GENDER-SPECIFIC CARE FOR NEUROLOGICAL DISORDERS: FOCUS ON EPILEPSY

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Epilepsy has a new definition. It has been legitimized and medicalized by being designated as a "disease" instead of its former status as a "disorder." Any person can have a seizure under physiologically vulnerable circumstances, but only those with epilepsy have the risk of ongoing unprovoked seizures. Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition[1].

- (1) At least two unprovoked (or reflex) seizures occurring >24 h apart;
- (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
- (3) diagnosis of an epilepsy syndrome.
- Epilepsy is considered to be resolved for individuals who either had an age dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure medicines for at least the last 5 years[1].

While metabolic derangements and toxins lower the seizure threshold in persons with and without epilepsy, for persons with epilepsy, it is the underlying pathophysiology that lowers the seizure threshold. This underlying factor may be structural or genetic, among other causes, but it is increasingly revealed that the seizure threshold for persons with epilepsy is lowered through genetic variations revealed by genomic analysis. This complexity unpins the concept that epilepsy of unknown cause, which comprises approximately 50% of persons with epilepsy, may be largely genetically determined while not familial. Genes for which abnormalities can be specifically disease-causing, such as nonsense mutations in the SCN1A gene resulting in the phenotype of Dravet Syndrome, can likely be disease- influencing when the genetic variation is more subtle in its differentiation from normal. In the specific example of SCN1A, polymorphisms of this gene are over-represented in patients with focal epilepsy of normal intellect and unrevealing MRI studies[2]. A group of susceptibility genes have been described, the M30 network, among which genetic alterations can be either sufficient or influential on the development of epilepsy[3]. This genetic influence on the manifestation of epilepsy naturally leads to the question as to what other co-morbidities are influenced by these variations. Do they contribute to the co-morbidities incorporated in the definition of epilepsy, specifically cognitive, psychosocial or in the instance of this discussion, with reproductive consequences? One recent paper addressed the concept of single gene variations that contribute to both epilepsy and co-morbidities, with compelling evidence put forth regarding epilepsy and depression (serotonin receptor variations such as 5HCT2) and epilepsy and dementia (Aβ accumulation)[4]. Alternatively, epilepsy –associated genes such as T-type calcium channel genes in Childhood Absence Epilepsy only cause a channelopathy confined to a specific neuronal population and produce no other neurologic problems[5].

This discussion is confined to the comorbidity of reproductive dysfunction and its management for men and women with epilepsy. While psychiatric and cognitive comorbidities of epilepsy have long been acknowledged as important, prevalent, worthy of study and intervention, reproductive comorbidity has been less accepted. This may be simply because the former two co-morbidities are obviously seated in the same human organ as epilepsy, while epilepsy-associated reproductive co-morbidities must come about due to complex endocrine effects for which the brain plays a key part, but the end sequelae is expressed in organs rather remote from the brain, the gonads. Further, reproductive adversity in the setting of epilepsy is associated with antiepileptic drugs and their effects on endogenous hormones, seizure occurrence is affected by both endogenous hormones and exogenous hormones in the form of hormonal birth control and hormone replacement in menopause and andropause, and most mysteriously and profoundly, epilepsy itself affects reproductive function through direct effects on hypothalamic pathways.

The antiepileptic drugs which are strong CY 3A4 inducers, carbamazepine, phenytoin, phenobarbital and to lesser degrees topiramate at greater than 200 mg per day, oxcarbazepine and eslicarbazepine, have the potential for decreasing the circulating levels of reproductive hormones including androgens through this metabolic pathway. This effect is present across genders and has been shown to be reversible when the AEDs are discontinued [6]. While suppressed progesterone and estrogen levels may have reproductive consequences for women in terms of menstrual irregularity and decreased fecundity, this effect is likely not clinically important for men. Valproate inhibits testosterone metabolism through CYP 2C19 inhibition and aromatase inhibition, and results in increased circulating testosterone levels for both men and women[7]. Levetiracetam has been shown to increase testosterone levels in men, and has not been studied in women[8]. Again, the physiologic consequences are more important for women in the form of an increased risk of polycystic ovarian syndrome and menstrual irregularity with valproate use[9].

Epilepsy itself may affect endogenous hormones, specifically the androgen system, recognized as an important regulator for many aspects of well-being. However, the endocrine effects appear to be opposite and adverse for each sex, in that androgens are overall increased in women with epilepsy[10], but decreased in men, with several reports of low testosterone and poor testicular function even in untreated men with epilepsy[11].

Further, endogenous hormones influence epilepsy, as evident for the 20% of women with epilepsy who have seizure exacerbations in association with menstrual cycling, called catamenial epilepsy. Treating these hormonally-influenced seizures with hormones now seems to be a reasonable approach for subset of these women. A recent study found that natural progesterone supplementation was beneficial and reduced seizure occurrence for women specifically with a clear premenstrual increase in seizure frequency (three-fold compared to other days of the cycle) [12]. Having a catamenial pattern appears to lend a susceptibility to increased seizure frequency at perimenopause and a decrease in seizure frequency at menopause[13].

Risks of exogenous hormone use are also important for women with epilepsy. A recent study reported an increased risk of seizures with combined oral contraceptive use for a significant minority of the study population[14]. Depo medroxyprogesterone acetate was more often associated with seizure decrease than seizure increase[14]. Further, hormone replacement therapy in the form of conjugated equine estrogens and medroxyprogesterone acetate increased seizures in a dose-related manner when used in menopausal women with epilepsy[15]. The effects of exogenous and endogenous hormones are remarkably consistent with the well-described neurophysiologic effects of estrogen which is excitatory and progesterone, which is neuro-inhibitory through its direct action on the progesterone receptor[16].

The strong CYP 3A4 enzyme-inducing AEDs appear to have an adverse effect on fertility[17], while emerging evidence indicates that fertility for women with epilepsy who are otherwise healthy and not taking enzyme-inducing AEDs are not at risk for not getting pregnant readily[18].

In differentiation from the disease of epilepsy, seizure occurrence likely adversely affects reproductive health in women. Earlier age at menopause has been reported in women with frequent seizures by as much as three years compared to those with rare seizures, who appear to have an expected age at menopause[19]. This adverse effect is supported by the finding of lower antimullerian hormone in women with epilepsy of reproductive age who have seizures versus those who are seizure-free[20], given that this hormone is a direct measure of ovarian follicular reserve.

There are more management interventions and concerns for women with epilepsy regarding reproductive health. But essentially the management approaches are the same across genders: 1) Clearly, the strong enzyme-inducing AEDs should be avoided in order to maintain an individual's physiologically normal endogenous reproductive hormone levels. Valproate should be avoided for women of reproductive age also due to its risk of teratogenesis, and for its endocrine disruptive effects including promoting metabolic syndrome through altering insulin metabolism are important for both genders. 2) Controlling seizures may extend the reproductive life epoch for women with epilepsy and may have as yet undiscovered beneficial effects for the reproductive life of men with epilepsy.

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