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The Effect of Menopause and Perimenopause on the Course of Epilepsy

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Summary: *Purpose:* The purpose of this study was to obtain preliminary information about the effect of menopause and perimenopause on the course of epilepsy, and to determine whether seizure type, use of hormone-replacement therapy (HRT), or a history of catamenial seizure pattern would influence this course.

Methods: We performed a questionnaire study of women with epilepsy currently in menopause and perimenopause, requesting information regarding the course of their epilepsy and treatment. Statistical analysis was performed by using Pearson χ^2 with 95% confidence limits.

Results: Forty-two menopausal women (ages 41–86 years) responded. Twelve subjects reported no change in seizures at menopause, 17 reported a decrease in seizure frequency, and 13 reported an increase. Sixteen (38%) took synthetic HRT. Sixteen (38%) additional subjects (having some overlap with the HRT group) reported having a catamenial seizure pattern before menopause. HRT was significantly associated with an increase in seizures during perimenopause ($p = 0.001$). A history of catamenial seizure pattern was significantly associated with a decrease in seizures at menopause ($p = 0.013$). Thirty-nine perimenopausal women (ages 38–55 years) responded. Nine subjects reported no change in seizures at perimenopause, five reported a decrease in seizure frequency, and 25 reported an increase. Eight (15%) subjects took synthetic HRT, and 28 (72%) reported having a catamenial seizure pattern before menopause. HRT had no significant effect on seizures; however, a history of catamenial seizure pattern was significantly associated with an increase in seizures at perimenopause ($p = 0.02$).

Conclusions: These pilot data suggest that synthetic HRT may be associated with an increase in seizure frequency in menopausal women with epilepsy. A catamenial seizure pattern may be associated with seizure decrease during menopause but with an increase during perimenopause. **Key Words:** Epilepsy—Menopause—Perimenopause—Hormones—Catamenial.

The course of epilepsy as women become menopausal is unknown. It is intriguing to postulate that women with epilepsy who experienced a relation of their seizures to their menstrual periods may have a decrease in seizure frequency after completion of their reproductive years. Backstrom in 1976 (1) described catamenial fluctuations in seizure frequency in relation to cyclic alterations in serum estrogen/progesterone ratios. The relatively high estrogen/progesterone ratio present at ovulation and just preceding menstruation may be more permissive for clinical seizures at these times because of the seizure-promoting effect of estrogen (2,3). Additionally, metabolites of naturally occurring progesterone bind at the γ-aminobutyric acid (GABA) receptor to produce an antiseizure effect (4). Therefore progesterone "withdrawal" at the end of the luteal phase just before or at the onset of menses is a particularly vulnerable time for seizure exacerbation (5). Further support of the influence of progesterone on cyclic seizures was put forth in the recent study of Herzog et al. (6) of catamenial epilepsy patterns. In this study, women with intractable complex partial seizures (CPSs) and low progesterone levels in the mid-luteal phase, indicating an anovulatory cycle or luteal phase defect, experienced more seizures throughout the second half of the menstrual cycle.

The effect of menopause on the course of epilepsy is of particular interest regarding patients who have catamenial seizure exacerbations. A prospective study of the course of epilepsy as women enter menopause would likely require 5–10 years of observation. Therefore we

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sought to obtain preliminary information from questionnaires about the change in the course of epilepsy over time as women achieved menopause. The perimenopausal period was addressed in the questionnaire as a separate life epoch, because during this time, the hormonal milieu also is changing. During perimenopause, estrogen levels gradually decline, and cyclic luteal phase progesterone surges also wane (7). The estrogen/progesterone ratio of perimenopause becomes generally higher and unpredictable, unlike the stable ratio of low levels of these reproductive hormones during menopause (8). Therefore it may be predicted that perimenopause would be associated with an increase in seizure frequency, and menopause would be associated with a decrease. To determine the natural course of epilepsy during perimenopause and menopause and potential influences of hormone replacement therapy (HRT), subjects were asked to report use of HRT and any antiepileptic drug (AED) changes over this time period.

METHODS

This study was approved by the human studies committee and was sponsored by a private donation. The human studies committee approved the study to be done only in an anonymous fashion. We mailed questionnaires to adult women (age > 24 years) with epilepsy, contacting them through the databases available from the local epilepsy consumer programs and through open solicitation in the Epilepsy Foundation of America newsletter.

No standardized questionnaire is mailed by epilepsy researchers to determine seizure history. The anonymous questionnaire devised by the investigators required completion of a six-page document that sought information about the respondent's epilepsy syndrome and treatment, age of onset, likely cause of epilepsy (including unknown), and seizure type, with a narrative description of all types of seizures experienced. The presence of a relation to menstrual periods also was questioned, and a detailed narrative of the relation was requested. For our study, catamenial seizure exacerbation was defined as seizures that occurred predominantly in a fixed relation to menses and occurred in the following time periods: in the week before menses, and/or during the first 3 days of menses, and/or at ovulation. This is adapted from the three patterns of catamenial epilepsy described by Herzog et al. (6) as easily extracted in a questionnaire format.

Women who were menopausal were asked to report the course of their epilepsy over time. Menopause was defined as not having a menstrual period for 1 year; medical and surgical menopause were included (9). Surgical removal of ovaries was specifically reported. Reporting of the course of epilepsy included the subjects completing a current monthly seizure rate and giving their impression of whether seizures had become more frequent, less frequent, or unchanged in the first 5 years of becoming menopausal. The subjects' impressions of their course of epilepsy was given priority over seizure counts because some subjects did not report seizure counts.

The course of epilepsy as the respondent entered perimenopause also was questioned in the same manner. Perimenopause was defined by the onset of irregular menses (9), "hot flushes," and mood changes. Mood changes alone were not sufficient to meet the criteria of perimenopause. Women currently in menopause were not used in analyzing the perimenopause portion of the study, to reduce the effects of time on recollection of their seizure patterns. Perimenopause was distinguished from amenorrhea by the presence of hot flushes associated with irregular menses, because vasomotor symptoms are characteristic of menopausal ovarian failure.

Finally, women were asked to state the exact number and severity of seizures per month before they began having perimenopausal symptoms. This was used to monitor the consistency of the reported seizure change during perimenopause and menopause.

Subjects were requested to report all medications used for seizure treatment over the course of their illness and the dates of these treatments. They also were requested to state the exact formulations and dates of all HRT including hormonal birth control. They were not asked if HRT seemed to have a specific effect on their seizure disorders.

Statistical analysis was performed by using Pearson χ^2 with significance set at the 95% confidence limits.

RESULTS

A total of 205 women responded. The response rate was 25% from one mailing without telephone follow-up. Sixty-four women were menopausal, 52 were in perimenopause, and 89 were premenopausal. Sixty-three (32%) of these subjects were from open solicitation, and the remainder were from consumer databases. The 89 premenopausal women who responded were not used in this study because they did not meet the criteria of reporting perimenopausal or menopausal characteristics.

Menopause

All subjects

Of the 64 menopausal women, 22 were excluded from the analysis because of the following factors: nine had confusing, incomplete, or inconsistent responses; seizures began after menopause in seven; the course was confounded by medication changes during menopause in three; one patient developed a brain tumor on reaching

menopause; one had a temporal lobectomy at menopause; and one was started on intramuscular medroxyprogesterone acetate (Depo-Provera), which resulted in cessation of menses and seizures.

The age range of the 42 remaining menopausal subjects was 41–86 years, with a mean age of 54 years and a median of 48 years. The age of onset of menopause (defined as the age at which the last menstrual period occurred) ranged from 29 to 56 years, with a median of 47 (mean, 45). This included four women who had surgical menopause at the ages of 29 and 36, and two subjects at 40 years; therefore the median age of natural menopause was 48 years (mean, 46). The duration of menopause was from 1 to 42 years, with a median of 4.5 (mean, 6).

Seizure change at menopause was reported as follows: 12 (28%) subjects reported no change, 17 (41%) reported a decrease in seizure frequency, and 13 (31%) reported an increase in seizure frequency. Sixteen (38%) of 42 women took synthetic HRT. Sixteen (38%) of 42 reported a pattern of catamenial seizure exacerbation before menopause.

Hormone replacement therapy

Of the 16 subjects who took HRT, 10 reported an increase in seizures, compared with three of the 26 subjects who did not take HRT (see Table 1). This difference in distribution was significant ($p = 0.001$), associating synthetic HRT and seizured increase.

Five menopausal subjects spontaneously reported an immediate increase in seizures after starting HRT, and several discontinued it after 1–2 months. There was no consistency in the AED regimens among the subjects who took HRT. However, almost all subjects were taking hepatic enzyme–inducing AEDs (see Table 2). Most subjects taking HRT took an estrogen combined with a synthetic progestin (see Table 2 for exact regimens).

The ages of the subjects who did not take HRT ranged from 40 to 86 years, with a median of 53.5 years (mean, 53). The number of years of education in this subgroup ranged from 8 to 21 years with a median of 12 years (mean, 14). The ages of the subjects who took HRT ranged from 41 to 58 years, with a median of 53 years (mean, 51). The number of years of education in this subgroup ranged from 11 to 20 years with a median of 14 years (mean, 14).

TABLE 1. *Effect of HRT on seizure change at menopause*

Seizure course at menopause	Without HRT (n = 26)	With HRT (n = 16)
No change in seizures	11 (42%)	1 (6%)
Decreased seizures	12 (46%)	5 (31%)
Increased seizures	3 (12%)	10 (63%)

$p = 0.001$.
HRT, hormone replacement therapy.

Catamenial pattern

Of the 16 subjects who reported a catamenial seizure pattern before menopause, 11 reported a seizure decrease, compared with six of the 26 subjects without a catamenial pattern (see Table 3). This distribution was significantly different ($p = 0.013$), relating catamenial pattern and seizure decrease, or the lack of catamenial pattern with no specific trend at menopause.

Interaction between catamenial pattern and HRT

The interaction between seizure change, catamenial seizure pattern, and HRT was evaluated by determining the effect of HRT on seizure change in two groups; the subjects with a history of catamenial seizure pattern ($n = 16$) and those without a catamenial seizure pattern ($n = 26$). In the 16 subjects with a catamenial seizure pattern, seizures were most often reported to decrease at menopause, but the use of HRT worsened seizure frequency in this group (see Table 4; $p = 0.031$). Of the 26 subjects without a catamenial pattern, 10 reported no change in seizures at menopause, and in this group, HRT also was associated with a worsening of seizures (see Table 5; $p = 0.005$).

Primary generalized epilepsy

Six menopausal subjects likely had primary generalized epilepsy based on their report of seizure description, age of onset, medications used, and stated etiology (such as "inherited"). None of these six subjects reported a catamenial seizure pattern. Three reported no change in their seizures at menopause, none of whom took HRT. Three reported seizure increase at menopause, two of whom took HRT.

Partial epilepsy

In the remaining 36 menopausal subjects with likely partial epilepsy, the effect of HRT on seizure increase remained significant ($p = 0.004$). However, the effect of catamenial pattern on seizure change in this patient subgroup was no longer significant, but suggested a trend ($p = 0.060$).

Temporal lobe epilepsy

Nineteen menopausal subjects were further assessed as having temporal lobe epilepsy (TLE) based on their given histories and seizure description, including onset of seizures with a rising abdominal sensation, episodes of *déjà vu,* observed staring and automatisms during the seizure, and the presence of postictal confusion. There was no significant difference in seizure change at menopause in the subgroups with and without TLE ($p = 0.100$); however, TLE appeared to be associated with a change in seizures at menopause, either increased or decreased, rather than no change. Seven of eight subjects with TLE whose seizures increased took HRT, compared with two of 11 in the no-change and decreased group combined. If HRT is associated with seizure increase,

TABLE 2. *Seizure course and HRT regimens in menopausal subjects taking HRT*

Patient no.	Menopausal seizure course	Hormone replacement regimen (subjects reported brand names)						
		PRE	PRO	PRP	E-derm	Ogen	NATPRO	NS
1 CBZ, PB	Unchanged	X	X					
2 PB	Improved				X			
3 PHT	Improved	X	X					
4 PHT	Improved			X				
5 CBZ, VPA	Improved	X					X	
6 PHT, PB	Improved			X				
7 CBZ	Worsened[a]	X						
8 PHT, CBZ	Worsened[a]				X			
9 CBZ, LTG	Worsened[a]			X				
10 CBZ, VPA	Worsened		X			X		
11 None	Worsened[a]	X	X					
12 PHT, PRM	Worsened	X	X					
13 PHT, CBZ	Worsened	X						
14 LTG	Worsened	X	X					
15 PHT, VPA	Worsened[b]	X						
16 PRM, DMX	Worsened[a]							X

[a] Spontaneously reported that seizures became worse with HRT.
[b] Surgical menopause.
PRE, Premarin [conjugated equine estrogens (CEE), 0.625 mg]; PRO, Provera [medroxyprogesterone acetate (MPA), 2.5 mg]; PRP, Prempro (CEE, 0.625 mg, and MPA, 2.5 mg); E-derm, Estroderm (17-β-estradiol); NATPRO, natural progesterone; NS, not specified; CBZ, carbamazepine; PHT, phenytoin; PB, phenobarbital; PRM, primidone; VPA, valproate; LTG, lamotrigine; DMX, acetazolamide (Diamox).

these findings suggest that subjects with TLE who do not take HRT are more likely to have a decrease rather than no change in their seizures at menopause.

Perimenopause

Fifty-two subjects were in perimenopause. Thirteen were excluded because of confusing answers or confounding medication changes. The age range of the remaining 39 subjects was from 38 to 55 years, with a mean of 46. Thirty-six subjects likely had partial epilepsy, and three likely had primary generalized epilepsy.

Nine (23%) subjects reported no change in seizures on reaching perimenopause, five (13%) reported a decrease in seizure frequency, and 25 (64%) reported an increase in seizure frequency. Eight (21%) subjects were taking HRT, and 28 (72%) reported a history of catamenial seizure exacerbation. There was no discernable effect of HRT on seizure change ($p = 0.203$). A history of a

TABLE 3. *Effect of reported catamenial seizure pattern on seizure change at menopause*

Seizure course at menopause	Without catamenial pattern (n = 26)	With catamenial pattern (n = 16)
No change in seizures	10 (38%)	2 (13%)
Decreased seizures	6 (24%)	11 (68%)
Increased seizures	10 (38%)	3 (19%)

$p = 0.013$.

TABLE 4. *Effect of reported HRT on seizure change at menopause in subjects with catamenial seizure pattern*

Seizure course at menopause	Without HRT (n = 10)	With HRT (n = 6)
No change in seizures	1 (10%)	1 (17%)
Decreased seizures	9 (90%)	2 (33%)
Increased seizures	0 (0)	3 (50%)

$p = 0.031$.

TABLE 5. *Effect of reported HRT on seizure change at menopause in subjects without catamenial seizure pattern*

Seizure course at menopause	Without HRT (n = 16)	With HRT (n = 10)
No change in seizures	10 (62%)	0 (0)
Decreased seizures	3 (19%)	3 (30%)
Increased seizures	3 (19%)	7 (70%)

p = 0.005.

catamenial seizure pattern was associated with a seizure increase (p = 0.009) (see Table 6) However, because we had previously found that HRT may worsen seizure frequency, we sought to determine an independent effect of catamenial epilepsy on seizure change in the perimenopausal group. To evaluate this effect, the 31 perimenopausal subjects who did not take HRT were evaluated separately for the effect of a catamenial pattern on seizure change at perimenopause. There was a significant interaction, relating a catamenial seizure pattern with an increase in seizure frequency at perimenopause, and a lack of catamenial pattern with no change in seizures at perimenopause (p = 0.039).

DISCUSSION

In this study, women with epilepsy who were menopausal, that is, 1 year without menstrual periods, reported nearly equal proportions of an increase, a decrease, or no change in seizure frequency as they became menopausal. These proportions argue against significant sample bias, in that the seizure change in the group as whole showed no trend. However, we acknowledge that the methods used in this study are subject to selection bias; specifically, it may be that women who experienced a seizure change during menopause and perimenopause are overrepresented.

Our results suggest that the course of epilepsy in women may be significantly influenced by several factors. One factor, which is endogenous, is that of a catamenial seizure pattern. The presence of experiencing a catamenial seizure pattern during cycling years appears to affect menopause and perimenopause in opposite ways. Having a catamenial seizure pattern was significantly associated with a decrease in seizures during menopause, but was significantly associated with an increase in seizures during perimenopause. Further, most subjects in perimenopause reported an increase in seizure frequency, which was even more pronounced in subjects with a catamenial seizure pattern. This is consistent with the effects of the estrogen and progesterone milieu on brain excitability during progression through these life epochs.

TABLE 6. *Effect of catamenial pattern on seizure change at perimenopause*

Seizure course at perimenopause	Without catamenial pattern (n = 11)	With catamenial pattern (n = 28)
No change in seizures	6 (54%)	3 (11%)
Decreased seizures	0 (0)	5 (18%)
Increased seizures	5 (46%)	20 (71%)

p = 0.009.

The fraction of subjects reporting a catamenial seizure exacerbation in the menopausal group is much smaller than that of the perimenopausal group (38 vs. 72%). This finding raises the question of the reliability of the reporting of catamenial seizure change, and this question has notoriously plagued researchers of this topic in the past. However, an interpretation of these differences other than reporting bias may be at play. That is, with the less predictable hormonal cycling of perimenopause, subjects may actually experience a more pronounced catamenial effect and are reporting this.

The most striking finding of this study is that there appears to be a strong effect of an exogenous factor, HRT, on influencing epilepsy in menopausal subjects. HRT use was strongly related to seizure increase, and several patients spontaneously reported an increase in seizures with HRT. This finding suggests that menopausal women with epilepsy may be at risk for an increase in seizure rate when they use HRT. All HRT regimens in this study that included a progestin consisted of synthetic progestins, except one subject who used Premarin and natural progesterone. Notably, her seizures decreased in menopause.

Women who use HRT are reportedly better educated and healthier than nonusers (10); however, there was no difference in the age or years of education between subgroups of our subjects who did or did not use HRT. Therefore this finding suggests that compliance with medications such as an AED regimen would not be different between groups. The fraction of study subjects who used HRT (38%) was similar to that in the general population. The percentage response to our questionnaire is typical of that expected for mailed questionnaires (11).

Although we found no further revealing factors in the subgroups of subjects with partial seizure or subjects with TLE, these groups were examined separately because the seizure-promoting effect of estrogen may be more important in localized brain structures. Through hormone autoradiographic binding techniques, it is known that sex-steroid binding in the brain is uniquely localized to nerve cell groups that control reproductive and sexual functions. These sites are the medial preoptic area, the medial cell groups in the midline hypothalamus, and limbic forebrain structures such as the medial amygdala and lateral septum (12). Therefore focal effects of estrogen on excitability become of interest and point to a possible overlap between structures involved in reproductive functions and in epilepsy.

Women with epilepsy are not known to have seizure worsening with oral contraceptive formulations (OCPs), and AED levels are thought not to be affected by concurrent OCP use, although careful interaction studies with large numbers of subjects have not been performed. The hormone doses used in HRT are similar to and generally lower than those used in OCPs. For example, the ethinyl estradiol dose in a low-estrogen OCP is 20 μg, and the dose used for relief of vasomotor symptoms in menopause is 20–50 μg per day. Therefore, an increased sensitivity to exogenous hormones by women with epilepsy during menopause compared with the cycling years is not readily explainable. It may be postulated that increased brain excitability is present during menopause because of alterations in estrogen and progesterone receptors in the setting of deficiency of these hormones, and in the setting of elevated levels of follicle-stimulating and luteinizing hormones.

In studies of Alzheimer's disease and HRT, no increase in seizure occurrence has been noted (13). Therefore, the proconvulsant effect of HRT may be confined to women with great epileptic potential; that is, they already have epilepsy. This is consistent with animal studies in which estrogen was more epileptogenic in animals with epileptic lesions than in normal control animals (3).

Previous efforts at evaluating the relation between perimenopause, menopause, and epilepsy have been published (14,15), and in general, these studies suggest that the hormonal influences during these life epochs may be important for women with epilepsy. However, the course of epilepsy during perimenopause and menopause is still poorly understood, and the data herein should be considered pilot data.

Our results, although somewhat limited by the nature of the methods used, reveal some important biologic and pharmacologic influences on the course of epilepsy during menopause and perimenopause. The effect of HRT on increasing seizure frequency is the most significant finding in that it raises an important clinical question regarding the use of HRT in this population. In an aging population in which HRT prescribing is likely to increase, the effects of HRT in specific disease settings must be evaluated. The purported antiseizure effect of natural progesterone may be applicable in this population. This study does suggest that women with epilepsy who begin HRT should be carefully monitored by their physicians for a change in seizure pattern.

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