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Gender differences in epilepsy

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Epilepsy is disorder of the central nervous system resulting in unprovoked seizures that happen more than once. Epilepsy affects children and adults, men and women, and persons of all races, religions, ethnic background and social classes. Individuals in certain populations are at higher risk. Epidemiological studies of epilepsy indicate that the overall incidence of epilepsy is slightly higher in male than in female subjects. For individual seizure types various sex ratios have been reported (1–5).

In two population based studies, gender differences in idiopathic generalized epilepsy were identified. In the outpatient study these differences were due to juvenile absence epilepsy and juvenile myoclonic epilepsy. It seems that women more frequently than man have idiopathic generalized epilepsy. The reason behind this difference is not established, but it is likely that sex hormones may play a role in the development of idiopathic generalized epilepsy. If this assumption is true, the gender difference would be more pronounced before menopause, and indeed, the female preponderance in idiopathic generalized epilepsy was highest for the age group 15–50 years and decline with age (6–8).

Symptomatic, localization reacted epilepsy was more frequent among men than among women, and this may reflect differences of structural damage of the brain and subsequent seizures. The gender difference was greatest in the age group 30–59 years (the age group with a high risk of traumatic brain injury), men also may be more vulnerable to seizure associated brain damage. It seems that nonsymptomatic epilepsy (both idopathic and criptogenic generalized) more often occurs in women in contrast to symptomatic location-related epilepsy which has preponderance in men (9).

Most studies in the literature find a female preponderance in psychogenic non-epileptic seizures (PNES) with the proportion of women of 75%. Men were significantly older than women at both attack onset and presentation at the NES clinic. In most pediatric series there is no sex imbalance. High rates of concomitant

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psychopathology in patients with PNES are frequently reported (10).

Both males and females with epilepsy have low bone marrow density (BMD) than controls. There are important gender differences in BDM. Males with longer duration of epilepsy (>6 years of epilepsy) experience the largest reduction in BDM compared to controls. Most studies in epilepsy have examined bone health and fractures and found evidence of increased bone turnover or a variable relationship to fractures. In women phenitoin and carbamazepine are associated with increased bone turnover suggesting that these antiepileptics may have long term effect. Men also appear to be vulnerable to bone adverse effects of epilepsy. Factors underlying such gender differences include genetic-ethnic factors, hormonal status, calcium intake physical activity, and weight. In twin study, heritability accounted for up to 80% of BMD accrual. Twins discordant for epilepsy demonstrated lowered BMD in the twin with epilepsy receiving AEDs for more than 2 years, particularly if an enzyme inducing AED was used. In menopause the decline in estrogen may be important factor in the pathogenesis of involutional osteoporosis. However, osteoporosis in adolescent patients may be related with application of AED, which are aromatase inhibitors, by disturbing skeleton maturation due to lowered oestrogen levels causing life long consequences if not properly treated (11,12).

Hormonal influences on seizure frequency

Experimental studies have shown that estrogen excites the brain cells and can make seizures more likely to happen (proconvulsive effect). In contrast, natural progesterone can inhibit or prevent seizures in some women and has anticonvulsive effect. The most important is the proportion of those two hormones, with occurrence of epileptic seizures with elevated estrogen concentration and normal progesterone concentration, as well as lowered progesterone concentrations with normal estrogen concentrations. Stable proportion of these hormones can have no influence on seizures (13–27).

Hormonal changes in men are less obvious than in women because men do not have a monthly cycle. However, in men, hormones (testosterone and breakdown products) also influence brain function and may have an impact on seizures. Normally, women also have low concentration of androgens in serum whose influence on epileptic activity has not been well investigated. Until now it has been noticed that women tend to have less frequent seizures when the levels of serum androgens are higher (28–30).

Some women with epilepsy experience changes in their seizure patterns at times of hormonal fluctuations. It is not unusual for certain kinds of seizures to disappear at puberty, while other seizure disorders may start at this time. Many women with epilepsy see changes in the number or the pattern of their seizures around the time of ovulation (mid-cycle), or just before and at the beginning of their menstrual periods. This is a condition called ''catamenial epilepsy'' and describes a tendency for increased seizures related to the menstrual cycle. In some women, seizures occur most frequently just before menstruation, during the first few days of menstruation and at mid-cycle, during ovulation. The balance between the two female sex hormones, estrogen and progesterone, may be disturbed, or you may not be producing enough progesterone during the second half of your menstrual cycle. It is also possible that the amount of antiepileptic drug (AED) circulating in your bloodstream may decrease before menstruation (31–34).

For both women and men, identifying hormonal influences on seizure patterns may lead to a better understanding of treatment options for seizure control. Women should keep a calendar of their menstrual cycles and of days they have seizures. It is important to keep track of other factors that may affect the menstrual cycle or seizure patterns, such as missed medication, loss of sleep, unusual fatigue, intense physical training, stress or an illness.

Most research on epilepsy in women has focused on the childbearing years, but as the population ages and older women take a more active role in the management of their health, more attention is being paid to the relationship between epilepsy and menopause (35). As a group, women with epilepsy who have gone through menopause have about the same frequency and severity of seizures as younger women, but this statistic hides a lot of individual differences. In one study, one-third of the women who had epilepsy before menopause reported no change in their seizures. A slightly larger proportion reported worsening of their seizures, and a slightly smaller number reported improvement. (There was even a group in which seizures occurred for the first time during or after menopause, with no known cause.) Another study similarly identified groups in which seizures were unchanged, increased, or decreased. This study found that women who had a pattern of catamenial epilepsy were more likely to have fewer seizures after menopause but they had more seizures during the period of changes just before menopause (called perimenopause). Women with catamenial epilepsy tend o have more frequent seizures during perimenopause when the level of progesterone is lower, and estrogen level is higher. In those cases progesterone therapy is recommended.

Larger studies are needed to better identify which women are likely to have improved or worsening seizures.

In menopause (low levels of estrogen and progesterone) there is reduced frequency of epileptic seizures due to stabilized proportion of the two hormones. In that period usage of hormone replacement therapy could lead to more frequent seizures. Low dosage of estrogen usually has no influence on seizure frequency.

Estrogen therapy is important in prevention of osteoporosis, therefore hormone replacement therapy has to be given individually, depending on the risks and benefits. One small study suggested that seizure frequency increased in women who used hormone replacement therapy (HRT), but another study found that women who used the type of HRT that includes progestin (a form of progesterone) were much less likely to have worsening of their seizures than those who took only estrogen. The role of HRT in preventing osteoporosis can be especially important for women with epilepsy, since seizures can increase the risk of falling and breaking weakened bones. The problem is worsened by the fact that certain seizure medicines can cause bone loss. These medicines include phenytoin (Dilantin or Phenytek), carbamazepine (Tegretol or Carbatrol), and phenobarbital which all binds oestrogen or act as aromatase inhibitors. Women who take these medications should be especially careful to get enough calcium, vitamin D, and exercise, however the efficiency of such additional treatment may be limited due to lack of oestrogen as a key molecule in bone mass turnover (36).

Antiepileptic drugs can contribute to the reproductive disfunction by lowering plasma steroid concentrations (carbamazepine, phenitoine, phenobarbital) or elevating gonadal androgen concentrations (valproate).

In one third of women with epilepsy, during pregnancy more frequent epileptic seizure are noted mostly at the end of the first or at the beginning of third trimester, due to physiological changes during pregnancy as well as non compliance. Physiological changes are attributable to weight gain, increased liver metabolism, and lower binding of AET to plasma proteins. The greatest difference in plasma concentration during pregnancy is noticed during first trimester (phenobarbital) and third trimester (carbamazepine). Lamotrigine dosage should be also adjusted due to frequent lowering of plasma concentrations. All AET dosages usually should be brought back to the initial dosage after labor (37–41).

Gestational epilepsy indicates idiopathic epilepsy which occurs for the first time during pregnancy.

One study analysed gender differences in mesial temporal lobe patients with regard to clinical history, seizure semiology and EEG

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data. Male patients experienced generalized seizures significantly more often and isolated auras significantly less often than female patients Analysing EEG data showed that seizure pattern lateralized to the side of hippocampal sclerosis occurred more often in female patients and they concluded that men had more often secondarily generalized tonic clonic seizures while women had isolated auras and lateralized EEG seizures pattern more often suggesting that seizure spread is more extended or occurs more frequently in men (42).

Recent results of oncological, neurological, developmental and biochemical studies suggest that the reproductive dysfunction in men and women, as a side effect related with antiepileptic therapy, points that the estrogens and estrogens receptors have more important role in epilepsy that was thought before. It seems that contrary to the present definition of oestrogen as a compound affecting seizure susceptibility, based on causal chains: of increased estrogen levels (such as alcohol intake) and seizure, fact that all antiepileptic drugs are aromatase inhibitors or have estrogen binding properties, described cases of seizures in epileptic patients taking quinine (which increases oestrogen levels) as preventive therapy against malaria, impact of photic activation and sleep on estrogen level, it can be assumed that estrogen may plays the leading role in the mutual origin of different types of epilepsy (43–58). Interdisciplinary and multiparameter approach in investigation of interaction between antiepileptic drugs and genetic polymorphisms of aromatase, canal membrane proteins, polymorphisms of metabolism and specific pattern of brain oestrogen receptors distribution of epilepsy patient in future may have impact on therapy improvement and possible application of gene therapy.

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