Original Article

Polycystic ovary syndrome in patients on antiepileptic drugs

Lakshminarayanapuram G. Viswanathan, Parthasarathy Satishchandra, Bipin C. Bhimani, Janardhan YC Reddy[1], Batchu S. Rama Murthy[2], Doddaballapura K. Subbakrishna[3], Sanjib Sinha

Departments of Neurology, [1]Psychiatry and [3]Biostatistics, NIMHANS, [2]Srinivasa Ultrasound Scan Center, Shankarpuram, Bengaluru, Karnataka, India

Abstract

Objective: This study aims to discuss the prevalence of polycystic ovary (PCO) and Polycystic ovary syndrome (PCOS) in women with epilepsy (WWE) on valproate (VPA), carbamazepine (CBZ), or phenobarbitone (PB), drug naive WWE and women with bipolar affective disorder (BPAD) on VPA. **Materials and Methods:** This prospective study included 190 women aged 18–45 years, who had epilepsy or BPAD (on VPA), and consented for study. Patients were grouped as Group 1 (n = 40): WWE on VPA, Group 2 (n = 50): WWE on CBZ, Group 3 (n = 50): WWE on PB, Group 4 (n = 30): drug naïve WWE, and Group 5 (n = 20): women with BPAD on VPA. All women were interviewed for medical, menstrual, drug and treatment history, nature of epilepsy, and seizure control. Chi-square test and Fisher's exact test were done to compare results between the groups. **Results:** Fifty-two women (52/190; 27.4%) had menstrual disturbances, in which oligomenorrhea was the most common (55.8%). There was a significant difference in the occurrence of PCOS in patients on VPA *versus* normal population (P = 0.05) and patients on other antiepileptic drugs (AEDs) (P = 0.02). There was, however, no significant difference in the occurrence of PCO between patients on VPA and the untreated epileptic women. VPA group (Epilepsy + BPAD) had a significantly higher occurrence of obesity than other treatment groups (P = 0.043, OR = 2.11). **Conclusions:** The study observed significantly higher occurrence of PCO in patients on VPA compared to other AEDs and the normal population. The importance of proper clinical evaluation before initiating VPA is highlighted.

Key Words

Antiepileptic drugs, epilepsy, Polycystic ovary syndrome, valproate

For correspondence:
Dr. Parthasarathy Satishchandra, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bengaluru - 560 029, Karnataka, India.
E-mail: drpsatishchandra@yahoo.com

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Introduction

Epilepsy is a common disorder affecting about 50 million in the world and about 50% of them are women.[1] Women with epilepsy (WWE) have a large psychosocial burden to bear along with other important issues related to fertility/pregnancy and marital life. Around half of the epileptic women have menstrual abnormalities and more of anovulatory cycles than the normal population.[2] One of the major causes of the menstrual abnormalities is polycystic ovary syndrome (PCOS) that affects 5–10% of women in the reproductive age group. Polycystic ovary (PCO) is defined as 10 or more subcapsular cysts, measuring 2–8 mm in diameter, found within an ovary that has thickened, echogenic stroma.[3] PCO occurs in 20% of premenopausal women[3,4] and does not indicate dysfunction alone. When patients with PCO have features of obesity and features of hyperandrogenism as well, they are diagnosed to have PCOS. The revised consensus definition of PCOS consists of the presence of polycystic ovaries and at least one of the two following criteria: (a) oligoovulation/anovulation and

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(b) clinical or biochemical evidence of hyperandrogenism [high levels of testosterone or increased luteinizing hormone/follicle-stimulating hormone (LH/FSH ratio)].[5] Studies with large groups of WWE have shown that PCOS and ovulatory dysfunction occur at higher than expected rates in WWE[6] with evidence of exacerbation of menstrual dysfunction associated with valproate (VPA) use.[7] VPA is a widely used antiepileptic drug (AED) and remains the drug of choice for various idiopathic generalized epilepsies. It is associated with high levels of serum testosterone and other androgens.[8,9] Isojarvi *et al*. in 1993 were the first group to report an association between VPA and PCO.[7] About 50% of the 28 WWE treated with VPA monotherapy had oligomenorrhea, amenorrhea, or prolonged menstrual cycles. More data might still be required to substantiate the role of hormonal abnormalities in WWE attributable to the disease *per se*, or treatment with AEDs such as VPA, or both, and among woman on VPA due to reasons other than epilepsy.

This study aims to discuss the prevalence of PCOS and PCO in WWE on AEDs such as VPA, carbamazepine (CBZ), or phenobarbitone (PB); drug naive WWE not on any treatment and women with bipolar affective disorder (BPAD) on VPA; and make an attempt to draw conclusions regarding the association of epilepsy, AEDs, and PCO/PCOS.

Materials and Methods

This prospective hospital-based study was conducted over 2 years at a tertiary care center and university hospital in South India for neuropsychiatric disorders. One hundred and ninety women (n = 190) in their reproductive age, *viz*., 18–45 years, and having epilepsy or BPAD (on VPA) were recruited. This was not a consecutive sampling. Epilepsy was defined as per the international league against epilepsy (ILAE), 1989 definition. The inclusion of BPAD was per Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) codes. Women who did not give consent for the study, who were on polytherapy, on hormonal preparations, did not undergo ultrasound examination for PCO, and had undergone hysterectomy/oophorectomy were excluded. Written informed consent was obtained from all the study subjects. Institute Ethics Committee approval was obtained.

After recruitment, 190 patients were divided into 5 groups: Group 1 (n = 40; age: 19.5 ± 3.1 years) included WWE on sodium VPA; Group 2 (n = 50; age: 20.3 ± 4.9 years) included WWE on CBZ and Group 3 (n = 50; age: 23.6 ± 6.8 years) included WWE on PB; Group 4 (n = 30; age: 22.3 ± 4.1 years) included WWE who were drug naïve at recruitment and Group 5 (n = 20; age: 29 4 ± 2.1 years) included women with BPAD on sodium VPA. The data of the study group was compared with the available data from normal population which is about 20%.[4,10]

All women were interviewed for medical and menstrual cycle history, type, and nature of seizures/epilepsy, AED history and duration of treatment, other treatment (if any), and seizure control. Subjects with epilepsy were evaluated by a team of neurologists with special interest in epilepsy (P Satishchandra, S Sinha, Bipin C Bhimani) and those with BPAD were evaluated by the psychiatrist (YC Janardhan Reddy), respectively. The following were considered menstrual disorders: Amenorrhea (no menstruation), oligomenorrhea (cycle length longer than 35 days), prolonged menstrual cycles (cycle lengths varying from <35 days to more than 35 days), and irregular cycles (cycle length between 22 to 35 days but more than 4 day variation between cycles). The height, weight, and body mass index (BMI) were calculated for all women. BMI >25 were considered to be preobese or overweight. Hirsutism was graded according to Ferriman-Gallwey scoring system. All the women underwent ultrasound examination of the abdomen for the diagnosis of PCO by a specialist sinologist (B.R.). They were diagnosed to have PCOS if ultrasound was suggestive of PCO (10 or more subcapsular cysts, measuring 2 to 8 mm in diameter, found within an ovary that has thickened, echogenic stroma) with evidence of hyperandrogenism on physical examination.[11] US evaluation was carried out and interpreted by specialists.

For the patients, who consented for hormonal assay, blood samples were drawn at 8AM after overnight fasting. Hormonal evaluation was done in the early follicular phase (day 3–7) in menstruating women and randomly in amenorrhea patients. Their lipid profile and AED levels were estimated, in addition, whenever possible. Normative data from the general population was taken for comparison with the study groups as well.

The demographic, clinical, investigation data were recorded in a digital excel spreadsheet. Statistical analysis was done using SPSS. Fisher exact test was done to compare results between the groups.

Results

The present study evaluated 190 women (170 with epilepsy and 20 with BPAD) for occurrence of menstrual abnormalities and PCO/PCOS. The demographics of the patients recruited in the study is shown in Table 1. The mean length of exposure to VPA in BPAD group was 23.2 ± 11.4 months (approximately 2 years). Group 2 had exposure to CBZ for 34.8 ± 70.4 months (about 3 years) and Group 3 to PB for 79.3 ± 53.4 months (6.5 years). Majority of the patients had generalized epilepsy (55.3%) The mean age of the patients varies from 19.5 to 29.4 years. Fifty-two women of the whole study group (52/190; 27.4%) had menstrual disturbances: oligomenorrhea, 29 women (55.8%), was the most common. Among them, 9 women reported menstrual abnormalities even before the diagnosis of epilepsy or BPAD was made. There was statistically significant difference in the occurrence of abnormal menstrual cycles as shown in Table 2 (P = 0.0325, 95% CI: 1.78–30.42).

In Table 2, the number of patients with PCO, PCOS, and menstrual irregularities are depicted. When the groups were compared in Table 3, it was observed that there was a significant difference in the occurrence of PCOS in patients on VPA *versus* normal population (P = 0.05) and patients on other AEDs (P = 0.02). There was, however, no significant difference in the occurrence of PCO between patients on VPA and the untreated epileptics. Additionally, there was no difference in the occurrence of PCO between patients of CBZ and PB *versus* normal population.

Table 1: The demographic and clinical details of study subjects

Patient group	Mean age (years)	Mean duration of disease (months)	Mean duration of Rx (length of exposure)	Mean exposure time (years)	GTC seizure	Partial seizure	Seizure freq. 0-1/month	Seizure freq. >1/month
Group 1 (*n*=40)	19.5±3.1	40.3±58.1	24.5±36.5	16.3±5.1	35	5	25	5
Group 2 (*n*=50)	20.3±4.9	70.4±96.4	34.8±70.4	15.6±4.7	17	33	42	8
Group 3 (*n*=50)	23.6±6.8	105±89.6	79.3±53.4	15±1.2	30	20	40	10
Group 4 (*n*=30)	22.3±4.1	30.7±42.1	NA	NA	12	18	14	16
Group 5 (*n*=20)	29 4±2.1	56.4±34.4	23.2±11.4	27.3±5.2	NA	NA	NA	NA

Table 2: Occurrence of menstrual irregularity in the patient group

Menstrual irregularity	Group 1 (*n*=40)	Group 2 (*n*=50)	Group 3 (*n*=50)	Group 4 (*n*=30)	Group 5 (*n*=20)	*P* value
Normal cycle	22	35	41	26	14	0.0325 (95% CI: 1.78-30.42)
Abnormal cycle	18	15	9	4	6	
Amenorrhea	4	5	1	1	0	Not possible
Oligomenorrhea	11	9	4	1	4	
Prolonged cycles	2	1	2	0	1	
Irregular cycles	1	0	2	2	1	
PCO+	15	10	8	5	3	
Frank PCOS	4	3	2	2	1	

Normative data for PCO prevalence in the population - 20%

Table 3: Comparison between the sub-groups

PCO	Comparison between various subgroups		*P* value
	Group 2 (*n*=50)	Normal data (100)	
Present	10	20	1.00
Absent	40	80	
	Untreated epileptics (*n*=30)	**Group 2**	
Present	5	10	0.94
Absent	25	40	
	Untreated epileptics (*n*=30)	**Normal data (100)**	
Present	5	20	0.85
Absent	25	80	
	Epileptics on valproate treatment (%) (*n*=40)	**BPAD on valproate (*n*=20)**	
Present	15 (37.5)	3	0.14
Absent	25 (62.5)	17	
	Epileptics on valproate treatment (%) (*n*=40)	**Normal data (100)**	
Present	15 (37.5)	20	0.05 (OR=2.4 CI: (0.99-5.80))
Absent	25 (62.5)	80	
	Epileptics on valproate treatment (*n*=40)	**Untreated epileptics (*n*=30)**	
Present	15	5	0.10
Absent	25	25	
	Epileptics on valproate treatment (*n*=40)	**Other AEDs treatment (*n*=100)**	
Present	15	18	0.02
Absent	25	82	

VPA group (epilepsy + BPAD) had a significantly higher occurrence of obesity than other treatment groups ($P = 0.043$, OR = 2.11). About, 36.7% of patients on VPA had BMI more than 25 and mean BMI in VPA group was 24.1 ± 4.2. Three WWE on VPA, three on CBZ, two on PB, one drug naïve, and one BPAD group on VPA had clinical features of hyperandrogenemia in the form of alopecia, acne, and/or hirsutism.

The frequency of occurrence of PCO on USG examination was unrelated to the type of epilepsy being 25.5% in women with generalized epilepsy, 19.14% in women with partial epilepsy and 20.7% in patients with seizure with secondary generalization ($P = 0.82$).

Hormonal evaluation was carried out in selected cases. Thirty cases consented for hormonal evaluation. Hormonal criteria (high testosterone level or high LH/FSH ratio) supported diagnosis in 11 patients (Group 1–4, Group 2–3, Group 3–2, Group 4–1, and Group 5–1). As numbers were small, group comparison was not done.

Discussion

Polycystic ovarian disease poses a great burden to women of the reproductive age group. WWE have an increased risk due to either the disease itself or the treatment. The aim of our study was to identify the association of VPA and PCOS. In this study, we divided patients into groups based upon the treatment they were receiving, which was VPA, CBZ, PB, or drug naive. The mean duration of therapy was about 3.5 years that is comparatively shorter compared to other studies such as Isojarvi *et al*. (1993), where the duration of therapy was 9 years; however, no correlation between the duration of AED therapy and frequency of PCOS was reported. Other studies as shown in Table 4 had duration of therapy ranging 1–9.5 years. Few studies[12-14] compared the results of the VPA patient group with untreated epileptic women.

We found no significant difference between the seizure type (generalized or partial) and occurrence of PCO. Similar findings were noted by Isojarvi *et al*. (1993) and Murialdo *et al*. (1997). Herzog *et al*. in their study in 1984, however, reported a higher incidence of PCO in patients with complex partial epilepsy.[14] Bilo *et al*. (1988) instead reported a higher incidence in idiopathic generalized epilepsy.[15] About 27.3% of the women in the study group had menstrual disturbance, oligomenorrhea being the most common. The menstrual disturbances were more common in VPA (45%) and CBZ (30%) treated groups compared to PB and the normal population. Luef *et al*. (2002) reported a higher frequency of menstrual irregularities in those treated with CBZ (16%) *versus* 11.5% in the VPA group.[16] However, Sahota *et al*. (2008) as well observed higher incidence of menstrual abnormalities in the group treated with VPA. The frequency of amenorrhea was higher in our study (10%) than reported by Sahota *et al*. (3%).

WWE receiving VPA have had a higher risk of developing PCO, indicating VPA may have a role in the etiopathogenesis of reproductive system abnormalities[5,17-20] (Bilo *et al*. 2001, Betts *et al*. 2003, Morrell *et al*. 2008, Sahota *et al*. 2008, and Gorkemli *et al*. 2009). However, Bauer *et al*. and Luef *et al*. did not find VPA to be associated with PCO. This study demonstrated that when compared with the CBZ and PB group, patients on VPA had a significantly higher prevalence of PCO. The occurrence of PCO was three times higher compared to patients with BPAD on VPA but due to small numbers, statistical analysis was not possible. However, there was no significant difference in the occurrence of PCO in women on VPA compared to untreated patients. As many of the patients were not tested for hormonal levels, PCOS could not be diagnosed in patients who had PCO but lacked clinical features of hyperandrogenism. Hu *et al*. (2011) in their metaanalysis concluded that VPA was associated with higher occurrence of PCOS compared to other AEDs. There was no significant difference between the occurrence of PCO in patients on CBZ and PB compared to untreated epileptics or normal population.[21]

VPA has been associated with causing obesity and the present study observed that 36% patients on VPA were obese. Though this was higher than obesity prevalence in the other groups it was not statistically significant. Isojarvi *et al*. (1993) reported 59% of patients on VPA were obese and Luef *et al*. (2002) obtained statistically significant difference in the BMI between the VPA group and CBZ group (24.4 ± 4.1 in VPA group vs 22.9 ± 2.4 in CBZ group).

There are few studies comparing the occurrence of PCO/PCOS in patients with bipolar disorder on VPA and other mood stabilizers with normal population. Rasgon *et al*. (2005) remarked that the rate of PCO/PCOS is higher in bipolar patients compared to the normal population and this increased occurrence of PCOS in these patients can be aggravated by

Table 4: Comparison between the results of various studies

Study	Age (years)	Seizure classification	Study design	Duration of Rx (years)	On SVA (*n*)	Other AEDs (*n*)	Drug naïve (*n*)	PCO (%)			PCOS (%)		
								SVA	Other drugs	Drug naive	SVA	Other drugs	Drug naive
Bauer *et al*. (2000)	20-50	Focal	Prospective cross sectional	-	34	40	19	-	-	-	11.10	10	10.50
Bilo *et al*. (2001)	16-42	Generalized and focal	Prospective cross sectional	-	13	21	None	38.50	28.60	31.20	23.10	23.8	31.20
Luef *et al*. (2002)	16-40	Generalized	Prospective cross sectional	2	22	21	None	12.40	14.30	-	3.80	3.8	-
Betts *et al*. (2003)	-	Generalized and focal	Prospective cross sectional	>1	54	51	None	50	33	-	30	6	14
Mikkonen *et al*. (2004)	8-18.5	Generalized and focal	Prospective	12.5-25.8	10	17	42	70	50	15	60	20	5
de Vries *et al*. (2007)	6-20	Generalized and partial	Prospective cross sectional	1-9.5	45	none	43	44	-	31	16	-	16
Morrell *et al*. (2008)	13-40	Idiopathic and symptomatic	Prospective multinational centers	1	222	225	none	40	40	-	36	23	-
Gorkemli *et al*. (2009)	17-39	Generalized and focal	Prospective cross sectional	2.0-3.7	40	31	none	55	45%	-	62.50	32.30	-
Sahota *et al*. (2008)	14-45	Generalized, focal andunclassified	Cross sectional	109	50	32 (mono)	none	23.50	25	-	11.80	450%	-
Present Study (2014)	16-31	Generalized and partial	Prospective cross sectional	3.5	40+20	100	20	37.50	18	16.70	10	5	6.6

VPA therapy.[22] A third of patients in our study on VPA for BPAD had PCO which was, however, lesser than patients with epilepsy on VPA. The number of recruited patients were too small to assess for statistical significance.

Epilepsy influences the reproductive endocrine system by affected the hypothalamic-pituitary axis. Harden *et al*. (2005) hypothesized that the discharges from the medial temporal lobe can stimulate the secretion of LH and Gonadotropin-releasing hormone (GnRH).[23] This may be the reason why some studies have reported higher menstrual irregularities in patients with partial epilepsy. The increased LH surge can cause stimulation of multiple follicles in the ovaries resulting in a polycystic condition. Ovarian theca cells show increased androgen synthesis when exposed to VPA in cultures.[24] This, coupled with an increased LH/FSH ratio results in hyperandrogenism and anovulatory cycles which characterize PCOS. In a 5-year follow-up study conducted by Mikkonen *et al*. (2004), it was found that these effects of VPA were reversible after discontinuing the drug.[25]

Conclusion

The limitation of this study, nonconsecutive sampling, with relatively small number of patients in each subgroup that may have impacted the statistical analysis. The results of this study might have been impacted by several confounding factors and readers should exercise caution in drawing a conclusion. However, this study brings into light the important association between VPA and reproductive system abnormalities in women. The present study observed significantly higher occurrence of PCO in patients on VPA compared to other AEDs, untreated WWE, and the normal population. This might have practical implications for clinicians who deal with such situations commonly.

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Conflicts of interest
There are no conflicts of interest.

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