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Sex and epileptogenesis, introduction to the special issue

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Despite the evident anatomical, behavioral, and biological differences between men and women, the inclusion of gender or sex related factors in neurological research has been slow coming. The National Institutes of Health Revitalization Act of 1993 (Public Law 103–43) required the inclusion of women and minorities in clinical trials. On the other hand, most preclinical studies have been usually done using male-only or mixed but unspecified sex or (less frequently) female-only groups of animals only few of the preclinical studies were designed to address potential sex differences in various anatomical, morphological, biological or functional features of the nervous system. It was only in 2014, while this special issue was in preparation, that a statement encouraged the inclusion of both sex and genders in the preclinical grant applications to NIH, recognizing the importance of investigating their role in mechanisms and treatments of neurological diseases (Clayton and Collins, 2014). The use of the terms sex and gender is often been done interchangeably. However “sex” typically refers to the biological differences and is very commonly used in the preclinical literature. In contrast, “gender” usually refers to the cultural or societal characteristics that compose a masculine or feminine identity and is the preferred term in the clinical studies.

A review of the available incidence and population-based studies on epilepsies of acquired or unknown etiologies yielded no consistent evidence of gender differences in the incidence or consequences of these epilepsies (Perucca et al., 2014b). The examined etiologies included tumors, perinatal brain insults, cerebrovascular disease, infections, trauma, neurodegenerative diseases, and autoimmune disorders. There was also no evidence that gender influences the prognosis of these epilepsies. However several study limitations exist that limit any definite conclusions, including the small numbers of affected patients, the retrospective nature of many studies, the fact that gender differences in the incidence or specific nature of insults were not accounted for.

Among epilepsies of known or presumed genetic etiology and within specific epilepsy syndromes, certain gender differences start to emerge. For genes that are located in the X chromosome, gender differences are not uncommon. Female predominance can be seen for example with defects in methyl CpG binding protein 2 (MeCP2; Rett syndrome), protocadherin 19 (PCDH19-related female limited epilepsy). In contrast, *fi19* (P A mutations can cause West syndrome in males (Masruha et al., 2006). Photosensitivity in

genetic generalized epilepsies or idiopathic photosensitive occipital epilepsy showed a striking female bias (Taylor et al., 2013). Similarly, female preponderance was reported in juvenile myoclonic epilepsy (Camfield and Camfield, 2009; Janz, 1998), childhood absence epilepsy, perioral myoclonia with absences and myoclonic encephalopathy in nonprogressive disorders (Panayiotopoulos, 2007; van Luijtelaar et al., 2014). Male preference is reported in special epilepsy syndromes like Landau–Kleffner syndrome, epilepsy with continuous spike and wave complexes in slow wave sleep, epilepsy with myoclonic absences, West or Dravet syndromes, benign epilepsy with centrotemporal spikes (Panayiotopoulos, 2007). However, in certain of these syndromes, the differences consist only reported trends, given the rarity of these conditions.

Although specific gene-related sex-specific functional effects may contribute to the gender preference of certain epileptic syndromes, there is also significant amount of clinical and preclinical evidence on the sexual dimorphism in the structure and connectivity of the brain, including limbic and other cortical and subcortical structures that are engaged in the seizure networks (reviewed in Savic and Engel, 2014). These structural and functional gender differences may contribute in determining the type of epileptic syndrome, its severity, but also the comorbid conditions that emerge in individuals affected by epilepsy (Savic and Engel, 2014).

Sex hormones act at various stages of development, including the fetal and perinatal periods, and not simply during the reproductive period. In fact, increasing recognition of specific “critical or sensitive” periods to the effects of sex hormones has emerged and these periods can be different for various studied endpoints and also across species (Giorgi et al., 2014; Kight and McCarthy, 2014). Furthermore, many other signaling pathways (e.g., GABA_A receptor signaling) or epigenetic processes effecting chromatin modifications (Kight and McCarthy, 2014; Qureshi and Mehler, 2014) are engaged to enhance these sex differences by eliciting different physiologic and cellular responses in males and females (Akman et al., 2014; Giorgi et al., 2014; Kight and McCarthy, 2014). The effects of these gender-specific molecular and signaling effects may be lasting influencing the organization, connectivity, and function of networks involved in seizure control and propagation (Giorgi et al., 2014), determine the consequences of early life seizures (Akman et al., 2014) or stressors (Akman et al., 2014; Jones et al., 2014).

During the reproductive period, sex hormones may influence the timing and frequency of certain seizures, as occurs in catamenial epilepsy (Koppel and Harden, 2014). Clinical trials conducted to determine the effects of progesterone treatments in women with catamenial epilepsy showed a beneficial effect only in a cohort of women with perimenstrual seizures (reviewed in Koppel and Harden, 2014). Further, seizures may have direct effects on the hypothalamic-pituitary-gonadal axis in both men and women, leading to reproductive dysfunction (Koppel and Harden, 2014).

In animal studies, sex hormones and neurosteroids have shown clear effects on pathways and brain regions controlling seizures, in both mature and immature animals (Akman et al., 2014; Giorgi et al., 2014; Reddy, 2014; Scharfman and MacLusky, 2014). In general, progesterone and neurosteroids have anticonvulsant and estradiol proconvulsant effects,

although dose and model specific effects have been described. Neuroprotection by supplementing estradiol levels, when deficient, has been demonstrated in certain models and all these studies have set grounds for testing new hormone-based treatment protocols in humans (Azcoitia et al., 1999; Scharfman and MacLusky, 2014; Veliskova et al., 2000).

In clinical trials, gender has an important role in pharmacokinetics and susceptibility to certain adverse effects of antiepileptic drugs (AEDs), specifically those that depend on sex hormone metabolism and teratogenic effects (Perucca et al., 2014a). Efficacy of AEDs can also be altered by endogenous or exogenous hormones (pregnancy, contraceptives) and these effects can be bidirectional (e.g., contraceptives) (Perucca et al., 2014a). In most clinical trials reviewed by the authors, typically drug-resistant seizures in adults, gender has not been explored as to its role in altering the AED efficacy and in the few that examined this, gender did not play a significant role (Perucca et al., 2014a). However, more systematic analyses may be needed, to conclusively decide whether certain types of seizures, in certain populations (pediatric vs adults), in certain AED types, gender may indeed affect efficacy towards specific endpoints (seizures, comorbidities).

There are currently no antiepileptogenic therapies for human epilepsies. Therefore, the question posed upon Pitkanen et al. (2014) was largely a conceptual issue: could gender influence antiepileptogenic treatments, based on what is known on the processes involved in epileptogenesis? The authors provide evidence from preclinical studies in adult animals that supports the idea that (a) sex can alter target expression during epileptogenesis, (b) there is cross-talk between many of the potential antiepileptogenesis targets and sex hormonal pathways, and (c) there is significant evidence that the consequences of seizures, the epilepsy-related pathologies and comorbidities may be gender or sex-specific. The importance of sex in epileptogenesis is also supported by the reviews in this special issue that discuss the studies in immature animals (Akman et al., 2014; Giorgi et al., 2014; Jones et al., 2014). In contrast to the evidence in humans (Perucca et al., 2014a), animal studies have either avoided or not studied the impact of gender on pharmacokinetics of tested antiepileptogenic drugs and have not looked at possible differences in blood brain penetration and target engagement. An important reason for this is the significant cost and large sample sizes required to evaluate antiepileptogenesis in both genders.

In summary, there is sufficient evidence from the preclinical studies in support of the importance of sex and gender related factors in the susceptibility, expression and course of seizures, epilepsies and comorbidities at all stages of development and reproductive maturity. However, these effects are not systematically studied, due to cost and sample size limitations as most preclinical studies utilize one or mixed gender populations and very few are specifically designed to study gender effects. In the clinical arena, it is clear that the role of gender cannot be extrapolated to all types of epilepsies, but knowing the etiology and syndrome classification is paramount. Currently, however, most clinical trials are specifically looking at drug-resistant, usually focal-onset epilepsies in adults, which is by far not the setting examined in most preclinical trials and cannot be extrapolated to all types of human epilepsies. Even though both genders are traditionally included in these trials, not all of them are powered or structured in a way that can definitively prove or disprove the importance of gender efficacy of an AED in epilepsies.

The disparity in methods and strategies between the preclinical and clinical studies is evident and will be the limiting factor in effective and accurate translation of preclinical discoveries to clinically-relevant findings (Brooks-Kayal et al., 2013; Galanopoulou et al., 2012, 2013). Increasing the power of preclinical studies to elucidate the role of gender and sex-related factors in specific pre-defined scenarios across the lifespan would help guide clinical studies to test the translatability of these discoveries in the clinical field and hopefully provide better, age-and gender-appropriate treatments.

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