FULL-LENGTH ORIGINAL RESEARCH

Lennox-Gastaut syndrome of unknown cause: Phenotypic characteristics of patients in the Epilepsy Phenome/Genome Project

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Summary

Purpose: **Lennox-Gastaut syndrome (LGS) is a devastating childhood-onset epilepsy syndrome. The cause is unknown in 25% of cases. Little has been described about the specific clinical or electroencephalography (EEG) features of LGS of unknown or genetic cause (LGS_u). The Epilepsy Phenome/Genome Project (EPGP) aims to characterize LGS_u by phenotypic analysis of patients with LGS_u and their parents.**

Methods: **One hundred thirty-five patients with LGS with no known etiology and their parents were enrolled from 19 EPGP centers in the United States and Australia. Clinical data from medical records, standardized questionnaires, imaging, and EEG were collected with use of online informatics systems developed for EPGP.**

Key Findings: **LGS_u in the EPGP cohort had a broad range of onset of epilepsy from 1 to 13 years, was male predominant ($p < 0.0002$), and was associated with normal development prior to seizure onset in 59.2% of patients. Despite the diagnosis, almost half of the adult patients with LGS_u completed secondary school. Parents were cognitively normal. All subjects had EEG recordings with generalized epileptiform abnormalities with a spike wave frequency range of 1–5 Hz (median 2 Hz), whereas 8.1% of subjects had EEG studies with a normal posterior dominant rhythm. Almost 12% of patients evolved from West syndrome.**

Significance: **LGS_u has distinctive characteristics including a broad age range of onset, male predominance, and often normal development prior to the onset of seizures. Cognitive achievements such as completion of secondary school were possible in half of adult patients. Our phenotypic description of LGS_u coupled with future genetic studies will advance our understanding of this epilepsy syndrome.**

KEY WORDS: **Lennox-Gastaut, Unknown, Slow spike wave, Phenotype, Epilepsy, Epilepsy Phenome/Genome Project.**

"In children with primary LGS, … the tragedy of a vicious seizure disorder or an "epileptic encephalopathy" gradually impairing a hitherto healthy brain, ought to be averted with great insight into genetic factors…" (Niedermeyer, 1986).

Lennox-Gastaut syndrome (LGS) is a severe childhood-onset epilepsy associated with multiple seizure types, characteristic electroencephalography (EEG) abnormalities, and developmental delay, originally described by Lennox in 1949 (Lennox & Davis, 1949; Lennox, 1960) and in the largest series of 100 patients by Gastaut in 1966 (Gastaut et al., 1966). The term Lennox-Gastaut syndrome was introduced

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in 1969 (Niedermeyer, 1969). Although precise definitions of LGS vary, most authors agree on childhood-onset refractory generalized epilepsy with multiple seizure types and either slow spike wave or generalized paroxysmal fast activity on EEG (Arzimanoglou et al., 2009). Given the clinical heterogeneity among cases, multiple pathophysiologic pathways or genetic factors likely exist that when elucidated will define the syndrome in more specific terms. Although rare, with a prevalence of 0.26 per 1,000 at 10 years (Trevathan et al., 1997), the disorder is associated with immense physical, emotional, and social consequences. LGS may evolve from West syndrome/infantile spasms (IS) in up to 20–30% of cases (Genton et al., 2000; Crumrine, 2002; Arzimanoglou, 2009). The pathogenesis of LGS is poorly understood, but it may involve a genetic influence on development of the immature nervous system, particularly during thalamocortical development, leading to structural or functional brain pathology (Blume, 2001; Markand, 2003). Approximately 25% of cases (previously referred to as cryptogenic) have an unknown cause, with underlying genetic factors suspected but as yet unconfirmed.

Few studies have separated cases of LGS of unknown cause (LGS_u) from cases with known structural or metabolic etiologies (LGS_s). Published series suggest that LGS_u has clinical characteristics distinct from LGS_s, including normal development or mild delay prior to the development of seizures, a later age of onset, a nonlocalizing neurologic examination, normal brain magnetic resonance imaging (MRI), and the absence of dysmorphic features. LGS_u was less likely than LGS_s to evolve from infantile spasms. Ten percent to 20% of patients with LGS have normal cognition, particularly if onset is later in the second decade or in cases of unknown etiology (Niedermeyer, 1986; Goldsmith et al., 2000). Outcome was better in cases of unknown cause, with a later age of onset, and in those with a normal examination (Oguni et al., 1996; Goldsmith et al., 2000).

Other LGS variants are reported, such as a "myoclonic variant" with a less severe phenotype, nocturnal only seizures, and unknown etiology (Chevrie & Aicardi, 1972). A higher rate of family history of seizures than the general population is reported in LGS_u (Boniver et al., 1987).

Systematic definition of the clinical phenotype of LGS_u is critical to expand our knowledge of this distinctive subgroup of LGS and to correlate with genetic studies. Availability of high quality phenotypic data in sufficient quantity has been the major limiting factor in phenome–genome association studies. To address this, the Epilepsy Phenome/Genome Project (EPGP) was formed as a multicenter collaborative effort of 27 epilepsy centers in the United States, Australia, New Zealand, and Argentina, funded by the National Institute of Neurological Disorders and Stroke (NINDS), to collect detailed phenotypic and genetic data on a large number of patients with epilepsy, including LGS_u (The EPGP Collaborative, 2013). The main hypothesis for the LGS_u component of the study is that de novo mutations are important causes for these patients, given that LGS does not show transgenerational transmission and most families do not have sibling recurrence. By collecting comprehensive phenotypic data on these subjects we will be well-positioned to understand the consequences of the mutations identified in a future genomic analysis.

Methods

Participants were identified primarily through the EPGP Clinical Centers by prospective screening of clinic patients, retrospective medical record reviews, and ongoing education of colleagues within the institution and from neighboring hospitals and practices. There was also an EPGP National Recruitment Campaign to recruit eligible families outside of the Clinical Centers through community advocacy groups, the Internet, news articles, advertising, and other forms of communication with patients and healthcare professionals (The EPGP Collaborative, 2013).

Detailed standardized phenotypic data were available from 135 patients with LGS_u, and their parents recruited from 19 centers in the United States and Australia (sites are listed in the Table S1). The local institutional review board approved the study at each center. All subjects were enrolled after eligibility criteria were confirmed and they (or their parents) provided written informed consent/assent.

Patients underwent a detailed, structured review of their history and records to define characteristics of their seizure history, seizure types, and additional medical conditions. A diagnostic interview was completed for 50 early patients, and was subsequently discontinued as sufficient data became available from medical record review. Clinical data were anonymized and entered into a secure centralized online database (Nesbitt et al., 2012). A final diagnosis form was completed by the local site principal investigator based on all collected information. A subset of cases was reviewed independently by two members of a Data Review Core to ensure data quality and consistency. A representative EEG was reviewed by a site investigator and an EEG Core member to assess data quality and EEG inclusion criteria. EEG findings accepted for inclusion were then reviewed and scored by two EEG Core members for specific EEG phenotypic features. The EEG source data included digital EEG files, scanned pages from paper EEG samples, EEG reports, or clinical notes describing EEG. Disagreements were resolved by consensus conference among two or more EEG Core members before the EEG data set was finalized. Some subjects had more than one EEG study, and such supplemental EEG findings were reviewed and scored in similar fashion. Brain MRI were reviewed by local investigators and an MRI Core member to exclude a structural lesion. All patients and their parents contributed blood samples that were processed for DNA

extraction and creation of immortalized cell lines, and stored at the NINDS Repository at the Coriell Institute for Clinical Research, Camden, NJ.

Inclusion/exclusion criteria

Inclusion and exclusion criteria for LGS_u are detailed in Table 1. EEG criteria included EEG background slowing or disorganization of the EEG background for age, and generalized spike and wave activity of any frequency or generalized paroxysmal fast activity (GPFA). Our protocol required that subjects with a clinical diagnosis of LGS but whose available EEG did not meet our EEG criteria for LGS, would be referred to the EPGP Phenome Core for further review. However, this scenario did not occur with any patient in our group. Background slowing was defined as <8 Hz posterior dominant rhythm in patients older than 3 years of age and <5 Hz in patients older than 2 years of age. EEG studies with normal backgrounds were accepted if the generalized spike and wave activity was 2.5 Hz or less or if GPFA was present. Generalized epileptiform abnormalities could be interictal or ictal. The MRI studies were normal or showed only mild diffuse atrophy.

Table 1. Inclusion and exclusion criteria for the LGSu arm of EPGP

Inclusion criteria
Generalized epilepsy with multiple seizure types
EEG background slowing or disorganization (normal background accepted if SWS <2.5 Hz or GPFA present)
Generalized spike and wave or generalized paroxysmal fast activity
Normal MRI (or mild diffuse atrophy)
Parental control with no history of epilepsy (febrile or provoked seizures allowed)
Adequate records
Exclusion criteria
Known genetic syndrome (known balanced translocations and small interstitial or telomeric deletions/duplications were included)
TORCH infection
Metabolic disease
Premature birth before 32 weeks
Structural MRI lesion
Hypoxic–ischemic encephalopathy
Meningitis/encephalitis
Stroke/intracerebral hemorrhage
Microcephaly <2.5 standard deviations from normal
Significant head trauma
Autism
Moderate to severe developmental delay prior to onset of seizures

EEG, electroencephalography; SWS, slow spike wave; GPFA, generalized paroxysmal fast activity.

Table 2. Morphology of epileptiform discharges in LGSu in 71 patients with available digital EEG

Single spike and wave – 39 (54.9%)
1 hertz – 13
2 hertz – 21
3 hertz – 2
4 hertz – 2
5 hertz – 1
Polyspike spike and wave – 16 (22.5%)
1 hertz – 3
2 hertz – 11
3 hertz – 2
GPFA – 9 (12.6%)
12 hertz – 1
13 hertz – 2
18 hertz – 2
20 hertz – 3
25 hertz – 1
Other – 7 (9.8%)

Patients with autism spectrum disorder (ASD) or moderate to severe developmental delay prior to the onset of seizures were excluded. Severe delay prior to seizure onset was defined by ≥50% delay in any area: motor, social, language, cognition, or activities of living; or global delay. Mild delay was defined as isolated delay of <50% of expected milestones in one area, or <30% of milestones across more than one area, which can result in normal development as a later time point. Details regarding developmental delay were obtained from parents through an eligibility interview and by local investigators from records via a standardized medical abstraction form. Borderline cases were adjudicated by the EPGP Phenome Core.

Patients with a history of epilepsy in either biologic parent were intentionally excluded to maximize the chance of finding de novo mutations in patients with LGS_u. Hence the study was not designed to identify pathogenic mechanisms in LGS with ASD or familial LGS.

Data were analyzed using the SAS or JMP programs (SAS Institute, Inc., Cary, NC, U.S.A.). Descriptive statistics were calculated for demographic, family history, and clinical data. Data are presented as means, standard deviations, and ranges for continuous variables, and frequencies and percents for categorical variables.

Results

Demographics

One hundred thirty-five patients were included in the analysis. The median age at enrollment was 14 years (range 2–51 years). Sixty-six percent of patients were male and 34% were female ($p < 0.0002$, compared with 50% expected). One hundred four (77%) patients were of white/Caucasian ethnicity, 10 (7.4%) were Hispanic, two were Asian, four were African American, and one was Native American/Alaskan. Fourteen patients were of mixed race with white/Caucasian along with Native American (8), African American (3), Asian (2), and Hawaiian (1). One hundred twenty-three patients (91%) were born in the United States. Eight patients from the Melbourne site were born in Australia. One patient each was born in Colombia, Canada,

Germany, and the United Kingdom. Of patients who were 18 years or older (n = 50), 21 were secondary school graduates (42%) and 2 (4%) had completed some college but did not graduate. This group had no developmental delay prior to seizure onset, and no reliance on special education was reported by parents. Twenty patients (40%) did not complete high school. In 13 (65%) of this group, mild developmental delay was documented prior to seizure onset, and special education was reported by parents. In seven patients, details of schooling were unknown or not asked.

Proband clinical characteristics

The median age at first seizure was 1 year (range <1–13 years). Most patients were diagnosed with LGS_u within a year of seizure onset (93%). Based on medical record review, 33 patients (24.4%) had mild developmental delay before onset of seizures, whereas 80 (59.2%) had normal development. Based on interviews of parents, mild developmental delay or a learning disability was present in one third of patients before onset of seizures. In 22 patients (16.2%), it was unclear from available records if developmental delay was present before seizure onset. Febrile seizures occurred in 12.5% (17) of cases. Four of these patients had more than one febrile seizure and five had complex febrile seizures (one with focal features and four with duration longer than 15 min). An abnormal neurologic examination within 3 months of the first seizure was observed in 12.5% (17) of cases, including findings such as hypotonia or increased tone.

Although records of older patients were often difficult to obtain, we tried to identify whether a genetic or metabolic workup had been completed and excluded those with positive results. A genetics consult was obtained in 32 patients (23.7%) and a metabolic evaluation was conducted in 39 (28.8%), and no abnormalities were identified. A normal chromosome analysis was documented for 37 probands (27.4%).

Parental background

The average age of the parents at the time of birth of the child who developed LGS_u was 31 years, with standard deviation of 5 years (maternal average 30 years, paternal average 32 years). Nine of the parents (3.3%) had febrile seizures as infants, most with single seizures, with two parents having two febrile seizures and one with 10. Six (2.2%) had single afebrile toxic/metabolic seizures in their lifetime. No parent had epilepsy, as dictated by inclusion/exclusion criteria. None of the parents had ever been treated with an antiseizure medication.

Forty-three parents from 41 different families had a family history of epilepsy, of which 11 (10 families, 7.4%) had a family history in a first-degree relative. Three probands had siblings with epilepsy (2.2%). Most parents were born in the United States (83.1%) and 80.1% were of white ethnicity. Other ethnicities were similar to those reported of the probands. Most parents had college education (some college 26.9%, completed college 29.5%, and 15.7% graduate school), and 17.9% completed secondary school. Only 5.6% had less than a high school education. 82.3% of the parents were right handed, 10.5% left handed, and 7.1% ambidextrous.

Clinical seizure types

The most common seizure types were absence (80%), atonic (65.1%), generalized tonic–clonic (60%), and tonic seizures (55.5%). Other seizure types included myoclonic seizures (55.5%), complex partial seizures (17%), and unclassifiable nonconvulsive seizures (6.6%); 21.4% had a history of infantile spasms. Reflex seizures were seen in seven patients (two with photoconvulsive seizures, and five with startle, touch, or sound-sensitive seizures). Only three patients had reported auras, including psychic, autonomic, somatosensory, sensory, or visual types.

EEG

One hundred sixty-eight inclusion and supplemental EEG or EEG reports were analyzed for the 135 patients with LGS_u. The mean posterior dominant rhythm (PDR) was 6.7 Hz (standard deviation [SD] 2.2). Eleven subjects (8.1%) had an age-appropriate PDR. Eighty (59.2%) had a slow PDR for age or disorganized background. Nine patients had absence of a PDR and no underlying EEG background organization (6.6%). For 35 patients (25.9%) there was insufficient information on waking EEG background. Generalized epileptiform abnormalities were seen in 100% of patients, as dictated by inclusion/exclusion criteria. Focal sharp waves were seen in 67 (49.6%) and focal slowing in 20 patients (15.2%).

Specific EEG phenotypic features could be assessed from digital EEG data from 71 patients (Table 2). Generalized single spike and wave complexes were seen in 39 (54.9%) with a frequency range of 1–5 Hz (median 2 Hz). Generalized polyspike and wave complexes were seen in 16 (22.5%) with a frequency range of 1–3 Hz (median 2 Hz). Seven patients had spike wave frequencies on available EEG ≥3 Hz. GPFA was seen in 9 (12.6%) with frequencies between 11 and 25 Hz (median 17).

Diagnosis and evolution

A final International League Against Epilepsy (ILAE) diagnostic code was applied to each patient based on clinical, EEG, and MRI data. A second code could be applied if one syndrome evolved into another at a later age. Sixteen patients (11.8%) had West syndrome (2210, 2211, or 2212), which evolved to LGS_u by a median age of 2 years (range 0–9). Two patients had a generalized epilepsy syndrome that evolved into LGS_u. Some patients' epilepsy evolved from LGS_u to another ILAE syndrome; two evolved to focal epilepsy, and two to epileptic spasms.

Discussion

We present the phenotypic characteristics of the largest series of LGS_u published to date. There is little insight into the pathogenesis and genetic origin of LGS_u (Blume, 2001). The need for improved disease-specific understanding is crucial to alleviate this devastating childhood epilepsy, as seizures are invariably refractory to treatment (Ferrie & Patel, 2009; Hancock & Cross, 2013).

We found a 2:1 male preponderance in our group of LGS_u, which has been previously observed in some mixed LGS_s and LGS_u series but not confirmed (Beaumonoir, 1982). Although not a population-based sample, LGS_u could be added to other early life neurologic disorders with male preponderance affecting brain development including autism, Attention Deficit/Hyperactivity Disorder (ADHD), dyslexia, and Tourette syndrome. This suggests that the vulnerability of the male brain extends to epilepsy in early life and may reflect a greater susceptibility of the male brain, possibly due to the initial early life pulse exposure to testosterone (Baron-Cohen et al., 2011). Alternatively, it may suggest mutations involving genes on the X chromosome.

Developmental delay has been a traditional hallmark of LGS. However, experience from some cohorts has suggested that development may be normal prior to seizure onset in LGS_u (Beaumonoir, 1982). In our group, 59% of patients had normal development prior to the onset of seizures, although this result was biased by the exclusion of patients with more severe delay. Development in patients with LGS_u invariably declines over time with continuing seizures (Niedermeyer, 1986; Crumrine, 2002; Markand, 2003). Despite this, in our group, 46% of adult patients were high school graduates. Inclusive education programs in EPGP countries to promote school completion may partly explain these figures. In addition, we recognize that enrollment bias exists that could have selected patients with higher cognitive function. What determines eventual cognitive outcome is unclear, and it is unproven whether interventions such as early and aggressive seizure control can improve outcomes compared to high mental retardation rates reported in older series of undifferentiated LGS.

No prior study has evaluated parental characteristics for probands with LGS. The majority of parents in our group were cognitively normal, and had attained some college education. The average parental age was 31 years, and was similar in other EPGP arms with parental controls. The average maternal age at birth in the United States is 27.4 years (Martin et al., 2007). The higher parental age and level of education in our cohort likely reflects the sociodemographic and educational background of the enrolled parents rather than the general population. Prevalence of a history of febrile seizures in the parents was similar to that expected based on population frequencies (Sillanpaa et al., 2008). The proportion of parents with a family history of epilepsy in first-degree relatives (7.4%) was also consistent with population rates. (Assuming four first-degree relatives at risk in each family and a lifetime risk of 2% in each relative, the probability ≥1 relative was affected is $[1-(1-0.02)^4] = 7.8\%$). These findings are consistent with an effect of de novo mutations on risk for LGS_u, in patients selected on the basis of the absence of a parental history of epilepsy. This was the original hypothesis that led to the design of this component of EPGP, and which will be tested through the genetic analysis planned through the Epi4K Center without Walls (Epi4K, 2012).

LGS patients typically have tonic or atypical absence seizures, but these seizure types were not always present in our subjects. The incidence of tonic seizures among our subjects (55.5%) is less than Gastaut's original estimate in mixed LGS of 70% (Niedermeyer, 1986). This may be explained by the delayed appearance of some seizure types, or by the variable documentation by sleep or video-EEG recordings available to EPGP investigators. In addition, clinical features in LGS are often variable, with the EEG being more consistent (Camfield, 2011). Despite the conventional association between LGS and tonic seizures, tonic seizures are not a requirement in the 1989 ILAE criteria for LGS, and not in expert reviews (Aicardi, 1996). Myoclonic seizures or other subtle seizure types (such as brief upgaze and alterations in respiration) may be confused with brief tonic seizures. Generalized tonic–clonic seizures were common (60%), in contrast to Gastaut's incidence of 15%. It remains to be seen whether seizure types or clusters of seizure types correlate phenotypically with specific genetic findings, such as is likely with the "myoclonic" and "occipital" variants of LGS.

The classic EEG finding in LGS is the interictal slow spike and wave pattern first described in 1939 (Gibbs et al., 1939). The interictal slow spike and wave pattern is typically 2 or 2.5 Hz in frequency (slower than the 3 Hz spike and wave pattern seen in Genetic [formerly termed "Idiopathic"] Generalized Epilepsy). In this cohort, although the median spike and wave frequency was 2 Hz, it varied between 1 and 5 Hz. Such variations including combinations of slow spike wave, a faster irregular spike wave, and GPFA within the clinical spectrum of LGS have been described in the literature (Markand, 1977; Aicardi, 1996).

Although smaller series suggest that LGS_u does not evolve from IS, several of our patients did evolve from West syndrome, although at a lower rate (11.8%) than that reported for structural/metabolic cases (20–30%) by other investigators (Genton et al., 2000; Arzimanoglou et al., 2009). The biologic basis and genetics of this phenomenon remain to be elucidated; further study of the EPGP cohort dedicated to infantile spasms may be revealing.

We acknowledge the potential selection bias introduced into our sample by the selection criteria. The goal of the LGS arm of EPGP was to exclude participants with structural/metabolic or known genetic causes to ensure the best

possible genetic cohort for the analysis of de novo mutations. The exclusion of parents with epilepsy also aided our search for these genes, but undoubtedly excluded certain genotypes and phenotypes. In addition, the need for complete phenotypic information and blood from both parents could have selected against patients from lower socioeconomic and racial groups who are limited by access to care and other sociodemographic factors.

The standardized phenotypic analysis of this large cohort of patients with LGS_u across several centers and countries demonstrates a spectrum of clinical, EEG, and developmental characteristics that will define the syndrome of LGS of unknown cause to a greater level. It is notable that this data should provide valuable clinical insight into the mutations or variants identified during the whole exome screening underway in Epi4K (Epi4K, 2012), thereby furthering our understanding of the disease.

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Disclosure

None of the 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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Appendix I:

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Distribution of patients among 19 clinical sites.