Epilepsy Currents
2024, Vol. 24(2) 79-83

DOI: 10.1177/15357597231213248
journals.sagepub.com/home/epi
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Epilepsy and Anti-Seizure Medications: Secret Agents for Endocrine Disruption

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Abstract

There is a reciprocal relationship between epilepsy and reproductive endocrine disorders. Seizures and anti-seizure medications (ASMs) can contribute to reproductive and endocrine dysfunction and reproductive dysfunction may exacerbate seizures. Epilepsy via neuroendocrine mechanisms affects the hypothalamic–pituitary-ovarian (HPO) axis, disrupting the regulation of gonadotropin secretion, and resulting in dystrophic effects on the ovaries and early menopause. Anti-seizure medications have endocrine-related side effects on sexual function and bone health. Long-term use of ASMs may result in menstrual irregularities, sexual dysfunction, anovulatory cycles, polycystic ovaries, and reduced fertility. Some ASMs also interfere with bone metabolism. Epilepsy patients treated with ASMs are at risk for bone loss and fractures. This article explores the endocrine and hormonal effects of seizures and ASMs.

Keywords

endocrine disruption, bone health, ASM, epilepsy, reproductive disorder, sexual dysfunction, PCOS, menstrual irregularities, menopause, catamenial epilepsy

There is a higher rate of menstrual disorders, polycystic ovary syndrome (PCOS), and sexual dysfunction in women with epilepsy. Menstrual disorders occur in a third of women with epilepsy compared with 12% to 14% in general population.[1] Polycystic ovary syndrome is characterized by enlarged ovaries, multiple cysts, androgen-secreting ovarian stroma causing symptoms of androgen excess including hirsutism, alopecia, acne, obesity, and menstrual disturbances.[2] It is seen in 4% to 7% of women of reproductive age but 10% to 25% of women with epilepsy.[3,4] In a study of 50 consecutive patients with temporal lobe epilepsy, Herzog and colleagues found that 56% reported amenorrhea, oligomenorrhea, and abnormal menstrual cycle intervals.[5]

Brain regulates sex hormones via the hypothalamic–pituitary–ovarian (HPO) axis. Gonadotropin-releasing hormone (GnRH) produced by hypothalamus stimulates the production of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland and eventually affects the production of estrogen and progesterone by the ovaries. The temporo-limbic system, implicated in the pathophysiology of more common adult-onset epilepsies, plays an integral role in endocrine regulation. There are direct projections from amygdala to hypothalamus and its neurosecretory cells. Seizures originating from the amygdala and temporo-limbic system can affect the pulsatile GnRH secretion, and therefore result in disruption of hypothalamic regulation of pituitary gonadotropin secretion and subsequent reproductive-endocrine disorders. The temporo-limbic system is in turn affected by the feedback of neuroactive reproductive steroids.[6-8]

In their study of women with temporo-limbic epilepsy and normal control subjects, Herzog and colleagues demonstrated

that there was a relationship among abnormal interictal epileptiform discharges, reproductive endocrine dysfunction, and menstrual disorders.[9] Furthermore, there is evidence that the laterality and focality of epilepsy is associated with specific types of endocrine disorders. There is increasing evidence that PCOS is associated with left temporal as well as right extra-temporal lobe epilepsies, whereas hypothalamic amenorrhea is seen more commonly in women with right temporal epileptogenic focus. Left temporal lobe epilepsy is associated with higher pulse GnRH secretion, resulting in higher LH/FSH ratio. This in turn causes failure of follicular ovarian maturation, chronic anovulation, and cyst formation. Right temporal lobe epilepsy is associated with lower pulse GnRH secretion, decreased LH and estradiol levels, characteristic for hypothalamic anovulation. The association of laterality of epilepsy with specific endocrine disorders further supports the important role of epilepsy as an endocrine disruptor.

In the quest to understand the endocrine disruptive effects of epilepsy, the name of a neuroactive peptide, Anti-Müllerian hormone (AMH) comes up in the literature. Anti-Müllerian hormone is a ligand of the transforming growth factor beta family (TGF-β), that is known to regulate sexual differentiation and gonadal function and have seizure protection properties. In females, granulosa cells of the ovary begin to produce AMH upon the initiation of follicular development to support ovarian function. Anti-Müllerian hormone receptors are also expressed in brain regions known to be involved in epileptic network including hippocampus, hypothalamus, and cortex. Women with epilepsy who have active seizures have a lower concentration of AMH compared with those without seizures and healthy controls. Anti-Müllerian hormone is hypothesized to protect neurons against N-Methyl-D-Aspartate mediated neurotoxicity both in vitro and in vivo.[10-12]

Women with epilepsy have a higher rate of premature ovarian failure and early menopause. In fact, there is a correlation between uncontrolled epilepsy and earlier age of menopause. This is attributed to endocrine effects of seizures on disruption of function of the HPO axis, leading to poor maturation and early loss of follicles discussed earlier.[13] There is increased risk for seizures during perimenopause period, when estradiol predominates with a net neuroexcitatory effect. Epilepsy is likely to improve after menopause is established and estradiol levels drop.[14]

Reproductive and Endocrine Effects of Anti-Seizure Medications

Anti-seizure medications (ASMs) can result in endocrine related side effects including polycystic ovaries, decreased libido, erectile dysfunction, and bone loss. Microsomal hepatic enzyme inducing anti-seizure medications (EIASM) may impact sex hormones and result in lower levels of bioavailable testosterone and estradiol and subsequently contribute to sexual dysfunction, menstrual irregularities, and problems with fertility. Some non-enzyme inducing ASMs such as valproic acid (VPA) are also associated with endocrine disturbances such as polycystic ovary and weight gain. Certain ASMs may contribute to sexual dysfunction by a variety of mechanisms. Anti-seizure medications have influence on the metabolism of the central and peripheral endocrine hormones and their binding proteins.[15] Some hepatic cytochrome P450 enzyme inducing ASMs increase the breakdown of biologically active testosterone resulting in hyposexuality in men and women with epilepsy. They also decrease bioavailability of estradiol, resulting in menstrual disorders, anovulatory cycles, and polycystic ovaries.[15] Most of the non-enzyme inducing ASMs such as gabapentin, pregabalin, benzodiazepines (BZDs), and VPA enhance GABAergic transmission, which in turn has specific effects on sexual function.[15]

Hepatic Enzyme Inducing ASMs

Carbamazepine (CBZ), phenobarbital (PB), and phenytoin (PHT) are all hepatic microsomal enzyme inducing ASMs (EIASMs). Oxcarbazepine (OXC) and topiramate (TPM) are weak hepatic enzyme inducers. Long-term treatment with these medications results in low levels of free testosterone and estradiol and therefore high levels of sex-hormone binding globulin concentrations in people with epilepsy.[16-19] This in turn may lead to menstrual irregularities, sexual dysfunction, and reduced fertility.

The effect of TPM on sexual function can be either central and related to interference at the limbic and cortico-striatal loop or through affecting peripheral spinal and autonomic neurons. Substitution or reduction in dose resulted in recovery of symptoms.[20]

Non-Enzyme Inducing ASMs

In women with epilepsy, valproate (VPA) is associated with increased risk of developing PCOS, hyperandrogenism, anovulatory cycles, and menstrual irregularities.[21-25] A cross-sectional study in 1993 of 238 women with epilepsy showed that menstrual disorders were common in women taking VPA monotherapy (45%). Polycystic ovary syndrome and hyperandrogenism were seen in 90% of women on VPA monotherapy especially if VPA was started before age 20.[26]

Lamotrigine (LTG) does not have hepatic enzyme inducing properties and LTG monotherapy is reported to cause minimal sexual effects in men and even improvement in sexual function in women.[19,27] Levetiracetam (LEV) was studied as monotherapy and was found not associated with drug-specific endocrine or sexual side effects in men and women. In a study by Svalheim and Colleagues women treated with LTG and LEV were found to be more satisfied with their sexual function than patients treated with CBZ and healthy control.[28] There are case reports of LEV associated hypersexuality[29] as well as loss of libido and anhedonia.[30] The effect is postulated to be due to changing in the balance of dopamine/serotonin ratio. There is lack of large population-based studies to provide conclusive guidance regarding the potential adverse sexual effects of lacosamide, zonisamide (ZNS), and some other newer ASMs.

Endocrine Effects of Epilepsy and ASMs on Bone Health

Osteoporosis is the most common bone disease. The WHO diagnostic classification defines osteoporosis as a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the young normal mean reference population. Osteoporosis is characterized by low bone mass or deterioration of bone tissue, disruption of bone architecture, compromised bone strength, with an increase in risk of fracture. Reduction in skeletal mass is caused by an imbalance between bone resorption and bone formation. Osteoporosis can be caused both by a failure to build bone and reach peak bone mass as a young adult and by bone loss later in life.

The peak bone mass is an important determinant of osteoporotic fracture risk. The peak bone mass is determined by the amount of bony tissue present at the end of the skeletal maturation. Factors influencing peak bone mass include sex hormones, insulin growth factor system, physical activity, calcium and protein intake, illness, and medications. Estrogen deficiency can accelerate bone loss and lead to excessive bone resorption accompanied by inadequate bone formation in postmenopausal women.

In people with epilepsy there is a 2-6-fold increased risk of fractures when compared to general population due to altered bone metabolism, decreased bone density, and a propensity to fall as a result of ASM-induced loss of balance.[31,32] Non traumatic fracture incidence is increased in younger age among ASM taking population peaking at 11 to 13 years, decreasing with the older age groups.[33] Other risk factors for bone loss include duration and severity of epilepsy, certain ASMs and prolonged duration of exposure, female sex, menopause, polytherapy, sedentary lifestyle, smoking, excessive alcoholic beverage intake, inadequate sun exposure, and certain endocrine conditions.[31]

Certain ASMs are independent risk factors for bone loss and Hepatic CYP450 enzyme inducing ASMs such as CBZ, PHT, PB, primidone, and BZDs have long been associated with decreased BMD and abnormal bone metabolism. There are several mechanisms suggested for ASM-induced bone disease. Enzyme inducing ASMs and VPA may affect specific isoenzymes involved in vitamin D metabolism and result in accelerated vitamin D metabolism, therefore lowering vitamin D levels and interfering with normal absorption of calcium. Secondary hyperparathyroidism has been reported in patients taking ASMs.[34] Anti-seizure medications may also affect the proliferation of chondrocytes in the growth plate, resulting in bone loss.[35] Enzyme inducing ASMs can reduce the capacity of thyroid chief cells to secrete calcitonin. Some ASMs can increase serum homocysteine by lowering the folate levels. Folate is thought to have a role in preserving nitric oxide synthase activity in bone cells, stimulating osteoblasts and inhibiting bone catabolism and loss. It has been found that (independent of age and sex) for each standard deviation increase in the homocysteine level, the risk of fracture increased by 30%.[36]

Several studies have reported decreased BMD, osteopenia and osteoporosis of hip and lumbar spine with CBZ,[15,37-39] PHT,[40-42] VPA,[15,40,41,43] TPM,[44,45] and OXC.[39,46] A recent study of adult patients newly diagnosed with epilepsy treated with VPA, LTG, and LEV monotherapy found that VPA altered bone turn over, while LTG and LEV did not exert harmful effects on bone health.[47] Koo and colleagues did not find any harmful effect of LEV on bone density.[48] However, at least one study has reported reduced BMD in adults treated with LEV.[49] One study of the effects of ZNS after 13 months of monotherapy in epilepsy patients concluded that long-term ZNS monotherapy does not negatively affect bone health in drug-naive patients with epilepsy.[50]

Epilepsy patients treated with ASMs are at risk for bone loss and fractures. Most ASMs irrespective of hepatic enzyme inducing or non-enzyme inducing may result in low BMD, hypocalcemia, and vitamin D deficiency, which may occur early during treatment and initially remain asymptomatic. Neurologists caring for patients with epilepsy should consider monitoring for calcium and vitamin D levels and periodic BMD examinations in their patients for early detection of upcoming bone loss.

In summary, this article explored the complex and reciprocal relationship among epilepsy, ASMs, and reproductive endocrine disorders. Epilepsy and its treatment can act as silent agents disrupting the endocrine pathways and contributing to reproductive and endocrine consequences. Physicians treating patients with epilepsy should be aware of these long-term endocrine disruptions including menstrual irregularities, sexual dysfunction, anovulatory cycles, polycystic ovaries, reduced fertility, and bone health issues and try to identify and address them as they care for their epilepsy patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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