CATAMENIAL EPILEPSY: THE ELUSIVE CONDITION

Frequency of Catamenial Seizure Exacerbation in Women with Localization-related Epilepsy

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This investigation assessed the frequency of catamenial epilepsy in 87 women who charted seizures and menses during three cycles. Catamenial epilepsy designation was made if two of three cycles showed at least one of three previously defined catamenial patterns. Among ovulatory cycles, average daily seizure frequency was significantly greater during the perimenstrual and preovulatory phases. Among anovulatory cycles, average daily seizure frequency was substantially less during the midfollicular phase than during the remainder of the cycle. Overall, 39.1% of the women had catamenial epilepsy.

COMMENTARY

The article by Herzog et al. provides data on the relation between seizures and hormonal cycling in women participating in a multicenter trial of hormonal therapy for refractory partial seizures. The data were collected during a 3-month untreated baseline, before randomization. Although the investigation provides statistical support for the existence of catamenial seizure exacerbation, it also demonstrates the complexity of the condition and the difficulty in studying it. Thirty-nine percent of women had catamenial epilepsy, as defined by the occurrence of a catamenial pattern in at least two of the three recorded cycles. However, as has been described previously by the same lead author, two distinct catamenial patterns were found: one with menstrual exacerbation (C1) and the other with ovulatory exacerbation (C2). Women could experience either or both patterns, even within a single cycle. Complicating matters further, 16.5% of cycles were anovulatory, and these cycles demonstrated a third pattern of exacerbation (C3) (1). The authors provide the majority of the data in terms of percentage of cycles, rather than percentage of subjects. For example, we are told that of 208 ovulatory cycles, 46 exhibited only the C1 pattern, 22, only the C2 pattern, and 22 had both in the same cycle. We have no way of knowing how many women had all ovulatory cycles, or how many of these had catamenial exacerbation for all observed cycles.

Although the authors claim that the women enrolled in the trial may provide a snapshot of women with epilepsy at large, it is quite possible that women who thought that their seizures were related to their menses would be drawn to a study of hormonal treatment. Several of the investigators are considered experts in treatment of catamenial epilepsy or related areas and might draw such women to their practice. This fact makes it difficult to determine whether the results can be generalized.

Several theories exist as to why seizures may be exacerbated during various times in the menstrual cycle. The prevailing theory is that progesterone is relatively antiepileptogenic, whereas estrogen may lower the seizure threshold. At times when estrogen is high relative to progesterone, as occurs before the menses, the likelihood of seizures would increase.

Good evidence exists that progesterone can act as an anticonvulsant. Progesterone raises the seizure threshold in several animal models of epilepsy, including kindled seizures (2,3). Strong evidence indicates, however, that this antiseizure effect is not related to binding with traditional progesterone receptors. It has recently been demonstrated, for example, that the antiseizure effect of progesterone is still present in progesterone-receptor knockout mice (4). This finding lends credence to the theory that progesterone exerts its effect after conversion to the progesterone metabolite allopregnanolone, a $GABA_A$-receptor–modulating neurosteroid, which also has been demonstrated to have anticonvulsant properties. In addition, a progesterone withdrawal effect may occur, which, in some animal models, leads to upregulation of $GABA_A$ receptors, with resultant hyperexcitability of hippocampal neurons (5).

Arguments that estrogen is involved in catamenial exacerbation also have been made. Estrogen potentiates the effects of the chemoconvulsants, kainate and pentylenetetrazole, and

increases neuronal excitability (6). Recently, it has been hypothesized that estrogen increases may increase hippocampal brain-derived neurotrophic factor (BDNF) levels, which in turn may lead to excess glutamate release in mossy fibers (7) and to hyperexcitability. This theory might suggest that patients with hippocampal seizure foci would be at particular risk. Other steroid hormones, such as androgens and corticosteroids, as well as changes in water and electrolyte balance, also may play a role (3).

What does this mean for treatment? Over the years, many relatively empiric treatments have been tried for catamenial exacerbation, none of which has been blinded, randomized, or controlled. These treatments have involved attempts at hormonal manipulation, including such drastic measures as hysterectomy or oophorectomy as well as administration of oral contraceptives, natural progesterone, and clomiphene (an estrogen-receptor antagonist) (3). Other therapies have included perimenstrual increases in AED doses, treatment with acetazolamide, and premenstrual introduction of short-term treatments, usually benzodiazepines (8). A pilot treatment trial of ganaxolone, a synthetic analogue of the neuroactive steroid allopregnanolone, was undertaken (9).

The authors conclude that identification of women who have particular sensitivity to hormonal fluctuation also may identify women who are most likely to respond to hormonal manipulation. In the presence of so many theories of potential mechanisms for catamenial exacerbation, what treatment is the best? Will treatment be the same for all women or even for all cycles of a single woman? To date, only uncontrolled, open studies of progesterone therapy have been undertaken. These studies showed that progesterone therapy substantially reduced seizures in some women (10). The placebo-controlled study from which the data on frequency of catamenial patterns of seizure exacerbation derive also will produce treatment results that may confirm or refute the benefits of progesterone therapy. The study also may identify the group of women who respond most predictably. If it turns out that different patterns respond differentially, treatment choices may be very complex.

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