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Expert Opinion Article

Assessing the Prevelance of Polycystic Ovary Syndrome by Sodium Valprate in Epileptic Patients, A Cross Sectional Study

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ABSTRACT

Background: The study explores the impact of antiepileptic drugs (AEDs), particularly valproate (VPA), on reproductive health in women with epilepsy, focusing on the development of Polycystic Ovarian Syndrome (PCOS).**Objectives:** The study aims to investigate the incidence and risk factors of PCOS in women with epilepsy undergoing AED therapy, with a focus on valproate's effects on reproductive hormones and ovarian function. **Methodology:** The study involved 102 women with epilepsy, aged 12-45 years, who were receiving AED therapy. Clinical evaluations, laboratory tests, and ultrasound examinations were conducted to assess reproductive health and diagnose PCOS. The study used the International League Against Epilepsy (ILAE) criteria for epilepsy diagnosis and classification.

Results: The study found that 12.7% of WWE developed PCOS, with a higher incidence in those taking valproate (VPA) therapy. Age at seizure onset (≤16 years old) was a significant risk factor for PCOS development. Valproate therapy was associated with increased testosterone levels, luteinizing hormone (LH) levels, and LH/FSH ratios, contributing to reproductive endocrine disorders. **Conclusion:** The study highlights the high prevalence of PCOS in women, particularly those taking valproate therapy. Age at seizure onset and valproate use are significant risk factors for PCOS development. Careful consideration of AED choice and monitoring of reproductive health are essential for WWE to minimize the risk of PCOS and related complications.

Introduction

Polycystic Ovarian Syndrome (PCOS) is a complex endocrine disorder affecting women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries [1-3]. The exact etiology of PCOS remains unclear, but genetic, environmental, and lifestyle factors are believed to contribute to its development. Women with PCOS often experience menstrual irregularities, infertility, weight gain, and acne, with increased risk of developing metabolic disorders, such as insulin resistance and type 2 diabetes [4]. Early diagnosis and management are crucial to mitigate long-term health consequences and improve quality of life for affected individuals.

The use of certain antiepileptic drugs (AEDs), particularly valproate (VPA), has been linked to an increased risk of developing Polycystic Ovarian Syndrome (PCOS) in women with epilepsy. Valproate's mechanism of action, which involves altering hormone regulation, may contribute to the development of PCOS symptoms, such as hyperandrogenism, menstrual irregularities, and polycystic ovaries[5-9]. Studies suggest that women with epilepsy taking valproate are more likely to experience reproductive endocrine disorders, including PCOS, compared to those taking other AEDs [10,11]. Careful consideration of AED choice and monitoring of reproductive health is essential for women with epilepsy to minimize the risk of PCOS and related complications.

The mechanisms underlying PCOS development in patients are not yet fully understood. Electrical discharges during seizures may disrupt pituitary and

gonadal hormone secretion, leading to reproductive dysfunction [12, 13]. While some studies suggest that seizure type and frequency are not primary factors contributing to PCOS, this study found that age at seizure onset (≤16 years old) is a significant risk factor. Valproate-associated weight gain and hyperinsulinemia may contribute to PCOS development [14], with over a third of patients with PCOS on valproate being overweight (BMI ≥24). Valproate therapy may also stimulate ovarian androgen production, leading to increased testosterone levels and reproductive disorders [15, 16].

The study found significantly elevated testosterone levels and luteinizing hormone (LH) levels in WWE taking valproate. This study underscores the high prevalence of PCOS inwomen, particularly those on valproate therapy. Age at seizure onset is a significant risk factor, and obesity may play a role in PCOS development. Further research is needed to clarify the underlying mechanisms and develop effective management strategies for PCOS in patients.

Methodology

This study was conducted at the Department of Neurology, Dow University of health sciences focusing on women of reproductive age. The study excluded individuals with progressive brain disease, existing diseases in other organs, pregnancy or lactation, use of psychiatric medicines, oral contraceptives or other hormonal preparations, and those who had undergone hysterectomy. A total of 139 patients matched the study design and were enrolled, with 102 patients completing the study process. The study received approval from the local Ethics Committee, and informed consent was obtained from all patients.

Patients were kept in contact via telephone, email, and face-to-face interviews at the hospital for clinical evaluation, laboratory investigations, and ultrasound examination. A detailed medical history was obtained, including age of seizure onset, seizure frequency, menstrual history, current medication, and other existing diseases.

Epilepsy diagnosis and classification followed the International League Against Epilepsy standards, with magnetic resonance imaging (MRI) performed on patients, except those diagnosed with other non-MRI assessments. Weight, height, and BMI were recorded, with overweight defined as a BMI of ≥24.Hirsutism was assessed using the Ferryman and Gallwey system, with scores ≥9 indicating hirsutism. Menstrual disorders were recorded as amenorrhea, oligomenorrhea, or irregular menstrual cycles.

Transvaginal or transabdominal B-mode ultrasonography detected ovarian volume, follicle number and size, and stromal echogenicity. Polycystic ovary was defined as ≥12 follicles with size >2 mm in diameter and/or ovarian volume >10 mL.Fasting blood samples were drawn at the early follicular phase (days 2-5) of the menstrual cycle, and serum concentrations of testosterone (T), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), dehydroepiandrosterone sulfate (DHEAS), estradiol (E2), and progestogen (P) were measured using chemiluminescent microparticle immunoassay kits. Hyperandrogenism was defined as serum T >10.0 μg/L, with positive clinical symptoms/signs typically present at this level. Patients with a single laboratory report of T >10.0 μg/L but no clinical symptoms/signs were not included as hyperandrogenism cases.

Ethical Considerations

The study was approved by the institutional IRB of Dow University of Health Sciences.

Statistical Analysis

Data analysis was performed using SPSS 22.0 software. Categorical variables were compared using Chi-square tests and Fisher's exact tests, while continuous variables were analyzed using ANOVA for multi-group comparisons. Binary logistic regression was employed to identify included means, standard deviations, frequencies and percentages. Chi-square tests compared treatment efficacy between groups, with effect modifiers controlled through stratification. A p-value of ≤ 0.05 was considered significant.

Results

The study involved 102 patients with epilepsy, mean age of 22 years, ranging from 12 to 45 years old, and approximately 88.2% of the patients were under 30 years old. The mean body mass index (BMI) was 21.9 ± 3.6 kg/m^2, indicating a relatively normal weight range for the population. The mean age at the initiation of antiepileptic therapy was 17.8 ± 7.0 years, and the average duration of treatment was 2.8 ± 3.3 years. Clinical manifestations of hyperandrogenism were observed in 4 patients (3.9%), presenting as hirsutism and/or acne, with only 1 case exhibiting elevated blood androgen levels.

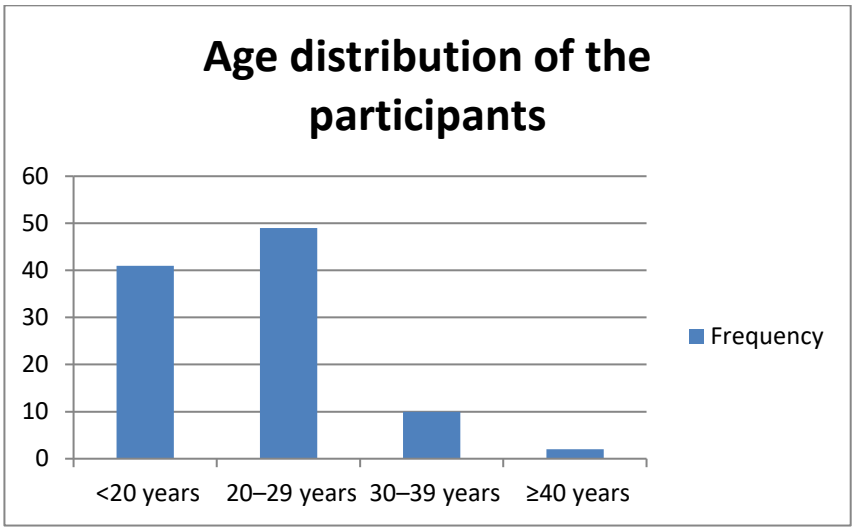

Figure 1. Showed the Age Distribution of the Participants

The average age of seizure onset was 16.3 ± 8.3 years old, and the mean duration of the disease was 6.2 years, with a range of 1 month to 29 years. The types of epilepsy represented in the study included simple or complex partial seizures (17 cases, 16.8%), primary generalized seizures or secondary generalized seizures originating from partial seizures (60 cases, 58.8%), and unclassifiable seizures (25 cases, 24.5%).

Table 1. Clinical Demographic Characteristics of the Study Participants

Mean age ± SD in years	22.0 ± 6.9
Mean BMI ± SD (kg/m^2)	21.9 ± 3.6
Mean age ± SD in years at the start of seizure	16.3 ± 8.3
Mean duration of epilepsy ± SD in years	6.2 ± 5.5
Type of seizures [*n* (%)]	
SPS, CPS	17 (16.7)
PG, PSG	60 (58.8)
Unclassifiable	25 (24.5)
Frequency of seizures [*n* (%)]	
Seizure-free in 3 months	52 (51.0)
Experienced seizures in 3 months	50 (49.0)
Accepting AEDs therapy [*n* (%)]	72 (70.6%)
Mean age at the start of AEDs ± SD in years	17.8 ± 7.04
Mean duration of AEDs therapy ± SD in years	2.80 ± 3.3
Type of AEDs	
Single drug therapy	49 (68.1)
VPA	21 (29.2)
CBZ	13 (18.1)
LTG	6 (8.3)
TPM	5 (6.9)
OXC	4 (5.6)
Multidrug therapy	23 (31.9)

Seventy-two patients (70.6%) were receiving regular antiepileptic drug (AED) therapy, with 32 cases (44.4%) using valproic acid (VPA) either as monotherapy (21 cases) or in combination with other AEDs (11 cases). The mean age at the initiation of AED therapy was 17.8 ± 7.0 years, and the average duration of treatment was 2.8 ± 3.3 years. Clinical manifestations of hyperandrogenism were observed in 4 patients (3.9%), presenting as hirsutism and/or acne, with only 1 case exhibiting elevated blood androgen levels.

Table 2. Incidence and Risk Factor Analysis of PCOS and Its Isolated Components in Study Participants

AEDs	Polycystic ovaries		A/oligomenorrhoea		Hyperandrogenism		PCOS	
Empty Cell	–	+	–	+	–	+	–	+
Number of cases (%)	73 (71.6)	29 (28.4)	82 (80.4)	20 (19.6)	95 (93.1)	7 (6.9)	89 (87.3)	13 (12.7)
Age of seizure start (mean ± SD years)	17.2 ± 8.6	14.0 ± 4.9	16.7 ± 8.5	14.6 ± 7.1	16.6 ± 8.4	11.0 ± 3.4*	16.7 ± 8.4	13.0 ± 7.2*
Duration of seizure (mean ± SD years)	6.3 ± 5.9	5.7 ± 4.6	6.1 ± 5.8	6.3 ± 4.5	6.0 ± 5.6	8.1 ± 3.7	6.0 ± 5.6	.3 ± 4.9
Type of seizure [*n* (%)]								
SPS/CPS (*n* = 17)	11 (64.7)	6 (35.2)	15 (88.2)	2 (11.8)	16 (94.1)	1 (5.9)	16 (94.1)	1 (5.9)
PG/PSG (*n* = 60)	46 (76.7)	14 (23.3)	48 (80.0)	12 (20.0)	55 (91.7)	5 (8.3)	52 (86.7)	8 (13.3)
Unclassified (*n* = 25)	16 (64.0)	9 (36.0)	19 (76.0)	6 (24.0)	24 (96.0)	1 (4.0)	21 (84.0)	4 (16.0)
Frequency of seizure								
Free in 3 months (*n* = 52)	36 (69.2)	16 (30.8)	40 (76.9)	12 (23.1)	46 (88.5)	6 (11.6)	49 (98.0)	1 (2.0)
Experience in 3 months (*n* = 50)	37 (74.0)	13 (26.0)	42 (84.0)	8 (16.0)	49 (98.0)	1 (2.0)	46 (92.0)	4 (8.0)
AEDs therapy [*n* (%)]								
No therapy (*n* = 30)	25 (83.3)	5 (16.7)	27 (90.0)	3 (10.0)	30 (100)	0 (0.0)	30 (100)	0 (0.0)
AEDs therapy (*n* = 72)	48 (66.7)	24 (33.3)##	55 (76.4)	17 (23.6)##	65 (90.3)	7 (9.7)#	59 (81.9)	13 (18.1)
Duration of AEDs therapy (mean ± SD years)	2.5 ± 3.1	3.7 ± 3.7	2.6 ± 3.2	3.6 ± 3.6	2.6 ± 3.2	5.0 ± 3.9*	2.5 ± 3.1	4.6 ± 3.9*

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Serum level of testosterone was significantly higher in patients who accepted valproate than those without VPA therapy, although the average level of the hormone did not reach to that of the defined hyperandrogenism. Serum LH level and LH/FSH ratio were also significantly higher in VPA-treated WWE ($p < 0.05$, compared to those without the AED therapy). There were no statistical changes in the levels of these hormones in patients who accepted non-VPA AEDs compared to those without AED therapy.

Table 3. Analysis of Pcos and its Isolated Components in Women Using Antiepileptic Drugs.

AEDs	Polycystic ovaries		A/Oligomenorrhoea		Hyperandrogenism		PCOS	
Empty Cell	–	+	–	+	–	+	–	+
Signal AED [*n* (%)]								
VPA (*n* = 21)	11 (52.4)	10 (47.6)*	13 (61.9)	8 (38.1)*	17 (80.9)	4 (19.0)	13 (61.9)	8 (38.1)*
Another AED (*n* = 28[a])	22 (78.6)	6 (21.4)	26 (92.9)	2 (7.1)	26 (92.9)	2 (7.1)	26 (92.9)	2 (7.1)
≥2 AEDs [*n* (%)]								
Non-VPA AEDs (*n* = 12)	10 (83.3)	2 (16.7)	10 (83.3)	2 (16.7)	12 (100)	0 (0.0)	12 (100)	0 (0.0)
VPA + other AEDs (*n* = 11)	5(45.5)	6 (54.5)	6 (54.5)	5 (45.5)*	10(90.9)	1 (9.1)	8(72.7)	3(27.3)*
AEDs therapy [*n* (%)]								
Non-VPA AEDs (*n* = 40)	32 (80.0)	8 (20.0)	36 (90.0)	4 (10.0)	38 (95.0)	2 (5.0)	38 (95.0)	2 (5.0)
VPA (*n* = 32)	16 (50.0)	16 (50.0)#	19 (59.4)	13 (40.6)#	27 (84.4)	5 (15.6)*	21 (65.5)	11 (34.4)#

Approximately 54.9% (56/102) of the patients exhibited one or more components of PCOS, including polycystic ovaries (28.4%), a/oligomenorrhoea (19.6%), and hyperandrogenism (6.9%). Among these patients, 13 cases (12.7%) met the diagnostic criteria for PCOS. Further analysis of risk factors for these reproductive disorders revealed that the mean age at seizure onset was 13.8 ± 6.5 years, with most cases occurring under the age of 16.

This was significantly younger than the age of seizure onset in patients without endocrine disorders (16.9 ± 8.6 years, $p < 0.05$)

Table 4. Analysis of Risk Factors of PCOS in Participants Used Valproic Acid Therapy.

Factors	With PCOS (*n* = 11)	Without PCOS (*n* = 21)
BMI (mean ± SD kg/m²)	23.6 ± 5.47	20.9 ± 3.61
<24 [*n* = 25, *n* (%)]	7 (28.0)	18 (72.0)
≥24 [*n* = 7, *n* (%)]	4 (57.1)	3 (42.9)
Age at VPA start (mean ± SD years)	15.7 ± 6.0	16.0 ± 7.5
≤18 [*n* = 20, *n* (%)]	9 (45.0)	11 (55.0)
>18 [*n* = 12, *n* (%)]	2 (16.7)	10 (83.8)
Dose of VPA (mean ± SD mg/day/kg)	14.7 ± 6.85	13.9 ± 5.78
≤15 [*n* = 19, *n* (%)]	6 (31.6)	13 (68.4)
>15 [*n* = 13, *n* (%)]	5 (38.5)	8 (61.5)
Duration of therapy (mean ± SD years)	5.03 ± 1.80	4.89 ± 1.85
<2 years [*n* = 13, *n* (%)]	4 (30.8)	9 (69.2)
≥2 years [*n* = 19, *n* (%)]	7 (36.8)	12 (63.2)

Although patients with reproductive dysfunction had a relatively long duration of seizures (average> 5 years), this was not statistically different from those without endocrine disorders Additionally, there were no significant differences in epilepsy type or frequency between patients with and without reproductive endocrine disorders. However, the occurrence of PCOS and its isolated components was associated with antiepileptic drug (AED) use, particularly valproate (VPA) therapy.

Discussion

Antiepileptic drugs (AEDs), particularly valproate (VPA), can alter serum concentrations of reproductive hormones, contributing to reproductive dysfunction, including PCOS [17]. This study focused on the incidence and risk factors of polycystic ovarian syndrome in women with epilepsy undergoing antiepileptic drugs (AED) therapy, revealing an increased frequency of PCOS and its components in those taking valproate. However, the relationship between valproate dosage and treatment duration and reproductive endocrine disorders could not be clarified due to the relatively small sample size[18-20]. While valproate therapy was associated with a higher incidence of polycystic ovarian syndrome, the study could not exclude potential side effects of valproate on reproductive function due to the small sample size for each non-VPA AED. Further research is needed to fully understand the complex relationships between epilepsy, antiepileptic drugs and PCOS [21].

The underlying causes and mechanisms of PCOS in women with epilepsy are not yet fully understood. Research suggests that electrical discharges during seizures, whether interictal or generalized, can disrupt the secretion of pituitary and gonadal hormones, leading to reproductive dysfunction [22]. Studies have shown that reproductive endocrine and sexual dysfunction are more prevalent in patients with partial epilepsy, particularly those with temporal lobe origin, compared to those with generalized epilepsy. However, this study found no significant difference in PCOS incidence between partial and generalized epilepsy in patients. The relationship between seizure type and PCOS incidence remains inconsistent across studies. Some research has found that reproductive endocrine disorders occur with similar frequency regardless of seizure type or frequency, suggesting that seizure type and frequency may not be primary factors contributing to polycystic ovarian syndrome [23]. Instead, this study found that the age at seizure onset, rather than seizure type, duration, or frequency, is related to polycystic ovarian syndrome (PCOS) incidence, with younger female (≤16 years old) exhibiting a higher incidence of the disorder.

The mechanisms behind the increased incidence of polycystic ovarian syndrome (PCOS) in women with epilepsy

using valproate therapy are not yet fully understood. Research suggests that valproate associated weight gain and hyperinsulinemia may contribute to the development of polycystic ovaries and hyperandrogenism in these patients. In this study, over a third of patients with PCOS who were taking valproate were overweight (BMI ≥ 24), compared to less than a fifth of those without polycystic ovarian syndrome (PCOS). Although the difference was not statistically significant due to the small sample size, the results suggest that obesity is linked to PCOS in patients using valproate therapy.

Valproate therapy may also impact sex hormone production, with in vitro studies showing that it stimulates ovarian androgen production, leading to increased circulating androgen levels and reproductive disorders, including PCOS. This study found significantly elevated testosterone levels in WWE taking valproate. Additionally, luteinizing hormone (LH) levels and LH/follicle-stimulating hormone (FSH) ratios were higher in patients taking valproate, but it is unclear whether this is a

primary effect of valproate or a secondary response to PCOS. While high LH levels may contribute to ovarian androgen synthesis, previous studies have not consistently linked valproate to elevated LH levels, making the role of LH in VPA-induced PCOS uncertain.

A previous prospective study in patients found an increased incidence of menstrual disturbances and polycystic ovaries within the first two years of valproate therapy. Similarly, this study found that approximately one-third of PCOS cases were diagnosed within the first two years of valproate therapy, with longer treatment durations not significantly increasing incidence. The minimum time required for valproate therapy to cause reproductive dysfunction remains unknown.

Another study identifies valproate (VPA) therapy as a substantial risk factor contributing to the development of PCOS in patients. Despite these findings, the underlying mechanisms driving this relationship remain unclear, underscoring the need for further investigation

The study emphasize the has revealed a significant prevalence of polycystic ovary syndrome (PCOS), affecting approximately 12.7% of this demographic in their reproductive years. Notably, this figure is more than double the incidence observed in healthy populations. The research highlights a correlation between the onset age of seizures and the occurrence of PCOS, as well as its isolated components, indicating that individuals who experienced their first seizure at a younger age (≤16 years old) are more likely to develop reproductive endocrine disorders, including PCOS.

Conclusion

In conclusion, this study highlights the high prevalence of polycystic ovary syndrome **(**PCOS) and its components in women with epilepsy, particularly those taking valproic acid therapy. The age at seizure onset, rather than seizure type or frequency, is a significant risk factor for reproductive endocrine disorders. Valproic acid therapy is associated with an increased risk of PCOS, and obesity may play a role in its development. Further research is needed to clarify the underlying mechanisms and to develop effective management strategies for polycystic ovary syndrome in women with epilepsy.

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