Archives of Epilepsy

Review

Sex Differences in Epilepsies: A Narrative Review

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Cite this article as: Asadi-Pooya AA, Alkhaldi M, Damabi NM, Dehkordi KF. Sex Differences in Epilepsies: A Narrative Review. *Arch Epilepsy.* 2024;30(4):100-103.

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Received: 05.05.2024 **Accepted:** 20.08.2024 **Publication Date:** xx

DOI: 10.4274/ArchEpilepsy.2024.24124

Abstract

Epilepsy affects people of all ages and sexes. The aim of the current narrative review was to summarize the sex differences in patients with epilepsy. In January 2024, we systematically searched PubMed for relevant articles. The following keywords were used: "Epilepsy" or "Seizure" and "Sex". The prevalence and symptomatology of many neurological conditions, including epilepsy syndromes, may differ between male and female patients. The reasons behind these sex differences are not yet clear. It is likely that sex hormones, neurosteroid, and sex chromosome gene differences play roles in the development of this phenomenon. The existence of sex differences in epilepsy is well recognized, but there is little discussion of their mechanisms and therapeutic implications. Future research should investigate the exact roles of sex hormones, neurosteroid, and genes in the development of sex differences in epilepsy. Similarly, future studies should investigate whether sex differences exist in seizure characteristics (e.g., seizure frequency, semiology, response to treatment, outcome) in different syndromes. These issues may have important clinical implications for designing appropriate sex-specific treatment strategies for various syndromes and conditions. Furthermore, sex should be considered as a biological variable in basic and clinical research.

Keywords: Epilepsy, gene, hormone, seizure, sex

INTRODUCTION

Gender and sex disparities exist in all aspects of human life; they may represent biology, bias, or both. In general, "sex" refers to the biological differences between males and females, while "gender" refers to the role of a male or female in society.[1] Sex differences in the characteristics of neurological conditions may be explained by the actions of sex hormones and also by sex chromosome gene-related brain differences.[2] These sex differences may influence the clinical characteristics, management, and even outcomes of neurological conditions.[3]

Evidence from human and animal studies supports a bidirectional relationship; the role of sex on seizures and epilepsy, as well as changes in the endocrine system and levels of sex hormones by epilepsy.[4] The aim of the current narrative review was to summarize the biological reasons for sex differences in people with epilepsy.

In January 2024, we systematically searched PubMed for relevant articles. The following keywords were used: "Epilepsy" or "Seizure" and "Sex". We included all original studies and articles written in English. Both authors independently participated in the screening, eligibility, and inclusion phases of the study. The authors collected the full manuscripts for all publications that appeared to meet the inclusion and exclusion criteria. The inclusion criteria were all human studies on sex differences in epilepsies (i.e., retrospective, cross sectional, case-control, case series, prospective trials, etc.), review articles, and articles written in English. The exclusion criterion was gray materials (i.e., letters, etc.) Because this was a narrative review, we did not follow the recommendations of the preferred reporting items for systematic reviews and meta-analyses statement; therefore, we did not track the number of identified papers in each step of the work.

Sex Differences in Patients with Epilepsy

The prevalence and symptomatology of many neurological conditions, including epilepsy syndromes, may differ between male and female patients. Although the sex differences in the incidence of epilepsy do not reach a significant difference, consistent trends across many

studies suggest that the incidence and prevalence of epilepsy are slightly higher in males than in females, in general.[4,5] Sex differences in seizure susceptibility may result from differences in factors, such as steroid hormone levels, cytochrome P450 activity, and biological factors in the brain.[6,7] These differences are most likely multifactorial phenomena, and many factors may contribute to these differences (e.g., environmental factors and lifestyle). In this review, we focused on the neurobiology of sex differences in various epilepsy syndromes.

Idiopathic Generalized Epilepsy

Female patients often outnumber male patients with idiopathic generalized epilepsy (IGE). The sex (female to male) ratio of the whole cohort of patients with IGE was approximately 1.5 in various studies.[8-10] This sex disparity is to some extent syndrome-related in patients with IGEs; the female-to-male ratio was significantly higher in patients with juvenile myoclonic epilepsy (JME) (of 1.8) compared with those in other syndromes of IGE (e.g., 1.33 in childhood absence epilepsy) in one study.[10] It is likely that sex hormones, neurosteroid, and sex chromosome gene differences play a role in the development of the aforementioned phenomenon (Figure 1).[11-13] Considering the peripubertal onset of JME, it is plausible to assume that the expression of genes that increase susceptibility to myoclonic seizures is regulated or affected by sex steroids.[14] In addition, it is hypothetically possible that mutant epilepsy genes have greater penetrance in females and males.[15]

Both female and male sex steroid hormones may influence brain excitability. Progesterone and its metabolites are anticonvulsants, whereas estrogens are mainly proconvulsants. The results from clinical studies have been supported by several animal studies that have demonstrated increased and decreased seizure frequencies after estrogen and progesterone administration, respectively.[11]

Androgens have more varied effects, although a generally antiseizure effect has been suggested; testosterone increases the electroconvulsive threshold in males at low doses and in both sexes at higher doses.[11] The effects of sex hormones on neuronal excitability and seizures involve complex mechanisms that are difficult to separate, as they range from regulation of gene expression to rapid effects via activation of various membrane receptors or acting as ligands on neurotrophin and ion-channel coupled receptors.[4] Furthermore, sex hormone surges during distinct maturation periods may also affect brain function and seizure outcomes (e.g., by inducing sexual differentiation of regions responsible for seizure control or initiation, or brain maturation).[4] Some epilepsy syndromes may either remit (e.g., childhood absence epilepsy) or have onset (e.g., JME) around the adolescence ages, indicating the likely influence of sex hormone changes and brain maturation occurring around puberty.[4]

Neurosteroids are key endogenous molecules in the brain that can affect many neural functions.[12] Neurosteroids are known for their nongenomic effects via the direct modulation of N-methyl-D-aspartate and gamma-aminobutyric acid (GABA)-A receptors. Neurosteroids are mainly responsible for the "fine tuning" of neuronal excitability by acting at synaptic and extrasynaptic receptors.[4] The neuronal GABA-A receptor chloride channel is a prime molecular target of neurosteroid.[12] At low concentrations, neurosteroid potentiate GABA-A receptor currents, whereas at higher concentrations, they directly activate the receptor.[16,17] Allopregnanolone-like neurosteroid are potent allosteric agonists and direct activators of synaptic and extrasynaptic GABA-A receptors.[12] The resulting chloride current conductance generates a form of shunting inhibition that controls brain network excitability and seizures. These mechanisms of neurosteroid provide potential innovative therapies for epilepsy and epilepticus.[12]

Finally, while sex differences in the brain have been largely attributed to the effects of sex hormones, it is becoming increasingly clear that brain sex differences are also mediated by the complement of genes encoded on sex chromosomes.[13] Sex chromosome gene expression is sexually dimorphic in the brain in a region-specific and cell type-specific manner.[13] Genes on the sex chromosome may influence neurological diseases by modifying the differentiation process of neurons, encoding proteins, neurotransmitter biosynthesis, and synaptic transmission (Figure 1).[13] Interestingly, evidence suggests the preponderance of female sex in the transmission of seizure liability in IGEs.[18] In one study of families with 82 index cases with IGEs, the highest risk for siblings was conferred by an affected mother. If a father was affected, the risk for proband siblings was almost equal to that in families with both parents unaffected.[18]

The relationship between menstrual cycle and seizure susceptibility in women is a well-known phenomenon (catamenial epilepsy); this is greatly influenced by hormonal fluctuations associated with the menstrual cycle phases. Catamenial seizures are considered neurosteroid withdrawal symptoms.[19] The pathophysiology of perimenstrual catamenial epilepsy involves withdrawal of progesterone-derived GABA ergic neurosteroid due to a decline in progesterone levels at the time of menstruation.[20] However, other mechanisms such as changes in water content, fluctuations in calcium levels, interactions between anticonvulsant drugs and steroid hormones, and thyroid hormone deficiency have also been implicated in the pathophysiology of perimenstrual catamenial epilepsy 4. A detailed review of catamenial epilepsy is beyond the scope of this manuscript, and readers should refer to other studies on this topic.[11,19,20]

Most of the abovementioned discussions on the neurobiology of sex differences in epilepsy also apply to other types of epilepsies [e.g., focal epilepsies, genetic epilepsies, status epilepticus (SE)]. Below, we highlight some sex differences that are specific to other epilepsy.

Focal Epilepsy

Generally, men may have a greater predisposition to behaviors that cause brain injury and acquired epilepsy.[21] In addition, animal studies have implicated that the presence of testosterone in intact and gonadectomized males with testosterone replacement increases their susceptibility to seizure. Seizures were either stronger (full limbic) or more frequent in animals with testosterone compared to animals devoid of testosterone.[22] In contrast, women

MAIN POINTS

- Systematically, PubMed was searched in January 2024.
- Keywords: "Epilepsy" or "Seizure" and "Sex".
- Epilepsy syndromes are affected by sex hormone, neurosteroid, and sex chromosome genes-related brain differences.

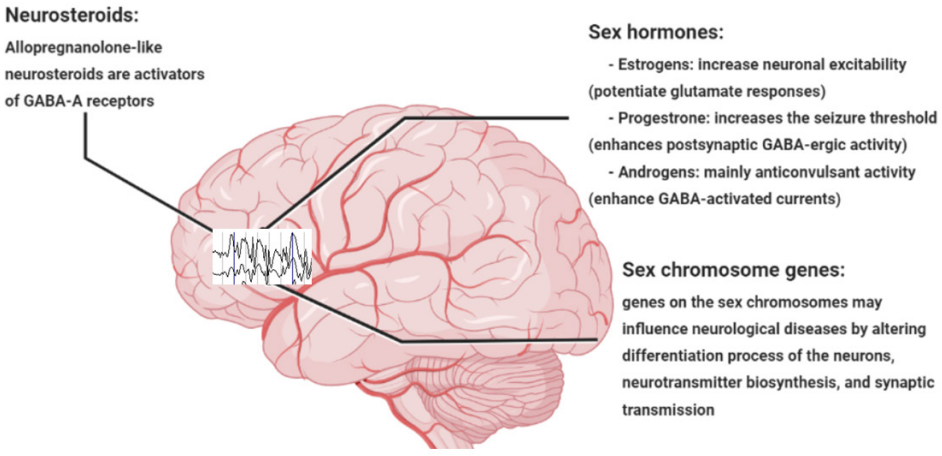

Figure 1. Potential reasons for sex differences in epilepsy

may be protected from brain injury by the neuroprotective effects of estrogens and progesterone.[21] Furthermore, some symptomatic (structural) focal epilepsy may be more frequent in men (e.g., focal cortical dysplasia, perinodular heterotopia).[7,21] In one study of non-acquired focal epilepsy, no sex differences were observed for seizure types with or without altered consciousness or progression to bilateral tonic-clonic seizures. However, autonomic, psychic, and visual symptoms are more frequently reported in females than in males.[3]

In temporal lobe epilepsy (TLE), which is the most common type of focal epilepsy, the sex distribution is almost similar between males and females,[23] but some clinical aspects appear to differ between men and women (e.g., auras are more common in women).[21,24] Interestingly, one study suggested the existence of sex differences in the spatial distribution of brain dysfunction in patients with mesial TLE, perhaps reflecting sexual dimorphism in regional cerebral connectivity.[25] Male patients more often exhibited frontal lobe hypometabolism ipsilateral to the seizure onset zone and epileptiform activity spread to this region. By contrast, female patients more often exhibited hypometabolism and ictal spread to the contralateral temporal lobe.[25]

Investigating sex differences in focal epilepsies may have important clinical implications; for example, in designing individualized sex-specific surgical plans for patients with drug-resistant mesial TLE, considering the extent of cerebral dysfunction in different sexes.

Symptomatic (Structural-Metabolic-Genetic) Generalized Epilepsy

Lennox-Gastaut syndrome (LGS) is the prototype of symptomatic (structural-metabolic-genetic) generalized epilepsy. Male patients often outnumber female patients in LGS. In one study, the sex (female to male) ratio of patients with LGS was 0.6;[26] this was consistent with other studies.[27] Male preponderance has also been reported in other epilepsy syndromes, such as Landau-Kleffner syndrome, epilepsy with myoclonic absences, Ohtahara syndrome, and Dravet syndrome.[4-7] Sex-dependent genetic disorders (e.g., X-linked syndromes such as Rett syndrome and fragile X syndrome) may explain some of these sex differences in symptomatic (structural-metabolic-genetic) generalized epilepsies.[28-31]

Status Epilepticus

SE is more prevalent in males than in females. In one large study from the USA, a higher incidence, earlier age at onset, and higher mortality of SE were observed among males.[32] In another study conducted in Taiwan, the male-to-female ratio of SE incidence rate was 1.57;[33] however, the in-hospital mortality was significantly lower in males (7.4%) than in females (11.1%).[33]

Sex Differences in the Adverse Effects of Antiseizure Medications

A recent systematic review suggested a higher frequency of general adverse effects of antiseizure medications in girls (than that in boys).[34] Higher risks of overweight, hyperammonemia, and carnitine deficiency were suggested in girls taking valproic acid. Similarly, an increase in height and an increased risk of weight loss were suggested to occur in girls on topiramate. Finally, a higher risk of retinal toxicity was observed in boys taking vigabatrin. However, the authors concluded that the effect of sex on the susceptibility to adverse effects of antiseizure medications is poorly investigated.[34]

The choice of antiseizure medications may have direct effects on hormonal cycles, hormonal contraception, pregnancy, fetal risk of major congenital malformation, and lactation in adolescents and adults with epilepsy. A detailed review of these issues is beyond the scope of this manuscript, and readers are encouraged to refer to other references.[35-37] For a comprehensive review of the molecular mechanisms of sex differences in epilepsy and seizure susceptibility in terms of chemical, genetic, and acquired epileptogenesis, readers may refer to the review by Reddy et al.[38]

CONCLUSION

The existence of sex differences in epilepsy is well recognized, but there is little discussion of their mechanisms and therapeutic implications. Future research should investigate the exact roles of sex hormones, neurosteroid, and genes in the development of sex differences in epilepsy. Similarly, future studies should investigate whether sex differences exist in seizure characteristics (e.g., seizure frequency, semiology, response to treatment, outcome) in different syndromes. These issues may have important clinical implications

for designing appropriate sex-specific treatment strategies for various syndromes and conditions. Furthermore, sex should be considered as a biological variable in basic and clinical research.

Footnotes

Authorship Contributions

Concept: A.A.A-P., Design: A.A.A., Data Collection or Processing: A.A.A., M.A., N.M.D., K.F.D., Analysis or Interpretation: A.A.A., Literature Search: A.A.A., M.A., N.M.D., K.F.D., Writing: A.A.A., M.A., N.M.D., K.F.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Sex and gender: What is the difference? Last Accessed Date: 02/26/2020. Available from: https://www.medicalnewstoday.com/articles/232363/ [Crossref]
2. Loke H, Harley V, Lee J. Biological factors underlying sex differences in neurological disorders. *Int J Biochem Cell Biol*. 2015;65:139-150. [Crossref]
3. Carlson C, Dugan P, Kirsch HE, Friedman D; EPGP Investigators. Sex differences in seizure types and symptoms. *Epilepsy Behav*. 2014;41:103-108. [Crossref]
4. Velíšková J, Desantis KA. Sex and hormonal influences on seizures and epilepsy. *Horm Behav.* 2013;63(2):267-277. [Crossref]
5. Beghi E. The Epidemiology of Epilepsy. *Neuroepidemiology*. 2020;54(2):185-191. [Crossref]
6. Reddy DS. The role of neurosteroids in the pathophysiology and treatment of catamenial epilepsy. *Epilepsy Res*. 2009;85(1):1-30. [Crossref]
7. Reddy DS. The neuroendocrine basis of sex differences in epilepsy. *Pharmacol Biochem Behav*. 2017;152:97-104. [Crossref]
8. Christensen J, Kjeldsen MJ, Andersen H, Laue Friis M, Sidenius P. Gender differences in epilepsy. *Epilepsia*. 2005;46:956-960. [Crossref]
9. Mullins GM, O'sullivan SS, Neligan A, et al. A study of idiopathic generalised epilepsy in an Irish population. *Seizure*. 2007;16(3):204-210. [Crossref]
10. Asadi-Pooya AA, Emami M, Sperling MR. A clinical study of syndromes of idiopathic (genetic) generalized epilepsy. *J Neurol Sci.* 2013;324(1-2):113-117. [Crossref]
11. Taubøll E, Sveberg L, Svalheim S. Interactions between hormones and epilepsy. *Seizure*. 2015;28:3-11. [Crossref]
12. Reddy DS, Estes WA. Clinical Potential of Neurosteroids for CNS Disorders. *Trends Pharmacol Sci.* 2016;37(7):543-561. [Crossref]
13. Pinares-Garcia P, Stratikopoulos M, Zagato A, Loke H, Lee J. Sex: A Significant Risk Factor for Neurodevelopmental and Neurodegenerative Disorders. *Brain Sci*. 2018;8(8):154. [Crossref]
14. Savic I. Sex differences in the human brain, their underpinnings and implications. Preface. *Prog Brain Res*. 2010;186:vii-ix. [Crossref]
15. van Luijtelaar G, Onat FY, Gallagher MJ. Animal models of absence epilepsies: what do they model and do sex and sex hormones matter? *Neurobiol Dis*. 2014;72 Pt B:167-179. [Crossref]
16. Harrison NL, Majewska MD, Harrington JW, Barker JL. Structure-activity relationships for steroid interaction with the gamma-aminobutyric acidA receptor complex. *J Pharmacol Exp Ther*. 1987;241(1):346-353. [Crossref]
17. Reddy DS, Rogawski MA. Stress-induced deoxycorticosterone-derived neurosteroids modulate GABA(A) receptor function and seizure susceptibility. *J Neurosci*. 2002;22(9):3795-3805[Crossref]
18. Doose H, Neubauer BA. Preponderance of female sex in the transmission of seizure liability in idiopathic generalized epilepsy. *Epilepsy Res*. 2001;43(2):103-114. [Crossref]
19. Joshi S, Kapur J. Neurosteroid regulation of GABAA receptors: A role in catamenial epilepsy. *Brain Res*. 2019;1703:31-40. [Crossref]
20. Reddy DS. Catamenial Epilepsy: Discovery of an Extrasynaptic Molecular Mechanism for Targeted Therapy. *Front Cell Neurosci.* 2016;10:101. [Crossref]
21. Scharfman HE, MacLusky NJ. Sex differences in the neurobiology of epilepsy: a preclinical perspective. *Neurobiol Dis*. 2014;72 Pt B:180-192. [Crossref]
22. Mejías-Aponte CA, Jiménez-Rivera CA, Segarra AC. Sex differences in models of temporal lobe epilepsy: role of testosterone. *Brain Res*. 2002;944(1-2):210-218. [Crossref]
23. Asadi-Pooya AA, Sharifzade M. Lennox-Gastaut syndrome in south Iran: electro-clinical manifestations. *Seizure*. 2012;21(10):760-763. [Crossref]
24. Toth V, Fogarasi A, Karadi K, Kovacs N, Ebner A, Janszky J. Ictal affective symptoms in temporal lobe epilepsy are related to gender and age. *Epilepsia*. 2010;51(7):1126-1132. [Crossref]
25. Savic I, Engel J Jr. Sex differences in patients with mesial temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry*. 1998;65:910-912. [Crossref]
26. Asadi-Pooya AA, Sharifzade M. Lennox-Gastaut syndrome in south Iran: electro-clinical manifestations. *Seizure*. 2012;21:760-763. [Crossref]
27. Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. *Epilepsia*. 1997;38:1283-1288. [Crossref]
28. Fehr S, Bebbington A, Nassar N, Downs J, Ronen GM, DE Klerk N, Leonard H. Trends in the diagnosis of Rett syndrome in Australia. *Pediatr Res*. 2011;70(3):313-319. [Crossref]
29. Berry-Kravis E, Raspa M, Loggin-Hester L, Bishop E, Holiday D, Bailey DB. Seizures in fragile X syndrome: characteristics and comorbid diagnoses. *Am J Intellect Dev Disabil*. 2010;115(6):461-472. [Crossref]
30. Choi MH, Yang JO, Min JS, Lee JJ, Jun SY, Lee YJ, Yoon JY, Jeon SJ, Byeon I, Kang JW, Kim NS. A Novel X-Linked Variant of IQSEC2 is Associated with Lennox-Gastaut Syndrome and Mild Intellectual Disability in Three Generations of a Korean Family. *Genet Test Mol Biomarkers.* 2020;24(1):54-58. [Crossref]
31. Shbarou R, Mikati MA. The Expanding Clinical Spectrum of Genetic Pediatric Epileptic Encephalopathies. *Semin Pediatr Neurol.* 2016;23(2):134-142. [Crossref]
32. Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. *Neurocrit Care.* 2014;20(3):476-483. [Crossref]
33. Ong CT, Sheu SM, Tsai CF, Wong YS, Chen SC. Age-dependent sex difference of the incidence and mortality of status epilepticus: a twelve year nationwide population-based cohort study in Taiwan. *PLoS One*. 2015;10(3):e0122350. [Crossref]
34. Giuliano L, Vecchio C, Mastrangelo V, et al. Epilepsy and Gender Commission of the LICE (Italian chapter of the ILAE). Sex differences in side effects of antiseizure medications in pediatric patients with epilepsy: A systematic review. *Seizure*. 2022;102:6-13. [Crossref]
35. Hophing L, Kyriakopoulos P, Bui E. Sex and gender differences in epilepsy. *International Review of Neurobiology.* 2022;164:235-276. [Crossref]
36. Tomson T, Marson A, Boon P, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. *Epilepsia*. 2015;56(7):1006-1019. [Crossref]
37. Tomson T, Battino D, Bromley R, et al. Breastfeeding while on treatment with antiseizure medications: a systematic review from the ILAE Women Task Force. *Epileptic Disord.* 2022;24(6):1020-1032. [Crossref]
38. Reddy DS, Thompson W, Calderara G. Molecular mechanisms of sex differences in epilepsy and seizure susceptibility in chemical, genetic and acquired epileptogenesis. *Neurosci Lett.* 2021;750:135753. [Crossref]