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REVIEW

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Epilepsy and polycystic ovary syndrome: where is the link?

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Abstract Several reports in the literature describe an increased prevalence of polycystic ovary syndrome (PCOS) in women with epilepsy. The possible pathogenesis of the association between epilepsy and PCOS is not clear yet, and different hypotheses have been proposed: while some authors suggest that epilepsy may affect the hypothalamic control of reproductive function, others propose a pathogenic role of the antiepileptic drug valproate. In this article we review the literature on the subject, and propose a pathogenic theory in which both epilepsy and valproate play different and significant roles in inducing reproductive endocrine disturbances in women with seizures.

Key words Epilepsy • Polycystic ovary syndrome • Valproate • Menstrual irregularities • Hyperandrogenism • Polycystic ovaries

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Epilepsy and PCOS: a long story, still controversial

The first description of an association between epilepsy and PCOS can be traced in the literature to as early as 1904, when Spratling [1] reported that women with epilepsy often present with enlarged and polycystic ovaries. This observation was apparently unnoticed by the medical community and 80 years had to pass before such problems were mentioned again in a scientific report. It was in fact 1984 when Herzog and his group [2] published a report describing a high frequency of polycystic ovary syndrome (PCOS) in women with temporal lobe epilepsy (TLE), followed by a second report in 1986 [3] describing similar results in a larger sample of TLE women. In 1988 Bilo and coworkers [4] reported similar findings in a smaller sample of women with idiopathic generalised epilepsy (IGE). In 1993, nearly 10 years after Herzog's report, Isojarvi and coworkers [5] published a report describing a high occurrence of menstrual disorders and/or polycystic ovaries and/or hyperandrogenism in women with epilepsy; in the following years this group published many other reports (see in [6]), always confirming their earlier findings. Finally, because of the growing concern for specific women's issues in epileptology, several recent studies have been devoted to the investigation of the reproductive endocrine status in women with epilepsy [6].

Unfortunately, the results emerging from these studies are widely contrasting, both with regard to the prevalence of PCOS among women with epilepsy, which varies widely in different reports, and with regard to the possible causes of this association, which have been attributed by some authors to a disturbing effect of epilepsy on the hypothalamus and by others to the effects of a widely used antiepileptic drug, sodium valproate (VPA).

In this article we will review the pathogenic theories regarding the association between PCOS and epilepsy and will briefly examine the data from literature regarding the prevalence of PCOS among women with epilepsy, with the aim of offering some tentative conclusions on this controversial issue.

PCOS: definition, prevalence and pathogenesis

What is PCOS? An answer to this question is of fundamental importance before discussing the association between PCOS and epilepsy. In the last few years a substantial uniformity has been reached in the diagnostic criteria for PCOS, and a National Institute of Health (NIH) Conference in 1990 standardised them, at least in the USA [7]. Table 1 summarises the clinical and laboratory findings of the "classical", full blown syndrome. This complete picture, however, is far from being the most common in women with PCOS, who most often present with only a few of these symptoms, which can, additionally, be differently represented at different times of their lives. Indeed, the diagnosis of PCOS in women who present with fewer of the classic symptoms has been the object of considerable controversy [8], and consequently the diagnostic standards emerging from the NIH Conference of 1990, rather than describing the complete pattern of the classical syndrome, do actually suggest the "minimal" diagnostic criteria for PCOS: that is, the clinical/laboratory findings that are both necessary and sufficient for the diagnosis of PCOS. As shown in Table 2, an association of menstrual irregularities and hyperandrogenism (either clinical or biochemical) must be present, and other causes of hyperandrogenic anovulation must be ruled out. It must be underlined that the "typical" (echographic) finding of polycystic ovaries has not been included in the NIH minimal diagnostic criteria, having been considered insufficient and unnecessary to make a diagnosis of PCOS. It is in fact now universally accepted that the isolated finding of polycystic ovaries should not be considered as an abnormal feature [8], as it is described on ultrasonography in nearly 20% of normal women [8].

Table 1 Clinical and laboratory findings of PCOS

Clinical data
Menstrual irregularities (oligomenorrhoea/amenorrhoea)
Hirsutism, acne, androgenic alopecia
Obesity
Laboratory data
Hyperandrogenism
Increased LH/FSH rate
LH hyperpulsatility
Hyperresponsivity of LH to GnRH
Reduced glucose tolerance/diabetes
Polycystic ovaries

Table 2 "Minimal" diagnostic criteria for PCOS (NIH Conference, 1990)

Menstrual irregularities (oligo/anovulation)
Hyperandrogenism either clinical or biochemical
Exclusion of other diseases (i.e., other known causes of female hyperandrogenism such as congenital adrenal hyperplasia, androgen-secreting tumours and hyperprolactinaemia)

In a recent workshop held in Rotterdam, the European and American Societies of Reproductive Medicine [9] actually proposed new diagnostic criteria, which also include the morphologic picture of polycystic ovaries. However, the new criteria are still the object of wide discussion [10–12], and presently the NIH criteria are still considered as the most authoritative guideline and as such are used in papers dealing with the diagnosis and epidemiology of PCOS.

It is worth noting that the most recent reports on PCOS prevalence in premenopausal women, obtained following NIH criteria for diagnosis, describe remarkably similar values, with a prevalence of 6.6% in USA [13], 6.5% in Spain [14] and 6.8% in Greece [15]. With these prevalence values, PCOS is considered the most frequent reproductive endocrine dysfunction in women. However, this syndrome involves far more than the reproductive system, as it is often associated with reduced glucose tolerance, type II diabetes and increased cardiovascular risk. Moreover, because of unbalanced oestrogen secretion, women with PCOS have an increased risk of developing endometrial cancer.

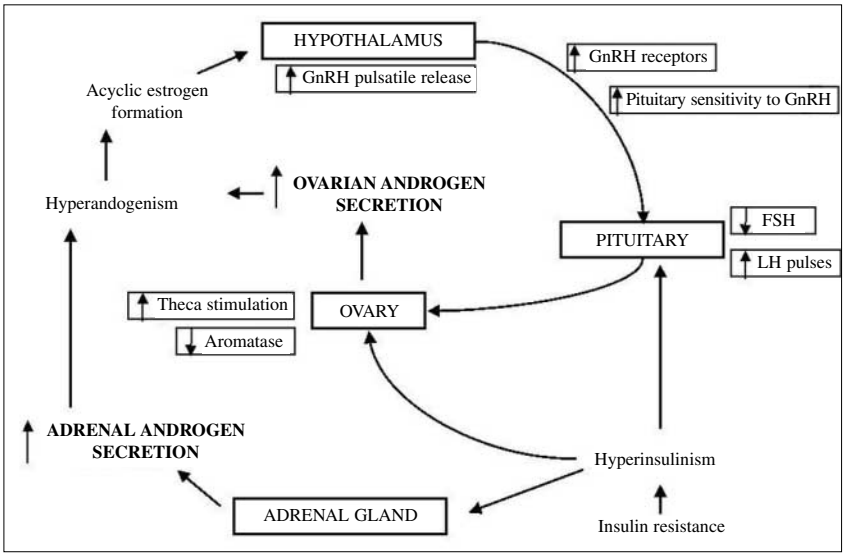

Fig. 1 Pathogenesis of PCOS: suggested mechanisms

The pathogenesis of PCOS is still poorly understood and it is unlikely that a single mechanism can be applied to all PCOS cases. A possible key role in pathogenesis has been attributed by different authors to the hypothalamic-pituitary unit, to the ovary, to the adrenal gland or, most recently, to insulin resistance. In the end, however, all these units do reciprocally interact in the maintenance of laboratory and clinical alterations (Fig. 1) and it is reasonable to suppose that different pathogenic mechanisms can be involved in different patients.

Polycystic ovary syndrome in women with seizures: the epilepsy theory

Between 1984 and 1988 two research groups described overrepresentation of PCOS in three series of women with epilepsy [2–4] (TLE in the two series from Herzog et al. and IGE in the series from Bilo et al.). Neither group found any significant association between occurrence of reproductive endocrine disturbances and use of antiepileptic drugs (AEDs), as most of the patients with PCOS and epilepsy were untreated at the time of the diagnosis or had already reported menstrual irregularities before AED therapy was started.

Considering these results, both groups independently focused their attention on the possible pathogenic mechanisms linking the epileptic disorder with the development of PCOS, and hypothesised that epilepsy itself might be responsible of a derangement of hypothalamic function leading to reproductive dysfunction.

How could epilepsy lead to PCOS? A possible disruptive effect of epileptic disorders on hypothalamic function has been suggested. The normal menstrual cycle is the result of complex interacting processes among hypothalamus, pituitary and ovaries. A key structure is a "pulse generator" in the mediobasal hypothalamus, responsible for rhythmic activation of hypothalamic GnRH neurons and consequent "pulsatile" release of GnRH from their terminals. The maintenance of pulsatile GnRH release within a critical range of amplitude and frequency is essential for normal gonadotropin secretion and therefore for normal folliculogenesis and ovulation [16].

Seizure disorders might have a definite role in altering the regularity of these events. Medial temporal lobe structures have extensive, reciprocal, direct connections with hypothalamic regions that are involved in reproductive endocrine regulation, and it is consequently possible that paroxysmal discharges involving these areas may disrupt normal hypothalamic-pituitary function [3]. Moreover, also the generalised epileptic discharges that characterise IGE may derange the normal functioning of the GnRH pulse generator, as supported by several reports [17–19] that describe significant increases in plasma PRL and, less consistently, in gonadotropins after epileptic seizures (primarily generalised tonic-clonic and complex partial seizures). These hormonal elevations are not due to a non-specific stress effect nor to the intense motor activity that may occur during seizures, but are thought to result from spreading of paroxysmal discharges within the hypothalamic areas, which control pituitary reproductive hormones [17, 18].

Further support for this theory comes from the finding of altered luteinising hormone (LH) pulsatility in untreated women with epilepsy. As LH pulsatility in peripheral circulation strictly reflects GnRH pulsatility in the pituitary portal circulation, the study of LH pulses is nowadays considered the most accurate way of studying reproductive endocrine function at the hypothalamic level in humans. Our group [20] assessed the basal hormone levels and the LH pulsatile pattern in midfollicular phase in a group of drug-free epileptic normal cycling women, compared to normal controls. No significant differences in hormone levels were found between patients and controls; ovulation was documented in all subjects. However, the LH pulse frequency was significantly higher in epileptic females. Both epileptic patients and control subjects had normal body weight and normal menstrual and ovulatory function; none received psychotropic or hormonal drugs or engaged in excessive physical activity. The only difference between patients and controls was the presence of epilepsy in the former group. We consequently suggested that the abnormal LH pulsatile pattern was most probably due to epilepsy itself, and that this epilepsy-related, subclinical abnormality of reproductive hypothalamic function might represent the first change leading in time to a clinically overt endocrine dysfunction such as PCOS. Alterations in LH pulsatility in treated epileptic patients were successively described by other groups [21–24], whose data also indicated a possible role of seizure disorders in disrupting LH pulsatile release.

Another report from our group [25] investigated the relationships between gonadotropin secretion and paroxysmal activity. Gonadotropin secretion was monitored for a 5-h period with blood samples taken every 10 min under continuous EEG monitoring in drug-free epileptic women and in controls. While in control subjects secretion of LH and follicle-stimulating hormone (FSH) showed a constant pattern throughout the study, in epileptic women these hormones showed a significant rise when paroxysmal activity increased, once again suggesting a possible spreading of epileptiform discharges within hypothalamic areas.

The possibility that a seizure disorder may be responsible for hypothalamic dysfunction is fascinating, but quite difficult to demonstrate. The impact of seizure disorders on the hypothalamus is probably very complex and not necessarily limited to the acute effects of spreading of paroxysmal activity. Seizure disorders are accompanied by, and in some cases probably caused by, neurotransmitter imbalance possibly related to genetic factors. Central neurotransmitters modulate brain susceptibility to

seizures, and probably also play an important role in the pathogenesis of human epilepsies. As many of the neurotransmitter systems involved in the control of the seizure threshold are also neuroendocrine modulators for the release of GnRH, it is reasonable to suppose that a neurochemical imbalance might at the same time be responsible for both the lowering of seizure threshold and the dysfunction of GnRH secretion [4, 20, 26]. This kind of imbalance probably acts as a pathogenic factor independently from actual seizure control, being only in part related to seizure frequency.

Polycystic ovary syndrome in women with seizures: the valproate theory

In 1993 Isojarvi and coworkers [5] reported a high occurrence of reproductive endocrine abnormalities in a large series of women with epilepsy, noticing a possible relationship of this phenomenon with the use of VPA.

Actually, the possible association between VPA use and menstrual dysfunction had already been suggested by several earlier anecdotal reports of individual epileptic patients or of small series of epileptic women using VPA [27–31]. However, the report from Isojarvi and coworkers was the first to describe such problems in a large series of patients, and was followed in the subsequent years by an impressive series of reports from the same group, all confirming their earlier data (see in [6]). In particular, an increased prevalence of polycystic ovaries, hyperandrogenism and menstrual irregularities (not necessarily associated in the same patient and, consequently, not necessarily giving rise to a picture of PCOS) were described in epileptic female patients treated with VPA significantly more often than in controls or in patients treated with other AEDs.

Several theories have been proposed to explain the possible pathogenic mechanisms of VPA-induced endocrine disturbances. As VPA use has often been associated with weight increase, in their earlier reports Isojarvi et al. suggested that weight gain could be the main pathogenic factor leading to reproductive endocrine disturbances [32] in women with epilepsy, proposing that VPA-induced obesity might lead to insulin resistance and consequently hyperinsulinaemia, resulting in direct and/or indirect hyperstimulation of the ovaries, hyperandrogenism and finally in ovarian polycystic changes. However, further studies from the same group [33] challenged the theory that VPA-induced obesity might have a primary role in inducing endocrine and metabolic changes and suggested that increase of androgen production might be the first abnormal finding originating from VPA use in epileptic women. However, VPA-related obesity is still considered to play a possible additional role in the development of endocrine disturbances, as polycystic ovaries, hyperandrogenism and menstrual disorders were more common in obese than in lean women treated with VPA [33].

How could VPA use lead to hyperandrogenism? A possible effect on gonadotropin release, mediated by a VPA-induced increase of GABA levels affecting GnRH secretion, is considered unlikely, as VPA-treated hyperandrogenic patients have normal LH levels [5]. Alternatively, a direct effect of VPA on androgen formation has been suggested [5]. Even though the evidence of an inhibitory effect of VPA on testosterone metabolism is indirect and only speculative at present, VPA is thought to inhibit the glucoronidation of several substances [34]. Consequently, a possible VPA-mediated inhibition of the conversion of testosterone to oestradiol could be hypothesised, with consequent increase of testosterone concentrations, arrest of follicular maturation and development of polycystic changes in the ovaries.

Recently, Nelson-Degrave and coworkers [35], testing the activity of VPA on androgen biosynthesis in ovarian theca cells isolated from follicles of normal cycling women, suggested that VPA may increase ovarian androgen biosynthesis, inducing changes in chromatin modifications (histone acetylation) that augment transcription of steroidogenic genes. The same research group [36], in a subsequent paper in which the gene expression profiles of untreated normal, VPA-treated normal and untreated PCOS theca cells were compared, reported that VPA-induced and PCOS-induced changes in gene expression were similar, resulting in enhancement of Akt/PKB signal transduction in human theca cells. These important data provide the first biochemical evidence to support a role for VPA in the genesis of PCOS-like symptoms.

The results of all these studies are very interesting and raise a very important point. The possibility that an effective, widely used AED may give rise to unwanted endocrine side effects, possibly resulting in reduced fertility and increased cardiovascular risk, deserves full consideration both from researchers and clinical epileptologists, and may suggest caution in prescribing VPA in women with epilepsy, particularly in the peripubertal period.

Polycystic ovary syndrome and epilepsy: review of the literature

After the reports from Isojarvi and coworkers, the possible association between PCOS and epilepsy received wide attention from the scientific community, and research groups from all over the world published reports describing the reproductive endocrine status of women with epilepsy. The increasing interest in this subject was a great opportunity to clarify the debated issues – is PCOS really overrepresented in women with epilepsy? And if this is

true, is this overrepresentation linked to VPA use, or is it independent from the use of this drug?

Exploring the literature: problems and pitfalls

Unfortunately, no consistency of diagnostic criteria and diagnostic tools is found in papers dealing with occurrence of PCOS in women with epilepsy, and consequently the results are very often difficult to interpret and virtually impossible to compare. Many authors still confuse the concept of PCOS with that of polycystic ovaries; others still invoke a supposed lack of uniformity of criteria for diagnosis of PCOS as an excuse to use personal views on this subject, completely ignoring the results of the 1990 NIH Conference or of other authoritative guidelines. Another frequent problem is presentation of results. Many authors, even when performing a complete evaluation of patients, present the results only as means of hormonal values or as percentages of abnormal findings observed in different subgroups, without giving any information on individual data that allow determination of the prevalence of PCOS in the studied sample.

However, even when patients are studied individually and information on menstrual cyclicity and androgen assessment are given, allowing a diagnosis based on NIH criteria, results emerging from different series are always difficult to compare, due to methodological problems in the collection and analysis of data. Collection of menstrual history from patients may give quite different results if patients are keeping menstrual diaries or if they are just recalling their menstrual pattern without a written record; prospective study of patients with direct recording of menstrual cyclicity over time surely gives the best results, provided that the time of observation is long enough. The use of software specifically devoted to the collection of clinical data over time, such as the Chronorecord software, could be useful in these situations. In addition, definition of menstrual irregularities is not given in all studies, and may vary in different series, so that results might actually not be comparable. Definition of hyperandrogenism also varies from series to series: many studies fail to evaluate clinical hyperandrogenism and/or the complete laboratory androgen pattern. Finally, in the evaluation of ovarian morphology the use of transabdominal or transvaginal scanning may have different degrees of accuracy, and consequently influence the results of the investigation. MRI scanning of the pelvis, recently proposed as a more accurate diagnostic tool [37], is employed only in a few studies.

The wide variability observed in the characteristics of the patient series in the different reports also gives rise to possible inaccuracies and poor comparability of results. Only in some of the study projects were patients enrolled consecutively, while this is probably the best way to avoid selection bias in a prevalence study. Patient groups in different reports differ widely as to the percentage of subjects with different epilepsy types or different AED therapy; most authors do evaluate results separately according to therapy groups but not according to epilepsy types, which might also be a relevant factor in influencing the endocrine status. Moreover, due to the concern about possible side effects of VPA on reproductive health, patients on AED polytherapy are usually divided into subgroups depending on the presence or absence of VPA in their therapeutic regimen; this choice may lead to overlooking other possible problems induced by other AEDs whose respective influence on the endocrine status is not investigated. Regarding reproductive endocrine status, duration of therapy regimens, age at which therapy was started, type of AEDs used in the past, epilepsy severity and location of seizure focus are all possible relevant factors, which vary greatly among patients within the same series and among different series. Finally, the small size of most patient series, especially when divided in subgroups, is a critical factor, as specifically underlined in other review articles dealing with this issue [38, 39].

Considering all these issues, the inconsistency of results in the different series is not surprising. With these limitations in mind, however, some tentative conclusions can be proposed. For the purpose of this review, we have compared only reports in which an estimation of prevalence of PCOS is possible employing NIH criteria for diagnosis, even though in some instances we had to correct the prevalence values given by the authors. Besides reviewing the prevalence of PCOS, we also compared the prevalence of menstrual irregularities, hyperandrogenism and polycystic ovaries in the reports that give such information, in order to have a better insight of the problem. The relationships between endocrine disturbances and VPA use have also been assessed.

Exploring the literature: is there an increased prevalence of PCOS in women with epilepsy? Is this related to the use of VPA?

Women with epilepsy seem to have a high prevalence of menstrual disturbances [3, 4, 33, 40–46]. With the exception of the report of Murialdo et al. [41], which describes a 10.8% prevalence of menstrual irregularities (for which no specific definition is given in the method section), in all the series in which such information is offered the prevalence of irregular menstruations, ranging from 21.8% to 56.0%, is quite higher than the 7% prevalence described in the general population in a recent epidemiological study [47] and is observed also in drug-free patients. Although comparisons with the general population must be evaluated with caution, it must be stressed that a high occurrence

of menstrual dysfunctions in women with epilepsy has been reported for a long time [48–54]. The use of VPA does not seem to be a relevant factor in the development of menstrual disturbances. While the series from Isojarvi et al. [33] reports a striking and significant difference in the prevalence of menstrual dysfunctions between VPA patients (59.5%) and CBZ subjects (11.4%), in the majority of the other reports distribution of menstrual irregularities is quite similar in different therapy groups [4, 41–45], with prevalence in VPA patients being usually even slightly lower. Besides Isojarvi, the only other series describing a higher, but not significant, prevalence of menstrual disturbances in VPA subjects is the one reported by Murialdo et al. [40] in which, however, the VPA group includes also CBZ patients and in which the prevalence of VPA monotherapy is not given.

Individual data on hyperandrogenism are more rarely given [3, 4, 33, 43–46]. Moreover, some of these reports only offer results on hirsutism without a laboratory evaluation of androgens, and are consequently hardly useful for comparison purposes. In the reports that offer laboratory data [3, 4, 33, 43], hyperandrogenism is usually overrepresented, with a single report describing a 4.5% prevalence [44] and all the others ranging from 15.0% to 26.0% [3, 4, 33, 43]. When a comparison among VPA users and non-VPA users is performed [4, 33, 43–46], prevalence of hyperandrogenism is higher in VPA patients in most reports [33, 44–46], although not significantly.

Finally, a high prevalence of polycystic ovaries (>30%) is reported in half of the studies [33, 43, 55, 56] in which this finding was systematically evaluated, most of which employed transvaginal scanning or MRI rather than transabdominal scanning, which is associated with a lower prevalence [4, 40, 41, 45]. Most reports describe a higher, but not significant, prevalence of polycystic ovaries in non-VPA users [4, 41, 45, 46, 55]; a significantly higher prevalence of polycystic ovaries in VPA users is once again observed only in Isojarvi's series [33].

How do all these data merge regarding PCOS prevalence in women with epilepsy? As we have already mentioned, the prevalence of PCOS in the general population is about 6.6% when NIH diagnostic criteria are employed. For comparative purposes, we will now necessarily consider only reports in which PCOS in patients with epilepsy is diagnosed, or may be diagnosed, using the same criteria [2–4, 33, 40, 43, 44]. In most of these reports, prevalence of PCOS is higher than 6.6%, but shows a high variability, ranging from 12.5% to 26.0%; there is only one report [44] in which it is considerably lower (2.3%). It must be stressed than the highest prevalence comes from the report [43] in which the evaluation of patients is most careful, with assessment not only of menstrual cyclicity but of ovulation status as well, and evaluation of both clinical and laboratory hyperandrogenism. Due to the small number of observations, the possible role of VPA in PCOS prevalence is difficult to evaluate if we consider only the reports in which a NIH diagnosis can be obtained; widening our analysis to all reports [4, 33, 42–46, 55, 56] in which prevalence of PCOS is given, even if with different criteria, we observe that most reports describe a higher prevalence of PCOS in VPA-treated patients [33, 44, 45, 55, 56], even though this finding is statistically significant only in two reports [33, 56].

In summary, we can conclude that women with epilepsy show menstrual dysfunctions significantly more often than the general population; this finding, which has been known for 50 years, does not seem to be related to the use of any AED and can be observed also in drug-free patients. Aspecific stress, caused by a chronic disease with a strong impact on quality of life, could play a relevant role in the pathogenesis of menstrual irregularities. However, women with epilepsy have also a high prevalence of polycystic ovaries and of hyperandrogenism. As we have mentioned earlier, the finding of isolated polycystic ovaries is not *per se* abnormal and, in the absence of large prospective studies monitoring reproductive health in epileptic women with isolated ovarian changes, there is no reason to consider it as a marker of endocrine abnormality. However, its elevated prevalence in women with epilepsy is intriguing, and its possible meaning is worth speculating. Polycystic changes are not specifically linked to the use of VPA in most series describing epileptic women and are frequently observed also in drug-free epileptic patients; for this reason, they seem to be related to the epileptic disorder rather than to AED therapy. However, both the finding of hyperandrogenism and the specific endocrine disorder of PCOS, with its well known impact on fertility and on cardiovascular health, are more frequently observed in epileptic women using VPA. Finally, the prevalence of PCOS in women with epilepsy is elevated in the majority of reports, even though there is considerable variability between series.

Polycystic ovary syndrome in non-epileptic women treated with valproate: settling the controversy

Recently, valuable help in settling the issue of the pathogenic mechanisms of PCOS overrepresentation in women with epilepsy has come from researchers who have evaluated the endocrine status in women receiving VPA for bipolar disorders, thus examining the effect of VPA separately from that of epilepsy.

The reports from O'Donovan et al., presented in a congress abstract [57] and then in a full report [58], display several shortcomings, which warrant caution in the interpretation of the results. To begin with, there are several differences between the results displayed in the congress presentation and those given in the full report, up to the point

that the conclusions are completely contrasting; as there are only minimal changes in the patient population between the two reports, it is difficult to explain such contrasting results. Information about menstrual irregularities and hyperandrogenism was obtained only from a self-reported questionnaire, and only patients who received VPA and had current menstrual abnormalities underwent a clinical and laboratory evaluation and could be diagnosed as having PCOS. However, no valid comparison is possible on this point with non-VPA bipolar patients, who were not submitted to any clinical or laboratory study. Finally, the pathogenic relationship between the endocrinological disturbance and the use of VPA remains to be proved, as the authors themselves underline that a temporal association between VPA use and clinical disturbances is lacking in several cases. For a more detailed analysis of these reports, we suggest a consultation of more extensive reviews on the subject [6, 59].

Rasgon et al. [60] evaluated the endocrine status of 80 bipolar women (in a previous pilot study the evaluation was limited to 22 subjects [61]) treated with VPA (alone or in association) or with other antimanic agents. Prevalence of PCOS in the total group of bipolar patients was 5%, specifically with 8% prevalence in VPA patients and 0% in non-VPA patients; when considering only PCOS cases with onset after VPA treatment, prevalence was 6% in the VPA group and 0% in the non-VPA group. We can conclude that prevalence of PCOS in bipolar patients does not differ from prevalence in the general population; it is (not significantly) higher in VPA users, but again with values only slightly different from the general population. In addition, bipolar women in this series showed a very high prevalence of menstrual abnormalities, often preceding the use of antimanic drugs but with a considerable increase after medication. This was true especially after VPA use. These disturbances, however, were most often limited to altered bleeding patterns (menorrhagia) while disturbances in menstrual cyclicity (oligomenorrhoea and amenorrhoea) consistent with ovulatory disorders and PCOS were less represented. The same group [62] recently reported a 2-year longitudinal evaluation in 25 women with bipolar disorder, treated with VPA, lithium or atypical antipsychotics, confirming high rates of menstrual abnormalities, hyperandrogenaemia and insulin resistance in the whole group. Valproate use was associated with an increase in total testosterone over time, but rates of oligomenorrhoea and clinical hyperandrogenism did not differ between medication groups.

In the report from McIntyre et al. [63], describing 38 bipolar female patients treated with VPA or lithium, menstrual irregularities and hyperandrogenism were, when considered separately, significantly more represented in VPA women than in lithium patients. PCOS prevalence was also higher in the VPA group (39% *vs*. 19%), but not significantly; on the whole, these results – in disagreement with those from Rasgon's group – show a very high prevalence of PCOS in bipolar patients, especially in VPA users, but with high values also in the lithium group.

Akdeniz et al. [64] compared the endocrine status of women with epilepsy and women with bipolar disorder, describing 15 bipolar patients treated with lithium, 15 bipolar patients treated with VPA and 15 epileptic patients treated with VPA. Menstrual irregularities were observed in 46.7% of the VPA-treated epileptic women, 20% of the VPA-treated bipolar women and 0% of the lithium-treated bipolar women. Laboratory hyperandrogenism was observed in both VPA groups but not in the lithium group; however, only in women with epilepsy was this finding associated with hirsutism. The authors conclude that even though VPA treatment is associated with raised testosterone levels in both bipolar and epileptic women, the latter have an increased susceptibility to clinical endocrine dysfunction.

Finally, in a very recent report Joffe et al. [65] evaluated 230 women with bipolar disorder, comparing the incidence of self-reported oligoamenorrhoea with hyperandrogenism that developed after antimanic treatment. Oligoamenorrhoea with hyperandrogenism developed in 9 (10.5%) of 86 women on valproate and in 2 (1.4%) of 144 women on other treatments (p=0.002), suggesting a significant association of PCOS with VPA use in bipolar women. Consequently, the authors suggest that VPA use rather than epilepsy *per se* could be responsible for overrepresentation of PCOS in epileptic women as well. The authors underline that the percentage of women developing PCOS features on VPA is much lower in their study than that reported in many of the studies describing epileptic populations [5, 56] and attribute this difference mainly to the fact that these studies have not utilised accepted criteria for the diagnosis of PCOS. However, there are also studies on epileptic populations in which well accepted criteria for diagnosis of PCOS have been employed [43] and in which a considerably higher percentage of women with epilepsy (26%) were diagnosed with PCOS, without a significant association with the use of VPA. However, the report of Joffe et al. is specifically focused on patients with new-onset of PCOS symptoms developed after medication use, and consequently reports incidence of PCOS rather than prevalence. Consequently, caution must be employed in comparing the results from this study to those coming from studies describing prevalence.

In conclusion, bipolar patients seem to show an increased risk of developing endocrine disturbances or PCOS when treated with VPA in respect to other antimanic medications. However, in most reports on this issue prevalence of PCOS in VPA-treated bipolar patients is lower than that reported in epileptic patients. One could speculate that the impact of VPA on endocrine status is not as strong in bipolar patients as in women with epilepsy, suggesting that these latter may have additional risk factors leading to the development of PCOS.

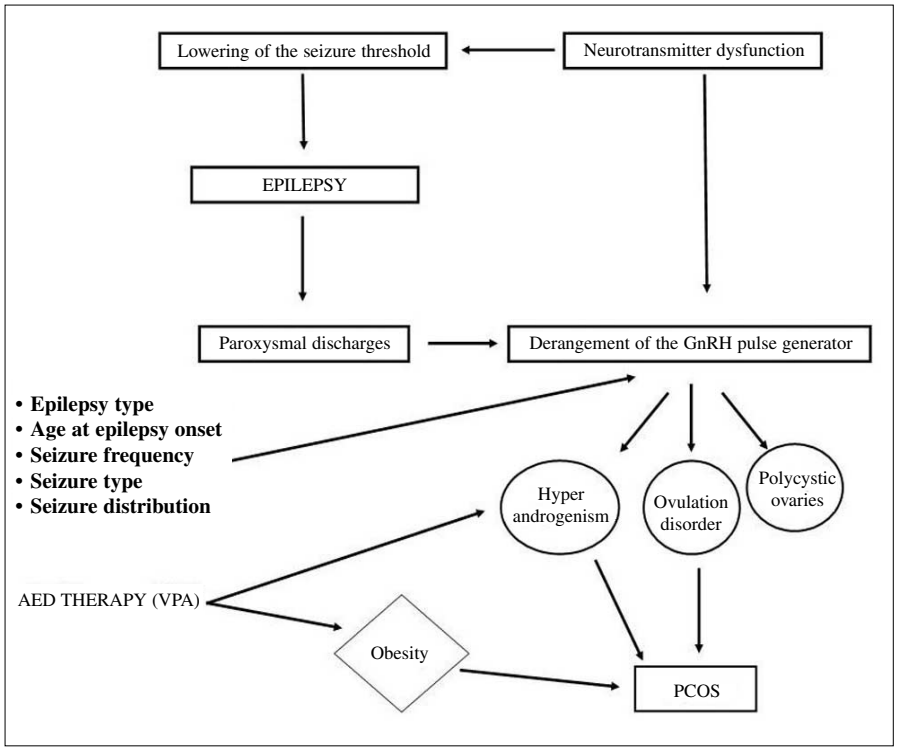

Fig. 2 Epilepsy and PCOS: suggested links. Epilepsy may lead to a derangement of the GnRH pulse generator because of spreading of paroxysmal activity within the hypothalamus and/or of neurotransmitter imbalances associated with the seizure disorder. The dysfunction of GnRH secretion may be subclinical or give rise to clinical disturbances such as hyperandrogenism and/or ovulation disturbances and/or polycystic ovaries. The possible evolution from the subclinical stage to an overt clinical disturbance is probably influenced by several additional factors, some of which could be related to the characteristics of the seizure disorder, others to the use of antiepileptic drugs. The use of valproate in particular seems to be associated with the development of PCOS. This VPA effect is most probably due to its hyperandrogenic activity, but also obesity, often associated with VPA use, possibly plays an additional role, as weight gain may act as a modifier that might contribute to the genesis and maintenance of hyperandrogenic chronic anovulation

Conclusions: different roles of epilepsy and VPA in development of PCOS

The association between epilepsy and PCOS is still a debated issue [66]. Based on the finding of abnormal LH pulsatility in drug-free, endocrinologically normal epileptic women reported in our previous study [20], we proposed [20, 26] that a derangement of the GnRH pulse generator might be observed in women with epilepsy, caused by spreading of paroxysmal activity within the hypothalamus and/or by neurotransmitter dysfunctions, which accompany seizure disorders; this abnormal finding is independent from AED use, may be observed in normally ovulating epileptic women and does not necessarily lead to clinical reproductive endocrine disturbances. The possible evolution towards a clinical dysfunction is probably dependent on several different additional factors, whose relative importance may be difficult to evaluate (Fig. 2). As a result of this increased susceptibility to hypothalamic dysfunction, a high percentage of women with epilepsy will present with menstrual disorders, and, possibly, polycystic ovaries. The further possible evolution towards a definite clinical disease, specifically PCOS, seems conversely to be more often related to the use of AEDs, and in particular of VPA. This VPA effect is most probably due to its hyperandrogenic activity, recently demonstrated *in vitro* on human theca cells; weight gain, often associated with VPA use, may also play an additional role. In fact, even though obesity is not considered as a prerequisite in the development of PCOS, weight gain may act as a modifier that might contribute to the genesis and maintenance of hyperandrogenic chronic anovulation [8].

Sommario *Diverse evidenze in letteratura suggeriscono che nelle donne con epilessia vi sia un'aumentata prevalenza di Sindrome dell'Ovaio Policistico (PCOS). Peraltro la possibile patogenesi di questo fenomeno non è ancora chiarita, e, mentre alcuni autori suggeriscono che l'epilessia di per sé disturbi il controllo ipotalamico della funzione riproduttiva, altri propongono che il farmaco antiepilettico valproato sia determinante nell'indurre la disfunzione endocrino riproduttiva. Questo articolo esamina la vasta letteratura sull'argomento e propone una teoria patogenetica unificatrice, in cui sia l'epilessia che l'uso del valproato giocano ruoli diversi e rilevanti nel determinismo della PCOS delle pazienti con epilessia.*

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