

Epilepsy and Women: How Changes in Hormone Levels Can Influence on the Seizure Index

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Abstract

Introduction: In 1857, the relationship between epileptic seizures and the menstrual cycle had been described for the first time. Epileptic seizures are influenced by the variation in the secretion of the sex hormones. When the frequency of seizure exacerbations is directly related to the menstrual cycle, it is called catamenial epilepsy and has three different patterns.

Materials and Methods: Women between 16 and 65 years with a diagnosis of epilepsy had been included. Prospective, descriptive, observational, cross-sectional and comparative study carried out at the Clinical's Hospital of Buenos Aires, from September 2019 to July 2020.

Results: Sample of 13 female patients with a diagnosis of epilepsy and suspected association of convulsive events with the menstrual cycle. Mean age of 36.4 years (SD+12.5) 84% did not receive oral contraceptives. 46% were being treated with 2 anticonvulsant drugs and 38% with 3 drugs. Mean age at menarche 12 years (SD ± 1 year). 61.5% (n=8/13) associated their menarche with the diagnosis of epilepsy. During menopause, 100% experienced a decrease in their seizure index. 77% of the population presented the C1 pattern (n=10/13).

Conclusion: A high proportion of women associate their menarche with the onset of seizures and an increase in the rate of events in perimenstrual periods and periovulatory. The highest proportion of patients presented the C1 pattern. There is a close relationship between hormonal changes and the rate of seizures.

Keywords: Epilepsy; Catamenial epilepsy; Menarch; Sex hormones; Menstrual cycle; Progesterone; Estradiol

Introduction

Epilepsy is one of the most frequent chronic neurological diseases worldwide, becoming a major health problem. It is estimated that more than 50 million people worldwide suffer

from this disease and every year 2.4 million new cases are registered [1].

According to the International League Against Epilepsy (ILAE) epilepsy can be defined as a brain disorder characterized by a long-lasting predisposition to generate epileptic seizures and by its neurobiological, cognitive, psychological and social consequences.

Although most epilepsy is adequately controlled with pharmacological treatment, approximately 25% of them are drug-resistant.

In 1857, Sir Charles Locock first described the relationship between epileptic seizures and the menstrual cycle. Hysterical epilepsy (from the Greek hystera, meaning 'uterus') was confined to women only and occurred with a regularity that was directly related to menstruation [2].

There is clear evidence that epileptic seizures are influenced by the physiological variation in the secretion of sex hormones during the menstrual cycle and throughout the reproductive life of women with epilepsy [3,4]. Estrogens (estradiol, estrone and estriol) are capable of crossing the blood-brain barrier and through various mechanisms have proconvulsant effects. Progesterone has opposite actions, decreasing epileptic discharges and increasing the seizure threshold.

Seizures, in most epileptic people, do not occur randomly; rather, they tend to cluster together, happening in a rhythm that shows an identifiable and predictable periodicity. When the frequency of seizure exacerbations in women is directly related to the menstrual cycle, it is called catamenial epilepsy (from the Greek "katamenios" meaning monthly) [5].

The frequency of catamenial epilepsy varies from 12% to 78% because there is still no established definition [2,4,6]. Thus, some authors consider it when the crises occur in 75% during the menstrual period and others consider it as just an increase in the frequency of the crises in this period comparing to a basal period.

Three patterns are described in catamenial epilepsy [6-8]. C1: Seizures occurs more frequently or occur in the perimenstrual

phase (days 26-3) of a normal ovulatory cycle. This pattern is seen in 25%-75% of women with this type of epilepsy; C2: Seizures are exacerbated in the periovulatory phase of a normal cycle (days 10-13); C3: In cycles with an inadequate luteal phase, the exacerbation of the seizures occurs from day 10 of one cycle to day 3 of the next cycle. An ovulatory cycle.

The main causes of catamenial epilepsy are due to the neuroactive properties of reproductive steroids and the variation in their levels during the menstrual cycle.

The neuroactive properties of estrogens are capable of modifying neuronal activity, through the inhibition of GABA and enhancing glutamatergic transmission, thus increasing neuronal metabolism and the frequency of epileptic discharges [4,9,10].

On the other hand, progesterone and its metabolites act as positive allosteric modulators at the GABA receptor, facilitating the opening of chloride channels and prolonging the inhibitory action of GABA on neurons. Thus, progesterone reduces hormonal metabolism and the frequency of discharges.

It has been shown that physiological variations in endocrine secretion during the menstrual cycle influence the generation of epileptic seizures [4]. In ovulatory cycles, the frequency of seizures shows a significant correlation with the estradiol/progesterone ratio. Thus, the increase in seizures rate on the premenstrual phase is due to the lack of the protective effect of progesterone and its metabolites in the hippocampus [4,9]. Exacerbations in the middle of the cycle could correspond to the preovulatory increase in estrogen not accompanied by an increase in progesterone.

Another factor for the exacerbation of epileptic seizures is due to the reduction in serum levels of antiepileptic drugs, since steroids and some drugs are metabolized in the liver in the same microsomal system. The decrease in the secretion of steroids in the premenstrual period allows the increase in the metabolism of drugs with the consequent decrease in their serum levels.

A several pharmacological treatments have been proposed through the years, although there is still no specific treatment [7].

Objectives

Primary objective

Describe the relationship between the menstrual cycle and the seizure rate.

Secondary objective

Within catamenial epilepsies, to assess the prevalence of each pattern (C1-C2-C3). There are few publications regarding catamenial epilepsy and most of these are narrative publications. It has been proposed to make a cadastre of patients with catamenial epilepsy to subsequently evaluate the better therapeutic alternatives and thus improve the quality of life of these patients.

Materials and Methods

Population

Women between the ages of 16 and 65 with a confirmed diagnosis of epilepsy through clinical findings, electroencephalography and imaging were included. Patients with other chronic diseases for which they had to receive additional pharmacological treatment, with the exception of oral contraceptives, were excluded.

Study design

This was a prospective, descriptive, observational, cross-sectional and comparative study carried out at the Clinical Hospital of Buenos Aires, from September 2019 to July 2020.

This study was approved by the teaching and research committee, together with the ethics committee of the Clinical Hospital "Jose de San Martin". Written informed consent was obtained from all patients included in the study.

Definitions

Epilepsy was defined according to the 2017 International League Against Epilepsy (ILAE) classification. Types of catamenial epilepsy were defined according to Herzog's criteria.

Sample size

This study included the participation of 13 women with a previous diagnosis of epilepsy.

Statistical analysis

Basic descriptive statistics were performed with the estimation of their respective 95% confidence intervals (alpha error=0.05%), for dichotomous variables, the Chi² test was used.

Results

13 female patients with a diagnosis of epilepsy and suspected association of convulsive events with the menstrual cycle were recruited from September 2019 to July 2020 at the Clinical Hospital of Buenos Aires. The mean age was 36.4 years old with a standard deviation of ± 12.5 years. 84% of the patients were not being treated with oral contraceptives. 46% of the population studied was being treated with 2 anticonvulsant drugs and 38% with 3 drugs.

The average age of menarche was 12 years with a standard deviation of ± 1 year and 61.5% of the population (n=8/13) associated their menarche with the diagnosis of epilepsy. 46% of the population (n=6/13) had to undergo prior treatment with more than 3 anticonvulsant drugs and even with such treatment his control of seizure only reached the few months of seizure-free permanence. Of the 3 patients who were already in menopause, 100% experienced a clear decrease or even a resolution of their seizures. 77% of the population presented the C1 type of catamenial epilepsy (n=10/13), the same as the data reported in the literature.

Discussion

Epilepsy is one of the most frequent chronic neurological diseases worldwide, becoming a major health problem. Although most epilepsy is adequately controlled with drug treatment, approximately 25% of them are drug-resistant.

There is clear evidence that epileptic seizures are influenced by the physiological variation in the secretion of sex hormones during the menstrual cycle and throughout the reproductive life of women with epilepsy.

Seizures, in the majority of epileptic people, do not occur randomly and when the frequency of exacerbations of seizures in women is directly related to the menstrual cycle, we speak of catamenial epilepsy, with a frequency that varies from 12% to 78%, with the C1 pattern being more frequent, which is observed in 25%-75% of women with this type of epilepsy.

The important thing about detecting patients with this type of epilepsy is to be able to offer them the best possible treatment, thus improving their quality of life. It has been shown that conventional treatments are not usually effective and patients do not achieve good crisis control. Thus, treatment with progestogens during the menstrual cycle is proposed.

The biggest drawback of unconventional treatments is due to their adverse effects or the tolerance that they produce in the long term.

Conclusion

In this work, it was found that a high proportion of these women associated their menarche with the onset of seizures and an increase in the rate of events with the perimenstrual and periovulatory periods, which coincides with the literature published to date. The highest proportion of patients presented the C1 pattern, coinciding with all the papers published to date.

With all the data previously described, it can be presumed that there is a close relationship between hormonal changes and the rate of seizures in these patients. For this reason, a thorough questioning is important in all epileptic women looking for the association of seizures with menstrual cycles.

Ethical Approval

The data was obtained from a brief questionnaire anonymously, without obtaining data that would allow the identification of the patient. The data sheet was stored in a computer with an alphanumeric code known only to the principal investigator.

Law 3301 of the Autonomous City of Buenos Aires on the protection of the rights of subjects in health research, Law 25326 of the Argentine Nation on the protection of personal data, its regulatory decrees and regulations and resolutions

derived from them, have been respected, adhering to the international principles enunciated in the declarations of Helsinki (in all its versions), in International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS/OMS), in Good Clinical Practice Standards (CIARM) and the Nuffield Report.

Conflict of Interests

The authors do not declare conflicts of interest with this study.

Study Limitations

Due to the SARS-CoV-2 pandemic coinciding with data collection and the suspension of face-to-face consultations, the sample size is small, which makes it difficult to draw statistically significant conclusions and inferences, so more studies will be required for the therapeutic decision in these patients.

Financing

The present study did not have economic financing for its realization.

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