Puberty and Epilepsy Onset in Women

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Abstract

Objective: The significance of the onset of seizure based on the medical and social aspects of epilepsy. The aim of this study was to investigate the age of seizure onset based on the specific characteristics of each age of seizure onset in many epilepsy syndromes to make an appropriate diagnosis.

Methods: The age at epilepsy was retrospectively studied in 155 women aged between 16 and 45 years with a verified diagnosis of epilepsy. The epidemiological method revealed the age at epilepsy onset, and females were divided into three groups: pre-puberty (10-11 years old), puberty (10-18 years old), and post-puberty (18+ years old). A correlation study of the frequency of onset with the periods of formation and function of the female reproductive tract was conducted.

Results: A statistically significant quantitative predominance of females with epilepsy onset during puberty ($p<0.001$) was identified. Statistically valid was the prevalence of epilepsy onset in the combined age range of 12 to16 ($p<0.001$). A direct link between menarche and epilepsy onset was detected in the general cohort in 13% of females, which is among the risk factors for catamenial seizure onset.

Conclusion: Epilepsy onset in females of reproductive age dominates during childhood development. In more than half of the cases, the epilepsy onset occurs in the puberty period. Epilepsy onset most often occurs between the ages of 12 and 16. Seizure onset occurs at the ages of 12-16 years during menstrual bleeding and ovulatory cycle development due to the proconvulsive effects of estrogens.

Keywords: Epilepsy, seizure onset, female sex, puberty, hormones, estrogens

INTRODUCTION

The topicality of the problem being researched results from the medical and social aspects of epilepsy onset. The significance of the age of seizure onset also results from the medical and social aspects of epilepsy.[1,2] The age of epilepsy onset is a determining factor in the development of the disease. A properly conducted differential diagnosis, timely diagnosis, and adequately selected antiepileptic treatment not only reduce social stigma but also determine the further course of the disease.[3] The opposite situation tends to progress to pharmacoresistant epilepsy. The age at onset is important in epileptology based on the specific characteristics of each age of the onset of many epilepsy syndromes, which helps to make the appropriate diagnostic testing.

Epilepsy onset is defined as the age at which the first unprovoked seizure occurs. However, the first unprovoked seizure and newly diagnosed epilepsy may not be synchronized (coincide with time of the onset). The accuracy of the determination of the age at epilepsy onset varies depending on the type of patient's seizures, as some types (e.g., absences, myoclonus) are often repeated for a long time before epilepsy is diagnosed. In recent years, the international league against epilepsy has formulated new definitions and classification systems of seizures and epilepsy that offer opportunities for the world community to communicate in a common language on many scientific and practical aspects of the disease.[4,5] This stems from the newly developed definitions of epilepsy in 2014. "Epilepsy is considered to be a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures occurring over the next 10 years; and (3) diagnosis of an epilepsy syndrome.[4] It is expected that the percentage of patients meeting the criteria for newly diagnosed epilepsy after the first unprovoked seizure will be higher because the diagnosis can now be made after a single unprovoked attack with a high risk of recurrence." This further highlights the importance of onset issues. The incidence and prevalence of epilepsy change with age, dominating in childhood and at a young age.[6] Most epidemiological studies show a general trend toward an increase in prevalence among adolescents and young adults.[7] Epilepsy onset is observed mainly in childhood (about 75% of all cases).[8] Testing has proven that an immature brain has an increased predisposition to seizures and a greater susceptibility to them.

Two peaks of morbidity are distinguished in childhood: infancy and puberty. The age between 12 and 16 years begins immediately after the epilepsy onset and can reach up to 3 years according to the criterion of a poor prognosis.[9] Most studies emphasize that the prevalence of epilepsy in males is higher than that in females; however, the absolute difference in prevalence between genders is minimal. At the same time, the level of social activity and family functioning in females with epilepsy is lower than in men.[10,11] Side effects of antiepileptic drugs and the development of reproductive endocrine complications reduce demographic rates in females with epilepsy.[12] Therefore, it is important to clarify the gender characteristics of the onset of female epilepsy. It acquires a special significance in puberty. However, puberty is considered a homogeneous period, and the change in the hormonal background within the period and the time dependence of epilepsy onset on these changes are not considered. The study of factors affecting reproductive health is necessary to improve the early diagnosis and prevention of reproductive endocrine complications.

The objective of this study was to study the correlation between the age at epilepsy onset and hormonal regulation of the female reproductive cycle in female epilepsy.

METHODS

This research paper is a follow-up study of a prospective observational non-randomized study on the side effects of antiepileptic drugs on the reproductive health of females with epilepsy.

Study Cohorts

Five hundred females of reproductive age 16-45 years were selected randomly in the cohort study. Only females diagnosed with epilepsy based on a combination of clinical, electro-neurophysiological, and neuroimaging data were included in this study. The criterion for age-related selection was the exclusion of reproductive life cycle progression (up to the age of 16) and decline (after 45 years) of the reproductive life cycle in females. The method of retrospective epidemiological analysis was used. For 155 females, the age at epilepsy onset was ascertained by the method for recording and analyzing anamnestic data and medical records. In accordance with the age of epilepsy onset, patients were divided into 3 groups: the first group included females with epilepsy onset before puberty, the second group included females during puberty, and the third group included females after puberty. In the second phase of the study, females of the second group with the onset of epilepsy in puberty were divided into 4 subgroups according to the age at the onset of this disease: subgroup A:10-11 years old, subgroup B:12-14 years old, subgroup C:15-16 years old, and subgroup D:16-18 years old. A correlation analysis of the frequency of epilepsy onset and reproductive life function was conducted.

The Ethics Committee of Almazov National Medical Research Centre approved this study on 22.04.2022 under the number 2304-22. All patients signed a consent form.

Statistical Analysis

The clinical evidence obtained in the research process was handled using the statistical 8.0 medical software system (StatSoft, Inc, USA). Quantitative comparison of parameters in the groups was accomplished using the Wilcoxon-Mann-Whitney test, Wald chi-squared test, median test, and ANOVA test.

RESULTS

Based on the age at epilepsy onset and the World Health Organization classification of puberty age periods (1977), the females were distributed into three groups: 23 females of the first group had the onset in pre-adolescence (between the ages of 1 and 10), 92 females of the second group had the onset at adolescence (between the ages 11 and 18), 40 females of the third group had the onset at postadolescence (aged 18 or more). The average age did not correlate reliably when averaging with the first group, 25.1, the second group, 24.6, and the third group, 28.3 (p=0.006) (Table 1).

The duration of epilepsy was 18±1.15 years in the first group, 1.47±0.69 years in the second group, 4.85±0.63 years in the third group, which correlated reliably (p=0.0001). The distribution by epilepsy type was not significantly different between the groups. Generalized epilepsy was diagnosed in 35% of female sand focal epilepsy in 65% of females. The dominance of focal epilepsy with a predominance of the temporal lobe among females who received combining antiepileptic drugs was noted, which confirms the predominance of pharmacoresistant forms in the polytherapy group.

The quantitative predominance of epilepsy onset in puberty was identified in the second group, 92 females (59%) (p=0.05). The epilepsy onset in post-puberty was half as many as in the second group (40 females, 26%). The epilepsy onset in pre-puberty in this cohort was even less common, with 23 females (15%), owing in part to the patients with the highest disability rate with epilepsy onset in childhood and their poor social skills in the female reproductive cycles.

Thus, a statistically significant quantitative predominance of females in the second group with epilepsy onset in puberty between the ages 10 and 18 (p=0.001) was identified. In general, epilepsy

Table 1. Age profiles of groups

Group	Valid (n)	Mean age	Error	Minimum age	Maximum age	Median age
1	23	25.1	1.21	16	41	25
2	92	24.6	0.63	16	44	25
3	40	28.3	0.99	19	45	27.5

In the combined interval between the ages of 12 and 16 compared with groups between the ages of 10 and 11 as well as of 17 and 18, the differences are significant (p=0.001).

MAIN POINTS

- Epilepsy onset predominates in childhood in females of reproductive age.
- Provoked seizures occur during puberty and are associated with sex steroid hormones.
- During puberty, epilepsy onset dominates in the combined age range of 12-16 years.
- During periods of the beginning of estradiol production and the development of the peak of estradiol, the proconvulsive effect of estrogen is most pronounced.
- The coincidence of epilepsy onset and menarche increases the risk of catamenial epilepsy and pharmacoresistant epilepsy development.

onset occurred in almost three-quarters of cases in childhood. Only about one-fourth of patients experienced epilepsy onset in post-puberty (Figure 1).

The maturation of the female reproductive system goes through several stages. The development of the hypothalamic-pituitary-ovarian system is a long and complex process. It is in the group with the onset in puberty. In accordance with the classification of this period, an additional clarification of the age of disease onset was carried out in the group of females with epilepsy onset in puberty. The age of disease onset was specified according to the classification of this period. Additionally, females were allocated into 4 subgroups: subgroup A:10-11-year-old females (pre-puberty sub period), subgroup B:12-14-year-old females (beginning of menarche), subgroup C:15-16-year-old females (establishment of a stable ovulatory cycle), subgroup D:16-18-year-old females (sub period of social maturation).[13] Additionally, females were allocated into 4 subgroups: subgroup A:10-11-year-old females (precocious puberty sub period), subgroup B:12-14-year-old females (the first experience of menstrual bleeding), subgroup C:15-16-year-old females (stabilization of ovarian cycle), subgroup D:16-18-year-old females (sub period of social maturation).[13] The study of the onset rate in subgroups of puberty, relevant to the four main periods of maturation of the hypothalamic-pituitary-ovarian system, showed the following frequency distribution. In first place, the onset rate in the second subgroup was 35 females (38%), the onset rate in the third subgroup was second at 24 females (26%), the onset rate in the first subgroup was third at 18 females (20%), and the onset rate in the fourth subgroup was fourth with 15 females (16%). Seizures onset at the age of 12-14 was more often observed statistically significantly than at the age of 10-11 (p=0.01) and 15-16 years (p=0.05). The prevalence of epilepsy onset was statistically significant in the 12-16 combined age range (p=0.001). Thus, the findings showed that hormonal changes that characterize the onset of the menstrual cycle and the formation of ovulatory cycles often trigger epilepsy onset (Figure 2).

The most significant and sensitive period of puberty is menarche, or the first menstrual cycle. In the cohort, the median age of menarche was 13 years, ranging between the ages of 12 and 14. No significant differences in groups reliably varied (p=0.49). There is a direct correlation between epilepsy onset and menarche in the general cohort: it was identified in 13% of females, which refers to risk factors for the formation of catamenial epilepsy. The total catamenial epilepsy in the study group was 32%. This type of epilepsy is typical of females only. Catamenial epilepsy, also known as menstrual seizures, refers to the gender characteristics of female epilepsy. It is a type of gender-based seizure in which seizure onset is closely associated with the menstrual cycle and its specific phases. Sex hormones not only determine epilepsy onset but also affect the frequency of seizures. Sex hormone concentration changes at various stages of the menstrual cycle, thus affecting the course of epilepsy.[14] The dominance of catamenial forms in females with epilepsy during puberty results from the catamenial pattern that emerges when menarche begins.

The disease onset during pregnancy and childbirth was observed in 4 females (3%), with one in a 16-year-old female. Thus, the correlation between epilepsy onset and menarche and changes in the hormonal background during pregnancy and delivery also indicates gender-related profiles of female epilepsy. Thus, the relationship between epilepsy onset and menarche and changes in the hormonal background during pregnancy and delivery reveal the gender traits of female epilepsy.

DISCUSSION

This research has confirmed the importance of puberty in the onset of epilepsy. The redefined epilepsy on one hand allows the detection of epilepsy earlier and the initiation of treatment, on the other hand, improves the accuracy of diagnostic. Approximately 8-10% of the population experience seizures over the course of their lifetime, but only 2-3% of them further develop epilepsy.[15] In the current circumstances, even the first seizure can be considered by doctors as epilepsy under the new definition: "one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years".[6] This increases the importance of studying epilepsy onset and conducting epidemiological studies. The main tasks of the epidemiology of non-communicable diseases are: risk group identification, risk of disease to change with time, and identification of risk factors to minimize their subsequent effects.[16] In particular, in cases of female epilepsy, the issues of time and risk factors for disease onset and cause-and-effect relationships in the development of reproductive endocrine complications during polytherapy with antiepileptic drugs are important.[17]

Research directions in epilepsy onset are diverse and multidirectional. The dynamics of health-related quality of life in children who have just been diagnosed with epilepsy are being studied through cognitive, emotional, physical, and functional

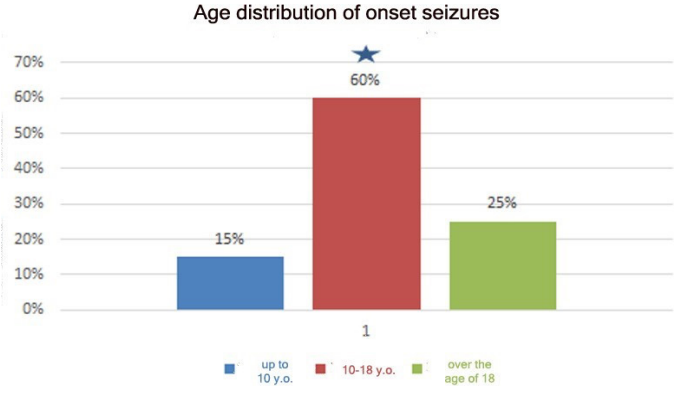

Figure 1. Age at seizure onset

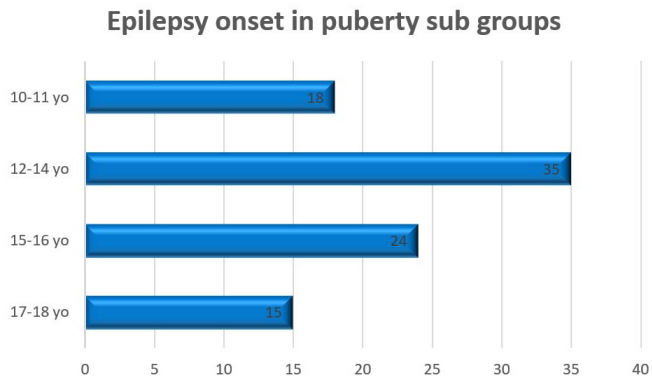

Figure 2. Epilepsy onset in puberty subgroups

status assessment.[18,19] A feature of the new classification of epilepsy is the addition of comorbid pathology to the classification structure. According to Kanner, psychiatric comorbidities should be recognized at the time of the initial evaluation of every person with epilepsy, and their treatment needs to be incorporated within the overall therapeutic plan.[20] It remains a huge challenge to make a differential diagnosis of a first-time seizure. Thus, the issues of epilepsy onset are topical and critical with a multi-directional range of research in this area and the prevalent issue of differential diagnosis of the etiology of a first-time seizure. In this regard, the gender features of seizure onset in female epilepsy patients are of particular importance, especially during puberty. The physiological instability of puberty and cycle hormonal imbalance often causes the collapse of mechanisms of antiepileptic protection and disease onset.[7,13]

Reproductive medicine is distinguished based on several anatomical and physiological characteristics of several stages in life: childhood, stages of puberty and sexual maturity, menopause transition, and postmenopausal period (advancing age, senility). The study included females of reproductive age, covering the stages of puberty and sexual maturity. Puberty is the time of hormonal storms that constitute the basis for the rapid development of all major disorders. Gynecologists call adolescence "crystal" in girls. Girls begin puberty at the ages of 10-11. The physiological course of puberty is important for physical and mental development. The period of 16-18 years completes puberty and enters adulthood. It is a flourishing of the functions of female reproductive organs. By the age of 16, in girls with normal sexual development, a stable ovulatory cycle is formed. By this age, delayed sexual development is identified (the first menstrual bleeding doesn't occurs after 15 years). The stage of sexual maturity (after 18 years) is marked by a high level of all specific body functions toward procreation. Puberty is one of the most turbulent years for the female body. Puberty includes a series of stages in the development of the female body at which the maturation of the female reproductive system emerges. This process is accompanied by markers of neuroendocrine and physiological changes in the reproductive system. Most pronounced is during the development of secondary sexual characteristics, the ability to ovulate, menstruate, and achieve fertility. This age is accompanied by intensive hormonal readjustment with an increase in estrogen levels and pronounced proconvulsive activity. In this period, in addition to maturation of the female reproductive system, physical development of the female body is completed, the body builds up, and female-type body fat and fat-free mass (muscle tissue) is distributed.

Puberty and formation of the female body normally have been completed by approximately 17-18 years. Puberty is initiated with a sustained increase in the pulsatile release of gonadotropin-releasing hormone "GnRH" from the hypothalamus, which stimulates the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the pituitary gland. Normally, menarche occurs at the age of 12-14 years. During this period, a stable circhoral (hourly) rhythm of GnRH secretion is established. In response to the rhythmic discharge of the releasing hormone, the release of LH and FSH increases. This process has been ongoing through the consistent inclusion of the links of the hypothalamic-pituitary-ovarian system.

There are several phases of puberty: preadolescence (ages 10 to 12) with an acyclic release of gonadotropins in the hypothalamus, which stimulates the production of LH and FSH hormones in the pituitary gland; the first phase of puberty (ages 12 to 14) with the formation of the rhythm of the release of gonadotropins and increased synthesis of estradiol in the ovaries; the second phase of puberty (ages 15 to 16) with a quantitative increase in ejection and the formation of a cyclic rhythm of gonadotropin release, creating the formation of a positive feedback mechanism. When a certain level of estradiol in the blood is reached, the release of LH and FSH and ovulation occur. The phase of social puberty is characterized by the end of restructuring of the hypothalamic structures that regulate the function of the reproductive system and the establishment of a constant rhythm of hormone secretion[14]. The functional heterogeneity of the phases was clearly confirmed by the data obtained in the second stage of the study. Sex hormones not only determine the onset of epilepsy but also determine the characteristics of female epilepsy. The prognosis of epilepsy in first-time diagnosis becomes evident within a few years after the treatment starts. This study showed that in 13% of epilepsy onset cases, the risk of pharmacoresistance therapy is evident. This risk is characterized by the coincidence of menarche and epilepsy onset. Menstrual or catamenial epilepsy is closely associated with seizures in certain phases of the menstrual cycle. The change in sex hormone concentration at different stages of the period influences disease development. According to the population study results, catamenial epilepsy is observed in 10-72% of cases. Patients with catamenial epilepsy more often accept pharmacoresistant forms, which should be considered in the disease prognosis and antiepileptic treatment prescription. Thus, adolescence is characterized as a risk period for epilepsy development compared with other periods of life. In the female population, it indicates an age-related risk group that is characterized by a higher incidence rate as compared to other age groups. These peculiarities impact disease prognosis, influence treatment plan choice, and indicate the necessity of preventive measures for pharmacosistance development.

Study Limitations

This is an anamnestic study with a limited sample size.

CONCLUSION

Epilepsy onset in females of reproductive age dominates in childhood. In more than half of the cases, epilepsy onset is observed at adolescence (ages 10 to 18). In subgroups of puberty, disease onset occurs more frequently between the ages of 12 and 16 during menarche and stabilization of the ovulatory peak, which is explained by the proconvulsive effect of estrogens.

Ethics

Ethics Committee Approval: The Ethics Committee of Almazov National Medical Research Centre approved this study on 22.04.2022 under the number 2304-22.

Informed Consent: All patients signed a consent form.

Authorship Contributions

Surgical and Medical Practices: G.O., Concept: G.O., N.D., Design: G.O., N.D., Data Collection or Processing: N.D., Analysis or Interpretation: G.O., N.D., Literature Search: N.D., Writing: G.O., N.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Karlov VA. epileptology - XX century. *Epilepsy and Paroxysmal Conditions.* 2014;6(2):71-79. [Crossref]
2. Mikhailov VA. Topical issues of epileptology - stigmatization, quality of life and rehabilitation of patients. *Epilepsy and Paroxysmal Conditions.* 2010;2(3):39-44. [Crossref]
3. Nesterova SV, Odintsova GV, Ivanova NE. Differential diagnosis of visual aura in migraine and epilepsy. *Translational Medicine*. 2016;3(6):32-39. [Crossref]
4. Zuberi SM, Perucca E. A new classification is born. *Epilepsia.* 2017;58(4):511. [Crossref]
5. Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017;58(4):531-542. [Crossref]
6. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia.* 2014;55(4):475-482. [Crossref]
7. Neznanov NG, Mikhailov VA. Epilepsy in children and adults, women and men. *Epilepsy.* 2021;13(1):47-51. [Crossref]
8. Forsgren L, Beghi E, Oun A, Sillanpää M. The epidemiology of epilepsy in Europe - a systematic review. *Eur J Neurol*. 2005;12(4):245-253. [Crossref]
9. Abramov K, Odintsova G, Khachatryan W. Epilepsy onset features in puberty period. *J Neurol Sci*. 2017;381(15):332. [Crossref]
10. Odintsova GV, Aleksandrov MV, Nesterova SV. The characteristics of social adaptation in reproductive-aged women with epilepsy and migraine. *Neurology, Neuropsychiatry, Psychosomatics.* 2018;10(1S):46-50. [Crossref]
11. Odintsova G, Saykova L. Sotsial'naya adaptatsiya i reproduktivnoe zdorov'e pri zhenskoy epilepsii: Aktual'nye aspekty i problematika. Russia, LAP LAMBERT Academic Publishing; 2013:1-112. [Crossref]
12. Anisimova DV, Magzhanov RV, Vlasov PN, et al. The pattern of female genital hormonal disease in juvenile myoclonic epilepsy. *Neurology Neuropsychiatry Psychosomatics*. 2016;(1):24-30. [Crossref]
13. Odintsova GV, Koroleva NY, Chugunova AA, Saykova LA. Monitiring of side effects of the antiepileptic drugs on reproductive health in women with epilepsy. *Epilepsy and Paroxysmal Conditions.* 2014;6(2):12-18. [Crossref]
14. Crawford P. Best practice guidelines for the management of women with epilepsy. *Epilepsia.* 2005;46(Suppl 9):117-124. [Crossref]
15. Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2129-2143. [Crossref]
16. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy-a review. *Epilepsy Res.* 2009;85(1):31-45. [Crossref]
17. Odintsova G, Chugunova A, Saykova L, Lobzin SV, Khachatryan W. Reproductive endocrine complications in women with epilepsy. *Giornale Italiano di Ostetricia e Ginecologia.* 2016;38(1):168-170. [Crossref]
18. Sajobi TT, Wang M, Ferro MA, et al. Multivariate trajectories across multiple domains of health-related quality of life in children with new-onset epilepsy. *Epilepsy Behav*. 2017;75:72-78. [Crossref]
19. Mula M, Cock HR. More than seizures: improving the lives of people with refractory epilepsy. *Eur J Neurol*. 2015;22(1):24-30. [Crossref]
20. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology.* 2018;91(2):82-90. [Crossref]