If it is shown that ischemia is one of the mechanisms for SUDEP, the use of anti-ischemic agents could save lives.

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Onset of epilepsy at the time of menarche

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Abstract—The authors compared the frequency of epilepsy onset in perimenarche with epilepsy onset in other childhood periods in 94 postmenarchial patients aged <55 years. Seizure onset was higher for the 12 to 15 year age bracket than for other ages and clustered around menarche. Epilepsy began during the year of menarche in 17% of patients vs 5.5% expected ($p < 0.001$), and during ±2 years of menarche in 38% patients vs 22% expected ($p < 0.001$). Seizures worsened during perimenarche in 29% of girls with pre-existing epilepsy. Perimenarche may be a risk for the development and worsening of epilepsy.

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Reproductive hormones affect seizure threshold and occurrence in adult women with epilepsy.[1] Reproductive hormonal changes during sexual maturation can also affect epilepsy. Hippocrates believed that epilepsy improved during menarche. Gowers thought the opposite, namely that epilepsy often began or worsened during menarche. Several studies have shown that in approximately one third of girls with epilepsy, seizures worsen during puberty or menarche.[2,3] Two studies have investigated seizure onset, as opposed to seizure exacerbation, during menarche.[3,4] In one study, 4/30 women related their first seizure to their first menstrual period.[4] In another study, 19% of 165 adult women with epilepsy reported seizure onset at menarche, including 33% of women with primary generalized epilepsy (PGE) and 14% women with localization related epilepsy (LRE).[3] However, the study was a mailed questionnaire survey with a 20% response rate, and it included elderly women who may have an imperfect recollection of early life events. The current study sought to determine whether perimenarche affects the risk of developing epilepsy by comparing epilepsy onset during menarche and perimenarche with other childhood periods.

Methods. We consecutively evaluated 94 postmenarchial girls/women aged 9 to 55 years with epilepsy onset between 4 months and 18 years with reproductive endocrine history interviews. Only girls/women who were cognitively normal (school attendance at grade or grade-1 level) or whose mothers could provide reliable histories (n = 4) were included. Women ≥55 years were excluded to maximize recall accuracy of reproductive history.

Questions included age at seizure onset, age at menarche, reproductive history, and change in seizure frequency or severity (e.g., change from partial to secondarily generalized seizures) during perimenarche in girls with pre-existing epilepsy. We defined perimenarche as the period from 2 years before until 2 years after menarche.

Histories of girls aged ≤18 years (n = 16) were corroborated in face-to-face interviews with their mothers. To reduce recall inac-

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Table *Age at menarche onset among girls and women with epilepsy onset before 18 years of age*

Parameter	No.*	Mean (SD)†	Median	Range	Significance‡
All subjects	94 (86)*	12.2 (1.6)	12.5	8–16.3	0.04
Controls	65	12.8	13	9.5–17	
White/Asian	75 (68)*	12.4 (1.6)	13	8–16.3	0.047
African American	19 (18)*	11.5 (1.4)	12	8.5–13.5	
Epilepsy onset before or during the year of menarche	53	12.4 (1.6)	12.5	9–16.3	0.04
Epilepsy onset after the year of menarche	33	11.7 (1.4)	12.1	8.5–16	

*Number of girls with known age at menarche onset in parentheses.
†SD rounded to a single decimal point.
‡Student's *t*-test.

curacies, 90% of subjects were interviewed on more than two separate occasions at least 1 month apart; 58% were interviewed on more than three occasions. Onset of epilepsy and menarche were determined with an accuracy of ≤3 months (as determined by seasons) or better in 32% subjects. Subjects in whom accuracy was less than 1 year or in whom the information could not be reproduced were counted as having nonreproducible information.

Evaluations included history, physical examination, EEG, and, if normal, sleep-deprived or long-term EEG, and MRI or CT. International League against Epilepsy classification was used to determine seizure type and epilepsy syndromes. Refractory epilepsy was defined as having more than one seizure per 4 months despite more than three monotherapy trials or two monotherapy and one polytherapy trials. Sixty-eight neurologically normal girls/women aged 17 to 53 years, of similar racial mix, consecutively seen in the sleep clinic served as control subjects for determination of age at menarche.

Statistical analysis included the χ^2 test, Fisher's Exact test, Student's t-test, and the Kolmogorov-Smirnov test.

Results. Seventy-three (78%) subjects had LRE, 20 (22%) had PGE and one had mixed epilepsy. Forty-one subjects had refractory seizures. Reproducible information was obtained in 93/94 subjects for seizure onset, 87/94 patients for menarche, and 86/94 subjects for both. Twenty percent of subjects were ≤20 years old; 59% were ≤32 years old at the time of the first interview.

Data and statistical results for menarche age are shown in the table. Mean age at menarche onset was less in epilepsy patients than in controls (12.2 vs 12.8 years, $p = 0.04$, Student's *t*-test). This was not explained by difference in distribution of race between the two groups. Menarche age was lower in African American girls or women with epilepsy (n = 19) than in the combined group of white/Asian epilepsy patients (n = 69) (11.5 vs 12.4 years, $p = 0.047$). Age at menarche could not be accurately determined in one African American and in seven white women. No correlation was found between the age at menarche and patients' age at evaluation, age at seizure onset, seizure type or refractoriness, and reproductive endocrine disorders.

Mean age at seizure onset was 10.1 years (SD 5.4, median 10.5, range 0.3–18). When seizure onset was divided chronologically into three-year brackets, it was higher for the 12–15 year bracket than for other ages ($p = 0.037$ by χ^2 goodness of fit test, figure 1).

Seizure onset clustered around the year of menarche (figure 2). Epilepsy began during the year of menarche in 15/86 patients with known age at seizure onset and at menarche (17.4% vs 5.5% expected, $p < 0.001$ by χ^2 test). It began in 19/86 (22%) patients during the 2-year period from 1 year before to 1 year after menarche (vs 11% expected, $p < 0.001$), and in 33/86 (38%) of patients during the 4-year period from 2 years before to 2 years after menarche (vs 22% expected, $p < 0.001$). Seven of 22 patients with PGE had onset of epilepsy within a 3-year period centered around menarche (five with juvenile myoclonic epilepsy, JME) vs 18/73 of patients with LRE, a nonsignificant difference.

Nine of 31 (29%) girls whose seizures began 3 or more years before menarche experienced seizure exacerbation during perimenarche; all had LRE.

Discussion. Our study indicates that there is an increased risk of developing epilepsy during perimenarche compared with other childhood periods for LRE and PGE. In girls 4 months to 18 years of age, 17% of epilepsy began during the year of menarche, 38% during ± 2 years of menarche. In girls with pre-existing epilepsy, 29% experienced seizure exacerbation during perimenarche (all with LRE), consistent with previous studies.[2,3]

The study's limitations include its retrospective,

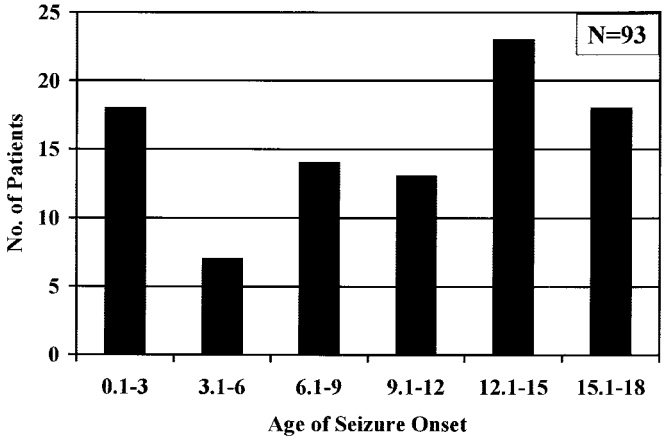

Figure 1. Age at seizure onset.

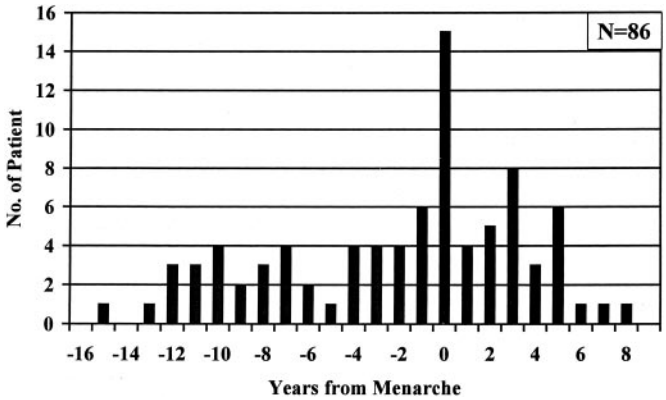

Figure 2. Seizure onset related to menarche.

report-based design, which is subject to recall bias and inaccuracy. We tried to reduce this by conducting multiple personal interviews and by excluding women older than 55 years.

In contrast to our findings, epidemiologic studies fail to show change in incidence of epilepsy during adolescence.[5] However, epidemiologic studies group patients by age, usually with 5-year brackets. This may miss the clustering of a disease around a physiologic event that spans several age brackets, such as perimenarche. In addition, some types of epilepsy (e.g., absence) remit spontaneously during adolescence, while others (e.g., JME) begin during adolescence, confounding epidemiologic studies.

Initiation or exacerbation of epilepsy during perimenarche may be related to changes in reproductive hormones. Estrogens promote seizures and epileptogenesis in animal models of epilepsy and facilitate seizures in adult women with epilepsy. Progesterone has the opposite effect. It inhibits neuronal excitability, seizures and epileptogenesis in animal models of epilepsy and lessens epileptiform discharges and seizures in women with epilepsy.[1,6–8]

During sexual maturation, secretion of the neuroexcitatory steroids, dehydroepiandrosterone sulfate, pregnenolone sulfate and estrogens starts with adrenarche and gonadarche between the ages of 8 and 10 years[9] but secretion of the neuroinhibitory steroid progesterone does not begin until menstrual cycles become ovulatory, about one to two years after menarche. Thus, neuroexcitatory steroids are present for a period of approximately 4 to 6 years before progesterone. This may promote excitatory synaptogenesis and the development of epilepsy. Further understanding of this process might lead to strategies of hormonal intervention to prevent epilepsy in girls during adolescence.

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