Research Article

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Journal of Neurology and Neuroscience
ISSN 2171-6625

2021
Vol.12 No. 10:9377

Sex Differences in Lennox-Gastaut Syndrome: Electroclinical Correlations

Ali A. Asadi-Pooya[1,2], **Mohsen Farazdaghi**[1*]

[1]Epilepsy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA

[*]**Correspondence to:** Mohsen Farazdaghi, Epilepsy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran, Tel: 989177125316; E-mail: m_farazdaghi@yahoo.com

Received: August 03, 2021; Accepted: October 13, 2021; Published: October 18, 2021

Citation: Farazdaghi M (2021) Sex Differences in Lennox-Gastaut Syndrome: Electroclinical Correlations. J Neurol Neurosci Vol: 12 No: 10

Abstract

Objectives: The aim of the current study was to investigate the sex and its associated factors in a large cohort of patients with Lennox-Gastaut syndrome (LGS). We hypothesized that sex has significant associations with the electroclinical characteristics of patients with LGS. This was a retrospective cross-sectional chart review study.

Methods: All patients with an electroclinical diagnosis of LGS were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran. The data were collected from 2008 through 2020.

Results: Three hundred patients (8%) were diagnosed as having LGS. One hundred and eighty-four patients (61%) were males and 116 were females (39%) (sex ratio of male to female: 1.59). Generalized paroxysmal fast activity (GPFA) in EEG was less often observed in female patients (OR= 0.58).

Conclusion: With regards to the etiology, there were no significant differences between males and females. Males outnumber females in LGS. Sex dependent genetic disorders may explain this observation. Electro-clinically, males and females with LGS have largely similar presentations. However, male patients more often have GPFA in their EEGs. This subtle electrical sex difference in patients with LGS should be studied in future investigations.

Keywords: Electroencephalogram; Epilepsy; Lennox-Gastaut; Seizure; Sex

Introduction

Sex differences in clinical characteristics of neurological conditions exist and these may be explained by the actions of sex hormones and also by sex chromosome genes-related brain differences [1, 2]. Evidence from both human and animal studies supports the role of sex on seizures and epilepsy syndromes [3]. Lennox-Gastaut syndrome (LGS) is the prototype of symptomatic (structural-metabolic-genetic) generalized epilepsies. Males often outnumber females in LGS [4, 5]. However, sex differences in clinical characteristics of LGS have never been specifically studied before.

Lennox-Gastaut syndrome is an epileptic encephalopathy characterized by a triad of multiple seizure types, a specific interictal electroencephalographic (EEG) pattern [i.e., generalized slow spike-wave (SSW) complexes and/or generalized paroxysmal fast activity (GPFA)], and intellectual/developmental disability [6, 7]. However, there are reports on patients with LGS and without intellectual/developmental disability [6]. Prevalence of LGS is estimated to be 1 to 2% of all patients with epilepsy and 1 to 10% of all childhood epilepsies [4, 5, 8]. The aim of the current study was to investigate the sex and its associated factors in a large cohort of patients with LGS. We hypothesized that sex has significant associations with the electroclinical characteristics of patients with LGS.

Methods

This was a retrospective cross-sectional chart review study. All patients with an electroclinical diagnosis of LGS were recruited at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran, from 2008 until 2020. The inclusion criteria were: multiple seizure types (i.e., tonic, atonic, and atypical absence seizures, among others), EEG pattern showing either bursts of SSW complexes or GPFA (or both), with or without intellectual/developmental disability (at the first visit) [9]. There were no exclusion criteria. This is the only epilepsy clinic in south Iran. The data were collected from 2008 through 2020. Electroencephalography was requested for all patients and the most informative EEG findings (at the first visit or during the course of follow-up) were considered for the purpose of this study. Brain imaging study [magnetic resonance imaging (MRI)] was performed, when possible. Brain MRI requires general anesthesia in these patients and therefore, has risks and additional costs; as a result, some families hesitate to perform the procedure for their children. Other tests (e.g., blood tests, metabolic tests, etc.) were requested based upon the clinical judgment. Genetic/metabolic tests are not widely available and are very expensive in Iran; they were requested exceptionally. Intellectual/developmental disability was defined as severe impairment in areas of functioning/development that affects learning, self-sufficiency, and adaptive skills (based on gross clinical judgement) [10].

Age, sex, age at seizure onset, seizure type(s) (at the first visit or during the course of follow-up), epilepsy risk factors [including history of pregnancy complications (e.g., hypoxia,

neonatal admission, etc.), positive family history of epilepsy, and parental consanguinity], EEG and imaging findings of all patients were registered routinely. Values were presented as mean ± standard deviation (SD) for continuous variables and as number (percent) of subjects for categorical variables. Pearson Chi-Square, Fisher's exact test, and t-test were used for univariate comparisons. The associations between clinical and EEG characteristics and sex were determined using the logistic regression analysis; the variables with $p < 0.2$ from comparison of the electroclinical characteristics in univariate analyses were entered into the model. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.

Standard Protocol Approvals, Registrations, and Patient Consents

The Shiraz University of Medical Sciences Institutional Review Board approved this study.

Data Availability Statement

The data is confidential and will not be shared as per the regulations of Shiraz University of Medical Sciences.

Results

During the study period, 3737 patients were registered at our epilepsy clinic. Three hundred patients (8%) were diagnosed as having LGS. Age at onset (mean ± standard deviation) was 3.3 ± 4.1 years. One hundred and eighty-four patients (61%) were males and 116 were females (39%) (sex ratio of male to female: 1.59). (Table 1) shows the clinical characteristics of the patients with LGS according to their sex in univariate analyses. Variables with a p value < 0.2 included: family history of epilepsy and tonic seizures (both were more common among male patients). (Table 2) shows the EEG characteristics of the patients with LGS according to their sex in univariate analyses. Variables with a p value < 0.2 included: abnormal background, GPFA, and multifocal spikes (all were more common among male patients).

We included all the variables with a p value < 0.2 in regression analysis. The results of the binary logistic regression analysis are shown in (Table 3). The model that was generated by this test was significant (p = 0.01). Generalized paroxysmal fast activity in EEG was less often observed in female patients (OR= 0.58).

Table1: Clinical characteristics of the patients with Lennox-Gastaut Syndrome according to their sex in univariate analyses.

	Males, N= 184 (%)	Females, N= 116 (%)	P value
Age at onset (mean ± standard deviation), years	3.2 ± 4.2	3.5 ± 3.9	0.58
Developmental disability	159 (86%)	105 (91%)	0.36
Family history of epilepsy	143 (78%)	80 (69%)	0.09
Parental consanguinity	106 (58%)	66 (57%)	0.90
Number of seizure types	2.47 ± 0.60	2.54 ± 0.62	0.30
Tonic seizures	124 (67%)	65 (56%)	0.05
Atonic seizures	31 (17%)	23 (20%)	0.53
Myoclonic seizures	79 (43%)	52 (45%)	0.81
Tonic-clonic seizures	99 (54%)	71 (61%)	0.23
Atypical absence seizures	53 (29%)	36 (31%)	0.69

Table2: Electroencephalographic characteristics of the patients with Lennox-Gastaut Syndrome according to their sex in univariate analyses.

	Males, N= 184 (%)	**Females, N= 116 (%)**	**P value**
Abnormal (slow) background	177 (96%)	107 (92%)	0.18
Slow spike-waves	163 (89%)	108 (93%)	0.23
Generalized paroxysmal fast activity	111 (60%)	50 (43%)	0.004
Multifocal spikes	33 (18%)	19 (16%)	0.19
Polyspikes	62 (34%)	39 (34%)	1.00

Table3: Associations between electroclinical characteristics and sex (female) in patients with Lennox-Gastuat syndrome*.

	Odds ratio	**95% confidence Interval**	**P value***
Family history of epilepsy	0.63	0.37-1.08	0.09
Tonic seizures	0.73	0.44-1.21	0.22
Abnormal EEG background	0.59	0.20-1.68	0.32
Generalized paroxysmal fast activity	0.58	0.35-0.96	0.03
Multifocal spikes	0.71	0.35-1.42	0.33

With regards to the etiology, there were no significant differences between males and females (Table 4). However, since identification of the etiology was the major weakness of our study, we will not elaborate on this.

Table4: Etiology of Lennox-Gastaut Syndrome according to the sex of patients.

	Males, N= 184(%)	Females, N= 116 (%)	P value
Hypoxic-ischemic encephalopathy in brain MRI	18 (10%)	10 (9%)	0.73

Developmental anomaly (agenesis of corpus callosom, polymicrogyria, lissencephaly, cortical dysplasia, etc.)	15 (8%)	10 (9%)	0.88
Tuberous sclerosis complex (TSC)	3 (2%)	0	-
Others (leukodystrophy, white matter disease, dysembryoplastic neuroepithelial tumor)	10 (5%)	8 (7%)	0.60
Brain atrophy	32 (17%)	14 (12%)	0.21
Normal Brain MRI	72 (39%)	50 (43%)	0.49
No imaging	34 (18%)	24 (21%)	-
Meningitis/ Encephalitis (Documented) (1 Hypoxic-ischemic MRI, 1 normal MRI, 3 atrophy, 3 without MRI)	7 (4%)	1 (1%)	-
Metabolic disorders [2 Fatty acid oxidation disorders (1 normal MRI, 1 Hypoxic-ischemic MRI), 1 Hyperammonemia (had vermis hypoplasia; probably a FBXL4 variant)]	2 (1%)	1 (1%)	-
Genetic disorders	0	1 (1%) (NALCN gene, no MRI)	-
Neonatal complications* (Documented)	47 (26%)	26 (22%)	0.53

* neonatal complications (Hypoxia, sepsis, hypoglycemia, hyperbilirubinemia, and hypothermia; all with hospital admissions).

Discussion

In this large study of patients with LGS, we observed that males outnumbered females (male to female ratio of 1.59). This is consistent with previous studies from other populations. Male preponderance is also reported in some other catastrophic childhood epilepsy syndromes such as Ohtahara syndrome, West syndrome, Dravet syndrome, and Landau-Kleffner syndrome. Sex dependent genetic disorders may explain some of the sex differences in LGS and other symptomatic (structural-metabolic-genetic) generalized epilepsies.

In the current study, we observed that most patients did not have identifiable etiologies (despite the shortcomings in their evaluations). Many of these patients probably suffer from genetic etiologies. Based on previous studies, the etiology of LGS is divided into two groups: identifiable (genetic-structural-metabolic) or unknown. The LGS of unknown etiology group (i.e., no apparent cause) accounts for approximately 25% to 35% of patients . However, the attribution of unknown is largely dependent on the sophistication of the investigations . In one previous study, 70% of the adult patients with LGS had unknown cause (were cryptogenic). When LGS has no apparent etiology, a genetic predisposition or etiology is likely. This probability increases the likelihood of sex dependent genetic differences in LGS. In a recent study, an X-linked variant of IQSEC2 was associated with LGS. Christianson syndrome is an X-linked intellectual disorder caused by mutations in the SLC9A6 gene; the affected patients may have LGS. However, LGS-related genes are largely unknown.

Electro-clinically, males and females with LGS have largely similar presentations. However, in this study we observed that male patients more often had GPFA in their EEGs. Lennox-Gastaut syndrome may be considered as “secondary network epilepsy”. In one fMRI-EEG study, in six patients with LGS, GPFA events showed almost uniform increases in blood oxygen level-dependent (BOLD) signal in “association” cortical areas, brainstem, basal ganglia, and thalamus. The authors concluded that GPFA is associated with activity in a diffuse network. Why males with LGS more often have GPFA in their EEGs is yet to be studied and explained.

Limitations

This was a clinic-based series and may not represent the full spectrum of patients with LGS; the mildest disease forms may not be referred to a busy university clinic and therefore, the possibility of selection bias exists. In addition, we did not have access to the imaging studies in some and to genetic and metabolic studies in most patients to identify the etiology of their condition. Finally, this was a retrospective chart-based review with all the associated limitations.

Conclusion

Males outnumber females in LGS. Sex dependent genetic disorders may explain this observation. Electro-clinically, males and females with LGS have largely similar presentations. However, male patients more often have GPFA in their EEGs. This subtle electrical sex difference in patients with LGS should be studied in future investigations.

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