Let’s Talk About Sex and Juvenile Myoclonic Epilepsy

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Sex-Specific Disease Modifiers in Juvenile Myoclonic Epilepsy

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Juvenile myoclonic epilepsy (JME) is a common idiopathic generalised epilepsy with variable seizure prognosis and sex differences in disease presentation. Here, we investigate the combined epidemiology of sex, seizure types and precipitants, and their influence on prognosis in JME, through cross-sectional data collected by The Biology of Juvenile Myoclonic Epilepsy (BIOJUME) consortium. 765 individuals met strict inclusion criteria for JME (female: male, 1.8:1). 59% of females and 50% of males reported triggered seizures, and in females only, this was associated with experiencing absence seizures (OR = 2.0, p < 0.001). Absence seizures significantly predicted drug resistance in both males (OR = 3.0, p = 0.001) and females (OR = 3.0, p < 0.001) in univariate analysis. In multivariable analysis in females, catamenial seizures (OR = 14.7, p = 0.001), absence seizures (OR = 6.0, p < 0.001) and stress-precipitated seizures (OR = 5.3, p = 0.02) were associated with drug resistance, while a photoparoxysmal response predicted seizure freedom (OR = 0.47, p = 0.03). Females with both absence seizures and stress-related precipitants constitute the prognostic subgroup in JME with the highest prevalence of drug resistance (49%) compared to females with neither (15%) and males (29%), highlighting the unmet need for effective, targeted interventions for this subgroup. We propose a new prognostic stratification for JME and suggest a role for circuit-based risk of seizure control as an avenue for further investigation.

Commentary

Juvenile myoclonic epilepsy (JME) is the most common type of generalized epilepsy, characterized by myoclonic seizures beginning at age 6 to 25 years, most often during the teen years, with or without absence and/or generalized tonic-clonic seizures. There is a female predominance and characteristic 2.5 to 6 Hz spike-and-wave and/or polyspike-and-wave discharges on electroencephalography (EEG). Seizures are most often lifelong without treatment although the majority are responsive to anti-seizure medication. Many patients report seizure precipitants, most often sleep deprivation, psychosocial stress, alcohol, and photosensitivity and a subset of individuals have seizures that are exclusively precipitated by specific identifiable triggers. Predictors of long-term seizure remission have been identified. Likelihood of poor response to pharmacologic therapy has been associated with sex including more prolonged epileptiform discharges on EEG and eye closure sensitivity in females and praxis induction as well as asymmetric EEG abnormalities in males. In clinical practice, valproate use is more common in males in part because of known risks of teratogenicity in women of childbearing potential such as neural tube defects and use of valproate has been correlated with better clinical outcome. In a large cross-sectional database from the Biology of Juvenile Myoclonic Epilepsy consortium consisting of 72 sites from 12 different countries, investigators studied sex-specific disease modifiers that may predict anti-seizure medication (ASM)-resistance in individuals diagnosed with JME. Examining 765 individuals (64% female) who met inclusion criteria, authors identified 3 factors that were associated with higher risk of treatment resistance including history of absence seizures, catamenial seizures, and psychological stress as a seizure precipitant among females with

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JME. The presence of absence seizures predicted ASM resistance in both males and females. Overall, one-third of participants were found to have ASM-resistant epilepsy. However, nearly 50% of females in the cohort with JME presenting with both absence and stress-precipitated seizures met criteria for ASM resistance, while only 15% of women with neither absence nor stress-precipitated seizures met criteria for ASM resistance. Catamnemal seizures were also independently predictive of poor response to ASMs without a prior history of absence seizures. Meanwhile, those individuals with a demonstrated photoparoxysmal response (PRP), most often manifesting as myoclonus, were more likely to become seizure-free with appropriate ASM. More females than males exhibited a PRP (42% vs 28%, p < 0.001). The authors accounted for prior history of valproate use and the potential bias introduced because of attempting to avoid it in women of childbearing potential in clinical practice and found that exposure to valproate did not account for the sex differences observed.

Based on their observations, the authors proposed a circuit-based explanation for variability in response to ASMs, a potential genetic predisposition in females to experience stress-induced and/or absence seizures, and possible influence of sex and steroid hormone concentrations on seizure intractability. Furthermore, they proposed behavioral modifications that could improve outcomes. As seen in prior studies, the most common patient-reported seizure precipitant was sleep deprivation in 34% of study participants. Surprisingly, only 2% of females who self-identified as having catamnemal seizures received menstrual management as a strategy for addressing seizures as compared to 64% who received counseling regarding optimal sleep hygiene. Better understanding and recognition of the impact of the menstrual cycle and hormonal manipulation may uncover additional management strategies for these individuals with ASM-resistant JME. Given that males also exhibit cyclical hormonal fluctuations, the impact on seizure control in this population is worth further investigation as well. Elucidation of specific neuroendocrine pathways involved with JME could provide evidence for certain hormonal or other pharmacologic interventions in susceptible patients. In addition, the authors proposed considering new strategies such as cognitive behavioral therapy and exercise to modify psychosocial stress responses that can trigger seizures.

Regarding conceptualizing seizures in JME into a circuit-based framework, studies have yet to fully identify regions of anatomic functional connectivity that are involved in certain seizure semiologies in patients with JME such as myoclonic, absence, or exclusively precipitated seizures although many neuroimaging, electrophysiologic, or combined approaches are currently being utilized.7,9 Neurostimulation-based interventions could be designed to target dysfunctional networks involved in generation of specific seizure types in individuals with JME and in particular, females with ASM-resistant absence and precipitated seizures.

The vast majority of participants (nearly 90%) in the study were of European ancestry and patients with JME over the age of 55 years were excluded from the analysis. Therefore, generalizability of the study findings to older adults and underrepresented minorities is potentially limited. An in-depth genetic evaluation and comparison of females with JME including whole exome sequencing and genetic pedigree (particularly in those individuals with the same seizure precipitants and responsiveness to anti-seizure treatments) may elucidate whether the complex inheritance pattern typically described in patients with JME10 is also responsible for the clinical presentation in these patients. Alternatively, the discovery of a single pathogenic variant may allow for the possibility of gene therapies for these individuals.

In conclusion, observed sex differences in clinical presentation and ASM resistance in patients with JME could shed light on underlying neuroendocrine, genetic, and functional anatomic influences. Once better understood, tailored therapies such as hormonal manipulation, pharmacologic therapy, neuromodulation, behavioral modification, or gene therapy could be implemented to improve seizure control.

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