Research Highlights

Highlights from the latest articles indicating the relevance of sex steroid pharmacogenetics

Sex steroids and seizure recurrence in women with epilepsy

Evaluation of: Murialdo G, Magri F, Tamagno G *et al.*: Seizure frequency and sex steroids in women with partial epilepsy on antiepileptic therapy, *Epilepsia* 50, 1920–1926 (2009).

It is widely acknowledged by various *in vitro* and animal model studies that sex steroids in women might play a role in modulating the risk factors associated with seizure frequency [1]. It has been hypothesized that an alteration in the relative levels of circulating sex steroids, mainly estradiol (E2) and progesterone (Pg), might act as trigger for excessive neuronal excitability during seizures, estradiol being a proconvulsant and progesterone being an anticonvulsant. Since premenopausal women exhibit cyclic variation in these sex steroids during their menstrual cycles, certain phases of the menstrual cycle are more vulnerable to seizure recurrence. A study by Backstrom *et al.* was the first to demonstrate the cyclic variability in serum levels of ovarian hormones and risk factors for seizure recurrence in a subset of women with epilepsy, popularly known as catamenial epilepsy [2]. Furthermore, medications might prove ineffective during high-risk periods of the menstrual cycle.

However, there has been a scarcity in research articles exploring the correlation of circulating E2/Pg levels with seizure frequency in patients with different seizure etiology. Murialdo *et al.*, have attempted to study the relationship of cyclic E2/Pg in women patients diagnosed with partial epilepsy who were already on drug regimens [3]. Furthermore, the authors have tried to address several other issues that might interfere with the conclusion. For instance, seizures alone could alter antiepileptic drug (AED) metabolism. On the other hand, AEDs could themselves alter the metabolism of sex steroids. Other factors like serum

proteins could influence the bioavailability of sex steroids and body weight, and adipose tissue reserves could also play a major role due to the lipophilic nature of sex steroids. As reproductive dysfunctions are commonly associated with epilepsy in women, the authors have also tried to correlate them with the severity of seizures. Lastly, healthy controls were also included in the study for observing differences in clinical parameters specific to disease state only.

Murialdo *et al.* failed to observe any association of E2/Pg or freely available (f)E2/Pg during luteal and the follicular phases of menstrual cycle with seizure frequency. In addition, steroid levels were similar in patients with different magnitudes of seizure severity. Although these levels were lower than healthy controls in the present study, the direct role of seizures influencing sex steroid levels is ruled out since seizure frequency did not show any significant associations with reproductive dysfunction. The author has also expressed several concerns with or limitations of this study, particularly regarding the small sample size for conducting monotherapy study, indirect assessment of reproductive dysfunction, and variability in phenotypic data including duration of AED treatment and body weight.

Recently, several reports have demonstrated the local synthesis of sex steroids in the brain, also known as neurosteroids, and it has been hypothesized that the sex steroid milieu in the brain might not be synchronous with cyclic variation in circulating steroids [4]. Furthermore, the magnitude of surge in the circulating E2 levels during the luteal phase of the menstrual cycle might not cause enough local concentration in the neurons to provide a trigger for reaching the seizure threshold [5]. Hence, this study by Murialdo might be considered as evidence that supports a greater role of neurosteroids

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in determining estrogenicity in the neuronal environment, and stresses the need for detailed understanding of hormonal milieu in the brain before coming to any clinically relevant conclusion.

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Sex steroid therapy & adiposity

Evaluation of: Karim R, Mack WJ, Hodis HN, Roy S, Stanczyk FZ: Influence of age and obesity on serum estradiol, estrone, and sex hormone binding globulin concentrations following oral estrogen administration in postmenopausal women. *J. Clin. Endocrinol. Metab.* 94(11), 4136–4143 (2009).

Impaired metabolism of endogenous estrogen is central to the pathogenesis of several diseases of the cardiovascular system and CNS [1]. This could be attributed to the marked variability in pharmacokinetics and pharmacodynamics of estrogen metabolism. In addition to genetic factors, gender, age and body weight might contribute to this variability [2,3]. Altered metabolism of estrogens could also influence the efficacy of exogenous estrogen therapy (ET) used for the treatment of estrogen-related diseases. Furthermore, prolonged administration or higher dose of ET might be associated with an increased risk of venous thrombosis and stroke in such patients [4].

Karim *et al.* have tried to evaluate the influence of age and body weight on circulating estrogen levels in postmenopausal women on exogenous estrogen treatment and an age matched placebo group (non ET users) [5]. The authors have used BMI

and waist:hip ratio as clinical parameters for judging body weight and obesity. Both BMI and waist:hip ratio showed positive associations with serum free estradiol (E2) levels, and an inverse relationship with serum hormone binding globulin (SHBG) levels in the placebo group. Lower SHBG levels are further indicative of higher E2 levels. These findings further demonstrate adipose tissue as being the primary source of estrogen synthesis after cessation of the menstrual cycle. On the other hand, association between age and serum free E2 levels as well as SHBG levels failed to reach any significance.

Karim *et al.* claim to be the first to investigate the influence of age and weight on estrogen levels in postmenopausal women on ET. Similar to the placebo group, both higher E2 levels and lower SHBG levels were characteristically associated with weight and central obesity in women on ET after adjusting for age. Use of reliable radioimmunoassay for purification and quantitation of E2 with repeated measurements further strengthens these observations, however, the authors have expressed concerns over limited sample size, and have stressed the need for revalidation in a larger epidemiological study. In summary, positive correlation of weight and central obesity with estrogens in older women on hormonal therapy further demonstrates their important utility

as clinical markers for deciding optimum duration and dosage of ET in postmenopausal women, specific to each patient, thus minimizing the risks associated with proinflammatory and prothrombotic effects of exogenous estrogens.

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