By Steven Karceski, MD

How Seizures and Medications Adversely Affect Men with Epilepsy

Male epilepsy patients, like female ones, can be subjected to unique, gender-specific adverse effects of AED use. Here's what to consider.

In the medical literature, there has been considerable attention focused on issues that are specific to women with epilepsy. The main concerns are decreased sexual function, diminished fertility and disruption of the normal menstrual cycle. Long-term medication side effects such as bone loss (osteopenia and osteoporosis) are also a problem with certain antiseizure medications; postmenopausal women are at the highest risk for developing these problems. Implicit in all the discussions about special considerations for women is the notion that our male patients are spared any gender-specific risks or adverse effects. Although the burden for men is indeed less severe vis-à-vis women, some male patients do experience sexual dysfunction while on an AED regimen.

In men, sexual dysfunction secondary to AED use manifests as impotence, diminished sperm count and abnormal sperm morphology. Although there may be several likely explanations for sexual dysfunction in men with epilepsy, recent studies have begun to clarify the link between seizures, AEDs and the serum concentration of testosterone.

Feedback Loop

There is a very sensitive feedback system which carefully regulates sex hormones in men. Leutinizing hormone-releasing hormone (LHRH), also called gonadotropin-releasing hormone (GnRH) is released by the hypothalamus. This stimulates the gonadotrophs, a small collection of cells in the anterior pituitary, to secrete both leutinizing hormone (LH) and follicle stimulating hormone (FSH). LH acts on the Leydig cells in the testes to produce testosterone. FSH, in combination with the testosterone which was produced by the action of LH on the Leydig cells, acts on the seminiferous tubules to increase sperm production. In other words, sperm production depends on both LH and FSH while testosterone production depends only on LH.[1]

Testosterone is metabolized, in its target tissues, to two active compounds: dihydrotestosterone and estradiol. Dihydrotestosterone is the substance that promotes virulization and male sexual differentiation. The total amount of circulating estrogen is in part due to the metabolism of testosterone. However, estrogen is also made in adipose tissue. As the amount of adipose tissue increases, so too does the total amount of circulating estrogen. All of these steroid hormones are broken down by the P450 system in the liver cells (hepatocytes).

When testosterone levels are low, the hypothalamus and pituitary respond by secreting GnRH and therefore LH and FSH. However, the serum concentration of testosterone will depend on the amount of sex hormone binding globulin (SHBG). The reason for this is that about 98 percent of the total amount of circulating testosterone is bound to SHBG. In other words, processes that increase the concentration of SHBG will reduce the amount available testosterone.

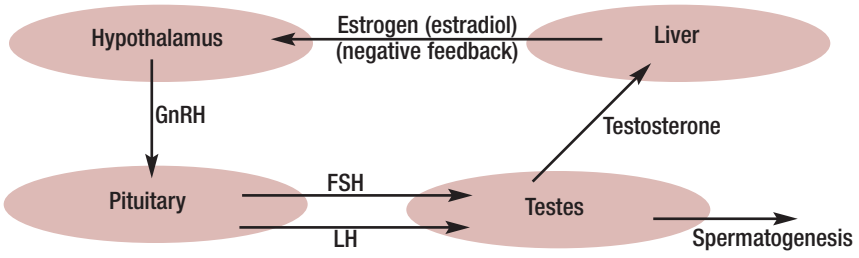
In addition to this, the levels of serum testosterone are affected by the levels of circulating estrogen, which negatively feeds back to the hypothalamus (see Figure 1). This makes sense as estrogen is one of the active metabolites of testosterone. However, estrogen is also be produced by fat cells. Greater amounts of adipose tissue translates into higher circulating levels of estrogen, and therefore lower serum testosterone levels. This can also lead to clinical changes such as abnormal breast development in men (gynecomastia).[1] In short, there are several points along the hypothalamic-pituitary-gonadal axis where hormone secretion and metabolism can be altered, resulting in sexual dysfunction in men with epilepsy.

AEs of Enzyme Inducers

Unfortunately, hepatic enzyme-inducing medications reduce the serum concentration of sex hormones. This has been the leading hypothesis to explain sexual dysfunction in men with epilepsy. Medications like phenytoin, carbamazepine, phenobarbital and to a lesser extent oxcarbazepine are inducers of the hepatic P450 system of drug metabolism. As a result, there is a reduction in the total levels of testosterone.

Dr. Herzog and his colleagues compared the serum concentrations of testosterone in several groups of men. They studied men with partial-onset seizures, also called localization-related epilepsy. They compared five groups: 25 men without epilepsy (the controls); 10 men who had epilepsy but had not taken an antiseizure medication for the previous six months as their seizures had remitted; 25 men who had seizures and were taking phenytoin monotherapy; 25 men who had partial seizures and were taking carbamazepine; and 25 men who had partial seizures and were taking lamotrigine. The groups did not differ in age, seizure fre-

Figure 1. The Hypothalamic-Pituitary Axis



GnRH = Gonadotropin-releasing hormone LH = Leutinizing Hormone FSH = Follicle Stimulating Hormone

quency or duration of their epilepsy.

When compared, those who were taking the enzyme-inducing medications (*i.e.*, the phenytoin and carbamazepine groups) had significantly lower testosterone levels. Interestingly, so did the group of men who had epilepsy but had been off medications for the preceding six months. One possible theory to explain this is that the effects of the medications may persist longer than six months.

The lamotrigine group had levels that were comparable to the control group. Lamotrigine is not a hepatic enzyme inducer. Instead, lamotrigine is metabolized through glucuronidation. Sex steroid hormones are not metabolized through this pathway. Therefore, it would be expected that lamotrigine should have no effect on sex steroid serum levels: this was in fact the result from this study.[2,3]

Dr. Herzog also used a questionnaire to determine the overall level of sexual function. The questions are designed to quantify sexual interest and potency, and was recorded as an S-score. As with the testosterone levels, the S-scores were significantly lower in the groups of men who were taking enzyme-inducing antiseizure medications. There was a direct correlation between these findings. In other words, lower testosterone levels correlated with decreased sexual function.

Looking for Answers

Given the normally high efficiency of the feedback system that regulates sex hormones, a natural question is this: if testosterone levels fall, shouldn't the hypothalamus recognize this and send more GnRH to the pituitary, signaling an increase in LH and FSH and ultimately an increase in testosterone? In other words, where did the feedback system "break down"?

SHBG. One answer to this question is that the levels of sex hormone binding globulin are increased in men who are taking enzyme-inducing medications. More SHBG means a lower free concentration of testosterone. Since the body only "sees" the unbound fraction, more SHBG essentially translates into less available testosterone. It has been reported that the effects of enzyme-inducing medications on SHBG dissipates six months after discontinuation of the antiseizure medication. Dr. Herzog's study might suggest that this effect is longer-lasting, as the men who had stopped their medications six months before entering the study still had sexual dysfunction.

Estradiol. One of the metabolic byproducts of testosterone is estradiol. Although this occurs in very small levels in men, it has a potent effect on the hypothalamic-pituitary feedback system. It has been shown in other studies that higher levels of estradiol in men correlates with reduced sexual function. The enzyme-inducing medications, by accelerating the metabolism of testosterone, increase the levels of estradiol, contributing to sexual dysfunction. Interestingly, valproate, which is a hepatic P450 enzyme inhibitor, also increases estradiol formation. It has been reported to cause sexual dysfunction in men.[2]

Other Questions. Epilepsy, the disorder of recurrent unprovoked seizures, also affects sexual function. People who have epilepsy often take medications for many years, making it difficult to determine the extent to which the illness itself contributes to the problem. Dr. Herzog tried to study this by including 10 men who had epilepsy, but who were no longer taking medications in order to sort through this challenging problem. Possibly due to small sample size, this question remains unanswered.

Conclusions

Although some questions remain unanswered, it is becoming clearer that many men with epilepsy experience sexual dysfunction. Several studies have shown that up to 20 percent of men with epilepsy experience this. The enzyme-inducing medications have been shown to lower testosterone levels and to increase levels of SHBG, both of which contribute to this problem. Medications which do not interact with the hepatic P450 system during metabolism, such as lamotrigine, do not affect sexual function. When treating men with epilepsy, physicians must be sensitive to these issues. When possible, a switch in medication might be needed to improve the situation. **PN**

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