Selected neurologic disorders related to polycystic ovary syndrome

Wybrane zaburzenia neurologiczne związane z zespołem wielotorbielowatych jajników

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Abstract

Epilepsy is one of the most common neurologic disorders. The epileptic seizures as well as antiepileptic drugs may disturb the reproductive system function. Polycystic ovary syndrome occurs more commonly in women with epilepsy, either treated or not with valproic acid. This article discusses the current knowledge about the relationships between epilepsy and polycystic ovary syndrome.

Key words: **PCOS** / **epilepsy** / **valproic acid** /

Streszcznie

Padaczka jest jedną z najczęstszych chorób neurologicznych. Zarówno napady padaczkowe, jak i stosowane w tej chorobie leki mogą zaburzać czynność układu rozrodczego. Zespół wielotorbielowatych jajników występuje częściej zarówno u nieleczonych, jak i leczonych kwasem walproinowym kobiet z padaczką. Artykuł przedstawia aktualny stan wiedzy na temat związków pomiędzy oboma schorzeniami.

Słowa kluczowe: **zespół wielotorbielowartych jajników (PCOS)** / **padaczka** / / **kwas walproinowy** /

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Polycystic ovary syndrome (PCOS) is a complex endocrine disorder. According to different authors, it affects 5-10% of premenopausal women [1]. The Rotterdam criteria suggest that PCOS is recognized when two of the following conditions are fulfilled: 1. menstrual disorders or amenorrhea with chronic lack of ovulation, 2. clinical and/or biochemical features of hyperandrogenism, 3. presence of the characteristic features of the ovaries in ultrasonography (polycystic ovaries - PCO). Other diseases such as congenital adrenal hyperplasia, Cushing syndrome, androgen-secreting tumors, hyperprolactinemia and thyroid disease should also be ruled out [1].

Epilepsy

Epilepsy is the most common neurological disease among people of all ages, including women of reproductive age. By definition, it is characterized by recurrent (two or more) epileptic seizures that are not provoked by any factor [2]. The incidence of epilepsy in Europe, according to an Italian study, is estimated as 2,7-3,3/1000 [2]. Many studies have shown an increased coincidence of epilepsy and polycystic ovary syndrome. Herzog has shown that PCOS occurs in 10-25% of women with temporal epilepsy, while in normal population it is observed in 5-10% [3, 4]. It is not clear whether epilepsy itself favors the occurrence of PCOS, or if there is an association between PCOS and antiepileptic drugs, particularly valproic acid (VPA). One theory says that seizures can affect the hypothalamic-pituitary-ovarian axis [3, 5]. It is suggested that seizures throughout the middle temporal area (medial temporal areas) stimulate the secretion of GnRH (gonadotropin-releasing hormone), and by changing the frequency of GnRH pulses increase the secretion of luteinizing hormone (LH), resulting in increased LH/FSH ratio (FSH – follicle-stimulating hormone), as it is seen in PCOS. Herzog and colleagues studied the frequency of LH pulses in women with epilepsy and found that it is higher, especially in the left temporal lobe epilepsy [3, 6, 7].

Neuroendocrine disorders (inappropriately low levels of FSH with normal or increased concentrations of LH) would cause lack of ovulation and the formation of immature ovarian follicles that produce testosterone, but with a deficit of aromatase, the enzyme which converts androgens into estrogens [3]. In addition, the increased level of LH would affect the increased androgen production in ovarian thecal cells [3, 8, 9].

Some authors suggest a connection between location of epileptic foci and the appearance of PCOS features. Foci located in the left temporal lobe would be associated with PCOS, and in the right temporal lobe with the occurrence of hypogonadotropic hypogonadism [3]. Other researchers postulate the relationship between the type of seizure with the emergence of PCOS. Generalized seizures are associated with the more frequent occurrence of menstrual disorders and PCOS. In the study of Morrell et al., PCO image on ultrasound was found in 41% of women with generalized epilepsy, and in 26% of women with partial seizures [5, 7, 10]. Results of other studies, however, did not confirm these observations [7,9].

Scharfman et al., in an animal model, confirmed the hypothesis that not only drugs used for treatment also but epilepsy itself affect the appearance of features of PCOS in the ovary. They showed that female rats with pilocarpine-induced temporal lobe epilepsy, had higher testosterone levels, increased body weight and more cysts seen on the ultrasonography of ovaries in comparison to rats in the control group [11].

Epilepsy is often associated with weight gain, and this usually affects women. Drugs used for treatment of epilepsy may have major influence on this phenomenon. There is no data assessing the impact of untreated epilepsy on energy metabolism in humans in the existing literature. But in an animal model increased body weight was observed in female rats with epilepsy induced by lithium and pilocarpine [11].

The fact that increased incidence of PCOS was demonstrated in patients treated for epilepsy with VPA may prove an existing relationship between epilepsy and PCOS. In teenagers with migraine who were treated with VPA or placebo, there were no differences in the prevalence of menstrual disorders and no increase in testosterone levels in any of the groups [12]. These results may indicate that epilepsy and bipolar disorder are conducive to the development of PCOS and the use of VPA is an additional, but not the sole pathogenetic factor.

Antiepileptic drugs

Antiepileptic drugs may affect levels of biologically active sex hormones. Many of them have long been used in the treatment of epilepsy. Drugs such as carbamazepine, phenobarbital or phenytoin increase the activity of hepatic cytochrome P450 involved in steroid hormone metabolism and increase the production of sex hormone binding globulin (SHBG), resulting in the reduction of biologically active hormone level [10]. Reduced incidence of PCOS in women treated with carbamazepine, compared to women who were not treated, was observed (13 and 30% respectively) [3]. Some other drugs, such as valproic acid, have the opposite effect: they inhibit hepatic enzymes, which results in significantly increased level of biologically active sex hormones, including androgens [9].

A common adverse effect of some antiepileptic drugs is weight gain. These drugs include valproic acid, carbamazepine, gabapentin and vigabatrin. Increased body weight augments insulin resistance and in women with genetic predisposition may favor the occurrence of PCOS [13].

Most data on the relationship between PCOS and antiepileptic drugs concern valproic acid. Valproic acid (VPA) and its metabolites are common antiepileptic drugs used for both generalized and partial seizures, as well as in other disorders such as bipolar disorder, migraine, or chronic neuropathic pain. Long-term treatment with VPA in women of reproductive age is associated with a higher incidence of polycystic ovaries in ultrasonography, hyperandrogenemia, weight gain, hyperinsulinemia and insulin resistance [13].

VPA is a short-chain fatty acid, which acts throughout the GABA-ergic (GABA γ-aminobutyric acid) and sodium channel activity. Its impact on cell function is also being postulated. VPA modulates intracellular signaling systems such as MAPK (mitogen-activated protein kinases), PCK (Protein kinase C), Akt / PBK (The serine / threonine protein kinase GDP Also known as the Act) [14]. Chronic treatment with VPA affects the activity of transcription factors. VPA reversibly inhibits the activity of histone deacetylases class I and consequently increases histone acetylation, which alters the expression of selected genes [15].

Nelson DeGrave et al., studied the effect of various doses of VPA on steroidogenic enzymes activity in thecal cell cultures obtained after hysterectomy from women with normal ovaries

and PCOS [8]. VPA in pharmacological doses (500uM) was found to increase synthesis of androgens (dehydroepiandrosterone and androstenedione) in ovarian thecal cells by increasing gene expression of CYP17 and CYP11 α. In subsequent studies, the same authors showed that the use of VPA caused changes in gene expression in normal thecal cells, similar to those observed in PCOS [8,14].

One of the most common side effects of VPA is weight gain. It was observed in approximately 43.6% of women and 23.5% of men on the long-term VPA treatment [13]. There is no relation between the dose and the degree of weight gain. Usually weight gain is observed during the first three months of treatment, with a maximum in the sixth month of therapy. It is noted more frequently in patients who started treatment during puberty or just after puberty. No relationship between weight gain and the type of seizures was found but there was an association with higher body weight at the beginning of treatment [13].

The precise pathogenetic background of the weight gain induced by administration of VPA is still unknown. It is postulated that several mechanisms can be involved [13]:

1) Impact on the hypothalamus

Patients receiving VPA showed an increase in appetite, thirst and desire for high-energy drinks. Similar feelings can be induced by activation of the hypothalamus. It was proved that VPA may interfere with the hypothalamic-pituitary-gonadal axis through the influence on GnRH pulse generator [16].

2) Induction of hyperleptinemia and resistance to leptin

Increased level of leptin was observed in patients taking VPA, but only in those who suffer from obesity. It seems that the increase in leptin levels is associated with weight gain, and not with the direct influence of VPA on the leptin metabolism [13]. This is supported by several facts. First, slim patients who are taking VPA do not show elevated levels of leptin. Secondly, there is no significant difference in levels of leptin in obese patients taking VPA and in the obese control group. Thirdly, in a group of obese patients treated with VPA, women have higher leptin levels than men, which corresponds to similar proportions of patients with obesity. The results of some studies have not shown the influence of VPA on leptin levels, or some were even counterproductive. Lagace et al., showed that VPA in a dose-dependent manner decreased the level of leptin mRNA in adipocytes, thus significantly reducing the secretion of the hormone [17].

3) Effects on adiponectin

It was shown that the use of VPA is associated with lower levels of adiponectin, but only in people who experienced weight gain during the treatment. These changes resemble those observed in adiponectin levels in simple obesity. In addition, Qiao and colleagues showed that VPA decreases adiponectin gene expression in mature adipocytes by inhibition of histone deacetylase activity [18].

4) Insulin resistance and hyperinsulinemia

Isojärvi et al. showed in 1996 that women who gained weight during VPA therapy had elevated levels of insulin [19]. Luef et al. confirmed in 2002 that patients taking VPA had a statistically higher BMI and higher postprandial insulin levels compared to the control group. In addition, higher concentrations of insulin was also observed after glucose load [20]. In another study Pylvänen and colleagues have shown that both lean and obese individuals using VPA had elevated insulin levels [21]. The use of VPA is associated with increased fasting insulin levels, but not with increased levels of proinsulin and C-peptide in the fasting state, suggesting that the drug has no effect on insulin secretion, but only affects the metabolism of insulin in the liver, increasing the concentration of the hormone in the periphery [22]. The exact mechanisms by which VPA induces insulin resistance and hyperinsulinemia are not yet known. It is suggested that VPA as a short-chain fatty acid, competes with other fatty acids (FFAs - free fatty acids) for binding to insulin, thus increasing their local availability, which contributes to the development of insulin resistance. Elevated levels of FFAs impair insulin synthesis and increase the proinsulin / insulin ratio [23].

Influence of VPA on reducing the activity of GLUT1 (Glucose transporter 1) and direct effect of VPA on pancreatic beta cells is also being considered [24]. It was observed that addition of VPA to the pancreatic beta cells cultures increased concentration of insulin in a time- and dose- dependent manner [25].

5) Genetic factors

Klein et al. observed five pairs of monozygotic twins treated with VPA. In all the twins effect of VPA on the change in body weight was the same. In four pairs of twins weight gain was observed, while in the fifth pair of twins, body weight has not changed. This seems to confirm that genetic factors may play a significant role in the development of obesity in humans treated with VPA [26].

Polycystic ovary syndrome is the most common endocrine disorder in reproductive women. On the other hand, epilepsy is one of the most common neurological diseases. Doctors involved in the treatment of epilepsy should not forget about the possibility of coexistence of PCOS and its long-term consequences that require careful observation and proper treatment.

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