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Sex hormones influence on epilepsy in young men

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Abstract. ***Background.*** *Hormonal changes in epilepsy have been studied mainly in women. Changes in sex hormones in men have hardly been studied, despite the possible significant impact of epilepsy on the hormonal spectrum in general and on sex hormones in particular. Hormonal dysfunction is also a known factor in worsening the clinical course of epilepsy. The purpose of this study was to investigate sex hormones in young male patients with epilepsy depending on the age of epilepsy onset, clinical course of the disease, type of seizures and form of epilepsy. The content of estradiol, progesterone, testosterone, prolactin was studied.* ***Materials and methods.*** *The study involved 80 male patients aged 18–44 (mean of 32.73 ± 7.23) years with epilepsy who were classified as young adults according to the WHO classification. The sample was random. All participants provided informed consent to participate in the study voluntarily. All patients with epilepsy were divided into three groups. The first group consisted of patients with age of epilepsy onset under 13. The second group included patients whose epilepsy onset occurred during puberty (13–17 years). The third group consisted of patients with epilepsy onset at the age of 18 years and older. All patients had a history of epilepsy for at least 1 year. The studies were carried out on the basis of clinical symptoms and instrumental data analysis. The hormonal status of the subjects was studied by determining serum level of sex hormones.* ***Results.*** *General trends were found in all patients with epilepsy: increased estradiol, decreased prolactin, and decreased testosterone. The degree of hormonal imbalance in patients with epilepsy depended on the age of epilepsy onset (prepuberty, puberty, post-puberty), the type of seizures and the clinical course of epilepsy. The present study established the relationship between the level of steroid hormones in young men and the age of epilepsy onset. It also examined the relationship between steroid hormone levels and the form of epilepsy, the type of epileptic seizures and their frequency.* ***Conclusions.*** *In men aged 20–44 years who are classified as young subjects by the WHO, epilepsy is accompanied by an imbalance in sex hormone. The nature of the hormonal imbalance depends on the age of epilepsy onset, although in all age subgroups, there was a tendency toward an increase in estradiol, a decrease in progestin and testosterone. Hormonal imbalance in men with epilepsy may be evidence that sex hormones are involved in the development of epileptogenesis in young age.*

Keywords: *epilepsy; sex hormones; testosterone; progesterone; prolactin; estradiol; young men; antiseizures medications*

Introduction

Reproductive and sexual dysfunctions are typical for patients with epilepsy and are not differentiated by gender [1]. It is known that the birth rate is reduced in both women with epilepsy and men [2].

The incidence of hyposexuality and decreased potency in men with epilepsy varies from 38 to 71 % [3–5]. Disorders of sexual desire and arousal are described in 30–60 % of patients with epilepsy. About one third of sexually active men with epilepsy have difficulty with erection or ejaculation [6, 7]. A decrease in libido or potency occurs in about 20 % of men with epilepsy [3, 8].

The previous studies, which used mostly structured or unstructured interviews, found a higher frequency — from 38 to 71 % [3, 9–15]. The abnormal semen analysis, including decreased sperm count, abnormal morphology, or

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impaired motility, is observed in 90 % of men with epilepsy [11, 13]. The etiology of these dysfunctions is multifactorial, as epilepsy itself, as well as drugs for its treatment, have a significant impact on the functioning of the reproductive system.

The comorbidity of epilepsy and neuroendocrine disorders accounts for up to 2/3 of all cases. Men suffering from epilepsy have prerequisites for the development of hormonal disorders from the very beginning, due to the presence of neuroendocrine regulation disorders. Epileptic seizures disrupt the cortical regulation of hormone release by the hypothalamus and can disrupt the integrity of the hypothalamic-pituitary-sexual system at all levels. In turn, antiseizure medications (ASMs) interfere with sex steroid metabolism by inducing or inhibiting liver microsomal enzymes [10].

Progesterone is an endogenous antiepileptic hormone that affects seizure susceptibility. Progesterone targets a variety of molecular and cellular mechanisms that have a role in epileptogenesis. The antiepileptic activity of progesterone is mediated mainly by its conversion to allopregnanolone with a wide range of anticonvulsant properties. Progesterone can modulate inflammatory signaling cascades, apoptosis, neurogenesis and synaptic plasticity, and thus can directly modify the effects that affect epileptogenesis [16].

Disturbances in progesterone levels in men can be manifested by metabolic disorders, create prerequisites for female obesity, causeless depression, drowsiness, mood swings, headaches, fatigue, irritability, testicular atrophy, and lowered blood pressure. Changes in blood progesterone levels also negatively affect sexual desire [17].

Testosterone has a marked effect on seizure susceptibility. Testosterone modulates seizure susceptibility through its conversion to neurosteroids with anticonvulsant and proconvulsant effects. Thus, the overall effect of testosterone on nervous excitability and epileptiform activity depends on the levels of various testosterone metabolites in the brain. Thus, testosterone has a bi-directional effect on seizures: at higher doses it acts as a proconvulsant, and at lower doses it has an antiepileptogenic effect [18, 19].

Prolactin is one of the hormones of the acidophilic cells of the anterior pituitary gland. It is a peptide hormone by chemical structure. In men, prolactin is involved in the process of testosterone production. This hormone plays a role in the immune system, affects body weight, participates in the development of secondary sexual characteristics and in the formation of sexual desire [19].

The purpose of the study was to investigate sex hormones in young male patients with epilepsy depending on the age of epilepsy debut, clinical course of the disease, type of seizures and form of epilepsy. The content of estradiol, progesterone, testosterone, prolactin was studied.

Materials and methods

The study involved men aged 18–44 years with epilepsy. According to the WHO classification, all men were classified as young adults. The average age of men was 32.73 ± 7.23 years.

All study participants were divided into groups depending on the age of epilepsy onset: group 1 — male patients with epilepsy onset before the age of 13, group 2 — patients with epilepsy onset during puberty (13–17 years), and group 3 — young men with epilepsy onset in the post-pubertal period. All patients had a history of epilepsy for at least 1 year. The control group consisted of 20 healthy men of comparable age.

The levels of sex hormones (estradiol, prolactin, progesterone, testosterone) were examined in all groups. Estradiol determination is based on a competitive enzyme-linked immunosorbent assay. The concentration of estradiol in the test samples is determined by the calibration graph of the dependence of optical density (OD) on the content of estradiol in the calibration samples. The reference interval in men was 0.029–0.3 nmol/L. Estradiol levels were determined using an ELISA and the Estradiol ELISA kit (Ukraine). Method for determining the concentration of prolactin in a one-step "sandwich" version of a solid-phase enzyme-linked immunosorbent assay using monoclonal antibodies to prolactin. The reference interval was 57–600 mIU/L. The level of prolactin was determined using a set of Prolactin ELISA-BEST reagents (Ukraine). The method for determining testosterone concentration is based on a one-step solid phase competitive enzyme immunoassay using monoclonal antibodies to testosterone. The reference interval for men is 4.5–35.4 nmol/L. Testosterone levels were determined using an ELISA and a set of reagents Testosterone ELISA-BEST (Ukraine). The serum progesterone level in young men with epilepsy was determined by a one-step solid-phase competitive enzyme immunoassay using polyclonal antibodies. Reference interval for men: 0.5–6.0 nmol/L. Progesterone levels were determined using ELISA and the Progesterone ELISA-BEST reagent kit (Ukraine).

In terms of ethics and bioethics, the study was conducted in accordance with the current international and Ukrainian legislation and industry regulations.

The results of the study were processed using the Statistica 10.0 software package and Microsoft Excel XP. The probability of differences in mean values was determined by the Student's t-test and Pearson's agreement test (χ^2). The difference was considered significant at $p < 0.05$.

Results

It is expedient to present the steroid hormone levels of young men with epilepsy and compare the data between the groups (Table 1).

We hypothesized that hormonal disorders may depend on the nature of the course of epilepsy, namely the age of onset, the form of epilepsy, the type of seizures, and their frequency. To test this hypothesis, we analyzed the detected hormonal changes depending on the above characteristics.

This study determined the relationship between changes in the level of sex hormones and the form of epilepsy in men in each group. Since the sample was random, only two forms of epilepsy could be distinguished in this study: symptomatic and cryptogenic. After statistical processing of the data, a relationship was established between the

Table 1. Steroid hormone levels in young men with epilepsy

Hormones	Group 1	Group 2	Group 3	Control group
Testosterone, nmol/L	15.53 [10.37; 20.27][4]	12.64 [9.35; 21.79][1, 4]	13.31 [7.49; 17.23][3, 4]	19.95 [4.5; 35.4]
Estradiol, nmol/L	0.31 [0.24; 0.34][4]	0.36 [0.26; 0.39][4]	0.33 [0.28; 0.39][4]	0.16 [0.129; 0.3]
Progesterone, nmol/L	3.53 [1.72; 3.82]	2.76 [2.16; 4.39][1, 4]	3.75 [2.43; 6.49][2]	3.4 [0.8; 6.0]
Prolactin, mIU/L	298 [226; 468.36][4]	323.25 [260; 394.65][1, 2]	301 [250; 430.24][4]	328.5 [57; 600]

Notes: [1] — significant difference between groups 1 and 2 (p < 0.05); [2] — significant difference between groups 2 and 3 (p < 0.01); [3] — significant difference between groups 1 and 3 (p < 0.05); [4] — significant difference compared to the control group (p < 0.01).

form of epilepsy and changes in estradiol levels in men of group 3 (young men with the onset of the disease in the postpubertal period). In men with epilepsy with the onset of the disease in the pre-pubertal and in the pubertal period (groups 1 and 2), no differences were found at a statistically significant level. In patients with the onset of epilepsy in the postpubertal period (group 3) with symptomatic epilepsy, estradiol levels ranged from 0.22 to 0.45 nmol/L with a median value of 0.34 nmol/L. In patients of group 3 with cryptogenic epilepsy, the level of estradiol was 0.319 [0.21; 0.42] nmol/L (Fig. 1).

Thus, in group 3, the estradiol level depends on the form of epilepsy at a statistically significant level (Mann-Whitney test; p = 0.011), unlike in groups 1 and 2.

There was a statistically significant dependence (median test (MT), p = 0.018) of changes in estradiol levels on the type of seizures in patients of group 1. The median estradiol value was 0.21 nmol/L in focal seizures, in generalized seizures — 0.28 nmol/L, in polymorphic seizures the median estradiol value was 0.35 nmol/L. Also, a statistically significant dependence of the type of seizures in patients of group 1 was observed on the level of testosterone (MT, p = 0.18). In focal seizures, the testosterone level was 4.9 nmol/L, in generalized seizures — 14.9 nmol/L, in polymorphic seizures the testosterone level was 23 nmol/L.

In addition, in patients of group 1, a statistically significant dependence (Kruskal-Wallis test (KWT), p = 0.001) of estradiol and testosterone levels on the frequency of seizures was observed. The level of estradiol in moderate frequency seizures was 0.1 nmol/L, and the level of testosterone was 3 nmol/L, and in frequent seizures — 0.3 and 16 nmol/L, respectively.

In the second group, patients showed a statistically significant dependence of estradiol (MT, p = 0.44), progesterone (KWT, p = 0.05) and testosterone (KWT, p = 0.003) on the type of seizures.

The median estradiol value was 0.32 nmol/L in generalized seizures, in patients with focal seizures the level of this hormone was 0.38 nmol/L, in polymorphic seizures — 0.35 nmol/L. The median testosterone value was 7 nmol/L in generalized seizures, in patients with focal seizures the level of this hormone was 15 nmol/L, in polymorphic seizures — 18 nmol/L (Fig. 2).

The median progesterone value was 1.5 nmol/L in generalized seizures. In patients with focal and generalized seizures, the level of this hormone was 2.8 nmol/L. In polymorphic attacks, the progesterone level was 4.5 nmol/L.

In contrast to group 1, patients in group 2 showed a statistically significant correlation (KWT, p = 0.001) between the frequency of seizures and testosterone levels. Testosterone

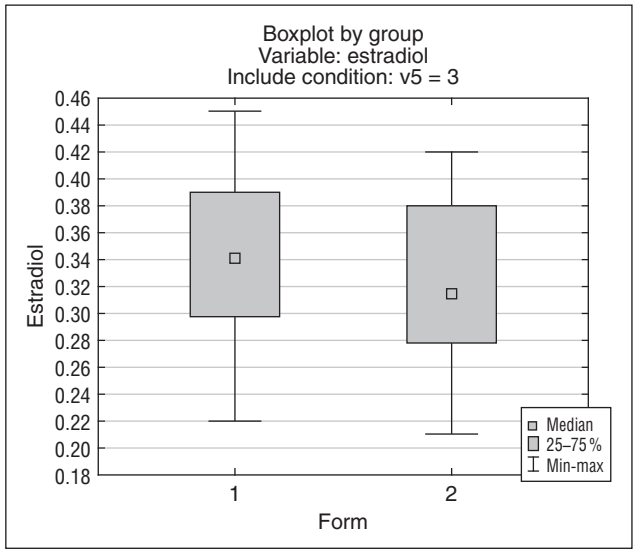

Figure 1. Changes in estradiol levels in patients of the third group depending on the form of epilepsy: 1 — symptomatic epilepsy, 2 — cryptogenic epilepsy

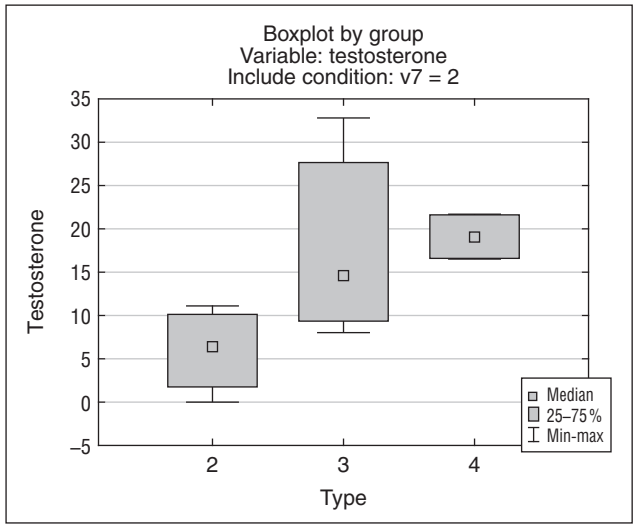

Figure 2. Changes in testosterone levels in patients of group 2 depending on the type of seizures: 2 — generalized seizures, 3 — focal seizures, 4 — polymorphic seizures

level in seizures of moderate frequency was 8 nmol/L, it was 18 nmol/L in frequent seizures.

In group 3, patients with epilepsy showed a statistically significant dependence of estradiol levels on the type of seizures (KWT, p = 0.07), prolactin (KWT, p = 0.017) and progesterone (KWT, p = 0.003). The median value of estradiol in focal seizures was 0.34 nmol/L, progesterone — 3.8 nmol/L and prolactin — 275 mIU/L. In generalized seizures, the level of estradiol was 0.31 nmol/L, progesterone — 2.9 nmol/L, prolactin — 300 mIU/L. In patients with focal attacks with transition to bilateral seizures, estradiol was 0.33 nmol/L, progesterone — 4.3 nmol/L and prolactin — 340 mIU/L. The median value of estradiol in polymorphic seizures was 0.35 nmol/L, progesterone — 4.1 nmol/L, prolactin — 260 mIU/L.

Discussion

The hormonal changes identified in the study confirm the presence of neuroendocrine regulation disorders in men with epilepsy. This, on the one hand, maybe due to the process of brain epileptization and impaired central neuroendocrine regulation of sex hormones. This opinion is in directly confirmed by a decrease in the level of "anti-epileptogenic" hormones when the disease debuts at puberty. On the other hand, the use of ASMs, which in any case affect the secretion and metabolism of steroid hormones. In turn, steroids have a multidirectional effect on brain excitability [16].

Estradiol levels were higher in all patients prescribed ASMs, regardless of the active ingredient. Given that estrogens are pro-epileptogenic, such an increase in estradiol in men with epilepsy, regardless of the duration of the disease, the form of epilepsy, the type of epileptic seizures, and the age of epilepsy onset, indicates a two-way relationship between epilepsy and changes in steroid hormones, as well as the involvement of neuroendocrine disorders in the pathogenesis of the disease [17]. An increase in estradiol, which is metabolized in the brain to a number of neurosteroids, leads to an increase in brain excitability through in direct effects on NMDA-and GABAergic mechanisms. Multidirectional changes in prolactin levels confirm the presence of sex hormone dysfunction in epilepsy in men [18].

A significant decrease in testosterone levels, which, on the contrary, is predominantly an antiepileptogenic hormone, also confirms the involvement of neurohormonal disorders in epileptogenesis. It is noteworthy that the development of epilepsy in puberty (patients of group 2) is accompanied by more significant hormonal disorders, although a decrease in testosterone relative to the control group was detected in all patients.

Also, low progesterone levels, especially in patients with a onset at puberty, indicate a weakening of antiepileptogenic mechanisms and the development of hormonal disorders that support epileptogenesis. Taking into account the broad neuroprotective and antiepileptogenic properties of progesterone, it can be concluded that its decrease against the background of general hormonal imbalance with a decrease in the level of antiepileptogenic hormones and an increase in proepileptogenic hormones maybe one of the links that supports the development of epileptogenesis in this group of patients.

In addition, analysis of the ratio of hormones in patients with different types of epileptic seizures and seizure frequency indicates that hormonal imbalance of sex hormones is associated with the development and persistence of epileptic seizures. That is, there is the formation of a self-sustaining epileptic system, which, on the one hand, is due to epileptic activity, and on the other hand, exacerbates the pathological condition.

Steroid hormones, which are synthesized and secreted from the ovaries, gonads, and adrenal glands, play a key role in the neuroendocrine control of nervous excitability and seizure susceptibility [20]. The mechanisms of sex steroid hormones' influence on brain excitability are associated with both classical, intracellularly mediated effects and non-classical membrane effects caused by binding to membrane receptors.

Thus, the present study revealed that the level of sex steroid hormones in young men depends on the form of epilepsy, frequency and type of epileptic seizures. Testosterone levels depended on the age of epilepsy debut, i.e., the highest rate was observed in males who had epilepsy debut in puberty. A significant decrease in testosterone levels, which, on the contrary, is predominantly a proepileptogenic hormone, also confirms the involvement of neurohormonal disorders in epileptogenesis. The development of epilepsy in puberty (patients of group 2) is accompanied by more significant hormonal disorders. The highest level of prolactin was observed in young men whose epilepsy debut occurred during puberty — 323.25 [260; 394.65] mIU/L.

Multidirectional changes in prolactin levels confirm the presence of sex hormone dysfunction in epilepsy in young men. The highest level of estradiol was observed in men whose epilepsy debut occurred during puberty. Progesterone levels differed statistically significantly from those of the control group. The highest progesterone level was observed in young men with epilepsy debut in the pre-pubertal period and amounted to 3.53 [1.72; 3.82] nmol/L. Also, low progesterone levels indicate a weakening of anti-epileptogenic mechanisms and the development of hormonal disorders that support epileptogenesis. Given the broad neuroprotective and antiepileptogenic properties of progesterone, it can be concluded that its decrease against the background of general hormonal imbalance with a decrease in antiepileptogenic hormones and an increase in proepileptogenic hormones may be one of the links that supports the development of epileptogenesis in this group of patients.

The study also found that the level of steroidal sex hormones depended largely on the ASMs. Patients whose taking carbamazepine had elevated levels of estradiol, levetiracetam — elevated levels of prolactin, valproic acid — progesterone, lamotrigine — testosterone. However, these changes were trend-like and did not reach statistically significant levels.

Conclusions

In men aged 20–44 years, who are classified as young subjects by the WHO, the presence of epilepsy is accompanied by an imbalance in sex hormone levels.

The nature of the hormonal imbalance depends on the age of epilepsy onset, although in all age subgroups there was a tendency to increase estradiol, decrease progestin and decrease testosterone.

The established imbalance of sex hormones in men with epilepsy may be evidence that sex hormones are involved in the development of epileptogenesis in men of a young age group.

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Вплив статевих гормонів на перебіг епілепсії в молодих чоловіків

Резюме. ***Актуальність.*** Гормональні зміни при епілепсії вивчалися переважно в жінок. Зміни статевих гормонів у чоловіків майже не досліджували, попри можливий значний вплив хвороби на гормональний спектр в цілому і на статеві гормони зокрема. Гормональна дисфункція також є відомим фактором погіршення клінічного перебігу епілепсії. ***Мета:*** вивчення статевих гормонів у молодих пацієнтів чоловічої статі з епілепсією залежно від віку початку захворювання, клінічного перебігу, типу нападів та форми епілепсії. Аналізували вміст естрадіолу, прогестерону, тестостерону, пролактину. ***Матеріали та методи.*** У дослідженні взяли участь 80 чоловіків віком 18–44 (у середньому 32,73 ± 7,23) роки з епілепсією, яких віднесено до категорії молодих дорослих за класифікацією ВООЗ. Вибірка була випадковою. Усі учасники добровільно надали інформовану згоду на участь у дослідженні. Пацієнтів з епілепсією розподілено на три групи. Першу групу становили хворі з віком початку епілепсії менше 13 років. До другої групи увійшли пацієнти, у яких дебют епілепсії припав на період статевого дозрівання (13–17 років), до третьої — чоловіки з дебютом у віці 18 років і старше. Усі пацієнти хворіли на епілепсію щонайменше 1 рік. Дослідження проводилися на основі клінічної симптоматики й аналізу інструментальних даних. Гормональний статус обстежених вивчали шляхом визначення рівня статевих гормонів у сироватці крові. ***Результати.*** У всіх пацієнтів з епілепсією виявлено загальні тенденції: підвищення естрадіолу, зниження пролактину й тестостерону. Ступінь гормонального дисбалансу залежав від віку дебюту хвороби (препубертатний, пубертатний, постпубертатний), типу нападів та клінічного перебігу епілепсії. У цьому дослідженні встановлено зв'язок між рівнем стероїдних гормонів у молодих чоловіків й віком дебюту епілепсії. Також розглядали залежність між рівнем стероїдних гормонів і формою епілепсії, типом епілептичних нападів та їхньою частотою. ***Висновки.*** У чоловіків віком 20–44 роки, які за класифікацією ВООЗ належать до категорії молодих суб'єктів, епілепсія супроводжується дисбалансом статевих гормонів. Характер гормонального дисбалансу залежить від віку дебюту захворювання, хоча в усіх вікових підгрупах мала місце тенденція до підвищення рівня естрадіолу, зниження прогестину й тестостерону. Гормональний дисбаланс у чоловіків з епілепсією може свідчити про роль статевих гормонів в епілептогенезі в молодому віці.

Ключові слова: епілепсія; статеві гормони; тестостерон; прогестерон; пролактин; естрадіол; молоді чоловіки; протинападові препарати