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Female reproductive factors and risk of Seizure or Epilepsy: Data from the Nurses' Health Study II

Barbara A. Dworetzky,
Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Mary K. Townsend,
Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Page B. Pennell, and
Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Jae H. Kang
Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Summary

Reproductive factors are associated with seizures in women with epilepsy. We prospectively examined the association between reproductive factors and the risk of adult-onset isolated seizure, epilepsy, or any unprovoked seizure (defined as single unprovoked seizure or epilepsy) among 114,847 Nurses' Health Study II participants followed from 1989–2005. Validated seizure questionnaires and medical records were used to confirm incident cases of isolated seizure (n=95) or epilepsy (n=151). Overall, there were no significant associations between any reproductive factor and risk of any unprovoked seizure (n=196). However, menstrual irregularity at ages 18–22 years was specifically associated with an increased risk of epilepsy (Relative Risk (RR) = 1.67, 95% Confidence Interval (CI), 1.12, 2.51). Menstrual irregularity during follow-up (RR = 2.21, 95% CI, 1.16, 4.20) and early age at menarche (<12 years vs. 12–13 years; RR=1.76, 95% CI, 1.10, 2.81) increased the risk of isolated seizure. Oral contraceptive use and parity were not associated with isolated seizure or epilepsy. Thus, menstrual factors were associated with risk of seizure/epilepsy.

Keywords

epidemiology; oral contraceptives; menstrual irregularities; hormones; women

Address: 75 Francis Street, Boston, MA 02115, Phone: 617-732-7547, Fax: 617-730-2885, bdworetzky@partners.org.

Disclosures:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Barbara A. Dworetzky receives support from an AAN education grant, a Harvard Catalyst grant, and has received travel reimbursement from the American Epilepsy Society. Page B. Pennell, M.D. has received salary support for research from the National Institutes of Health, the Milken Family Foundation, and the Epilepsy Foundation, and travel reimbursement from the National Institutes of Health, the Milken Family Foundation, the Epilepsy Foundation, American Epilepsy Society, and the National EpiFellows Foundation.

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Female sex hormones and their fluctuations are associated with seizure threshold and frequency.(Backstrom, 1976)Estrogen lowers seizure threshold and increases seizure frequency; in female rats, the electroshock seizure threshold is lowest with highest endogenous estrogen levels.(Woolley & Timiras, 1962)In one-third of premenopausal women with pharmaco-resistant epilepsy, seizure frequency was higher in menstrual phases with a higher estrogen/progesterone ratio (Herzog, et al. 1997; Logothetis et al., 1959), and studies have demonstrated decreases in seizures during the mid-luteal menstrual phase (with highest progesterone levels).(Backstrom, 1976) Progestin infusions suppress epileptic discharges on EEGs of women with epilepsy,(Backstrom et al., 1984) and progesterone has been used to treat partial seizures in women.(Herzog et al., 1997) To date, no prospective studies have evaluated whether female reproductive factors may be associated with adult-onset incident seizure or epilepsy. Thus, we prospectively evaluated this relationship in 114,847 women in the Nurses' Health Study II (NHS II) from 1989 to 2005.

Methods

The NHS II was initiated in 1989 with 116,430 female nurses aged 25–42 years. Participants are followed biennially with mailed questionnaires that update health and lifestyle information. To date, >85% follow-up has been maintained. From 1989, participants reported new isolated seizure or epilepsy diagnoses and their dates by writing in a box provided for "other major illnesses". "In 2001, we included specific questions on diagnoses of isolated seizure or epilepsy, including dates of occurrence (<1991<1991–1995–1995–1999–2000–2001+); a similar question was asked in 2005. We excluded 98 participants with seizure/epilepsy (except febrile seizure before age 6 years) occurring before 1989 and 1,485 participants lost to follow-up within two years of 1989, leaving 114,847 participants who were followed from 1989 to a diagnosis of seizure/epilepsy, loss–to-follow-up, death or 2005 (end of this study). This study was approved by the institutional review board.

Exposure Data

In 1989, data were collected on age at menarche, usual menstrual cycle length and pattern during ages 18–22 years, parity (the total number of pregnancies lasting 6+ months), age at first birth, and oral contraceptive use; where relevant, this information was updated biennially. In 1993 (when participants' mean age was 38 years), the current menstrual pattern was assessed.

Outcome Data

To identify incident cases, we mailed participants who self-reported new seizure/epilepsy diagnoses after 1989 a validated seizure supplementary questionnaire (Dworetzky et al., 2009) and requested permission to access medical records. The questionnaire assessed detailed information regarding the age at first seizure, number of lifetime seizures, family history, medication history, etiology provided by physician, seizure description (i.e., limb jerks, warnings, alteration in awareness), and diagnostic procedures (MRI, CT, EEG, video EEG, neurologic consultation). Both the questionnaire and medical records were received from 66.0% of respondents, and the questionnaire alone was received from 34.0%. Finally, two epileptologists independently reviewed all relevant confirmatory information and came to a consensus on the final confirmation and classification.

For analysis, we defined three types of cases: 1) "isolated seizure", including single unprovoked seizure (28%) as well as acute symptomatic seizure (single seizure with systemic causes, 38%; single seizure with neurologic causes, 19%; and recurrent provoked seizure, 15%); 2) "epilepsy", including symptomatic partial epilepsy (49%), idiopathic/cryptogenic partial epilepsy or partial epilepsy of unknown cause (33%), idiopathic

generalized epilepsy (5%), and nonclassifiable epilepsy (13%); and 3) “any unprovoked seizure”, defined as single unprovoked seizure or epilepsy. (Commission on Epidemiology and Prognosis—International League Against Epilepsy, 1993). The date of diagnosis was the date of the first reported seizure.

Covariate Data

Multivariable models adjusted for family history of isolated seizure or epilepsy, cigarette smoking, hypertension, high cholesterol, type 2 diabetes mellitus, stroke, brain tumor, parity, history of oral contraceptive use, menstrual regularity at age 18–22 years, age at menarche, and body mass index. In the analysis of each reproductive factor, the other factors were also adjusted.

Analyses

We used Cox proportional hazards models(Cox & Oakes, 1984) stratified by age (in months) and the specific 2-year period at risk to calculate relative risks (RR) and their 95% confidence intervals (CIs).

Results

From 1989 to 2005, we accrued over 1.7 million person-years of follow-up and ascertained 95 cases of isolated seizure and 151 cases of epilepsy.

Age at menarche

The mean age at menarche in the study population was 12.4 years (SD=1.4 years). Compared with menarche at age 12–13 years, menarche at <12 years was significantly associated with risk of isolated seizure (RR=1.76; 95% CI 1.10, 2.81). However, age at menarche was not associated with risk of epilepsy or any unprovoked seizure (Table 1).

Menstrual irregularity and cycle length

Menstrual irregularity at age 18–22 years was found in 24% of women (Table 1). Menstrual irregularity at age 18–22 years was significantly associated with risk of epilepsy (RR=1.67, 95% CI 1.12, 2.51), but not with risk of isolated seizure or any unprovoked seizure. After additional adjustment for cigarette smoking and body mass index at age 18, which predict menstrual irregularity at age 18, results were similar.

Menstrual irregularity in 1993 was found in 10% of women. This irregularity was associated with a 2.21-fold (95% CI 1.16, 4.20) increased risk of isolated seizure. Similarly, extreme menstrual cycle lengths in 1993 were positively associated with risk of isolated seizure (RR = 2.50, 95% CI 1.16, 5.40 for cycle lengths of 40+ days).

Oral contraceptive (OC) use

Most women had used OCs, with 77% past users and 9% current users (mean duration of use 4.4 years (SD=3.7 years)). Compared with past OC use, current use or never use was not associated with risks of isolated seizure, epilepsy, or any unprovoked seizure (Table 1). Duration of use also was not associated with seizure/epilepsy. Among past users, time since stopping use was not significantly related to risk (data not shown).

Parity

We did not observe any significant associations between increasing parity or age at first birth and the risk of seizure/epilepsy (data not shown).

Secondary analyses

To determine whether the significant associations may be mediated by stroke or tumor, analyses were repeated after excluding participants with either a history of brain tumor or stroke. The results were similar and no significant findings became non-significant (data not shown).

Discussion

In this large prospective study of women followed for 10+ years, we observed that menstrual irregularity at ages 18–22 years was associated with increased risk of new adult-onset epilepsy. Menstrual irregularity assessed during follow-up and early menarche was related to increased risk of new adult-onset isolated seizure. Oral contraceptive use and parity were not associated with any outcome.

Menstrual cycle irregularities (e.g., amenorrhea, oligomenorrhea, or abnormally short or long cycles) have been reported in >50% of women with epilepsy.(Herzog, et al. 1986)In our study, menstrual irregularity at age 18 was associated with a 1.67-fold increased risk of epilepsy. It is possible that the early irregular cycles are a marker for abnormalities of the neuroendocrine axis that also render women more susceptible to develop epilepsy. Alternatively, the relatively higher proconvulsant estrogen to progesterone ratio in anovulatory cycles in women with irregular menses at age 18–22 years, when the brain is still undergoing development and organization, may decrease the threshold for seizures, and thereby make them susceptible to later epilepsy development. Finally, it is possible that women had a first undetected seizure in adolescence or young adulthood and afterwards developed menstrual irregularities followed by later epileptic seizures that led to their epilepsy diagnosis; however, this is unlikely, especially as menstrual irregularity in 1993 was not associated with epilepsy. In our study, women with current irregular menstrual cycles had an increased risk of isolated/provoked seizure but not epilepsy. One explanation for the differential results of menstrual irregularities by timing may be that recent proconvulsant exposures rather than those from the remote past may be more etiologically important for isolated seizures versus epilepsy, leading to the stronger association with more recent menstrual irregularity.

OC use was not associated with isolated seizure, epilepsy, or any unprovoked seizure. This is consistent with studies that found that oral contraceptive use was not related to seizure exacerbation in women with epilepsy. (Guberman, 1999; Vessey et al., 2002)

Our study has some limitations. Although this was a large study, the case numbers for isolated seizure and epilepsy were relatively small, thus limiting the statistical power of the study and precluding our ability to explore potential interactions between reproductive variables and other factors. In addition, the outcome of “isolated seizures” included both single unprovoked seizures as well as acute symptomatic seizures (systemic and neurologic). A single unprovoked seizure may progress to epilepsy, and the risk of acute symptomatic seizures after stroke or metabolic disturbances may be modestly influenced by small hormonal changes due to differences in reproductive factors. These may be difficult to interpret and need confirmation. The report of early menstrual histories (e.g., age at menarche, menstrual pattern at age 18–22 years) in 1989 may have involved some recall bias; however, this misclassification is likely to be random, which would have biased results towards the null. The prospective design, large population, and high follow-up rate contribute to the validity of results.

Overall, the observed elevated risk of isolated seizure with early age at menarche and menstrual irregularity during follow-up and the elevated risk of epilepsy with early

menstrual irregularity support the hypothesis that reproductive hormones may be altered in neuroendocrine axis disorders, especially those involving limbic structures such as the most common types of adult epilepsy. Early menstrual irregularity may be a marker of neuroendocrine disturbances that precede rather than result in the development of epilepsy in susceptible women.

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Table 1

Reproductive factors and risk of seizure/epilepsy (1989–2005)*

Variable	%		Isolated seizure†		Epilepsy†		Any unprovoked seizure†
Age at menarche		cases	RR (95%CI)*	cases	RR (95%CI)*	cases	RR (95%CI)*
<12 years	24%	33	1.76 (1.10,2.81)	33	0.83 (0.55, 1.26)	48	0.97 (0.68, 1.38)
12–13 years	58%	41	1.00	89	1.00	109	1.00
14+ years	18%	21	1.67 (0.98,2.84)	28	0.90 (0.58, 1.39)	38	1.02 (0.69, 1.49)
Menstrual regularity at age 18‡							
Regular	76%	60	1.00	83	1.00	112	1.00
Irregular	24%	19	0.87 (0.51,1.49)	38	1.67 (1.12, 2.51)	44	1.40 (0.97, 2.02)
Menstrual cycle length at age 18‡							
≤ 25 days	11%	6	0.53 (0.23,1.26)	17	1.40 (0.81,2.44)	21	1.28 (0.78, 2.09)
26–31 days	66%	55	1.00	72	1.00	94	1.00
32–39 days	15%	14	1.16 (0.63,2.12)	21	1.34 (0.80,2.25)	28	1.37 (0.88, 2.14)
≥ 40 days	8%	8	1.08 (0.50,2.35)	13	1.71 (0.90, 3.23)	16	1.51 (0.85, 2.66)
Menstrual regularity during follow-up‡							
Regular	90%	50	1.00	94	1.00	119	1.00
Irregular	10%	13	2.21 (1.16,4.20)	8	0.54 (0.25,1.16)	12	0.70 (0.37, 1.31)
Menstrual cycle length during follow-up‡							
≤ 25 days	17%	13	1.40 (0.74,2.67)	18	1.04 (0.60,1.81)	23	1.04 (0.64, 1.68)
26–31 days	68%	38	1.00	62	1.00	81	1.00
32–39 days	10%	7	1.27 (0.55,2.93)	16	1.55 (0.86,2.78)	20	1.51 (0.90, 2.54)
≥ 40 days	5%	9	2.50 (1.16,5.40)	6	0.90 (0.36,2.21)	9	1.11 (0.53, 2.31)
Oral contraceptives							
Never	14%	12	1.04 (0.55,1.94)	17	0.87 (0.51,1.48)	22	0.88 (0.55, 1.41)
Past	77%	67	1.00	105	1.00	136	1.00
Current	9%	6	1.04 (0.43,2.47)	15	1.20 (0.67,2.12)	20	1.38 (0.84, 2.27)

[*] Multivariate models adjusted for family history of seizure or epilepsy, smoking (never, past current), hypertension, high cholesterol, type 2 diabetes mellitus, stroke, brain tumor, parous state, history of oral contraceptive use, menstrual regularity at age 18–22 (regular or not regular), age at menarche (years), body mass index (kg/m^2). The missing exposure categories and the corresponding case numbers are not shown.

[†] "Isolated seizure" includes single unprovoked seizure and acute symptomatic seizure (single seizure with systemic causes, single seizure with neurologic causes, and recurrent provoked seizure). "Epilepsy" includes symptomatic partial epilepsy, idiopathic/cryptogenic partial epilepsy or partial epilepsy of unknown cause, idiopathic generalized epilepsy, and nonclassifiable epilepsy. "Any unprovoked seizure" includes single unprovoked seizure or epilepsy.

[‡] The study period was from 1993 – 2005 for menstrual irregularity variables.