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Neurological Disorders Associated with Polycystic Ovary Syndrome

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Abstract

This article presents a general analysis of contemporary data on the correlation between polycystic ovarian syndrome (SOPC) and neurological diseases. The most frequent neurological disorder associated with SOPC is epilepsy, which is a serious health problem. Data show a higher frequency of SOPC in women suffering from epilepsy, and some of the authors link this phenomenon to the adverse effects of treatments with valproic acid. Other the neurological diseases associated with SOPC also include non-convulsive disorders.

Key words: polycystic ovarian syndrome, epilepsy, neurological disorders.

Неврологические нарушения при синдроме поликистозных яичников

Дан анализ современных представлений о взаимосвязи синдрома поликистозных яичников (СПКЯ) и патологий нервной системы. Частота сочетания СПКЯ и неврологических нарушений представлена, в первую очередь, эпилепсией при СПКЯ, что является актуальной медицинской проблемой. Имеются данные о повышении частоты СПКЯ у женщин больных эпилепсией, причем ряд авторов связывают этот феномен с применением препаратов вальпроевой кислоты. Среди неврологических патологий, сочетающихся с СПКЯ, встречаются также и бессудорожные нарушения.

Ключевые слова: синдром поликистозных яичников, эпилепсия, неврологические нарушения.

Introduction

Polycystic ovarian syndrome (PCOS) was originally reported by Stein and Leventhal in 1935 when they studied a group of women suffering from amenorrhea, infertilty, enlarged polycystic ovaries and hirsutism. Most women who suffer from this condition experience infrequent or irregular menstrual cycles.

Polycystic ovary syndrome is an endocrine disorder that affects between 5% and 15% of all women of reproductive age [1]. It occurs among all races and nationalities, and is a leading cause in 73% of women with anovulatory infertility [2, 3]. The majority of specialists consider PCOS a heterogenous pathology, whose principle features are obesity, anovulation, acne and excessive amounts or effects of androgenic hormones. The symptoms and severity of the syndrome vary greatly among women. Insulin resistance, diabetes and obesity are all strongly correlated with PCOS, although the causes are still disputable.

Other names for this syndrome include polycystic ovary disease (PCOD), functional ovarian hyperandrogenism, Stein-Leventhal syndrome (original name, not widely used in modern literature), ovarian hyperthecosis and sclerocystic ovary syndrome.

Common symptoms of PCOS include:

- Oligomenorrhea, amenorrhea
- Infertility
- Hirsutism
- Hair loss
- Acne vulgaris
- Seborrhoeic dermatitis
- Obesity or weight gain
- Deepening of voice

Mild symptoms of hyperandrogenism, such as acne or hyperseborrhea, are frequent in adolescent girls and are often associated with irregular menstrual cycles. In most instances, these symptoms are transient and only reflect the immaturity of the hypothalamic-pituitary-ovarian axis during the first years following menarche [4].

The heterogeneity in the signs and symptoms of PCOS has led to considerable controversy in this area due to the difficulty in establishing a uniformly accepted definition of PCOS. What is clear, however, is that women with the disorder do not ovulate in a predictable manner and women with PCOS also produce excessive quantities of androgens (particularly testosterone). Polycystic ovaries are not present in all women diagnosed with PCOS. Also, many women with regular menstrual periods and normal levels of testosterone have cystic ovaries.

Two definitions are commonly used to describe the pathology:

1) The National Institutes of Health (**NIH 1990**) criteria for PCOS require both:

a) the presence of ovulatory dysfunction;

b) clinical and/or biochemical evidence of hyperandrogenism with exclusion of other endocrinopathies [5].

2) The revised European Society of Human Reproduction and Embryology (Rotterdam 2003) criteria for PCOS require 2 out of 3 symptoms mentioned below:

a) oligoovulation and/or anovulation;

b) clinical and/or biochemical evidence of hyperandrogenism;

c) polycystic ovaries and exclusion of other endocrinopathies [6].

The Rotterdam definition is wider and includes many more patients; notably, patients without androgen excess are included whereas in the NIH 1990 definition androgen excess is a prerequisite [6].

PCOS is traditionally divided in Russian and ex-Soviet scientific literature into "primary," which manifests in puberty and is considered a separate nosological form, and "secondary," which develops due to different endocrinopathies (adrenogenital, metabolic, Cushing's syndrome etc.) [7].

Several metabolic abnormalities are characteristic of PCOS. Impaired glucose tolerance, as evidence of insulin resistance, is present in about 31% to 35% of women with PCOS and can occur in both lean and obese women. In contrast, insulin resistance occurs in about 8% of the general population [8]. Further, hyperinsulinemia resulting from insulin resistance perpetuates the development of PCOS. Insulin inhibits hepatic production of insulin-like growth factor binding protein-1 (IGFBP-1) and testosterone-binding globulin. The free fraction of both IGFBP-1 and testosterone, therefore, will be increased, but this is only part of the cascade of events. Insulin and IGFBP-1 both stimulate thecal androgen production; therefore, the net effect of hyperinsulinemia is higher androgen production in the ovary as well as a greater bioactive fraction of androgen [8].

Another key hormonal feature of PCOS is elevated luteinizing hormone (LH) secretion from the pituitary and an increased ratio of LH to follicle-stimulating hormone (FSH). LH stimulates ovarian steroidogenesis, and an elevated LH-to-FSH ratio will produce follicles that do not fully mature, but instead become numerous and cystic. Immature follicles are deficient in aromatase, the enzyme that produces estrogen in the ovary by converting it from its precursor, testosterone. In this manner, the PCOS ovarian follicle manufactures primarily androgens. The abnormality is reinforced further by the conversion of androgen to estrogen by aromatase in the periphery, which results in elevated circulating estrogens that feed back to the pituitary and disrupt normal LH secretion [7].

Among the variety of clinical manifestations and pathophysiology of PCOS, the correlation to neurological disorders is an issue worthy of further investigation. Most reports given in this regard have discussed an interrelation between PCOS and epilepsy, which is a serious health problem.

PCOS and Epilepsy

The correlation between PCOS and epilepsy has been reported by many authors during recent decades [9]. Previous studies have described an association between epilepsy and features of the polycystic ovarian syndrome (PCOS) among women receiving treatment with antiepileptic drugs (AEDs), including valproic acid (VPA) [10]. This association with PCOS has been attributed to epilepsy itself by some investigators [11], and to the use of VPA by others [10].

Table 1

Association between epilepsy and PCOS

Study	No.	No. (%) with PCOS	Odds ratio	95% CI	P
Herzog et al., 1986	50	10 (20%)	3.4	1.2–9.1	0.01
Bilo et al., 1988	20	3 (15%)	2.4	0.4–10.1	0.18
Isojarvi et al., 1993	2381	3 (3.1%)	0.4	0.1–1.6	0.28
		to	to	to	
		7 (7.1%)[2]	1.1	0.3–3.0	1.1
Bauer et al., 2000	93	6 (6.5%)	0.9	0.3–2.8	1.0
Bilo et al., 2001	50	13 (26%)	4.8	1.9–12.2	<0.001

Note: Odds ratios, 95% confidence intervals (95% CI), and two-sided Fisher's exact test are used to compare prevalence of PCOS in each study with the maximum estimated community prevalence of 6.8% (13 of 192 women). [1]Ninety-eight women of 238 total subjects had complete evaluation for PCOS (31 VPA, 49 carbamazepine, 18 clonazepam, phenobarbital, clonazepam and/or carbamazepine). [2]The proportion with PCOS calculated from data available on 98 women for whom menstrual cycle irregularity (n = 47), hirsutism (n = 4), and menstrual irregularity with hyperandrogenemia (n = 3) was reported. The range is reported because it is unclear whether women with hirsutism were the same as those with menstrual irregularity and hyperandrogenemia.

The percentage of women reported in each study to have PCOS varies widely because different researchers have used different definitions of the syndrome and have studied different groups. Estimates range from as low as 3.1% to as high as 26% of all women in the studies (Table 1) [12, 13,

14, 15, 16]. This information is derived from a total of five clinical case series involving between 20 and 238 premenopausal women receiving outpatient care in epilepsy centers in the United States [13], Italy [14, 16], Germany [15] and Finland [12]. In population-based studies, PCOS has been estimated to occur in 4.0–6.8% of premenopausal women [10, 11]. The prevalence of PCOS in epileptic populations was elevated in three of five studies when compared to the maximum predicted community prevalence of 6.8% (Table 1) [13],[14] and significantly so in two studies, including the study by Bilo et al. [16].

Thus, reproductive endocrine disorders, such as PCOS, are common in women with epilepsy [10], however, there is uncertainty as to whether it is epilepsy or its treatment that predisposes them to PCOS. Both epilepsy and antiepileptic drugs (AEDs) can have an effect on the feedback loop of the hypothalamic–pituitary–gonadal axis, which controls the synthesis and concentrations of sex hormones [17].

An examination of the reports, mentioned above, and other clinical series reveals significant disagreement among them in their conclusions about the association between epilepsy and PCOS. Several factors may explain the discrepancy in the findings. The studies are all relatively small, permitting chance observations and selection bias to exert substantial effects. The referral pattern for each of the epilepsy clinics in which studies were conducted may differ such that some may over-represent women with reproductive-endocrine disorders. In addition, the type of epilepsy (generalized, focal), the location of seizure focus (temporal lobe, extra-temporal) and the responsiveness to therapy of study subjects varies among the clinical reports. Associations between PCOS and generalized epilepsy [13], temporal-lobe epilepsy [12], and no specific epilepsy type or seizure focus location [12, 16] have been reported. Moreover, the frequency of use of specific AEDs and the proportion of women receiving no treatment for their epilepsy varies substantially among the clinical reports. If an association of epilepsy with PCOS is mediated or caused by one or more AEDs, the number of subjects receiving that medication must be large enough to permit accurate analysis. Finally, personal characteristics of study subjects that may modulate the relationship between epilepsy and PCOS—such as ethnicity and body weight—vary markedly among the clinical reports.

In another study, the same group (Herzog et al.) found that there was a significant difference between the EEG laterality distributions associated with polycystic ovarian syndrome and those associated with hypogonadotrophic hypogonadism [18]. Patients with PCOS and untreated temporal lobe epilepsy had predominantly left-sided interictal epileptiform discharges in the EEG. This distribution differed significantly from that of women with epilepsy who had no reproductive endocrine disorders. The fact that PCOS appears to be more frequent with left-sided than with right-sided unilateral temporal lobe epileptogenic discharges would also suggest that epilepsy induces PCOS [19].

Features of PCOS Associated with Valproate

An alternative explanation for the association between epilepsy and PCOS, is that PCOS is induced by use of VPA [19]. Several studies have been conducted in order to determine the effects, if any, of AEDs on endocrine disorders. Scandinavian studies have suggested that there is a possible link between valproate and PCOS [12],[20],[21]; however, the impact of AEDs on endocrine disorders is debated. In 1993, Isojarvi et al. [12] reported the first association between valproate and cystic ovaries. The authors stated that nearly half of the 28 women treated with valproate monotherapy for epilepsy had amenorrhea, oligomenorrhea, or prolonged menstrual cycles, compared with 19% of the 120 women taking Carbamazepine monotherapy. The presence of menstrual disturbances was associated with elevated free testosterone in women taking valproate alone or valproate plus Carbamazepine. Forty-three percent of women receiving valproate alone had PCOS, compared with 22% of women taking Carbamazepine alone. This study does not clearly differentiate between the possibility of an effect of valproate administration and the effects of epilepsy itself on menstrual disturbances or elevated free testosterone. However, it is supportive of an association between valproate administration and cystic ovaries. In 1996, a second report from the same group demonstrated that 11 of 22 obese women with epilepsy, taking valproate, had insulin resistance and elevated androgen levels [20].

The results of Isojärvi et al. have been widely publicised. However, they are not supported by the results of two recent studies [22],[23]. Bauer et al. [22] conducted a prospective study in 93 women with partial epilepsy in order to determine whether PCOS is a common finding in women treated with AEDs. In this study the incidence of PCOS in patients treated with valproate monotherapy (11.1%) was similar to that for patients treated with Carbamazepine (10%) and also to that in patients receiving no medication (10.5%). This suggests that the manifestation of PCOS in women with focal epilepsy is not related to the administration of either valproate or Carbamazepine [22]. In another study investigating the effects of valproate, Phenobarbital and Carbamazepine on sex hormones and luteal function, Murialdo et al.[23] found that the prevalence of PCOS did not differ significantly between treatment groups.

The theory that VPA induced weight gain leads to increased insulin resistance with consequent hyperinsulinemia, and finally PCOS, does not explain why PCOS and/or hyperandrogenism was also high in lean VPA-treated patients. In an editorial comment on this study, Herzog [19] proposed that epilepsy may induce PCOS and that PCOS is treated by enzyme-inducing AEDs, but not by valproate, which is an enzyme-inhibiting AED. By inducing hepatic enzymes that reduce biologically active testosterone in the serum and by increasing the binding and metabolism of testosterone, some AEDs may inadvertently treat hyperandrogenism and thus PCOS, while valproate therapy may not. SHBG is uniformly elevated by chronic treatment with Phenytoin, Carbamazepine, Primidone and Phenobarbitone, but not with valproate [23]. Weight gain is a well-known side effect of valproate,

but it is not a primary diagnostic feature of PCOS. Insulin resistance can be produced by weight gain itself; however, it is present as an independent endocrine dysfunction in both obese and lean women with PCOS. It is unknown whether valproate is associated with insulin resistance in patients who do not gain weight while taking the drug. Menstrual dysfunction and anovulation have been reported more frequently in women with epilepsy, but their association with valproate and epilepsy is mixed. PCOS seems to be overrepresented in women with epilepsy and, in some reports, is specifically associated with valproate. The clinical significance of this fact as an independent finding is unclear, but it is likely to at least be a harbinger of anovulation and subfertility.

PCOS and Other Neuropathies

In 2006, a case of **thoracic myelopathy due to ossification of the posterior longitudinal ligament** (OPLL) in a patient with policystic ovary syndrome was reported by authors from Japan [24]. A 24-year-old woman presented with a three-week history of muscle weakness and sensory disturbance in her bilateral lower extremities. She also exhibited "moon-face," hepertrichosis, obesity and hyperglycemia. Myelography and computer tomography were performed, and OPLL was recognized at levels T3 to T9 of the spine. Hypercholesterolemia and abnormally high testosterone levels were found. She also had polycystic lesions in both ovaries on magnetic resonance imaging, thus the diagnosis of polycystic ovary syndrome was established. Her neurological symptoms worsened rapidly and she developed paraplegia.

The characteristic findings of obesity, insulin resistance with compensatory hyperinsulinemia, increased levels of free insulin-like growth factor-I (IGF-I) and hyperandrogenemia in patients with polycystic ovary syndrome were suspected to be related to the occurrence of OPLL. The stature of female patients with OPLL in the thoracic spine corresponded to patients with polycystic ovary syndrome. IGF-I was reported to be involved in the development of OPLL. It was proposed that hormonal surveys for patients with OPLL in the thoracic spine might be useful for clarifying the pathogenesis of OPLL.

In 2007 a case of **benign intracranial hypertension (pseudotumor cerebri), visual impairment, and hypothyroidism in association with polycystic ovary syndrome** was reported in Austria [25]. A 20-year-old obese woman developed menstrual cycle irregularities beginning at 14 years of age, initially accompanied by bitemporal headache and later by diffuse headache, as well as bilateral visual impairment, described as sparkling black points. Ophthalmologically there was a recurrent papilledema. Clinical neurologic investigations revealed sore neck muscles. Magnetic resonance imaging of the brain, orbita and cervical spine, and investigations of cerebrospinal fluid were non-informative. Visually evoked potentials revealed demyelination of the optic nerves. Gynecologic investigations revealed PCOS and endocrinologic investigations hypothyroidism and hyperandrogenism. A possible relationship between pseudotumor cerebri and the ophthalmologic, gynecologic, and endocrinologic abnormalities is discussed.

In 2008, a study was conducted by a group of specialists from Iran; the aim was to assess the prevalence and characteristics of **headache, especially migraine, in patients with PCOS** compared with women without this disease [26]. One hundred thirty-three women with PCOS and 107 controls were interviewed by two neurologists experienced in headache diagnosis. The headache disorders were classified according to the International Headache Society criteria. Forty-five women (33.8%) of the 133 cases without PCOS complained of headache. Of the PCOS patients, 48 women (44.9%) suffered from headache. Thus migraine was not more frequent in women with PCOS. It was concluded that male sex hormones, and especially testosterone, do not play an important role in the exacerbation of migraine headache.

In 2008, a case of **multiple cerbral infarctions associated with polycystic ovaries and ovarian hyperstimulation syndrome (OHSS)** was reported by a group of scientists from Korea [27]. A 31-year old woman was admitted with a chief complaint of left-sided motor weakness and motor aphasia. She had been diagnosed at an infertility clinic 6 months previously as having oligo-ovulation, infertility and polycystic ovaries. Her medical history was unremarkable: no history of hypertension, migraine or obesity. Induction of ovulation began 28 days prior to focal neurological symptoms. The patient received oral clomiphene citrate (100 mg/day for 5 days) and injections of human menopausal gonadotropin (75 IU/day for 5 days). Two weeks later, oocytes were retrieved and eventually 6 embryos were transferred to her endometrium.

Laboratory tests demonstrated that the serum white blood cell count and levels of liver enzymes were elevated, while serum albumin was decreased. Human chronic gonadotropin (hCG) was 8.3 mIU/ml (normal range at 2nd week after conception: 0–400 mIU/ml); serum estradiol and progesterone levels increased up to 4,300 pg/ml (normal range during 1st trimester: 100–5,600 pg/ml) and 60.0 ng/ml (normal range during 1st trimester: 11.2–90.0 ng/ml), respectively. Blood urea nitrogen, serum creatinine, prothrombin time, activated partial thromboplastin time, homocysteine and protein C were within normal limits. Anticardiolipin antibody, lupus anticoagulant and activated protein C resistance were negative. MRI of the brain revealed an acute ischemic lesion on diffusion-weighted and T 2 -weighted imaging in the territory of the right middle cerebral artery, but no occlusions of the major intracranial arteries and extracranial carotid and vertebral arteries were found on MR angiography.

The patient was started on intravenous heparin (21,600 U/day) to prevent further thromboembolic complications; however, nystagmus and vomiting developed on day 3 after admission. A repeated brain MRI showed newly developed left cerebellar infarction. On hospital day 12, serum hCG was found elevated to 3,463 mIU/ml (normal range at 4th week after conception: 1,000–20,000 mIU/ml), with subsequent abdominal ultrasonographic examination showing a triple pregnancy in the uterus. Therapeutic surgical abortion was performed on hospital day 21, and serum hCG, estrogen and progesterone levels returned to normal after the operation.

The patient was placed on 100 mg/day aspirin prophylaxis, and a follow-up examination at 6-months revealed residual, mild, left-arm weakness and motor aphasia. It was concluded that the occurrence of progressive, multi-territorial infarctions, without atherosclerotic lesions in cerebral arteries visible on MRA and the absence of a cardioembolic source suggested that systemic conditions conducive to a hypercoagulable state may have been responsible for cerebral infarction in this case. It was speculated that sustained high levels of hCG due to triple pregnancy, combined with a prior history of polycystic ovaries, might have led to severe OHSS and subsequent cerebral infarction, despite anticoagulation treatment. In addition, hyperactivation of the hemostatic system likely played a role in the development of thromboembolism. Therefore, the alterations of hemostatic factors may also have contributed to the development of cerebral infarction. OHSS occurs more frequently and severely when combined with polycystic ovary syndrome [28, 29]. Although the exact mechanism of this phenomenon is not clearly defined, it may be related to the exaggerated response to gonadotropin in polycystic ovary syndrome.

Conclusions

PCOS has multiple etiologies; none is fully understood [10]. Its occurrence is under genetic influence as well as related to ovarian, hypothalamic, and glucose-modulating dysfunctions. In this light, it is difficult to state which is the specific reproductive dysfunction related to epilepsy.

One explanation for the connection between PCOS and epilepsy: women whose seizures begin in the left temporal lobe may be more likely to have certain hormonal abnormalities that prevent ovarian follicles from maturing. This leads to anovulation, the collection of cysts, and the release of more male hormones — all the criteria for a diagnosis of PCOS.

PCOS has another link to epilepsy: it may increase or worsen seizures. The hormonal abnormalities related to anovulation include a lack of progesterone, which the ovaries usually produce in the days after ovulation. Progesterone has antiseizure and mood-stabilizing properties. The ovaries of women with PCOS, on the other hand, continue to produce estrogen, which promotes seizures and anxiety.

Theories underlying the occurrence of PCOS in epilepsy concern the mechanism of elevated LH. Investigators speculate that epilepsy affects the brain in such a manner that it secondarily influences the reproductive system; by affecting the hypothalamic–pituitary axis (HPA), for example. This hypothesis was first proposed by Herzog et al. in 1986 but has been studied very little since then. The sequence of events leading to elevated LH secretion begins as follows: seizure discharges, either ictal or interictal and involving medial temporal areas, stimulate the secretion of gonadotropin-releasing hormone (GnRH). Next, increased GnRH pulse frequency promotes the secretion of LH at greater levels than the secretion of FSH, resulting in an elevated LH/FSH ratio [18].

Herzog et al. [19] studied LH pulse frequencies in women with epilepsy and found that the pulse frequency is increased with an especially marked increase in left temporal lobe epilepsy. Furthermore, evidence for reproductive dysfunction in epilepsy based on a mechanism of HPA dysfunction has been reported. Earlier-than-expected menopause has been described in women with high seizure rates - a finding that is also likely a manifestation of subtle HPA dysfunction, leading to early ovarian failure. Therefore, the reproductive abnormalities in women of reproductive age with epilepsy (that is, ovulatory dysfunction and elevated circulating androgens,) which either look like or actually are PCOS, could be the result of seizures or interictal discharges affecting the HPA.

Mechanisms by which valproate can cause elevation of androgens and PCOS result from induction of androgen synthesis in the ovary, likely as a result of multiple processes. One study using human, ovarian, thecal cell cultures showed that valproate induced ovarian androgen synthesis by augmenting transcription of steroidogenic genes [20]. Another report used ovarian follicles in culture with ovarian thecal and granulosal cells (so as to replicate an ovary,) and showed that valproate increased testosterone secretion from follicles but had differing effects based on the degree of LH stimulation in the culture and on maturity of the follicles. Further, valproate decreased the conversion of testosterone to estradiol, suggesting an inhibitory effect on the converting enzyme, aromatase [21].

Valproate produced ovarian cysts in nonepileptic Wistar rats at very high, supratherapeutic doses. A study more applicable to humans, however, evaluated the effects of valproate on nonepileptic, normally cycling female Rhesus monkeys. The monkeys were treated for 12 to 15 months, having achieved therapeutic levels of valproate similar to those in seen in humans, and compared with control monkeys. No effects on menstrual cycling (which normally is nearly identical to that in humans), ovulation, androgen levels, LH/FSH ratio, insulin response, or lipid profiles were found. The ovaries, on pathologic evaluation, were normal as well. These results suggest that the effects of valproate in women with epilepsy could be due to valproate exacerbating an already disturbed system, which is unable to compensate for its androgen-promoting actions.

More information is needed about the use of valproate in women with epilepsy and its risk of inducing PCOS. Common sense would dictate that, for a woman with epilepsy who has evidence of PCOS, the use of valproate should be judiciously considered.

Finally, it appears that PCOS occurs significantly more often in women with epilepsy than in others, especially among certain groups. Studies using much larger groups will be needed for doctors to find out the details of how PCOS is related to the many types of epilepsy and seizure medicines. The exact mechanisms of other reported cases of correlation between PCOS and neurological disorders are not clearly defined; it may be related to a dis-hormonal state in PCOS.

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