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Neurology 2003;60;495-497

This information is current as of May 2, 2008

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http://www.neurology.org/cgi/content/full/60/3/495
If it is shown that ischemia is one of the mechanisms for SUDEP, the use of anti-ischemic agents could save lives.

Acknowledgment

The authors thank subjects who participated in the study as well as Viggo-Kamp Nielsen (Aarhus University Hospital, Denmark) for neurophysiologic advice and assistance, Michael Rehling (Skejby University Hospital, Aarhus, Denmark) for advice and assistance related to the myocardial scintigraphy imaging, and Gertrud Næs Schmidt (Skejby University Hospital) for EKG technical assistance. They also thank Lene Nielsen, Krista Nielsen, Birgitte Jensen, Emma Stenfeldt, and Rud Sørensen (Aarhus University Hospital) for EKG, video, and patient assistance. They also thank Gregory D. Cascino and Jeffrey R. Buchhalter for assistance with this manuscript.

References


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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% of 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.

NEUROLOGY 2003;60:495–497

Reproductive hormones affect seizure threshold and occurrence in adult women with epilepsy. 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. Two studies have investigated seizure onset, as opposed to seizure exacerbation, during menarche. In one study, 4/30 women related their first seizure to their first menstrual period. 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). 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-
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.

The study’s limitations include its retrospective,
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. 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.

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 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.

Acknowledgment

The authors thank Theresa Ingram, Epilepsy Unit Coordinator, Georgetown University Hospital, for assistance in the manuscript preparation.

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