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REPRODUCTIVE-ENDOCRINE OUTCOMES IN PATIENTS WITH EPILEPSY STARTED AT MENARCHE

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Summary

Introduction: Reproductive-endocrine disorders (RED) are distributed more often among women with epilepsy than in population. In patients with epilepsy and RED epilepsy is more often characterized by catamenial seizures in comparison with women without RED. It is thought that epilepsy manifested in puberty in one third of cases develop as catamenial seizures. **Aim:** To study distribution of RED and catamenial seizures among women with epilepsy manifested at menarche. **Methods:** 43 women with epilepsy manifested at menarche and with age range 12 -34 years were chosen (23 with cryptogenic partial and 20 with idiopathic generalized epilepsy). Interrelation between seizure exacerbation and phases of menstrual cycle (MC) was investigated during four months. By means of investigation of hypothalamic-gonadal hormones and suprapubic ultrasound two groups of the patients were defined: women with epilepsy (WWE - 19 cases) and women with coexisting epilepsy and RED (ERED group - 24 patients). 13 patients were antiepileptic drug (AED) free. **Results:** Catamenial exacerbation of seizures was shown in 46.5% of patients and was 3 times more often among patients of ERED group than of WWE group (66.7% vs 21%). MC disturbances 3.5 times more often prevailed in patients with RED ($p>0.001$). RED was almost equally distributed among treated and AED free groups (56.7% and 53.8%, $p>0.05$); RED was more often found among patients who were on valproate (VPA) therapy ($p>0.2$). **Conclusions:** The risk of RED development is high among the patients with epilepsy manifested at menarche and it does not depend on AED treatment as RED distribution was equally found in both treated and AED free groups. In women with epilepsy manifested at menarche and with catamenial course of seizures from the beginning may indicate on RED existence and could be served as an indicator of RED development.

Key Words: women, epilepsy, menarche, reproductive, endocrine disorders.

Introduction

Women with epilepsy have several problems related with epilepsy as well as reproductive dysfunction. 14% to 20% of women with temporal lobe epilepsy have amenorrhoea (Jensen and Vaernet 1977), fertility is reduced in 69% of patients (Dansky et al. 1980), 17.8%-25% have reproductive endocrine disorders (Herzog et al. 1986; Bilo et al. 1988; Kasradze et al. 1998) such as polycystic ovarian syndrome (PCOS) or hypogonadotropic hypogonadism (HH). The cause of these reproductive endocrine disorders (RED) in women with epilepsy is thought to be as a spreading of epileptic discharges upon limbic structures that could modify pulsative secretion of gonadotropin releasing hormone and facilitate dysfunction of reproductive endocrine system. On the other side proconvulsive effect of oestrogen and anticonvulsive properties of progesterone may influence epileptic discharges in case of RED with high oestrogen activation (Herzog 1989; Morrell 1999; Zahn 1999). The existence of equal etiological factors for both epilepsy and RED is also possible (Herzog 1989; Zahn 1999). Antiepileptic drugs (AED) may also have some influence on ovarian steroid hormones and hypothalamic-pituitary-gonadal axis (Jensen and Vaernet 1977; Murialdo et al. 1997; Isöjarvy et al. 1998).

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Seizure exacerbation or modification are common during "critical" periods of reproductive cycle in women (menarche, menstruation, pregnancy, breastfeeding, menopause). Epilepsy is a most problematic in adolescence. Establishment of the female pattern of cyclical changes in hypothalamic-pituitary-gonadal hormone release is an important factor influencing seizure frequency and phenomenology during puberty. It is well known that some epileptic syndromes cease or improve during puberty, some persist, some become worse and some turn into another syndrome (Janz and Christian 1957; Jeavons et al. 1968; Niijima and Wallance 1989). More than one third of women with genetically determined idiopathic generalized epilepsies have onset of seizures within six months of menarche. But it is not clear how often women develop catamenial epilepsy in case of epilepsy manifested at puberty (Bäckstrom and Rosciszewska, 1987).

There is no consensus on definition of catamenial seizures. According to the current opinion seizures are catamenial if they are influenced by cyclic changes of ovarian sex hormones (Herzog et al. 1997). Recent studies found that 7-12% of women with epilepsy have catamenial exacerbation of seizures (Crawford 1991; Kasradze et al. 1998). In women with intractable epilepsy the percentage of catamenial seizures(Herzog et al. 1986, 1997; Rosciszewska 1987) and/or reproductive dysfunction (Kasradze et al. 1998) is much higher: from one third to one half of cases. Propensity for seizure exacerbation in such patients depends on fluctuations in plasma concentration of ovarian steroid hormones (oestrogen and progesterone) and on serum oestrogen/progesterone ratio. Concentration of ovarian hormones is different in several phases of menstrual cycle (MC). Herzog et al. (1997) suggest three patterns of catamenial exacerbation of seizures: C1 - perimenstrual, C2 - periovulatory : both observed in ovulatory cycles; and C3 - pattern consisting of clustering of seizures in entire second half of anovulatory cycles (progesterone < 0.5 ng/ml).

According to our previous investigations, 60.8% of the patients with catamenial epilepsy have any type of RED and the idea that catamenial seizures might be an indicator of PCOS or HH has been drown. Recently we have shown that 46.4% of patients with epilepsy manifested during pregnancy have catamenial seizures. 64.3% out of them had any type of RED (Kasradze et al. 2002). At the same time epilepsy manifested during puberty often get catamenial seizures (Diamantopulos and Crumsrine 1986; Rosciszewska 1987). These facts led us to a hypotheses that RED could be highly expected in patients with epilepsy manifested at menarche.

The aim of this study was to reveal the prevalence of catamenial epilepsy and reproductive endocrine disturbances in patients with epilepsy started at menarche.

Methods

The study was conducted in the Epilepsy Center of Sarajisvili Institute of Neurology and Neurosurgery. Reproductive status of patients was evaluated in Jordania Institute of Human Reproduction. The type of epilepsy was classified according to the recommendations of the International League Against Epilepsy (Commission 1989) and syndromes of reproductive dysfunction were defined according to the criteria given by several investigators of the problem of women and epilepsy (see below).

We examined reproductive-endocrine system and studied interrelation of epileptic seizures with menstrual cycle in 43 female patients with age range 12-34 years (mean 18.7± 0.8 years) and with epilepsy manifestation at menarche time (before or after 3 months). 13 patients were recruited in the study after 2-24 months from the first epileptic seizure (mediana = 13 months) and 30 patients were enrolled 3-15 years later (mediana = 4.8 years). All patients were evaluated for a history of the menstrual problems. To establish MC rhythm, its type and frequency of seizures the patients had to fill calendar during four months. Using the criteria proposed by Herzog et al. (1997) C1, C2 and C3 catamenial patterns of seizure exacerbation were determined. The seizures were considered catamenial if the average daily frequency of seizures calculated before (- 10. + 1 days), during- and after (1. +3 days) menstrual flow was at least two fold greater than the average daily frequency during the remainder of MC.

All these patients were fully investigated by reproductologist-endocrinologist. Pelvic Ultrasound was performed on the 7^{th} or 8^{th} day of MC and randomly in case of amenorrhoea. Venous blood samples were taken at 9:00-11:00 a.m. on day 21^{st} and 22^{nd} of MC or randomly in case of amenorrhoea. The hormones assayed were: progesterone, estradiol, luteinizing hormone (LH), follicule-stimulating hormone (FSH), prolactine, testosterone, cortizole, TSH, T3 and T4. Laboratory investigations of blood samples were carried out using ELISA method (enzyme-linked immuno-sorbent assay, multichannel spectrometry, E4 301 wave strength-450 nm). Before study none of the patients were pregnant, breastfeeding or took any hormonal pills for treatment or contraception. 13 patients had never taken AED treatment before admittance and the rest 30 patients took AED treatment regularly (Table 3).According to hormonal profile and clinical condition of reproductive-endocrine system the patients were divided into two groups: 24 patients with epilepsy and RED (ERED), and 19 patients with epilepsy only (WWE). 23 patients had cryptogenic partial epilepsy (CPE) and 20 patients had idiopathic generalized epilepsy (IGE). In the table 1 it is summarized the final distribution of all patients according to epilepsy syndromes and presence or absence of RED.

Two types of RED were confirmed in the patients by reproductologists: polycystic ovarian syndrome (PCOS) - 6 patients, and hypothalamic hypogonadism (HH) - 18 patients. PCOS was defined as a combination of the multiple ovarian cysts, raised level of testosterone (>0.7 ng/ml) and oligomenorrhoea or amenorrhoea (Bauer et al. 2000). Hypothalamic hypogonadism (HH) was diagnosed in patients with low concentration of luteinizing hormone or declined LH/FSH ratio, with menstrual irregularities: oligomenorrhoea or amenorrhoea (Herzog et al. 1986). 21 patients had oligomenorrhoea (MC duration more than 35 days). 7 patients had amenorrhoea (MC frequency less than six episodes per year). Two patients with oligomenorrhoea suffered from the episodes of amenorrhoea since menarche (duration of amenorrhoea from six months up to two years), three patients with amenorrhoea had complains of oligomenorhoea at the beginning and then amenorrhoea. Statistical analyses were carried out using the Studient's and χ^2 tests.

Results

Age of epilepsy manifestation at menarche. The mean age of patients at menarche and first epileptic seizure was 12.7±0.4 years (Table 1). The first epileptic seizure was developed earlier in ERED group than in WWE group (12.5±0.3 and 13.1±0.4 years accordingly, p>0.01) and earlier in patients with IGE than in CPE group (12.1±0.4 and 13.3±0.3 years accordingly, p>0.001).

Table 1. Distribution of patients according to epilepsy and RED syndromes

Patients	Cryptogenic partial epilepsies			Idiopathic generalized epilepsy's				
	T n=16	O n=6	F n=1	JAE n=2	JME n=10	GMA n=4	GTCS n=3	PSR n=1
WWE n=19	9	1	1	2	2	2	1	1
PCOS n=6	4	-	-	-	2	-	-	-
HH n=18	3	5	-	-	6	2	2	-

T - temporal, O - occipital, F - frontal, JAE - Juvenile absance epilepsy, JME - Juvenile myoclonic epilepsy, GMA - Grand mal of awakening, GTCS - Generalized tonic-clonic seizures, PSR - Photosensitive reflex-epilepsy

Catamenial exacerbation of seizures. According to anamnesis, epilepsy had catamenial course from the beginning in 20 patients (46.5%). It was confirmed by four months calendar charting in 17 cases, three patients already had amenorrhoea (one with CPE and RED and two with IGE and RED). Catamenial seizures had 66.7% of ERED patients (16 cases) and 21% of WWE patients (4 cases) (χ^2=8.87, p<0.001). Catamenial patterns of seizures are given in table 2.

Table 2. Patients' age at menarche and epilepsy manifestation, number of patients with several patterns of catamenial exacerbation of seizures and several types of menstrual irregularities during four months follow-up

Patients		Age at menarche and epilepsy manifestation (M±SD years)	Catamenial exacerbation of seizures and their patterns (number of patients)				Type of menstrual cycle irregularities (number of patients)		
			All n=17	C1 n=9	C2 n=0	C3 n=8	Normal n=21	Oligomenorrhoea n=15	Amenorrhoea n=7
WWE n=19	CPE n=11	13.5±0.3	2	2	-	-	8	3	-
	IGE n=8	12.6±0.7	2	2	-	-	7	1	-
ERED n=24	CPE n=12	13.2±0.4	6	3	-	3	4	6	2
	IGE n=12	11.8±0.3	7	2	-	5	2	5	5

CPE - cryptogenic partial epilepsy; IGE - idiopathic generalized epilepsy;

Menstrual cycle and menstrual irregularities. According to the data of four months-follow-up and evaluation of hormonal plasma concentrations 22 patients (51.2%) out of 43 had anovulatory cycles. This disturbance of MC significantly prevailed among patients with RED than in WWE patients (75% vs 21.1%, χ^2=13.7, p>0.001). Regardless of patients' age MC irregularities from menarche revealed in 17 patients (oligomenorrhoea in 12 cases and amenorrhoea in 5 cases). In two patients oligomenorrhoea was developed in 8 and 12 years after menarche and the beginning of AED therapy (both patients were from WWE group).

AED usage. Our patients had different duration of AED usage - from two months up to 13 years. 13 patients with epilepsy duration from two months to seven years had never taken any AED therapy. In seven of them (53.8%) RED was confirmed (five of them had MC irregularities, three - catamenial seizures). The rest 30 patients took AED regularly (Table 3). 56.7% of these patients (17 cases) had any type of RED and this figure is almost equal to the RED distribution among non-treated patients (χ^2=4.3, p>0.05).

Table 3. AED usage and mean duration of treatment at the study recruiting time

Antiepileptic treatment (M±SD year)	WWE n (%)	Patients with PCOS n (%)	Patients with HH n (%)
No treatment n=13 (2.6±0.5 years)	6 (46.2%)	2 (15.4%)	5 (38.5%)
VPA n=7 (5.1±1.5 years)	1 (14.3%)	1 (14.3%)	5 (71.4%)
CBZ n=10 (3.9±0.7 years)	4 (40 %)	2 (20%)	4 (40%)
PB n=5 (5±1.6 years)	3 (60%)	-	2 (40%)
Polytherapy* n=8 (6.4±1.5 years)	5 (62.5%)	1 (12.5%)	2 (25%)

**Polytherapy - CBZ+PB in 3 patients and CZP+PB in 5 patients VPA -Valproic acid; CBZ - Carbamazepine; PB - Phenobarbital; CZP - Clonazepam.*

Discussion

The period of puberty occupies quite a long interval of time expanding from pre-adolescence up to adulthood (from 9-10 years up to 17-18 years). It consists of consecutive stages of sex maturity governed by development of hypothalamo-pituitary-gonadal system. Menarche is a time point of establishment of feminine type of hormone secretion. Therefore for our investigation we had chosen patients of different ages but with practically simultaneous appearance of menarche and epilepsy. Analysing our data we revealed that menarche and the first epileptic seizure developed earlier in the patients with IGE than in patients with CPE (p>0.001).

Prevalence of RED among patients with epilepsy manifested at menarche is unknown. According to our study in 55.8% of such adolescent patients we can expect statistically non-significant coexistence of epilepsy with RED or possibility of further development of reproductive endocrine disorders (χ^2=2.8; p>0.3). This figure (55.8%) is higher for women with epilepsy manifested at menarche than for women with epilepsy in general (17.8%- 25%) (Herzog et al. 1986; Bilo et al. 1988; Kasradze et al. 1998). At the same time recently we revealed statistically reliable prevalence of RED (48.4%) among 31 patients with the first epileptic seizure during pregnancy (Kasradze et al. 2002).

One can speculate that seizure manifestation during these "critical" periods of reproductive system in women may indicate an existence of clinically veiled dysfunction of reproductive system. This idea can be supported by the high rate of MC disturbances in our study (51.2%). This figure is significantly higher than those found in 92 healthy adolescent girls in Georgian population (11.9%), and in 81 juvenile patients with diabetes type 1 (22.2%) (Chanturia et al. 2000). Higher prevalence of menstrual irregularities in women with epilepsy than in general female population is well known (Betts and Crawford 1998; Bauer et al. 2000). Based on our previous investigation of 281 CPE and 62 IGE consecutive patients it was revealed that 22.6% of these patients were complaining of menstrual irregularities at the moment of admission to our clinic (Kasradze et al. 1998). The same incidence of MC irregularity was revealed by the similar investigation (Murialdo et al. 1997).

The reliability of our investigation is based on anamnestic data and four months calendar monitoring of MC irregularities. 17 patients with RED had irregular MC from the menarche. This is characteristic for initial stage of MC formation. But mean age of

these patients was higher (18± 0.8 years) at the time of hormonal tests and the diagnosis of RED than the age of the beginning of MC formation. Thus, the irregularity of MC in combination with epileptic seizures begun from the menarche could be served as an indicator of RED rather then initial transient MC irregularities. Studying influence of MC phases on seizure exacerbation we found out some difference between the two groups of patients with epilepsy manifested at menarche: the prevalence of catamenial epilepsy was higher in patients with RED than in patients without RED (66.7% vs 21%, $p<0.001$). Seizure exacerbation in WWE group was revealed perimenstrually or in the first two days of menstruation whereas in ERED group seizure exacerbation was revealed mostly during inadequate luteal phase (8 cases out of 13). In two patients seizure exacerbation was defined as C3 type with regular MC and both patients had RED. So it could be thought that the patients with seizure exacerbation during midluteal phase may have anovulatory cycle even in case of regular MC. According to the current view the main hormonal mechanisms of catamenial seizure exacerbation are elevated oestrogen at ovulation, progesterone withdrawal at menses and elevated oestrogen/progesterone ratio in anovulatory cycles (Herzog et al. 1997; Morrell 1999). It seems that these mechanisms are more active in women with seizure onset at menarche.

Certain AEDs appear to increase the risk for specific reproductive dysfunction. Valproic acid is associated with a syndrome resembling PCOS (Isöjarvi et al. 1998). In contrast of this idea in our study RED was confirmed in 7 out of 13 non-treated patients (53.8%).

The same figure of RED distribution (54%) among non-treated epileptic women was shown in our previous study. (Toidze et al. 2000). However RED was found more often among the patients on VPA therapy (85.7%) and least often among the patients on Phenobarbital (PB) and on polytherapy (3 cases on PB+CBZ, 5 cases on PB+CZP). These data are similar to our previous study results when under AED therapy RED developed more rapidly on VPA monotherapy despite of the type of epilepsy. One can speculate that VPA may facilitate RED development but the number of study patients is not enough to make conclusions. But there is an evidence to suggest that menstrual disorders, altered pulsatile secretion of LH and PCOS are usually common among untreated women with epilepsy (Herzog et al. 1986), whereas HH was more common among the treated women (Bilo et al. 1988).

On the basis of this study we cannot formulate interrelation of RED and epilepsy syndromes although we can indicate that the patients of IGE group are different from the patients of CPE group with the age of menarche, higher distribution of catamenial epilepsy and hypothalamic hypogonadism. These data need further investigation.

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