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Onset of epilepsy and menarche—Is there any relationship?

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Summary

Purpose: Women with epilepsy have increased frequency of reproductive health problems compared to women without epilepsy. In puberty, reproductive hormonal changes during sexual maturation may affect epilepsy and induce the debut of seizures as indicated in some studies. On the other hand, epileptic activity affects sex hormone function, which may induce alterations in pubertal endocrine maturation and thereby menarche age. We wanted to investigate the relation between epilepsy and menarche age in a larger population of female epilepsy patients.
Methods: A retrospective, questionnaire study of a cohort of 265 female outpatients from three Norwegian hospitals and 142 controls, aged 18—45 years was conducted. Parameters regarding epilepsy and reproductive health issues were registered. Perimenarche was defined as 2 years before and 2 years after the year of menarche.
Results: There was a significantly higher frequency of patients with epilepsy debut between 10 and 18 year compared to 0—9 years ($p < 0.01$). There was, however, no significant difference in occurrence of epilepsy debut in the perimenarche period compared to the 5 year periods before and after perimenarche, and no significant difference in epilepsy debut in the year of menarche compared to the 5 years before or after. Menarche age was not significantly different in those with epilepsy debut before or after menarche. Epilepsy type (idiopathic generalised or partial) did not influence the menarche age.
Conclusions: The study did not confirm the former observations of clustering of epilepsy debut at menarche or in the perimenarche period or alterations in menarche

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age in girls with epilepsy. However, onset of epilepsy is more frequent in the adolescent years (10—18), than in childhood (0—9).

Introduction

In puberty, girls experience large hormonal changes. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are increasing from the onset of puberty, followed by a gradual increase in estrogens.[1] When menarche is reached the sex-steroid hormones starts to follow a cyclic pattern and the production of progesterone starts. The pubertal sequence of accelerated growth, breast development, adrenarche and menarche requires a period of 4.5 years (range 1.5—6 years).[1] Estrogens are known to lower the seizure threshold and thereby increase seizure susceptibility while progesterone has the opposite effect.[2—5] This leads to increased seizure frequency in relation to certain phases of the menstrual cycle, so-called catamenial epilepsy, in as much as one-third of all women with epilepsy.[3] The knowledge about the hormonal influence on brain excitability has therefore led to a hypothesis about menarche and/or puberty as an important trigger for epilepsy.[6,7] In accordance with this, some studies have shown a relation between onset of epilepsy and menarche in as much as 20—30% of all female patients.[6,7] Large population based studies, like the Rochester study by Hauser et al.,[8] have not been able to confirm an increased incidence of epilepsy around puberty. In that study, the age-specific incidence of epilepsy in both men and women showed a U-shaped curve, with high incidence the first year of life and in the oldest age group.

On the other hand, sex hormone function can be affected by epileptic activity.[9—11] Epileptic activity has been shown to affect endocrine function at the hypothalamic level, including altered LH pulsatility.[12,13] Regular LH pulsation is essential for induction of ovulation and thereby for menstruation. This raises the question of whether having epilepsy in childhood and adolescence affects the time of menarche.

On this background there are two main questions: (1) Do the endocrine changes in puberty lead to increased frequency of epilepsy debut in adolescence, and if so, is this related to menarche? (2) Do epilepsy affect the time of menarche?

Methods

The study was retrospective and based on a questionnaire. The questionnaire was sent to a cohort of 500 female epilepsy out-patients from three different Norwegian hospitals: Rikshospitalet University Hospital, Ullevål University Hospital and Telemark Hospital. All female patients with a diagnosis of epilepsy and on antiepileptic drug therapy registered in the outpatient clinics computer database, and aged between 18 and 45 years were asked to participate. When sending out the questionnaires, the only exclusion criterion was major mental retardation. After receiving the schemes, patients with progressive neurodegenerative diseases or acute brain disorders receiving complex and constantly varying treatment due to their underlying disease, were excluded from further examination. The questionnaire contained questions regarding the age of menarche, fertility, reproductive health and about the epilepsy. Each patient received two questionnaires; one for themselves and one for a close female friend without epilepsy. The friends served as a non-epileptic control group. The Regional Ethical Committee approved the study.

The epilepsy type was classified according to the classification system of the International League Against Epilepsy.[14] Perimenarche was defined as 2 years before and 2 years after the year of menarche.[6]

Statistical analyses

The Chi-square test and Fisher's exact test were used for analyses of categorical data. Independent sample *t*-test was used for analyses of normally distributed, continuous data. A value of $p < 0.05$ (two tailed) was considered significant.

Results

Answers were received from 265 patients and 142 controls (Table 1). Thirty patients were excluded because their epilepsy was related to progressive neurodegenerative disease or acute brain disorders (i.e. brain tumour, progressive neurofibromatosis, cerebral haemorrhage, Fahrs syndrome, central nervous system infections and progressive multiple sclerosis). Mean age when answering was 32.0 years both for the epilepsy patients and for the controls. Mean age at the first epileptic seizure was 15.7 years (range 0—41). In all epilepsy patients, 53.4% had partial and 39.4% had primary generalised epilepsy.

Table 1 Summary of clinical findings—all women

Parameter	Controls (n = 142)	Patients (n = 236), responders	Patients (n = 45), non-responders
Age, years (mean, S.D.)	32.0 (7.66)	32.0 (6.90)	30.7 (7.08)
Age of menarche (mean, S.D.)	13.0 (1.46)	13.1 (1.50)	
Epilepsy debut age (mean, S.D.)		15.7 (10.36)	13.5 (8.25)
Type of epilepsy			
Partial (%)		53.4	53.3
Generalised (%)		39.4	46.7
Unclassified (%)		7.2	0
Seizure frequency the last year before answering the forms			
Seizure free (%)		52.1	46.7
1—5 seizures (%)		16.5	11.1
>5 seizures (%)		25.4	22.2
No information (%)		5.9	

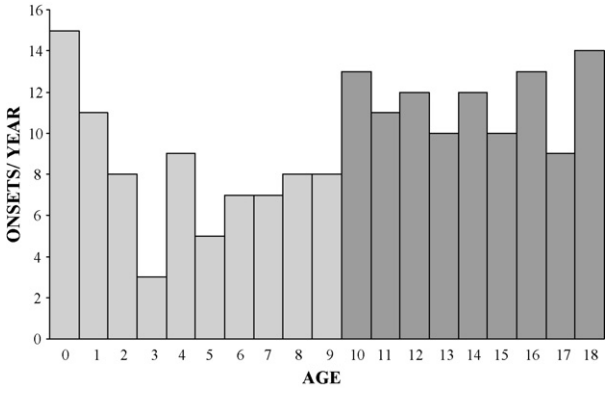

Figure 1 Number of patients with epilepsy debut per year in women with epilepsy onset between 0 and 9 years (light gray), and 10 to 18 years (dark gray) (n = 185).

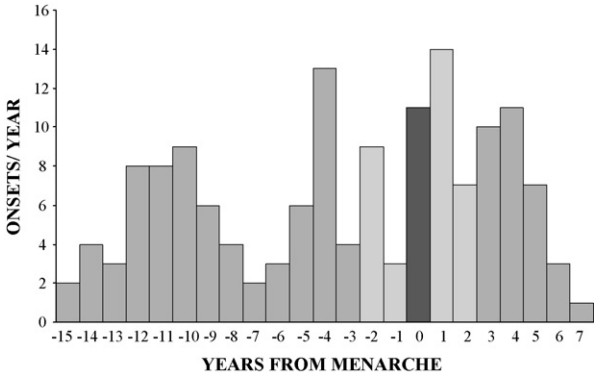

Figure 2 Epilepsy onset related to menarche in patients with epilepsy debut between 0 and 18 years (n = 148). Year of epilepsy debut is subtracted from year of menarche. Black: year of menarche. Years −2 to +2 (light gray and black) represents perimenarche.

In 7.2% of the patients, the epilepsy type could not be defined. One hundred and eighty-five patients had their first epileptic seizure between 0 and 18 years of age.

In the group of patients with debut of epilepsy between 0 and 18 years (n = 185) we found a significantly higher frequency of patients with epilepsy debut between 10 and 18 years (11.6 patients/year) compared to epilepsy debut between 0 and 9 years (8.1 patients/year) (p = 0.01) (Fig. 1).

One hundred and fourty-eight patients with epilepsy debut between 0 and 18 years gave sufficient information about menarche. The relation between age at onset of epilepsy and menarche age is shown in Fig. 2. Eleven patients experienced their first epileptic seizure in the year of menarche, which was not statistically different from the mean yearly number of seizure onsets during the 5-year period before (7.0 patients/year) or after (9.8 patients/year).

There was neither no significant difference in epilepsy debut in the perimenarche period (8.8 patients/year) compared to the 5-year period before (5.6 patients/year) or after (6.4 patients/year) perimenarche ($p > 0.05$).

Mean age at menarche for all epilepsy patients was 13.1 years, compared to 13.0 in the control group (Table 1). Patients, who had the first epileptic seizure before menarche, reached menarche at 13.2 years (Table 2). The patients who had epilepsy debut after the year of menarche reached menarche at 12.7 years (n.s., p = 0.071). A power analysis of our data supported the finding that this difference was non-significant, with an 82% probability of finding a difference of 0.5 years when standard deviation was 1.5 (observed in our study) and n = 150 patients. Among patients with epilepsy debut before menarche, there was no significant difference in menarche age in patients with partial and generalised epilepsy (13.1 years versus 13.0 years).

Table 2 Menarche age in women with epilepsy debut between 0 and 18 years of age

Group investigated	Age of menarche		
	Mean	Range	*p*
Patients	13.1	8.0—17.5	
Controls	13.0	9.0—18.0	n.s.
Epilepsy debut before or in the year of menarche	13.2	10.0—17.0	
Epilepsy debut after the year of menarche	12.7	8.0—17.5	n.s. (0.071)
Partial epilepsy	13.1	8.0—17.5	
Generalised epilepsy	13.0	10.0—17.0	n.s (0.882)

Discussion

The study demonstrates a significantly higher frequency of seizure onset in adolescence (10—18 years of age) compared to childhood (0—9 years of age) in this patient group. This finding may be related to an effect of puberty and hormonal changes related to it. Increase in serum estrogens starts gradually 2—4 years before the first menstruation, while progesterone increases after the first ovulation. Increased estrogens from the age of 9—10 years may therefore be one factor involved in the higher amount of epilepsy onsets in the age group 10—18 years.

Our observation of a higher frequency of seizure onset in adolescence contrasts the findings by Hauser from 1993.[8] Our study did, however, not follow the whole female epilepsy population; only those between 18 and 45 were participating. Those with early epilepsy debut and recovery from epilepsy before the age of 18 years were not included in the study. The difference in methodology may explain why our result shows a higher incidence of epilepsy onset in the adolescents than in early childhood. However, both the present study and prior large studies such as the Hauser et al. study[8] might contain substantial numbers of cases with symptomatic etiology causing seizure onset at a particular age that is entirely unrelated to and uninfluenced by hormones. This may mask the effects of hormonal influence in smaller subsets of patients. In future studies, the frequency of seizure onset at different ages has to be specified for different kinds of epilepsies.

We did not find a direct relation between onset of epilepsy and menarche or perimenarche. This contrasts previous studies[6,7] which found a higher frequency of epilepsy onsets and increased seizure frequency during the menarche year and in perimenarche. One reason for the discrepancies may be the design of the studies. Morrell's et al. study[7] was a mailed questionnaire study with a 21% response rate. The participants were aged 18—83 years, and the recall accuracy may have been inadequate at least in the old age group. Klein's et al. study[6] was based on interviews of 94 women aged 9—55 years. Ninety percent of them were interviewed two times, 58% were interviewed three times. This method can either improve the recall accuracy, or it can over alert the women. In our questionnaire there were several questions concerning different female epilepsy patient issues, and it was not obvious for the patients that there could be a connection between menarche age and seizure debut age. This might, on the other hand, have underestimated a possible effect. The difference in methodology between these two studies may therefore account for some of the difference between the results. However, in addition to a possible effect on epilepsy debut, menarche and the hormonal changes around puberty might exacerbate seizures or produce a loss of remission in patients suffering from epilepsy from childhood.[6,7] Because our study was a retrospective questionnaire based study in women at a mean age of 32.0 years, we were unfortunately not able to get reliable information about the seizure frequency in the perimenarche period.

A problem with all retrospective, questionnaire-based studies is the responder rate. In this study, however, it was 53% (265/500). In order to find out if the non-responders differed from the responders in important areas, we managed to find 45 of the non-responders from one of the hospitals (Rikshospitalet University Hospital). Medical records from these non-responders were reviewed and information analysed as for the patients (Table 1). The non-responders did not differ from the responders regarding any of the parameters available. We therefore consider the responding patients as representative for the whole group.

There are possible limitations interpreting the results from the present study; the women were aged 18—45 years. Patients who suffered from epilepsy as children and recovered before 18 years of age, and women older than 45 years were not included. We therefore know little about these women's epilepsy debut and how it would influence the results.

Patients who had their first epileptic seizure before menarche, reached menarche at a mean age of 13.2 years. Patients with epilepsy debut after menarche reached menarche at 12.7 years. This was not significantly different. With a difference between groups of 0.5 years, one might speculate that the number of patients included in this analysis (148 patients) was too low to detect a significant difference. However, the power analysis of our data demonstrated a more than 80% probability of finding a difference of 0.5 years in our study. Further, the menarche age in the control group was 13.0 years which is in between of the two patient groups. An age matched control group reached menarche at 13.0 years. We could not find significant differences in menarche age in generalised versus partial epilepsies. These findings may indicate that menarche age in our patient population is unaffected by the patients epilepsy type, and age of epilepsy onset.

In conclusion, we did find a significant increase in onset of epilepsy for adolescents (age: 10—18 years) compared to children (age: 0—9 years), but this increase was not directly related to menarche or the perimenarche period. This may however, still suggest a relation between puberty with its hormonal changes and the onset of epilepsy, although this is not necessarily directly related to menarche. Secondly, we did not find changes in menarche age in patients with epilepsy debut before menarche compared to patients with epilepsy debut in adulthood.

This study is performed in a large unselected patient group. Although a clear relation between epilepsy and menarche age cannot be found in a large patient population as in this study, a relation may be present in subsets of patients. Further studies should now be directed towards selected and well characterized patient groups like patients with well defined epilepsy syndromes and seizures, like patients with primary generalized epilepsies, partial epilepsies and patients with well defined right or left temporal foci. Prospective studies in girls with epilepsy, studying the effect of seizure frequency and menarche through childhood and adolescence should be encouraged.

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