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REVIEW

Sexual dysfunction in women with epilepsy

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Summary Sexual dysfunction in women with epilepsy (WWE) is an important comorbidity. A significant minority of WWE have markedly decreased sexual interest and it appears that orgasmic dysfunction occurs more frequently in WWE than in control women. Enzyme-inducing antiepileptic drugs can adversely affect sexual functioning by decreasing bioactive testosterone levels. Temporal lobe epilepsy of right-sided versus left-sided origin may also be a risk factor for sexual dysfunction. In addition to these factors, emerging evidence suggests that the serotonin transporter protein is related to temporal lobe epilepsy and it is postulated that this transporter may play a role in altered sexual functioning in epilepsy, perhaps through the serotonergic effects of antiepileptic drugs (AEDs). Strategies for modifying the contributors to sexual dysfunction in WWE will be discussed as well as the role of the neurologist in initiating management of this challenging comorbidity.

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Introduction

Sexual dysfunction in persons with epilepsy is a comorbidity that has been incompletely explored. However, there are several reasons to consider its importance. The high rates of sexual dysfunction in persons with epilepsy likely are, in some cases, a manifestation of hypothalamic dysfunction related to seizures and interictal discharges. This association between neurophysiologic brain dysfunction and reproductive abnormalities is clearly relevant for neurologists. Further, as difficult as it may be to explore with patients in the office, sexual well-being is a high priority for almost everyone. Therefore, an understanding of the spectrum of sexual dysfunction in women with epilepsy (WWE) and approaches to management are worthy of discussion.

In this brief review, evidence for the spectrum of sexual difficulties in WWE will be presented, as well as risk factors for such. Potentially modifiable contributors to sexual dysfunction in WWE will be discussed as well as initial approaches to management.

The scope of sexual dysfunction in women: prevalence and type

The International Consensus Development Conference on Female Sexual Dysfunction has divided sexual dysfunction in women into four major categories: sexual desire disorders, sexual arousal disorders, orgasmic disorders (either primary or secondary), and sexual pain disorders.[1] These are further subtyped according to duration, timing of occurrence (situational or generalized), and etiology. In the psychological realm, the Diagnostic and Statistical manual of mental disorders, fourth edition (DSM-IV-TR; Am. Psychol. Assoc. 2000) defines two main categories of female sexual disorders, hypoactive sexual desire disorder, and female sexual arousal disorder. These desire and arousal disorders as defined by the DSM-IV-TR often occur together.[2] The sexual dysfunction described in the reports discussed herein for WWE will be described generally within these accepted categories.

Type of sexual dysfunction in WWE

One of the first and most insightful reports on sexuality in WWE was published by Bergen et al.[3] The investigators evaluated 50 WWE in a tertiary epilepsy care center; 32 of 50 women had partial epilepsy, and 28 of 50 were taking only one AED. WWE and a comparison group of women of similar age were asked how often they had the desire for sex, and how often they actually had intercourse. Equal proportions of women in both groups had a frequent desire for sex, but several more controls had very frequent desire compared with none in the epilepsy group. Further, a much greater proportion of WWE than comparators had very infrequent sexual desire, with about 20% reporting that they almost ''never'' had sexual desire; very few women in the comparison group reported this low level of sexual desire. The bimodal distribution persisted for the actual rate of sexual intercourse and for married WWE who had a current sexual partner. Therefore, this difference was not accounted for by access to a sexual partner. Some WWE had sexual desire more frequently than they had intercourse, however the reverse was true in the comparison group. The investigators found no correlation to age, antiepileptic drugs (AEDs) used, duration of epilepsy, or seizure type. This report is revealing regarding the overall picture of sexual dysfunction in WWE: many WWE have normal sexuality, but there is a significant fraction who have markedly decreased sexual desire and this fraction is not present in the general population.

Several reports suggest that orgasmic dysfunction is over-represented among WWE. Jensen et al.[4] studied sexuality in 48 WWE and compared their findings to their own previously reported data on sexuality in persons with diabetes mellitus and healthy controls. Although the authors found no difference in sexual desire between the three groups, 19% of the WWE had orgasmic dysfunction compared with 11% of the diabetes mellitus group and 8% of the controls ($P = 0.081$). They found no correlation between sexual dysfunction and type and duration of epilepsy, or AED use. None of the WWE had out-of-range testosterone levels, either free or total, or testosterone-binding globulin levels.

Inadequate orgasmic satisfaction in WWE, significant compared with controls, was also reported by Duncan et al. in their study of 195 WWE from a hospital-based clinic.[5] They also found that sexual experience scale scores indicated that WWE are more ''moral'' and less open to sexual experiences, but, in general, WWE in relationships seemed to desire intercourse as much as controls.

In an investigation of self-reported sexual functioning and sexual arousability in 116 WWE, anorgasmia was also reported by one third of 17 women with primary generalized epilepsy and 18 of 99 women with localization-related epilepsy. Compared with historical controls, this group of women did not have less sexual experience, and reported less sexual arousability and more sexual anxiety.[6]

Therefore, in addition to what seems like a physiologic impairment of sexual functioning, that is, inadequate orgasms or anorgasmia, psychosocial factors are likely to contribute to self-reported sexual dysfunction in WWE. For example, living with the stigma of epilepsy may be an impediment to social activities. According to a survey of quality of life in persons with epilepsy across Europe, many subjects reported low satisfaction with sexual relationships in the context of feeling stigmatized by having epilepsy.[7]

Therefore, many studies support the idea that although most WWE have normal sexual lives, a significant minority, about 20—30%, may have some degree of sexual dysfunction. Orgasmic dysfunction appears to be specifically over-represented in WWE.

Seizures related to orgasm: a rare form of reflex epilepsy

An obvious reason for anxiety related to sexual activity is if intercourse seems to precipitate seizures. In a recent report of the rare form of reflex epilepsy in which orgasm-induced seizures, six subjects, all women, were described as having seizures within minutes to hours of orgasm during intercourse.[8] The seizures were of varying types, including primary generalized convulsions and complex partial seizures. Interestingly, four of the six subjects had seizures of right temporal origin.

Decreased genital blood flow in WWE

Morrell et al.[9] reported on genital blood flow (GBF) measured by vaginal plethysmography in women with temporal lobe epilepsy as they watched either erotic or sexually neutral videos. GBF was significantly decreased in WWE compared with controls during erotic visual stimulation. There was no difference in mood scales between the two patient and control groups, however, epilepsy subjects were less sexually experienced than the controls, and reported more anxiety upon imagining sexual situations than did controls. Due to small numbers of subjects, the effect of AEDs on plethysmography results was not assessed in this study.

The authors proposed a central mechanism for this effect, that disruption of relevant regions of cortex by epileptic activity, specifically limbic, and frontal areas, could be the cause of sexual dysfunction. The occurrence of decreased GBF in WWE could, at least in part, contribute to inadequate orgasm. There is laboratory evidence however, that testosterone increases vaginal blood flow.[10] Therefore, decreased free testosterone levels associated with hepatic cytochrome P-450 enzyme induction in women taking enzyme-inducing AEDs may account for this altered GBF.

AEDs and sexual dysfunction

It is well-established that hepatic cytochrome P-450 3A4 isoenzyme-inducing AEDs can lower free testosterone levels. This was most recently shown in an elegant study by Lossius et al.[11] in which seizure-free epilepsy patients appropriate for AED withdrawal were evaluated for changes in reproductive hormone levels 4 months after discontinuing the AED. Their main findings were that total testosterone and free androgen index (FAI) ($100 \times$ testosterone/sex hormone binding globulin) significantly increased after withdrawal from the most frequently used AED, carbamazepine, for both genders. In contrast, withdrawing valproate resulted in nonsignificant decreases in these parameters. These results indicate that the choice of AED can effect hormones important for sexual functioning, and that such alterations are reversible.

All enzyme-inducing AEDs are not the same. In a report of alterations in reproductive hormone levels in WWE taking carbamazepine or oxcarbazepine, both AEDs were associated with relatively total testosterone level and FAI.[12] However, oxcarbazepine-treated subjects had higher dihydroepiandrosterone (DHEA) and androstendione than controls, which may be related to the mild inhibitory effect of oxcarbazepine on the isoenzyme 2C19 metabolic pathway.

Alternatively, there is evidence that AEDs which do not induce cytochrome P-450 enzymes have little effect on these important reproductive hormones. In a recent study of persons with epilepsy aged 13—80 years randomized to either valproate or lamotrigine monotherapy, no changes in total testosterone of FAI were found after 6 or 12 months of treatment either within each treatment group or by comparing treatment groups.[13]

Lamotrigine has specifically been associated with improvement in sexual functioning, as reported recently by Gil-Nagel et al.[14] In an open study of 141 epilepsy patients changed to lamotrigine monotherapy, an overall improvement in self-reported sexual functioning was found, measured 4 and 8 months after changing AEDs. Women in the study reported a significant overall improvement in five dimensions of sexuality including desire/frequency, desire/interest, pleasure, arousal/excitement, and orgasm. Men reported an improvement only in the pleasure dimension. The reason for this improve-

ment in association with lamotrigine is unclear; seizure reduction, changes in overall side effects or perhaps elevated mood could be contributing factors.

Right-sided epilepsy has more impact on sexuality than left-sided epilepsy

Reports from different aspects of the epilepsy literature suggest that seizures of right temporal origin are particularly associated with reproductive dysfunction and possibly even sexual ictal phenomenon. From the epilepsy surgery literature, Baird et al. reported that one third of their 58 temporal lobectomy patients had an increase in sexual activity after surgery, compared with one quarter of patients having decreased postsurgical sexual activity.[15] Change in sexuality was more likely to occur in women and in patients with right-sided resections. This lateralization of change in sexuality after surgery is consistent with a report by Herzog et al.[16] that right temporal epileptic discharges in WWE were associated with hypogonadotropic hypogonadism that included, for many subjects, decreased sexual interest. These findings would suggest, therefore, that right temporal resection could improve sexual functioning.

In a carefully performed questionnaire study of sexual functioning in men and women with either right or left temporal lobe epilepsy, Daniele et al.[17] found that sexual interest specifically was decreased in patients with right temporal lobe epilepsy compared to left for both genders, although most aspects of sexual performance were not different. Ictal sexual behaviors and ictal orgasm have been specifically associated with right temporal epilepsy as well.[8]

There is also lateralization in the central regulation of gonadotropin secretion: experimental evidence indicates that the right hypothalamus is predominant in the control of reproductive functioning.[18] Therefore, a body of evidence from divergent sources, both clinical- and laboratory-based, suggest that right-sided epilepsy and right temporal lobe epilepsy specifically, may be associated with a risk of sexual and reproductive dysfunction.

Is serotonin a factor in epilepsy-related sexual dysfunction?

Serotonin (5-hydroxytryptamine or 5-HT) is a neurotransmitter for which decreased serotonergic activity, can facilitate seizure activity and exacerbate seizure severity in animal models.[19] The serotonin transporter (5-HTT) is important for 5-HT inactivation since it is the reuptake site, and is a target for selective serotonin reuptake inhibitors (SSRIs). SSRI are known to have anticonvulsant activity in the laboratory, and further, have as a major side effect, sexual dysfunction, indicating that serotonin activity plays an role in sexual functioning. A recent report has associated a specific 5-HTT genetic polymorphism with temporal lobe epilepsy, suggesting that the serotonin transporter gene may be etiologically important for the development of temporal lobe epilepsy.[20] This emerging information, combined with evidence that several AEDs affect brain serotonin concentration, including valproate,[21] oxcarbazepine,[22] carbamazepine,[23] and lamotrigine,[24] indicate that sexuality in persons with epilepsy may be affected through mechanisms that do not involve alterations in reproductive hormone levels or psychosocial influences on behavior. Perhaps some persons with epilepsy are genetically susceptible to sexual dysfunction via the serotonin transport mechanism, or may be vulnerable to the serotonergic effects of AEDs.

Conclusion

How the sexual difficulties of WWE differ from controls?

WWE have a higher rate of profound lack of sexual interest and have high rates of orgasmic dysfunction, including anorgasmia.

What epilepsy-related factors contribute to sexual dysfunction in WWE?

AEDs that induce cytochrome P-450 isoenzyme 3A4 and therefore decrease free testosterone are associated with sexual dysfunction. Right temporal lobe epilepsy also appears to be associated with sexual dysfunction compared to left temporal lobe epilepsy. Lack of seizure freedom could adversely impact psychosocial aspects of living with epilepsy, including sexuality.

Which contributors to sexual dysfunction in WWE are modifiable?

Consideration of changing from a highly enzyme-inducing AED such as carbamazepine, phenytoin, or phenobarbital when clinically appropriate may be helpful for persons with epilepsy complaining of sexual dysfunction. AEDs that are not enzyme inducers could be considered, such as lamotrigine, for which there is some evidence for improved sexual

functioning in this setting, especially for women. Valproate and levetiracetam are also not enzyme inducers, and may be reasonable alternatives, depending on the clinical situation. Clearly, seizure control is of utmost importance in maximizing quality of life, including the sexual life, of persons with epilepsy.

What should the neurologist do?

One of the most refreshing things a neurologist could do would be to simply ask patients about their sexual functioning. Although this seems awkward, it may be an easy segue from the discussion about bowel or bladder functioning, or from inquiries about social relationships. Since decreased sexual interest can be due to depression, the presence of mood disorders should be screened for when sexual dysfunction arises as a complaint. Maximizing seizure control and the possibility of adverse sexual effects due to AEDs should be considered. It is inherently difficult for a physician to actively inquire about a medical condition far outside their comfort zone for initiating treatment. For most neurologists, it would be most appropriate to refer such patients to a gynecologist for further evaluation and treatment; an initially laboratory evaluation for women would include total and free testosterone, sex hormone binding globulin, estrogen follicle-stimulating hormone, and luteinizing hormone levels.

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