Clinical Research

Effects of Menopause on Seizures in Women with Epilepsy

*†Fariha Abbasi, *†Allan Krumholz, †‡Steven J. Kittner, and ‡Patricia Langenberg

*Maryland Epilepsy Center, and the Departments of †Neurology and ‡Epidemiology, University of Maryland School of Medicine, Baltimore, Maryland, U.S.A.

Summary: *Purpose:* Although important associations between epilepsy and women's hormonal phases are described, the relation of menopause to epilepsy has received little attention.

Methods: By using a structured interview, we studied menopausal women with epilepsy seen at the University of Maryland Epilepsy Center over a 1-year period from 1994 to 1995. We analyzed the characteristics and temporal relation of the seizures to menopause and compared the frequency and severity of the seizures with those in a similar group of premenopausal women.

Results: We identified 61 menopausal women (46 who were postmenopausal and 15 perimenopausal) and compared them with 46 premenopausal women. No statistically significant differences were noted in either the frequency or the severity of seizures comparing all menopausal or only postmenopausal with premenopausal women. However, 12 (20%) of the 61 menopausal women noted that their seizures first began during or after menopause, with eight having no proven cause for their seizures. Many individual women described changes in their seizures with menopause. Among the 61 menopausal women, 49 had established epilepsy before the onset of menopause, and 20 (41%) reported worsening of their seizures with menopause, 13 (27%) noted improvement, and 16 (33%) described no changes. These observations were similar for peri- and postmenopausal women. Of the 15 menopausal women taking hormone replacement therapy, the six taking progestin were significantly less likely to report worsening of their seizures.

Conclusions: These findings support the view that hormonal influences are important in women with seizures. Although, in aggregate, menopausal (combined perimenopausal and postmenopausal) and postmenopausal women's seizures were similar in frequency and severity to those of other women, menopause was associated with changes in seizures for some women. Moreover, menopause may be a previously unrecognized factor for some new-onset seizures. The relations between menopause and epilepsy deserve to be more fully investigated. **Key Words:** Menopause—Epilepsy—Seizures—Women—Hormones.

Women with epilepsy are increasingly recognized to have special problems resulting from the complex and significant effects of reproductive phases on their seizures. The interactions of puberty, menarche, menstruation, and pregnancy with epilepsy have been studied and reviewed by several investigators (1–7). Still, little is known about the associations of epilepsy with another important female hormonal phase, menopause. Understanding this issue will be of increasing importance as the percentage of older individuals in the population increases.

Indeed, menopausal women with epilepsy present a potential major public health concern. Menopause generally occurs in American women between the ages of 48 and 55 years. Current census figures indicate that we now approach a figure of 50 million American women older than 50 years. Because the American woman can expect to live an average of 30 years after menopause, she will spend approximately one third of her life after ovarian failure (8). Furthermore, although epilepsy characteristically has its onset at a young age, and often persists as a life-long problem, it does not necessarily shorten the life span; many women with epilepsy will therefore live many years after menopause. Recent studies indicated that the incidence of epilepsy in the older population has been underestimated and increases considerably after age 50 years (9). However, other than a few case reports and one study from Poland by Rosciszewska (10,11), very little is known about the relation of menopause to epilepsy. The purpose of this study was to investigate the effects of menopause on women with epilepsy.

METHODS

Our study population comprised women with epilepsy seen at the University of Maryland Epilepsy Center from July 1994 to July 1995. We focused on menopausal women, both perimenopausal and postmenopausal, but a comparison group of premenopausal women was selected from the same population. To be included in the study, a patient must have been diagnosed with epilepsy, which we defined as recurrent (at least two) unprovoked epileptic seizures (8). Patients with idiopathic, cryptogenic, and remote symptomatic seizures were included in each of our study groups (Table 1; 12).

Women were classified into two major groups (Table 1): premenopausal and menopausal. Menopausal women were further subdivided to two subgroups: (a) postmenopausal and (b) perimenopausal. The operational definitions for this classification are given in the Table 1. We used the World Health Organization proposed definition of 1 year of amenorrhea to define our postmenopausal women (13), a standard also used in other major clinical studies of menopause (14). However, we appreciate that menopause is a dynamic transition and that longer postmenopausal periods would potentially define women with greater hormonal deficiency (15). Also, we include perimenopausal women in our analysis because we and others recognize that this is a major and important phase of the menopausal transition during which the hormonal changes typical of menopause first manifest (13,15,16). For our statistical analyses, however, perimenopausal and postmenopausal women were considered both as a combined "menopausal" group and separately as "perimenopausal" and "postmenopausal" groups.

Informed consent was obtained from all subjects, and a structured questionnaire was administered by one of the investigators (F.A.). We obtained background demographic information for each patient and acquired details of the seizure history, which included both the present seizure frequency and seizure severity. Seizure severity was determined by the standardized Chalfont severity scale (17). In addition to background demographic information and details regarding her seizures, each patient was questioned specifically about the relation between

TABLE 1. *Classification of menopausal status*

I. Premenopausal	Women younger than 45 years with regular menstrual cycles who are not experiencing any menopausal symptoms
II. Menopausal	
A. Perimenopausal	Women older than 45 years with irregular menstrual cycles who are experiencing menopausal symptoms
B. Postmenopausal	Women older than 45 years with the absence of menses for ≥12 months or Women younger than 45 years with surgically induced (oophorectomy) and medically confirmed menopause (14)

the applicable hormonal phases and the frequency and severity of her seizures. These hormonal phases included puberty, the menstrual cycle, pregnancy, and menopause. When appropriate based on the history, we additionally inquired about the relation between a patient's seizures and hormonal therapy with oral contraceptives or hormone replacement therapy (HRT) for menopause. Menopausal women taking HRT that included progestin were compared with those using HRT with estrogen preparations that did not include progestin.

We then analyzed and compared results from menopausal with those from premenopausal women by using the t test for comparison of means, and the χ^2 and Fisher's Exact tests for categoric analysis. We considered menopausal women (perimenopausal and postmenopausal) as a group but also compared perimenopausal and postmenopausal women separately in our analyses. Specific questions addressed included whether there were significant differences in the frequency or severity of seizures in menopausal (perimenopausal and postmenopausal) as compared with premenopausal women. We also attempted to determine whether menopausal women with epilepsy experienced characteristic patterns of change in their seizures as they passed through menopause.

RESULTS

A total of 107 women participated in the study. We identified 61 menopausal women: 46 were classified as postmenopausal and 15 perimenopausal (Table 2). These 61 menopausal women were compared with a group of 46 premenopausal women. The median age of epilepsy onset for our premenopausal women was 13.5 years; 18.5 years for the postmenopausal women, and 19.5 years for the perimenopausal women. The groups were demographically similar in terms of such variables as marital status, education, and occupation. No statistically significant differences between all menopausal (combined peri- and postmenopausal) and premenopausal women were found regarding types of seizures, medication profiles, or demographic variables other than age.

Some representative characteristics of our study population of 107 women were as follows: Seventy percent were married, divorced, or widowed. Seventy-two percent had one or more pregnancies. Fifty percent had some college or technical school education after high school. Forty-three percent were employed outside of the home, and 29% received disability. Antiepileptic medications (AEDs) were being taken by 98% of the patients at the time of the interview. The relative annual seizure frequencies in our population were as follows: 29% of patients reported zero to one; 24%, two to 12; 27%, 13–60; and 19% reported ≥60 seizures.

An analysis of the frequency or the severity of seizures in menopausal (combined perimenopausal and post-

TABLE 2. *Characteristics of epileptic seizures in women by menopausal status*

| | Premenopausal | Menopausal | | |
		Perimenopausal	Postmenopausal	All menopausal
Number	46	15	46	61
Age in years	33.3 (7.2)	44.7 (2.9)	53.4 (10.8)	51 (10.2)
Number of seizures annually	45.1 (64.2)	11.0 (18.0)[b]	50.5 (69.0)	40.8 (62.8)
Severity of seizures[a]	38.5 (38.9)	45.1 (38.4)	46.2 (37.3)	46.2 (37.2)
Seizure type				
% GTC	57	60	52	54
% CPS	70	73	78	77

Values expressed as mean (standard deviation).
[a] Based on Chalfont Scale (17).
[b] Perimenopausal mean significantly different from premenopausal (p = 0.048) and postmenopausal (p = 0.033).
GTC, generalized tonic–clonic; CPS, complex partial seizures.

menopausal) compared with premenopausal women revealed no significant differences between these two groups (Table 2). The only difference noted was with a separate analysis of perimenopausal subgroup (Table 1). There was a lower seizure frequency but not severity for the perimenopausal women as compared with both premenopausal and postmenopausal women (Table 2).

Many individual women reported a change in their seizures with menopause. In fact, among the 61 menopausal women, 45 (74%) reported either that their epilepsy changed or first began during menopause. In particular, 49 (80%) of 61 menopausal women had a history of seizures before their menopause. In this group, 20 (41%) of 49 reported worsening, 13 (27%) of 49 improvement, and 16 (33%) of 49 no definite change in their seizures with menopause. Worsening of seizures for the purpose of this analysis was judged on the basis of a change in seizure frequency. Also, these proportions were similar for both perimenopausal and postmenopausal women when those subgroups were separately considered.

An unanticipated finding was the substantial proportion of patients who related the first onset of their seizures to menopause. Among the 61 menopausal women we questioned, 12 (20%) first started to have seizures in menopause, nine of whom noted the first seizure during the perimenopausal phase or within 2 years of becoming postmenopausal, whereas three had seizures starting ≥2 years after becoming postmenopausal. For four of these 12 women, epilepsy was the consequence of an known cause (i.e., stroke or brain tumor). For these four women, menopause could not be considered a causative factor for the seizures (so-called remote symptomatic epilepsy; 12). However, it is interesting to note that all three of the women with postmenopausal seizure onset had a known cause for their epilepsy, whereas only one of nine women with seizures starting perimenopausally or within 2 years of becoming postmenopausal had a definable cause for her epilepsy.

Puberty and pregnancy also were associated with new-

onset epilepsy or seizures in some of our patients. For example, among menopausal women, nine (15%) of 61 reported that their first seizure occurred at puberty, and one (2%) woman experienced her first seizure during pregnancy.

The effects of HRT on epilepsy also were considered in the menopausal women in our study. Thirty-one (51%) of our 61 subjects had some experience with HRT. Of these 61 women, 15 were undergoing such therapy at the time of our study, and 16 had tried HRT in the past but discontinued it. Of the 31 women with epilepsy who had experience with hormonal therapy for menopause, 22 (71%) noted no change in their seizures while receiving treatment, five (16%) reported some improvement in their seizures, and four (13%) described worsening. Three women reported that their physicians specifically advised against HRT because of fear of exacerbating the seizures. We observed no correlation between the reported effect of oral contraceptives on our patients' seizures and the seizure changes noted with either menopause or HRT for menopause.

The types of hormonal replacement preparations and dosages prescribed varied considerably, and many of the women who had previously been taking HRT could not identify exactly what they had been prescribed, so we were unable to perform complete analyses of this issue. However, we could reliably determine the nature of the HRT for the 15 menopausal women who were taking HRT at the time of the study. We determined whether the women were taking HRT with or without progestin. There were six women taking HRT that included progestin, and nine taking estrogen without progestin. Of the six women taking some progestin, three (50%) described a decrease, none an increase, and 3 (50%) no change in their seizures. In contrast, of the nine women taking only estrogen; none noted a decrease, one (11%) an increase, and eight (89%), no change in their seizures. The numbers of subjects are small, but the difference between the estrogen group and the estrogen plus progestin group was statistically significant (p = 0.045); only women

taking progestin noted a decrease in their seizure activity. The risk of seizures worsening with HRT was low for all women with only one (7%) of 15 menopausal women currently taking HRT and only four (13%) of 31 menopausal women ever reported to have taken HRT describing worsening, whereas women taking progestin were more likely to report improvement in their seizures.

In general, the number of patients in our series was relatively small, which limited our ability to detect associations among variables. We could not demonstrate associations between the reported influence of various hormonal phases (puberty, menstruation, or pregnancy) on our patients' seizures and the changes attributed to menopause. For example, women who reported that seizures worsened with their menstrual cycles, so-called catamenial epilepsy, were not more likely to report that their seizures worsened with menopause.

DISCUSSION

Our study of menopausal women provides supporting evidence that hormonal changes may affect women with seizures. Although puberty and pregnancy have been well identified previously as risk factors for epilepsy, few studies have explored the similar risks posed by menopause. Many reviews discuss the changes that occur in epilepsy during various hormonal stages of a woman's life (1–7), but data on the influence of menopause is very limited. In view of the known hormonal effects on seizures in women, it seems reasonable to presume that menopause may also affect epilepsy.

In our study, seizures in postmenopausal and all menopausal (combined peri- and postmenopausal) women proved similar in frequency and severity to those of premenopausal women (Table 2). The only difference noted was that the 15 perimenopausal women had a lower seizure frequency than both the pre- and postmenopausal women. Given the small sample size of the perimenopausal subgroup and the nominal significance of the p value, this could be a chance finding and is of doubtful relevance.

Menopause did influence seizure patterns for some individuals. For example, among the menopausal women with epilepsy, the majority reported some change in their seizures with menopause. Indeed, among the 49 women in our series whose epilepsy preceded the onset of menopause, 67% noted a change in their seizures with menopause. The highest proportion, 41%, reported worsening, but 27% noted that their seizures improved. This was similar for both peri- and postmenopausal women. These observations differ somewhat from the only other study on the interaction of menopause and seizure frequency (10,11), which is in the Polish literature. In that study of 41 menopausal women, 21 (51%) described no change in their seizures, eight (20%) reported improvement, and 12 (29%) noted worsening (10,11). We cannot completely

account for the differences between ours and the earlier study. Both studies do, however, suffer from some methodologic limitations that could have contributed to the somewhat different observations: each involved relatively small numbers of women, was retrospective, and depended on the patients' self-reports. There may also have been selection biases. In particular, our study was based at a tertiary care epilepsy center, which tends to draw patients with intractable or more difficult epilepsy problems. This patient population may, in part, account for the somewhat higher incidence of reported seizure worsening with menopause among our patients. In addition, our study included both perimenopausal and postmenopausal women (Table 1), whereas the study from Poland did not similarly categorize patients, stating only that the women were investigated during menopause (10,11). Still, this is unlikely to be a major factor because we did not discern significant differences in the seizure changes reported with menopause between our postmenopausal and perimenopausal groups. Indeed, despite some differences, both our study and the previous study by Rosciszewska (10,11) suggested that menopause may affect seizure activity for many women.

One particularly interesting finding of our study that was not noted by Rosciszewska's report (10,11) was that 12 (20%) of 61 menopausal women first began having seizures during menopause. For four (33%) of these 12, the cause of epilepsy was clearly defined as a stroke or tumor, and these individuals are classified as having remote symptomatic epilepsy due to a known cause, whereas eight (67%) women had no defined established cause for their seizures and are classified as having idiopathic or cryptogenic epilepsy. Interestingly, in seven (88%) of these eight women, epilepsy onset occurred sometime between the start of menopause and 2 years after the complete cessation of menses. These findings suggest that some women may have a kind of "menopausal" epilepsy, influenced by hormonal changes in perimenopausal or early postmenopausal phases, and perhaps similar to what has been termed gestational epilepsy in pregnancy (2).

There is considerable evidence that female sex hormones and their fluctuations affect seizure thresholds and may influence seizures in women with epilepsy. Gowers (18) was the first to note, in 1855, a higher prevalence of new-onset seizures between the ages of 10 and 20 years, which he proposed might be related to the hormonal changes of puberty. Although the influence of hormones is a highly complex issue, studies in both humans and animals support the general view that estrogen may lower seizure threshold and increase seizure frequency, whereas progestin appears to have an opposite effect (19,20). Indeed, pharmacologic and physiological studies demonstrated the existence of estrogen and progestin receptors in various locations of the CNS (21).

Extensive evidence supports the potential seizure-provoking influence of estrogen. For example, positive correlation has been observed between the follicular phase of the menstrual cycle, a time of high estrogen, and increased frequency of seizures (22). Moreover, animal studies indicate that estrogen has a seizure-activating effect. For example, the electroshock seizure threshold in rats is lowest during periods of the estrus cycle when estrogen levels are high, or after i.v. estrogen is administered to female rats (23,24). In other studies, estrogen applied topically created new seizure foci and activated previously present cortical epileptogenic foci (24), and on a neuronal level, estrogens enhance glutamate excitation (25). Some questions remain regarding the significance of this estrogen seizure-provoking effect in humans because studies involving catamenial epilepsy have not consistently confirmed that high levels of estrogen are responsible for exacerbation of seizures (1,22,26,27). Nonetheless, the concept that estrogen may lower the seizure threshold in some individuals is reasonably well accepted.

Progestin, on the other hand, has been shown to protect against pentylenetetrazol-induced seizures and to elevate the electroshock threshold in animals (23). In a rat model, progestin enhanced the inhibitory response of neurons to γ-aminobutyric acid (GABA) and suppressed excitability of neurons to glutamate (28). Clinical studies described a consistent decrease in seizures during the midluteal phase of the menstrual cycle, associated with high progestin levels (27,29). Other clinical research indicated that progestin infusions suppress epileptiform spikes in women with epilepsy and that progestin therapy decreases seizure frequency in women refractory to standard drug therapy (20).

One particularly concerning observation from our clinical study is the difficulty women reported obtaining information about menopause and its potential influence on their seizures. Although many women voiced long-standing concern about the relation between menopause and epilepsy, and several reported that they had sought counsel from their physicians, only one woman reported that her physician offered information about this issue. Moreover, she obtained this information only after being referred to a tertiary epilepsy center shortly before entering this study.

Our study of menopausal women supports the concept that hormonal influences are important in epilepsy and offers some potential directions for future investigation. Overall, 74% of our menopausal women described some change in their seizures with menopause, with 20% noting that their seizures first began during menopause. It is not yet understood to what extent menopause is responsible for these reported changes, but it is clear that menopausal effects on seizures are a serious concern and highly relevant issue for many mature women with epi-

lepsy. The complex potential interactions between menopause and epilepsy must be better understood by physicians and better communicated to women with epilepsy.

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