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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

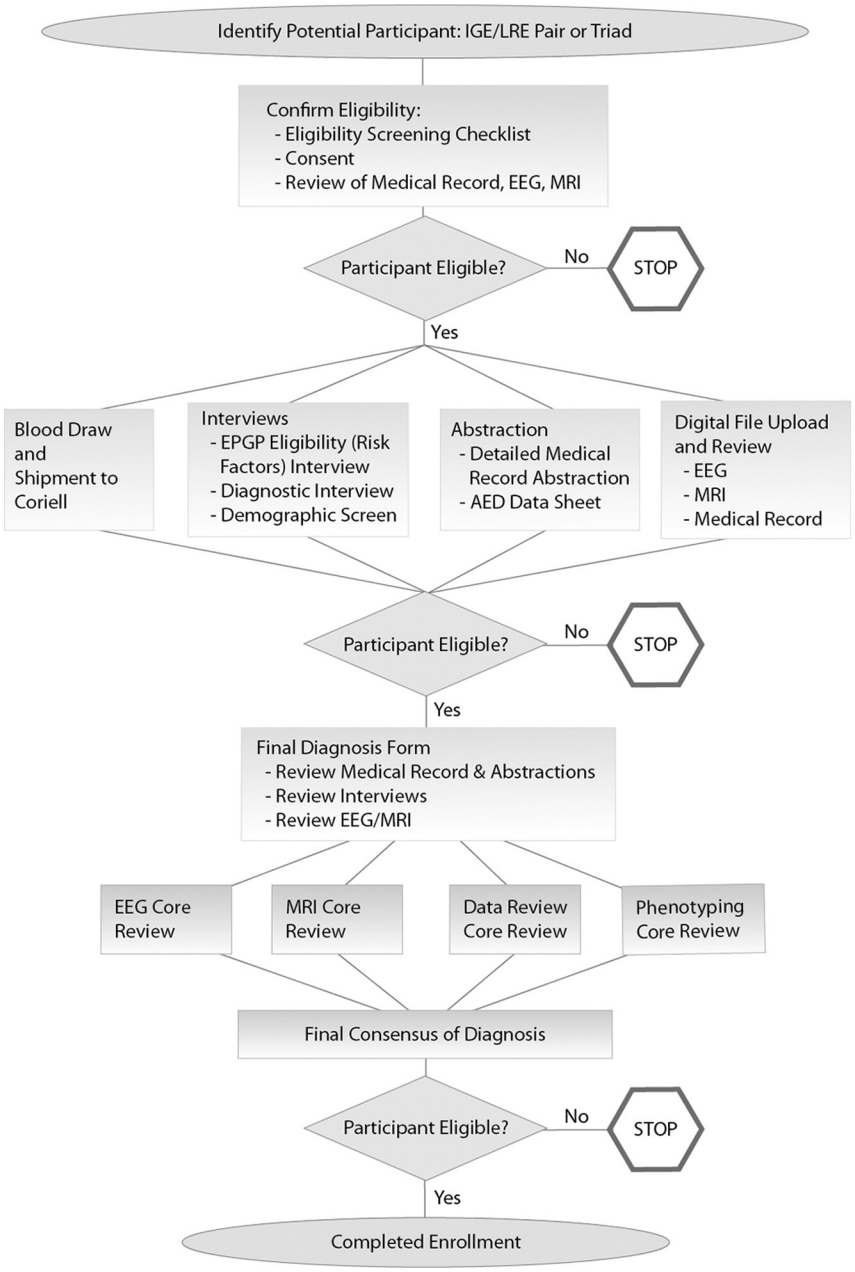

Fig. 1. The EPGP patient enrollment process. Following the initial eligibility screen, two additional eligibility screens occurred after additional data were gathered and reviewed prior to final enrollment.