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Sex differences in seizure types and symptoms

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ABSTRACT

Background: Despite the increasing interest in sex differences in disease manifestations and responses to treatment, very few data are available on sex differences in seizure types and semiology. The Epilepsy Phenome/Genome Project (EPGP) is a large-scale, multi-institutional, collaborative study that aims to create a comprehensive repository of detailed clinical information and DNA samples from a large cohort of people with epilepsy. We used this well-characterized cohort to explore differences in seizure types as well as focal seizure symptoms between males and females.

Methods: We reviewed the EPGP database and identified individuals with generalized epilepsy of unknown etiology (GE) (n = 760; female: 446, male: 314), nonacquired focal epilepsy (NAFE) (n = 476; female: 245, male: 231), or both (n = 64; female: 33, male: 31). Demographic data along with characterization of seizure type and focal seizure semiologies were examined.

Results: In GE, males reported atonic seizures more frequently than females (6.5% vs. 1.7%; $p < 0.001$). No differences were observed in other generalized seizure types. In NAFE, no sex differences were seen for seizure types with or without alteration of consciousness or progression to secondary generalization. Autonomic (16.4% vs. 26.6%; $p = 0.005$), psychic (26.7% vs. 40.3%; $p = 0.001$), and visual (10.3% vs. 19.9%; $p = 0.002$) symptoms were more frequently reported in females than males. Specifically, of psychic symptoms, more females than males endorsed déjà vu ($p = 0.001$) but not forced thoughts, derealization/depersonalization, jamais vu, or fear. With corrections for multiple comparisons, there were no significant differences in aphasic, motor, somatosensory, gustatory, olfactory, auditory, vertiginous, or ictal headache symptoms between sexes.

Conclusions: Significant differences between the sexes were observed in the reporting of atonic seizures, which were more common in males with GE, and for autonomic, visual, and psychic symptoms associated with NAFE, which were more common in females.

1. Introduction

Epilepsy affects ~50 million people worldwide and has a lifetime risk of ~3% [1,2]. The incidence and prevalence of unprovoked seizures are higher in men than women [3–5], and status epilepticus is more frequent in men than women [6,7]. However, some idiopathic generalized epilepsies are more common in women [4,8–12], particularly juvenile myoclonic epilepsy [8–11] and absence epilepsy [4,8,12]. There are no sex differences for patients with hippocampal sclerosis on MRI [13]. Sex disparities after epilepsy surgery are reported with more favorable outcomes in women [14] as well as men [15–18].

A few studies have examined sex differences in seizure semiology. A retrospective review of patients with medial temporal lobe epilepsy identified less frequent isolated auras and more frequent secondarily generalized seizures in men but no other significant semiologic differences between sexes [19]. Others reported an increased incidence of sexual auras [20,21] and increased frequency of affective, particularly negative affective, ictal symptoms [22] in women. These observations suggest that there may be underlying sex differences in the neurobiology of seizures and epilepsy. Using the prospectively gathered seizure and semiology data from the multicenter Epilepsy Phenome/Genome Project database, we aimed to explore differences in both seizure types and semiology.

2. Materials and methods

2.1. Subjects

All patients were identified from the Epilepsy Phenome/Genome Project (EPGP). This multi-institutional, collaborative network of 27 academic epilepsy centers throughout the U.S., Australia, New Zealand, and Argentina carried out detailed clinical phenotyping of participants from 2006 to 2013. Enrolled participants in the generalized

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epilepsy of unknown etiology (GE) or nonacquired focal epilepsy (NAFE) arms had a family history (either a sibling or a parent) of epilepsy. Participants were identified through a combination of prospective screening of clinic patients, retrospective review of medical records, and education and recruitment of colleagues within the primary EPGP institutions and neighboring institutions [23]. After obtaining informed consent from the subject, all clinical and demographic data were gathered prospectively through semistructured interviews as well as review of medical records, EEG, and imaging data. Fig. 1 depicts the data collection and review processes and the three points at which eligibility was reassessed following obtaining informed consent. Subjects with GE had to have generalized onset seizures, normal neuroimaging if it was performed, and an EEG showing generalized epileptiform activity with a normal posterior dominant rhythm. If the EEG was normal, there had to be clear clinical history and the data were sent for review and adjudication [23]. For NAFE, subjects had neuroimaging which was either normal or demonstrated mesial temporal sclerosis or focal cortical dysplasia and an unambiguous clinical semiology consistent with focal seizures and/or focal EEG abnormalities. Patients with benign rolandic epilepsy based upon clinical presentation were not required to have neuroimaging.

2.2. Seizure classification

Seizures were classified utilizing the International League Against Epilepsy Classification for both generalized and focal (partial) seizure types [24]. Generalized seizures were as follows: absence, atypical absence, tonic, clonic, tonic–clonic, atonic, and myoclonic. Focal seizures were classified utilizing the older terminology of simple partial seizures for focal seizures without dyscognitive features and complex partial seizures for focal seizures with dyscognitive features. Both types of

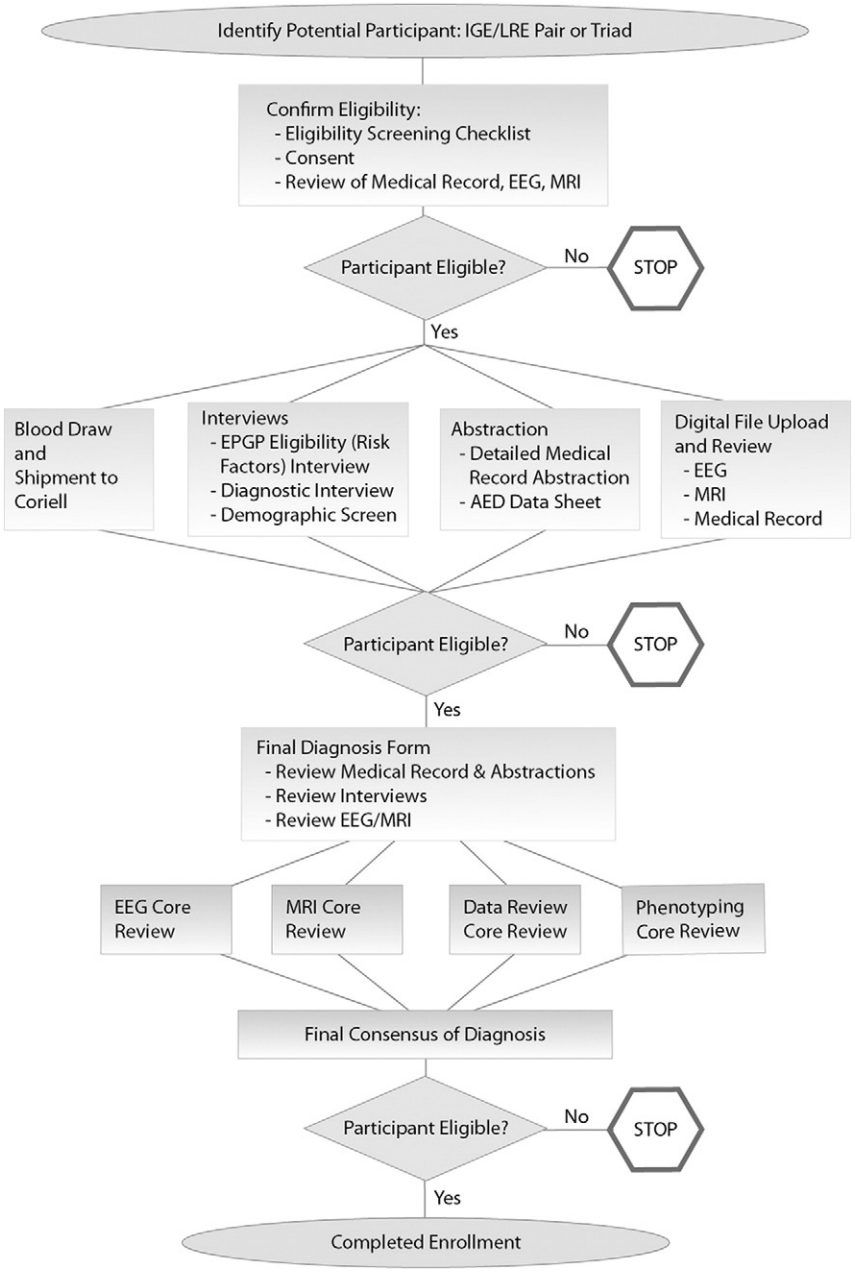

Fig. 1. The EPGP patient enrollment process. Following the initial eligibility screen, two additional eligibility screens occurred after additional data were gathered and reviewed prior to final enrollment.

seizures could progress to a secondarily generalized tonic–clonic convulsion. Patients were not restricted to a single seizure type.

2.3. Semiologic descriptions

Semiology information was gathered through a structured interview (by telephone or in person) and by medical record review [23]. The interview was modified from a previously validated instrument [25,26]. When necessary, data were reviewed and adjudicated by the Phenotype Core. Ictal semiologies were grouped into the following categories: aphasia, autonomic, motor, psychic, gustatory, olfactory, somatosensory, or visual. These data were gathered at the time of enrollment in the EPGP.

2.4. Data surveillance and quality control

Systematic quality reviews were conducted to identify and correct errors in phenotypic data [23]. All data were stored electronically in a central repository [27]. The following activities are conducted on an ongoing basis: 1) Qualitative and quantitative data monitoring activities by the EPGP statistician; 2) automated error checks programmed by the Informatics Core; 3) in-person data review meetings to examine forms and medical records for a subset of participants; 4) expert reviews by EPGP scientific cores, including EEG, MRI, AED, Phenotype, and Data Review Cores; and 5) review of final diagnoses by two independent members of the Data Review Core.

2.5. Statistical analysis

All data were analyzed utilizing SPSS version 21 for Windows. For continuous variables (i.e., age at enrollment, age at seizure onset, and duration of epilepsy), generalized linear models were employed. For categorical variables (e.g., seizure types, semiology), binary logistic regression was utilized. For all analyses, generalized estimating equations were utilized to adjust the confidence intervals for the nonindependence of observations within each family. A Bonferroni correction was used to address multiple comparisons. For generalized seizure types, a corrected alpha level of $p \leq 0.006$ was used. For focal seizure symptoms, a corrected alpha level of $p \leq 0.005$ was used to address multiple comparisons across the 11 primary symptom classes. For both autonomic and psychic symptoms, additional exploratory analyses of symptoms within those classes were done with an alpha level of $p < 0.05$.

3. Results

Out of a total of 2751 patients that consented for enrolment, 545 males and 691 females were analyzed. After obtaining informed consent, there were 813 participants that were ineligible after obtaining and screening their enrolment data. Another 544 participants did not complete the study protocol for data collection and review and were lost to the study; these "inactive" participants were not included in the final data set. An additional 76 males and 82 females were not classifiable due to inadequate clinical data; these patients were excluded from analyses. Table 1 shows the number of males and females enrolled in each of three groups: 1) NAFE, 2) GE, and 3) both GE and NAFE. For each group, the mean age at enrollment, age at onset of epilepsy, and duration of seizures are shown (in years) along with the standard deviations. The mean age at the time of enrollment was younger for males than females for both NAFE ($p = 0.02$) and GE ($p < 0.001$). The duration of epilepsy was shorter for males for both NAFE ($p = 0.012$) and GE ($p < 0.001$). The age at onset was younger for males with GE ($p = 0.001$); there was no significant difference for NAFE. For all subsequent analyses, patients in group 3 (both GE and NAFE) were included in both the NAFE and GE calculations.

Table 2 shows the frequency of generalized seizure types for both sexes. Atonic seizures were seen more frequently in males than females ($p < 0.001$); otherwise, no differences were seen.

Table 3 shows the frequency of focal seizure types. No differences between the sexes were seen. Table 4 shows the frequencies of the categories of ictal semiologies for both males and females. Motor phenomena were the most commonly reported semiologic element for both males and females followed by psychic features. For males, aphasia and then autonomic symptoms were the next most common features, whereas for females, autonomic symptoms and aphasia were the next most common. Autonomic features ($p = 0.005$), psychic phenomena ($p = 0.001$), and visual phenomena ($p = 0.002$) were more frequent in females compared to males with NAFE. Within autonomic features, visceral/epigastric sensations ($p = 0.003$) were more common in females; no difference was seen for chest tightness, dyspnea, cardiac symptoms, or diaphoresis. Within the category of psychic ictal symptoms, déjà vu ($p = 0.001$) was more common in females; ictal fear, forced thoughts, jamais vu, and derealization/depersonalization had similar frequencies for both males and females.

The overall reporting of symptoms was higher for females than it was for males in subjects with NAFE; females reported a mean of 4.9 different symptoms for their seizures with males reporting 4 ($p = 0.002$). For generalized seizures, there was no difference between genders.

4. Discussion

This large, prospective sample of patients with rigorous phenotypic classification identified several sex differences with regard to seizure type and semiology. Although no differences in the frequency of focal seizure types were seen between sexes, an increased frequency of autonomic, psychic, and visual features was seen in females compared to males. For generalized seizures, atonic seizures were seen with greater frequency in males than females.

Semiologic differences between sexes have been largely unstudied in the literature. A retrospective study restricted to medial temporal lobe epilepsy identified no differences for psychic auras [19], in contrast

Table 1
Age at enrollment, age at onset of seizures, and epilepsy duration.

	Number	Age at enrollment			Age at onset			Duration of epilepsy		
		Mean	SE	p	Mean	SE	p	Mean	SE	p
Focal epilepsy										
Male	231	22.3	1.1	0.02*	12.1	0.8	0.27	10.2	0.8	0.012*
Female	245	25.9	1.2		13.2	0.8		12.6	0.7	
Generalized epilepsy										
Male	314	18.6	0.7	<0.001*	9.8	0.4	0.001*	8.8	0.6	<0.001*
Female	446	23.5	0.7		11.5	0.4		12	0.6	
Focal epilepsy and generalized epilepsy										
Male	31	15.8	2	0.11	8.4	1	0.3	7.4	1.5	0.14
Female	33	20.5	2.2		10.1	1.3		10.4	1.4	

* Denotes statistically significant differences.

Table 2
Sex differences in generalized epilepsy of unknown etiology seizure types.

	Male			Female			Statistical significance
	Yes	No	% yes	Yes	No	% yes	
Absence	193	146	56.9%	292	176	62.4%	$p = 0.12$
Atonic	22	318	6.5%	8	466	1.7%	$p < 0.001$*
Atypical absence	17	318	5.1%	13	462	2.7%	$p = 0.08$
Gen. clonic	4	335	1.2%	3	468	0.6%	$p = 0.34$
Gen. tonic	9	329	2.7%	5	463	1.1%	$p = 0.1$
GTC	174	165	51.3%	238	229	51.0%	$p = 0.92$
Myoclonic	107	233	31.5%	169	307	35.5%	$p = 0.25$

* Denotes statistically significant differences after correction for multiple comparisons.

to the findings in this series. Our data were not limited to a particular epilepsy localization (e.g., temporal lobe epilepsy) nor restricted to the aura. Although the overall rates of reported psychic symptoms are higher in our study compared to the data reported by Janszky et al. (27% males and 40% females versus 24% males and 31% females, respectively), the frequency of psychic symptoms for each sex was not statistically different between the studies for males ($p = 0.76$) nor for females ($p = 0.16$) [19]. In our study, more detailed information on the nature of the psychic features of seizures revealed increased reporting of déjà vu for females but no other differences for specific psychic symptoms.

Similarly, in our study, autonomic features including visceral/epigastric sensations were more frequent in females with NAFE. In contrast to our findings, Janszky et al. reported no difference in frequency of reported abdominal auras between males and females. Notably, a higher frequency of abdominal auras was seen in their series compared with ours for both males (58% versus 5.0%, $p = 0.0001$) and females (69% versus 11.9%, $p = 0.0001$). It is unclear what accounts for the marked difference in frequency of this symptom between series. It is possible that this is due, in part, to how symptoms were ascertained as well as to the differences in patient populations, as Janszky et al. limited enrollment to temporal lobe epilepsy. In addition, the broader range of ictal symptoms explored within the questionnaire for our cohort likely impacts the identified ictal symptoms.

Visual ictal symptoms were more common in females; sex differences for ictal visual symptoms have not been assessed by any previous studies. As was observed in the study by Janszky et al., we found no differences in olfactory, motor, or language symptoms [19].

In contrast to previously reported studies, we did not observe an increased rate of absence seizures in females [4,8,12]. With the exception of atonic seizures, which were seen more frequently in men, no differences were seen amongst generalized seizure types. Although the reason for this finding is not known, it is possible that the increased frequency of atonic seizures may be related to Doose or Doose variants (myoclonic–astatic epilepsy). This syndrome is known to be more frequent in males [28,29]. Given the EPGP methodology which enrolled patients with a family history of epilepsy, it is possible that there was a relative increase in enrollment of patients with Doose syndrome which could lead to more frequent atonic seizures in males.

Table 3
Sex differences in nonacquired focal epilepsy seizure types.

	Male			Female			Statistical significance
	Yes	No	% yes	Yes	No	% yes	
SPS	72	188	27.7%	92	184	33.3%	$p = 0.13$
SPS to CPS to GTC	18	238	7.0%	25	250	9.1%	$p = 0.38$
SPS to GTC	36	219	14.1%	48	227	17.5%	$p = 0.32$
CPS	152	106	58.9%	173	104	62.5%	$p = 0.38$
CPS to GTC	74	181	29.0%	84	189	30.8%	$p = 0.7$

Table 4
Sex differences in nonacquired focal epilepsy seizure semiology.

	Male			Female			Statistical significance
	Yes	No	% yes	Yes	No	% yes	
Aphasia	45	217	17.2%	56	222	20.1%	0.37
Autonomic	43	219	16.4%	74	204	26.6%	0.005*
Dyspnea	5	257	1.9%	16	262	5.8%	0.05
Chest tightness	3	259	1.1%	3	275	1.1%	0.93
Visceral or epigastric sensation	13	249	5.0%	33	244	11.9%	0.003*
Cardiac	4	258	1.5%	12	265	4.3%	0.07
Diaphoresis	27	235	10.3%	34	244	12.2%	0.49
Motor	180	74	70.9%	187	82	69.5%	0.74
Psychic	70	192	26.7%	112	166	40.3%	0.001*
Fear	30	230	11.5%	42	234	15.2%	0.19
Déjà vu	27	233	10.4%	56	222	20.1%	0.001*
Jamais vu	1	258	0.4%	8	269	2.9%	0.06
Derealization/ depersonalization	17	245	6.5%	26	252	9.4%	0.22
Forced thoughts	1	260	0.4%	4	274	1.4%	0.23
Gustatory	16	245	6.1%	19	255	6.9%	0.71
Olfactory	8	253	3.1%	16	258	5.8%	0.13
Somatosensory	17	245	6.5%	32	244	11.6%	0.04
Visual	27	235	10.3%	55	221	19.9%	0.002*
Auditory	17	245	6.5%	26	250	9.4%	0.22
Vertigo	7	254	2.7%	14	259	5.1%	0.15
Ictal headache	9	253	3.4%	4	269	1.5%	0.15

* Denotes statistically significant differences after correction for multiple comparisons.

Differences in the approach to phenotyping may account for some of the discrepancies in results between our study and those reported above. The EPGP inclusion criteria for focal epilepsy required either normal neuroimaging or the findings of mesial temporal sclerosis or focal cortical dysplasia along with EEG findings or clinical semiology consistent with focal seizures. Data were obtained through medical records as well as diagnostic interviews. In contrast, Janszky et al. utilized review of the medical records on admission for presurgical evaluation and the video-EEG ictal data for inclusion and characterization [19]. Also, the population in the EPGP cohorts with GE and NAFE was enriched for genetic factors; families were required to have at least two affected first degree relatives to be enrolled. The study reported by Janszky et al. excluded patients with a family history of epilepsy [19]. These differences both in phenotypic characterization and in patient population may account for some of the differences observed between previous studies and the EPGP data. Lastly, the EPGP population here was relatively young with mean ages well below 30 for both males and females, reflecting the inclusion of both adults and children (ranging from one to 82 years of age).

Differences in symptom reporting based upon sex may account for the observed findings [30]. Whether these known reporting differences are psychological, biological, or sociological remains unclear, and the impact of one or all of these factors on our results is uncertain. It is possible that sex differences in the frequency of specific seizure symptoms may reflect underlying differences in how males and females engage limbic and other regions for memory and emotional tasks. There is evidence supporting differences between the sexes in the processing of memory and emotion. Differences have been observed using fMRI activations associated with emotional memory [31] and autobiographical memory [32] as well as differences in cerebral blood flow utilizing SPECT in limbic regions in response to procaine infusion [33]. These sex differences in cognitive and emotional processing may lead to differences in activation patterns, and thus semiologies, for seizures.

Given the increasing evidence over the past several decades of the importance of hormones such as estrogen, progesterone, and androgens in neurodevelopment, neuroprotection, memory, and seizures, these differences in focal seizure semiologies may reflect responses to different levels of these important hormones between sexes [34–36]. It is plausible that differences in both brain-derived and systemically

derived estrogens between sexes may lead to differences in responses to the inciting event leading to seizures or the subsequent seizures themselves. It is reasonable to hypothesize that these differences might result in increased involvement of limbic pathways, leading to the experiential phenomena seen with greater frequency in females in this study.

The unique EPGP study population poses some limitations for this study. The EPGP was designed to address the role of genetic variations in the development of epilepsy and treatment resistance by enrolling patients with a family history of epilepsy [23]. Although the study presented here utilized generalized estimating equations to address the nonindependence of observations within families, it is possible that the observed sex differences may not be generalizable to a sample of patients without a family history of epilepsy. As patients were recruited primarily from epilepsy centers, they had sought treatment or evaluation leading to a potential bias for patients with less well-controlled epilepsy; families who have well-controlled epilepsy (i.e., do not need to have regular visits to a neurologist or epileptologist) may be underrepresented in this sample. Similarly, patient populations derived primarily from epilepsy centers may not be representative of a nontertiary center-derived sample. These factors may have led to the higher proportion of females compared to males in the overall study population.

5. Conclusions

The findings presented here show differences in several subjective ictal symptoms between males and females. Although our data cannot directly assess the neurobiological bases of these findings nor can they rule out the possibility of the findings being driven by differences in symptom reporting and recognition, they raise important questions as to differences that exist between the sexes. Nonetheless, these findings may allow for further explorations of processing differences and the ways in which seizures impact these complex systems.

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Conflict of interest

Drs. Carlson, Dugan, and Kirsch have no conflicts of interest to disclose.

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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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