# Incidence of PCOS in epileptic women on Valproic acid

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Abstract Epilepsy is the most common neurological disease among people of all ages, including women of reproductive age. It is affecting about 50 million in the world and about 50% of them are women. By definition, it is characterized by recurrent (two or more) epileptic seizures that are not provoked by any factor. To study the incidence of PCOS in epileptic women taking valproic acid for treatment. This cross sectional study was carried out to find the incidence of PCOS among epileptic women. between July 2017 to December 2017. It is suggested that obesity and associated hyperinsulinemia contribute to the development of polycystic ovaries and hyperandrogenism in WWE who use VPA therapy. Key Words: PCOS, epilepsy.

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# INTRODUCTION

Epilepsy is the most common neurological disease among people of all ages, including women of reproductive age. It is affecting about 50 million in the world and about 50% of them are women. By definition, it is characterized by recurrent (two or more) epileptic seizures that are not provoked by any factor<sup>1</sup>. Treatment of epilepsy includes antiepileptic drugs like valproic various acid. carbamazepine, gabapentin, viabetrin, combination of above and many more. Anti epileptic drugs can have clinically significant effects on hormonal homeostasis. VPA (valproic acid) is a short-chain fatty acid, which acts throughout the GABA-ergic (GABA γ-aminobutyric acid) and sodium channel activity. Its impact on cell function is also being postulated. VPA modulates intracellular signaling systems such as MAPK (mitogen-activated protein kinases), PCK (Protein kinase C), Akt/ PBK (The serine / threonine protein kinase GDP Also known as the

 $Act)^{2}$ . Chronic treatment with VPA affects the activity of transcription factors. VPA reversibly inhibits the activity of histone deacetylases class I and consequently increases histone acetylation, which alters the expression of selected genes<sup>3</sup>. Reproductive endocrine disorders are more common among women with epilepsy. These abnormalities include menstrual disorders such as oligomenorrhoea or amenorrhoea, hyperandrogenism, functional hyperprolactinemia, and polycystic ovary syndrome (PCOS). A common adverse effect of some antiepileptic drugs is weight gain. Increased body weight augments insulin resistance and in women with genetic predisposition may favor the occurrence of PCOS. Polycystic ovary syndrome (PCOS) is a complex endocrine disorder. According to different authors, it affects 5-10% of premenopausal women<sup>[4]</sup>. The Rotterdam criteria suggest that PCOS is recognized when two of the following conditions are fulfilled:

- 1. Menstrual disorders or amenorrhea with chronic lack of ovulation,
- 2. Clinical and/or biochemical features of hyperandrogenism,
- 3. Presence of the characteristic features of the ovaries in ultrasonography(polycystic ovaries PCO).

Other diseases such ascongenital adrenal hyperplasia, Cushing syndrome, androgen secreting tumors, hyperprolactinemia and thyroid disease should also be ruled out<sup>4</sup> PCOS is a common cause of infertility and is associated with dyslipidemia. glucose intolerance and endometrial cancer. This study was done to find prevalence of PCOS in women taking valproic acid.

## **MATERIAL AND METHODS**

This cross sectional study was carried out to find the incidence of PCOS among epileptic women. between July 2017 to December 2017. All 147 women in age group of 18yrs to 45 yrs with history of epilepsy were interviewed. These patients were followed up for epilepsy in tertiary care center. 106 normal women in same age group were interviewed as control group.

# **Exclusion Criteria**

- Pregnancy or lactation,
- Use of psychiatric medicines or oral contraceptives
- Those who had undergone hysterectomy
- Not willing to participate

The study was approved by the local Ethics Committee. Informed consent was taken from all patients. Patient were interviewed. thorough history and clinical examination was done. Ultrasound examination was done and hormonal blood levels were measured. Detailed medical history included age of start of seizure, frequency of seizures, duration of seizure, medication using for seizure, menstrual history etc. Menstrual disorders were recorded as amenorrhea (absence of a menstrual period), oligomenorrhea (cycle length longer than 35 days during the last 6 months), and irregular menstrual cycles (cycle length varying more than 4 days, at least once during the last 6 months). All women underwent pelvic examination, examination for hirsuitism and ultrasound examination in the hospital. On ultrasound examination Polycystic ovary was defined as each ovary existing with 12 or more follicles with size >2 mm in diameter and/or volume of ovary >10 mL. Hirsutism was determined and scored using the Ferryman and Gallwey system.<sup>5</sup> Weight, height, BMI were recorded. Patients were classified into Overweight and obese if BMI  $>25^6$ . For determining hormonal blood levels patient were called for fasting levels of LH, FSH, testosterone, estrodial and progesterone Serum concentration of T > 10.0 mg/L with clinical symptoms was defined as hyperandrogenism. PCOS is defined as presence of any 2 or more of the followings 1) amenorrhoea/oligomenorrhoea 2) serum T > 10 microgram 3) polycystic ovary on ultrasound examination

## **RESULTS**

	Table 1: Clinical characterstics of patients									
		Sr M	o Clinical characterstics			Val	ues	Range		
	1			Mean ag	Mean age		.8 yrs	18-36yrs		
		2 Mean age at start of treatment					17±1.7yrs 12-23			
		3 Mean duration of treatment				6.8± 1	6.8± 1.7 yrs 2- 8			
	4			Mean BN	AI .	23±1.9 kg/m2		21-28		
	Table 2: Frequency of menstrual disturbances in epileptic women									
Sr No	Treatment N		No of cases	o of cases Amenrrh		ea oligomenrrhoea		onged cases	Irregular m	enses
1	Valproic acid		61	11(18.0	)3) 12	12 (19.67)		1(1.63) 0		
2	Oth	ner AED	86	2 (2.32	2) 4	4(4.65)		1(1.16)	0	
3	N	ormal	106	0	2	2(1.88)		1(0.94)	0	
	1	Гotal	253	13(5.1	3) 18	3(7.11)		3(1.18)	0	
	Table 3: Analysis of PCOS and isolated components in study subjects									
	Sr No 1 Valproic acid		No t of cases	Polysystic ovaries	oligomenor	rhoea ł	nyperand	rogonadism	PCOS	
			id 61	28(45.94)	23(37.7	7)	10(1	16.39)	24(39.34)	
	2	Other AEI	D 86	18(20.93)	6(6.97	)	5(5	5.81)	5(5.81)	
	3	Normal	106	9(8.49)	7(6.60	)	2(1	L.88)	2(1.88)	
		Total	253	46(18.18)	29(11.4	6)	15(	5.92)	29(11.46)	
	Table 4: Circulating hormonal levels in study subjects									
		Sr No Hoi		nes	Valproic acid	l Oth	er AED	Normal		
	1		Testosterone (ng/ml)		0.76± 0.29	0.46	5± 0.19	0.44±0.3		
		2	LH (IU/L)		6.18± 3.32	4.3	3± 1.9	4.13± 2.29	)	
		3	FSH (IU/L)		5± 1.33	4.26	6± 1.13	5.09± 1.8		
	4		Estradial (	Estradial (pg/ml)		52.07	52.07±35.26 41.22±2		25	
	5		Progesteron	rogesterone (ng/ml)		0.29	9± 0.12	0.22± 0.1		

The mean age of all women was 27±2.8 yrs years, ranging from 18-36 year-old. The mean BMI was 23±1.9 kg/m2. Range of BMI was 21-28 kg/m2. The average age of start of seizures was 17±1.7yrs. It was ranging from 12-23 yrs. The mean duration of disease was  $6.8 \pm 1.7$  yrs ranging from 2-8 years. Out of 147, 61 patients received valproic acid for treatment and 86 received other anti epileptic drugs. Patients receiving valproic acid in combination with other AED were included in valproic group. There were 4 patients receiving this combination. We included 106 normal women for study purpose. Table no 2 showed Frequency of menstrual disturbances in epileptic women. Most common menstrual disturbance was oligomenorrhoea (7.11%). In valproic acid receiving patients 12 out of 61(19.67%) had oligomenorrhoea followed by other AED where occurance was 4.47%. Amenrrhoea was most commonly observed in patients receiving valproic acid (18.3%) followed by other AEDs (2.32%). None of the patient had irregular menses. 2.83 % of normal women had menstrual disturbances. Among them oligomenorrhoea was common. Table no 3 showed occurance of PCOS and isolated components in patients receiving different AEDs. Several risk factors for these reproductive disorders were further analyzed. In patients receiving valproic acid Occurance of PCOS's components, includes polycystic ovaries (28/61, 45.94%), oligomenorrhoea (23/61, 37.7%),a/ and hyperandrogenism (10/61, 16.39%), and among them 24 cases (39.34%) were diagnosed as PCOS. In patients receiving other AED Occurance of PCOS's components, includes polycystic ovaries (18/86, 20.93%),a/ oligomenorrhoea (6/86, 6.97%), and hyperandrogenism (5/86, 5.81%), and among them 5 cases (5.81%) were diagnosed as PCOS. In normal women polycystic ovaries (9/106 8.49%) were most common. only 2 patients were diagnosed as PCOS. Thus occurance of PCOS was more in patients receiving valproic acid than using other AEDs. Difference between them is statistically significant (p<0.05). Similarly occurance of PCOS is more in valproate than normal women (statistically significant p<0.001) Table no. 5 showed circulating hormonal levels Serum level of testosterone was significantly higher in patients who were treated by valproic acid than those without it. Serum LH level and LH/FSH ratio were also significantly higher in Valproic acid treated women (p < p0.05), compared to normal. There were no statistical changes in the levels of these hormones in patients who accepted other AEDs compared to normal women.

## DISCUSSION

The mean age of all women was  $27\pm2.8$  yrs years. The mean BMI was  $23\pm1.9$  kg/m2. The average age of start of seizures was  $17\pm1.7$ yrs. It was ranging from 12-23 yrs.

The mean duration of disease was  $6.8 \pm 1.7$  yrs range 2-8 years. Similar findings were seen in various studies<sup>6,7</sup> menstrual disturbance common Most oligomenorrhoea (7.11%). In valproic acid receiving patients 12 out of 61(19.67%) had oligomenorrhoea followed by other AED where occurance was 4.47%. Amenrrhoea was most commonly observed in patients receiving valproic acid (18.3%) followed by other AEDs (2.32%). Similar findings were seen in Jue-Qian Zhou et  $al^7$  The study found that 31 out of 147(21.08%) cases have at least one of the major isolated components of PCOS, such as polycystic ovaries, hyperandrogenism, and a/oligomenorrhea. The incidence rate of PCOS in Chinese WWE was  $12.7\% (13/102)^6$ , our study had more rate than a study reported in Indian WWE (about 11.8%),<sup>8</sup> and similar results were seen in in some reports in Western WWE (up to 26%).<sup>9</sup> The causes and mechanisms underlying the occurrence of PCOS in WWE are still not fully clear. Electrical discharges during generalized and partial seizures, may alter the secretion of pituitary and gonadal hormones<sup>,9,10,11</sup> which may result in reproductive dysfunction. Incidence of PCOS was more in patients receiving valproic acid than using other AEDs. Difference between them is statistically significant (p<0.05). Similarly occurance of PCOS is more in valproate than normal women (statistically significant p < 0.001). Similar findings were seen in other studies<sup>7</sup> As the use of VPA is often associated with increased weight and hyperinsulinemia, it is suggested that obesity and hyperinsulinemia associated contribute to the development of polycystic ovaries and hyperandrogenism in WWE who use VPA therapy.<sup>12,13</sup> Our study showed that circulating levels of testosterone were significantly elevated in Women with VPA therapy. Similar findings were observed in Jue-Qian Zhou *et al*<sup>14</sup> Nelson *et al*<sup>14</sup>

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