamide	Retrospective study ($N = 62$)[12]	↓>50% in all-seizure frequency in 33 (51.6%) patients	Somnolence, anorexia, weight loss, oligohidrosis, renal calculi	It can cause metabolic acidosis and skin rash. Only night time use may prevent a problem with sedation
Clobazam	Multicenter, double-blind, phase 2, dose-ranging (high- versus low-dose) ($N = 68$)[13] Phase 3, double-blind, placebo-controlled[14] Open-label extension ($N = 267$)[15]	↓≥40% in drop seizures from baseline in high-dose group ↓68.3% in seizure frequency in high-dose group versus 12.1% in the placebo group ↓91.6% in frequency of drop seizures at 2 years	Somnolence, lethargy, sedation, drooling, constipation, aggression, hypomania, insomnia	Tolerance and physical and/or psychic dependence may develop and discontinuation may result in withdrawal or rebound phenomenon Concomitant use with cannabidiol may have a synergistic effect, but has higher risk of sedation due to many folds increase in active metabolite desmethylclobazam
Rufinamide	Multicenter, double-blind, randomized, placebo-controlled trial ($N = 138$)[20] Open-label extension ($N = 124$)[21] Multicenter, double-blind, randomized, placebo-controlled trial ($N = 59$)[22] Open-label extension ($N = 54$)[23]	↓32.7% in median total seizure frequency versus 11.7% in placebo group ($p = 0.0015$) ↓≥50% in frequency of seizures in 45.1% of patients ↓32.9% in median total seizure frequency versus 3.1% in placebo group ($p < 0.001$) ↓36.1%(median) reduction of tonic-atonic seizures at 52 weeks	Vomiting, somnolence, rash.	It is contraindicated in familial short QT syndrome. Valproate may increase the serum concentration of rufinamide. Rapid titration is possible by increasing the dose every other day to reach a daily target dose over one week
Cannabidiol	Multicenter open-label interventional trial ($N = 214$ epileptic patients, 30 LGS)[29] Randomized, double-blind, placebo-controlled phase 3 trial ($N = 171$)[30] Randomized, double-blind, placebo-controlled phase 3 trial ($N = 225$)[31]	↓ > 50% in all-seizure frequency in 37% LGS patients (the highest response rate in patients with atonic seizures) ↓43.9% in monthly drop seizure the cannibidiol group compared to 21.8% in the placebo ↓41.9% in drop seizures the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group	Diarrhea, somnolence, decreased appetite, pyrexia, fatigue, vomiting, convulsion and status epilepticus	Concomitant use with valproate increases risk of liver enzyme elevation. See interaction with cannabidiol above.
Levetiracetam	Open-label, multicenter, observational clinical trial ($N = 55$)[35]	>50% in all-seizure frequency in 58.2% patients (the highest response rate, 66.7%, in epileptic spAEDs and the lowest, 50.0%, in myoclonic seizures)	Hyperactivity	A combination regimen of levetiracetam, valproic acid and clobazam is an acceptable option
Perampanel	Prospective, single-center ($N = 13$)[36]	↓ >50% in all-seizure frequency in 69.2% Patients	Behavior disturbance, agitation, and fatigue	It has a boxed warning for dose-related serious or life-threatening neuropsychiatric events (most often in the first 6 weeks of therapy). It has a long half-life and has the advantage of a once-daily regimen

Table 1 (*continued*)

AED	Trial design	Efficacy	Reported common side effects	Other considerations
Lacosamide	Multicenter, retrospective, open-label ($N = 18$)[38] Retrospective, open-label ($N = 19$)[39]	↓29% in frequency of all-seizures, 31% in tonic seizures and 20%, drop-attacks ↓ >50%-seizure frequency in 3/19 adult LGS patients	Worsening of seizures, aggressiveness, irritability weight loss, tremor, memory problems, nausea or dizziness	It binds selectively to the slow-inactivated state of sodium channels, in contrast to drugs like carbamazepine and phenytoin, which bind tightly to fast-inactivated states Worsening of tonic, atonic seizures and behavior may occur

has been maintained from the beginning of the treatment. Isojarvi et al. showed that the increase in the clobazam dose could further improve seizure control in >80% of patients with LGS who had responded to a lower dose of clobazam during the initial part of treatment [22]. Though clobazam has a different chemical structure (1,5-benzodiazepine) compared to other commonly used benzodiazepines, increased sedation, drooling, and cognitive deterioration can occur, and the patients need to be closely monitored for such adverse effects and action needs to be taken. Intermittent use may be necessary for some patients if effectiveness diminishes after a certain period of treatment. Although the prescription cost of clobazam is high, it can be an attractive option due to its ability to reduce seizure-related medical utilization and costs [23]. In 2018, a new formulation of an oral soluble film of clobazam has been approved by the FDA for the treatment of LGS [24].

2.1.7. Rufinamide

Rufinamide, a third-generation AED, is much underutilized in adult LGS patients. Rufinamide was approved in 2008 by the FDA for LGS patients ≥4 years old. Two RCTs and open-label extension studies demonstrated that rufinamide could decrease total seizures, particularly drop seizures with acceptable adverse effect profile [25–28]. A further European phase IV, noninterventional, multicenter registry confirmed its favorable safety profile [29]. Valproate may increase the serum concentration of rufinamide by inhibiting hydrolysis, and dose modification is necessary to prevent adverse effects. Rapid titration of rufinamide is possible by increasing the dose every other day to reach a daily target dose over one week, but a lower dose and slower titration may increase the tolerability. Rufinamide is contraindicated in familial short QT syndrome as it can cause QT interval shortening [30]. Kessler et al. demonstrated in a retrospective cohort study that patients with LGS compared with other epilepsy syndromes were twice more likely to continue rufinamide without additional therapy, suggesting better effectiveness in LGS [31]. McMurray and Striano showed in a post-hoc subgroup analysis from a phase III study that rufinamide had a favorable efficacy compared to placebo in adults [32]. Among 31 patients (18–37 years), 33.3% favorably responded to rufinamide versus 0% for placebo for all seizure types and 57.1% versus 10.0% ($P = 0.020$) for drop seizures. Rather than counting drop seizure rates, a novel outcome –a measurement of the seizure-free days, which can be more closely associated with quality-of-life– was investigated in LGS patients receiving rufinamide with positive outcomes [33].

2.1.8. Epidiolex (purified pharmaceutical-grade cannabidiol oil)

An initial open-label intervention study and two placebo-controlled phase III trials of pharmaceutical-grade cannabidiol oil (CBD oil) demonstrated a significant reduction of drop seizures compared to placebo in LGS patients [34–36]. A systemic review of the two randomized trials showed a responder rate (≥50% seizure reduction) of 40% for drop seizures and approximately 50% for the non-drop seizures [37]. In 2018, the FDA approved the pharmaceutical-grade CBD for LGS patients (>2-year-old). However, Epidiolex is expensive, and many patients will continue to use artisanal cannabis products with variable CBD concentrations, dubious quality, and unknown safety profiles. Although there was high-profile (some might say, excessive) reporting on the effectiveness of CBD oil, the effectiveness of artisanal CBD products has not been rigorously tested.

Cannabidiol oil increases active metabolite of clobazam (desmethyl clobazam) by many fold, and the combination of clobazam and CBD oil can have a synergistic effect [38]. Epidiolex has been associated with adverse effects, such as diarrhea, sedation, appetite suppression, and elevation of bilirubin and liver enzymes. Abnormal liver function tests occur most commonly when patients are co-medicated with valproic acid but usually reversible with dose modification of either or both of these AEDs. Significant improvement in alertness and sleep were also reported from CBD. Long-term (median treatment duration of 78.3 weeks) safety and efficacy data have been available from the expanded access program of pharmaceutical-grade CBD. In this cohort of 607 patients, 94 had LGS. After 12 weeks of add-on CBD treatment, a reduction of median monthly major motor seizures by 50% and total seizures by 44% were noted, with persistent reductions in both seizure types up to 96 weeks. In this study, CBD was noted to have an acceptable safety profile, with the most common adverse effects were somnolence (30%) and diarrhea (24%) [39].

2.1.9. Levetiracetam

Though levetiracetam has not been specifically approved for LGS, it typically gets introduced early in the treatment process due to a favorable adverse effect profile. Other than relatively common behavioral adverse effects, it is usually well-tolerated and stays in the medication list longer compared to other AEDs. An open-label multicenter study of levetiracetam in 55 LGS patients showed >50% seizure reduction in >50% of patients with surprising seizure freedom rate of 27.3% [40]. However, further studies, particularly controlled trials, are needed for confirmation of this finding. Due to favorable drug-drug interaction profile, levetiracetam will continue to be used in combination with other specifically approved AEDs for LGS. A combination regimen of levetiracetam, valproic acid, and clobazam is an acceptable option for the treatment of LGS.

2.1.10. Newer AEDs

Perampanel, a novel AMPA receptor antagonist, has shown early promise for the treatment of LGS in retrospective and a small prospective study [41]. A large multicenter study is currently ongoing. However, many LGS patients have significant behavioral issues, and perampanel has a black box warning relating to behavioral alteration.

Data regarding the efficacy of lacosamide in patients with LGS are scarce. Cuzzola et al. reported three LGS patients who had worsening of tonic seizures after the introduction of lacosamide. One patient also developed tonic status epilepticus. Tonic seizures improved after the withdrawal of lacosamide in all 3 patients [42].

Grosso et al. reviewed data of 18 LGS patients who received adjunctive oral lacosamide therapy [43]. Though none of them became seizure-free, during a follow-up period of 9 months, 33% had more than >50% seizure reduction. However, four patients had worsening of seizures and discontinued lacosamide. Additionally, Andrade-Machado et al. showed in a retrospective, open-label study that only three patients out of 19 adult LGS patients had >50% seizure reduction [44]. Additionally, 9 (47.4%) patients had worsening behavior during treatment with lacosamide. Worsening of tonic and drop seizures was reported in 16 (78.9%) and 7 (38%) patients, respectively.

Fenfluramine, an amphetamine derivative, has a proposed antiepileptic action by increasing serotonin transmission. It has been studied as a potentially effective therapy for LGS. A phase II open-label study in 13 LGS patients showed >50% seizure reduction in >60% patients both during the first 20 weeks and an extension period of 15 months of treatment [45]. A phase III RCT is currently ongoing. Though cardiac monitoring for valvulopathy is necessary, the previous pilot study did not reveal any echocardiographic signs of cardiac valvulopathy or pulmonary hypertension. Lorcaserin, selective serotonin receptor (5-HT_{2C}) agonist, has been investigated in 9 patients with LGS with a reduction of motor seizures in 50% of the patients [46].

3. Ketogenic diet (KD)

Data regarding the efficacy of the KD for LGS has been investigated in children. Although recent studies highlighted the efficacy of the KD in adults with intractable epilepsy, specific efficacy and safety data regarding LGS have not been explored. A Johns Hopkins study retrospectively reviewed 71 children with LGS on high fat and low carbohydrate diet, and >50% patients had >50% reduction of seizures at 6 months after the initiation of the KD, which persisted during the one-year follow-up [47]. Additionally, approximately 25% of the patients had >90% of seizure-reduction. This study also reviewed data of 189 other pediatric patients with LGS from 18 previous studies with an outcome similar to the Johns Hopkins study. Adverse effects of the KD are mostly benign, such as constipation, weight loss, hyperlipidemia, etc. Rarely more severe adverse effects such as kidney stones and metabolic decompensation can occur. The KD formula is easy to administer in patients with a gastrostomy tube, but adult patients without gastrostomy tube may tolerate less restrictive– modified Atkins diet (MAD) and low hypoglycemic index diet– better. Most studies on the KD in adult patients with intractable epilepsy classified the individuals in symptomatic versus cryptogenic intractable epilepsy without specifying an epilepsy syndrome diagnosis, such as LGS. Ye et al. calculated an efficacy rate of 52% from the KD (with or without medium-chain triglyceride) and 34% from the MAD in a meta-analysis of multiple studies involving adult patients [48]. Adherence was noted to be better with the MAD (56%) than the KD (38%). Adverse effects due to long term use of the restrictive diets are understudied. Cervenka et al. published a prospective open-label observational study from Johns Hopkins Adult Epilepsy Diet Center, where 106 adult patients naïve to diet therapy were exposed to the MAD [49]. At three months, 36% of these patients had >50% seizure reduction, and 16% became seizure-free. At one and 4-year follow-up evaluation detected 30% and 21% of patients continued to have >50% seizure reduction, respectively, and 13% and 7% of the patients remained seizure-free completely, respectively. Hyperlipidemia and weight loss were the most common adverse effects. In summary, it should be emphasized that there is a lack of specific evidence of the efficacy of the KD or MAD in adult patients with LGS, and appropriate trials should be performed to determine its usefulness in adult patients with LGS.

4. Vagus nerve stimulation (VNS)

Several studies demonstrated the effectiveness and safety of VNS in patients with LGS [50–58]. In general, seizures reduce by >50% in more than half of the patients. Atonic and tonic seizures respond more favorably than focal, tonic-clonic, or absence seizures. In contrast to AEDs, improvement in seizure-control progressively gets better, presumably due to chronic neuromodulation. Patients tolerate VNS well with rare incidence of infection, local pain, cough, voice change, drooling, and throat discomfort. Serious adverse effects such as bradycardia, vocal cord paralysis, and sleep apnea are extremely rare. Besides seizure reduction, the patients may be benefited from an improvement in the alertness and mood, reduced doses of AEDs, decreased ictal and post-ictal periods, decreased incidence of status epilepticus, and reduced rate of hospitalization.

5. Epilepsy surgery

Douglass et al. reviewed surgical options for patients with LGS [59]. Standard pre-surgical evaluation with Video-EEGs, structural high-resolution epilepsy protocol MRIs, and other advanced neuroimaging techniques as appropriate should be employed to identify surgical candidates for focal, lobar, or multilobar resective surgeries. However, the surgical outcome is much better, both for seizure control and improvement in the development, if the appropriate procedure is done in early childhood. However, approximately 40% of LGS patients older than 15 years of age were free of disabling seizures (Engel class I) after resective surgeries [60,61]. Focal structural pathology in the neuroimaging makes a patient an excellent candidate for resective surgery. Lennox-Gastaut syndrome patients with diffuse EEG abnormalities may still be considered for resective surgery in the presence of a localized lesion in the brain. Willey et al. reported good surgical outcomes in patients with generalized or contralateral (to the structural abnormality in the MRI) EEG abnormality in the presence of congenital or early acquired structural abnormality [62]. However, Liu et al. reported favorable surgical outcomes in the presence of asymmetric EEG abnormality in amplitude, synchronicity, onset, or duration. Though it would be rare for an adult LGS patient to undergo resective surgery for LGS, palliative surgery such as corpus callosotomy (CC) should be considered for appropriate patients with disabling drop seizures. Other than a remarkable decrease in the drop seizures, improvement in the attention level is consistently reported after CC. Cukiert et al. reviewed 76 patients with LGS or similar patients who underwent one-stage CC and noted >90% patients had >50% reduction in the generalized seizures (most improvements in atonic seizures followed by atypical absence seizures) [63]. More importantly, more than two-thirds of the patients had >90% reduction of seizures, and approximately 10% became seizure-free. A similar but slightly modest improvement was reported from a prospective study done in Taiwan [64]. Approximately two-thirds of the patients had >50% reduction of seizures during follow-up; moreover, 18.9% of patients remained seizure-free after the procedure in combination with AEDs. Physicians and families use CC as a last resort due to concerns related to surgical complications: specific to CC (disconnection syndrome with hemiparesis, mutism, and impairments due to interhemispheric transfer of tactile or visual information) and nonspecific due to neurosurgical procedures, such as cerebral infarction, extra-axial fluid or blood collection, ventriculitis, meningitis, and hydrocephalus. The risk of hemiparesis, a particularly permanent one, is very small. Cukiert et al. reported that no individuals developed hemiparesis after CC in a cohort of 76 patients. However, 72 patients showed postoperative signs or symptoms of an acute cal-

losal disconnection syndrome (68 patients developed apathy, 54 experienced urinary incontinence, 8 had right hemineglect, and 6 developed low-verbal output). They had a subsequent improvement over the next 1–7 weeks.

Though symptoms of disconnection syndrome typically improve over time, the newer surgical techniques such as radiosurgical CC may further reduce the risk of complications. Feichtinger et al. reported the use of radiosurgical CC, performed using 3–4 target centers via a collimator helmet, in two adult LGS patients with a 60% reduction of drop attacks [65].

6. Management of status epilepticus

Although the incidence of SE in adult LGS patients is unknown, these patients may present with nonconvulsive status with variable clinical features such as mild confusion to a comatose state. Rather than an abrupt change in behavior, an insidious decline in the mental status also can be a presenting feature, and a high index of suspicion is necessary with a comparison of the current EEG with the patient's baseline EEG. Importantly, changes in the antiepileptic regimen can induce status epilepticus in these patients. Treatment for nonconvulsive status should be less aggressive than convulsive status and in most situations, can be controlled without IV anesthetic agents. Experts recommended clobazam, steroid, or high dose IV valproate as preferred agents for the management of nonconvulsive status [66].

7. Transitioning to adult care

The plan for transition may need to start during early adolescence; the failure in planning may lead to poor seizure control, increased risk of morbidity and sudden unexpected death in epilepsy (SUDEP), and deficient management of comorbidities [67,68]. A transition clinic with the availability of both pediatric and adult neurologists is optimum; nonetheless, in most settings, it is difficult to establish due to various reasons. However, a formal transition plan can alleviate some of the challenges. Several years before this transition, essential details of the process should be discussed among the patient, family, and provider. Responsibility of transition should be not be endowed to the pediatrician or primary care provider; as in most LGS patients, neurologists are most familiar with the active issues– epilepsy, intellectual impairment, and other common comorbidities associated with the epileptic encephalopathy. Through advanced practice providers can provide extensive help with the transition process, ultimately an experienced epileptologist – with in-depth knowledge about LGS, including the evolution of electroclinical phenotype during adulthood and expert skills in pharmacological and nonpharmacological management of LGS– needs to map out the most appropriate treatment plan. It is not unusual to discover that LGS patients are taking 4–5 different AEDs concurrently. Over the years, medications are added to the regimen due to continuing seizures without weaning ineffective AEDs. Some AEDs such as sodium channel blockers can potentially worsen drop seizures. However, rapid weaning from these can trigger convulsive seizures. Both carbamazepine and phenytoin can be effective in controlling tonic and tonic-clonic seizures. Careful assessment is necessary to identify the most effective 1 or 2 AEDs and then, the other ineffective AEDs can be slowly weaned. However, periodic worsening of seizure control can occur in LGS without any external triggers and can be difficult to differentiate from the worsening related to the withdrawal of a particular AED. A careful seizure counts– several months before, during, and after the weaning– may help objectively determine the impact of the AED-withdrawal. Potentially synergistic combinations such as valproic acid with lamotrigine or clobazam with CBD can be preferably selected at this time. A comprehensive note can be included in the patient's chart with the following information: A plan for seizure clusters, alternative AEDs to be introduced if the current regimen becomes ineffective, and documentation of previously discontinued AEDs whether due to adverse effects or ineffectiveness. As health insurance coverage of the patient may change after adulthood, knowledge about potential coverage of any particular service or AEDs may guide specific treatment choices. As much as possible, diagnostic workup, as well as necessary repeat neuroimaging and EEG, should be completed if prior studies were performed many years ago. That may help to decide if any new therapy can be useful or change in the treatment plan is necessary before the transition. As patients may continue with the fixed AED regimen for decades, special consideration should be given to the adverse effect profile, particularly cognitive and behavioral consequences. Due to excessive sedation, benzodiazepines (other than clobazam), phenobarbital, and other 1st generation AEDs may not be ideal choices. Some newer AEDs such as topiramate in higher doses can cause significant cognitive slowing, and vigilant monitoring is necessary. Some caregivers may not come forward with the concern of adverse effects, and direct questioning about cognitive slowing is necessary. Occasionally improved alertness and cognition after weaning of the culprit medicine proves the impact of the adverse effects. During careful planning of the AEDs, not only seizure count but the quality of life issues-sleep, alertness, behavior, and cognition- should be carefully considered.

8. Management of other comorbidities

8.1. Cognitive impairment

Cognitive impairment brings new challenges during adolescence and adulthood. Severe intellectual impairment reported in 43% of patients with cryptogenic LGS and 76% with symptomatic LGS [69]. To describe the employment status in LGS patients, Yagi et al. investigated the job situation of 102 adult LGS patients [70]. In this cohort, only 12 individuals had been involved in a regular job. Although 36 additional patients had part-time or sheltered jobs, the majority (54 individuals) were unemployed. Later onset LGS may be associated with better cognitive prognosis. Ferlazzo et al. reported moderate to severe intellectual impairment in 26/27 patients and behavioral abnormalities in 14/27 patients (age 40–59 years) in a long term (average 35 years) follow-up study [71]. With the transition of care during adulthood, several other difficulties arise for the family related to legal guardianship, residential planning, financial planning, availability of ancillary services, and employment challenges. Parents typically accept the severity of the LGS diagnosis after passing through a difficult grief stage but continue to be anxious about receiving adequate treatment of their offspring throughout adulthood. Besides a high risk of early death and physical disability, poor health-related quality of life is prevalent in adult patients with LGS. Nevertheless, more research regarding quality of life issues is needed [72,73]. Several useful tips to deal with these challenges has been provided in the LGS foundation website and summarized in table 2 [74,75].

8.2. Psychiatric and behavioral issues

Psychiatric issues, especially oppositional behaviors, intermittent explosive outbursts, anxiety, and depression, may become more prevalent with age. Cognitive impairment increases the risk of these psychiatric comorbidities; however, confirmation of the psychiatric diagnosis may be particularly problematic in the presence of intellectual impairment. Communication difficulties and frustration may mimic psychosis, and non-pharmacologic intervention with behavioral therapy can be surprisingly effective.

Prompt evaluation and treatment by mental health care providers especially valuable for these patients. Psychopharmacologic treatment should be managed under the care of a physician with particular experience managing this complex group of patients, who are already on polypharmacy for seizure management. Although there is a general fear of worsening seizure control from antidepressants and antipsychotics, the actual risk is relatively minor, with rare exceptions, such as during treatment with clozapine. However, close monitoring for seizure worsening and behavioral changes are necessary after the addition of psychotropic medications, as well as the use of a low starting dose, slow escalation of the dose, maintenance of the minimal effective dose, and avoidance of complex drug–drug interactions.

8.3. Sleep dysfunction

Sleep dysfunction is a common comorbidity in LGS. Adult LGS patients may cease to have frequent day time seizures, but continue to suffer from nocturnal tonic seizures. Sforza et al. reported that in adult LGS patients, interictal abnormalities are significantly higher in the first 3 h of sleep with a progressive decline during later part, possibly related to sleep homeostatic influences on the epileptic threshold [76]. The authors also found that epileptiform activities were more prevalent during stage II and slow-wave sleep, which might be responsible for sleep alteration and poor sleep quality compared with stage I and rapid eye movement (REM) sleep. This paper suggested nocturnal video telemetry study to identify the period of increased epileptogenicity and consideration of a high dose of AED at night to counteract increased epileptogenicity. Eisensehr et al. reported that a higher level of activation during the cyclic alternating pattern of non-REM sleep was associated with more generalized polyspike bursts and seizures than the lower levels of arousal phase [77].

8.4. Gender-specific issues for women

Women with LGS are susceptible to have unplanned, high-risk pregnancies. Young maternal age, single parenthood, and poor antenatal care are other potential risk factors. The risk of premature birth is higher in patients with intractable epilepsy. Folic acid supplementation and appropriate contraceptive plan need to be discussed early with adolescent women [78]. The risk of unintended pregnancy is high in women with LGS due to reduced or poorly effective (withdrawal or barrier methods) contraceptive use. Moreover, enzyme-inducing AEDs such as phenobarbital, phenytoin, carbamazepine, oxcarbazepine, topiramate (in dosages above 200 mg daily), and glucuronidated AEDs (lamotrigine) can decrease the effectiveness of systemic hormonal contraceptives. Sexually active patients who are on enzyme-inducing AEDs should take advantage of the intrauterine devices (IUD; progestin or copper) or tubal ligation to prevent pregnancy. Women with LGS should be educated about prevention strategies against sexual exploitation, abuse, sexually transmitted diseases (including HIV infection).

8.5. Falls and other injuries

Recurrent falls may continue to cause physical injuries and poor quality of life [79]. These patients may suffer progressive gait deterioration and appearance of extrapyramidal features. Seizure related adverse incidents such as drowning, near drowning, burns, fractures, faciomaxillary, and soft tissue injuries are common in patients with LGS. Due to the high frequency of seizures and drop seizures, the risk of injury may be higher than other adult patients with epilepsy. Moreover, associated intellectual impairment increases the risk of falls and injuries. Many of these patients also take medicines that increase the risk of falls, such as anxiolytics, antidepressants, antipsychotics, and sedatives. In spite of significant diminution of quality of life due to recurrent falls, high-quality evidence regarding various intervention strategies is lacking. However, a comprehensive approach is necessary to increase mobility and encourage physical exercise in these patients. Careful assessment of the medications is necessary to identify any agent that is potentially provoking falls. If falls are primarily due to seizures, an aggressive management strategy to control seizures should be undertaken. Environmental modification and use of a helmet may be necessary to prevent severe injury, particularly head and faciomaxillary injuries. Daily exercise and physical movement may reduce the risk of nonseizure induced fall risk. Moreover, other potentially effective strategies – the provision of adaptive devices, modification of the environment, education about safety, aggressive management of epilepsy, and scrutiny of the medication-related adverse effects- can mitigate fall risk and improve the quality of life of adult patients with LGS. Also, special attention should be given to the bone health.

Table 2
Planning for the future challenges for adolescents and adults with Lennox-Gastaut syndrome.

- Establishing care in a transition clinic to facilitate transfer to an adult neurologist
- Implementing a formal transition plan early in the process
- Fostering an excellent relationship between parent and the pediatric provider
- Developing skills necessary for parental advocacy
- Networking among LGS families
- Building a strong support group within and outside the family
- Expanding parent- support groups
- Promoting knowledge in families to be able to interpret information related to insurance and adult health care providers
- Providing information to help access to adult providers specific to the geographic location
- Advancing parental and caregiver education (especially about the importance of guardianship or power of attorney, necessary changes related to providers, insurances, and the loss of services with the end of special education

8.6. SUDEP (sudden unexpected death in epilepsy)

Sudden unexpected death in epilepsy risk is higher in LGS due to the high-frequency of seizures and intractability of chronic epilepsy [80,81]. Intellectual impairment and nocturnal seizures also potentially increase SUDEP risk. It is essential to discuss SUDEP risk with the patients, families, and other support workers (if the patient is living in a residential unit) and address all the modifiable risk factors. Nocturnal supervision by auditory monitors or other sophisticated commercial epilepsy alarms can be helpful to detect seizures. In some rare cases, the caregiver may need to sleep in the same room or provide physical checks intermittently during nights.

8.7. Healthcare utilization

Reaven et al. demonstrated that significantly higher healthcare utilization and costs were associated with LGS patients rather than patients with other types of epilepsies [82]. Pina-Garza et al. similarly showed that total healthcare and medical costs had been much higher in LGS patients than other epilepsy patients in all age groups, suggesting that the price- burden has a lifelong impact without diminution after childhood [83]. In this study, a considerable proportion of patients were not treated with broad-spectrum AEDs, including clobazam and rufinamide. Appropriate AEDs are underutilized in older patients due to various reasons, including diagnostic difficulty. Classical drop seizures of LGS are less fre-

quent in adult patients. Although paroxysmal fast discharges during sleep persist, diffuse slow spike-wave discharges may disappear in adult LGS patients. A Refractory Epilepsy Screening Tool for LGS (REST-LGS) has been developed to improve the identification of patients with LGS [84]. As the clinical features of LGS may change over time, adult patients with epilepsy and intellectual impairment (particularly if no prior etiologic diagnosis) should undergo genomic evaluation. Due to genetic heterogeneity of LGS, a genome wide assessment such as CNVs (comparative genomic hybridization array testing) and/ or gene sequencing (targeted multiple gene panels, whole exome sequencing, or whole genomic sequencing) is most appropriate. Besides improved diagnosis in adult patients, genetic evaluation may provide enhanced understanding about the natural history of the disease. Additionally, identifying the genetic cause may unravel the underlying disease mechanism with future provision of precision medicine. For example, a distinct phenotype of SCN2A encephalopathy patients may have favorable response to sodium channel agents.

9. Conclusion

There are no consensus recommendations or guidelines on the management of LGS beyond childhood. However, expert-opinion favors valproate as one of the first-line therapies in LGS except in women of childbearing age. Based on several phase 3 studies, several AEDs are available for intractable seizures to be used sequentially or in combinations: lamotrigine, rufinamide, topiramate, clobazam, and CBD oil. Head to head studies to compare these AEDs have not been performed. Prescribing pattern of AEDs is primarily dependent on physician and patient preferences, presence of other comorbidities, and available coverage from the payors. During combination therapy, restricting the number of AEDs to 2 or 3 is justified to minimize adverse effects, and careful consideration should be given to the synergistic combinations such as valproate and lamotrigine and clobazam and pharmaceutical-grade pure CBD oil. Due to the risk of aplastic anemia and hepatic failure, felbamate should not be used as a first or second-line therapy. Nonpharmacologic therapies such as the KD, VNS, and palliative surgeries can be useful in patients with intractable seizures and can be considered after failure of two appropriately chosen AEDs. Care providers should give high priority to the cognitive, behavioral, educational, and social requirements of these patients and shift the perspective from only seizure management to a more global approach in the improvement of quality of life in patients with LGS. [the author's opinion] Caregivers and providers should be also aware of the unique challenges of LGS beyond childhood and use appropriate resources to incorporate these patients into the social structure of society [the author's opinion].

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Review

Expert opinion: Proposed diagnostic and treatment algorithms for Lennox–Gastaut syndrome in adult patients

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ABSTRACT

Lennox–Gastaut syndrome (LGS) is a severe developmental epileptic encephalopathy diagnosed in childhood that persists through adolescence and into adulthood. While the characteristics of LGS in pediatric patients are well defined, including "drop attacks", interictal slow spike and wave electroencephalogram (EEG) activity, and intellectual disability, these features can evolve over time, and different EEG activities may be present in adult patients with LGS. This may result in missed diagnoses in these patients and subsequent challenges for the adequate treatment of their seizures. Based on discussions held during the LGS Transition of Care advisory board meeting and thereafter, we developed proposed diagnostic and treatment algorithms for LGS in adult patients.

We highlight readily available assessments to facilitate diagnosis of LGS, based on past medical history and physical examination. The LGS diagnostic algorithm recommends that clinicians consider the occurrence of wider seizure types and abnormal EEG activities to be potentially indicative of LGS. Seizure types may include atypical absence seizures, myoclonic seizures, focal seizures, and tonic–clonic seizures, and EEG may demonstrate background slowing, focal or multifocal epileptiform discharges, and diffuse fast rhythms during sleep, among other activities. Extended EEG during sleep and video-EEG should be used in equivocal cases.

Treatment of LGS in adult patients should incorporate both antiseizure drug (ASD) therapy and nonpharmacologic approaches. Frequent reassessment of patients is considered a central aspect. ASDs were categorized based on order of preference for use in the treatment of LGS; Tier 1 comprises recommended first-line ASDs, and includes valproate, clobazam, lamotrigine, rufinamide, topiramate, and cannabidiol. Other treatment options include diet, neurostimulation, and surgical approaches.

Developments with the potential to improve diagnosis in the future include genetic screening, while novel ASDs and advances in neurostimulation techniques may provide valuable treatment options. These algorithms should be frequently revisited to incorporate improved techniques and therapies.

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Abbreviations: AAN, American Academy of Neurology; ASD, antiseizure drug; BCP, birth control pill; BRV, brivaracetam; CBD, cannabidiol; CBZ, carbamazepine; CLB, clobazam; CNZ, clonazepam; DBS, deep brain stimulation; DZP, diazepam; EEG, electroencephalogram; FBM, felbamate; FBTC, focal to bilateral tonic–clonic; FDA, Food and Drug Administration; GBP, gabapentin; GTC, generalized tonic–clonic; HSV, herpes simplex virus; ID, intellectual disability; KD, ketogenic diet; LCM, lacosamide; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; OXC, oxcarbazepine; PBT, phenobarbital; PDD, pervasive developmental disorder; PER, perampanel; PGB, pregabalin; PHT, phenytoin; RNS, responsive neurostimulation; RUF, rufinamide; SCN1A, sodium channel, neuronal type I, alpha subunit; SCP, spastic cerebral palsy; SE, status epilepticus; SGE, symptomatic generalized epilepsy; SSW, slow spike and wave; STP, stiripentol; TC, tonic–clonic; TGB, tiagabine; TMD, trimethadione; TPM, topiramate; TS, tuberous sclerosis; V-EEG, video-electroencephalogram; VGT, vigabatrin; VNS, vagus nerve stimulation; VPA, valproate; ZNS, zonisamide.

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1. Introduction

Lennox–Gastaut syndrome (LGS) is a severe developmental epileptic encephalopathy [1,2], with onset usually occurring between the ages of 3 and 5 years, and typically before the age of 8 years [3]. Diagnosis of LGS still relies upon the presentation of the classical triad of characteristics, which include: multiple seizure types (including tonic, atonic, and atypical absence seizures) [2,4]; abnormal electroencephalogram (EEG) activity (consisting primarily of an interictal pattern of diffuse slow spike and wave (SSW) activity, occurring during wakefulness) [2,4]; and intellectual disability [2]. Gastaut originally described this triad of characteristics in 1966 [2], and these historical criteria now present challenges for the effective and reliable diagnosis of LGS in adult patients, since the classic signs of LGS can evolve in patients over time [1,4,5]. This evolution could potentially result in differences in EEG activities emerging in patients with LGS with increasing age, as demonstrated in a patient with LGS and tuberous sclerosis in Fig. 1, and the occurrence of seizure types beyond those most commonly associated with LGS. Consequently, adult neurologists may look for signs of LGS that are no longer present in adult patients; therefore, patients could be incorrectly characterized as having generalized epilepsy, rather than receiving a correct diagnosis of LGS. In addition, many patients may present to an adult neurologist for the first time, providing little or no medical history from infancy, further complicating the detection of any preceding signs of LGS that may have occurred during childhood [5]. Additional challenges to diagnosis may arise from LGS having very diverse etiologies, including genetic, structural, and cryptogenic [1].

American Academy of Neurology (AAN) and American Epilepsy Society (AES) treatment guidelines for LGS, based on the assessment of evidence available in the literature (during 1987–2015), indicate that lamotrigine, topiramate, and rufinamide are established as effective in treating LGS; based on clinical experience, clobazam is also established as an effective treatment for LGS [6,7]. These four antiseizure drugs (ASDs) have each received approval from the Food and Drug Administration (FDA) for the treatment of seizures associated with LGS [8–11] and along with valproate, which has not been approved for the treatment of LGS, comprise the most commonly used medications for the treatment of LGS [4]. Since the publication of the AAN and AES treatment guidelines, cannabidiol has also received FDA approval for the treatment of seizures associated with LGS [12]. Felbamate is considered to be effective in the treatment of LGS; however, in the context of LGS and due to its unfavorable safety profile, felbamate is only recommended for use in patients over 4 years of age who are unresponsive to the primary ASDs [13]. However, long-term cessation or control of seizures with ASD treatment may not be a realistic goal for most patients with LGS due to the refractory nature of the seizures

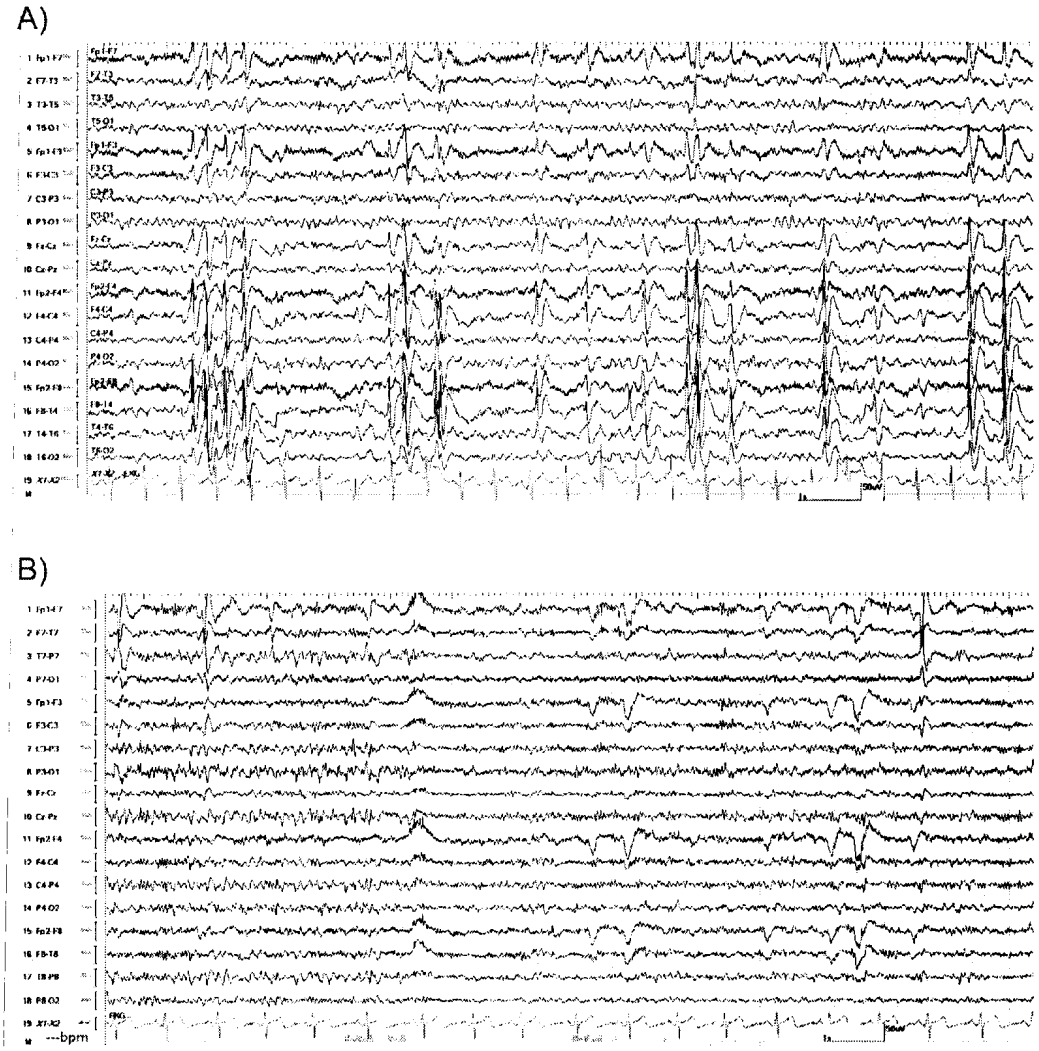


Fig. 1. EEGs demonstrating activities from a patient with LGS and tuberous sclerosis at the ages of (A) 13 years and (B) 25 years. EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome.

associated with the syndrome, and challenges in balancing ASD polytherapy and adverse effects [14,15].

As patients mature, the transition of care from a pediatric to an adult neurologist is particularly relevant in the context of LGS. As LGS persists through adolescence and into adulthood, a more effective and comprehensive transition of care from pediatric to adult care services is required in order to avoid patients becoming lost in the care system and to maintain continued access to specialist care [16]. Notably, behavioral issues may be exacerbated in patients with intellectual disabilities during the transition to adult services, as a result of anxiety experienced in leaving a pediatric neurologist with whom they have developed a relationship over time for an unfamiliar adult neurologist, and also due to disruption to an established routine [16–18]. Adolescent patients can face challenges receiving treatment from pediatric care services, which may prefer to move patients on to adult services rather than retain them in pediatric care due to limited resources and a shortage of pediatric neurologists [4,16,19]. However, adult healthcare services may not always be suitably prepared for patients with intellectual disabilities, may have a significantly different culture and approach to care compared with pediatric services, and will not usually accept patients aged under 18 years [4,16]. Further issues can arise from the changes occurring in an adolescent patient's life surrounding their sexual maturity, and social, financial, and legal status [16].

While the management of LGS has been reviewed previously [4], approaches for the diagnosis and treatment of LGS specifically in adolescent and adult patients are not as well established, potentially due to the belief that LGS is a childhood syndrome. The underdiagnosis of LGS in adult patients needs to be addressed in order to prevent patients from receiving ineffective and unsuitable medications, and therefore a broader definition of LGS and improved awareness of additional indicators of LGS may reduce missed diagnoses. In addition, current treatment algorithms are considered suboptimal for adults newly diagnosed with LGS and for adult patients with LGS undergoing a transition of care, especially as many patients with LGS are refractory to ASDs, with reported rates of patients experiencing seizures that persist long-term ranging from 66 to 100% [20–23]. In order to discuss the development of proposed diagnostic and treatment algorithms for LGS in adult patients, the LGS Transition of Care advisory board convened in November 2017, with the objectives of supporting a smoother transition of care and facilitating reliable and effective diagnosis and treatment of LGS in adult patients. Here, we present the two proposed algorithms that emerged from these discussions, both of which have been further developed subsequent to the advisory board meeting.

2. A proposed diagnostic algorithm for LGS in adult patients

2.1. Development of the LGS diagnostic algorithm

Given that the previous definition of LGS was considered outdated, attendees of the advisory board devised a diagnostic algorithm based upon their own clinical experience and expert opinion. In addition, attendees each developed two case studies prior to the meeting, which described real patients or hypothetical or composite cases. The first was based on an adult or adolescent patient with LGS, who was either in the process of transitioning from pediatric care or had recently transitioned from pediatric care, and the second was based on an adult patient with LGS who had already transitioned. Cases were reviewed and one case from each advisor was presented at the advisory board meeting. A summary of these cases is provided in Table 1. Notably, these cases highlight the challenges associated with diagnosing and treating LGS in adult patients. During the advisory board meeting, a rudimentary diagnostic framework was created to facilitate discussions around the core criteria that are essential for making a clinical diagnosis of LGS in adults. The primary focus of discussion was to identify readily available assessments to facilitate the diagnosis of LGS in adult patients with refractory seizures and in a community setting. Since the advisory board meeting, advisors continued to discuss the diagnostic algorithm to produce the version presented here.

2.2. Proposed diagnostic algorithm for LGS in adult patients

Readily available assessments to form the basis of the diagnostic algorithm were identified, which can be applied on presentation of an adult patient with refractory seizures. These assessments include past medical history, physical examination, and review of medical records (Fig. 2).

Although the occurrence of multiple seizure types during childhood is already understood to be indicative of LGS [3], a wider array of seizure types should be considered when making assessments based on a patient's medical history. The presence or history of two or more seizure types that are often resistant to medical treatment may contribute to a diagnosis of LGS. These seizure types include, but are not limited to, drop attacks (including tonic, atonic, and myoclonic atonic seizures), atypical absence seizures, myoclonic seizures, focal (partial) seizures, and tonic–clonic seizures (including focal to bilateral tonic–clonic [secondarily generalized] seizures and generalized-onset tonic–clonic [primary generalized tonic–clonic] seizures).

Age at onset of LGS symptoms should also be considered. Although Gastaut originally noted that a range from 1 to 6 years of age was generally the most common period for the onset of symptoms [2], our proposed diagnostic algorithm is consistent with more contemporary guidelines that recognize that onset usually occurs between 3 and 5 years of age, and typically occurs before 8 years of age (Table 2) [3]. Childhood onset of developmental delays and cognitive impairment should also be regarded as potential signs of LGS, and these may occur alongside behavioral disturbances, such as aggressiveness, autistic traits, and hyperactivity [24].

Findings from physical examination of an adult patient with refractory seizures may reveal neurological deficits or could inform the etiology of their refractory seizures. Indicators from physical examination that may suggest a diagnosis of LGS include the presence of symptoms of neurocutaneous syndromes (such as tuberous sclerosis), hemiparesis, quadriparesis, and cognitive impairment.

While the absence of medical records, case summaries, and referral letters from pediatric neurologists may be problematic, the review of such documentation, where available, may contribute towards the diagnosis of LGS. A possible history of West syndrome should be investigated as this can often develop into LGS, as reported in 34% of patients with West syndrome by Camfield et al. [25], and it may be regarded as an antecedent syndrome to LGS. However, a history of West syndrome should not be considered a requirement for a diagnosis of LGS.

In adults with LGS, EEG assessment has shown slow background activity, diffuse slow spike–wave discharges during wakefulness, and bursts of diffuse fast rhythms during sleep [26]. In equivocal cases, where a diagnosis of LGS is not conclusive after readily available assessments have been conducted, a routine EEG should be performed to distinguish abnormal activity that may be indicative of LGS, including SSW activity (Fig. 3A). However, given that EEG activities in patients with LGS commonly evolve as patients mature, SSW activity may no longer be present in adult patients. Instead, other abnormal activities may be detected and should be recognized as possible signs of LGS. These include, but are not limited to, diffuse bilateral background slowing, focal spike and wave discharges, multifocal epileptiform discharges, generalized polyspike and wave discharges, and generalized paroxysmal fast discharges (Fig. 3B–F). When a diagnosis of LGS remains uncertain after EEG, admission of the patient to an epilepsy monitoring unit for a multihour EEG with sleep features should be considered [26].

Based on this algorithm, if a diagnosis of LGS in an adult patient is probable or possible, treatment of LGS should be initiated. While the proposed treatment algorithm is outlined later in this paper, in patients where multiple ASDs fail, referral to a tertiary center for video-EEG and/or to an epileptologist is recommended. A summary to compare the criteria

Table 1
Summary of case studies presented at the LGS Transition of Care advisory board.

Patient	Age, years	Summary of patient history	EEG/V-EEG activities	Treatments		Course of care/challenges
				Current	Past	
Patient 1	33	Recurrent seizures since SE episode at 5 months old; infantile spasms at 9 months, and hypsarrhythmia; cerebral palsy; frequent falling	Generalized slowing; multi-focal epileptiform discharges; generalized slow spike–wave discharges	VPA, RUF, CBZ, ZNS, LEV, CLB, VNS	RUF, LEV, CBZ, LCM, VPA, CNZ, CLB, ZNS, valaciclovir (for dizziness)	*Challenges:* Limited medical records at first visit *Treatment plans:* History/EEG suggested drop seizures; family reluctant with some options, including ASDs, VNS, and surgery *Outcomes:* Significantly reduced drop seizures and related injuries – patient more alert, talkative, and in better mood
Patient 2	32	Decreased muscle tone; episodes of myoclonus and several drop attacks per day; developmental delay; never developed speech *Seizure types:* myoclonic jerks with falls; tonic posturing; brief losses of muscle tone (10–15/month)	Generalized slowing; epileptiform discharges; slow spike and wave discharges; tonic seizures with generalized discharges	RUF, VPA, CLB, BRV, PER, ZNS	VPA, CNZ, CBZ, ZNS, PHT, GBP, TPM	*Challenges:* Lack of records from pediatric neurologist – only records for previous 1–2 years received from the general neurologist; relied on recollect on of patient's mother and description of initial seizures; mother reluctant to consider VNS and some medication changes; aggressive behavior
Patient 3	18	PDD, TS, LGS *Seizure types:* focal unaware (2–4/day), drop attacks (several/week)	Tonic seizures (generalized paroxysmal fast activity) with focal features; multiple independent spike foci; multifocal delta slowing; asymmetric diffuse polymorphic delta-theta slowing; frontal rhythmic delta activity	BRV, LCM, PER, PBT, VGT, VNS	Everolimus, CLB, LTG, LEV, PHT, RUF, TGB, TPM	*Challenges:* Tuberous sclerosis, behavioral issues (chance of harming self), and drop attacks *Treatment plans:* Rechallenge with RUF (previously RUF caused vomiting); decrease LCM; taper off PER; taper PBT; consider VPA. Multidisciplinary team for TS; comprehensive epilepsy team to seamlessly continue care, full-time psychiatry services
Patient 4	16	Mitochondrial disorder, LGS, developmental delay. Referred to palliative care; hospitalized for increase in tonic seizures, lethargy, inability to eat *Seizure types:* gelastic; tonic; TC; atypical absence; atonic	Tonic seizures with spike–wave discharge followed by generalized paroxysmal fast activity; generalized slow spike–wave discharges; electrodecrements in sleep; background disorganization and slowing	RUF, VPA, CLB, VNS	LEV, STP, VGT, ZNS	*Challenges:* Mitochondrial encephalopathy, epilepsy; complex transitions and re-challenging with medications require trust between patient/caregivers and providers; comprehensive epilepsy team to seamlessly continue care *Treatment plans:* Increase RUF as needed and as tolerated; consider increasing CLB and moving to bedtime dosing
Patient 5	17	ID; HSV meningo-encephalitis at 1 month; aspiration pneumonia; SCP; LGS *Seizure types:* Atypical absence; drop attacks; FBTC; nocturnal TC seizures (rare); clusters (2–3/month); 1 episode of SE	Background slowing with slow spike and wave discharges, more prominent in sleep	VPA, CLB, VNS	LTG, LEV, OXC, PBT, PHT, RUF, TPM, CBD, KD	*Challenges:* Separated parents; comorbidities; bond with pediatric team (years); transitional care team required at both ends *Treatment plans:* Adult epileptologist identified and detailed clinical summary provided; continue current regimen and consider PER or FBM; callosotomy an option for refractory drop seizures
Patient 6	22	SGE from 1 year of age; ID; SCP; premature birth; LGS; (+) SCN1A mutation *Seizure types:* TC seizures (monthly); seizure clusters (2–3/month); SE	Background slowing with multifocal spikes; slow spike and wave discharges	LEV, (+ LTG)	PBT, OXC	*Transition of care:* Adult neurologist identified and detailed clinical summary provided; mother complained that she didn't feel as comfortable with the adult care facility; LTG added, resulted in increased seizures *Recommendations from pediatric epileptologist:* LTG may worsen patients with SCN1A mutations; add RUF; BCP for catamenial seizures; social service referral
Patient 7	48	Intractable seizures (from 2 years); developmental delay; LGS diagnosis at 8 years *Seizure types:* Drop attacks; GTC; tonic (2–5/day)	Multifocal sharp waves; complex partial seizure; multiple tonic type seizures	LEV, LTG, CBZ, RUF	CBZ, LTG, PBT, PHT, VPA, CNZ	*Recommendations:* Genetics workup; VNS; stop CBZ; consider FBM, CLB, and diet
Patient 8	36	Febrile SE; residual left hemiparesis; developmental delay; LGS diagnosis at 6 years *Seizure types:* GTC (1/week); tonic (1/day); atonic (1/day)	Diffuse background slowing with multifocal sharp discharges; electrodecremental generalized fast activity with tonic seizures; generalized asymmetric slow spike and wave activity	LEV, LTG, VPA, CNZ, VNS	CBZ, LTG, PBT, PHT, ZNS, CLB, FBM	*Challenges:* ID; intractable epilepsy, severe developmental disability; failed multiple regimens

Table 1 (*continued*)

Patient	Age, years	Summary of patient history	EEG/V-EEG activities	Treatments		Course of care/challenges
				Current	Past	
Patient 9	32	Infantile spasms (9 months); LGS (3 years) *Seizure types:* TC; tonic; atonic; myoclonic; absence; focal (partial)	*Previous:* Slow spike and wave *Reevaluation at transition of care:* Spike and wave activity; background slowing; generalized and focal spikes	LCM, LEV, VNS	PBT, LTG, TPM, CBZ, ZNS, FBM, CLB, RUF, VPA, GBP, PHT, PGB; TMD	Patient had no long-term response to any ASDs; full-time care by mother and/or father
Patient 10	18	Cognitive delay; hypotonia; crying; aspiration pneumonia; fever; weight loss; LGS (2 years) *Seizure types:* GTC (2–4/month); tonic stiffening (1–3/day); absence (4/day); myoclonic jerks; partial	*Previous:* bilateral frontal spikes; multifocal epileptiform spikes *Reevaluation at transition of care:* Generalized spike and wave activity; multifocal spike discharges	LTG, OXC, LEV, CBD, DZP	CLB, ZNS, CNZ, VPA	*Challenges:* Anxiety over switching from pediatric neurologist to adult neurologist *Services available:* Direct nurse to nurse and doctor to doctor care

for diagnosis based on this proposed algorithm compared with those of the classical LGS diagnostic criteria based on Gastaut et al. (1966) is provided in Table 2 [2].

2.3. Future directions for the diagnosis of LGS in adult patients

Given the challenges associated with diagnosing LGS in adult patients, the implementation of novel assessments to facilitate swifter diagnoses is desirable, as this may allow treatment with appropriate ASDs to be initiated sooner and for more targeted treatments to be identified. In addition, earlier diagnosis of LGS can help the medical provider in discussing the prognosis with families and caregivers. One possibility to improve upon current approaches to LGS diagnosis is the development of genetic testing. Currently, such testing is used in the diagnosis of Dravet syndrome in pediatric patients, by screening for mutations associated with the syndrome, including in sodium channel SCN1A, which are believed to be present in 70–80% of patients with Dravet syndrome [27,28]. As numerous de novo and heritable mutations across multiple loci are believed to be associated with LGS [29], this would require the development of a multigene panel to be tested. Such screening would not be able to rule out a diagnosis of LGS, as structural or cryptogenic etiologies unrelated to genetic mutations cannot be eliminated by such approaches [1]. However, a significant proportion of the estimated 25% of patients with LGS of a cryptogenic etiology may benefit from an additional diagnostic assessment based on genetic testing [30,31].

3. A proposed treatment algorithm for LGS in adult patients

3.1. Development of the LGS treatment algorithm

As previous treatment algorithms were considered to be suboptimal for informing treatment decisions for adult patients with LGS, coupled with its multiple etiologies (structural, metabolic, and genetic) [32], attendees of the advisory board devised a treatment algorithm based upon their own clinical experience and expert opinion. Advisors completed premeeting surveys, which included questions surrounding their preferred ASD for the treatment of seizures associated with LGS (Table 3). The ASDs most frequently used to treat LGS in adult patients were collated and the output served as the basis for categorizing ASD treatment preferences into three tiers. Tier 1 represents ASDs that are FDA-approved for the treatment of LGS and are recommended as first-line therapies; Tier 2 represents ASDs that are commonly used for the treatment of LGS; and Tier 3 represents ASDs that are less frequently used for the treatment of LGS and may have limited systematic trial data to support their efficacy and/or associated safety concerns. An additional group of ASDs to be avoided in the treatment of seizures associated with LGS was also defined. The case studies described earlier in relation to the diagnostic algorithm were also used to inform the development of the treatment algorithm. Nonpharmacologic interventions complementary to ASD treatments were also discussed and included in the development of the treatment algorithm. Since the advisory board meeting, further discussions have been held to revise the treatment algorithm and account for recent developments, such as the approval of cannabidiol by the FDA for the treatment of LGS [12].

3.2. Proposed treatment algorithm for LGS in adult patients

Based on the discussions to develop the treatment algorithm, frequent reassessment and follow-up of adult patients with LGS is recommended as a cornerstone of the proposed treatment algorithm (Fig. 4). Reassessment may occur at least once every three, six, or 12 months, and this should be determined based on seizure frequency, changes in medication, and other medical needs. The management of behavioral symptoms should also be considered when assessing treatment options. Patients with vagus nerve stimulation (VNS) implants may require more frequent visits for programming.

Antiseizure drug polytherapy is recommended alongside complementary non-ASD interventions; because of the refractory nature of the seizures associated with LGS, successful treatment with ASD monotherapy is rare. FDA-approved ASDs specifically indicated for the treatment of LGS have been categorized into Tier 1 of ASDs in the treatment algorithm, and these currently include clobazam, lamotrigine, rufinamide, topiramate, and cannabidiol [8,9,11,12]. Based on the most common survey responses, valproate was also included in Tier 1 and was chosen as the top ASD for the treatment of seizures associated with LGS, despite not being FDA-approved for the treatment of LGS [33]. Reasons for the frequent use of valproate in the treatment of seizures associated with LGS include the wealth of clinical experience of its use to treat LGS, cost effectiveness, its effect as a mood stabilizer on comorbidities, and the existence of multiple formulations. Lamotrigine is also recommended as first-line therapy for the treatment of LGS, while clobazam and rufinamide were the most commonly selected ASDs for add-on therapy. To date, only one formulation of cannabidiol has received FDA approval for the treatment of patients with LGS aged 2 years and older, and other pharmaceutical formulations are currently still under investigation. In addition, while artisanal preparations of cannabidiol are available, none are approved for the treatment of LGS. Based on the approval of cannabidiol (June 2018) and the relative lack of clinical experience of its use in the treatment of LGS compared with the other Tier 1 ASDs, cannabidiol has been included in the LGS treatment algorithm as the last-choice Tier 1 ASD [12].

Tier 2 ASDs include those which are commonly selected for the treatment of seizures associated with LGS, and include levetiracetam, perampanel, and zonisamide [34–36]. Lacosamide and brivaracetam are considered potentially valuable in the treatment of LGS but lack systematic trial data to support their efficacy. Lacosamide may also aggravate seizures in patients with LGS [37,38]. Both treatments are therefore included in Tier 3 [39,40]. Felbamate has also been placed into Tier 3, due to the increased risk of aplastic anemia and liver failure associated with felbamate treatment [13,41], and therefore its use for

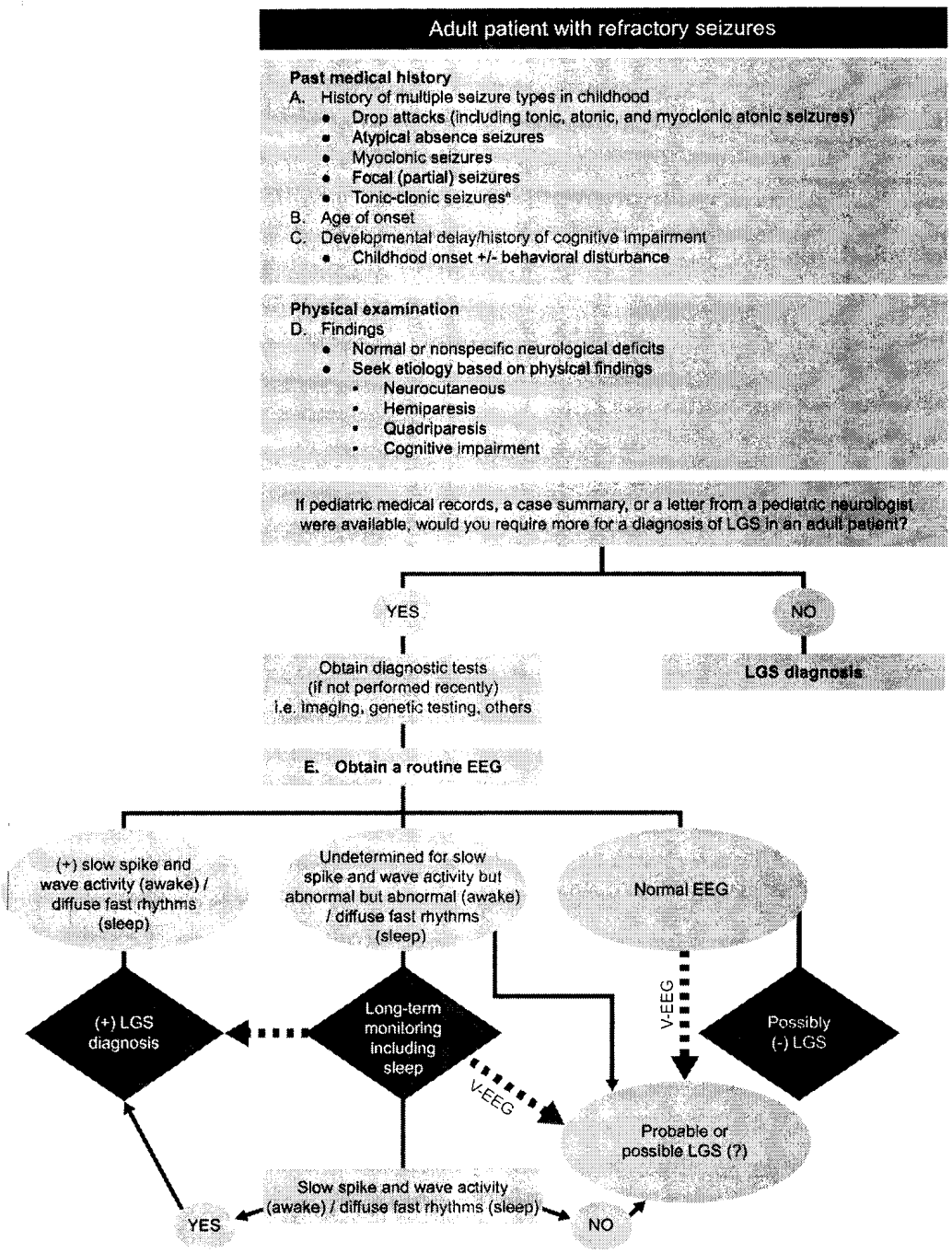


Fig. 2. Summary of the proposed LGS diagnostic algorithm for adult patients with refractory seizures proposed by the LGS Transition of Care advisory board. [a]Including focal to bilateral tonic-clonic (secondarily generalized) seizures and generalized onset tonic-clonic (primary generalized tonic-clonic) seizures. EEG, electroencephalogram; LGS, Lennox-Gastaut syndrome; V-EEG, video-electroencephalogram.

the treatment of seizures associated with LGS should be considered carefully. Cenobamate has recently been approved by the FDA for the treatment of focal (partial) seizures [42], and on this basis, has been included in Tier 3 of the treatment algorithm. This positioning of cenobamate will be reviewed as further evidence becomes available from clinical trials and clinical experience.

Antiseizure drugs that should be avoided in the treatment of LGS were also identified. These include ASDs less frequently used in the treatment of LGS and ASDs that have the potential to exacerbate certain seizure types. This category includes carbamazepine, eslicarbazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, and vigabatrin [9,39,43–47]. It is important to observe any potential adverse effects relating to behavioral dysfunction following the selection of an ASD for the treatment of LGS.

Complementary interventions that may be applied in parallel with ASD therapy include nonpharmacologic treatments, community services, and psychosocial approaches. The implementation of a ketogenic diet is a common approach for the control of refractory seizures, and its use for the treatment of seizures associated with LGS in pediatric patients has been reported elsewhere [48]. Assessment of the ketogenic

Table 2
Comparison of the classical criteria used for the diagnosis of LGS and criteria based on the proposed LGS diagnostic algorithm.

	Classical LGS diagnostic criteria[a]	Proposed LGS diagnostic criteria
Presence of intellectual disability	Yes	Yes
Seizure types	Drop attacks (tonic and atonic seizures)	Drop attacks (tonic, atonic, and myoclonic atonic seizures) Atypical absence seizures Myoclonic seizures Focal (partial) seizures Tonic–clonic seizures[b]
EEG activity[c]	Slow spike and wave	Slow spike and wave (awake), diffuse fast rhythms (sleep) Background slowing Focal epileptiform discharges or slowing Multifocal spike and wave discharges Generalized polyspike and wave discharges Generalized paroxysmal fast discharges
Other considerations		
Age at onset	Generally between 1 and 6 years	Between 3 and 5 years, typically before 8 years
Physical examination	–	May reveal neurological deficits or etiology of seizures

EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome.
[a] Based on Gastaut H et al. Epilepsia 1966; 7: 139–179.
[b] Including focal to bilateral tonic–clonic (secondarily generalized) seizures and generalized onset tonic–clonic (primary generalized tonic–clonic) seizures.
[c] In equivocal cases, the proposed diagnostic algorithm recommends the use of extended EEG to identify abnormal EEG activity.

diet in adult patients with LGS suggests that it is a useful therapy to contribute towards seizure control, although sustained seizure freedom may not be consistently achieved [21]. The modified Atkins diet, a variant of the ketogenic diet, may also be beneficial for adult patients with LGS [21], as it is better tolerated and can be initiated as an outpatient.

Vagus nerve stimulation has been investigated as a treatment for adult patients with drug-resistant epilepsy and in pediatric patients with LGS [49,50]; however, its application in adult patients with LGS has not been as extensively studied. Based on the assessment of available studies, AAN guidelines recommend that VNS should be considered for the treatment of seizures associated with LGS [51]. The latest iteration of VNS (SenTiva®, LivaNova) allows detection of seizure activity by time (during sleep vs wakefulness) and in prone vs supine positions. This can be used as a surrogate marker to assess risk of sudden unexpected death in epilepsy. In addition, if confronted with predominant nocturnal seizures, the nocturnal duty cycle can be preferentially increased over the daytime cycle. Deep brain stimulation (DBS) also presents a potential non-pharmacologic treatment [52]; however, there is currently limited experience of DBS in adult patients with LGS.

Other more invasive surgical interventions that may be considered for the treatment of seizures associated with LGS include resective surgery and corpus callosotomy [53]. While resective surgery may be suitable for selected patients with surgically accessible epileptogenic foci, corpus callosotomy and VNS are potential options for the treatment of atonic seizures in non-lesional patients [53–55].

Patient and family education is also required to improve treatment outcomes during the transition of care. Furthermore, the typical features of LGS change over time and reassessment will be required to adapt treatment to the patient's condition [18]. With continuing developments in the field, assessments in future may also include genetic testing. Ultimately, the transition of care from pediatric care to adult care requires a significant level of trust to be developed between the patient, caregivers, and providers, and the difficulties experienced during this transition may be allayed by establishing transition clinics and implementing a multidisciplinary management team [16].

3.3. Redefining goals of treatment during transition

Changes in the features of LGS during the period of transition call for reassessment of treatment goals, and as quality of life becomes more important in the longer term than measurements of seizure outcome, goals should be tailored to include measures of behavioral symptoms and cognition. For example, the International Classification of Function, Health, and Disability (ICF) have developed a model that provides examples of the different aspects of global assessment that should be considered across the lifespan, and is applicable to patients aged 4, 12, and 35 years. In the ICF model, assessments related to the functioning of the patient are described as three dimensions: body function or structure (e.g., seizure freedom and cognitive improvements), activity and participation (e.g., improvement in self-independence and relationships), and environmental factors (e.g., burden on the family or partner). However, this classification was intended for assessment of stable disorders and its application in patients with LGS requires further investigation [3].

3.4. Future directions in the treatment of LGS in adult patients

As further clinical experience is accumulated for the current therapies included in the treatment algorithm, and new therapies that may be suitable for the treatment of LGS are in development, revisions to the proposed LGS treatment algorithm will be required. Several medications have the potential to be introduced into the treatment algorithm in the future, depending on their performance in the treatment of LGS and their safety profiles. Fenfluramine, which was previously approved as an appetite suppressant, does not have approval for the treatment of epilepsy. However, in pediatric patients, fenfluramine has demonstrated efficacy for the treatment of seizures associated with Dravet syndrome in phase III studies (NCT02682927 and NCT02826863) [56] and for the treatment of seizures with LGS in an open-label pilot study (NCT02655198) [57]. An ongoing phase III study (NCT03355209) is assessing the efficacy of fenfluramine in pediatric and adult patients with LGS and is estimated to complete in December 2019 [58]. Based on a case series of patients with childhood-onset epilepsies including LGS and Dravet syndrome, lorcaserin, which also does not have FDA approval for the treatment of these syndromes [59], may have some efficacy in controlling motor seizures in these patients [60]. Other drugs under investigation for the treatment of LGS include carisbamate (phase I; NCT03731715) and TAK-935 (phase II; NCT03635073 and NCT03650452) [61–63].

Responsive neurostimulation (RNS) may also present an effective therapeutic approach for the treatment of LGS in adult patients; however, RNS is not currently approved for the treatment of LGS and further understanding on which patients may benefit from RNS is required before any recommendations can be made as part of the LGS treatment algorithm [64,65]. A potential advantage of RNS is in its provision of chronic electrocorticography, which may be valuable as a diagnostic application [65].

4. A note on nomenclature

Finally, it should be noted that there has been a move in the medical community away from the naming of conditions and diseases after individuals, particularly considering information that has later come to light on Hans Asperger's and Fredreich Wegener's links to the Nazi regime. This has led to the renaming of Wegener's

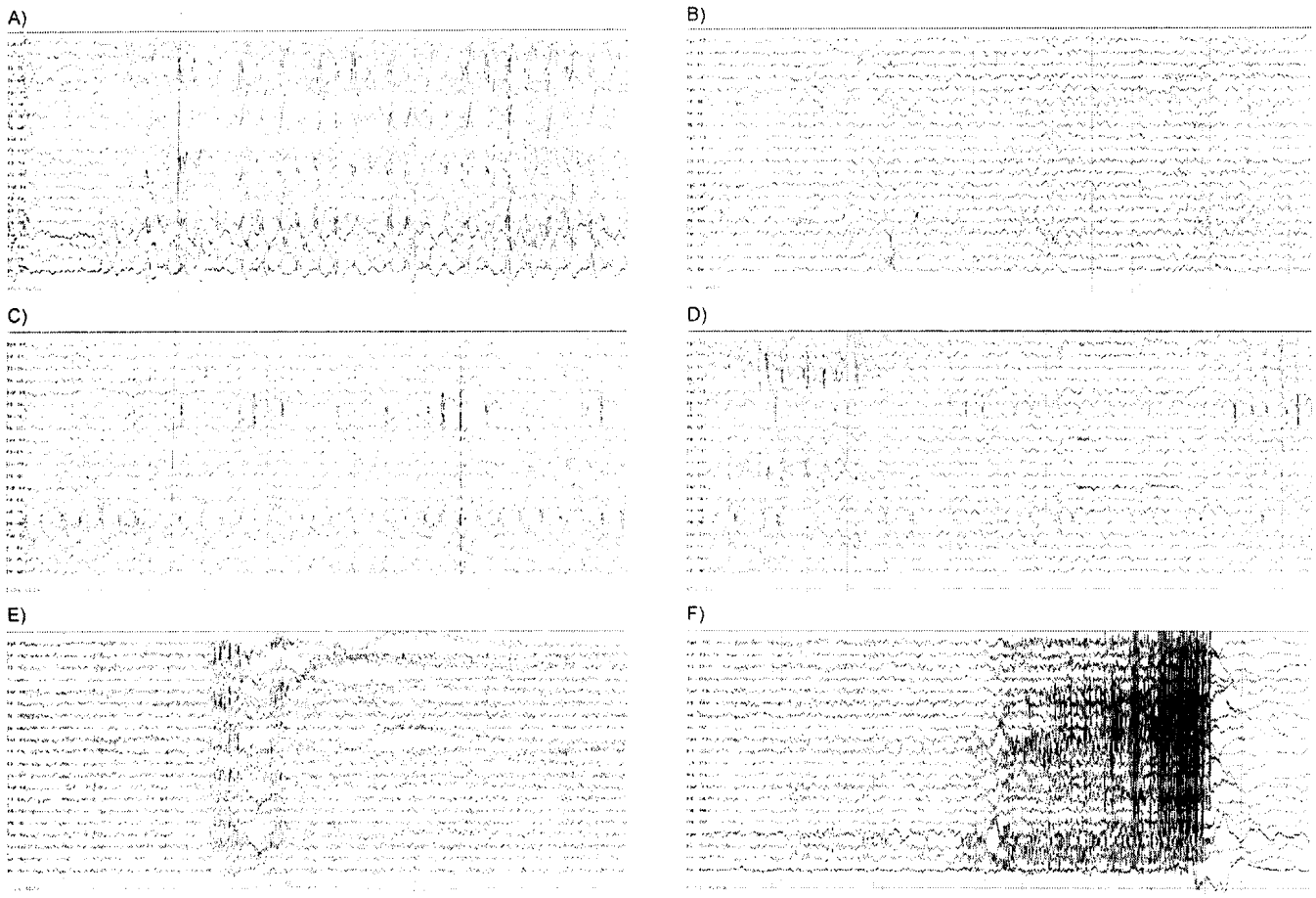


Fig. 3. EEGs demonstrating activities associated with LGS in adult patients, including (A) generalized slow spike and wave discharges, (B) diffuse bilateral background slowing, (C) focal spike and wave discharges, (D) multifocal epileptiform discharges, (E) generalized polyspike and wave discharges, and (F) generalized paroxysmal fast discharges during tonic seizure. EEG, electroencephalogram; LGS, Lennox–Gastaut syndrome.

granulomatosis as 'granulomatosis with polyangiitis', whereas Asperger's syndrome is no longer considered a separate condition, but has been incorporated into the broader category of autism spectrum disorder [66]. Similarly, there may be an argument for the phasing out of the term 'Lennox–Gastaut syndrome', considering that the condition was named after the neurologist William G. Lennox (along with Henri Gastaut) and the former's support of eugenics [67]. However, ultimately this is an issue for consideration by the scientific and patient communities moving forwards.

Table 3
Summary of advisory board ASD survey for the development of the LGS treatment algorithm.

ASD	Check √ all that apply	ASD dosage	Therapeutic response		
			Yes	No	If "No", provide reason(s) and action taken
Clobazam					
Divalproex sodium					
Ethosuximide					
Felbamate					
Lamotrigine					
Levetiracetam					
Oxcarbazepine					
Phenobarbital					
Phenytoin					
Rufinamide					
Topiramate					
Valproic acid					
Vigabatrin					
Zonisamide					
Other (describe)					

ASD, antiseizure drug; LGS, Lennox–Gastaut syndrome.

5. Conclusions

Based on our clinical experience and following discussions held during and since the LGS Transition of Care advisory board in November 2017, we have proposed diagnostic and treatment algorithms for the management of adult patients with LGS. Several readily available assessments have been identified to facilitate diagnosis of LGS in adult patients, and these form the basis of the diagnostic algorithm. Many adults may present with refractory seizures but without a previous diagnosis of LGS; the widening of the criteria used for the diagnosis of LGS, and raised awareness of a broader group of indicators of LGS, should reduce the frequency of missed diagnoses, and allow adult patients diagnosed with LGS to receive appropriate treatment.

The treatment of LGS in adult patients or in patients undergoing a transition from pediatric care to adult care can be challenging, as patients are often refractory to ASDs, and current treatment algorithms are considered suboptimal. Here, we have proposed a treatment algorithm to outline therapies that should be considered for the treatment of adult patients with LGS. Antiseizure drugs considered to be effective in the treatment of LGS in adult patients have been placed

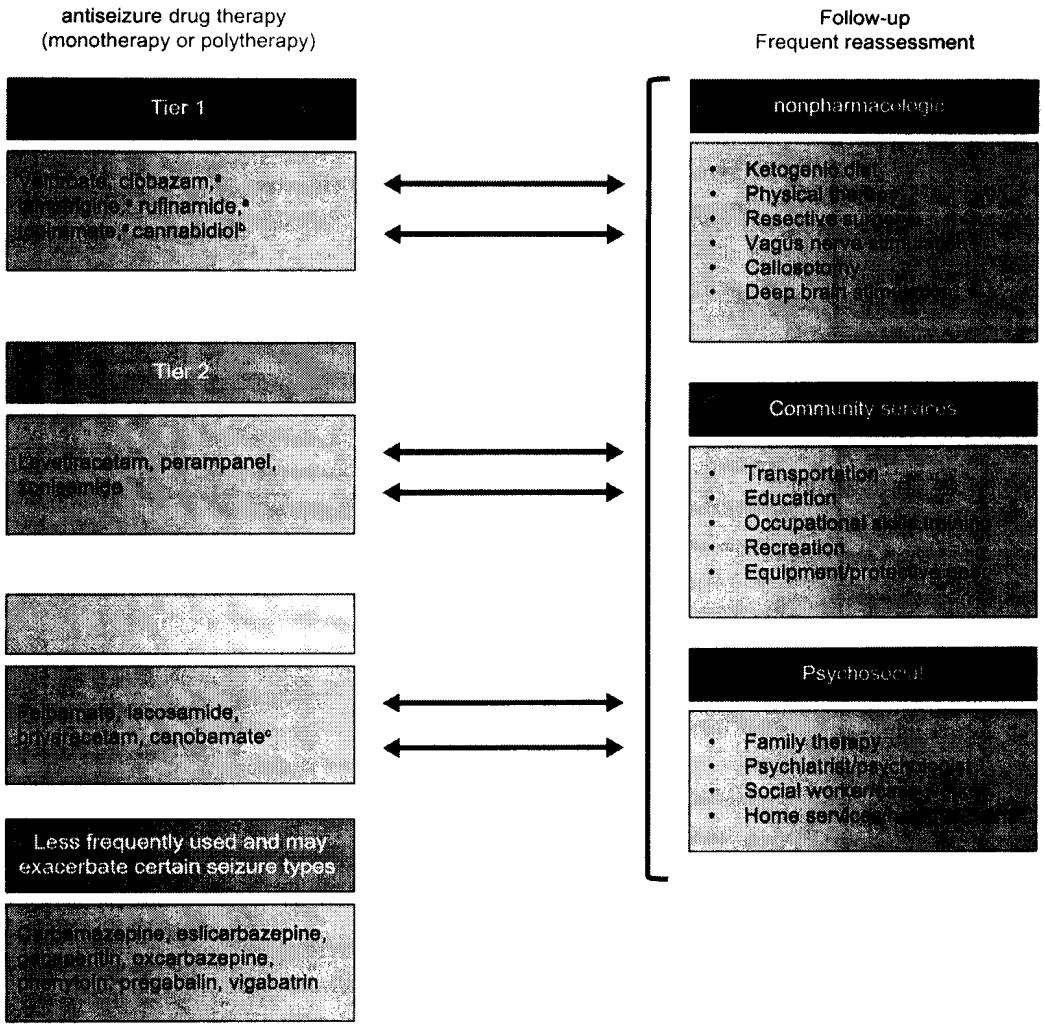


Fig. 4. Summary of the proposed treatment algorithm for adult patients with LGS proposed by the LGS Transition of Care advisory board. Consider patient factors when selecting ASDs. [a]FDA-approved for LGS. [b]Cannabidiol is included as the last-choice Tier 1 ASD treatment. At present, only one formulation of cannabidiol is FDA-approved for the treatment of LGS; other pharmaceutical formulations are currently under investigation. [c]Cenobamate is included in Tier 3, but may be re-positioned in future based on trial data and clinical experience. [d]There is limited experience of deep brain stimulation in adults with LGS. ASD, antiseizure drug; FDA, Food and Drug Administration; LGS, Lennox–Gastaut syndrome.

into Tiers 1 and 2; the recommended first-line medications are valproate, lamotrigine, clobazam, rufinamide, topiramate, and cannabidiol. Complementary interventions, to be used in parallel with ASD therapy, include nonpharmacologic treatments, community services, and psychosocial approaches.

Limitations of these algorithms include their development being based on our own clinical experience and case studies, rather than on a systematic review of clinical trial data. However, a previous systematic review was unable to determine the most effective treatment for LGS, due to the low number of randomized clinical trials in LGS and heterogeneity across the trials that have been conducted [14]; given this, the review and discussion of case studies can provide valuable evidence to inform treatment decisions.

Lastly, we have also identified ongoing developments that may result in updates to the diagnostic and treatment algorithms. Further advances in genetic testing for LGS may present innovative tools to facilitate more effective diagnosis, while additional treatment options could include novel ASDs and neurostimulation therapies. Based on this, we encourage ongoing discussion to reassess the recommendations of the diagnostic and treatment algorithms, to improve outcomes in this highly refractory patient population.

Author contributions

All authors were participants of the advisory board and were involved in the reviewing and approval of the manuscript, and in the decision to submit the article for publication. All authors also confirm accountability for the accuracy and integrity of the work.

Declaration of competing interest

Georgia Montouris has served on advisory boards for Eisai and SK Life Science, and has served on a safety board for UCB Pharma. Sami Aboumatar has served on advisory boards and/or has carried out consulting work for Eisai and Sunovion. David Burdette has served on advisory boards for Eisai and SK Life Science; has received speaker bureau honoraria from Eisai, Greenwich Biosciences, NeuroPace, Sunovion, and UCB Pharma; and has received research grant support from Eisai, NeuroPace, and Zogenix. Sanjeev Kothare and Ruben Kuzniecky have served on an advisory board for Eisai. William Rosenfeld has served on advisory boards for Eisai and SK Life Science; serves as a consultant for SK Life Science; has received speaker bureau honoraria from Eisai, Sunovion, and UCB Pharma; and has received research grant support from Greenwich Biosciences, Neurelis, Ovid Therapeutics, SK Life

Science, Takeda, and UCB Pharma. Steve Chung has served on advisory boards for Eisai, SK Life Science, Sunovion, and UCB Pharma; has received speaker bureau honoraria from Eisai, Lundbeck, Sunovion, and UCB Pharma; and has received research grant support from SK Life Science and UCB Pharma.

Acknowledgments

The advisory board was convened and funded by Eisai Inc. Members of the advisory board were selected based on the following criteria: adult neurologists/epileptologists who have expertise in treating patients with epilepsy and have patients who meet the criteria for LGS. The role of Eisai in the advisory board was to bring together neurologists/epileptologists with the necessary expertise to provide input on the transition of care and treatment of patients with LGS. The specific objectives of the meeting were as follows: 1. Obtain expert insight on the differences between pediatric and adult patients with LGS; 2. Gain expert feedback on key attributes necessary for adult neurologists to successfully identify and treat patients with LGS; 3. Develop an outline for a proposed diagnostic algorithm for LGS in adults and a proposed treatment algorithm for LGS in adults; 4. Obtain advisor feedback on educational needs with respect to transition of care in LGS; and 5. Obtain advisory feedback on data gaps in the treatment of adults with seizures associated with LGS.

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CEPHALGIA

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ТЕРАПИЯ ПРИ СИНДРОМ НА LENNOX-GASTAUT

РЕЗЮМЕ

ТЕРАПИЯ ПРИ СИНДРОМ НА LENNOX-GASTAUT

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Синдромът на Lennox-Gastaut е тежка епилептична енцефалопатия, характеризираща се със значителна терапевтична резистентност, като терапията се усложнява от наличието на полиморфни пристъпи. Наличните антиепилептични медикаменти помагат за редукция на пристъпната честота и подобряване на качеството на живот, но рядко се постига трайна ремисия на пристъпите. Руфинамид, ламотрижин, топирамат и бензодиазепини са основните медикаменти на избор като допълваща терапия. Лечението при всеки пациент е индивидуално като се взимат предвид потенциалните предимства от всяка терапия и се отчитат възможните странични ефекти.

Ключови думи: синдром на Lennox-Gastaut, терапевтична резистентност, руфинамид, топирамат, ламотрижин

ABSTRACT

TREATMENT OF LENNOX-GASTAUT SYNDROME

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Lennox-Gastaut syndrome is a severe epileptic encephalopathy, characterized by a therapeutic resistance. The therapy is significantly complicated by the persistence of polymorphic seizures. The antiepileptic drugs help to reduce the seizure frequency and improve the quality of life of the patients, but rarely a complete remission of the seizures is achieved. Rufinamide, lamotrigine, topiramate and benzodiazepines are the first line add-on drugs. The treatment of each patient is individual and is guided by the potential benefits and the possible side effects of the antiepileptic drugs.

Key words: Lennox-Gastaut syndrome, therapeutic resistance, rufinamide, topiramate, lamotrigine

ВЪВЕДЕНИЕ

Синдромът на Lennox-Gastaut (LGS) е тежка епилептична енцефалопатия, която се характеризира с клиничната триада от: 1) терапевтично резистентни полиморфни пристъпи; 2) типична ЕЕГ находка с наличие на бавни комплекси остриe/бавна вълна в будност и бърза активност по време на сън; 3) когнитивен дефицит (16,24). Нарушение в когнитивните функции се наблюдава при 20-60% от пациентите към момента на поставяне на диагнозата, а в рамките на 5 год. когнитивен регрес се отчита при 75-95% от случаите (16). Отчитат се поведенчески нарушения и психиатрична симптоматика.

Синдромът на Lennox-Gastaut е един от най-трудните за лечение епилептични синдроми като терапията значително се усложнява от наличието на полиморфни, терапевтично резистентни пристъпи (12,16). Наличните антиепилептични медикаменти помагат за редукция на пристъпната честота и подобряване на качеството на живот, но рядко се постига трайна ремисия на пристъпите, а ефектът на медикаментите обикновено е преходен (12,29). Основните използвани медикаменти са ламотрижин, топирамат, бензодиазепини и руфинамид.

ЛАМОТРИЖИН (LTG)

Антиепилептичният ефект на LTG е свързан с блокиране на натриевите канали (17). Ефикасността на LTG е изследвана при 169 пациенти на възраст между 3 и 25 години в двойно-сляпо плацебо-контролирано проучване, където медикаментът е прилаган като допълваща терапия (19). Титрирането на LTG е започнато с 5 до 50 mg в зависимост от телесното тегло и съпътстващо лечение с валпроат, а максималната доза е 100-200 mg/дневно при комбинация с валпроат и 300-400 mg/дневно при монотерапия. В групата на пациентите, приемащи LTG, е отчетена 32% редукция на пристъпната честота, за разлика от плацебо групата, в която намалението е 9 %. При 33% от случаите, лекувани с LTG, е отчетена редукция на пристъпната честота ≥50% (19). Сигнификантно по-голяма е редукцията с ≥50% на drop-атаките и на генерализираните тонично-клонични пристъпи (ГТКП) при приемащите LTG пациенти в сравнение с плацебо групата. При анализ на групата с ≥50% редукция на пристъпите е установен по-добър ефект върху drop-атаките (тонични и атонични пристъпи) спрямо генерализираните миоклонии и генерализираните тонично-клонични пристъпи (ГТКП). От изследването са отпаднали само 1 пациент, лекуван с LTG, и 6 пациенти - с плацебо, поради значително затруднено честяване на пристъпите (19).

Ефектът на LTG е описан и от други автори (1,6,7,16,27). Понижаване на пристъпната честота е отчетено и в изследване на Donaldson и съавт. (6). Авторите описват добър ефект върху тоничните и атоничните пристъпи, ГТКП и атипичните абсанси, но не и върху миоклоничните пристъпи. Петдесет и три процента от случаите са с ≥50% редукция на пристъпната честота, при същия процент от случаите е отчетеното и подобрение в качеството на живот. Обрив е описан при 13% от пациентите като при един от тях това е довело до изключване на медикамента (6). Кожен обрив е наблюдаван при около 1 на 300 възрастни и при 1 на 100 деца, приемащи LTG (17). Изявата му е по-често при бърза титрация или съпътстваща терапия с валпроат, което изисква спазване на схемите за бавно включване на LTG. Описани са и случаи на хепатотоксичност при прием на LTG като се обсъждат възможни алергични механизми.

ТОПИРАМАТ (TPM)

Механизмът на действие на TPM се свързва с блокиране на волтаж-зависимите натриеви канали, потискане на обратния захват на GABA, антагонизъм на AMPA/каинат субтиповете на глутаматните рецептори и инхибиране на карбоанхидразата (16). Ефектът на TPM при LGS е оценен в двойно-сляпо, плацебо-контролирано изследване на 98 пациенти на възраст между 1 и 30 год., като таргетната доза на TPM е 6 mg/kg (25). Установена е редукция на честотата на drop-атаките при 14.8% от приемащите медикамента в сравнение с увеличаване на пристъпната честота при 5.1% от пациентите в плацебо групата. При 25.8% от пациентите, лекувани с TPM, е постигната редукция на средната честота на пристъпите (drop-атаки и ГТКП) в сравнение с влошаване на пристъпите при 5.2% в плацебо групата. Четирима пациенти са с ≥75% редукция на

пристъпната честота. Родителската оценка показва двукратно намаляване на тежестта на пристъпите в сравнение с плацебо групата. Най-честите странични ефекти са сомнолентност, анорексия, нервност, поведенчески проблеми, умора, замайване, загуба на тегло (25). Деветдесет и седем от случаите са преминали в последствие в отворено проучване (9). При пациентите, приемали TPM за ≥3 месеца или ≥6 месеца, е отчетена ≥50% редукция на drop-атаките съответно при 57% и при 55% от случаите. Към края на проведеното изследване 15% от пациентите не са имали drop-атаки за период ≥ 6 месеца.

Ефикасността на медикамента е проследена и в няколко други отворени проучвания, включващи случаи с LGS (1,4,11,18). Като цяло, при изследваните пациенти е описана редукция в честотата на пристъпите между 33 и 75%. В изследване на Coppola и съавт. е установена редукция в пристъпната честота при около 40% от пациентите (4). Авторите не откриват зависимост между клиничния ефект на TPM, етиологията и комбинацията с други антиепилептични медикаменти.

РУФИНАМИД

Механизмът на действие на Руфинамид е свързан с повлияване на натриевите канали (17). Ефективността му е проследена в двойно-сляпо, плацебо-контролирано проучване при 138 пациенти с LGS на възраст между 4 и 30 год. с анамнеза за полиморфни пристъпи (тонични и атонични пристъпи, атипични абсанси) (10). Първоначалната доза от 10 mg/kg е титрирана в рамките на 14 дни до максимум 45 mg/kg. Отчетена е редукция на общата пристъпна честота с 32.7% при приемащите Руфинамид пациенти. Средната честота на тоничните и атоничните пристъпи е намаляла с 42.5% при лекувани с Руфинамид пациенти и се е повишила с 1.4% при плацебо групата (10). Установено е и статистически значимо по-добро повлияване (дефинирано като процент на пациентите, при които е отчетено ≥50% намаляване на пристъпната честота) както на тоталната пристъпна честота, така и поотделно на тоничните пристъпи и на тежестта на пристъпите при лечение с Руфинамид в сравнение с плацебо групата. Наблюдавано е и повлияване на атипичните абсанси и на атоничните пристъпи.

Сто двадесет и четири пациенти са взели участие в отворено проучване с продължителност от 44 месеца (13). Пациентите, които са приемали плацебо, са преминали на лечение с Руфинамид с първоначална доза от 10 mg/kg и последваща титрация до 25-60 mg/kg. Отчетено е понижаване на тоталната честота на пристъпите, както и на честотата на тоничните пристъпи. През последните 6 месеца на наблюдение ≥50% редукция на тоталната пристъпна честота е постигната при 45.1% от случаите, а ≥75% - при 27.9%, двама пациенти са били без пристъпи (13). По отношение на тонични-атонични атърчове, 47.9% са имали ≥50% редукция на пристъпната честота, а 35.9% - ≥75% редукция, 9.4% са били без пристъпи. Най-честите странични реакции са повръщане, сънливост, инфекции на горните дихателни пътища, описани при над 10% от пациентите. Дванадесет пациенти са напуснали проучването поради странични реакции. Сериозни, свързани с терапията странични реакции, са обрив, констипация, езофагит, загуба на тегло, гастрит, анорексия, повръщане, летаргия, описани при 9 случая (13).

В изследване на Ohtsuka и съавт. (22) се установени подобни резултати на тези на Glauser (10), касаещи повлияването на тоталната пристъпна честота, но по-лоши резултати при повлияване на тонични-атонични пристъпи (24.2% спрямо 42.5%) (22). Описано е повлияване на тоничните, миоклоничните и фокалните пристъпи спрямо плацебо групата. Авторите не отчитат влияние върху ефикасността на Руфинамид от

страна на фактори като възраст, пол, вид на епилептичните пристъпи, предшестващ синдром на West, придружаваща терапия (22). Подобни са резултатите на Lee и съавт., които описват задоволителен ефект при 34.8% от своите пациенти, които след 6 месеца са били с ≥50% редукция на пристъпната честота (15).

КЛОБАЗАМ (CLB)

Клобазам е GABA-ергичен медикамент (14,17). Ефективността му е анализирана в мултицентрово двойно-сляпо изследване като са сравнени резултатите при ниска (0.25 mg/kg/дневно) и висока доза CLB (1 mg/kg/дневно) (3). Изследвани са 68 деца с LGS на възраст между 2 и 26 години. Дозата на лекарството е определена спрямо килограмите при тегло до 37.6 kg, а при по-голямо тегло прицелната доза е 10 mg/дневно за групата с ниска доза CLB и 40 mg/дневно за групата с висока доза. Основната цел на изследването е установяване на ефекта на CLB върху drop-атаките, а основен показател е намаляване на средната седмична честота на тези пристъпи (3). При всички пациенти, приемащи CLB във висока доза, е отчетено ≥40% намаляване на drop-атаките. При пациентите, лекувани с ниски дози на CLB, е отчетено известно подобрение при 78%, докато 22% са били с увеличаване на пристъпната честота. Отчетен е значително по-изразен ефект във високо-дозовата група - ≥25% редукция в седмичната пристъпна честота на drop-атаките при 89% от случаите спрямо 56% от ниско-дозовата група, ≥50% редукция на пристъпите при 83% спрямо 38% и ≥75% редукция при 67% спрямо 25%. По-голям процент пациенти, лекувани с висока доза CLB, са с пълно повлияване на пристъпите - 22% спрямо 6% от случаите, лекувани с ниска доза CLB, въпреки че разликата не достига статистическа значимост. Страничните ефекти, отчетени в двете групи, са подобни – сънливост, хиперсаливация, констипация, агресия, инсомния, хипомания (3).

В друго двойно-сляпо плацебо-контролирано проучване за оценка ефективността на CLB върху drop-атаките са включени 3 групи пациенти с различни дози на медикамента (20). Титрирането на CLB е осъществено в рамките на 3 седмици, трите групи пациенти са приемали съответно ниска доза - 0.25 mg/kg/дневно (максимум 10 mg/дневно, n=58), средна доза - 0.5 mg/kg/дневно (максимум 20 mg/дневно, n=62) и висока доза - 1 mg/kg/дневно (максимум 40 mg/дневно, n=56) CLB, като резултатите са съпоставени с тези на плацебо групата (n=59). Отчетено е 41.2% намаление на средния седмичен брой на drop-атаките в ниско-дозовата група, 49.4% намаление - при лечение със средна доза на CLB и 68.3% - при прилагане висока доза (20). Ефект е отчетен върху всички типове пристъпи със съответна редукция 34.8%, 45.3% и 65.3% в трите групи. Отчетена е 100% редукция на пристъпната честота при 25% от високо-дозовата група и ≥50% при 75% от случаите от същата група.

Двеста шейсет и седем от пациентите от двете предхождащи изследвания са включени в отворено проучване, резултатите от което са публикувани през 2012 год. (21). Средната доза на CLB е 0.94 mg/kg/дневно, а максималната - 1.22 mg/kg/дневно. Тринадесет пациенти са изключени поради странични реакции. На трети и двадесет и четвърти месец от наблюдението е установено съответно 71.1% и 91.6% намаление на средната седмична честота на drop-атаките и 64.8% и 81.5% редукция на честотата на всички епилептични пристъпи (21). Процентът на пациентите с ≥50% редукция на drop-атаките се е увеличил от 61.5% на 3 месец на 79.5% на 24 месец, а процентът на пациентите с ≥50% редукция на всички типове пристъпи - от 61.5% на 3 месец на 60.3% на 24 месец. Отчетено е и задържане на постигнатия положителен ефект с CLB във времето. Според авторите, въпреки че толерансът

може да е проблем при някои случаи, обикновено той не е сигнификантен фактор при лечението (21). Те взимат предвид данните за: липса на намаляване на степента на повлияване на пристъпите за първите две години от лечението; липса на промяна (към увеличаване) на средната доза CLB във времето; наличие на тенденция за намаляване на броя на съпътстващите антиконвулсанти. Поради липсата на плацебо-контролирана група те обаче допускат и възможността за наличие на други фактори, повлияващи честотата на пристъпите – напр. естествената тенденция за намаляване на пристъпната честота във времето, независимо от лечението.

ФЕЛБАМАТ

Фелбамат е първият одобрен от FDA (US Food and Drug Administration) медикамент като допълваща терапия при пациенти с LGS (16). Действието му е свързано с инхибиране на N-metil-D aspartate (NMDA) рецепторите и потенцииране на GABA свързаните отговори (16). Това двойно действие върху ексцитаторни и инхибиторни пътища с умерено GABA-ергично действие и по-изразен антиглутаматергичен ефект допринася за широкия спектър на действие на медикамента. Пациенти на възраст над 4 години, без ефект от първоначалната терапия, се считат за кандидати за започване на терапия с фелбамат (17). Взима се предвид обаче и възможността за значителни странични реакции – апластична анемия и чернодробна недостатъчност. Между 1994 и 2006 год. са описани 34 случая на апластична анемия и 18 случая на чернодробна недостатъчност в САЩ, поради което медикаментът се счита за подходящ само при липса на рискови фактори, например анамнеза за цитопения, автоимунни заболявания, позитивни антинуклеарни антитела или чернодробна патология (17).

Фелбамат е първото лекарство с доказан ефект върху пристъпите при LGS, който е анализиран в рандомизирано, двойно-сляпо, плацебо-контролирано проучване. Изследването включва 73 пациенти на възраст между 4 и 36 год. (8). Първоначалната доза от 15 mg/kg е титрирана в рамките на 14 дни до максимум 45 mg/kg или 3600 mg/дневно. При пациентите, лекувани с фелбамат (n=37), са отчетени 34% намаление на дропатаките и 19% редукция на тоталната честота на епилептичните пристъпите в сравнение с плацебо групата (n=36), където тези проценти са съответно 9% и 4% (8). Установено е и намаляване на ГТКП при пациентите, лекувани с фелбамат, както и подобрение в качеството на живот. Като цяло 50% от участниците в проучването са имали поне 50% редукция на честотата на пристъпите. Повечето съобщени странични реакции са леки или умерени по тежест и са подобни в двете групи (8). Анорексия, повръщане и сънливост са най-честите странични реакции при лечението с фелбамат. Почти всички пациенти са включени след това в отворено изследване (5). Пациентите, които са били първоначално на плацебо, а в последствие са преминали на лечение с фелбамат, имат същите показатели на подобрение, както пациентите с първоначален прием на фелбамат. Отчетена е около 50% редукция на пристъпната честота при 55% от тези пациенти в рамките на първия месец от лечението като този ефект се е задържал за периода на наблюдение от 12 месеца (5).

ДРУГИ АНТИЕПИЛЕПТИЧНИ МЕДИКАМЕНТИ

Използването на други антиепилептични медикаменти се основава на клиничен опит и на данните от предимно малки, плацебо-неконтролирани проучвания (16,17). Обикновено се описва цялостното влияние на медикаментите върху всички типове пристъпи, без винаги да се диференцира ефектът върху отделните типове епилептични пристъпи.

ВАЛПРОАТ (VPA)

VPA се използва за лечение на ГТКП, фокални пристъпи и grop-атаки (1,17,24). При наблюдение на 38 деца с LGS е отчетено 100% повлияване на пристъпите при 21% от случаите и ≥50% - при 55% от случаите. Основните наблюдавани странични ефекти са леки и не са довели до изключване на медикамента - основно гастроинтестинални оплаквания, увеличаване на телесното тегло, временна сънливост, тромбоцитопения, неутропения, нарушение в чернодробните ензими. Има данни, че VPA е по-ефективен при първично генерализираните тонично-клонични пристъпи спрямо вторично генерализираните.

ДРУГИ БЕНЗОДИАЗЕПИНИ

Клоназепам повлиява GABA трансмисията като се използва за лечение на различни типове пристъпи при деца и възрастни (17,24). В изследване на 37 деца с резистентни на лечението пристъпи, 24 от които с инфантилни спазми и 13 - с LGS, са отчетени подобрение при 3 деца с LGS за минимум 6 месеца и временна ремисия на пристъпите също при 3 случая с LGS (30). Странични ефекти са наблюдавани при 19 от 37 деца - основно хиперсаливация, мукозна обструкция на назофаринкс, проблеми в преглъщането. Пет деца са изключени от изследването поради по-сериозни странични реакции - атаксия, объркаост, сънливост.

Ефектът на нитразепам е изследван в малка кохорта от пациенти с терапевтично резистентни епилептични спазми и пристъпи при LGS, като е отчетен ефект при ¼ от децата (2).

При лечение с бензодиазепини трябва да се има предвид рискът за екзацербация на тоничните пристъпи (26).

ЛЕВЕТИРАЦЕТАМ (LEV)

Ефектът на LEV е описан при ограничен брой болни с LGS (23). Reyes и съавт. проследяват 6 пациенти, лекувани с медикамента като допълваща терапия (23). При 4 от тях авторите отчитат 100% редукция на честотата на миоклоничните пристъпи, при 2 - ≥50% намаление на атоничните пристъпи и при 4 - 100% намаление на честотата на ГТКП.

ЗОНИСАМИД (ZNS)

Механизмът на действие на ZNS е свързан с блокиране на натриевите и на Т калциевите канали (17). Ефектът на медикамента при пациенти с LGS е оценен в отворено проучване като резултатите показват, че ZNS е ефективен и добре толериран (28). Изследвани са 62 пациенти с LGS. При 4.8% от тях е постигнат 100% контрол на пристъпите, докато при 22.6% - над 75% редукция на пристъпната честота (28). Над 50% редукция в честота на атоничните пристъпи е отчетена при 15 от 24 пациенти (62.5%), ≥50% намаление в честотата на миоклоничните пристъпи - при 9 от 17 (52.9%) пациенти и в честотата на ГТКП - при 3 от 8 (37.5%) случая.

ЗАКЛЮЧЕНИЕ

LGS се отличава със значителна терапевтична резистентност. Проведените изследвания не показват предимство на определен медикамент по отношение на ефективността. Руфинамид, ламотрижин, топирамат и фелбамат са потенциални медикаменти на избор като допълваща терапия, а клобазам има предимства по отношение на grop-атаките. Лечението при всеки пациент е индивидуално като се взимат предвид потенциалните предимства на всяка терапия и се отчитат възможните странични ефекти.

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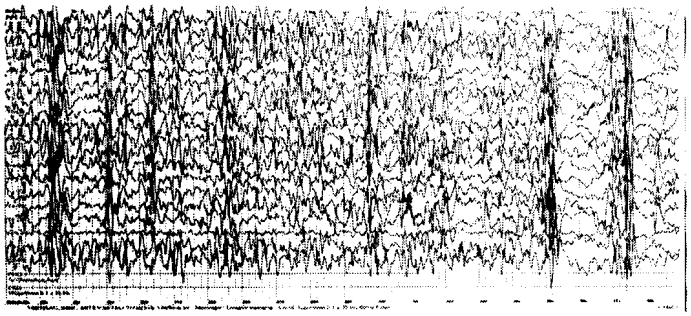
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Резюме

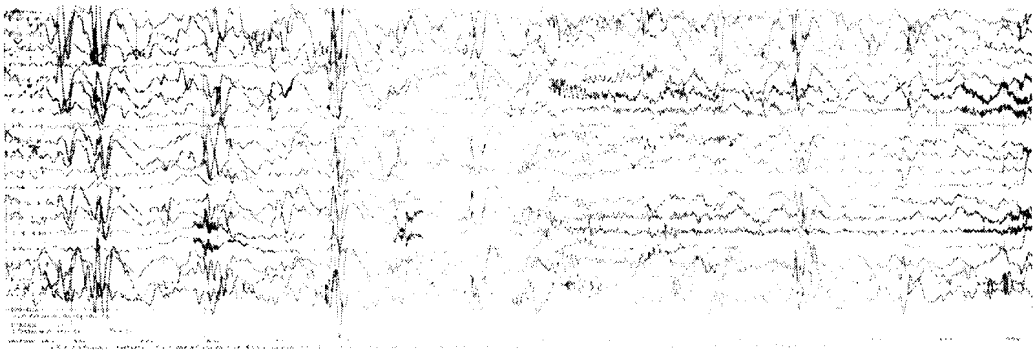
„Епилептични енцефалопатии" и „енцефалопатии на развитието" се дефинират като фамакорезистентни епилепсии, при които пристъпите и/или ЕЕГ разрядите увреждат невро-психичното развитие и когнитивните функции. Енцефалопатиите на развитието протичат със забавено нервно-психично развитие или интелектуален дефицит, обусловен от непрогресираща мозъчна увреда, съчетано или не с епилепсия; Неврокогнитивният и поведенчески дефицит остава, независимо от контролиране на епилепсията Нова концепция за енцефалопатите на развитието и за епилептичните енцефалопатии са че епилепсията и забавеното развитие са две състояния с обща етиология (структурни и генетични причини), при което агресивното антиепилептично лечение е необходимо. Епипептичните енцефалопатии се дефинират като процес на неврологична увреда, причинен от епилептичната активност с вариабилен потенциал за лечение. Епилептичната активност въздейства на неврогенезата, синаптогенезата нормалната организация на невроналните мрежи, тригерира невровъзпаление, с възможни патофизиологични механизми за невронална увреда. Според възрастта на изява епилептичните енцефалопатии са: *ранни инфантилни* (синдром на Otahara, синдром с епилептични инфантилни спазми или синдром на West, мигриращи фокални пристъпи, синдром на Dravet) и *късни (*синдром на Lennox-Gastaut, епилептични енцефалопатии с острие – бавна вълна активация в сън, синдром на Landau Kleffner, атипична бенигнена фокална епилепсия в детството, хемиконвулсия- хемиплегия синдром, епилептичен синдром свързан с фебрилни инфекции; С начало в различна възраст са епилептични синдроми с прогресивни неврологични увреди, синдром на Rasmussen, прогресивна миоклонична епилепсия, Фебрилно-инфекциозно свързани епилептични синдроми. При тях непрекъснатата епилептична активност или честите епилептични пристъпи обуславят когнитивен регрес. Неврокогнитивните и поведенчески отклонения могат да се подобрят при контрол на епилептичните пристъпи редукция на интерикталната епилептична активност. Своевременното диагностициране на епилептичните енцефалопатии при познание на основните им клинични характеристики, особено на синдрома на Lennox-Gastaut и на Dravet и ранното им лечение подобрява тяхната прогноза. Терапевтичните подходи за лечението на епилептичните енцефалопатии са с монотерапия и рационална политерапия включително с нови антигърчови лекарства (АГЛ). Представя се информация за клиничната характеристика и съвременно лечение на синдрома на Lennox-Gastaut и на Dravet, вкл. с Fenfluramin.

Епилепсията е социално значимо заболяване, с висока заболяемост в детската възраст (120 - 240/100 000), като 50-60% от епилепсиите започват преди 16 годишна възраст, а 40% от децата с епилепсия до 3 г. са с епилептични енцефалопатии. „Епилептични енцефалопатии" и „енцефалопатии на развитието" се дефинират като

фамакорезистентни епилепсии, при които пристъпите и/или ЕЕГ разрядите увреждат невро-психичното развитие и когнитивните функции, а често има и поведенчески промени. Дисутира се ролята на абнормно невронно развитие и съзряване на бялото мозъчно вещество. **Енцефалопатии на развитието** протичат със забавено нервно-психично развитие или интелектуален дефицит, обусловен от непрогресираща мозъчна увреда, съчетано или не с епилепсия; Неврокогнитивният и поведенчески дефицит остава, независимо от контролиране на епилепсията (1) Specchio N, Curatolo P 2021). **Епипептична енцефалопатия** се дефинира като процес на неврологична увреда, причинен от епилептичната активност с вариабилен потенциал за лечение. Епилептичната активност въздейства на неврогенезата, синаптогенезата нормалната организация на невроналните мрежи, тригерира невровъзпаление, с възможни патофизиологични механизми за невронална увреда. Нова концепция за енцефалопатия на развитието ("developmental encephalopathy") и за епилептична енцефалопатия са че епилепсията и забавеното развитие са две състояния с обща етиология (структурни и генетични причини) , при което агресивното антиепилептично лечение е необходимо. (1,2,3,4,5,6) (Kalser J, Cross JH. The epileptic encephalopathy jungle - from Dr West to the concepts of aetiology-related and developmental encephalopathies. Curr Opin Neurol. 2018;31(2):216-222; Scheffer IE, Berkovic S , Capovilla G, et al. ILAE classification of the epilepsies: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58: 512–521; Specchio N, Curatolo P. Developmental and epileptic encephalopathies: what we do and do not know. Brain. 2021 Feb 12;144(1):32-43. Zuberi SM, Wirrell E, 22 ; Specchio N, Wirrell EC 2022). **Епилептичните енцефалопатии**, според възрастта на изява са: *ранни инфантилни* с начало в *неонаталния период и ранната детска възраст* - синдром на Otahara, синдром с епилептични инфантилни спазми (синдром на West), мигриращи фокални пристъпи, синдром на Dravet (4) (Zuberi SM, Wirrell E, 22); *с начало в детска възраст* са основно синдромът на Lennox- Gastaut, епилепсия с миоклонично-атонични пристъпи, епилептични енцефалопатии или енцефалопатии на развитието с острие – бавна вълна активация в сън, синдром на Landau Kleffner, атипична бенигнена фокална епилепсия в детството, хемиконвулсия- хемиплегия синдром, епилептичен синдром свързан с фебрилни инфекции (остър енцефалит с рефрактерни, повтарящи се фокални пристъпи, или напредваща енцефалопатия при деца в училищна възраст) (5) (Specchio N, Wirrell EC 2022); С начало в различна възраст са епилептични синдроми с прогресивни неврологични увреди, синдром на Rasmussen, прогресивна миоклонична епилепсия, фебрилно-инфекциозно свързани епилептични синдроми (FIRES) (6) (Riney K, Bogacz A 2022). При тях непрекъснатата епилептична активност или честите епилептични пристъпи обуславят когнитивен регрес (1) (Specchio N, Curatolo P 2021). (**Фигури 1 а, б**). Неврокогнитивните и поведенчески отклонения могат да се подобрят при контрол на епилептичните пристъпи редукция на интерикталната епилептична активност. При **енцефалопатиите на развитието и епилептичните енцефалопатии** когницията и поведението са увредени, независимо от началото на епилепсията, която е с висока честота на пристъпите и с епилептиформена активност; Когнитивните и поведенчески увреди остават, дори при овладяване на епилептичните пристъпи; може за има известно подобрение (1) (Specchio N, Curatolo P 2021).



Фиг. 1 а. ЕЕГ с хипсаритмия и епилептични спазми при синдром на West



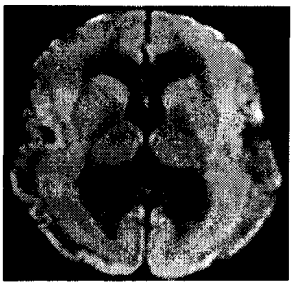
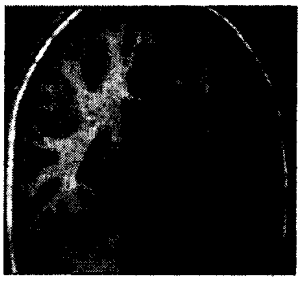
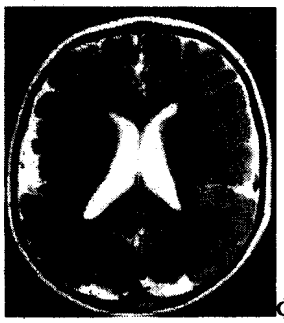
Фиг. 1 б. ЕЕГ с генерализирани бавни комплекси остнрие бавна вълна и бързи ритми при тоничен пристъп при дете със синдром на Lennox-Gastaut

Причините за фармакорезистентност при епилептичните енцефалопатии и енцефалопатиите на развитието епилепсии е обусловено от генетични причини, най-често с генни дефекти –патологични варианти) причиняващи натиево-йонни или калиево йонни каналопатии, комплекс туберозна склероза (TSK) (**Табл. 1**) и структурни мозъчни увреждания като вродени мозъчни малформации, основно корови малформации и дисплазии, вкл. туберозна склероза комплекс (**Фиг. 2 а, б, в, г, д**) , хипоксично- исхемични увреждания в пре- и перинаталния период (**Фиг. 3 а, б**) и енцефалити, често при Herpes simplex енцефалит (**Фиг. 3 в**), енцефалит на Rasmussen (**Фиг. 3 г**)

Таблица 1. Генетични прилини при енцефалопатии на развитието и епилептични енцефалопатии (DEE) (1) [Specchio N, Curatolo P., 2021]

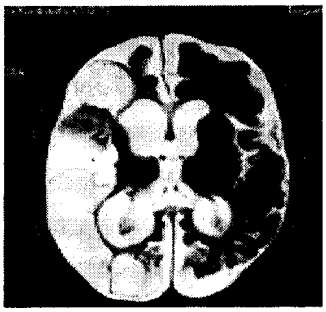
Ген	**Протеин**	**Вид пристъпи**	**Синдром**	**Характеристика на енцефалопатията на развитието**	**Отговор към лечение с АГЛ**
SCN1A	Na^+ channel: $Na_v1.1$	Различен, типични ГТКП при Т°	Dravet, GEFS+, ранна инфантил	Dravet , умствен дефицит, забавено НПР	Na^+ канални агонисти-влошават

			на ЕЕ (West)		
SCN2A	Na^+ channel: $Na_v1.2$	Различни-фокални, миоклонични, атонични	West, Ohtahara, Lennox-Gastaut, рядко BFNE	Умствен дефицит, забавено НПР, ASD	Na^+ канални антагонисти подобрява или влошават
SCN8A	Na^+ channel: $Na_v1.6$	Различно фокални, ГТКП, спазми, миоклонии, абсанси	West, Lennox-Gastaut, и др	Умствен дефицит, забавено НПР	Отговор към Na^+канални-антагонисти
CDKL5	Kinase	Спазми, миоклонии Тонични, тонично-клонични	CDKL5 deficiency disorder (CDD)	Умствен дефицит, двигателен дефицит	Резистентна
KCNQ2 /KCNQ 3	K^+ channels: $K_v7.2$, $K_v7.3$	Различни Типични фокални към ВГТКП	Ohtahara-, BFNE	Умствен дефицит	Различен ± отговор към Ретигабин
PCDH1 9	Protoc adheri n 19	Фокални, провокация от То		Умствет дефицит, ASD	
TSC1/ TSC2	mTOR kinase	Спами, фокални, тонични	TSC	Умствен дефицит, ASD	Резистенност; Vigabatrin, rapamycin


Фиг.2.а

Фиг.2 б.

Фиг.2в

Фиг 2 г

Фиг.2 д

Фиг. 2. МРТ на главен мозък при епилептични енцефалопатии с вродени мозъчни малформации а. Лисенцефалия; б. Двойна мозъчна кора и полимикрогирия; в. Субкортикална хетеротопия; г. Едностранна полимикрогирия и контралатерална пахигирия; д. Туберозна склероза


Фиг.3 а

Фиг.3 б

Фиг. 3 в

Фиг.3.г

Фиг. 3. Епилептични енцефалопатии а. Пренатални хипоксии с поренцефални кисти;

б. Перинатална хипоксично исхемична енцефалопатия; в. Прекаран Herpes simplex енцефалит; г. Енцефалит на Rasmussen

Терапевтичните подходи за лечението на епилептичните енцефалопатии са с монотерапия и рационална политерапия антигърчови лекарства (АГЛ) с различен механизъм на действие, като през последните 23 г. са регистрирани и 19 нови антигърчови лекарства (АГЛ), 7 от които през последните 10 г.: За генерализирани и фокални епилепсии, епилептични енцефалопатии се прилагат широкоспектърните АГЛ Lamotrigine (LTG), Topiramat (TPM), Levetiracetam (LEV). За фокални епилепсии- Oxcarbazepine (OXC), Gabapentin (GBP), Tiagabin (TGB), Lacosamid (LGM), Brivaracetam (BRV), Eslicarbazepin (ESC). За епилептични енцефалопатии, регистрирани от

EMA са Vigabatrin (VGB), Zonizamid (ZNS), Clobazam, Rufinamid (RFM), Stiripentol (STR), Cannabidiol, Fenfluramin от които в списъка на лекарства по чл. 266 т.2 от ЗЛСХМ)- Наредба 10 от 2011 г. са Rufinamid (RFM), Stiripentol (STR), Cannabidiol, Fenfluramin (7,8,9,10,11) (Национален консенсус за диагностика и лечение на епилепсията, 2022, 2023). За епилептичните енцефалопатии се прилага следните АГЛ (Таблица 2, Таблица 3) Arzimanoglou A. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009;8(1):82-93. Cross JH,. Front Neurol. 2017 Sep 29;8:505. doi: 10.3389/fneur.2017.00505. eCollection 2017. *Asadi-Pooya, Ali A. Lennox-Gastaut syndrome: a comprehensive review Neurological Sciences. 2018; 39 (3): 403–41;* Specchio N, Wirrell EC, 2022; Riva A, 2022): (Таблица 2, Таблица 3)

Таблица 2. Епилептични енцефалопатии- избор на антигърчови лекарства (АГЛ) в детската възраст - I, II монотерапия, допълваща терапия (Национален консенсус за диагностика и лечение на епилепсията, Българска неврология 2022, 2023) (7)

Епилепсия/Синдром	**I монотерапия**	**Алтернативна моно-/допълваща терапия**
Синдром с инфантилни спазми (синдром на West)	ACTH, VPA	CZP, LTG, TPM, VGB**, ZNS**
Синдром на Lennox-Gastaut	LTG, TPM, VPA	CBZ, CZP, PB, PHT, Rufinamide*, с Cannabidiol* с Clobazam**, Fenfluramine*, ZNS**
Синдром на Dravet (SMEI)	VPA,TPM	LEV, Stiripentol*, Cannabidiol* с Clobazam**, Fenfluramine*
Епилептична енцефалопатия с CSWS или електричен статус по време на бавновълнов сън (ESES)	VPA, ESM	LEV, бензодиазепини, Clobazam**, кортикостероиди

**регистрирани от EMA са Vigabatrin (VGB), Zonizamide (ZNS), Clobazam

включени в списъка на лекарства по чл. 266 т.2 от ЗЛСХМ)- Наредба 10 от 2011 г. Rufinamide, Stiripentol*, Cannabidiol* с Clobazam**, Fenfluramine*, ZNS**

Таблица 3. Видове и дозиране на АГЛ с индикации за детска възраст, нерегистрирани в България, регистрирани от EMA, 2023 (Национален консенсус за диагностика и лечение на епилепсията, Българска неврология 2022, 2023)

АГЛ mg	**Монотерапия**	Допълваща терапия
Vigabatrin** от 4 mg/kg титриране до 100-150 mg/kg	Синдром на West	**Синдром на West**

Rufinamide* - 45 mg/kg	-	**Синдром на Lennox-Gastaut ≥ 4 години, възможно при епилептични спазми, миоклонично-астатична епилепсия**
Stiripentol* - 50-100 мг/кг	-	**Синдром на Dravet (SMEI) ≥ 3 години** **Резистентни фокални пристъпи, епилептичен статус**
Sulthiam от 3 mg/kg, титриране до 5 - 10 mg/kg	-	**Роландова епилепсия след неуспех от други АЕЛ; фокални пристъпи и ВГТКП, синдром на Rett, епилептични енцефалопатии**
Clobazam** 0.4-1 mg/kg		**Синдром на Lennox-Gastaut ≥ 2 години-Фокални и генерализирани пристъпи с терапевтична резистентност**
Zonisamide** ≥ 6 г. и юноши ≥50 kg- 1 mg/kg титриране до 8-12 мг/кг		**Фокални и ВГТКП** ≥ 6 години **ИГЕ с ГТКП, ЮМЕ; Синдром на West, Lennox-Gastaut, миоклонично-астатична епилепсия**
Felbamat** от 15 mg/kg титриране до 30-60 mg/kg до 12 г.		**Синдром на West, Lennox-Gastaut, West, Landau-Kleffner, ЮМЕ, но при неуспех от други АЕЛ поради сериозни нежелани лекарствени реакции (чернодробни увреди, апластична анемия и др.).**
Canabidiol*-- 5 mg/kg/дневно, титриране до 20 mg/kg		**Синдром на Lennox-Gastaut syndrome и синдром на Dravet, в комбинация с clobazam за пациенти ≥ 2 години. Лечение при епилепсия при туберозна склероза**
Fenfluramin*- 0.2- 0.7 mg/kg		**Синдром на Dravet, синдром на Lennox-Gastaut**

Нови възможности при пациентите с епилептичните енцефалопатии със синдром на Dravet и на Lennox-Gastaut са Cannabidiol (Epidiolex) и Fenfluramin (Fintepla), чиято ефективност при тези синдроми и доказана в двойно слепи плацебо- контролирани изследвания (12,13,14,15,16) (Devinsky O, Patel AD, Cross JH, Villanueva V.Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. New England Journal of Medicine 2018; 378(20):1888-1897) Thiele EA, Marsh ED, Jacqueline A

French JA et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018; 391(10125)); Thiele EA, Marsh ED, Jacqueline A French JA et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018; 391(10125). Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, Devinsky O, Cross JH, Guerrini R, Talwar D, Miller I, Farfel G, Galer BS, Gammaitoni A, Mistry A, Morrison G, Lock M, Agarwal A, Lai WW, Ceulemans B; FAiRE DS Study Group. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019;394(10216):2243-2254. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, Stephani U, Laux L, Wirrell E, Knupp K, Chiron C, Farfel G, Galer BS, Morrison G, Lock M, Agarwal A, Auvin S; FAiRE, DS Study Group. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 2020;77(3):300-308. Knupp KG et al 2022.

Fenfluramin е с нов, различен от извествите механизъм на действие:

а/Ефект върху серотонинергичната система

- Serotonin или 5-hydroxytryptamine (5-HT) е невротрансмитер и невромодулатор с въздействие върху различни физиологични функции (17,18) (**Ciranna L. *Curr Neuropharmacol* 2006;4:101–14; Bagdy et al. *J Neurochem* 2007;100:857–73**); вкл. при връзката при дисфункция в 5-HT невротрансмисия и епилепсия, както и като агонист на специфични серотонинови рецептори в мозъка, вкл. 5-HT_{1D} и 5-HT_{2C}[1] , а така също 5-HT_{2A} и 5-HT_4 (19) (**Sourbron J et al. *Front Pharmacol* 2017;8:191**)

б/Ефект върху σ1 (sigma-1) рецептори

- позитивен модулатор върху σ1 рецептора (20) (**Martin P et al. *Epilepsy Behav* 2020;105:106989**). σ1 рецепторите са протеини, локализирани предимно в ендоплазмения ретикулум на митохондриите на много органи, вкл. в ЦНС (21) (**Ryskamp DA et al. *Front Neurosci* 2019;13:862**) и действат чрез: потискане навлизането на калций в неврона и редукция на ексцесивния калций и модулиране на йонните канали – Ca^{2+}, Na^+, K^+ канали и NMDA рецептори, което засяга невронната възбудимост и синаптичната активност и синаптичната пластичност, обучение и памет (21) (**Ryskamp DA et al. *Front Neurosci* 2019;13:862**)
[2]

Точното и ранно диагностициране на синдрома на Dravet и на Lennox-Gastaut е необходимо за своевременното лечение на тези епилептични енцефалопитаии, при които честите епилептични припадъци и непрекъснатата продължителна епилептична активност, регистрирана в ЕЕГ водят до регрес в нервно-психичното развитие.

СИНДРОМЪТ НА DRAVET (SMEI) е епилептична енцефалопатия с прогресиращ полиморфен епилептичен синдром, протичащ с 4 типа резистентни пристъпи с установени мутации основно в *SCN1A* (80%), както и в *SCN1B, SCN2A, SCN8A, SCN9A, PCDH19, GABRA1, GABRG2, STXBP1, HCN1, CHD2, KCNA2.* (22,23) (Shorvon SD, Guerrini R, Cook M, eds. (2013). *Oxford textbook of epilepsy and epileptic seizures*. Oxford: Oxford Univ. Press. p. 13. ISBN 978-0-19-965904-3 Berkovic SF 2019). Протича с Усложнени фебрилни гърчове - 6.0 ± 1.5 месеца - 100%; Генерализирани припадъци (Тонично-клонични - 92%; Клонични; Асиметрични тонични / клонични - 72%; Хемиклонични с постиктални хемипарези - 72%); Миоклонични пристъпи с начало между 1 - 5 г. - 72%; Атипични абсанси с начало между 1- 12 г.; ЕЕГ- абсансен ЕС - 30-40%; Комплексни

парциални- с начало между 4 мес.- 4 г. (43-79%); Вторично генерализирани тонично- клонични припадъци (ВГТКП) или или фокални пристъпи с еволюция към двустранни тонично-клонични; Прости фокални- по-редки; Чести епилептични статуси. Пристъпите често са провокирани от T°, фотостимулация. Прогнозата е неблагоприятна поради висока смъртност поради епилептични статуси или внезапна неочаквана смърт при *епилепсия* (SUDEP). Провежда се лечение с VPA, LEV, CLZ, TPM, ESM, PHB, Stiripentol*, CBD* в комбинация с Clobazam**, Fenfluramine* ≥ 2 г. , ZNS**; Кетогенна диета (7,14,15) (Lagae L,2019;. Nabbout R, Mistry A Clinical Trial. JAMA Neurol. 2020, Миланов 2022),

Fenfluramine (Fintepla) е показан за лечение на пристъпи, свързани със синдром на Dravet като допълваща терапия при пациенти над 2 г. , на основание на завършили клинични проучвания, доказващи ефикасността при лечение с Fenfluramine без Stiripentol в доза 0.7 mg/kg/дневно с редукция на пристъпите с 62.3% спрямо изходното ниво (14) (Lagae L, Lancet. 2019;394(10216):2243-2254) и при комбинация на Fenfluramine със Stiripentol в доза 0.4 mg/kg/дневно с редукция на пристъпите с 54. 0 % (15) (Nabbout R, JAMA Neurol. 2020;77(3):300-308).

Препоръки за дозиране

	Без stiripentol	**Със stiripentol**
Единична доза – първа седмица	0.1 mg/kg два пъти дневно (0.2 mg/kg/day)	
Ден 7 – втора седмица	0.2 mg/kg два пъти (0.4 mg/kg/day)	Поддържаща доза 0.2 mg/kg два пъти дневно (0.4 mg/kg/day)
Ден 14 – Ако е необходимо, по-нататъшна титрация	0.35 mg/kg twice daily (0.7 mg/kg/day)	.
Максимално препоръчвана доза	26 mg (13 mg два пъти дневно i.e. 6.0 mL два пъти дневно)	17 mg (8.6 mg два пъти дневно ,т.е.. 4.0 mL два пъти дневно)

СИНДРОМЪТ НА LENNOX-GASTAUT (LGS) се отнася към епилептичните енцефалопатии с начало в детската възраст (1,8) (Arzimanoglou A,2009; Specchio N, Wirrell,2022) Той е чест- 1-2% от всички епилепсии, около 5-10% от децата с епилепсия. Началото е между 1 - 7 г. (3 - 10 г.) с пик- 3-5 г. В 70- 80% е симптоматичен, с преход от синдром на West в 30- 50% (8) (Arzimanoglou A,2009). Критерии за типичен LGS са:

1. *Полиморфни, терапевтично резистентни пристъпи-* тонични, атонични, атипични абсанси (2 от тези 3 типа); Възможни епилептини спазми, тъй като LGS се развива след

синдром на West при около 30% и тези пациенти продължават да имат и епилептични спазми и по време на LGS; Неконвулсивен епилептичен статус: при 50–75% от пациентите с LGS – продължителни атипични абсанси със степенно увредено съзнание, периодично кратки тонични пристъпи; Фокални пристъпи със или без двустранна генерализация още в началото или на по-късните стадии; Миоклонични пристъпи: при 11–28% - внезапно падане; с ГТКП (~ 56%), прости фокални, миоклонични (11-28%), епилептични спазми, атипични абсансни статуси.

2. *ЕЕГ* - генерализирани разряди от дифузни бавни острия и комплекси острие-бавна вълна < 3 Hz в будно състояние и генерализирани бързи ритми (≥ 10 Hz) по време на сън 3. *Увредени интелектуални функции - когнитивни, поведение*. Патофизиология е корова свръхвъзбудимост в критични периоди за мозъчното развитие. Симптоматичен LGS е налице при 70-80%- мозъчни увреждания: Мозъчни малформации (лисенцефалия, лентовидна хетеротопия (Double cortex syndrome), двустранна перисилвиева полимикрогирия, корови дисплазии при туберозна склероза, агенезия на corpus callosum), постхипоксична енцефалопатия, постенцефалитна енцефалопатия. При идиопатичните случаи (до 20%) са налице различни de novo мутации (патологични варианти), които се срещат и при други видове епилепсии и епилептични енцефалопатии и енцефалопатии на развитието (CHD2- и миоклонична енцефалопатия; -и при синдром на Rett , Разстройсва от аутистичния спектър (PAC); *SCN1A*- и при GEFS+, синдром на Dravet и др.; *SCN8A*- и при инфантилни спазми, тонични, фокални пристъпи; *STXBP1*- и при инфантилни спазми, ранни епилептични енцефалопатии, PAC; *ALG13*- и при инфантилни спазми, епилептична енцефалопатия; *DNM1*-при инфантилни спазми, епилептична енцефалопатия; *GABRB3*- и при инфантилни спазми, синдром на West; *GRIN2A*- и при инфантилни спазми, синдром на West; *IQSEC2* (Xp11.22)-епилептична енцефалопатия, PAC).

Електро-клинични особености и прогресия при LGS (8) [Arzimanoglou A,2009] са: 1. *В началото на заболяването* са наличието при криптогенните случаи на атонични (астатични) пристъпи (Drop attaks), след това и други пристъпи; След синдром на West остават епилептични спазми; ЕЕГ в началото е абнормна, но със запазена реактивност; ЕЕГ по време на сън - нормална; Неврологичен дефицит липсва, освен има ако определена причина; Психомоторно развитие е нормално или забавено. 2. *При разгъната характеристика*: Видовете пристъпи са атипични абсанси, атонични (астатични) с внезапно падане, загуба на съзнание; миоклонични, тонични пристъпи, ГТКП; Наличие на неконвулсивен епилептичен статус- дълги атипични абсанси, поведенчески промени, ЕЕГ е със залпове или дифузни бавни комплекси 2-2,5 в сек в будност, залпове от бързи ритмични вълни 10 хц по време на сън; Налице е забавено развитие, прогресиращо във времето. Прогноза на LGS е неблагоприятна поради висока смъртност (5%), интелектуален дефицит (85-92%, тежък - 44-50%); персистиращи епилептични припадъци (78% - 90% - 96%, като без припадъци са само 4%, криптогенни случаи).

Еволюцията в ЕЕГ при LGS е 3 типа: Типична за LGS (симптоматични и от с-м на West); Главно с фокална абнормност - най-добра прогноза; Множествени независими спайкови фокуси при снижение на IQ при 40%, и "малки" припадъци. Най-честа е клинико - ЕЕГ еволюцията с клиника на LGS- тонични пристъпи, абсанси (34%),

последвана от тежка епилепсия с независими множествени спайкови фокуси (31%) (8) (Arzimanoglou A,2009).

Диференциална диагноза при LGS основно включва: 1. Миоклонично-астатична епилепсия (Синдром на Doose) - миоклонични пристъпи, абсанси, ГТКП, няма когнитивен регрес; при LGS – тонични пристъпи, атипични абсанси, миоклонии, прогресия, ПП, КП ; 2. Синдром на Dravet (SMEI), ранна тежка миоклонична епилепсия)- характерна комбинация от пристъпи с начало с фебрилна провокация от кърмаческа възраст (ФГ, хемиконвулсивни, ГТКП, миоклонични, абсанси, КП), генетична причина (основно *SCN1A*); 3. Атипична бенигнена фокална епилепсия с центротемпорални спайкове (Роландова)= Pseudo-Lennox Gastaut syndrome - характерна ЕЕГ, активация в сън с ESES.

LGS е терапевтично резистентен, не е възможен пълен контрол на пристъпите (8,9) (Cross JH, Auvin S, Falip M, Striano P, Arzimanoglou A. Expert Opinion on the Management of Lennox-Gastaut Syndrome: Treatment Algorithms and Practical Considerations. Front Neurol. 2017). Провежда се лечение с VPA, TPM, LTG, кортикостероиди; Алтернативни- CBZ, Clz, ESM, LEV, GBP, PB, PHT, Rufinamid* над 4 г., CBD* в комбинация с Clobazam над 2 г- **, ZNS**. Оперативното лечение включва хирургия на лезии, калозотомия при резистентни drop attacks. При епилептичен статус - IV бензодиазепини + кортикостероиди. (7,8,9,10,11,12,13,14,15,16) (Cross JH, Auvi S, Falip M, Striano P, Arzimanoglou A. Expert Opinion on the Management of Lennox-Gastaut Syndrome: Treatment Algorithms and Practical Considerations. Front Neurol. 2017 Sep 29;8:505. doi: 10.3389/fneur.2017.00505. eCollection 2017. ; *Asadi-Pooya, Ali A. Lennox-Gastaut syndrome: a comprehensive review Neurological Sciences. 2018; 39 (3): 403–414 Миланов И, Божинова В.*; Devinsky O, Patel AD, Cross JH, Villanueva V.Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. New England Journal of Medicine 2018; 378(20):1888-1897) ; Thiele EA, Marsh ED, Jacqueline A French JA et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018; 391(10125); Riva A, Coppola A, Di Bonaventura C, et al. An Italian consensus on the management of Lennox-Gastaut syndrome. Seizure 2022; 101: 134-140; Knupp KG et al. Efficacy and safety of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome A randomised controlled trialJAMA Neurol. 2022;79:554–564.) Италиански консенсус за лечение на синдрома на Lennox-Gastaut, 2022 (11) (Riva A, Coppola A, 2022) с позоваване на: American Academy of Neurology (AAN) и American Epilepsy Society (AES) с правила за лечение на LGS (2004 г.), последни от 2018 г. са с препоръка за Valproate- първа линиа за LGS, последвани от lamotrigine, topiramate, rufinamide и clobazam- най-ефективни при LGS. От Европейската литература: Valproate-основен АЕЛ, lamotrigine, rufinamide, topiramate, cannabidiol, clobazam, прибавяне и на perampanel, zonisamide, fenfluramine, cannabidiol подходящи за определени пациенти с LGS. Изводи към 2022 г.: Valproate, lamotrigine, topiramate, rufinamide, clobazam; zonisamide, fenfluramine, cannabidiol при някои пациенти LGS.

Fenfluramin е нова терапевтична възможност при лечение на синдрома на Lennox-Gastaut, в публикувано клиничното проучване за ефикасност и безопасност на фенфлурамин за лечение на пристъпи, свързани със синдрома на Lennox-Gastaut - Рандомизирано контролирано проучване (16) (Knupp KG et al. 2022):

- Това проучване е фаза 3 при пациенти с високо рефрактерен на лечение Lennox-Gastaut (LGS) и постигна своята първична крайна цел, като допълнителната терапия с **Fenfluramin** 0,7 mg/kg/ден демонстрира значително подобрение в честотата на атоничните /астатичните (drops)/ пристъпи (изчислена средна разлика [Hodges-Lehmann] от плацебо : –19,9%)
- **Fenfluramin** като допълнителна терапия също е ефективен за намаляване на генерализираните тонично-клонични пристъпи (GTCS), с 46% и 58% редукция, наблюдавани съответно в групите с 0,7 и 0,2 mg/kg/дневно **Fenfluramin**, в сравнение с влошаване от 3,7% в плацебо групата; демонстрира се общо подобрение на всички моторни пристъпи, по-висока ефективност за дозата на **Fenfluramin** 0.7 mg/kg/дневно, отколкото 0.2 mg/kg/дневно спрямо плацебо
- **Fenfluramin** обикновено се понася добре от пациенти със синдром на Lennox-Gastaut (LGS), като най-честите нежелани реакции включват намален апетит, сънливост, умора, повръщане, диария и пирексия
- В това проучване не са наблюдавани клапно сърдечно заболяване или белодробна артериална хипертония

Ограничение на това проучване е кратката продължителност, необходими са дългосрочни оценки на безопасността и ефикасността. От гореизложеното е видно, че при терапевтично-резистентните епилептични енцефалопатии, синдромите на Lennox-Gastaut, Dravet и корови дисплазии (тубери) при туберозна склероза (TSC) са необходими нови лечения за повлияване на рефрактерния епилептичен синдром.

ИЗВОДИ

- Детските епилептични енцефалопатии/ енцефалопатии на развитието са най-сериозния проблем в епилептологията: чести припадъци, епилептични статуси, SUDEP, когнитивен регрес, снижено качество на живот
- Необходима е терапия, редуцираща пристъпите, подобряваща качеството на живот: широкоспектърни LTG, TPM и LEV; Strilentol за синдром на Dravet (SMEI); Rufinamid за синдром на Lennox-Gastaut; Cannabidiol за синдром на Lennox-Gastaut и синдром на Dravet в комбинация с Clobazam и при пристъпи при туберозна склероза; Fenfluramine за синдром на Dravet и синдром на Lennox Gastaut, регистрирани за употреба от EMA и възможни за прилагане у нас по чл.266, ал. 2 от Наредба №10 от 2011 г. от Закона за лекарствените продукти в хуманната медицина (ЗЛПХМ); регистрирани от EMA, но нерегистрираните у нас Vigabatrin за синдром на West; Clobazam за синдром на Lennox-Gastaut; Felbamat за синдром на Lennox-Gastaut и на West.

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The burden of illness in Lennox–Gastaut syndrome: a systematic literature review

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Abstract

Background Lennox–Gastaut syndrome (LGS) is a severe developmental and epileptic encephalopathy characterized by drug-resistant epilepsy with multiple seizure types starting in childhood, a typical slow spike-wave pattern on electroencephalogram, and cognitive dysfunction.

Methods We performed a systematic literature review according to the PRISMA guidelines to identify, synthesize and appraise the burden of illness in LGS (including "probable" LGS). Studies were identified by searching MEDLINE, Embase and APA PsychInfo, Cochrane's database of systematic reviews, and Epistemonikos. The outcomes were epidemiology (incidence, prevalence or mortality), direct and indirect costs, healthcare resource utilization, and patient and caregiver health-related quality of life (HRQoL).

Results The search identified 22 publications evaluating the epidemiology (n = 10), direct costs and resource (n = 10) and/or HRQoL (n = 5). No studies reporting on indirect costs were identified. With no specific ICD code for LGS in many regions, several studies had to rely upon indirect methods to identify their patient populations (e.g., algorithms to search insurance claims databases to identify "probable" LGS). There was heterogeneity between studies in how LGS was defined, the size of the populations, ages of the patients and length of the follow-up period. The prevalence varied from 4.2 to 60.8 per 100,000 people across studies for probable LGS and 2.9–28 per 100,000 for a confirmed/narrow definition of LGS. LGS was associated with high mortality rates compared to the general population and epilepsy population. Healthcare resource utilization and direct costs were substantial across all studies. Mean annual direct costs per person varied from $24,048 to $80,545 across studies, and home-based care and inpatient care were significant cost drivers. Studies showed that the HRQoL of patients and caregivers was adversely affected, although only a few studies were identified. In addition, studies suggested that seizure events were associated with higher costs and worse HRQoL. The risk of bias was low or moderate in most studies.

Conclusions LGS is associated with a significant burden of illness featuring resistant seizures associated with higher costs and worse HRQoL. More research is needed, especially in evaluating indirect costs and caregiver burden, where there is a notable lack of studies.

Keywords Burden of illness, Direct costs, Indirect costs, Caregiver burden, Health-related quality of life, Developmental and epileptic encephalopathy, Epilepsy, Lennox–Gastaut syndrome, Seizures

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Background

The recognition of a specific disease entity is vital for every aspect of patient care, from diagnosis, management and treatment to advancements in health outcomes through research and health policy (Fig 1). The definition of Lennox–Gastaut syndrome (LGS) has been evolving since Lennox and Davis (1950) [1] and Gastaut et al (1960) [2] described the electroclinical features of a severe, refractory, childhood epileptic encephalopathy with slow spike and wave electroencephalogram (EEG) formations (Fig 1A). Studies elucidating LGS over the years have established a triad of classical features that can be used in clinical practice and research [3–5] (Fig 1B): 1. Multiple types of drug-resistant seizures, including tonic, atonic, and atypical absences, with onset generally before the age of 8 years (peak age of onset between 3 and 5 years). Tonic seizures and atypical absences are mandatory for diagnosis. 2. Interictal EEG pattern of diffuse, slow spike-wave complexes; and 3. developmental delay. However, importantly, it has also become clear that there are caveats to these features which can make LGS challenging to define and diagnose [5]. For example, none of the 3 features alone is pathognomonic, the main seizure types are not always present, and the features and progression of LGS is variable [6–11]. In addition, LGS is associated with multiple etiologies, as opposed to the known monogenetic causes that can be diagnostic for other epilepsy syndromes such as Dravet syndrome (DS) and tuberous sclerosis complex (TSC). Indeed, LGS can often arise from another severe infantile epilepsy syndrome including infantile spasms syndrome, early infantile developmental and epileptic encephalopathy, epilepsy of infancy with migrating focal seizures and TSC [12].

Despite the challenges of defining LGS, there have been significant clinical improvements over the years [5, 13–16]. There are now seven anti-seizure medications (ASMs) specifically indicated in patients with LGS in the US [15]—clobazam, felbamate, lamotrigine, topiramate, rufinamide, cannabidiol and fenfluramine, with efficacy demonstrated in clinical trials for seizures associated with drops in LGS patients (Fig 1A) [17–23]. Other interventions include the ketogenic diet, vagus nerve stimulation, and corpus callosotomy [5, 13–16].

The term "burden of illness" encompasses outcomes including the epidemiology (prevalence/incidence and mortality), healthcare resource utilization, costs, and patient and caregiver health-related quality of life (HRQoL) [24, 25]. In addition to clinical research investigating therapies, evaluating the burden of illness is key to understanding the challenges and needs of patients and their caregivers, together with understanding the impact and challenges on healthcare systems and society. Systematic literature reviews (SLRs) evaluating the burden of illness in DS and TSC have recently been published [25, 26]. However, there are no SLRs on this topic for LGS.

We conducted an SLR with a narrative synthesis to comprehensively identify, synthesize and appraise the evidence associated with the burden of illness in individuals with LGS, as well as to identify gaps in the evidence. The focus of this SLR was on the overall burden as opposed to the impact of specific interventions.

Methods

We carried out an SLR following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. The protocol was registered with Prospero (CRD42022333410).

Literature search

We searched MEDLINE, Embase and APA PsychInfo (all via OVID), Cochrane's database of systematic reviews (CDSR, Wiley), and Epistemonikos. The search strategy took the following form: ((terms for Lennox–Gastaut syndrome) AND (modified search filters for epidemiology, resource use, and health-related quality of life)) and it was developed by an information specialist and checked by the authors [28–31]. Conference proceedings were searched via Embase and we checked the reference lists of eligible studies and relevant systematic reviews [32]. The search was not limited by language and it was reported in web-only material using a search narrative [33]. The search terms used to identify the relevant literature can be seen in the Additional file 1: (Supplementary information: Search terms). The databases were searched from inception to 10th September 2021.

Eligibility criteria

A summary of the eligibility criteria for this review according to population, intervention, comparator, outcomes and study design (PICOS) is presented in Table 1. Eligible studies were those that reported original data on the above outcomes without the impact of an intervention. In vitro and in vivo studies, preclinical studies, review articles, SLRs, editorials, and case studies were not eligible, however the reference lists of reviews and SLRs were searched to ensure all relevant studies were captured. In addition, economic evaluations (e.g cost-effectiveness, cost-utility and budget impact models) reporting on specific interventions without any original data on e.g HRQoL (e.g utilities) and healthcare resource utilization were excluded, however the reference lists were searched for publications containing original data. No limits were applied (e.g regarding publication dates or language), except for

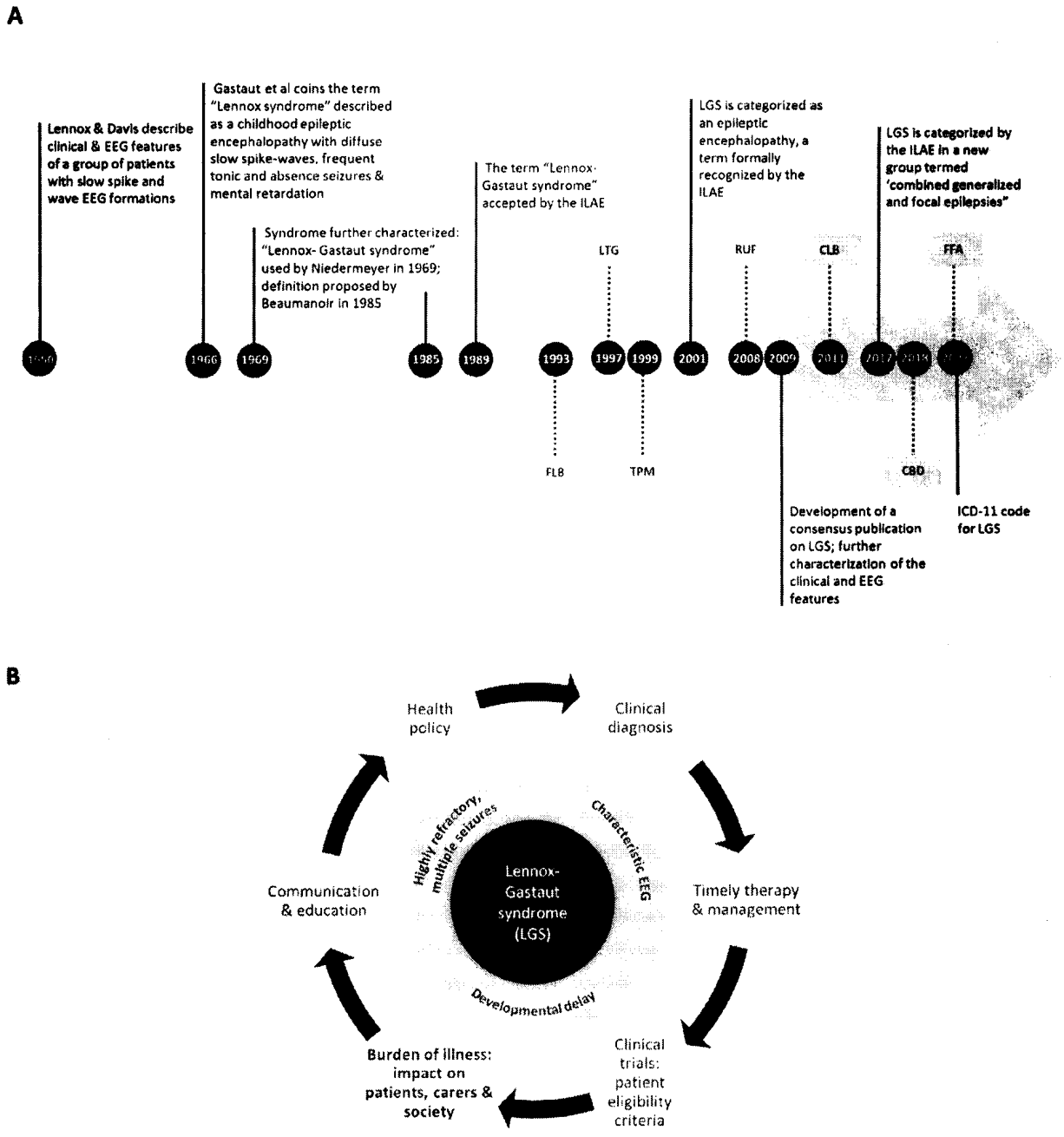


Fig 1 Timeline to show **A** the history of the characterization and treatment of LGS **B** the triad of symptoms characteristic of LGS and the clinical implications of the characterization of the syndrome. From: Lennox et al (1950) [1], Gastraut et al (1966) [2], Niedermeyer (1969) [90], Beaumanoir (1985) [91], ILAE 1989 [92], Engel (2001) [93], Arzimanoglou et al (2009) [3], Scheffer (2017) [94], World Health Organization (ICD-11) (2022) [64]. CLB, clobazam; CBD, cannabidiol; EEG, electroencephalogram; FFA, fenfluramine; FLB, felbamate; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; LTG, lamotrigine; RUF, rufinamide; TPM, topiramate

Table 1 PICOS criteria for inclusion and exclusion of studies

PICOS	Inclusion	Exclusion
Population	Patients with LGS, including clearly defined "probable" LGS	Other DEEs
Intervention	Studies assessing the overall burden of illness of LGS without the impact of an intervention	Studies assessing the impact of interventions[a]
Comparator	N/A	-
Outcomes	Prevalence/incidence Economic burden Direct and indirect costs Resource use Patient and caregiver HRQoL and broader patient-reported outcomes Mortality	-
Study designs/ publication type	Publications reporting original data, including: Healthcare insurance claims data Chart reviews Registry studies Electronic healthcare databases studies Epidemiologic surveys Observational studies Economic evaluations if they contain original data on resource utilisation and HRQoL	*In vitro* and *in vivo* studies Preclinical studies Case reports and case series Clinical studies reporting only efficacy and safety data Economic evaluations reporting on specific interventions[b] Reviews[c], SLRs[c], comments, letters, editorials and press releases
Limits	Searches of conferences in Embase were limited to the previous 3 years (conferences 2018-current)[d]	None

HRQoL, health-related quality of life; LGS, Lennox–Gastaut syndrome; N/A, non-applicable; SLR, systematic literature review

[a] The focus is on the overall burden as opposed to the impact of specific interventions

[b] Economic evaluations reporting on specific interventions without any original data on e.g HRQoL (utilities) and healthcare resource utilisation will be excluded, however, the reference lists will be searched to ensure all relevant studies are captured in this SLR.

[c] Reviews and SLRs will be excluded from final inclusion but the reference lists will be searched to ensure all relevant studies are captured in this SLR.

[d] The rationale for excluding conference abstracts > 3 years is that this should be sufficient time for the data to be published in peer-review journals if they are of sufficient importance and quality. The rationale for including conference abstracts ≤3 years is to include the most up-to-date data.

conference abstracts that were limited to the previous 3 years.

Study selection

Publications identified via the bibliographic database searches were managed and screened in Covidence, which is an online tool that helps to facilitate the systematic review process [34]. To ensure the accuracy of the screening process, two independent reviewers assessed relevant articles. Initially, primary screening was performed by reviewing the title and abstract and articles were excluded if they were clearly not relevant according to the PICOS eligibility criteria (e.g if the article was about a different condition and clearly not about patients with LGS etc). For all potentially relevant articles, full articles were obtained, and secondary screening was performed by reviewing the full text against the PICOS criteria. The reasons for exclusion at secondary screening were clearly documented according to the PICOS criteria. Disagreements regarding the inclusion and/or exclusion of studies at both primary and secondary screening were generally resolved by discussion between the two reviewers, or if needed by a third reviewer.

Data extraction and synthesis

Data were extracted into tables in MS Word by one reviewer, which was checked for accuracy by a second independent reviewer. The prespecified variables were as follows: Study and population characteristics i.e study type, observation period, population definition and number, age (mean, standard deviation [SD], median, range), percentage of male patients, and outcomes reported; epidemiology outcomes i.e incidence, prevalence and mortality as reported by the authors; healthcare resource utilization (mean and SD per person per year [PPPY]) as reported by the authors including inpatient, outpatient, home nursing, equipment, physiotherapy, medications; annual hospitalisation rates; length of hospital stay; anti-seizure medication use; direct costs i.e total direct costs and a breakdown of costs for individual healthcare resources as reported by the authors (mean and SD PPPY); indirect costs (e.g costs from loss of productivity). In addition, quantitative HRQoL measures for patients or caregivers (measure used, patient or caregiver and value) and qualitative HRQoL studies were described descriptively. Data were extracted for patients with LGS, LGS subpopulations (patients with and without seizures and

with and without rescue medication) and control populations used by the authors (e.g age matched non-LGS patients).

During the development of the protocol (Prospero: CRD42022333410), it was anticipated that the studies identified in this SLR would be diverse with regard to study design, definition of LGS (especially as there is no specific ICD-9 or 10 code for LGS in some regions and diagnosis can be challenging), size of the populations, the ages of the patients and the length of the follow-up period, and therefore the synthesis of the data was planned to be narrative in nature, without any statistical analyses/comparisons (e.g meta-analyses). Costs were extracted as given in the source. Summaries of the costs across the different studies were provided in the narrative synthesis in US dollars ($) using a simple conversion from Euros (€) to US dollars at an exchange rate of €1.00 Euro =$1.06 (xe.com on 21st June 2022).

Quality assessment/risk of bias

The quality assessment of the prevalence studies was performed using a tool developed by Hoy et al. [35]. The quality of the cost of illness studies was assessed using a tool from the British Medical Journal Checklist for economic submissions [36] that was adapted by Molinier et al. [37]. The quality assessment of the qualitative and quantitative HRQoL studies was conducted using the Critical Appraisal Skills Programme, CASP; https://casp-uk.net/ that was adapted by Gallop et al. [38].

Results

Search results

The electronic database searches initially identified 868 articles, of which 595 were screened after the removal of duplicates. After the primary screening, a total of 149 articles were retrieved for secondary screening (full-text assessment), and of these, 22 met the eligibility criteria (Fig 2). The study characteristics are summarized in Table 2, epidemiology data are summarized in Table 3 and the costs and resource data are presented in Additional file 2: Table S1. The results of the quality assessments/risk of bias are presented in Additional file 2: Tables S2–5.

Epidemiology: Incidence/prevalence and mortality

Overall, 9 studies (10 publications) reported on the epidemiology of LGS (Table 3). Prevalence, reported in 7 studies, varied from 4.2–60.8 per 100,000 people across studies for probable LGS and 2.9–28 per 100,000 people for a confirmed/narrow definition of LGS [15, 39–44]. Incidence, reported in 2 studies, was estimated at approximately 1.9 per 100,000 people in both studies [42, 45]. In addition, 3 studies reported on the proportion of LGS among epilepsy patients, varying from 4 to 8.4% during childhood [43, 44, 46] [42, 45]. The risk of bias in the studies reporting on prevalence/incidence was low in 3 studies [40, 41, 47] and moderate in 5 studies [39, 42–45] (Additional file 2: Table S2).

Trevathan et al (1997) reported the lifetime prevalence of LGS at the age 10 years to be 26 per 100,000 people (0.26 per 1000 people) [44]. The study used data from the Metropolitan Atlanta Developmental Disabilities Study (MADDS) that encompassed children aged 10 years who were born from January 1, 1975, through December 31, 1977; children with LGS were identified via multiple sources including public schools, special education programs, hospitals, selected physicians' offices, and EEG laboratories [44]. More recent studies (2019–2021) have used databases covering large populations including claims databases in the USA [41] and Germany [47] and the Clinical Practice Research Datalink (CPRD) database of health records in the UK [40]. These studies have estimated the prevalence of probable LGS to be 13.0–60.8 per 100,000 people in the USA [41], 39.2 per 100,000 people in Germany [47], and 4.2 per 100,000 people in the UK [40]. Using a more stringent definition of LGS resulted in prevalence rates of 6.5 per 100,000 people in Germany [47] and 2.89 per 100,000 people in the UK [40]. Other older, smaller population-based studies have reported the prevalence of LGS to be 10 per 100,000 people in Estonia [39], 2.1–28 per 100,000 people in Finland [42, 45], and 20 per 100,000 people in Sweden [43]. While LGS is a rare syndrome, Piña-Garza et al. [46] reported that LGS accounts for 8.4% of epilepsy cases at age 10 decreasing to 2% in the 60-year-old cohort in the USA. In addition, Trevathan et al (1997) (MADDS study) [44] reported that it accounted for 4% of childhood epilepsy cases, while the study in Sweden [43] found that among the childhood epilepsy syndromes, 5.8% of patients had LGS (Table 2).

Mortality was reported in 3 studies, although with different methods (mortality ratio, mortality rate as a percentage of patients who died divided by the total number of patients in the study, and mortality rate per 1000 person-years) [40, 47, 48]. Overall, the studies showed that mortality was substantially higher in LGS patients than in children with epilepsy and controls (Table 3) [40, 47, 48]. For example, using the MADDS data source, Autry et al. [48] reported a mortality ratio (ratio of observed-to-expected deaths) of 13.92 (95% confidence interval [CI] 7.19–24.31) for children with LGS versus 3.11 (95% CI 2.39–3.98) for all children with epilepsy over a 26-year follow-up period. The retrospective claims analysis from Germany reported a mortality rate (the percentage of patients who died divided by the total number of patients in the study) over the

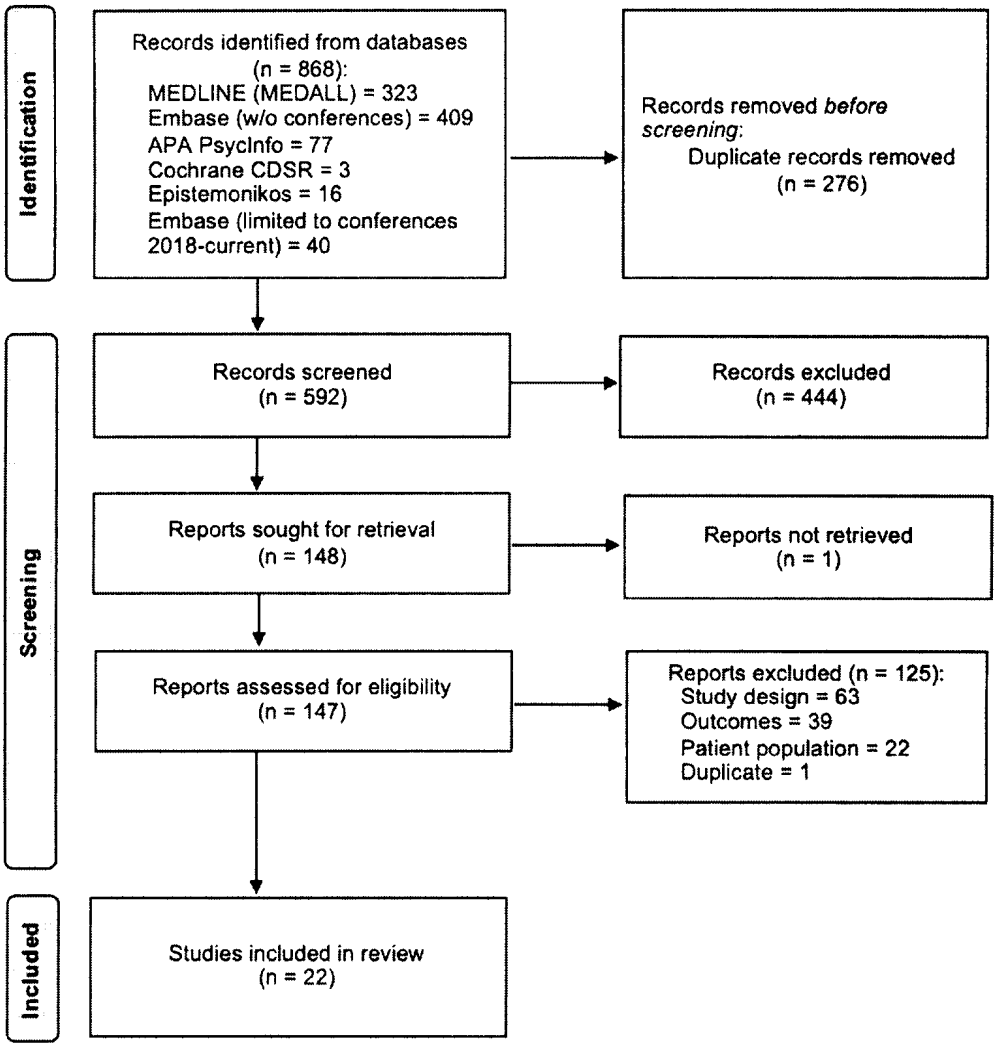


Fig 2 PRISMA flow diagram. Adapted from Page et al (2021) [95]

10-year study period of 10.01% for patients according to the broad definition of LGS and 2.88% for the narrow definition versus 0.01% for the age- and sex-matched control population ($p < 0.001$) [47]. Using data from the CPRD (electronic health records) linked to mortality data from the Office of National Statistics (ONS) in the UK, Chin et al. [40] estimated the mortality rates to be 6.12 deaths per 1000 person-years for confirmed LGS and 4.17 deaths per 1000 person-years for probable LGS over a follow-up period of 1796 and 1679 patient-years, substantially higher than the mortality rates for the general population and the epilepsy population (0.6 per 1000 person-years in England in 2018 [49], and 0.9 per 1000 person-years in the UK [50], respectively).

Healthcare resource utilization and costs

Overall, 9 studies (9 publications), all published from 2017 to 2021, were identified that reported on resource utilization and/or direct costs; 7 reported on both resource utilization and direct costs [46, 47, 51–55] (6 from the USA and 1 from Germany), and 2 reported on resource utilization only (1 from the USA using insurance claims databases and 1 from the UK using electronic health records) [40, 56] (Table 2 and Additional file 2: Table S1). By country, most of the studies were from the USA (7 out of 9 studies). All of the costs studies were retrospective analyses of insurance claims databases and the mean annual direct costs were €22,787 in Germany (n = 1 study), and varied from $28,461 to $80,545 in the

Table 2 Study characteristics

Study, year (Publication type) Country Database	Study type and source of data	Time period	Population: Number	Definition of LGS	Characteristics: Age, mean (SD; median [range]), years; Male, %	Outcomes
Burden-of-illness/costs and resource						
Piña-Garza [46] (Full) USA MEDLINE and Embase	Retrospective insurance claims analysis: Medicaid multi-state database of six states	Observation period: mean (SD): 11.1 (4.5) years (1997/98–2012/13)	*Probable LGS:* N=14,712	≥2 medical claims ≥30 days apart for specified epilepsy or unspecified epilepsy (ICD-9-CM codes) Machine-learning technique based on a number of clinical variables (including use of rufinamide during the testing & training period)	16.3 (15.7); 52.5% male	Epidemiology Resource Direct costs
Strzelczyk 2021 [47](Full) Germany MEDLINE, Embase and APA PsycInfo	Retrospective insurance claims analysis: Vilua Healthcare research database, entries for >4 million people i.e ~5% of the German population	10 years (2007–2016)	*Broad LGS:* N=545 *Narrow LGS:* N=102	*Broad definition*: Algorithm considering: ≥1 ICD-10 diagnosis of G40 (epilepsy)/G41 (status epilepticus) and ≥1 claim of either rufinamide or felbamate (during the year of identification), OR ≥2 different ASMs in combination with ≥1 developmental delay diagnosis and no diagnosis code for competing etiologies *Narrow definition*: ≥1 documented G40/G41 claim before their 6th birthday	*Broad LGS:* 31.4 [2–89]; 53% male *Narrow LGS:* 7.4 [2–44]; 52% male	Epidemiology Mortality Resource Direct costs
Chin 2021 [40] (Full) UK MEDLINE and Embase	Retrospective analysis using electronic medical records from healthcare databases: Primary care data (CPRD) linked to secondary care data (HES), and general population mortality data (ONS)	~31 years (1987–2018) Follow-up: mean (SD; median [range]): 11.7 (8.2; 9.6 [0.2; 32.2]) years	*Confirmed LGS*: N=110 *Probable LGS*: N=146 *Full cohort:* N=256	*Confirmed LGS*: CPRD read code for LGS *Probable LGS*: ICD-10 code/ CPRD read code for epilepsy Rufinamide within a year of diagnosis	*Confirmed LGS*: 7.0 (10.0; 3.5 [0–61]); 66% male *Probable LGS:* 8.9 (11.0; 4 [0–54]); 56% male *Full cohort:* 8.1 (10.6; 4 [0–61]); 60% male	Epidemiology Mortality Resource

Table 2 (continued)

Study, year (Publication type) Country Database	Study type and source of data	Time period	Population: Number	Definition of LGS	Characteristics: Age, mean (SD; median [range]), years; Male, %	Outcomes
Reaven 2018 [54] (Full) (LGS vs controls) USA MEDLINE, Embase and APA PsycInfo	Retrospective insurance claims analysis: Truven Health Analytics MarketScan® Research Databases, entries for ~60 million people with commercial or Medicaid insurance coverage	2010–2015	*Probable LGS:* *Commercial:* N=2270 *Medicaid:* N= 3749	A diagnosis code for refractory epilepsy and A diagnosis code for developmental delay/ intellectual disability and A prescription for at least one selected ASM. Excluded patients with diagnosis codes for conditions suggestive of other etiologies Modified version of the algorithm developed by Piña-Garza et al [45] (above)	*Commercial:* 13 (9.8 [0–62]); 53.0% male *Medicaid:* 13 (10.5 [0–60]); 52.9% male	Resource Direct costs
Reaven 2019 [53] (Full) (LGS vs other DEEs; seizure events vs no events) USA MEDLINE, Embase and APA PsycInfo			*Probable LGS:* *Commercial:* N=2269 *Medicaid:* N= 3730		*Commercial:* 13 (9.8 [0–62]); 53.0% male *Medicaid:* 13 (10.5 [0–60]); 52.8% male	
Stockl 2019 [56] (Abstract) (Hospitalizations) USA Embase			*Probable LGS: Commercial:* N=2520 *Medicaid:* N=4613	As above, but also patients with an acute inpatient hospitalization (≥1 day LOS)	NR	Resource
Stockl 2019 [55] (Abstract) (Commercial; Costs & Resource) USA Embase	Retrospective insurance claims analysis: IBM® MarketScan® Commercial & Medicaid databases	2015–2016	*Probable LGS:* *Commercial:* N=1296	≥1 ASM claim and medical claims with ≥1 diagnosis code for LGS or refractory epilepsy or ≥1 claim for clobazam or rufinamide. The LGS cohort required a diagnosis code for LGS or all of the following: ooooooo≥1 diagnosis code for refractory epilepsy ooooooo≥1 diagnosis code for intellectual disability/ developmental delay, ooooooNo diagnosis codes that preclude LGS	*Commercial:* 16.5; NR	Epidemiology Resource (ASM use only) Direct costs
Hollenack 2019 [52] (Abstract) (Medicaid; Costs & Resource USA Embase		2014–2015	*Probable LGS:* *Medicaid:* N= 5186		*Medicaid:* 18.3; 58.2% male	
Hollenack 2019 [41] (Abstract) (prevalence) USA Embase		*Commercial:* 2016– 2017 *Medicaid:* 2016	*Probable LGS: Commercial:* N=2273 *Medicaid:* N=4786		NR	

Table 2 (continued)

Study, year (Publication type) Country Database	Study type and source of data	Time period	Population: Number	Definition of LGS	Characteristics: Age, mean (SD; median [range]), years; Male, %	Outcomes
François 2017 [51] (Full) USA MEDLINE	Retrospective insurance claims analysis: Truven Health MarketScan® claims databases, entries for >40 million people with commercial or Medicaid insurance coverage	2010–2014	LGS pre-clobazam initiation *Commercial/medicare:* N=1384 *Medicaid:* N=1365	≥2 medical claims with a diagnosis of generalized convulsive or non-convulsive epilepsy ≥30 days apart, or ≥1 medical claim with a diagnosis of generalized convulsive epilepsy and ≥1 medical claim with a diagnosis of non-convulsive epilepsy (≥30 days apart (ICD-9-CM codes) ≥1 of the epilepsy diagnosis codes in the primary position ≥1 medical claim with a diagnosis for developmental disorder or cognitive impairment (ICD-9-CM codes)	*Commercial/medicare:* 31.0 (23.2); 49.3% male *Medicaid:* 24.1 (17.9); 51.8% male	Resource Direct costs
Umeno 2019 [57] (Full) Japan Embase	Retrospective study on the use of the welfare system in children with DEEs in Japan	2015–2016	LGS: N=30	Children aged 0 to 16 years diagnosed at the Department of Child Neurology, Okayama University Hospital	NR	Resource (welfare system)
Epidemiology alone						
Trevathan 1997 [44] (Full) MADDS study USA MEDLINE and Embase	Population-based, cross-sectional study: (MADDS): a multiple-source, EEG laboratory-based, case ascertainment system across Atlanta	1975–1977	Children with LGS: N=23	Epilepsy Two or more seizure types that included tonic, atonic, atypical absence, and/or myoclonic seizures with multiple falls Interictal EEG that demonstrated slow spike-wave discharges	NR; 73.9% male	Prevalence
Autry 2010 [48] (Full) MADDS study USA		1975–2001	LGS: N=34		NR; NR	Mortality
Sidenvall 1996 [43] (Full) Northern Sweden MEDLINE and Embase	Observational study: Active epilepsy assessed in children aged 0–16 years in an area of northern Sweden with ~ 250,000 inhabitants (~50,000 children)	1985–1986	LGS: N=9	Diagnosed using standard ILAE criteria	NR; NR	Prevalence

Table 2 (continued)

Study, year (Publication type) Country Database	Study type and source of data	Time period	Population: Number	Definition of LGS	Characteristics: Age, mean (SD; median [range]), years; Male, %	Outcomes
Rantala 1999 [42] (Full) Finland MEDLINE and Embase	Retrospective study: Children seen at the Department of Pediatrics University of Oulu	1976–1993	LGS: N=25	At least two types of the most common seizure types (tonic-axial, atonic, and absence seizures) Slow spike waves	13.0 [6.5–17.9]; 56% male	Prevalence and incidence
Heiskala 1997 [43] (Full) Finland MEDLINE and Embase	Retrospective study: Health records from the Helsinki metropolitan area & the province of Uusimaa	1975–1985	LGS: N=75	A minimum of two types of typical though non-specific epileptic seizures (e.g. astatic seizures, tonic seizures during sleep, and atypical absence seizures) Mental deficiency Bursts of diffuse slow spike-waves in the EEG	NR; NR	Incidence
Beilmann 1999 [39] (Full) Estonia MEDLINE	Observational study: Patients with epilepsy seen at the Tartu University Hospital, sourced through multiple methods	1995 –1997	NR	Diagnosed using standard ILAE criteria	NR; NR	Prevalence
HRQoL						
Auvin 2021 [61] (Full) UK and France	Observational study: On-line surveys	2018–2019	Patients and/or caregivers of individuals with DEEs estimated a patient's health state from vignettes of hypothetical patients	NA	NA; NA	Patient HRQoL: quantitative (VAS)
Radu 2019 [62] (Abstract) NR Embase	Observational study: On-line surveys	2018		NA	NA; NA	Patient HRQoL: quantitative (VAS)
Gallop 2010 [58] (Full) US, UK & Italy MEDLINE, Embase and APA PsycInfo	Observational study: Open-ended interviews and HRQoL instruments	NR	Parents of patients with LGS recruited through support groups and websites (UK and US) and through clinicians (Italy): N=40	NR	12 [4–43]; 63% male	Caregiver HRQoL: Quantative (SF-36v2, HADS) and qualitative Patient HRQoL: Qualitative
Murray 1993 [60] (Full) Australia MEDLINE, Embase and APA PsycInfo	Observational study: Questionnaires & in-depth interviews	NR	Parents of patients with LGS who attended a self-help group: N=41	NR	13 [3–34]; NR	Caregiver HRQoL: Qualitative
Gibson 2014 [59] (Full) USA MEDLINE, Embase and APA PsycInfo	Observational study: General experience and parent survey	NR	Parents of patients with LGS who had contacted a support hotline: N=96 surveys returned	NR	[3.5–36 years]; NR	Caregiver HRQoL: Qualitative

ASM anti-seizure medication; *CPRD* Clinical Practice Research Datalink; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; HADS, Hospital Anxiety and Depression Scale; HES, Hospital Episode Statistics; HRQoL, health-related quality of life; ILAE, International League Against Epilepsy; LGS, Lennox–Gastaut syndrome; LOS, length of stay; NA, non-applicable; MADDS, Metropolitan Atlanta Developmental Disabilities Study; NR, not reported; ONS, Office for National Statistics; SD, standard deviation; VAS, visual analogue scale

Table 3 Epidemiology: Incidence/prevalence and mortality in patients with LGS

Study	Country	Study type	Year	Population (n)	Incidence/prevalence		Mortality
					Parameter	Value	
Piña-Garza 2017 [46] (Full)	USA	Retrospective claims analysis	2012/13	Probable LGS patients N=14,712	Proportion of epilepsy patients with probable LGS (10-year age groups)	8.4% at age 10 decreasing to 2% in the 60-year-old cohort	NR
Strzelczyk 2021 [47] (Full)	Germany	Retrospective claims analysis	2016	*Broad LGS* N=545 *Narrow LGS* N=102	Prevalence (standardized to German GKV population)	*Broad LGS:* 39.2 per 100,000 people *Narrow LGS:* 6.5 per 100,000 people	*Broad LGS: 10.01% [157 events] Narrow LGS:* 2.88% [six events] ($p < 0.001$ vs control) *Control:* 0.01% [one event]
Chin 2021 [40] (Full)	UK	Retrospective analysis of electronic medical records	2017	*Confirmed LGS:* N=74 for prevalence *Probable LGS:* N=106 for prevalence *Full cohort:* N=180 for prevalence; N=122 for mortality	Prevalence (standardized to UK CPRD population)	*Confirmed LGS:* 2.89 per 100,000 people* *Probable LGS:* 4.20 per 100,000 people* *Full cohort:* 5.78 per 100,000 people*	Crude mortality rate per 1000 person-years: *Confirmed LGS:* 6.12 [11 events] *Probable LGS:* 4.17 [7 events] *Full cohort:* 18 events
Hollenack 2019 [41] (Abstract)	USA	Retrospective claims analysis	2016/ 2017	*Probable LGS: Commercial:* N=2273 *Medicaid: N*=4786	Prevalence	*Commercial:* 13.0 per 100,000 people* *Medicaid:* 60.8 per 100,000 people*	NR
Trevathan 1997 [44] MADDS study (Full)	USA	Population-based, cross-sectional study	1975–1977	LGS: N=23	Prevalence of LGS at age 10 years Proportion of epilepsy patients with LGS	26 per 100,000 people* 4% of epilepsy patients	NR
Autry 2010 [48] MADDS study (Full)			Original cohort: 1975–1977 Follow-up: 1975 to 2001	LGS: N=34	NR	NR	Mortality ratio (95% CI): 13.92 (7.19-24.31) for LGS vs 3.11 (2.39-3.98) for all epilepsy
Sidenvall 1996 [43] (Full)	Northern Sweden	Observational	1985	LGS: N=9	Prevalence N (%) of epilepsy patients with LGS	20 per 100,000 people* n=9 (5.8%) of all epilepsy cases	NR
Rantala 1999 [42] (Full)	Finland	Retrospective	1976–1993	LGS: N=25	Prevalence	28 per 100,000 people (95% CI: 18–41)*	NR
					Annual incidence	1.93 per 100,000 children <15 years (95% CI: 1.25-2.85/100,000)	
Heiskala 1997 [45] (Full)	Finland	Retrospective	1975–1985	LGS (broad definition): N=75 LGS children 0–14 years: N=NR	Annual incidence	Broad definition: 2.1 per 100,000 people Children 0–14 years: 1.9 per 100,000	NR
Beilmann 1999 [39] (Full)	Estonia	Observational	1997	LGS: N=NR	Prevalence	10 per 100,000 people*	NR

CI confidence interval; *CPRD* UK Clinical Practice Research Datalink; *GKV* German population covered by statutory health insurance (Gesetzliche Krankenversicherung; GKV); *NR* not reported

*Converted to per 100,000 people

USA across studies (n = 6 studies). The risk of bias in the studies reporting on costs and/or resources was assessed to be low in 6 studies [40, 46, 47, 51, 53, 54] and moderate in 3 studies, which were conference abstracts that provided limited information [52, 55, 56] (Additional file 2: Table S3). No study reporting the indirect costs of patients with LGS or their caregivers was identified, although one paper reported that a large proportion of caregivers of patients with LGS struggled to access the available medical expense subsidies in Japan [57] (Table 2).

Total healthcare costs and healthcare resource utilization associated with LGS were substantially higher than matched controls [54], non-LGS epilepsy patients [46], and patients with other DEEs, including DS and TSC [52, 53, 55] (Fig 3A, Additional file 2: Table S1). For example, Reaven et al. [54] reported that, compared to matched controls, annual costs for services were 17 to 20 times higher for patients with possible LGS, and annual costs for drugs were 16 to 38 times higher (Fig 3B). In addition, among LGS patients, costs and healthcare resource utilization were reported to be higher in patients with a seizure event versus those without (Fig 3C) [53], and costs and hospitalizations/ length of stay (LOS) were higher in those prescribed rescue medication vs those not [47] (Additional file 3: Fig S1).

The studies showed that patients with LGS require a multitude of healthcare resources including general/family practitioner visits, outpatient visits to the neurologist/ epilepsy clinic, laboratory and radiology services, medication, physiotherapy/habilitation services and other physical therapies, inpatient and emergency department visits, as well as home-based nursing [40, 47, 51, 53, 54, 56] (Additional file 2: Table S1). Across the studies, inpatient care and home-based care were significant cost drivers, whereas pharmacy costs, particularly for ASMs, generally represented a smaller share of all healthcare costs (Fig 4A, Additional file 2: Table S1) [46, 47, 51–55]. In Germany the greatest contributors to healthcare costs were inpatient care (33%) especially hospital stays related to epilepsy, followed by home nursing care (including intensive home nursing) (13%), and medication (10%) (Fig 4A, Additional file 2: Table S1) [47]. ASMs represented only 14% of the overall medication costs despite their ubiquitous use. Similarly, Piña-Garza et al. [46] reported that the main contributor to healthcare costs was home-based care in children aged 1–18 years (mean costs of $12,396 to $18,360 PPPY across across different pediatric age groups) and long-term care in the 60-year-old cohort ($16,215 PPPY), whereas mean pharmacy costs encompassed a smaller proportion of the costs at $1592–$5630 PPPY across all age groups. In the study by Reaven et al. [54], the largest contributors to the healthcare costs in LGS patients were inpatient care in the commercial-insured cohort and home health services (home-based nursing, personal care, and residential habilitation services) in the medic aid-insured cohort (Fig 4A, Additional file 2: Table S1).

While the costs of ASMs may account for a relatively small proportion of the overall healthcare costs, data from several studies suggest that the burden of ASMs on patients and the overall pharmacy costs is high. For example, in a study based on IBM® MarketScan® medic aid database, the mean number of distinct ASMs during the 12-month study period averaged 2.4, 2.3, and 2.2, in probable LGS, probable DS, and other refractory epilepsies, respectively, accounting for 67.3%, 62.8%, 52.3% of the pharmacy costs [52]. Likewise, using the IBM® MarketScan® commercial database, the mean number of distinct ASMs was 3.4, 2.6, and 2.1, respectively, representing 72.6%, 70.8%, and 65.8% of the pharmacy costs [55]. In addition, Chin et al (2021) reported that in patients with confirmed LGS the mean number of ASMs was 6.7 (SD 3.4) during the 8–12 years follow-up period, with only 3.7% being prescribed only one ASM during this period, while the mean number of ASMs per year was 1.06 during 2010–13 and 1.12 during 2014–17 [40]; this suggests that patients had to switch to different ASMs many times over the course of the study period. Similarly, in the study in Germany, patients generally received 1–3 different ASM combinations each year (range: 1–9) and most patients received 2–4 different ASMs [range: 1–12] over the entire 10-year observable period [47]. Of note, the use of other drugs was also substantially higher in LGS patients than in control populations (Fig 2B) [54]. In both Germany [47] and the UK [40] the most commonly prescribed ASMs were valproate, lamotrigine, clobazam, oxcarbazepine (in Germany) and levetiracetam (in the UK); in the UK rufinamide was prescribed in 27% of patients with confirmed LGS. In the US, Pina-Garza et al. [46] reported LGS patients may be inadequately treated; the majority, but importantly not all probable LGS patients had ≥1 claim for an ASM (62.6–82.3% across age cohorts), while clobazam and rufinamide, both specifically licensed for LGS in the US, were infrequently used, especially in the older cohorts (17.5% for clobazam and 7.4% for rufinamide in patients ≤5 years, 5.5% for both ASMs in the 20-year cohort and <1.0% of patients in the 60-year cohort).

Regarding hospitalizations and LOS, in Germany there was a large variation between patients, with some being hospitalized many times (median hospitalization rate: 1 [range: 0–13 PPPY]) with a median LOS of 3 days (range: 0–804 days) [47]. In a study describing the nature of acute hospitalizations in LGS patients, 46–58% were considered epilepsy-related across health

plans (Commercial and Medicaid) compared to 63–70% for DS, 26% for TSC, and 37–51% for other DEEs; 6–7% were pneumonia-related, and approximately 2% were injury-related [56]. Across the different DEEs, admission to the intensive care unit (ICU) accounted for 31% of all hospitalizations, and ICU use was associated with a longer LOS (mean 8.0 [SD 16.8] days vs. 4.0 [SD 7.9] days for non-ICU use). Furthermore, readmission rates were high, with approximately 9–10% of patients readmitted within the month and 42–45% within a year of discharge [56]. Concerning injuries, 67% of LGS patients reported at least one injury over the 10-year study period in Germany [47], while in the study by Reaven et al. [53], 22% (2329 of 10,618) of LGS patients with a medically-treated seizure event across insurance types had an injury.

Health-related quality of life

Five studies, published between 1993 and 2021, were identified that reported on the HRQoL of patients with LGS and/or their caregivers using qualitative and/or quantitative methods; one study reported on both caregiver and patient perspectives [58], 2 focused on caregivers [59, 60] and 2 on patients [61, 62] (Table 2). Three studies used qualitative methods (one for both patient and caregiver HRQoL, and two for caregiver HRQoL); the quality of the qualitative studies was assessed to be grade I (highest methodological and reporting quality) in one study and grade III (limitations in methodological and reporting quality) in 2 studies (Additional file 2: Table S4). Three studies used quantitative methods (one assessed caregiver HRQoL using the SF-36 and the HADS (Hospital Anxiety and Depression Scale), while two studies used a VAS (visual analog scale). The quality of the quantitative studies was assessed to be grade II (moderate-high methodological and reporting quality) in 2 studies and grade III in one study (Additional file 2: Table S5).

All three studies reporting on the HRQoL of caregivers found that LGS had substantial negative effects. Gallop et al. [58] investigated the HRQoL of parent caregivers (N = 40) both quantitively and qualitatively. Using the SF-36v2, a widely used generic instrument to measure health status, the parents' mental health summary score (a composite of social functioning, vitality and mental health) was found to be below average (45 for LGS parents vs. 50 for US general population). In addition, 58% of parents experienced anxiety according to the HADS. Using semi-structured interviews with the parents, the authors determined that the parents were impacted physically, emotionally, socially and financially. Gibson [59] similarly reported that LGS had a significant physical, emotional, social and financial impact on parents, while siblings were also affected, frequently taking on a caregiver role themselves early in life. Furthermore, Murray reported in 1993 that parents had to deal with a lot of uncertainty around diagnosis, etiology, seizure activity, treatment and prognosis, which caused feelings of guilt and stress in some parents [60].

Gallop et al. [58] also investigated parents' perceptions of how LGS impacted their children, describing the profound impact that the syndrome conferred on the daily lives of children with LGS; in particular, physical, social, cognitive and behavioral aspects of their lives were disrupted. Studies by Auvin et al. [61] and Radu et al. [62] used an alternative method of measuring patient HRQoL in a quantitative manner whereby patients and/or caregivers of patients with LGS, DS, or other epilepsies were asked to score the patient HRQoL based on hypothetical vignettes of patients with LGS (or DS) according to how many seizures and seizure-free days the hypothetical patient experienced. These studies have suggested that fewer seizures and additional seizure-free days are associated with better patient HRQoL, with seizure-free days having the greatest consequence on HRQoL (Fig 4B). Of note, this vignette-based method for estimating HRQoL focused specifically on the impact of seizure frequency/seizure-free days as opposed to a more holistic HRQoL assessment. The values were used in the NICE (National Institute for Health and Care Excellence) appraisal in the UK to inform the cost-effectiveness of cannabidiol for the adjuvant treatment of seizures associated with LGS [63].

(See figure on next page.)

Fig 3 **A** Total direct costs in LGS patients (blue) versus control patients (grey), patients with other epilepsies (lilac), and in LGS patients with seizure events vs without seizure events and LGS patients in years where patients were prescribed with rescue medication vs years where patients were not prescribed rescue medication (blue) **B** resource utilization and costs in LGS patients vs controls; **C** resource utilization and costs in LGS patients with seizure events vs without seizure events. Adapted from: Reaven et al (2018) [54], Piña-Garza et al (2017) [46], Stockl et al (2019) [55], Hollenack et al (2019) [52], Reaven et al (2019) [53] and Strzelczyk et al (2021) [47] .* Costs were converted from Euros to US dollars on 21st June 2022 (exchange rate 1.00 Euro =1.06 US Dollars [xe.com]). ASM, anti-seizure medication; DS, Dravet syndrome; ED, emergency department; LGS, Lennox–Gastaut syndrome; PPPY, per person per year; OP, outpatient; TSC, tuberous sclerosis complex

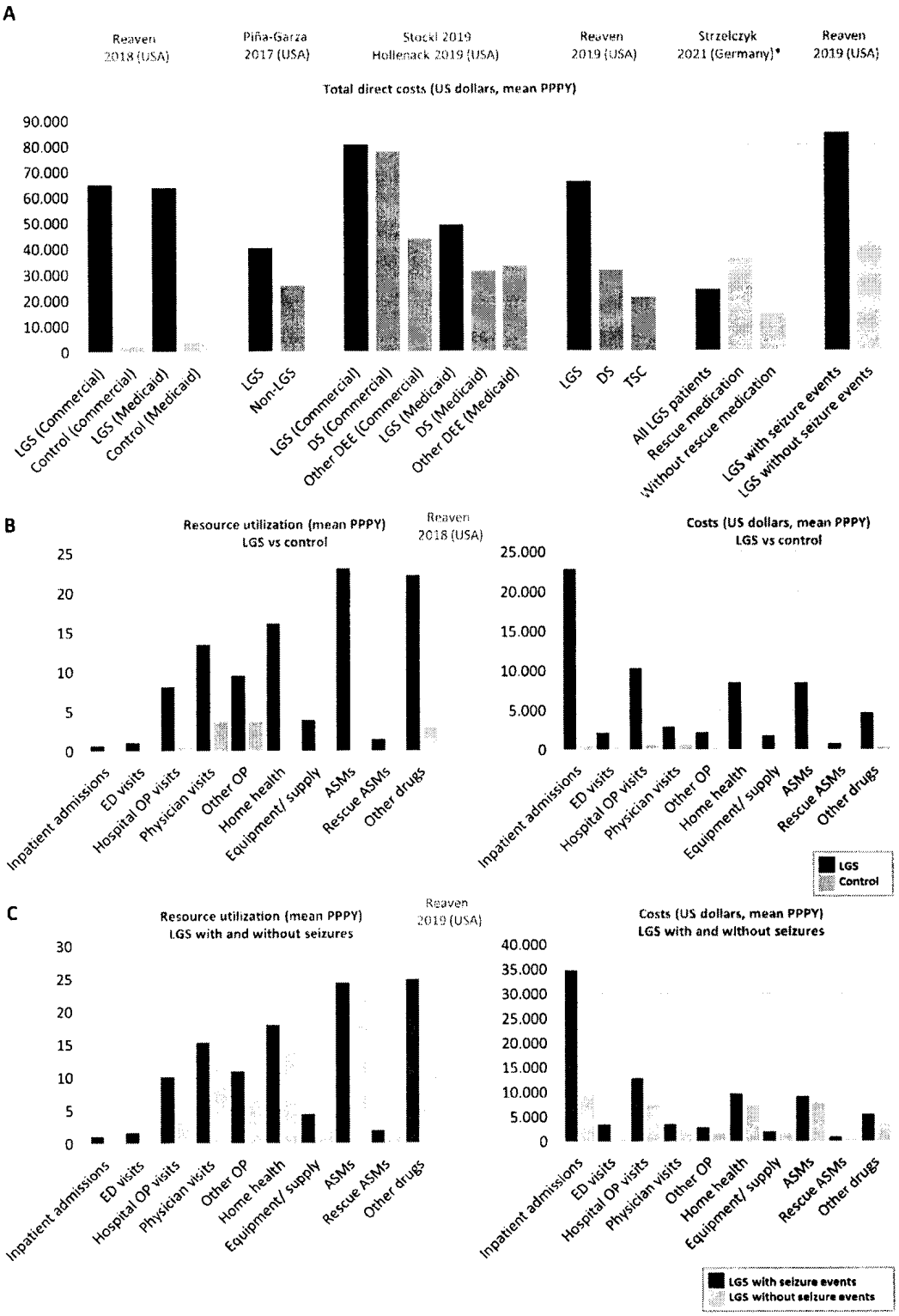


Fig 3 (See legend on previous page.)

Discussion

We conducted a comprehensive SLR following pre-specified inclusion/exclusion criteria to understand the burden of LGS, providing a descriptive summary of the literature while identifying gaps in the current knowledge. The epidemiology studies confirm that LGS is a rare syndrome, whereby the prevalence varied from 4.2 to 60.8 per 100,000 people across studies for probable LGS and 2.9 to 28 per 100,000 people for confirmed/narrow definition of LGS. Annual costs per patient and healthcare resource utilization were substantial across all studies, confirming the high economic burden associated with LGS. In addition, studies showed that the HRQoL of patients and caregivers was adversely affected, and seizure events were associated with higher costs and worse HRQoL. Furthermore, LGS was associated with high mortality rates compared to the general population and those with epilepsy in general.

The burden of illness studies relies heavily on how the disease is defined. However, for LGS there are inherent difficulties in using the currently available source data where there has been no specific code for LGS in the ICD coding in many regions. An extension code for LGS in the ICD-10-CM coding system (G40. 812) has only been available since 2015, and it is only used in some regions. The recent release of ICD-11 includes a specific code for LGS (8A62.1 Lennox–Gastaut syndrome) [64], however, it may be many years before the benefits are seen in real-world research, including the burden of illness studies, which require a sufficient number of patients and observation period. Without a precise definition of LGS and a lack of consistency in using recent and specific diagnostic codes for LGS, there was considerable heterogeneity between studies on how LGS was defined. The retrospective claims analysis studies generally used a "probable LGS" definition that included appropriate ICD-9 or ICD-10 codes for epilepsy and developmental delay and a prescription for a relevant ASM. Piña-Garza et al (2017) developed a machine-learning classification model to identify patients with LGS [46], which was subsequently used and modified for other studies [53, 54, 56]. The methods were latterly reported in more detail by Vekeman et al (2019), showing that an LGS classifier that used input variables including the number of distinct ASMs received, epilepsy-related outpatient/inpatient visits, electroencephalogram procedures and claims for delayed development, showed high sensitivity and specificity in identifying LGS patients [65]. On the other hand, Chin et al (2021) was able to circumvent the limitations of the ICD coding by using the electronic medical records from the CPRD in the UK that included a code for LGS (the confirmed LGS group) [40]. Other smaller retrospective, observational studies reporting on the epidemiology of LGS included patients who had been diagnosed based on standard diagnostic/ILAE criteria [39, 42–45, 48], while the HRQoL studies generally recruited caregivers and/or patients through support groups, patient associations, clinicians and/or websites [58–62]. Other areas of heterogeneity across the studies included the size of the populations, the ages of the patients and the length of the follow-up period. Another limitation is that LGS is likely to be underdiagnosed/ misdiagnosed, especially in adults [11, 14], and therefore many aspects of the burden of illness may have been underestimated.

Many of the studies identified are recently published, particularly those on costs and healthcare resources, which may reflect the development of new treatment options, whereby the data can be used to inform payers and health technology assessment agencies. We did not look at the impact of interventions on our outcomes. However, compared to standard of care, studies have estimated that rufinamide is a cost-effective treatment [66, 67], while cannabidiol was found to be cost-effective in a model that was based on absolute seizure frequency and seizure-free days and took account of the impact of caregivers' burden [68], but in a different model, it was determined not to be cost-effective at a willingness-to-pay threshold of $150,000/ quality-adjusted life-year [69]. As with DS [70–73], studies have suggested that seizure events in LGS are associated with higher costs and worse HRQoL, and therefore it is hoped that current and future improvements in the treatment will help to alleviate some of the burdens on healthcare resources and costs and improve the HRQoL of patients and caregivers.

We found only a few studies evaluating the HRQoL in patients and caregivers. In a recent SLR describing the impact of a range of DEEs (including LGS) on the HRQoL of caregivers and the wider family unit Gallop et al. [58] identified only one study of sufficient quality regarding caregivers of patients with LGS (also identified hererin) [38]. However, across the DEEs, the authors found that most of the studies reported a negative impact on the

(See figure on next page.)

Fig 4 **A** Cost drivers according to inpatient and emergency department admissions (red), outpatient visits (orange), home health (home nursing and physiotherapy; blue), equipment (yellow) and medication (green) costs (where reported) **B** Patient and caregiver HRQoL according to number of drop seizures per month and number of seizure-free days in the UK and France. Mean health state utility scores for a hypothetical patient with LGS and a hypothetical caregiver of a patient with LGS. **A** Adapted from: Strzelczyk et al (2021) [47] and Reaven et al (2018) [54]. Home health= home-based nursing, personal care, and residential habilitation services. **B** Adapted from Auvin et al (2021) [61]. ASM, anti-seizure medication; ED, emergency department; HRQoL, health-related quality of life; OP, outpatient

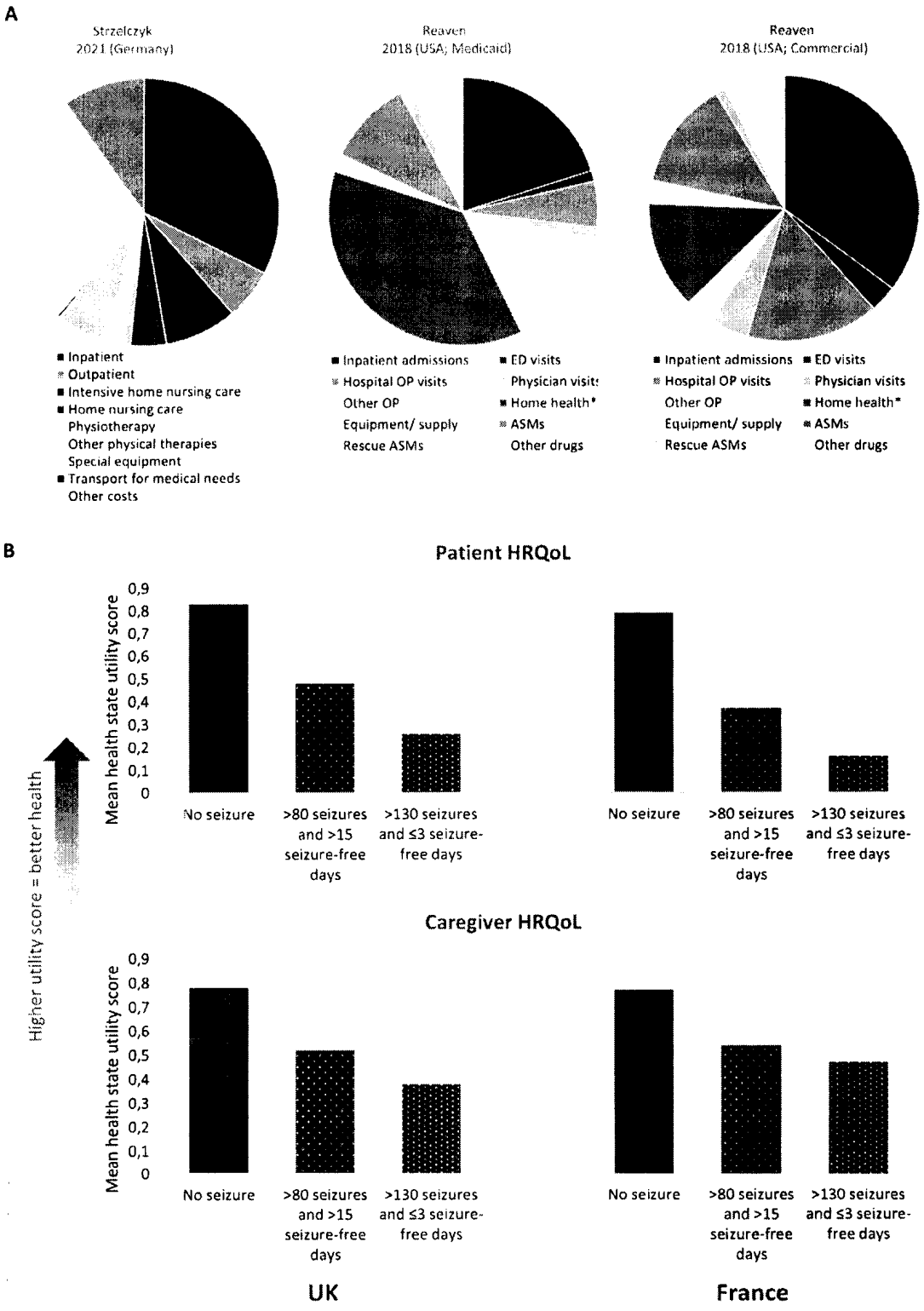


Fig 4 (See legend on previous page.)

HRQoL of caregivers, and they highlighted the challenges of evaluating caregiver HRQoL, especially using generic instruments, because parents of young children with complex chronic diseases adapt and become habituated to their decrease in quality of life [38]. The same can apply to patients, although measuring HRQoL in patients with LGS generally requires a parent proxy because of the patient's young age and/or cognitive dysfunction, as well as not knowing a time before their condition with which to compare to.

We identified no studies reporting on indirect costs, and therefore it is likely that the overall economic burden has been underestimated due to studies only reporting on direct costs. Indeed, the financial burden among patients and caregivers has also been little studied across other DEEs including DS and TSC [25]. However, the few studies that are available on DS caregivers and TSC patients or caregivers have shown that indirect costs are relevant [72, 74–76], with a particular impact on mothers having to reduce their working hours or stop working completely [72, 74, 77]. Overall, evaluating the caregiver burden including indirect costs, productivity losses and HRQoL requires complex, preferably prospective, studies that may have been hindered by a lack of having large patient advocacy groups from which to recruit participants, as well as a lack of priority for health research funding, among other factors.

Strengths and limitations

As far as we are aware this is the first SLR on the burden of illness in LGS. The SLR has several strengths in that it was a comprehensive review performed according to the PRISMA guidelines, with no limitations on language or date (except for abstracts), whereby the search terms were developed by an experienced information scientist.

The main limitations have been discussed above, including the challenges around identifying the LGS population and the paucity of studies, especially on caregiver HRQoL and indirect costs. Furthermore, many of the studies, especially regarding costs and resources, were conducted in the USA, with limited evidence in Europe, and no evidence from other parts of the world despite not having any language restrictions. This country-bias may reflect the lack of research funding as described above, with perhaps some publication bias against non-native English speaking countries [78, 79]. The situation in low and middle income countries is especially complex and many aspects of the burden of illness, especially mortality, costs, and resources are likely to be very different from high income countries. For example, a study of the global burden of epilepsy (among other conditions) reported that 81% of epilepsy-deaths occurred in low and middle countries [80], reflecting both the larger number of people with epilepsy and the limited resources with which to effectively manage and treat patients [81]. Overall, there is an imperative need for innovative solutions to improve the outcomes of patients in these countries [82, 83].

We restricted the search specifically to LGS, excluding studies which encompassed refractory epilepsy in general, even if they had a few LGS cases within a more general population of refractory epilepsy patients, which may have limited our evidence base, especially as LGS can evolve from or be part of other epilepsy syndromes, e.g. TSC [84]. In addition, while the literature was searched in major electronic databases, we may still have missed some studies from other databases or from the grey literature. We did not identify any extra relevant studies when we searched the reference lists of other SLRs, reviews and economic evaluations suggesting that our methods, including the search terms and databases used, were robust.

Future research directions

In this SLR we have found that there is lack of studies reporting on indirect costs, and patient and caregiver HRQoL. These are extremely important and relevant outcomes for this complex syndrome that goes beyond seizures. In addition, there is a lack of studies on all aspects of the burden of illness in low and middle income countries, and more research is needed in these areas, possibly through enhanced collaboration with established research groups in high income countries and the pharmaceutical industry. Patient advocacy groups for LGS should be empowered across all countries, perhaps through the use of virtual events and an increase in online resources and communities.

Studies in this SLR have reported that seizure events are associated with higher resource and costs, and lower patient HRQoL. Cannabidiol and fenfluramine are the most recently approved therapies for the treatment of seizures associated with LGS (Fig 1). ASMs in clinical development include soticlestat and carisbamate. Soticlestat has recently successfully completed Phase 2 clinical deveopment as an adjunctive therapy in pediatric patients with DS or LGS [85], with Phase 3 trials underway (NCT04938427 and NCT05163314). A Phase 3 clinical trial assessing carisbamate in patients with LGS has also been initiated (NCT05219617). It will certainly be of interest in the future to determine the impact that these potential and new ASMs [89] have on the burden of illness in LGS, especially patient and caregiver HRQoL. Of concern though is the apparent lack of other therapies in development for patients with LGS at present.

Also of note is that LGS has multiple and varied etiologies, and with advances in neuroimaging and genetics the conditions within this syndrome are now largely defined

and named by their etiology. These etiologies are a more precise guide to prognosis and management than the designation of LGS. William Lennox's views on eugenics [87, 88] have resulted in his name being removed from named lectures in the USA. The International League Against Epilepsy (ILAE) decided to keep the term Lennox–Gastaut in the 2022 ILAE Syndromes Definitions arguing that this was because medications are licensed for LGS and that a better collective name had not been coined for DEE with slow spike and wave and tonic seizures in childhood [86]. However, the term Lennox–Gastaut may gradually be retired in the next decade.

Conclusions

LGS is associated with a substantial burden of illness, with seizure events associated with higher costs and worse HRQoL. However, with no ICD-10 coding for LGS available in many regions, several studies had to rely upon indirect methods to identify their patient populations. More research is needed, especially in evaluating the caregiver burden, including HRQoL, productivity losses and indirect costs, where there is a notable lack of studies.

Abbreviations

ASMs	Anti-seizure medications
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
DEE	Developmental and epileptic encephalopathy
DS	Dravet syndrome
EEG	Electroencephalogram
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
ICU	Intensive care unit
LGS	Lennox–Gastaut syndrome
LOS	Length of stay
MADDS	Metropolitan Atlanta Developmental Disabilities Study
NICE	National Institute for Health and Care Excellence
ONS	Office of National Statistics
PICOS	population, intervention, comparator, outcomes and study design
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PPPY	Per person per year
SD	Standard deviation
SLR	Systematic literature review
TSC	Tuberous sclerosis complex

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13023-023-02626-4.

Additional file 1. Search terms.

Additional file 2. Supplementary Table S1: Healthcare resource utilization and costs in patients with LGS; **Table S2:** Quality assessment checklist for prevalence studies; **Table S3:** Quality assessment checklist of cost-of-illness studies; **Table S4:** Quality assessment checklist for qualitative HRQoL studies; **Table S5:** HRQoL: Quality assessment checklist for quantitative HRQoL studies.

Additional file 3. Supplementary Figure S1: Costs, annual hospitalization rate and length of stay (LOS) in LGS patients in years wherepat ents were prescribed with rescue medication vs years where patients were not prescribed rescue medication.

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Author contributions
AS and SSB developed the idea for this study and conceived the paper. AS, SZ, PS, FR and SSB wrote the paper, discussed the results, and contributed to the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
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Epilepsia

SPECIAL REPORT

International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions

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Abstract

The 2017 International League Against Epilepsy classification has defined a three-tier system with epilepsy syndrome identification at the third level. Although a syndrome cannot be determined in all children with epilepsy, identification of a specific syndrome provides guidance on management and prognosis. In this paper, we describe the childhood onset epilepsy syndromes, most of which have both mandatory seizure type(s) and interictal electroencephalographic (EEG) features. Based on the 2017 Classification of Seizures and Epilepsies, some syndrome names have been updated using terms directly describing the seizure semiology. Epilepsy syndromes beginning in childhood have been divided into three categories: (1) self-limited focal epilepsies, comprising four syndromes: self-limited epilepsy with centrotemporal spikes, self-limited epilepsy with autonomic seizures, childhood occipital visual epilepsy, and photosensitive occipital lobe epilepsy; (2) generalized epilepsies, comprising three syndromes: childhood absence epilepsy, epilepsy with myoclonic absence, and epilepsy with eyelid myoclonia; and (3) developmental and/or epileptic encephalopathies, comprising five syndromes: epilepsy with myoclonic–atonic seizures, Lennox–Gastaut syndrome, developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep, hemiconvulsion–hemiplegia–epilepsy syndrome, and febrile infection-related epilepsy syndrome. We define each, highlighting the mandatory seizure(s), EEG features, phenotypic variations, and findings from key investigations.

KEYWORDS

benign occipital epilepsy, childhood epilepsy with centrotemporal spikes, continuous spike-and-wave in sleep, eyelid myoclonia, febrile infection-related epilepsy syndrome, hemiconvulsion–hemiplegia–epilepsy syndrome, Landau–Kleffner syndrome, Lennox–Gastaut syndrome, myoclonic absences, myoclonic atonic, Panayiotopoulos syndrome

1 | INTRODUCTION

The goal of this paper is to describe epilepsy syndromes that begin in childhood (age 2–12 years). Additional syndromes that have a variable age at onset, including in childhood, are described in the paper on epilepsy syndromes with onset at a variable age.[1] The childhood onset syndromes can be broadly divided into three main groups: (1) self-limited focal epilepsies (SeLFEs); (2) generalized epilepsy syndromes, which are thought to have a genetic basis; and (3) developmental and/or epileptic encephalopathies (DEEs), which often have both focal and generalized seizures, including Lennox–Gastaut syndrome (LGS), developmental epileptic encephalopathy with spike-and-wave activation in sleep (DEE-SWAS), and epileptic encephalopathy with spike-and-wave activation in sleep (EE-SWAS), or may have generalized seizures alone, such as epilepsy with myoclonic atonic seizures (EMAtS), or focal/multifocal seizures alone, such as hemiconvulsion–hemiplegia–epilepsy syndrome (HHE) and febrile infection-related epilepsy syndrome (FIRES).

Key Points

- The ILAE produced a classification of epileptic syndromes presenting in childhood
- Syndromes with onset in childhood are divided into three categories: self-limited focal epilepsies, generalized epilepsies, and developmental and/or epileptic encephalopathies
- Each syndrome has mandatory seizure types, EEG features, age at onset, and findings from key investigations
- Precise identification of an epileptic syndrome can provide useful information on prognosis and management

Childhood is also the typical age of onset of childhood absence epilepsy (CAE); this syndrome is covered in a separate paper on the idiopathic generalized epilepsy (IGE) syndromes.[2]

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Recognition of these childhood syndromes requires careful analysis of seizure semiology, evolution over time, and the developmental course of the child, as well as electroencephalographic (EEG) features (background, interictal, and ictal patterns) and, in some cases, brain magnetic resonance imaging (MRI) and genetic studies. At times, childhood syndromes may have evolved from other epilepsy syndromes or types, such as infantile epileptic spasms syndrome, which may evolve to LGS, or self-limited epilepsy with centrotemporal spikes (SeLECTS; formerly known as benign rolandic epilepsy or benign epilepsy with centrotemporal spikes) or structural focal epilepsy evolving to EE-SWAS. In other syndromes, children with prior normal development present with a severe, acute encephalopathy followed by drug-resistant epilepsy, as typically seen in FIRES, or HHE. Moreover, for some SeLFEs, there may be overlap with the IGEs or even evolution to them, reflecting the patient's underlying susceptibility to epileptic seizures.[3,4]

The exact proportion of children with epilepsy who meet criteria for a specific syndrome has not been well studied prospectively; however, retrospective data suggest that an epilepsy syndrome is identified in at least one third of cases.[5,6]

This paper will address the specific clinical and laboratory features of epilepsy syndromes that begin in childhood and provide rationale for any significant nomenclature or definitional changes. Table 1 summarizes the epilepsy syndromes, with updated nomenclature and acronyms used in this paper.

2 | METHODOLOGY

The methodology for syndrome definitions is described in "Methodology for Classification and Definition of Epilepsy Syndromes with List of Syndromes: Report of the ILAE Task Force on Nosology and Definitions."[7] A working group consisting of Task Force members with expertise in pediatrics was convened. One member of the group was assigned to draft a template for each proposed syndrome, using data from a literature review through July 2019, the

TABLE 1 Childhood epilepsy syndromes

Self-limited focal epilepsies		Genetic generalized epilepsies		DEEs	
Epilepsy syndromes with focal seizures	Formerly known as	Epilepsy syndromes with generalized seizures	Formerly known as	DEEs	Formerly known as
SeLECTS	Childhood epilepsy with centrotemporal spikes, (benign) Rolandic epilepsy, (benign) epilepsy with centrotemporal spikes	CAE[a]	Pyknolepsy, petit mal	EMAtS	Doose syndrome
SeLEAS	Panayiotopoulos syndrome, early onset (benign) occipital epilepsy	EEM	Jeavons syndrome	LGS	No changes
COVE	Late onset (benign) occipital epilepsy or idiopathic childhood occipital epilepsy–Gastaut type	EMA	Bureau and Tassinari syndrome	DEE-SWAS EE-SWAS Landau–Kleffner syndrome (subtype of EE-SWAS)	Epileptic encephalopathy with continuous spike-and-wave in sleep, atypical (benign) partial epilepsy (pseudo-Lennox syndrome)
POLE	Idiopathic photosensitive occipital lobe epilepsy			FIRES HHE	AERRPS, DESC No changes

Note: This table includes identified syndromes of this age group and not all epilepsy types.

Abbreviations: AERRPS, acute encephalitis with refractory, repetitive partial seizures; CAE, childhood absence epilepsy; COVE, childhood occipital visual epilepsy; DEE, developmental and/or epileptic encephalopathy; DEE-SWAS, developmental epileptic encephalopathy with spike-and-wave activation in sleep; DESC, devastating epileptic encephalopathy in school-aged children; EEM, epilepsy with eyelid myoclonia; EE-SWAS, epileptic encephalopathy with spike-and-wave activation in sleep; EMA, epilepsy with myoclonic absence; FIRES, febrile infection-related epilepsy syndrome; HHE, hemiconvulsion–hemiplegia–epilepsy syndrome; LGS, Lennox–Gastaut syndrome; POLE, photosensitive occipital lobe epilepsy; SeLEAS, self-limited epilepsy with autonomic seizures; SeLECTS, self-limited epilepsy with centrotemporal spikes.

[a]CAE is addressed in the paper on idiopathic generalized epilepsies.[2]

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most recent edition of "Epileptic Syndromes of Infancy, Childhood and Adolescence,"[8] and current criteria listed on www.epilepsydiagnosis.org, which was circulated to all members. Every draft was discussed at either an online or an in-person meeting of Task Force members and modified based on further input and clinical experience of Task Force members, together with additional literature searches.

For each syndrome, mandatory features (must be present for diagnosis) and exclusionary features (must be absent for diagnosis) were proposed, along with alerts (features that are absent in the vast majority of cases, but rarely can be seen). Alerts should lead to caution in diagnosing the syndrome and consideration of other conditions. A Delphi process was then undertaken, surveying all Task Force members, in addition to recognized external experts in pediatric epilepsy, from all International League Against Epilepsy (ILAE) regions (Europe, Oceania/Asia, North America, Latin America, Africa, and the Eastern Mediterranean region), to reach consensus.

For each syndrome, the core diagnostic criteria, along with a summary of other features, are provided. Based on the Delphi process, tables with the mandatory and exclusionary criteria and alerts for each syndrome are provided at the end of the article.

Proposed syndromes are subdivided into (1) SeLFEs of childhood, (2) genetic generalized epilepsies, and (3) developmental and/or epileptic encephalopathies of childhood.

3 | SELF-LIMITED FOCAL EPILEPSIES OF CHILDHOOD

Focal epilepsies with onset during childhood are often self-limited and usually of unknown cause.[9,10] Many self-limited childhood focal epilepsies have a characteristic electroclinical presentation and fall within one of the SeLFE syndromes (Figure 1). These conditions have been referred to in the past as "benign" or "idiopathic."

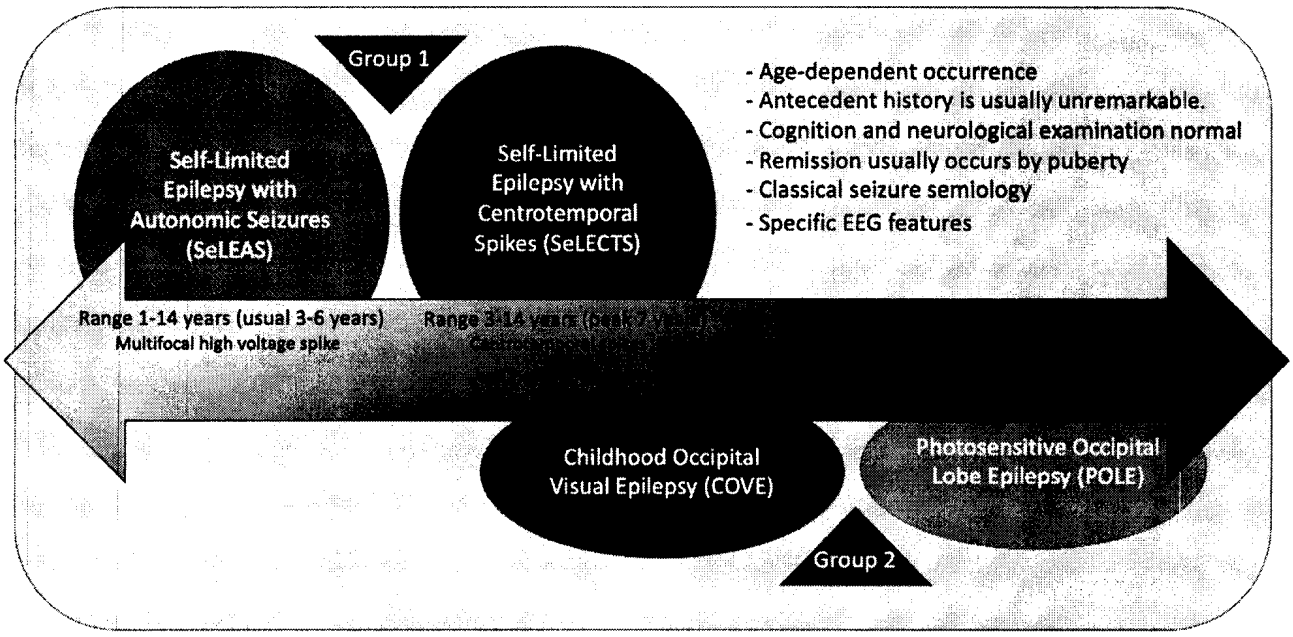


FIGURE 1 Self-limited focal epilepsies of childhood (SeLFE) syndromes are a group of conditions characterized by age-dependent occurrence in otherwise normal children. Cognition and neurological evaluation are typically normal. Remission occurs in almost all patients by puberty. Presumed genetic factors have an important role. Seizure semiology and electroencephalographic (EEG) features are specific for each of the syndromes included in this group. Within the SeLFEs, we recognize two levels of syndromes, based on the long-term prognosis. The first subgroup (Group 1) includes two syndromes: the former syndromes of childhood epilepsy with centrotemporal spikes or benign epilepsy of childhood with centrotemporal spikes or benign Rolandic epilepsy, now renamed as self-limited epilepsy with centrotemporal spikes; and of Panayiotopoulos syndrome or early onset benign occipital epilepsy, now renamed as self-limited epilepsy with autonomic seizures. The second subgroup (Group 2) includes two syndromes: the former syndromes of late onset benign occipital epilepsy or Gastaut syndrome or idiopathic childhood occipital epilepsy–Gastaut type, now renamed as childhood occipital visual epilepsy; and of idiopathic photosensitive occipital lobe epilepsy, now renamed as photosensitive occipital lobe epilepsy. In Group 1, remission is expected in all cases. In Group 2, remission is highly likely; however, a few patients may have persistence of seizures after adolescence. In the figure are represented the age at onset and EEG findings for each of the syndromes

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The term "benign" is no longer recommended, as it fails to acknowledge the comorbidities present in some individuals. The term "idiopathic epilepsy" is now restricted to describing the four syndromes termed the idiopathic generalized epilepsies. Given the typical evolution of these conditions, with age-dependent onset and remission, it has been proposed to use the term "self-limited" when referring to such epilepsies.[11] The Nosology and Definitions Task Force of the ILAE proposes the term "self-limited focal epilepsies of childhood" to encompass this group of epilepsy syndromes.

Presumed genetic factors play an important etiological role, as supported by the higher incidence of a positive family history of epilepsy and age-dependent, focal EEG abnormalities. However, no specific genetic variants have been identified so far. Rarely, genetic variants may be associated with more severe phenotypes of these syndromes (i.e., *GRIN2A* in SeLECTS evolving to EE-SWAS).[12–15]

The SeLFEs account for up to 25% of all pediatric epilepsies.[16,17] These syndromes share the following features:

1. Age-dependent occurrence, specific for each syndrome.
2. No significant structural lesion of the brain.
3. Birth, neonatal, and antecedent history is usually unremarkable.
4. Cognition and neurological examination are typically normal.
5. Remission usually occurs by puberty.
6. Pharmacoresponsiveness if treated.
7. Genetic predisposition for the EEG trait.
8. Classic seizure semiology for each syndrome. Seizures are focal motor or sensory with or without impaired awareness and may evolve to bilateral tonic–clonic seizures.
9. Specific EEG features: epileptiform abnormalities with distinctive morphology and location (depending on the epilepsy syndrome), often activated with sleep. The EEG has a normal background.

In most cases, children with SeLFEs have features characteristic of one specific syndrome. However, some have a mixed picture, or may evolve from one syndrome to another over time.[18] Furthermore, rare cases also show overlap with the IGEs.[3,4]

Within the SeLFEs, we recognize two levels of syndromes, based on the long-term prognosis.

The first subgroup includes two syndromes:

1. Self-limited epilepsy with centrotemporal spikes (SeLECTS; formerly called childhood epilepsy with centrotemporal spikes, benign epilepsy of childhood with centrotemporal spikes, or benign Rolandic epilepsy).
2. Self-limited epilepsy with autonomic seizures (SeLEAS; formerly called Panayiotopoulos syndrome or early onset benign occipital epilepsy).

The second subgroup includes two syndromes:

1. Childhood occipital visual epilepsy (COVE; formerly called late onset benign occipital epilepsy, Gastaut syndrome, or idiopathic childhood occipital epilepsy–Gastaut type; rare cases may begin around puberty/adolescence).
2. Photosensitive occipital lobe epilepsy (POLE; formerly called idiopathic photosensitive occipital lobe epilepsy).

In the first group, remission in both SeLECTS and SeLEAS is expected in all cases by adolescence, and if treatment is started it should not be continued beyond that age.

In COVE and POLE, the remission is highly likely; however, a few patients may experience a persistence of seizures after adolescence. Chronic treatment with antiseizure medications (ASMs) is often prescribed. In most cases, ASMs can be successfully discontinued without seizure recurrence; however, rare cases may require a longer duration of ASM treatment.

All the above nomenclature changes were carefully evaluated by our working group. The main goal was to have a uniform classification and terminology for the self-limited childhood focal epilepsy syndromes. Our aim was to improve diagnosis and management of these epilepsy syndromes, for both counseling and treatment purposes.

3.1 | Self-limited epilepsy with centrotemporal spikes

SeLECTS is a self-limited epilepsy syndrome, formerly known as benign Rolandic epilepsy or benign epilepsy with centrotemporal spikes, which begins in children in their early school years (Table 2).[19] Seizures are often brief, and typically involve focal clonic or tonic activity of the throat/tongue and one side of the lower face, which may then evolve to a focal to bilateral tonic–clonic seizure. This epilepsy syndrome occurs in children who are otherwise neurologically and cognitively normal, and imaging studies, if done, show no causal lesion. The EEG shows a normal background with high-amplitude centrotemporal sharp-and-slow-wave complexes, which are activated in drowsiness and sleep.[20] Seizures cease by puberty. The finding of a positive family history and focal EEG abnormalities in family members supports underlying genetic factors contributing to the etiology of SeLECTS.[21,22]

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TABLE 2 Self-limited epilepsy with centrotemporal spikes

	Mandatory	Alerts	Exclusionary
Seizures	Focal seizures with dysarthria, sialorrhea, dysphasia, and unilateral clonic or tonic–clonic movement of mouth in wakefulness or sleep and/or nocturnal focal to bilateral tonic–clonic seizures in sleep only If seizures occur during sleep, they are seen within 1 h of falling asleep or 1–2 h prior to awakening	Focal motor or generalized convulsive status epilepticus >30 min Usual seizure frequency more than daily Daytime seizures only	Generalized tonic–clonic seizures during wakefulness Atypical absences Seizures with gustatory hallucinations, fear, and autonomic features
EEG	High-amplitude, centrotemporal biphasic epileptiform abnormalities	Sustained focal slowing not limited to the postictal phase Persistently unilateral centrotemporal abnormalities on serial EEGs Lack of sleep activation of centrotemporal abnormalities	
Age at onset		>12 years	<3 years or >14 years
Development at onset		Moderate to profound intellectual disability	Neurocognitive regression with a continuous spike-and-wave pattern in sleep (suggests EE-SWAS)
Neurological exam		Hemiparesis or focal neurological findings, other than Todd paresis	
Imaging			Causal lesion on brain MRI
Course of illness	Remission by mid to late adolescence No developmental regression		Neurocognitive regression with a continuous spike-and-wave pattern in sleep suggests evolution to EE-SWAS

An MRI is not required for diagnosis but should be strongly considered in cases with alerts.
An ictal EEG is not required for diagnosis.

Syndrome without laboratory confirmation: In resource-limited regions, SeLECTs can be diagnosed without EEG and MRI in children without alerts who meet all other mandatory and exclusionary criteria.

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: EEG, electroencephalogram; EE-SWAS, epileptic encephalopathy with spike-and-wave activation in sleep; MRI, magnetic resonance imaging; SeLECTs, self-limited epilepsy with centrotemporal spikes.

3.1.1 | Epidemiology

SeLECTS is the most frequent SeLFE and accounts for approximately 6%–7% of all childhood epilepsies.[5,23] Its incidence is approximately 6.1 per 100 000 children aged <16 years per year.[24,25]

3.1.2 | Clinical context

The age at onset is usually between 4 and 10 years (range = 3–14 years) in 90% of patients, with a peak at approximately 7 years.[26] Both sexes are affected, with a slight male predominance (60%).[25,27,28]

Antecedent, birth, and neonatal history is typically normal. A history of febrile seizures is seen in 5%–15% of cases. Rarely, a history of SeLEAS may be present.[29] Development, cognition, neurological examination, and head size prior to seizure onset are typically normal. SeLECTS may be seen in children with a history of prior neurological injury or intellectual disability, but these features are considered coincidental and not causal. Prior to epilepsy onset, attention-deficit/hyperactivity disorder and specific cognitive function deficits, mainly related to language and executive function, may be seen.[30]

3.1.3 | Course of illness

Seizures usually resolve by puberty but can occasionally continue until 18 years of age.[31] While the epilepsy

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is active, behavioral and neuropsychological deficits may rarely emerge or worsen, particularly in language and executive functioning.[32,33] These deficits often improve or resolve with age.[34] The social outcome in adults is very good.[35] Seizures typically respond well to ASM. The prognosis for seizure remission is excellent even for those whose seizures are initially difficult to control.[36]

3.1.4 | Seizures

Focal seizures with characteristic frontoparietal opercular features and/or nocturnal bilateral tonic–clonic seizures are mandatory for diagnosis. Seizures are brief, typically <2–3 min, usually few in number (most children have fewer than 10 lifetime seizures), and may occur sporadically, with frequent seizures seen over a few days or weeks and then several months passing before the next seizure.

Characteristic semiology of the focal seizures includes (1) somatosensory symptoms, with unilateral numbness or paresthesia of the tongue, lips, gums, and inner cheek[27]; (ii) orofacial motor signs, specifically tonic or clonic contraction of one side of the face, mouth, and tongue, then involving one side of the face; (iii) speech arrest—children have difficulty or are unable to speak (dysarthria or anarthria) but can understand language; and (iv) sialorrhea, a characteristic ictal symptom—it is unclear whether this is due to increased salivation, swallowing disturbance, or both. In some cases, focal seizures in sleep evolve rapidly to tonic–clonic activity of the ipsilateral upper limb, to an ipsilateral hemiclonic seizure, or to a focal to bilateral tonic–clonic seizure. Todd paresis may occur postictally. In nocturnal seizures, the initial focal component may often not be witnessed.

Seizures occur during sleep in 80%–90% of patients and only while awake in <20% of children.[37] In seizures associated with SeLECTS, cognitive (e.g., gustatory hallucinations), emotional (e.g., fear), and autonomic features are not seen. Moreover, focal motor or focal to bilateral tonic–clonic status epilepticus, defined as seizure persisting for >30 min, is rare[37] and, if present, should lead to review of the diagnosis. The occurrence of atypical absence seizures, focal atonic seizures, and focal motor seizures with negative myoclonus with loss of balance and falls should suggest evolution to EE-SWAS, and evidence of cognitive impairment or regression should be sought.

Generalized tonic–clonic seizures, as distinct from focal to bilateral tonic–clonic seizures, during wakefulness are exclusionary, but may be difficult to differentiate clinically.

3.1.5 | Electroencephalogram

Background activity is typically normal, with the presence of normal sleep architecture. If sustained focal slowing without centrotemporal spikes or diffuse slowing is recorded, another epilepsy syndrome or a structural lesion should be considered, and brain imaging is recommended.

High-amplitude (>200 μV, peak to trough),[38] centrotemporal sharp-and-slow-wave complexes that activate in drowsiness and sleep are mandatory for diagnosis. They are triphasic, high-voltage (100–300 μV) sharp waves (initial low-amplitude positivity, then high-amplitude negativity followed again by low-amplitude positivity), with a transverse dipole (frontal positivity, temporoparietal negativity), often followed by a high-voltage slow wave.[37,39] The abnormalities may be isolated or occur in trains of doublets and triplets, and focal, rhythmic, slow activity is occasionally observed in the same region as the spikes. The abnormalities may be unilateral or bilateral and independent (Figure 2A). There may be abnormalities seen outside the centrotemporal region (midline, parietal, frontal, occipital). If a continuous spike-and-wave pattern is present in sleep, the child should be evaluated for progressive language or cognitive impairment or regression. This EEG pattern should only lead to a diagnosis of EE-SWAS if developmental plateauing or regression is present.[21,40]

A marked increase in the frequency of epileptiform activity in drowsiness and sleep is typical. The EEG pattern may also change such that sharp waves or spike-and-wave complexes have a broader field and become bilaterally synchronous (Figure 2B). In 10%–20% of children, centrotemporal sharp waves or spike-and-wave complexes may be activated by sensory stimulation of the fingers or toes.[41]

Seizures are typically infrequent; it is rare to obtain an ictal recording, and there are few published reports in the literature.[42] Seizures may be accompanied by a brief decrease in amplitude of the background EEG, followed by diffuse sharp wave abnormalities of increasing amplitude, predominantly in one centrotemporal region,[42] followed by high-amplitude slowing and then a return to the usual interictal EEG (Figure 2C). With focal to bilateral tonic–clonic seizures, ictal rhythms may become bilaterally synchronous (as opposed to generalized) sharp wave or spike-and-wave activity.[43–45]

3.1.6 | Imaging

Neuroimaging is normal or may show nonspecific findings. If the electroclinical diagnosis of SeLECTS is made and there are no atypical features, neuroimaging is not required. If there are clinical, developmental, or EEG features or evolution inconsistent with this diagnosis,

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neuroimaging should be considered. Nonspecific MRI findings, such as hippocampal asymmetry, white matter abnormalities, and enlargement of the lateral ventricles, should not exclude a diagnosis of SeLECTS.[46] Patients with focal epilepsy due to structural abnormalities such as focal cortical dysplasia, heterotopia, or low-grade brain tumors may mimic SeLECTS but usually show atypical features such as unilateral EEG abnormality or drug resistance.

3.1.7 | Genetics

Genetic factors play an important etiological role, as supported by the higher incidence of a positive family history for epilepsy or febrile seizures, and age-dependent, focal EEG abnormalities in the relatives of SeLECTS patients. Siblings may show the EEG trait of centrotemporal abnormalities in an age-dependent, autosomal dominant fashion without clinical seizures.[22] However, the clinical epilepsy syndrome is likely complex in inheritance, as pedigrees with multiple individuals with SeLECTS are very rare.[42] At this time, there are no identified pathogenic gene variants found in most children with SeLECTS. Heterozygous pathogenic variants in *GRIN2A* can be found in individuals with SeLECTS, who may show evolution to EE-SWAS, with associated language and cognitive impairment.[13–15] Also, copy number variants have been detected in rare cases.[47] Other genetic etiologies such as fragile X syndrome (FraX) should be considered.

3.1.8 | Differential diagnosis

Other epilepsies:

- DEE-SWAS or EE-SWAS: Patients with DEE-SWAS may present with similar seizures but can be distinguished by cognitive and language regression. Children with SeLECTS may rarely evolve to this syndrome.
- Focal seizures due to structural brain abnormality.
- Other SeLFEs: The morphology of the EEG abnormalities in the various SeLFEs may overlap, and their seizure localization may change with age. If patients present with prolonged focal nonmotor seizures with prominent autonomic features, especially ictal vomiting, SeLEAS should be considered.
- FraX should be excluded in males with intellectual impairment, as EEG changes in FraX may mimic those seen in SeLECTS.[48,49] In FraX, seizures are most commonly focal impaired awareness seizures, and less likely focal motor without impaired awareness or focal to bilateral tonic–clonic seizures.

3.2 | Self-limited epilepsy with autonomic seizures

SeLEAS, formerly known as Panayiotopoulos syndrome or early onset benign occipital epilepsy, is characterized by the onset in early childhood of focal autonomic seizures that are often prolonged. EEG shows high-amplitude (>200 μV, peak to trough)[38] focal spikes with variable localization that are typically activated by sleep. Seizures are infrequent in most patients, with 25% only having a single seizure. The epilepsy is self-limited, with remission typically within a few years from onset.[50] The mean duration of the disease is approximately 3 years (Table 3).[51]

3.2.1 | Epidemiology

The prevalence of SeLEAS depends on the age range studied. It accounts for 5% of childhood epilepsies between 1 and 14 years[51] and 13% of childhood epilepsies between 3 and 6 years.[52] SeLEAS is the most common cause of afebrile nonconvulsive status epilepticus in childhood.[53]

3.2.2 | Clinical context

The usual age at onset is between 3 and 6 years (70% of cases), and ranges from 1 to 14 years.[54] Both sexes are affected equally. Antecedent and birth history is normal. A history of febrile seizures is seen in 5%–17% of patients. Head size and neurological examination are normal. Development and cognition are normal.[51,55,56]

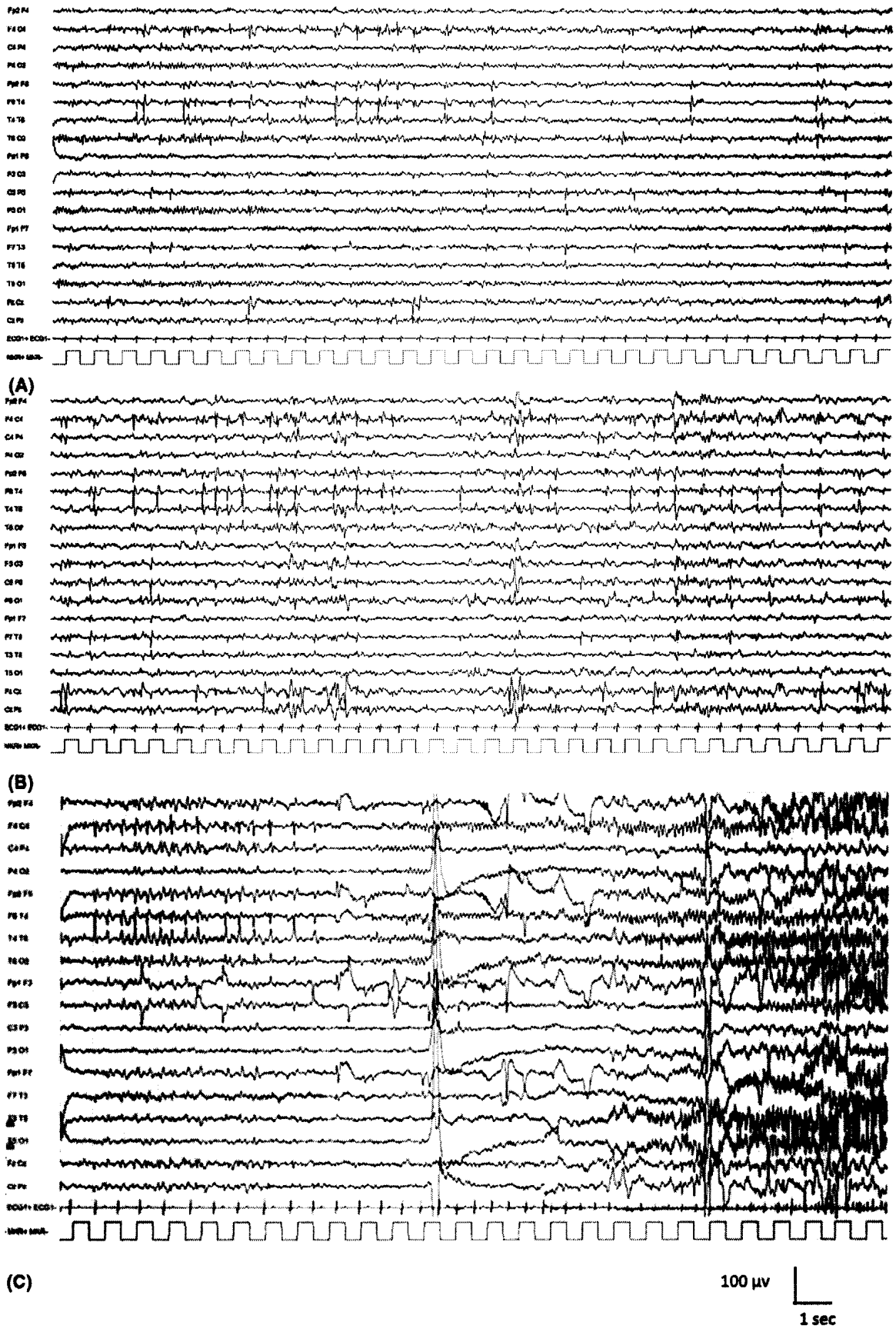
3.2.3 | Course of illness

Seizure frequency is typically low, with approximately 25% of children having a single seizure only, and the majority having fewer than five seizures in total.[57] Seizures typically remit within 1–2 years, with normal neurodevelopment, although approximately 20% of patients may evolve to other SeLFEs, most commonly SeLECTS.[57] Rarely, SeLEAS may evolve to EE-SWAS.

3.2.4 | Seizures

Focal autonomic seizures, with or without impaired awareness, are mandatory for diagnosis. Autonomic features at onset may vary, but most frequently include retching, pallor, flushing, nausea, malaise, or abdominal pain. Vomiting, the most common autonomic manifestation, occurs in approximately 75% of children and leads

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FIGURE 2 Self-limited epilepsy with centrotemporal spikes. Interictal and peri-ictal electroencephalographic (EEG) patterns seen in a 9-year-old child are shown. (A) Awake EEG showing high-amplitude, spike-and-wave abnormalities over C4 and T4 electrodes, in the right centrotemporal region. Abnormalities are isolated or occur in brief sequences. Synchronous or asynchronous stereotypic spikes are seen also over the left central region or over the anterior vertex. (B) Sleep EEG shows an increase in interictal epileptiform abnormalities and a higher amplitude. (C) Peri-ictal EEG. Repetitive spike-and-wave abnormalities are evident over right central and temporal regions. This activity suddenly disappears, and over the right central and temporal region there is low-voltage fast activity that increases in amplitude and decreases in frequency

TABLE 3 Self-limited epilepsy with autonomic features

	Mandatory	Alerts	Exclusionary
Seizures	Focal autonomic seizures, with or without impaired awareness Autonomic symptoms often involve prominent retching and vomiting, but may also include malaise, pallor, flushing, abdominal pain, and pupillary or cardiorespiratory changes	Seizure frequency greater than monthly	
EEG	High-amplitude, focal or multifocal epileptiform abnormalities that increase in drowsiness and sleep	Sustained focal slowing not limited to the postictal phase Unilateral focal abnormalities in a consistent focal area across serial EEGs	
Age at onset		<3 years or >8 years	<1 year or >14 years
Development at onset		Moderate to profound intellectual disability	Neurocognitive regression with a continuous spike-and-wave pattern in sleep (suggests EE-SWAS)
Neurological exam		Hemiparesis or focal neurological findings, other than Todd paresis	
Imaging			Causal lesion on brain MRI
Course of illness	Remission by early to mid adolescence No developmental regression		Neurocognitive regression with a continuous spike-and-wave pattern in sleep suggests evolution to EE-SWAS

An MRI is not mandatory for diagnosis but should be done in the presence of any alerts.
An ictal EEG is not required for diagnosis.
Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an interictal EEG is required to confidently diagnose this syndrome.

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: EEG, electroencephalogram; EE-SWAS, epileptic encephalopathy with spike-and-wave activation in sleep; MRI, magnetic resonance imaging.

to misdiagnosis of acute gastroenteritis or migraine. Additional autonomic features include pupillary (e.g., mydriasis), temperature, and cardiorespiratory (breathing, pallor, cyanosis, and heart rate) changes. Syncope may rarely occur. Seizures frequently evolve with eye and/or head deviation, generalized hypotonia, and focal clonic (hemiclonic) or focal to bilateral tonic–clonic seizure activity. Awareness is usually preserved at seizure onset and may fluctuate in degree of impairment as the seizure progresses. More than 70% of seizures occur from sleep. Seizures are often prolonged and can last longer than 30 min.[17]

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3.2.5 | Electroencephalogram

The background activity is normal. If persistent focal slowing is present, a structural brain abnormality should be sought as an alternative etiology. Diffuse slowing is not seen except in the postictal period.

Multifocal, high-voltage sharp waves or spike-and-wave complexes are typically seen, often over the posterior regions at disease onset. Abnormalities may show marked variability in terms of localization in sequential EEGs, and the predominance of abnormalities might move to either centrotemporal region or frontopolar region. Generalized abnormalities may also be seen.[29] EEG abnormalities are activated both by sleep deprivation and by sleep, when abnormalities often have a wider field and may be bilaterally synchronous (Figure S1A,B). Eye closure (elimination of central vision and fixation-off sensitivity) typically activates posterior abnormalities, but this finding is not pathognomonic of this syndrome.

If seizures are recorded, ictal onset varies, but most have posterior onset. The ictal pattern shows rhythmic slow activity intermixed with small spikes and/or fast activity (Figure S1C).[58]

3.2.6 | Imaging

Neuroimaging, if performed, shows no causal lesion. MRI should be considered in cases with recurrent seizures or atypical presentations. Nonspecific MRI findings should not exclude a diagnosis of SeLEAS.

3.2.7 | Genetics

SeLEAS is probably genetically determined; however, no causative gene variants have been detected so far. There is a higher prevalence of febrile seizures in first-degree relatives and case reports of siblings with other SeLFEs.[18,51] There is no clear indication to perform genetic testing in most patients; however, rare cases with *SCN1A* pathogenic variants have been reported.[59–61]

3.2.8 | Differential diagnosis

Other epilepsies:

- Focal seizures due to structural brain abnormalities. Temporal lobe epilepsy in early childhood and structural occipital epilepsies may present with ictal vomiting.
- SeLECTS should be diagnosed if seizures have prominent frontoparietal–opercular features.
- COVE is distinguished by prominent visual symptoms, as opposed to autonomic features.
- Familial focal epilepsy with variable foci. Different focal epilepsies occur in other family members, but SeLEAS is not usually seen.

Other conditions:

- Migraine-associated disorders such as benign paroxysmal vertigo.
- Syncope.
- Other medical disorders associated with intermittent vomiting.

3.3 | Childhood occipital visual epilepsy

COVE syndrome, formerly known as late onset benign occipital epilepsy, Gastaut syndrome, or idiopathic childhood occipital epilepsy–Gastaut type, begins in later childhood and is self-limited in the majority of patients. This syndrome occurs in developmentally normal children, with frequent, brief seizures during wakefulness, with visual phenomena without altered awareness, which are often followed by headaches with migrainous features. Seizures may be controlled, and remission of seizures often, but not invariably, occurs within 2–7 years from onset (Table 4).[62]

3.3.1 | Epidemiology

COVE has a prevalence of 0.3% of children with newly diagnosed, afebrile seizures.[26]

3.3.2 | Clinical context

Age at onset is typically at 8–9 years, with a range from 1 year to 19 years.[63] Both sexes are equally affected. Antecedent and birth history is normal. Patients have normal development and cognition, although mild cognitive impairment has been described. Head size and neurological examination are normal.[64]

3.3.3 | Course of illness

Remission occurs in 50%–80% of patients by puberty with or without administration of ASM.[65,66] Seizures are often responsive to ASM. Remission is more likely in the 90% of patients who only have focal seizures.[64] Occurrence of bilateral tonic–clonic seizures is associated with a lower rate of remission. Development usually remains normal.

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TABLE 4 Childhood onset visual epilepsy

	Mandatory	Alerts	Exclusionary
Seizures	Focal sensory visual seizures with elementary visual phenomena (multicolored circles), with or without impaired awareness, and with or without motor signs (deviation of the eyes or turning of the head) Seizures arise predominantly or exclusively from wakefulness	Prolonged seizure lasting >15 min GTCS during wakefulness	Drop (tonic or atonic) seizures Atypical absences Progressive myoclonus
EEG	Occipital spikes or spikes-and-wave abnormalities (awake or sleep)	Sustained focal slowing not limited to the postictal phase	
Age at onset		<6 years >14 years	<1 year or >19 years
Development at onset		Intellectual disability	Neurocognitive regression
Neurological exam		Any significant neurological examination abnormality	Persistent visual field deficit
Imaging			Causal lesion on brain MRI Cerebral occipital lobe calcifications
Course of illness			Neurocognitive regression Development of myoclonic seizures, ataxia, spasticity
An MRI is required for diagnosis to exclude a causal lesion. An ictal EEG is not required for diagnosis. Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an interictal EEG and MRI are required to confidently diagnose this syndrome.			

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: EEG, electroencephalogram; GTCS, generalized tonic–clonic seizures; MRI, magnetic resonance imaging.

3.3.4 | Seizures

Focal sensory visual seizures during wakefulness are mandatory for diagnosis. They have abrupt onset, are brief (typically seconds, most lasting <3 min, rarely up to 20 min), and frequent without treatment. Typically, elementary visual phenomena occur, described as small multicolored circles seen in the peripheral vision, increasingly involving more of the visual field and moving horizontally across to the other side. This may be followed by deviation of the eyes or turning of the head (to the side ipsilateral to the hemisphere of seizure onset).[67]

Other features consistent with occipital lobe onset may occur, including ictal blindness, complex visual hallucinations or illusions (such as palinopsia, micropsia, metamorphopsia), orbital pain, eyelid fluttering, or repeated eye closure.[68,69] The seizure may spread outside the occipital lobe, resulting in hemiparesthesia, impaired awareness (14%), and hemiclonic (43%) or focal to bilateral tonic–clonic (13%) seizure.[63] Typical absence seizures may rarely occur in some patients after onset of the focal sensory seizures.[70]

There may be ictal or postictal headache, nausea, or vomiting. Postictal headache with migrainelike features is common (in 50% of patients) and may be associated with nausea and vomiting.

3.3.5 | Electroencephalogram

The background activity is normal. Interictal occipital sharp waves or spike-and-wave complexes are typically seen but may only occur in sleep. Centrotemporal, frontal, or generalized abnormalities are also present in 20% of cases.[71] Fixation-off sensitivity (facilitation of epileptiform abnormalities with elimination of central vision) is seen in 20%–90% of patients but is not pathognomonic of this syndrome.[63,66,72] EEG abnormalities are enhanced by sleep deprivation and sleep (Figure S2A,B). COVE may rarely evolve to EE-SWAS; therefore, if cognitive regression occurs, a sleep EEG should be performed.

At ictal onset, there is a decrease in the usual background occipital spikes or spike-and-wave complexes with the sudden appearance of unilateral occipital fast rhythms

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with spikes of low amplitude. There may be slower spike-and-wave abnormalities during oculoclonic seizures or ictal blindness (Figure S2C).[68,69]

3.3.6 | Imaging

Neuroimaging is normal. Brain MRI is required to exclude a structural brain abnormality.[73]

3.3.7 | Genetics

Genetic testing is not required, as there are no genes identified for this epilepsy syndrome. It is presumed that the etiology is genetic, and likely complex/polygenic in inheritance.[18] A family history of febrile seizures or epilepsy occurs in up to one third of cases, and a family history of migraine is reported in 9%–16% of cases.[63,66]

3.3.8 | Differential diagnosis

Other epilepsies:

- Focal seizures due to a structural brain abnormality.
- Celiac disease, epilepsy, and cerebral calcification syndrome is distinguished by occipital lobe calcification, best seen on brain computerized tomography scan.
- Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS).
- Lafora disease is distinguished by the presence of regression, prominent myoclonus, progressive ataxia, and spasticity.

Other conditions:

- Migraine with visual aura can be distinguished by the more gradual development and longer duration of the aura, and the character of the visual phenomena (linear, zig-zag, or fortification spectral phenomena as opposed to colored circles or light flashes that change in size or move horizontally).
- Posterior reversible encephalopathy syndrome presents with acute symptomatic seizures, which resolve with control of hypertension.

3.4 | Photosensitive occipital lobe epilepsy

POLE is a rare epilepsy syndrome that has onset in childhood and adolescence and is characterized by the presence of photic-induced, focal seizures involving the occipital lobe in individuals with normal development, neurological examination, and intellect (Table 5). At seizure onset, the patient experiences a visual aura with involuntary head version with intact awareness. Prognosis is variable.

3.4.1 | Epidemiology

The prevalence of POLE is low. Epidemiological data are limited, but estimates suggest that POLE accounts for 0.7% of childhood epilepsies.[74]

3.4.2 | Clinical context

Age at onset is between 1 and 50 years, but is most commonly between 4 and 17 years (mean = 11 years), although rare cases with adult onset are also reported.[75] There is a strong female predominance.[74] Antecedent and birth history is unremarkable, and development is normal. Head size and neurological examination are normal.

3.4.3 | Course of illness

Prognosis varies; some patients will have only a few seizures, others have seizure remission over time, and others continue to have photic-induced seizures.[76]

3.4.4 | Seizures

Photic-induced, focal sensory visual seizures (induced for example by flickering sunlight) are mandatory for diagnosis and the main seizure type. Young children may find the aura hard to describe but they can sometimes draw a picture of what they see. Visual sensory symptoms include lights, colored spots, formed visual hallucinations, or visual blurring/loss that moves across the visual field. There is associated head and eye version in which the patient feels they are following the visual phenomenon. Seizures can be induced by video games or other photic stimuli, and in the past were often induced by older analog televisions with slower frequency outputs.[77]

Seizures are typically brief (<3 min), although prolonged seizures may occur. Seizures may progress to a cephalic sensation (including headache), autonomic epigastric sensation or vomiting, and impaired awareness or to a focal to bilateral tonic–clonic seizure.[74,78] Infrequently, seizures can arise from sleep without photic induction.

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TABLE 5 Photosensitive occipital lobe epilepsy

	Mandatory	Alerts	Exclusionary
Seizures	Focal sensory visual seizures (see text), which may evolve to bilateral tonic–clonic seizures Seizures are triggered by photic stimuli, such as flickering sunlight	Prolonged seizures lasting >15 min	Eyelid myoclonia Progressive myoclonus
EEG	Occipital epileptiform abnormalities facilitated by eye closure and IPS	Sustained focal slowing not limited to the postictal phase Photoparoxysmal response at slow photic frequency (1–2 Hz; suggest CLN2 disease)	
Age at onset		<4 years or >17 years	<1 year or >50 years
Development at onset		Moderate to profound intellectual disability	Neurocognitive regression
Neurological exam		Any significant neurological examination abnormality	Permanent visual field deficit
Imaging			Causal lesion on brain MRI

An MRI is required for diagnosis to exclude a causal lesion.
An ictal EEG is not required for diagnosis.

Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an EEG and MRI are required to confidently diagnose this syndrome.

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: CLN2, ceroid lipofuscinosis type 2; EEG, electroencephalogram; IPS, intermittent photic stimulation; MRI, magnetic resonance imaging.

Some patients also have focal sensory visual occipital seizures without visual induction.[74] An overlap between this syndrome and the IGEs is well described,[79–81] and thus myoclonic, absence, and generalized tonic–clonic seizures may also be seen. The frequency of seizures is variable.

3.4.5 | Electroencephalogram

The background EEG is normal. Interictal occipital spikes or spike-and-wave abnormalities may be seen. Generalized spike-and-wave complexes or centrotemporal spikes may coexist. Occipital spike-and-wave or polyspike-and-wave complexes are facilitated by eye closure and intermittent photic stimulation (Figure S3). Generalized spike-and-wave or polyspike-and-wave (with posterior predominance) complexes may also occur with photic stimulation.[74] Epileptiform activity is elicited by sleep deprivation and by sleep.

Ictal onset is in the contralateral occipital lobe to the visual field containing the visual sensory phenomena, and to the direction of head and eye deviation.[74,76] Occipital ictal patterns may spread to the ipsilateral temporal lobe or the contralateral occipital lobe.

3.4.6 | Imaging

Neuroimaging is normal.

3.4.7 | Genetics

A family history is reported in one third of patients.[74] A few families with affected members in multiple generations have been reported.[79,82,83] There is considerable overlap with the IGEs and with SeLECTS.[80,84] No known gene exists.

3.4.8 | Differential diagnosis

Other epilepsies:

- Epilepsy with eyelid myoclonia (EEM) is differentiated by the prominent eyelid myoclonia and by the absence of visual hallucinations and head and eye version.
- SeLEAS is differentiated by prominent dry retching/vomiting and other autonomic features that are seen at seizure onset.

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- COVE is distinguished by frequent focal sensory seizures with visual symptoms that are not triggered by photic stimuli.
- Focal seizures due to a structural brain abnormality: If present, focal sensory seizures with visual symptoms are not triggered by photic stimuli.
- Ceroid lipofuscinosis type 2 (CLN2) disease presents in younger children (<5 years of age), and the EEG characteristically shows a photoparoxysmal response at low frequencies (1–3 Hz). Children have progressive cognitive regression, ataxia, and visual loss.
- Lafora disease presents with focal sensory visual seizures but is associated with a progressive myoclonic epilepsy with disabling myoclonus, cognitive impairment, and ataxia.

Other conditions:

- Migraine with visual aura has visual phenomena that are longer in duration and qualitatively different (linear, zig-zag, or fortification spectral phenomena as opposed to colored circles or light flashes that change in size or move horizontally).

4 | GENETIC GENERALIZED EPILEPSY SYNDROMES OF CHILDHOOD

Essentially all generalized epilepsy syndromes that have onset in childhood have a genetic etiology. They are regarded as following complex inheritance, which means they have a polygenic basis, with or without a contribution from environmental factors. Among the genetic generalized epilepsies with onset in childhood, the most common and best delineated is the IGE syndrome of CAE, which is discussed in the IGE paper.[2] Recent studies have highlighted that some IGE syndromes may also be due to monogenic disorders such as glucose transporter 1 (GLUT1) deficiency syndrome.[85] Genetic etiologies such as Angelman syndrome or 15q inversion-deletion are important causes of the more severe DEEs, and typically arise de novo in the patient.

Other childhood genetic generalized epilepsy syndromes include two distinct syndromes, epilepsy with myoclonic absence (EMA) and epilepsy with eyelid myoclonia (EEM). These syndromes have a more variable prognosis than CAE, with a higher proportion of cases having drug-resistant seizures and more frequent cognitive comorbidities. Although there is often a positive family history of epilepsy, the type of epilepsy in family members may include IGE syndromes as well as genetic epilepsy with febrile seizures plus. Epilepsy with myoclonic-atonic seizures (EMAtS) is also a generalized epilepsy syndrome that is classified under the DEEs, as children typically show developmental stagnation or regression during the period of frequent seizures. See Figure 3.

4.1 | Epilepsy with eyelid myoclonia

4.1.1 | Overview

This syndrome (previously known as Jeavons syndrome) is characterized by the triad of frequent eyelid myoclonia, with or without absences, induced by eye closure and photic stimulation. Eyelid myoclonia is often most prominent on awakening (Table 6).

A subgroup of patients with EEM have prominent photic induction of eyelid myoclonia (with or without absence), and absence or myoclonic seizures.[86] This subgroup has previously been referred to as "sunflower syndrome," due to sun-seeking behavior, as they may turn their faces to the sun as a light source at seizure onset.[87] This subgroup can be termed "EEM with prominent photic induction."

4.1.2 | Epidemiology

This syndrome is rare, and there are no population-based studies on incidence. Several studies from epilepsy centers have shown that it accounts for 1.2%–2.7% of all epilepsy cases seen.[88,89]

4.1.3 | Clinical context

The peak age at onset is 6–8 years, with a range of 2–14 years.[89–91] There is a 2:1 female:male predominance.[89–91] Antecedent and birth history is normal. Development and cognition are often normal, although individuals with borderline intellectual functioning and intellectual disability are seen. In the subgroup with prominent photic induction, approximately half have intellectual disability or attentional problems, which may become more apparent with age.[87] Neurological examination is normal.

4.1.4 | Course of illness

EEM is often, but not invariably, drug-resistant.[92–94] Generalized tonic–clonic seizures are often controlled with ASMs, whereas eyelid myoclonia are not fully controlled. In adult life, eyelid myoclonia alone may not be associated with EEG change, and thus represents a movement disorder.[95] EEM is often a life-long condition.[93,94]

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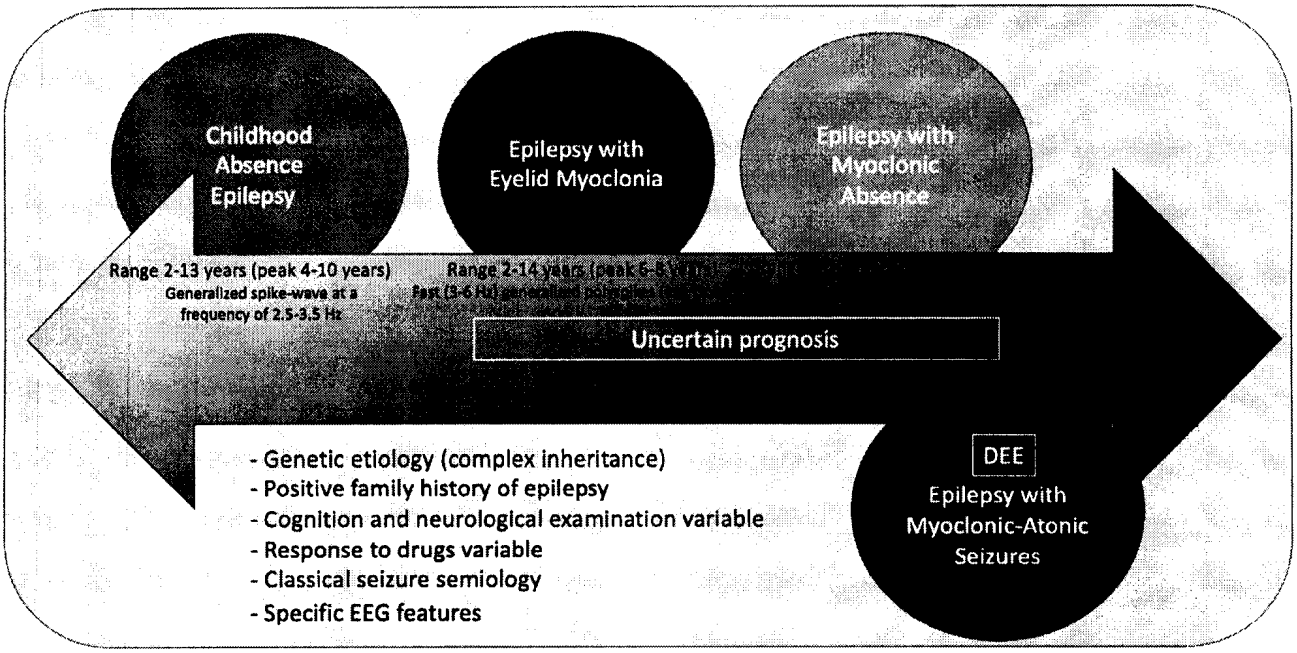


FIGURE 3 Genetic generalized epilepsies of childhood are a group of conditions characterized by genetic etiology with complex inheritance, namely, with polygenic basis. A positive family history of epilepsy is frequent. Cognition, neurological examination, and response to drugs are variable. Seizure semiology and electroencephalographic (EEG) features are specific for each of the syndromes included in this group. Genetic generalized epilepsies of childhood encompass childhood absence epilepsy, which is discussed in the paper on idiopathic generalized epilepsy syndromes,[2] epilepsy with eyelid myoclonia, epilepsy with myoclonic absence, and epilepsy with myoclonic atonic seizures. Epilepsy with myoclonic absence and epilepsy with eyelid myoclonia have a variable prognosis. Epilepsy with Myoclonic Atonic Seizures is classified under the developmental and/or epileptic encephalopathies (DEEs), as children typically show developmental stagnation or regression. In the figure are represented the age at onset and EEG findings for each of the syndromes

In the subgroup with prominent photic induction, behavioral management may be important to avoid excessive medication, but is very challenging, particularly in those with intellectual disability. Environmental measures to reduce light exposure are important in these patients, which include wearing wide-brimmed hats and wrap-around sunglasses. Specific blue lenses (Z1) may attenuate the photosensitive response in some patients.[96]

4.1.5 | Seizures

Eyelid myoclonia, consisting of brief, repetitive, and often rhythmic 3–6-Hz myoclonic jerks of the eyelids, with simultaneous upward deviation of the eyeballs and extension of the head, is mandatory for diagnosis. These seizures are very brief (typically <1 to 3 s, always <6 s) and occur multiple times each day, even many times per hour. They are typically induced by involuntary or voluntary slow eye closure or exposure to bright light or sunlight.[97] During eyelid myoclonia, awareness may be intact or mildly impaired; impaired awareness may be subtle and not recognized by the patient.

Up to 20% of patients develop eyelid myoclonic status epilepticus, with repetitive, recurrent eyelid myoclonia associated with mildly impaired awareness and responsiveness. Eyelid myoclonia may also be associated with absence seizures, with mildly impaired awareness. In addition, some patients have typical absence seizures without eyelid myoclonia.

Generalized tonic–clonic seizures occur in the majority of cases but are usually infrequent. They may be provoked by sleep deprivation, alcohol, or photic stimulation.

In the patients with prominent photic induction, eyelid myoclonia (with or without absence), absence, or myoclonic seizures are typically associated with behaviors such as facing a light source and hand-waving in front of the eyes, rubbing the forehead, going up close to an analog television, or using other means to create a flickering effect of light.[86,87,98] Sustained triggering can result in a generalized tonic–clonic seizure.

Febrile seizures occur in 3%–13% patients.[92,99] Patients may also have myoclonic and typical absence seizures even if at relatively lesser frequency than eyelid myoclonias. The presence of frequent limb myoclonus should suggest an alternative syndrome diagnosis. Focal seizures are exclusionary.

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TABLE 6 Epilepsy with eyelid myoclonia

	Mandatory	Alerts	Exclusionary
Seizures	Eyelid myoclonia (see text)	Inability to induce eyelid myoclonia in the office by slow eye closure during exposure to bright light in an untreated patient Myoclonic jerks affecting limbs—strongly consider JME	Any of the following seizure types: • Myoclonic–absence seizures • Focal seizures
EEG	Eye closure and intermittent photic stimulation elicits fast (3–6 Hz) generalized polyspikes or polyspike-and-wave complexes		Focal slowing Consistently unilateral focal spikes Generalized slow spike-and-wave pattern at frequency < 2.5 Hz (unless it is at the end of a higher frequency burst) Diffuse background slowing that is not limited to the postictal period Lack of EEG correlate with typical clinical event
Age at onset			<2 years or >14 years
Neurological exam		Focal neurological findings	
Imaging		Potentially relevant abnormal neuroimaging, excluding incidental findings (see text)	Abnormal neuroimaging with causative lesion
Course of illness			Progressive cognitive decline over the course of the epilepsy

An MRI is not required for diagnosis.

An ictal EEG is not required for diagnosis, provided that eyelid myoclonia has been observed clinically by the diagnosing provider and the interictal study shows fast (3–6 Hz) generalized polyspikes or polyspike-and-wave complexes induced by eye closure or intermittent photic stimulation. However, most untreated patients will have recorded photoparoxysmal response with eyelid myoclonia on a routine EEG performed during intermittent light stimulation.

Syndrome without laboratory confirmation: In resource-limited regions, epilepsy with eyelid myoclonia can be diagnosed in persons who meet all other mandatory and exclusionary clinical criteria if they have eyelid myoclonia witnessed by the examiner or captured on home video.

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: EEG, electroencephalogram; JME, juvenile myoclonic epilepsy; MRI, magnetic resonance imaging.

4.1.6 | Electroencephalogram

The background activity is normal; significant EEG background slowing should suggest an alternative diagnosis. Interictally, brief bursts of fast (3–6 Hz) irregular generalized polyspike-and-wave complexes are frequent. Fixation-off sensitivity, which can be induced by eye closure, and intermittent photic stimulation activate the epileptiform abnormality and often elicit eyelid myoclonia with/without absence seizures (Figure 4).[100,101] Young patients typically show photic sensitivity, which becomes less apparent with age and ASM. Similarly, sensitivity to eye closure may reduce with age. The epileptiform activity is also elicited by hyperventilation.

In the subgroup with photic induction, generalized spike-and-wave abnormalities are also provoked by photic induction. In those patients, intermittent photic stimulation may trigger brief eyelid myoclonia, typical absence, or myoclonic seizures.

Bursts of generalized spike-and-wave activity often become briefer and fragmented in sleep. Fragmented generalized spike-and-wave complexes can appear as focal or multifocal spike-and-wave complexes but are not consistently localized to one area. The morphology of the focal spike-and-wave complexes resembles that of the generalized spike-and-wave pattern.

Ictal recordings of eyelid myoclonia show high-amplitude, irregular generalized polyspike or polyspike-and-wave complexes, which may be followed by rhythmic spike or polyspike-and-wave complexes at a frequency of 3–6 Hz. Eyelid myoclonia with/without absence is terminated with complete elimination of light. Eyelid myoclonia may or may not be associated with loss of awareness.

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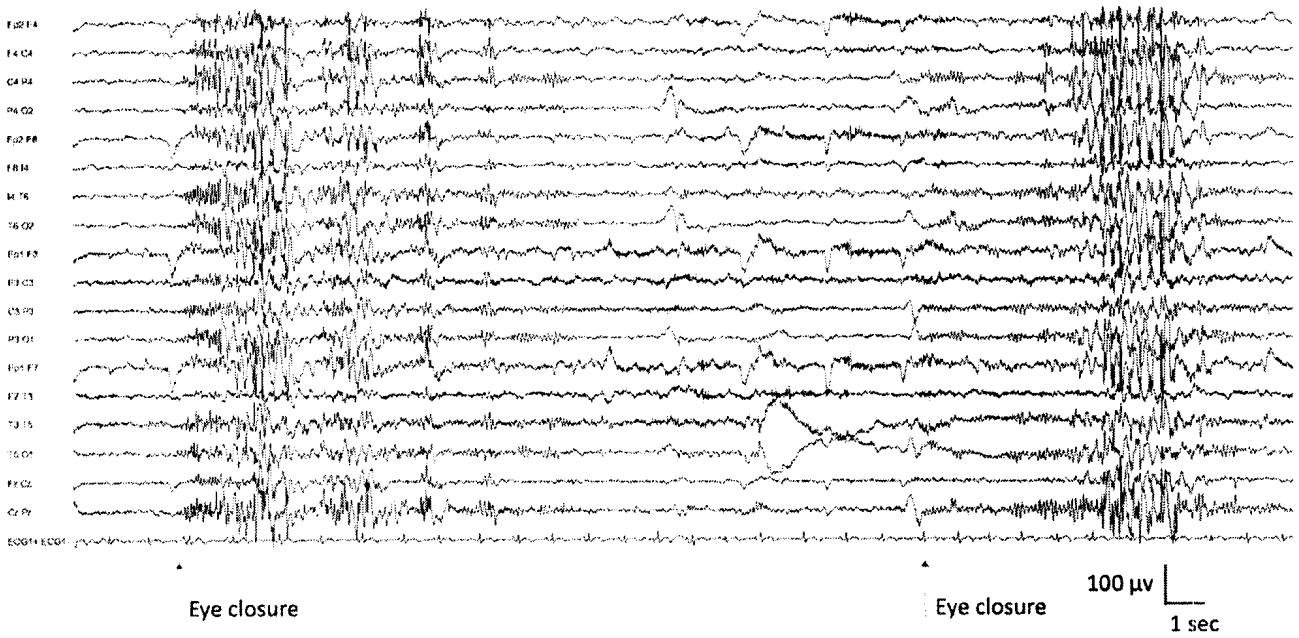


FIGURE 4 Ictal electroencephalogram of 14-year-old patient with epilepsy with eyelid myoclonia. Background activity is normal. Each time the patient closes the eyes (eye closure artifact is seen), there is a generalized polyspike-and-wave discharge lasting between 6 and 8 s, clinically associated with eyelid myoclonia. During the second event, soon after eye closure, there is a fast activity discharge that builds up

4.1.7 | Imaging

An MRI is not required with a typical clinical presentation, but if done, shows no causal abnormality.

4.1.8 | Genetics

This syndrome likely has shared genetic etiologies with other idiopathic generalized epilepsies. A family history of seizures or epilepsy is present in 25%–83% of cases, with nearly all affected relatives having generalized seizures.[92,99] In approximately 20% of cases, there is a family history of an IGE—CAE, juvenile absence epilepsy, juvenile myoclonic epilepsy, or generalized tonic-clonic seizure alone—and nearly half the patients have a family history consistent with genetic epilepsy with febrile seizures plus.[99]

No single pathogenic gene variant is identified in the majority of patients. In patients with this syndrome in the setting of a DEE, several monogenic disease genes have been implicated, including *CHD2*,[102] *SYNGAP1*[103] and *NEXMIF*[104] (formerly known as *KIAA2022*); some patients with pathogenic variants in these genes have this syndrome without a DEE.

4.1.9 | Differential diagnosis

Other epilepsies:

- IGE syndromes with absence seizures (CAE, juvenile absence epilepsy, and juvenile myoclonic epilepsy) may have photosensitivity on EEG; however, prominent eyelid myoclonia is not seen.
- POLE presents with visually induced seizures but without eyelid myoclonia.
- Other early onset epilepsies with myoclonus and photosensitivity,[97] including rare monogenic epilepsies such as neuronal ceroid lipofuscinosis.

Other conditions:

- Facial tics.
- Compulsive blinking.

4.2 | Epilepsy with myoclonic absence

EMA is a very rare childhood epilepsy syndrome that presents with daily myoclonic absence seizures (Table 7).

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TABLE 7 Epilepsy with myoclonic absences

	Mandatory	Alerts	Exclusionary
Seizures	Myoclonic absence seizures as predominant type (see text)		Focal seizures Atonic, myoclonic–atonic, or tonic seizures
EEG	Regular 3-Hz generalized spike-and-wave pattern time-locked with myoclonic jerks		Focal slowing Consistently unilateral focal spikes Generalized slow spike-and-wave pattern at frequency <2 Hz (unless it is at the end of a higher frequency burst) Diffuse background slowing that is not limited to the postictal period
Age at onset			<1 year or >12 years
Neurological exam		Moderate or greater intellectual disability Focal neurological findings	
Imaging			Abnormal neuroimaging with causative lesion
Course of illness			Progressive cognitive decline over the course of epilepsy

An MRI should be considered to exclude other causes.

An ictal EEG is not required for diagnosis, provided that myoclonic absences have been observed clinically by the diagnosing provider and the interictal study shows regular 3-Hz generalized spike-and-wave complexes. However, most untreated patients will have recorded myoclonic absence seizure on routine EEG.

Syndrome without laboratory confirmation: In resource-limited regions, epilepsy with myoclonic absences can be diagnosed in persons who meet all other mandatory and exclusionary clinical criteria if they have myoclonic absence seizures witnessed by the examiner or captured on home video.

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging.

4.2.1 | Epidemiology

The exact incidence is unknown. This syndrome accounted for 0.5%–1% of all epilepsies observed in a specialty epilepsy clinic, Saint Paul Center in Marseille.[105]

4.2.2 | Clinical context

Peak age at onset is approximately 7 years, with a range of 1–12 years, and males are more commonly affected (70%).[105,106] The antecedent and birth history is unremarkable; however, at presentation approximately half of patients have developmental impairment. Intellectual disability may become evident with age, and is ultimately seen in 70% of cases.[105–107] Neurological examination is typically normal.

4.2.3 | Course of illness

The evolution of EMA is variable.[105,106] Remission occurs in approximately 40% of patients. In the remainder, myoclonic absences persist, or the epilepsy may evolve with the development of other generalized seizure types. Prognosis is more favorable if myoclonic absence seizures are the only seizure type and are controlled with medication.[105]

4.2.4 | Seizures

Myoclonic absence seizures are mandatory for diagnosis.[105] Absence seizures are associated with rhythmic 3-Hz jerks of the upper limbs, superimposed on tonic abduction of the arms during the seizure (giving a ratcheting appearance). The seizures have an abrupt onset and offset. The patient, if standing, typically bends forward during the

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seizure, but falling is uncommon. The myoclonic jerks are typically bilateral and symmetric but can be unilateral or asymmetric. Perioral myoclonia and rhythmic jerks of the head and legs may also occur. Seizures last 10–60 s and occur multiple times per day.[107] Alertness varies from complete loss of awareness to retained awareness. Occasionally, autonomic manifestations, such as a change in breathing or urinary incontinence[105] or complex gestural automatisms, may be seen.[108] Myoclonic absences are the only seizure type seen in one third of patients. Myoclonic absence status epilepticus is rare. Generalized tonic–clonic (seen in 45%), clonic, atonic, or typical absence seizures may also occur; multiple seizure types may indicate a more unfavorable prognosis. Only 4% of patients also have typical absence seizures without myoclonic jerks. Focal seizures are exclusionary.

4.2.5 | Electroencephalogram

The background activity is normal. Occipital intermittent rhythmic delta activity is typically not seen.[105] Interictal 3-Hz generalized spike-and-wave and polyspike-and-wave abnormalities may occur (approximately one third of cases). Focal abnormalities that arise consistently from one region should raise consideration of an alternative diagnosis of a structural etiology.

Generalized spike-and-wave discharges may be provoked by hyperventilation, which may also trigger myoclonic absence seizures. Intermittent photic stimulation triggers generalized spike-and-wave abnormalities in a minority of patients (14%). Generalized spike-and-wave complexes are also activated by sleep deprivation, drowsiness, and sleep. Similar to other generalized epilepsies, generalized spike-and-wave complexes often become fragmented with sleep deprivation or sleep. The pattern may appear as focal or multifocal spike-and-wave complexes but is not consistently seen in a single area. The morphology of the focal abnormalities appears similar to the generalized spike-and-wave activity.

Regular 3-Hz generalized spike-and-wave complexes accompany myoclonic absence seizures. The 3-Hz discharge is time-locked with the myoclonic jerks (Figure 5). The electromyographic (EMG) recording shows that the myoclonic jerks precede the marked tonic contraction of both deltoids.[105]

4.2.6 | Imaging

An MRI should be considered to exclude other causes, but if done, it should be normal or may show mild diffuse atrophy.

4.2.7 | Genetics

A family history (usually of generalized seizures) is present in 20% of cases. Rarely, there is a family history of febrile seizures. Although EMA is considered to be genetic,

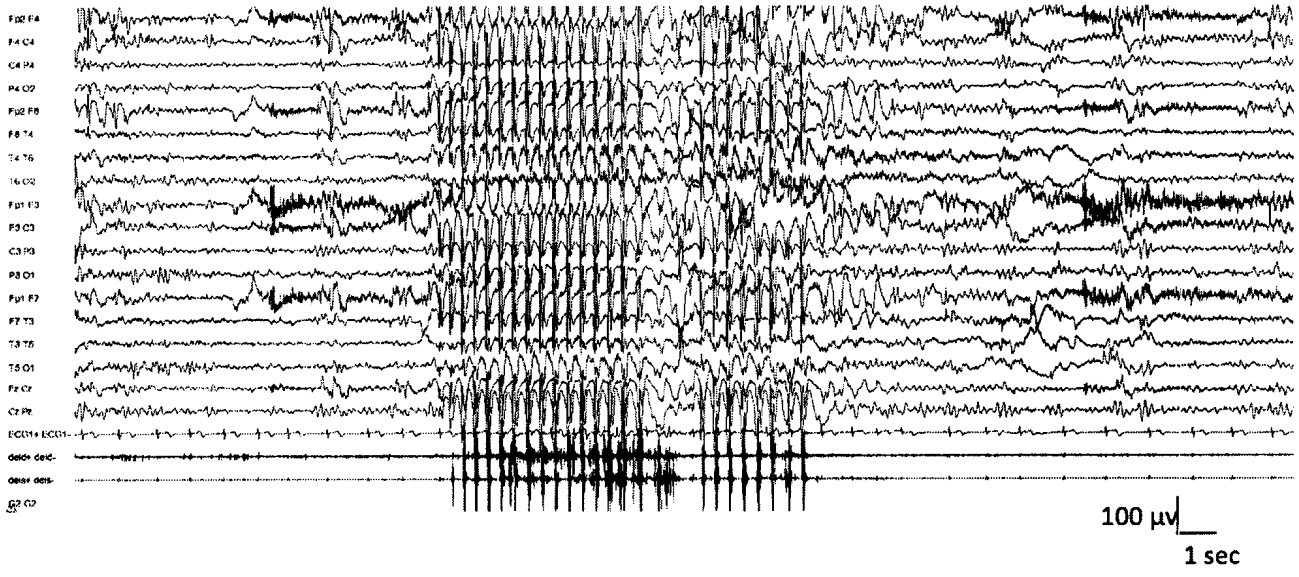


FIGURE 5 Ictal polygraphic electroencephalographic recording in an 8-year-old child with epilepsy with myoclonic absences, showing a paroxysmal generalized 3-Hz spike-and-wave discharge. Electromyographic channels (right and left deltoids) show bilateral myoclonic jerks synchronous with epileptiform abnormalities, and between jerks there is a sustained increase in muscle tone

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there are only isolated case reports of specific pathogenic genetic variants,[109,110] with most cases likely to be polygenic. This syndrome is presumed to have shared genetic etiologies with the IGEs.[111]

4.2.8 | Differential diagnosis

Other epilepsies:

- CAE: Although subtle myoclonic jerks may be seen with absences in CAE, they are low amplitude, do not have the sustained rhythmicity, and are not associated with the stepwise (ratcheting) tonic abduction of the arms.
- LGS often has atypical absences with rhythmic jerking or loss of tone; however, the presence of slow spike-and-wave (≤2.5 Hz), generalized paroxysmal fast activity and tonic seizures should suggest the diagnosis.
- Myoclonic absence seizures may rarely be seen in other DEEs but are not the predominant seizure type.[110]

5 | DEES OR EPILEPTIC ENCEPHALOPATHIES WITH ONSET IN CHILDHOOD

"Epileptic encephalopathies" are defined as diseases in which the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond that expected from the underlying etiology alone. These disorders are characterized by frequent epileptiform activity associated with developmental slowing and often regression. They may occur on a background of normal or abnormal development.

In the 2017 Classification of the Epilepsies, additional terminology was introduced with the word "developmental" added to denote those children who had abnormal development secondary to the underlying cause in addition to an epileptic encephalopathy.[112] This term was introduced because many pathogenic gene variants cause developmental impairment in their own right, with the epileptic encephalopathy superimposed on the pre-existing impairment, further impacting developmental outcome.[113]

Conversely, a "developmental encephalopathy" refers to developmental impairment without frequent epileptiform activity, such as in a child or adult with intellectual disability.[112]

Moreover, the task force reviewed the use of the term "developmental encephalopathy" in persons who had fully completed development and agreed to establish a wider term "epilepsy syndromes with progressive neurological deterioration" in addition to developmental encephalopathy. This can be applicable in older individuals with FIRES or Rasmussen syndrome.

In this section, we describe EMAtS, LGS, and DEE-SWAS. We also include two syndromes characterized by acute encephalopathy, followed by a developmental and epileptic encephalopathy, namely, FIRES and HHE.

5.1 | Epilepsy with myoclonic atonic seizures

EMAtS, formerly known as Doose syndrome, begins in early childhood, in the setting of normal development in two thirds of cases.[114] The full complement of clinical and EEG features may be absent early in the course and take time to appear. These children typically show developmental stagnation or even regression during the active seizures (stormy) phase, which improves once seizures are controlled. See Table 8.

5.1.1 | Epidemiology

EMAtS has an incidence of approximately 1 in 10 000 children and accounts for approximately 2% of childhood epilepsies.[115]

5.1.2 | Clinical context

EMAtS typically begins at between 2 and 6 years (range = 6 months to 8 years). Boys are more commonly affected.[116] Approximately one quarter of children have a history of a febrile seizure,[117–120] and such a history is associated with a more favorable long-term outcome.[120] Development prior to seizure onset is normal in two thirds of patients, and neurological examination is typically unremarkable at onset. Moderate to severe developmental delay preceding seizure onset should be considered as an alert for diagnosis.[121]

5.1.3 | Course of illness

The onset of EMAtS is often abrupt, with explosive "stormy" onset of many seizures and seizure types often generalized tonic–clonic and myoclonic. In other cases, it evolves more slowly, requiring careful follow-up over the first year to distinguish it from LGS. Seizures often are drug-resistant, particularly during the high seizure frequency (explosive or stormy) phase, and recurrent bouts of nonconvulsive status epilepticus with increased frequency of other generalized seizure types are seen. During this phase, developmental plateauing or even regression,

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TABLE 8 Epilepsy with myoclonic atonic seizures

	Mandatory	Alerts	Exclusionary
Seizures	Myoclonic–atonic seizures	Tonic seizures within 12 months of epilepsy onset	Epileptic spasms or IESS prior to diagnosis Focal seizures
EEG	Generalized 2–6-Hz spike-wave or polyspike-and-wave abnormalities	Generalized paroxysmal fast activity in sleep Generalized slow spike-and-wave complexes of <2 Hz Photoparoxysmal response at low frequencies (suggests *CLN2* disease)	Persistent focal abnormalities Hypsarrhythmia
Age at onset			<6 months or >8 years
Development at onset		Moderate to severe developmental delay preceding seizure onset	
Neurological exam		Focal neurological findings	
Imaging			Causal lesion on MRI

An MRI is not required for diagnosis but is typically done to exclude other causes.

An ictal EEG is not required for diagnosis. However, in a child with alerts or with clinical features that may suggest Lennox–Gastaut syndrome or infantile epileptic spasms, a video at least is essential and ideally an ictal EEG should be recorded.

Syndrome-in-evolution: Epilepsy with myoclonic atonic seizures should be suspected in the case of explosive onset of multiple generalized seizure types in an appropriately aged child without other alerts or exclusionary features.

Syndrome without laboratory confirmation: In resource-limited regions, epilepsy with myoclonic atonic seizures can be presumptively diagnosed without EEG if the clinician has personally witnessed myoclonic atonic seizures, either directly by observing the patient, or on video provided by the family. However, an EEG is strongly recommended.

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: CLN2, ceroid lipofuscinosis type 2; EEG, electroencephalogram; IESS, infantile epileptic spasms syndrome; MRI, magnetic resonance imaging.

predominantly on behavior and executive functions, and ataxia are often evident. Behavior disorders such as hyperactivity and aggression, and sleep disturbances are also common during the active phase, and typically improve or remit after seizure control is achieved.

Despite seizures being drug-resistant initially, two thirds of children achieve remission, usually within 3 years of onset, and can be weaned off antiseizure therapies.[120,122] In the remaining third, persisting seizures, cognitive impairment, aggression, and hyperactivity are often seen. Once seizures are controlled and the EEG improves, developmental progress is seen. Development may return to premorbid levels of function, or the child may be left with a variable degree of intellectual disability. Factors predictive of poorer outcome include tonic seizures, recurrent nonconvulsive status epilepticus, and an EEG showing very frequent or nearly continuous irregular generalized spike-and-wave, slow spike-and-wave, or generalized paroxysmal fast activity.[120,122–125]

5.1.4 | Seizures

Myoclonic–atonic seizures are mandatory for diagnosis and are characterized by a brief myoclonic jerk affecting the proximal muscles, often associated with a slight vocalization, followed by a very brief atonic component, which may be subtle, with a head nod, or more prominent, with an abrupt fall (Video S1). Conversely, pure atonic seizures, which are also commonly seen, lack the myoclonic component at onset, and lead to an abrupt but brief loss of axial tone, with head nods or a sudden fall.

Other seizures that are frequently seen include myoclonic (which are brief [<100 ms] and can also lead to falls),[126] absence, and generalized tonic–clonic seizures. The latter may occur with or without fever and are the presenting seizure type in approximately two thirds of cases.[117,119,122]

Tonic seizures appear in some patients later in the course and are associated with a poorer long-term outcome.[120]

Nonconvulsive status epilepticus is also common and may be inaugural. It manifests as impaired awareness, lasting hours to days, with atypical absence, myoclonic, and atonic features, associated with somnolence, unsteadiness, drooling, speech disorders, and erratic myoclonus predominating in the face and upper limbs. Recurrent nonconvulsive status epilepticus is associated with a less favorable outcome.[120,124] Epileptic spasms and focal seizures are exclusionary.

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5.1.5 | Electroencephalogram

The background activity shows a normal, age-appropriate posterior dominant rhythm at onset. Monomorphic, biparietal theta rhythms are characteristic of EMAtS but are not seen in all patients. With increased seizure frequency, generalized, higher amplitude background slowing may be seen.

Interictal abnormalities comprised of generalized 2–6-Hz spike-and-wave or polyspike-and-wave complexes often occurring in bursts lasting 2–6 s are seen (Figure 6A). Long sequences of generalized irregular spike-and-wave discharges should raise the question of nonconvulsive status epilepticus. The generalized discharges can become fragmented, and a consistent spike focus is not seen. Generalized spike-and-wave abnormalities are activated with sleep. Generalized paroxysmal fast activity, consisting of bursts of diffuse or bilateral fast (10 Hz or more) polyspikes during sleep, is rarely seen and should suggest LGS. Hyperventilation may elicit generalized spike-and-wave discharges and absence seizures. Photosensitivity is rare.

Ictal recordings of myoclonic–atonic seizures show generalized polyspike or spike discharges with the myoclonus, followed by a high-voltage slow wave accompanying the atonic component (Figure 6B,C). Simultaneous recording of EMG with EEG is recommended for ictal recordings; polyspikes correlate with brief myoclonus in the neck muscles, whereas the slow wave correlates with loss of muscle activity in the proximal limb muscles. Absence seizures are associated with 2–6-Hz generalized spike-and-wave complexes.

During nonconvulsive status epilepticus, the EEG shows long runs of high-amplitude, 2–3-Hz irregular, generalized spike-and-wave activity, with background slowing.

5.1.6 | Imaging

The MRI is normal.

5.1.7 | Genetics

A family history of epilepsy or febrile seizures is found in approximately one third of cases[117,119,122,123,127] and is associated with a more favorable long-term outcome.[120] The familial epilepsy syndrome of genetic epilepsy with febrile seizures plus is seen in families of probands with EMAtS.[128,129]

In the majority of children, EMAtS has complex inheritance with a polygenic pattern. In some cases, pathogenic variants have been seen in genes including *SCN1A*,[130] *SCN1B*,[131] *SCN2A*,[132] *STX1B*,[133] *SLC6A1*,[134] *CHD2*,[102] *SYNGAP1*,[103] *NEXMIF*[104] *KIAA2022*.[135] Approximately 5% of patients with EMAtS have GLUT1 deficiency associated with pathogenic variants in *SLC2A1*.[85]

5.1.8 | Differential diagnosis

Other epilepsies:

- LGS can be distinguished by the presence of tonic seizures early in the disease and the EEG, which shows slow spike-and-wave <2.5-Hz and generalized paroxysmal fast activity in sleep. Additionally, children with LGS more commonly have delayed development prior to seizure onset and may have a history of infantile spasms syndrome.
- Myoclonic epilepsy of infancy is distinguished by the lack of myoclonic–atonic and atypical absence seizures, and typically presents earlier than EMAtS.
- Dravet syndrome is distinguished by prolonged, hemiclonic seizures triggered by fever/illness in the first year of life and absence of myoclonic–atonic seizures.
- DEE-SWAS or EE-SWAS is associated with regression and marked activation of epileptiform abnormalities in sleep, with nearly continuous diffuse spike-and-wave complexes; myoclonic–atonic seizures are not seen.
- Subacute sclerosing panencephalitis is a rare condition associated with fulminant/rapid progression of myoclonic seizures, and episodes of falls. The EEG pattern is diagnostic.
- CLN2 disease typically begins in children with normal development or isolated speech delay. Children may present with a phenotype of EMAtS; however, there is progressive motor and cognitive decline and ataxia. The EEG shows a photoparoxysmal response at 1–3 Hz, so low-frequency testing is important.

5.2 | Lennox–Gastaut syndrome

LGS is a DEE associated with a wide range of etiologies. It results from high-frequency, synchronized activity in bilaterally distributed brain networks that develops in a susceptible age period in childhood.[136] This syndrome is characterized by the presence of (1) multiple types of drug-resistant seizures with onset prior to 18 years (one of which must include tonic); (2) cognitive and often behavioral impairments, which may not be present at

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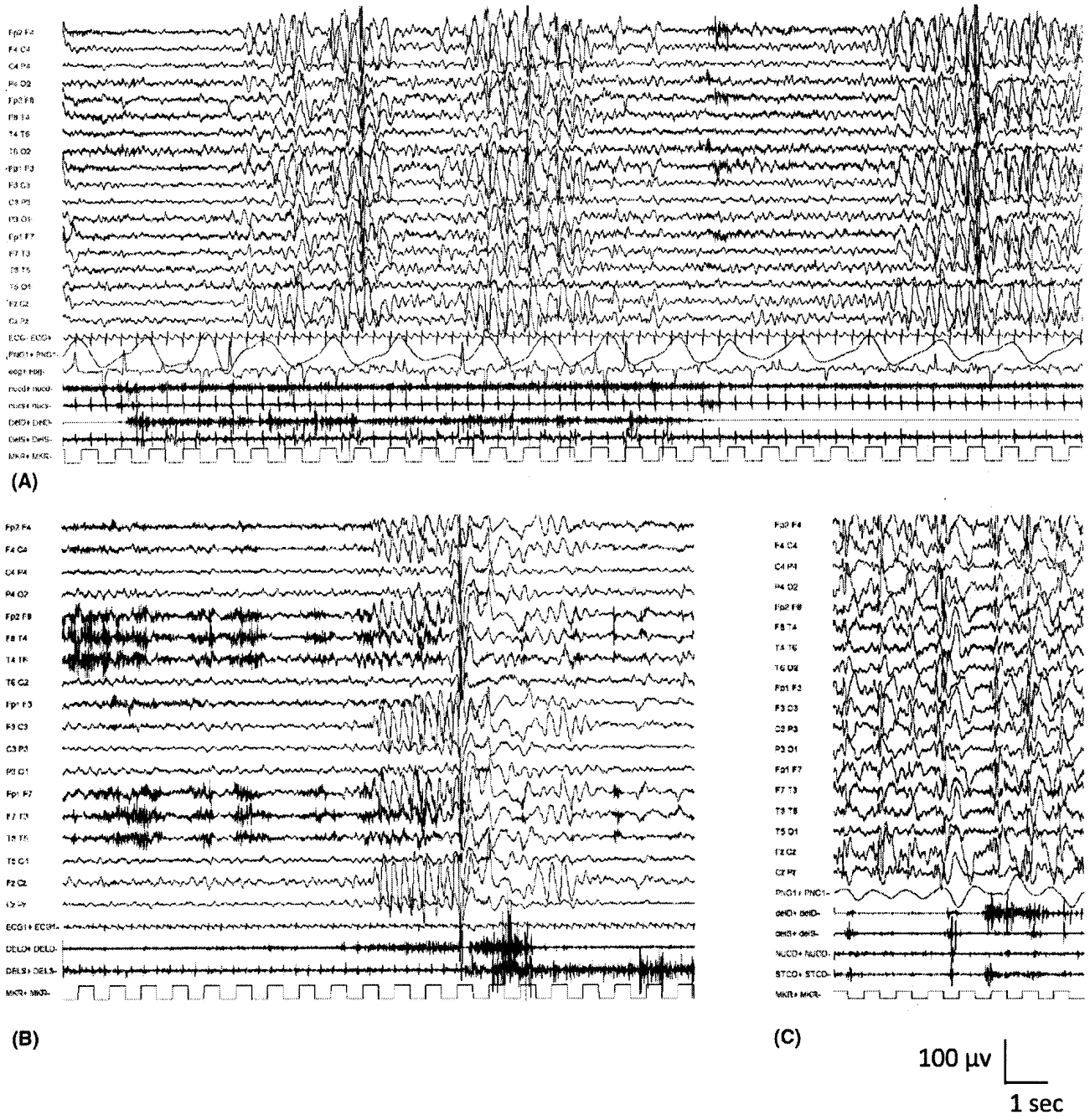


FIGURE 6 Interictal and ictal polygraphic electroencephalographic (EEG) recordings in a 3-year-old child with epilepsy with myoclonic atonic seizures. (A) Interictal EEG shows bilateral posterior slow waves (4–6 Hz). There are generalized abnormalities characterized by high-amplitude spikes and spike-and-wave abnormalities intermingled with high-amplitude delta waves without any clinical changes. (B, C) Examples of myoclonic atonic seizures associated with a generalized spike-and-wave discharge of brief duration. Electromyographic channels show loss of tone in the deltoids (B) and in nuchal and sternocleidomastoid muscles (C). Clinically, the child experiences abrupt falls with both events

seizure onset; and (3) diffuse slow spike-and-wave and generalized paroxysmal fast activity on EEG (Table 9). Many clinicians use the term "LGS" to describe any severe, early onset epilepsy with intractable seizures leading to falls. This approach is incorrect, as it fails to recognize the specific features of LGS, and to distinguish it from EMAtS, which often has a markedly better outcome, and many other severe epilepsies starting

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TABLE 9 Lennox–Gastaut syndrome

	Mandatory	Alerts	Exclusionary
Seizures	Tonic seizures (see text) 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		

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 Lennox–Gastaut syndrome.

Syndrome without laboratory confirmation: In resource-limited regions, at a minimum, an interictal EEG showing characteristic generalized slow spike-and-wave pattern during wakefulness is required for diagnosis.

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: CLN2, ceroid lipofuscinosis type 2; IESS, infantile epileptic spasms syndrome; DEE, developmental and/or epileptic encephalopathy; EEG, electroencephalogram; MRI, magnetic resonance imaging.

in childhood. The full complement of clinical and EEG features is often absent early in the course and takes time to appear. Young children presenting with characteristic seizure types but lacking all the features need close follow-up for evolution to LGS. In particular, a number of severe infantile epilepsy syndromes, such as infantile epileptic spasms syndrome, early infantile DEE, and epilepsy of infancy with migrating focal seizures, often evolve to LGS. Repetitive assessment for LGS criteria may be helpful to access to ASMs licensed for LGS.

5.2.1 | Epidemiology

LGS accounts for approximately 1%–2% of all persons with epilepsy. In children, LGS is rarely diagnosed at initial seizure onset (0.6%). LGS often evolves from another severe infantile epilepsy syndrome or etiology, with approximately 20% of cases evolving from infantile epileptic spasms syndrome.[137] Ultimately, 3.6% of all children with epilepsy, and 19% of children with seizures starting in infancy, evolve to LGS.[138]

5.2.2 | Clinical context

LGS usually begins between 18 months and 8 years of age, with a peak age at onset of 3–5 years. Onset in the second decade is rare.[139] It is slightly more common in males. Abnormalities on neurological examination (for example pyramidal signs) are often found and are related to the underlying etiology. Most children have developmental impairment that predates seizure onset in LGS, but developmental stagnation or decline can occur with onset of frequent seizures. Less commonly, development and behavior may be normal at seizure onset.

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5.2.3 | Course of illness

LGS persists into adulthood in nearly all cases, and seizures remain drug-resistant.[139] Atypical absence and tonic seizures remain frequent in adults, whereas atonic seizures often settle.[140]

Over time, there is developmental slowing, plateauing, or regression, culminating in moderate to severe intellectual disability in >90% of patients.[140–142] Behavior disorders such as hyperactivity, aggression, autism spectrum disorder, and sleep disturbances are common in childhood and adolescence.[140,141]

5.2.4 | Seizures

Tonic seizures, consisting of a sustained increase in axial and limb muscle contraction lasting from 3 s to 2 min, are mandatory for diagnosis and are most prominent in sleep. They may be subtle, with slow upward eye rolling or deviation, at times with facial grimace or flexor movements of the head and/or trunk, or more clinically obvious, with a brief cry, apnea, abduction, and elevation of the limbs with a vibratory component and bilateral fist clenching. If occurring while the patient is standing, they may forcefully throw the patient off balance, leading to a fall (drop attack), with the patient often sustaining an injury. Tonic seizures may be exacerbated by medications that lead to increased sleepiness, such as acute use of high-dose benzodiazepines.

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

1. Atypical absence seizures: These are often frequent and consist of periods of impaired awareness. They may be challenging to identify with confidence due to their gradual onset and offset in a patient with underlying cognitive impairment.
2. Atonic seizures: These lead to an abrupt loss of axial tone, with head nods or a sudden fall (drop attacks), often causing injury. They are frequent, particularly in younger children with LGS. They are typically brief, lasting only one to a few seconds.
3. Myoclonic seizures: Myoclonic seizures are also very brief (<100 ms) and may lead to falls (drop attacks). If myoclonic–atonic seizures are present, the diagnosis of EMAtS should be strongly considered.
4. Focal impaired awareness seizures: These may remain focal or evolve to bilateral tonic–clonic seizures.
5. Generalized tonic–clonic seizures.
6. Nonconvulsive status epilepticus: Approximately half to three quarters of patients with LGS have one or more episodes of nonconvulsive status epilepticus, which consist of ongoing atypical absence seizures with altered awareness, with erratic, generalized, or multifocal myoclonic and atonic components, and interspersed clusters of brief tonic seizures.
7. Epileptic spasms.

5.2.5 | Electroencephalogram

The background activity is abnormal, with diffuse theta–delta slowing, which may be more pronounced focally, depending on the underlying etiology. If prominent biparietal theta rhythms are seen, EMAtS should be considered. Two interictal patterns are mandatory for the diagnosis of LGS:

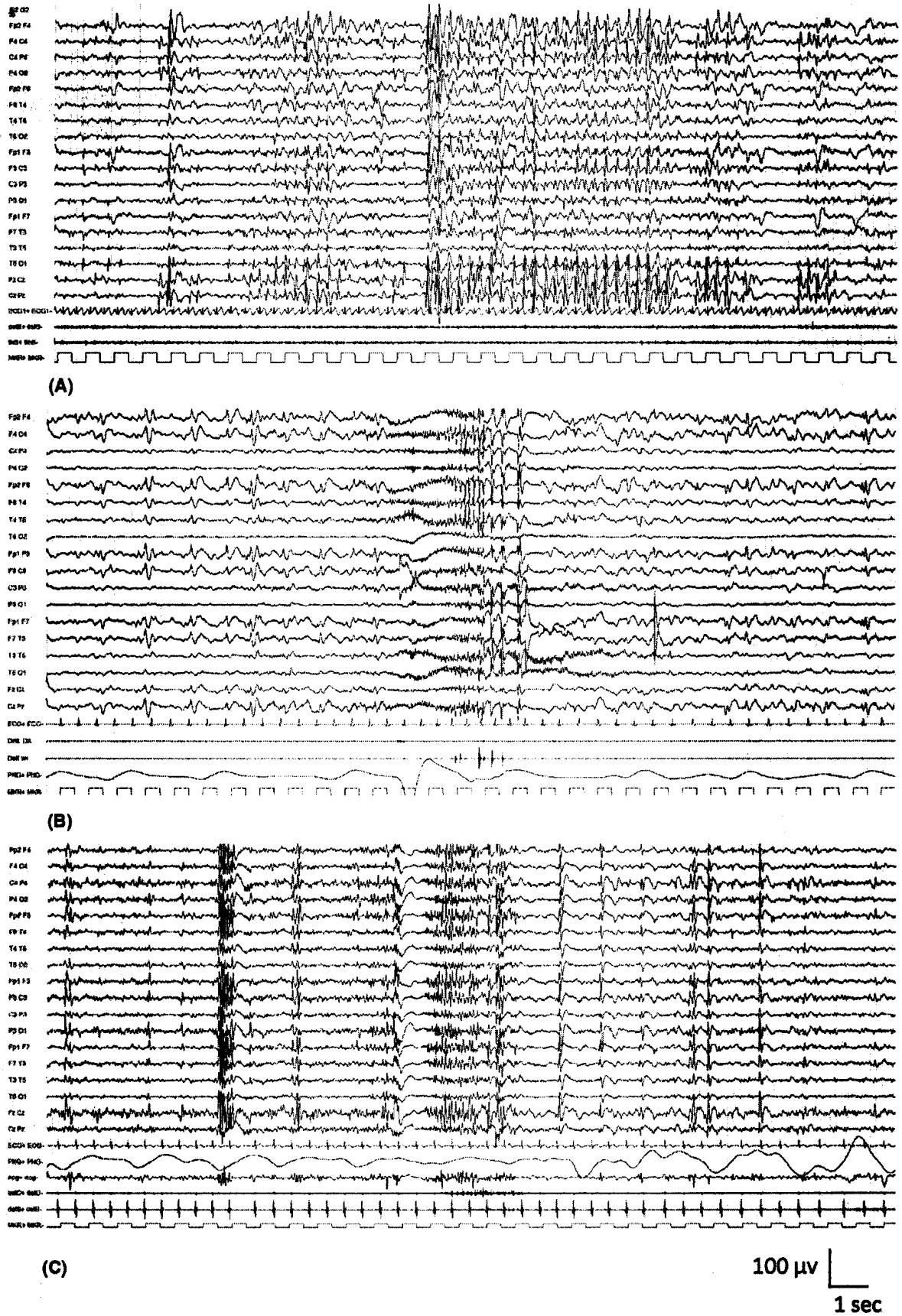
1. Generalized slow spike-and-wave: This interictal slow spike-and-wave pattern is characterized by spikes (<70 ms) or sharp waves (70–200 ms), followed by negative high-voltage slow waves (350–400 ms), which are bilaterally synchronous, often anterior predominant, and occur at a frequency of ≤2.5 Hz (Figure 7A). The slow spike-and-wave pattern is abundant and often occurs in runs. It can be associated with atypical absence seizures, but often waxes and wanes without any clinical correlate both in wakefulness and particularly in sleep. Generalized slow spike-and-wave (≤2.5 Hz) complexes are more frequently present in young children, whereas in adolescence and adulthood there is a decrease in the frequency of the spike-and-wave pattern. After the age of 16 years, the majority of patients no longer exhibit the typical slow spike-and-wave pattern.[143–145]
2. Generalized paroxysmal fast activity: This pattern consists of bursts of diffuse or bilateral fast (10 Hz or more) activity often seen during sleep. These typically are brief, lasting a few seconds or less (Figure 7B).

Focal or multifocal slow spike-and-wave pattern may also be seen. Abnormalities are not typically activated by photic stimulation.

Tonic seizures, which are often subtle, and may not be recognized by families, are typically recorded on sleep EEG. The EEG pattern of tonic seizures consists of a burst of bilateral 10-Hz or higher frequency fast activity with a recruiting rhythm—an initial diffuse decrement followed by gradual increase in amplitude (Figure 7C). Polygraphic recordings during tonic seizures often show a brief apnea with electromyographic axial muscle contraction. Because of these characteristic findings, a sleep recording can be beneficial to distinguish LGS from other epilepsy syndromes.

Atypical absence seizures are associated with slow spike-and-wave (<3 Hz) complexes, although it can be

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FIGURE 7 Lennox–Gastaut syndrome. Interictal and ictal polygraphic electroencephalographic (EEG) recordings are shown. (A) Generalized slow spike-and-wave abnormalities (between 2 and 2.5 Hz) are seen, lasting 8 s, not associated with any clinical signs. (B) Generalized paroxysmal 10-Hz fast activity. The discharge is seen during sleep and is not associated with any clinical signs. (C) Ictal EEG showing a generalized electrodecremental response lasting 4 s associated with bilateral tonic contraction of the upper limbs, consistent with a generalized tonic seizure

challenging to clearly distinguish between ictal and interictal slow spike-and-wave patterns.

5.2.6 | Imaging

As structural causes are the most common etiology, MRI at onset is strongly recommended, as this may impact on treatment decision-making.[146] A variety of structural etiologies may be found, including focal or diffuse cortical malformations, tuberous sclerosis complex, tumors, or acquired brain injury such as hypoxic–ischemic encephalopathy. Reinvestigation of older patients with LGS can result in identification of structural etiologies missed on previous imaging.[147] MRI may also be normal.

5.2.7 | Genetics

Pathogenic variants in many genes have been associated with the etiologies that causes LGS and are usually de novo in the child.[148,149] A range of chromosomal abnormalities and copy number variants have been associated with LGS, so chromosomal microarray is essential. A range of next generation sequencing approaches can be taken, ideally with whole exome sequencing, or an epilepsy gene panel, particularly if no etiology is found after clinical examination and MRI. Furthermore, genetic testing should also be considered for patients with structural brain disorders suggestive of an underlying genetic cause.

5.2.8 | Metabolic testing

Rarely, LGS can be due to a neurometabolic disorder. Metabolic testing should be considered if an underlying etiology is not found with imaging or genetic studies.

5.2.9 | Differential diagnosis

Other epilepsies:

- Infantile Epileptic Spasms syndrome may progress to LGS, and distinction between these syndromes during the transition can be challenging. In distinction to spasms, tonic seizures are typically longer than 3 s and do not occur in clusters on waking.
- EMAtS is distinguished by normal development prior to seizure onset in many cases, myoclonic–atonic seizures, and faster generalized spike-and-wave pattern, which is typically >3 Hz.
- Dravet syndrome is distinguished by prolonged, hemiclonic seizures triggered by seizures in the first year of life; tonic seizures (if present) do not occur until later.
- Other early onset DEEs with multiple seizures types.
- DEE-SWAS or EE-SWAS is associated with regression and marked activation of epileptiform abnormalities in sleep, with nearly continuous diffuse spike-and-wave complexes.
- Ring (20) syndrome is associated with refractory epilepsy, intellectual disability, and behavioral abnormalities; tonic seizures usually appear during sleep, whereas awake patients frequently experience nonconvulsive status epilepticus.
- Frontal lobe epilepsy may present with bilateral tonic seizures, often with asymmetrical features. Slow spike-and-wave and generalized paroxysmal fast activity are not seen.
- Rare metabolic disorders may lead to an LGS phenotype. CLN2 disease typically begins in children with normal development or isolated speech delay. Following onset of seizures, there is progressive motor and cognitive decline and ataxia. The EEG characteristically shows a photoparoxysmal response at 1–3 Hz.

5.3 | DEE-SWAS and EE-SWAS

DEE-SWAS and EE-SWAS refer to a spectrum of conditions that are characterized by various combinations of cognitive, language, behavioral, and motor regression associated with marked spike-and-wave activation in sleep. Regression is seen within weeks from the EEG pattern. DEE-SWAS and EE-SWAS share similar clinical features (Table 10) and management implications. They are grouped together because they carry similar implications, and the syndrome highlights the need to inquire about specific clinical features when seeing a child, such as auditory agnosia, global regression of behavior and motor skills, and negative myoclonus. This syndrome is intended to replace syndromes previously named epileptic encephalopathy

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TABLE 10 Developmental and epileptic encephalopathy with SWAS and epileptic encephalopathy with SWAS

	Mandatory	Alerts	Exclusionary
Seizures		Tonic seizures during sleep	Epileptic spasms
EEG	Slow (1.5–2 Hz) spike-and-wave abnormalities in N-REM sleep Abnormalities are markedly activated in sleep	Generalized paroxysmal fast activity in sleep (consider Lennox–Gastaut syndrome) Generalized slow spike-and-wave complexes of <2.5 Hz in both awake and asleep states (consider Lennox–Gastaut syndrome)	
Age at onset		>1 and <2 years	<1 year or >12 years
Development at onset	Cognitive, behavioral, or motor regression or plateauing temporally related to SWAS on EEG		
Long-term outcome	Remission of SWAS pattern on EEG by mid adolescence, although EEG often remains abnormal		
An MRI is not required for diagnosis but is often performed to evaluate for underlying etiology. A sleep EEG is mandatory for diagnosis.			
Syndrome without laboratory confirmation: In resource-limited regions, this syndrome cannot be presumptively diagnosed without a sleep EEG.			

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging; N-REM, non-rapid eye movement; SWAS, spike-and-wave activation in sleep.

with continuous spike-and-wave in sleep and atypical benign partial epilepsy (pseudo-Lennox syndrome). Landau–Kleffner syndrome (LKS) is a specific subtype of EE-SWAS, where regression affects mainly language, with an acquired auditory agnosia, and the eponym used to describe this syndrome should be retained (Figure 8).

Sleep EEG must be performed to confirm the diagnosis. The EEG pattern associated with EE-SWAS and DEE-SWAS was known as electrical status epilepticus in sleep (ESES).[11,150] Historically, ESES was defined as nearly constant epileptiform activity that occupies >85% of slow wave sleep; however, lower percentages of sleep may also be associated with significant regression in cognitive or behavioral function.

EE-SWAS is now recognized in patients with pre-existing normal development with an activation of slow (1.5–2 Hz) spike-and-wave complexes in non-rapid eye movement (N-REM) sleep.

DEE-SWAS occurs in patients with pre-existing neurodevelopmental disorders and is defined on the basis of a documented persisting worsening of various combinations of cognitive, language, behavioral, and motor functions concomitant with significant activation of spike-and-wave complexes during sleep. Caution is needed not to overdiagnose the syndrome in the absence of clear and persisting regression.

Specific focal epilepsy syndromes, such as SeLECTs and SeLEAS, or other structural focal epilepsies, may evolve to EE-SWAS, either transiently or for a prolonged period.

5.3.1 | Epidemiology

DEE-SWAS and EE-SWAS are rare, accounting for 0.5%–0.6% of all epilepsy presentations seen at pediatric tertiary epilepsy centers.[151–153]

5.3.2 | Clinical context

DEE-SWAS and EE-SWAS are characterized by onset of seizures at between 2 and 12 years of age (peak = 4–5 years), with the EEG developing spike-and-wave activation in sleep 1–2 years after seizure onset in association with cognitive/behavioral regression or plateauing. Both sexes are affected equally. Antecedent and birth history are often normal; however, structural brain lesions are a risk factor for DEE-SWAS and EE-SWAS. Specifically, thalamic injury in early life[154] and malformations such as bilateral perisylvian polymicrogyria are associated with this syndrome; therefore, neuroimaging, particularly MRI, is recommended whenever possible. Neurological examination and developmental level may be normal or reflect an underlying structural brain abnormality. Regression in cognitive, behavioral, or psychiatric functioning is the cardinal symptom of this syndrome. All cognitive domains can be affected, including language and communication, temporospatial orientation, attention, and social interaction. Motor regression with dyspraxia or dystonic features may also occur.[155] Follow-up visits with clinical assessment, EEGs, and neuropsychological

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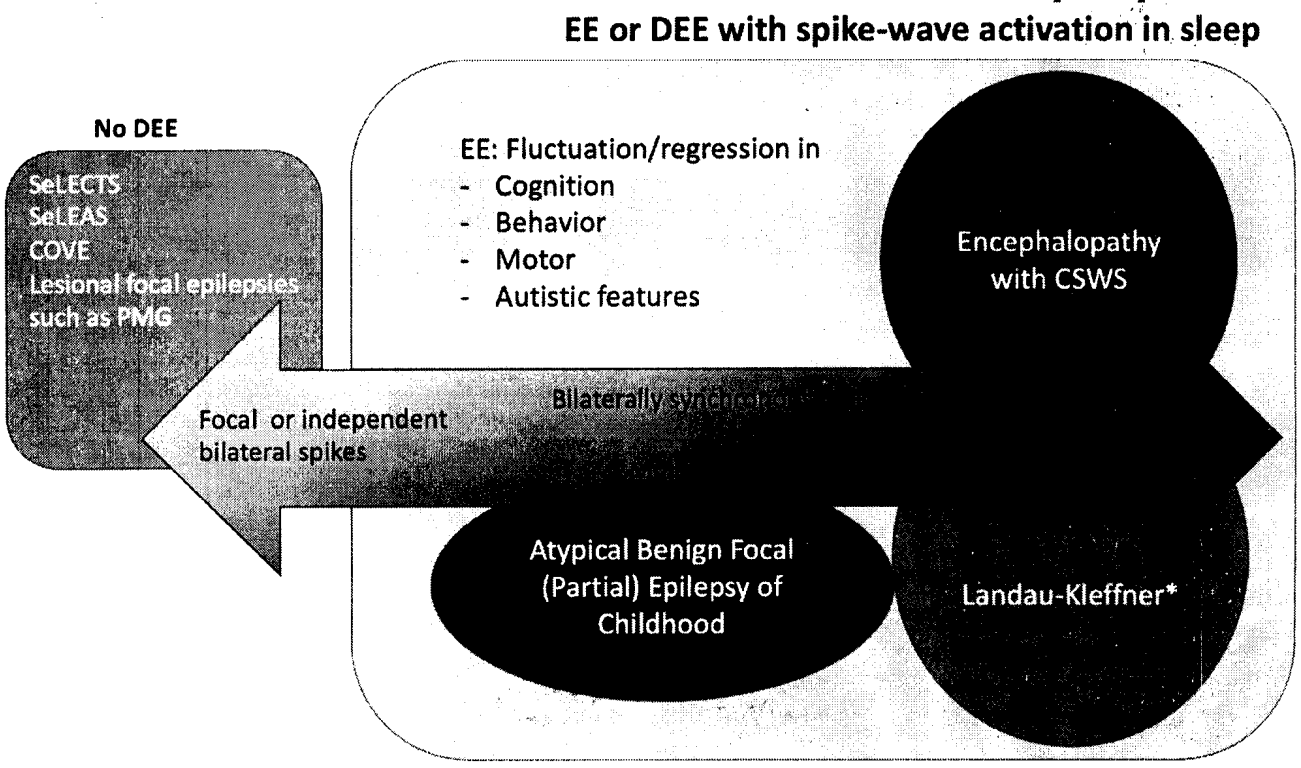


FIGURE 8 Developmental and/or epileptic encephalopathy (DEE) and epileptic encephalopathy (EE) with spike-and-wave activation in sleep (SWAS) refer to a spectrum of conditions that are characterized by various combinations of cognitive, language, behavioral, and motor regression associated with marked spike-and-wave activation in sleep. Regression is seen within weeks from the electroencephalographic pattern. This syndrome is intended to replace syndromes previously named Epileptic Encephalopathy with Continuous Spike-and-Wave in Sleep and Atypical Benign Partial Epilepsy (pseudo-Lennox syndrome). *Landau–Kleffner syndrome is a specific subtype of EE-SWAS, where regression affects mainly language with an acquired auditory agnosia. Specific focal epilepsy syndromes, such as self-limited epilepsy with centrotemporal spikes (SeLECTS) and self-limited epilepsy with autonomic seizures (SeLEAS), or other structural focal epilepsies, may evolve to EE-SWAS, either transiently or for a prolonged period. CSWS, continuous spike-and-wave complexes during sleep, N-REM, non-rapid eye movement; PMG, polymicrogyria

testing should be scheduled at baseline and during the follow-up to assess the evolution.[156]

5.3.3 | Course of illness

Clinical seizures typically remit around puberty, even in patients with a structural lesion.[157] Resolution of clinical seizures may precede, coincide with, or follow the resolution of the EEG pattern.[157] The SWAS pattern on EEG also resolves, typically by adolescence.[158,159] Focal abnormalities may persist during both wakefulness and sleep. Sleep architecture normalizes with resolution of SWAS.[158]

Neurocognitive and behavioral improvement is typically seen, with resolution of the SWAS on EEG.[160] However, many patients have residual impairment, which is severe enough to limit independent functioning in approximately half of the patients.[161,162] The duration and etiology of DEE-SWAS and EE-SWAS are the most important predictors of cognitive outcome; the risk of poor outcome is higher if it is present for >2 years.[163] Poorer outcomes are also seen with younger onset of DEE-SWAS.[163] Thus, early diagnosis is of paramount importance to enable initiation of treatment to improve long-term outcome even if some causes are not treatable (the etiology prevails), and there may be no clinical improvement for some when the EEG pattern is abolished. Nevertheless, residual deficits may remain following remission of seizures and SWAS, which may occur from months to 7 years after onset.

5.3.4 | Seizures

There is no mandatory seizure type. Seizure type is dependent on the underlying etiology. Furthermore, EE-SWAS and DEE-SWAS may occur in patients who do not have clinical seizures.

In most patients, infrequent and drug-responsive seizures are observed during the initial phase at between 2 and 5 years of age. These early seizures are typically focal

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motor, with or without impaired awareness, and focal to bilateral tonic–clonic seizures. Seizures typically worsen with the evolution of multiple seizure types. These include focal seizures with or without impaired awareness, typical and atypical absence seizures, atonic seizures, and focal motor seizures with negative myoclonus.

5.3.5 | Electroencephalogram

The EEG pattern depends on the underlying etiology. The background activity during wakefulness may show focal or diffuse slowing and often contains focal or multifocal abnormalities, but it may be normal (Figure 9A). Epileptiform abnormalities during wakefulness are not continuous. In drowsiness and sleep, there is marked activation of epileptiform activity, with slow (1.5–2 Hz) spike-and-wave complexes in N-REM sleep. Typically, this activity is also seen in Stage II sleep (Figure 9B). SWAS is usually diffuse but may occur more focally (typically frontally) or multifocally. In rapid eye movement sleep, the abnormalities become less frequent or may even be absent. Normal sleep architecture (vertex sharp waves, sleep spindles, and K complexes) is absent or difficult to distinguish. An overnight sleep EEG may be required, as slow wave sleep may not be achieved on an outpatient sleep EEG. The ictal EEG correlates with the seizure type.

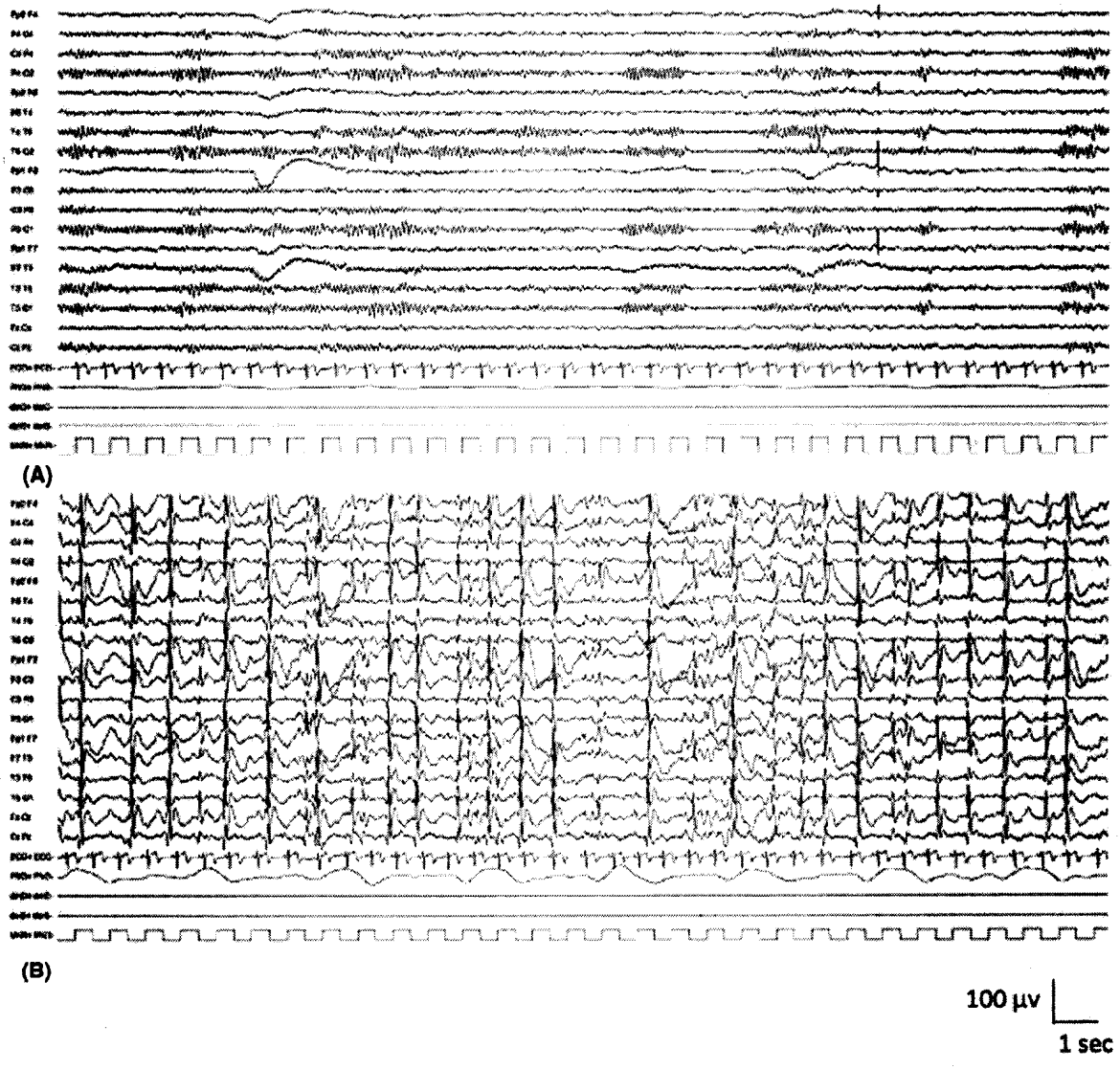


FIGURE 9 Epileptic encephalopathy with spike-and-wave activation in sleep. Awake and sleep polygraphic electroencephalographic (EEG) recordings are shown. (A) Awake EEG shows a background activity characterized by 9–10-Hz alpha rhythm, with lower amplitude, fast activity seen over the bilateral anterior regions. There are no epileptiform abnormalities. (B) During sleep, there are continuous generalized spike-and-wave abnormalities

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5.3.6 | Imaging

Neuroimaging may be normal or demonstrate underlying structural brain abnormalities that may be developmental (e.g., perisylvian polymicrogyria) or acquired (thalamic abnormalities can be observed).

5.3.7 | Genetics

Some cases have a genetic basis and may follow monogenic or complex inheritance. A family history of seizures is seen in up to 50% patients with DEE-SWAS or EE-SWAS.[164] The major monogenic cause is *GRIN2A*, which encodes the N-methyl-D-aspartate (NMDA) receptor glutamate receptor alpha 2 subunit.[12] Pathogenic variants are associated with a range of severity of DEE-SWAS phenotypes.[13–15] These individuals have a characteristic speech pattern, which may persist into adult life.[165]

5.3.8 | Differential diagnosis

Other epilepsy syndromes:

- SeLFEs can have marked activation of epileptiform abnormalities in sleep, but there is not temporally related cognitive or behavioral regression with the EEG finding of SWAS.
- Structural focal epilepsies may have abundant focal abnormalities that may activate in sleep, but there is not temporally related cognitive or behavioral regression with the EEG finding of SWAS.
- LGS is distinguished by the EEG, which shows prominent slow spike-and-wave complexes during both wakefulness and sleep, and by the sleep EEG, which shows generalized paroxysmal fast activity, and often tonic seizures are captured.

Other conditions:

- Children with autism spectrum disorders with or without intellectual disability but without regression may show activation of epileptiform abnormalities in sleep.
- Cognitive regression due to other etiologies.

5.4 | Febrile infection-related epilepsy syndrome

FIRES (previously also known as acute encephalitis with refractory, repetitive partial seizures, or devastating epileptic encephalopathy in school-aged children) is one cause of new onset refractory status epilepticus, which occurs predominantly in children and adolescents (Table 11). A prior febrile infection occurs, starting between 24 h and 2 weeks, prior to an explosive onset of superrefractory status epilepticus; there may or may not be fever at onset of status epilepticus.[166] The acute phase, during which the seizure burden is very high, lasts 1–12 weeks,[167] and during this phase, mortality and morbidity are significant. This is followed by a chronic phase, where most survivors are left with drug-resistant multifocal epilepsy and a variable degree of intellectual disability or learning difficulties. The cause is not known, but growing evidence suggests a heterogeneous etiology resulting in fulminant non-antibody-mediated neuroinflammation.[168,169]

5.4.1 | Epidemiology

This is a rare syndrome, which is likely underrecognized, with an estimated incidence of 1 per million.[170]

5.4.2 | Clinical context

FIRES occurs most commonly in school-aged children (mean = 8 years) with a typical range of 2–17 years.[166,169,171] It is exceedingly infrequent under the age of 2 years and can begin at a variable age, but may rarely occur in young adulthood. Both sexes are affected, with a slight male predominance.[171] Perinatal history is typically normal. At presentation, children are developmentally normal, without a history of prior neurological disease including epilepsy, and have normal head size.

All children have a history of a prior febrile infection, most commonly upper respiratory or gastrointestinal, between 24 h and 2 weeks before onset of refractory status epilepticus. At the time of seizure onset, patients may still be febrile, or may have had recent resolution of the fever.

At presentation, patients are typically encephalopathic and have frequent seizures despite ASMs. Head size is normal. Persistent focal abnormalities on examination are unusual, but transient Todd paresis may be seen.

5.4.3 | Course of illness

The prognosis is variable but often poor.[171] Mortality is approximately 10% in the acute phase, due to intensive care complications such as sepsis, or uncontrolled status

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TABLE 11 Febrile infection-related epilepsy syndrome

	Mandatory	Alerts	Exclusionary
Seizures	History of nonspecific febrile illness in the 2 weeks preceding seizure onset Focal and multifocal seizures that often evolve to bilateral tonic–clonic seizures Seizures progress in frequency and severity to culminate in superrefractory status epilepticus typically within 2 weeks of onset		History of epilepsy prior to onset of symptoms
EEG	Slowing of the background activity with multifocal epileptiform abnormalities and frequent, focal electrographic and electroclinical seizures	Unifocal seizures	
Age at onset		<2 years	<1 year or >30 years
Development at onset	Acute encephalopathy with onset of frequent seizures	Intellectual disability prior to seizure onset	
Neurological exam		Neurological exam abnormalities prior to onset of seizures	
Imaging			At presentation, MRI shows an epileptogenic lesion concordant with seizure onset (see text)
Other testing			Lumbar puncture showing evidence of central nervous system infection Causal antibody on CSF or plasma autoimmune testing Documented metabolic or genetic etiology Documented toxic encephalopathy
Long-term outcome		Lack of drug-resistant focal or multifocal epilepsy Lack of learning difficulties or intellectual disability Lack of variable degrees of cerebral atrophy on MRI	
An MRI is required for diagnosis to exclude a causal lesion. An ictal EEG is required for diagnosis to confirm frequency and multifocality of seizures.			
Syndrome without laboratory confirmation: In resource-limited regions, this syndrome cannot be presumptively diagnosed without EEG and MRI studies.			

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging.

epilepticus. Following the acute phase, most children are left with drug-resistant, multifocal epilepsy.

Developmentally, in the acute stage, most children regress, and at follow-up, in the chronic phase, the majority are left with varying degrees of intellectual disability.[171] Approximately one third of survivors have normal or borderline cognition (often learning disorders), one third have mild to moderate intellectual disability, and one third have severe to profound disability or are vegetative. Poorer outcome was associated with longer duration of medically induced burst-suppression coma and younger age at onset.[171] Attention and behavior problems, including aggression, are also common in survivors.

In the chronic phase, many patients will have evidence of motor dysfunction.

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5.4.4 | Seizures

Focal or multifocal seizures are mandatory for diagnosis and may evolve to bilateral tonic–clonic seizures. Common ictal symptoms are eye deviation and hemifacial twitching. Seizures progress in frequency and severity rapidly to culminate in superrefractory status epilepticus (defined as >24 h) in the acute phase.

5.4.5 | Electroencephalogram

The EEG background activity is typically abnormal, with slowing and multifocal abnormalities. Recurrent extreme delta brush, consisting of a paroxysmal beta–delta complex of 15–18-Hz beta superimposed on 1–3-Hz delta in the frontal and central head regions, is often seen (Figure S4A,B).[172] This pattern may be modified by anesthetic agents used for the treatment for status epilepticus.

Prolonged video-EEG monitoring at diagnosis shows a gradual increase in seizure burden over the first days to week of illness. Initially, seizure burden may be low, but over time, frequent, multifocal subclinical and clinical seizures are recorded, usually with a frequency of several per hour.[172] A typical seizure pattern, consisting of focal activity of >10 Hz of low to moderate amplitude, evolving to well-formed, rhythmic spikes and spike-and-wave complexes, is seen, and ictal activity often shifts from one hemisphere to the other (Figure S4C).[172]

5.4.6 | Neuroimaging

During the acute stage, the MRI is normal in approximately two thirds of cases. Approximately one third may show T2 hyperintense changes in bilateral temporal regions, insula, basal ganglia, and/or thalami, which may be subtle. Leptomeningeal enhancement may also be seen but is not specific to this syndrome.[173]

During the chronic stage, the MRI usually shows variable degrees of diffuse cerebral atrophy, and/or signal changes over the temporal lobes, cerebral cortex, periventricular white matter, hippocampi, and basal ganglia.[173]

5.4.7 | Genetics

This disorder is not suspected to be genetic, and no causal genes have been identified. There is usually no family history of seizures.

5.4.8 | Other laboratory studies

Examination of cerebrospinal fluid (CSF) is required to exclude infection. The CSF is typically normal but may show a mild pleocytosis. CSF protein and lactate are normal. Oligoclonal bands are negative. An immune etiology should be excluded, but in FIRES, no causal antibodies have yet been found.[169] Serum and CSF autoimmune panels are negative. It has been reported that Th1 chemokines (CXCL9, CXCL10, etc.) are predominantly upregulated in CSF, independently of interleukin-1 receptor (IL-1R) signaling.[174] Metabolic studies are unremarkable. In some cases, excessive neuroinflammation, which may be secondary to functional deficiency in IL-1R antagonist, has been reported.[175,176]

5.4.9 | Differential diagnosis

Other epilepsy syndromes:

- Dravet syndrome is distinguished by its presentation predominantly in the first year of life, and history of intermittent prolonged seizures with interval recovery, as opposed to a singular superrefractory status epilepticus with the development of persistent morbidity.
- *PCDH19* clustering epilepsy is distinguished by its presentation in the first 3 years of life, and history of a cluster of seizures usually induced by fever. Superrefractory status epilepticus is unusual.

Other conditions:

- Meningitis or encephalitis.
- Specific autoimmune-mediated encephalopathies such as anti-NMDA receptor encephalitis.
- Toxic encephalopathies.
- Metabolic disorders such as mitochondrial disease.

5.5 | Hemiconvulsion–hemiplegia–epilepsy syndrome

HHE is a rare consequence of focal motor status epilepticus in infancy and early childhood (Table 12). The initiating event for this syndrome is a focal clonic status epilepticus typically occurring in the context of a febrile illness in children <4 years of age.[177] Neuroradiological studies at the time of the status epilepticus show unilateral edematous swelling of the affected hemisphere. The acute phase is followed by hemispheric atrophy with subsequent appearance of

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TABLE 12 Hemiconvulsion–hemiplegia–epilepsy syndrome

	Mandatory	Alerts	Exclusionary
Seizures	Diagnosis requires both a history of acute stage and chronic stage disease Acute stage: Episode of febrile, hemiclonic status epilepticus, which is immediately followed by permanent hemiparesis Chronic stage: After a variable time (usually <3 years after initial status epilepticus), unilateral focal motor or focal to bilateral tonic–clonic seizures appear		Transient hemiparesis (Todd paresis) Unilateral focal motor seizures that progress in a crescendo pattern over months to years, with late development of progressive hemiparesis (consider Rasmussen encephalitis)
EEG	Slowing of background activity over the affected hemisphere Focal or multifocal epileptiform abnormalities over the affected hemisphere in the chronic phase		
Age at onset		>4 years	>6 years
Development at onset		Intellectual disability prior to seizure onset	
Neurological exam		Focal neurological abnormalities prior to initial episode of febrile status epilepticus Facial angioma suggestive of Sturge–Weber syndrome	
Imaging	MRI immediately following febrile status epilepticus (acute stage) shows diffuse signal change with T2 hyperintensity and restricted diffusion of the subcortical region of the affected hemisphere, often with severe edema Over time (chronic stage), there is atrophy of the affected hemisphere		Other structural causes predisposing to focal status epilepticus
Other testing			Alternative cause of hemiparesis found such as acute ischemic stroke, intracranial infection, etc.
Long-term outcome	Drug-resistant epilepsy Permanent focal motor deficit		

An MRI is required to diagnosis.

An ictal EEG is not required for diagnosis.

Syndrome-in-evolution: Children with acute permanent hemiparesis following an episode of focal convulsive febrile status epilepticus, with mandatory MRI findings, but who have not yet progressed to the chronic phase of the disease with recurrent, drug-resistant focal motor or focal to bilateral tonic–clonic seizures should be suspected of having emerging hemiconvulsion–hemiplegia–epilepsy syndrome.

Syndrome without laboratory confirmation: In resource-limited regions, hemiconvulsion–hemiplegia–epilepsy syndrome can be presumptively diagnosed without EEG in cases that meet all mandatory and exclusionary clinical criteria without alerts. However, an imaging study (CT or MRI) is required to exclude other causes.

Note: Alert criteria are absent in the vast majority of cases, but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions.

Abbreviations: CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.

focal seizures, which are drug-resistant. The majority of patients have a resultant permanent motor deficit. The etiology and the underlying mechanisms are not understood.

5.5.1 | Epidemiology

HHE is a rare syndrome and its incidence has declined markedly in resource-equipped countries over the past

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30 years since the instigation of aggressive treatment for prolonged seizures or status epilepticus.[178]

5.5.2 | Clinical context

Age at onset is typically <4 years, and there is no sex predilection.[178,179] Birth and antecedent history are noncontributory, and previous development and neurological examination are normal. Children present with prolonged focal status epilepticus and then develop immediate hemiparesis. The diagnosis of HHE should be considered when a persistent hemiplegia is observed after febrile status epilepticus in a child younger than 4 years. Aphasia may also be present acutely in up to one quarter of cases, if the dominant hemisphere is involved.[180]

5.5.3 | Course of illness

The majority of children are left with a permanent motor deficit. However, this deficit may be minimal or resolve within 12 months in 20%.[177] If present, aphasia most commonly resolves within 2 months[180] but may persist.[181] Subsequent focal seizures appear after a variable duration, with 85% having seizure onset within 3 years of the initial status epilepticus.[178] Focal seizures during the chronic phase are typically drug-resistant,[179] but may be amenable to surgical treatment, such as hemispherotomy.[178,182] Many children are also left with variable degrees of intellectual disability.[178]

5.5.4 | Seizures

The first seizure is typically focal clonic febrile status epilepticus. The clonic component may be subtle. There is typically a seizure-free period after the focal status epilepticus that can last months to years. After a variable period, focal motor seizures and/or focal to bilateral tonic–clonic seizures appear, and usually become drug-resistant. Seizures may localize solely to the temporal lobe or may arise from extratemporal regions or be multifocal.[182]

5.5.5 | Electroencephalogram

If an EEG is obtained during the acute focal status epilepticus, the ictal discharge is characterized by rhythmic (2–3 Hz) slow waves that are usually bilateral with higher amplitude over the affected hemisphere (Figure S5A,B).[178] In addition, over the affected hemisphere, recruiting rhythms (10 Hz) are frequently seen.[178] The background activity may be normal at onset, but during the chronic phase, there is excess slowing (often asymmetric) and epileptiform abnormalities, which are most prominent over the affected hemisphere, but may be bilateral.

5.5.6 | Imaging

MRI immediately following the status epilepticus demonstrates diffuse hemispheric signal abnormalities with T2 hyperintensity and restricted diffusion, predominantly of the subcortical white matter of the affected hemisphere.[183] Edema of the affected hemisphere can be severe, leading to mass effect and possible herniation (Figure S5C–F).[178] If magnetic resonance spectroscopy is done, it shows decreased N-acetyl aspartate and mildly increased lactate in the affected hemisphere. On Day 8–15 after status epilepticus, cytotoxic edema decreases, with normalization of apparent diffusion coefficient images and ongoing T2 hyperintensity, with evolving volume loss. Within 1 month, atrophy of the affected cerebral hemisphere is clearly evident. Hippocampal sclerosis is also commonly seen (Figure S5G–J).[182]

5.5.7 | Genetics and other testing

Genetic testing and evaluation for coagulation, metabolic, infective, and immune disorders are typically normal.[178,184]

5.5.8 | Differential diagnosis

Other epilepsy syndromes:

- Dravet syndrome presents in infancy with prolonged hemiclonic seizures in the context of a febrile illness, which may result in transient Todd paresis. However, this deficit resolves, and the typical MRI abnormalities of HHE are not present.
- Sturge–Weber syndrome may present with focal motor status epilepticus, but the skin lesions and MRI showing the typical features of this syndrome should suggest the diagnosis.
- Rasmussen syndrome presents with unilateral focal motor seizures, but the progression is much slower, and focal status epilepticus is seen later in the evolution and is a more persistent feature when it occurs. MRI may be normal at seizure onset or show

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mild insular atrophy but evolves to focal white matter changes and hemispheric atrophy over months to years.
- Focal febrile status epilepticus or focal status epilepticus due to other etiologies can be followed by Todd paresis, which typically resolves within 24 h.

Other conditions:

- Meningitis and encephalitis.
- Hemorrhagic or ischemic stroke.
- Polymerase gamma- or MELAS-related mitochondrial disease.

6 | DISCUSSION

Although not every child with epilepsy can be classified as having a specific epilepsy syndrome, identification of a syndrome can provide guidance on management and prognosis. An electroclinical approach, combining a detailed clinical history and an EEG recording, is needed to reach a syndrome diagnosis. Most of the syndromes described above have a mandatory seizure type or types and often mandatory interictal EEG features. A diagnostic hypothesis is crucial to ensure adequate EEG studies, including both wakefulness and sleep, are recorded to inform syndrome diagnosis. A sleep EEG is required to identify mandatory EEG patterns in some syndromes, such as LGS, DEE-SWAS, and EE-SWAS. Moreover, detailed seizure semiology based on history is adequate to diagnose many seizure types without obtaining an ictal recording. However, for seizure types in certain syndromes, an ictal EEG recording is required for diagnosis. For example, it is not easy to determine a specific seizure type for a "drop attack" based on history alone. Even the use of home video recordings, which are undoubtedly helpful in many cases, cannot always confirm a definitive seizure type. Based on the diagnostic hypothesis, a specific EEG type (sleep-deprived, prolonged video-EEG) may be required to confirm a syndrome diagnosis.

In many but not all cases, syndrome identification informs likely etiology. This allows clinicians to initiate the highest yield investigations to minimize discomfort and invasive investigations for the patient, and to reach a specific diagnosis, in the most cost-effective manner. Specific comorbidities also correlate strongly with specific syndrome, and thus identification of an epilepsy syndrome may assist in their earlier recognition and management. In the context of a specific epilepsy syndrome, the occurrence of comorbidities is of paramount importance, as they may be responsible for a greater burden for the patient than the seizures. Increasingly, precision therapies are being identified that target specific etiologies, and recent clinical trials in epilepsy are targeting specific syndromes.

Whereas some syndromes are highly correlated with specific etiologies, others are associated with a diverse group of etiologies. Despite well-recognized electroclinical epilepsy syndromes, evolution and outcome are often still challenging to predict accurately and often depend upon the underlying etiology. With rapid advances in genetics, immunology, and imaging, it is likely that further etiology-specific syndromes will be identified, and it might be possible to predict which patients will respond best to a specific treatment, or to identify a specific or novel therapy based on the causative genes or pathway responsible for the disorder. Use of therapies that target the underlying neurobiological process that leads to epileptogenesis may significantly ameliorate comorbidities as well as seizures.

Furthermore, it is well recognized that specific ASMs may exacerbate certain conditions, such as sodium channel agents for many of the IGEs. Moreover, some ASMs are more likely to be effective for several seizure types, such as absence seizures and generalized tonic–clonic seizures. Thus, early syndrome identification will allow for selection of the optimal therapy, which is most likely to lead to early seizure control and to prevention of other seizure types that may evolve into a specific syndrome.

Accurate syndrome definition will often inform natural history and likelihood of remission. Some syndromes are self-limited over time. For these, we can provide reassurance to families of the favorable long-term outcome and can also avoid excessively prolonged use of chronic ASMs, and unnecessary diagnostic tests or treatments. Conversely, other syndromes have a much poorer outcome, such as LGS, HHE, or FIRES. In those, we understand from their onset that evolution will be unfavorable, typically with drug-resistant and life-long seizures and adverse neurodevelopmental sequelae. In such cases, a more aggressive treatment approach may be undertaken, with regular review, to attempt to ameliorate overall function and quality of life outcomes. However, it should be acknowledged that treatment options for these syndromes are often limited, the choice of the most appropriate medication is not always clear from studies to date, and polytherapy might increase the risk for adverse events or in some cases, cause seizure aggravation. Many patients with these syndromes might benefit from participation in future clinical trials of novel medications. Some syndromes do not fall clearly into a self-limited epilepsy or DEE, but rather they might have an uncertain evolution: EMA, EEM, EMAtS, and EE-SWAS. Outcome is variable, in terms of both seizure remission and cognitive and

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psychiatric comorbidities. In these latter conditions, there is a spectrum of severity: patients might present with or evolve to intellectual disability ranging from mild to severe, with variable degrees of neurological impairment. Sometimes, even if seizures remit, neurological sequalae persist.

As described above, some syndromes may evolve to another syndrome over time, such as SeLEAS to SeLECTS, and SeLECTS to EE-SWAS. This raises the question of the possible neurobiological links between these syndromes. To date, it is unclear why the majority of children have just one syndrome, whereas others evolve. Such evolution is likely to be due to underlying neurobiological factors. As future research provides insights into the underlying etiology, we may be able to more accurately distinguish the patients who will not show progression from one syndrome to another. Such insights will modify therapeutic approaches from the onset of their epilepsy. Identification of biomarkers may allow intervention to prevent such evolution.

The most significant nosological changes in the childhood syndromes are in the SeLFEs, which were formerly known as "benign" or "idiopathic" focal epilepsies, and DEE-SWAS or EE-SWAS, which was formerly known by the terms LKS, ESES, and epileptic encephalopathy–continuous spike-and-waves during sleep.

The nomenclature "SeLFE" was chosen to reflect the key features of the natural history, and the clinical phenotype. The term "benign" is inappropriate, as many children have associated cognitive and psychiatric comorbidities. For each syndrome, the nomenclature used reflects the major phenotypic features, such as centrotemporal spikes in SeLECTs, autonomic seizures in SeLEAS, occipital semiology and EEG findings in COVE, and photic-induced focal sensory visual seizures and genetic predisposition in POLE. Similarly, the terms DEE-SWAS and EE-SWAS comprise the two essential components, cognitive regression and the characteristic EEG pattern.

We elected to keep the term LGS for several reasons. Most importantly, the term LGS is crucial in allowing patients to acquire the multiple supports including medical and disability support therapies that they require on a daily basis. Replacing this term would lead to a lapse in services that these patients critically require. Additionally, the syndrome comprises multiple seizure type and etiologies, which would be challenging to capture in a succinct name.

Our hope is that using clearer language, with terms directly expressing the seizure semiology that are consistent with the 2017 Epilepsy and Seizure classification, will facilitate both recognition and accurate diagnoses, for health care professionals and families caring for children with epilepsy. The definitions for epilepsy syndromes provided in this paper will require validation in longitudinal studies and may be further refined as new data are published over time. Future work may expand on the definitions of more etiology-specific epilepsy syndromes. This may aid earlier clinical recognition of some etiologies that benefit from prompt targeted treatment.

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CONFLICT OF INTEREST

N.S. has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Eisai, BioMarin, LivaNova, and Sanofi; and has served as an investigator for Zogenix, Marinus, BioMarin, UCB, and Roche. E.C.W. has served as a paid consultant for Encoded Therapeutics and BioMarin. She is the Editor-in-Chief of Epilepsy.com. I.E.S. has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, Chiesi, Encoded Therapeutics, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, BioMarin, and Eisai; has served as an investigator for Zogenix, Zynerba, Ultragenyx, GW Pharma, UCB, Eisai, Anavex Life Sciences, Ovid Therapeutics, Epigenyx, Encoded Therapeutics, and Marinus; and has consulted for Zynerba Pharmaceuticals, Atheneum Partners, Ovid

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Therapeutics, Care Beyond Diagnosis, Epilepsy Consortium, and UCB. R.N. has served as principal investigator in clinical trials for Novartis, Nutricia, Eisai, UCB, GW Pharma, and LivaNova. She received consulting fees from Biogene, BioMarin, GW Pharma, Zogenix, Novartis, Nutricia, Stoke, Ionis, Targeon, and Takeda and honoraria from Nutricia, Biocodex, Zogenix, GW Pharma, Advicennes, and Eisai. She has received unrestricted research grants from Eisai, UCB, LivaNova, and GW Pharma and academic research grants from EJP-RD (horizons 2020) and IDEAL-EPISTOP. S.M.Z. has received research support from Epilepsy Research UK, Tenovus Foundation, Glasgow Children's Hospital Charity, and Scottish Government Technology Enabled Care. He has received honoraria for educational symposia, advisory boards, and consultancy work from GW Pharma, Zogenix, Arvelle Therapeutics, and Encoded Therapeutics. J.M.W. has received paid honorarium for activities as Associate Editor of *Epilepsia*. R.P. is an investigator for studies with UCB and does consultancy work for Kephala, Ireland. She has served as a speaker and/or on advisory boards for Natus, GW, Eisai, and UCB. E.H. has received honoraria from UCB, Eisai, LivaNova, Novartis, and GW Pharmaceuticals. S.W. has received unrestricted educational grants from UCB Pharma, Eisai, and Sunovion. H.J.C. has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo, and Marinius. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. Her research is supported by the NIHR Biomedical Research Centre at Great Ormond Street Hospital. She holds an endowed chair at UCL Great Ormond Street Institute of Child Health; she holds grants from NIHR, EPSRC, GOSH Charity, ERUK, and the Waterloo Foundation. P.T. received speaker's or consultancy fees from Arvelle, Eisai, GW Pharma, LivaNova, UCB Pharma, Xenon Pharma, and Zogenix. S.A. has served as consultant or received honoraria for lectures from Biocodex, Biomarin, Eisai, GW Pharma, Neuraxpharm, Nutricia, UCB Pharma, Xenon, and Zogenix. He has been an investigator for clinical trials for Eisai, UCB Pharma, and Zogenix. He is an Associate Editor for *Epilepsia*. K.R. has received speaker honoraria, advisory board payments, and/or research funding from UCB, Eisai, Novartis, Zogenix, SK Lifesciences, AFT Pharmaceuticals, LivaNova, Queensland Genomic Health Alliance, Department of Health (Australia), Medicure International, Novartis, and Janssen-Cilag. S.L.M. serves as an Associate Editor of *Neurobiology of Disease*. He is on the editorial board of *Brain and Development*, *Pediatric Neurology*, *Annals of Neurology*, *MedLink*, and *Physiological Research*. He receives compensation from Elsevier for his work as Associate Editor of *Neurobiology of Disease* and from *MedLink* for his work as Associate Editor; and royalties from two books he coedited. E.P. has received speaker and/or consultancy fees from Angelini, Arvelle, Biogen, Biopas, Eisai, GW Pharma, Sanofi, SK Life Science, Takeda, UCB Pharma, Xenon Pharma, and Zogenix, and royalties from Wiley, Elsevier, and Wolters Kluwer. None of the other authors has any conflict of interest to disclose. 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.

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