CURRENT LITERATURE

SEX, DRUGS, AND EPILEPSY

Epilepsy Syndrome, Focus Location, and Treatment Choice Affect Testicular Function in Men with Epilepsy

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OBJECTIVE: To evaluate testicular function in men with epilepsy treated with different antiepileptic drugs (AEDs) versus no drugs.
METHODS: Two hundred men with epilepsy (mean age, 36 years) were investigated. Inclusion criteria included one or no AEDs, no comedication, and no endocrine comorbidity. Findings were compared with those from 105 healthy men (mean age, 33.9 years). Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), free testosterone (free T), and inhibin B were measured.
RESULTS: One hundred seventy-eight men had focal epilepsy (117 of these had temporal lobe epilepsy [TLE]) and 22, idiopathic generalized epilepsy (IGE). Thirty-three men were not taking an AED; 124 men received enzyme-inducing AEDs. Free T was lowered in all patient subgroups, and the T/LH ratio was lowered in all groups except patients with IGE and patients receiving valproate (VPA). T was lower in patients with temporal than extratemporal focal epilepsy. Compared with TLE patients taking carbamazepine (CBZ), patients treated with VPA had higher total T and lower LH values, resulting in a significantly lower T/LH ratio with CBZ.
CONCLUSIONS: Epilepsy, especially TLE, adversely affects testicular endocrine function. CBZ may increase the negative effects of epilepsy on serum levels of reproductive hormones.

Effect of Epilepsy and Antiepileptic Drugs on Male Reproductive Health

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BACKGROUND: Men with epilepsy have reduced fertility, and antiepileptic drugs (AEDs) may affect semen quality. Moreover, animal studies suggest that valproate (VPA) may be associated with testicular atrophy.
OBJECTIVE: To evaluate reproductive function in men with epilepsy.
METHODS: Sixty men with epilepsy and 41 control men were evaluated for their reproductive health. Fifteen men were taking carbamazepine (CBZ), and 18 men, oxcarbazepine (OXC) for partial epilepsy, and 27 men were taking VPA for generalized epilepsy. Reproductive hormones were assayed from serum samples; semen analysis and ultrasonography of the testicles were performed; and testicular volume was calculated.
RESULTS: Men taking CBZ had low serum dehydroepiandrosterone sulfate concentrations ($P < 0.001$), and men taking VPA had high concentrations of serum androstenedione ($P < 0.001$). The frequency of morphologically abnormal sperm was higher among CBZ-treated ($P < 0.01$), OXC-treated ($P < 0.05$), and VPA-treated men ($P < 0.01$) than among the control men. Moreover, both CBZ and VPA were associated with poor motility of sperm ($P < 0.05$). In addition, the frequency of abnormally low sperm concentration was high in men taking CBZ ($P < 0.001$), and the frequency of any sperm abnormality was high in men taking VPA ($P < 0.01$). The VPA-treated men with abnormal sperm had smaller testicular volumes than the control men ($P = 0.003$).
CONCLUSIONS: CBZ, OXC, and VPA are associated with sperm abnormalities in men with epilepsy. In addition, VPA-treated men with generalized epilepsy who have abnormal sperm may have reduced testicular volume.

COMMENTARY

These two interesting articles focus on antiepileptic drugs (AEDs) as a cause for abnormal reproductive parameters in men with epilepsy. An alternative analysis of these articles would be that the epileptic condition itself, with or without AED use, is associated with impaired reproductive parameters in men with epilepsy. In the article by Bauer et al., men with

partial epilepsy of temporal lobe origin plus a small group with idiopathic generalized epilepsy were studied. Those patients not using AEDs had low bioactive testosterone and an associated impaired hypothalamic response. The abnormal response was evidenced by a lack of increase in luteinizing hormone (LH) in this group. Their data also suggest that carbamazepine (CBZ) imparts an extra measure of testicular resistance to the stimulating effects of LH, because LH was increased, but testicular production of testosterone was even lower with CBZ use in men with temporal lobe epilepsy (TLE). With valproate (VPA), the total testosterone levels and LH levels were normal; therefore testicular dysfunction with VPA was not implied by these results. However, the lowest levels of free testosterone occurred with VPA use.

One key finding of this article is that TLE itself produces low free testosterone, and the mechanism by which a brain disorder causes a testicular disorder is inexplicable. One mechanism by which this may occur is that subtle derangements in hypothalamic and pituitary function, caused by nearby epileptic discharges, produce elevations in circulating hormones, such as prolactin or estrogen. Estrogen can induce sex-hormone–binding globulin production in the liver, and thus, reduce free fraction of testosterone.

In the article by Isojärvi et al., AED-treated men with partial epilepsy, but not specifically TLE, and a group of men with generalized epilepsy on VPA, were evaluated for sperm and semen characteristics. All epilepsy subjects, as a group compared with controls, had significant decreases in percentage of normal sperm, percentage of motile sperm, and in spermatozoa concentration. Specific AED effects on sperm were that CBZ, but not oxcarbazepine (OXC), was associated with low spermatozoa concentration and that OXC, in general, had less negative effects on sperm and semen than CBZ or VPA. One major confounding factor in attributing these alterations to *any* AED, and not to epilepsy, is that all subjects took AEDs for an extended period. For example, all subjects with generalized epilepsy took VPA for a mean of 4.7 years.

These articles are among the first to document reproductive variations in men with epilepsy and, when taken together, provide powerful evidence that brain dysfunction can cause reproductive dysfunction and, indeed, gonadal dysfunction. One puzzling finding, however, is that the Bauer et al. article found significant increases in FSH and LH, whereas these hormone levels were normal in patients in the Isojärvi et al. study. The types of epilepsy treatments, specifically monotherapy treatment, and types of assays were very similar in the two studies and would not account for the differences in hormone levels. However, the Bauer et al. population was about 10 years older than the Isojärvi et al. population (mean, 36 years, compared with 26 years). In men, as in women, FSH and LH increase as a result of an aging of the hypothalamopituitary axis. This process may be accelerated in men with epilepsy and, at least, may provide a partial explanation for the profound differences between the findings in these two studies. Additionally, the subject groups were relatively small—between 15 and 60 subjects in any given epilepsy type, therefore, differences might be less if larger groups were studied.

Two caveats of these data should be kept in mind. First, the studies actually found that no specific AED can be solely implicated as causing reproductive abnormalities; the common features of the subjects was that they had epilepsy, and the AEDs produced further variations (or corrections) in parameters. Second, the findings cannot be readily used to advise individual male patients about the risk of impotence or infertility. Bauer et al. stated it best in saying: "the real value of a study like the one presented is in the analysis on a group level."

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