Original Article

Obesity, polycystic ovarian syndrome and thyroid dysfunction in women with epilepsy

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Abstract

Introduction: Women with epilepsy (WWE) have an increased risk for several endocrine disorders. Obesity and Polycystic Ovarian Syndrome (PCOS) are common side-effects of anticonvulsant drugs. **Aim:** To study the prevalence of Obesity, PCOS, Thyroid dysfunction in WWE on monotherapy with Carbamazepine (CBZ), Sodium Valproate (VAL) and Phenytoin (DPH) **Material and Methods:** Sixty WWE in the reproductive age group (13 – 45 yr) who are on atleast 6 months of monotherapy with either CBZ (20) or VAL (20) or DPH (20) are subjects of the study. Their Anthropometric data is recorded. They are interviewed and investigated for PCOS and thyroid dysfunction. Twenty healthy women in the reproductive age group served as controls. BMI>25 is taken as cut-off for Obesity. PCOS is defined as menstrual irregularity and/or clinical /biochemical hyperandrogenism with ultrasound evidence of PCO as per the Rotterdam criteria. TSH <0.1 and >4 is taken as evidence of thyroid dysfunction. Women are grouped according to the anticonvulsant drug received and the data analyzed in each group. **Results:** The mean BMI among VAL and CBZ users is significantly higher than among DPH users (23.3 & 23.4 vs 20.4). There is no significant difference in incidence of PCOS among WWE using either DPH or VAL or CBZ. Elevated TSH>4 is seen more often in WWE on VAL (9/20) compared to CBZ (6/20) and DPH (3/20). WWE on CBZ, VAL and DPH did not differ in mean BMI, Obesity, PCOS compared to healthy controls. As compared to healthy controls, more WWE on drug therapy had significantly elevated TSH (1/20 vs20/60). **Conclusions:** WWE on VAL and CBZ had significant weight gain compared to DPH users. Despite weight gain, there was no difference in the incidence of PCOS between the users of VAL, CBZ and DPH. As compared to healthy controls, more WWE on drug therapy had significantly elevated TSH, more so in the VAL group.

Key Words

Body mass index, polycystic ovarian syndrome, phenytoin, sodium valproate, carbamazepine, thyroid stimulating hormone, women with epilepsy

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Introduction

Women with epilepsy (WWE) have an increased risk for several endocrine disorders. Obesity, polycystic ovarian syndrome (PCOS) and metabolic bone disease are common side-effects of anticonvulsant drugs. An association between epilepsy and reproductive disturbances with an apparent increase in PCOS has been reported in previous studies. Whether this association can be attributed to epilepsy itself or is related to antiepileptic drug therapy, in particular valproate, remains controversial. Subsequent studies did not confirm the increased incidence of PCOS in valproate users. Sahota *et al* from North India reported the occurrence of reproductive endocrine disorders in WWE receiving various antiepileptic drugs [1]. A common finding in WWE on AED is the alteration in thyroid hormone levels and obese WWE are often referred to the endocrinologist with an elevated thyroid stimulating hormone (TSH) for evaluation. With this background, the present study was performed to evaluate the prevalence of obesity, PCOS and thyroid dysfunction in WWE on monotherapy with the three commonly used antiepileptic drugs, Carbamazepine (CBZ), Valproate (VAL) and Phenytoin (DPH).

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Aim of the study

The aim of the study is to evaluate the prevalence of obesity, PCOS and thyroid dysfunction in WWE on monotherapy with CBZ , VAL and DPH. WWE are also compared with healthy controls for obesity, PCOS and thyroid dysfunction.

Materials and Methods

Sixty WWE in the reproductive age group (13 – 45 years) who were attending the Neurology OPD at Andhra Medical College, Visakhapatnam during the period Jan 2009 to June 2009 were included in the study. They were on at least 6 months

of monotherapy with either CBZ (20) or VAL (20) or DPH (20). Age of onset of epilepsy, duration of seizures, epilepsy syndrome and AED drug used and the dose were documented. Their age, weight, height and body mass index (BMI) were recorded and they were interviewed for menstrual disturbances and signs of hyperandrogenism.

Menstrual disturbances are defined as amenorrhea (absence of menstruation for 6 months), infrequent uterine bleeding (oligomenorrhea defined as interval between episodes of uterine bleeding greater than 35days), menorrhagia (excess uterine bleeding) or irregular episodes of excessive uterine bleeding. Clinical hyperandrogenism is defined as presence of acne/hirsutism/androgenic alopecia. Hirsutism is scored as per the modified Ferriman - Gallway Score[2] and a score of more than eight was considered significant for a diagnosis of hirsutism . Biochemical hyperandrogenism is defined as serum total testosterone values 0.6 ng/mL or more. All women had a basal serum testosterone (8 am), serum prolactin and serum T3, T4, TSH estimation. Serum testosterone and prolactin were assayed by enzyme-linked immunosorbent assay, T3, T4 by radioimmunoassay and TSH was analyzed by immunoradiometric assay. A transabdominal ultrasound was performed using a 3.5 MHz transducer to look for ovarian diameter, number and mean size of ovarian follicles and stromal echogenicity. A positive finding of polycystic ovaries required either 12 or more follicles measuring 2–9 mm in diameter, or increased ovarian volume (10 cc) in at least one of the ovaries [3]. WWE on polytherapy, thyroid disorders, history of menstrual disturbances and endocrine disorders causing androgen excess were excluded from the study.

Twenty healthy women in the reproductive age group served as controls.

The study had approval from the ethics committee of King George Hospital, Visakhapatnam. Informed consent was obtained from all patients.

Mean duration of seizures and AED usage was calculated. BMI>25 was taken as the cut - off for obesity. PCOS is defined as per the Rotterdam criteria [4] shown in Table 1. We looked for three criteria, i.e. menstrual irregularity, clinical and/or biochemical evidence of androgen excess and ultrasound of ovaries for PCO. If a woman had two of three criteria, we established the diagnosis of PCOS.

The normal range of TSH was taken as 0.3-4mIU/mL. TSH <0.1 and >4 was taken as evidence of subclinical thyroid dysfunction. Women were grouped according to the anticonvulsant drug received and the data were analyzed in each group. A student's t test and Chi Square test were performed for comparison between the different groups. The level of significance was established at *P* less than 0.05. Data are presented as the mean ± SD.

Results

The base line characteristics of the 60 women in the study group are shown in Table 2. The mean AED dose in CBZ, VAL and DPH is 640 mg, 645 mg and 260 mg, respectively, with a mean AED therapy duration between 4.5 and 5.48 years. The seizure type in each group was classified according to the International League Against Epilepsy (1981), and included generalized and partial seizures. Menstrual irregularity, clinical/biochemical evidence of hyperandrogenism, ultrasound evidence of PCO and PCOS are shown in Table 3. The diagnosis of PCOS was fulfilled only if two of three criteria are present. Serum prolactin was normal in all subjects except in two patients with PCOS – one in the Val group where the prolactin was 32ng/mL and the other in the CBZ group with a serum prolactin of 40ng/mL. Four women were infertile – two in the VAL, and two in the CBZ group.

Obesity, PCOS and thyroid dysfunction in the three groups are analyzed and shown in Table 4.The mean BMI was significantly higher in the VAL and CBZ groups compared with the DPH group. Of the 60 WWE, 12 had BMI >25. A significantly higher number was found in the VAL [5] and CBZ [6] groups. In the controls, five of 20 had BMI >25, and the mean BMI was 23 as compared with 12 of 60 in WWE whose mean BMI was 22.4. There was no statistically significant increase in BMI in WWE as compared with controls.

Of the 60 WWE in the present study, 12 had PCOS - four in CBZ, six in VAL and two in DPH users. PCOS was seen in 12/60 in WWE (20%) and 3/20 in the controls (15%). There was no statistically significant difference among the three groups and also when compared with controls. Serum TSH >4 was seen

Table 1 : Criteria for the definition of polycystic ovarian syndrome (Rotterdam), 2003 (2)

To include two of the following, in addition to exclusion of related disorders*

- Oligo–anovulation or anovulation (eg., amenorrhea or irregular uterine bleeding)
- Clinical and/or biochemical signs of hyperandrogenism (eg., hirsutism and/or elevated serum total or free testosterone)
- Polycystic ovaries (by ultrasound)

*Cushing's syndrome, non- classic congenital adrenal hyperplasia, hyperprolactinemia, hypothyroidism , neoplastic androgen secretion.

Table 2: Baseline characteristics of the study group

Drug	Number of patients	Mean AED dose in mg/day	Mean duration of seizures in years	Mean AED duration in years
CBZ	20	640 ± 264.4	7.68 ± 6.79	5.485 ± 3.506
VAL	20	645 ± 270.9	6.43 ± 4.67	4.88 ± 4.63
DPH	20	260 ± 59.8	7.29 ± 6.14	4.51 ± 4.55

CBZ = Carbamazepine; VAL = Valproate; DPH = Phenytoin; AED = Antiepileptic drugs

Table 3: Menstrual irregularity, hyperandrogenism, ultrasound showing PCO and PCOS in the various study groups and controls

Group	Menstrual irregularity	Clinical/biochemical hyperandrogenism	PCO on ultrasound	PCOS
CBZ	6	6	4	4
VAL	12	4	8	6
DPH	3	7	2	2
Controls	5	3	3	3

CBZ = Carbamazepine; VAL = Valproate; DPH = Phenytoin; PCOS = Polycystic ovarian syndrome

Table 4 : Endocrine abnormalities in the various groups

Drug	Mean BMI	S.D	No. with B.M.I >25 (%)	No. with PCOS (%)	No. with TSH >4 (%)
CBZ	23.4	4.321	6 (30)	4 (20)	6 (30)
VAL	23.3	5.64	5 (25)	6 (30)	9 (45)
DPH	20.6	2.234	1 (5)	2 (10)	3 (15)

CBZ = Carbamazepine; VAL = Valproate; DPH = Phenytoin; PCOS = Polycystic ovarian syndrome; BMI = Body mass index; TSH = Thyroid stimulating hormone

Table 5 : Comparison of endocrine abnormalities among the different drugs

Drug	Mean B.M.I	B.M.I >25	PCOS	TSH >4
CBZ and VAL	NS	NS	NS	NS
DPH and VAL	*P* = 0.05	*P* =0.05	NS	*P*= 0.01
CBZ and DPH	*P* =0.01	*P* =0.04	NS	NS

CBZ = Carbamazepine; VAL = Valproate; DPH = Phenytoin; PCOS = Polycystic ovarian syndrome; BMI = Body mass index; TSH = Thyroid stimulating hormone

Table 6: Comparing BMI, PCOS, TSH among the study groups (*n*=60) and healthy controls (*n*=20)

Parameter	Study group (*n*=60)	Control group (*n*=20)	*P* value
Mean BMI	22.433 ± 4.424	23 ± 4.565	0.631
B.M.I >25	12 (20)	5 (25)	0.659
PCOS	12 (20)	3 (15)	0.404
TSH >4	18 (33)	1 (5)	0.01

PCOS = Polycystic ovarian syndrome; BMI = Body mass index; TSH = Thyroid stimulating hormone

in 18/60 in WWE (33%) and 1/20 in the controls (5%), which was significantly higher in WWE. TSH >4 was seen in 6/20 in CBZ, 9/20 in VAL and 3/20 in DPH users. TSH elevation was significantly higher in the VAL group. Table 5 compares the findings of BMI and PCOS and TSH >4 among the three drugs – DPH, VAL and CBZ. The findings reveal significant difference in mean BMI in the VAL and CBZ users when compared with the DPH users. PCOS did not differ in the three groups. However, TSH >4 was significantly more common in VAL group as compared with the DPH group. The BMI, PCOS, and TSH >4 were compared between the study group and healthy controls in Table 6. Except TSH > 4 being more common in the study group, there was no difference between BMI and PCOS in the two groups.

Discussion

A side-effect of AED therapy observed in our study was obesity in the VAL and CBZ groups as compared with DPH users. Sahota *et al* in their study from PGIMER, Chandigarh, reported significant weight gain and obesity in the valproate group when compared with the other AEDs. [1] This has also been previously reported in earlier studies [5, 6, 7]. Animal studies, in which rhesus monkeys were therapeutically exposed to VAL, showed a significant increase in mean body weight [8].The mechanisms leading to weight gain during VAL medication are however still unknown. In WWE, this VAL related weight gain has been associated with hyperinsulinemia[9]. WWE did not differ in body weight as compared with healthy controls in our study. We could not establish weight gain after the onset of AED therapy in view of the study being cross- sectional. Secondly, majority of our patients were illiterate and could not give history of their previous weight nor was there documented weight prior to AED therapy.

The association between reproductive disorders and epilepsy has been reported in various earlier studies. Whether this can be attributed to epilepsy itself or is related to antiepileptic drug therapy, in particular valproate, remains controversial. An acceleration of the GnRH pulse generator, which has been suggested as an intrinsic defect of PCOS, could in epileptic subjects be related to the spreading of paroxysmal discharges within the hypothalamus [10]. An alternate explanation for the association between epilepsy and PCOS is the induction of PCOS by AEDs, which may affect pituitary hormone function via a direct effect on cortical input to the hypothalamic-pituitary-ovarian axis or alter gonadal hormonal feedback, which could affect sex steroid output [11]. Data from animal studies, in which non-epileptic normally cycling rhesus monkeys were exposed to VAL over 12-15 months, did not induce cyclic hormonal or morphological ovarian abnormality characteristic of the PCOS [8]. In this study of WWE, the prevalence of PCOS is similar in women treated with either

VAL or CBZ or DPH and in controls. These results do not support the hypothesis that endocrine dysfunction is more common in women treated with VAL, as suggested by Isojarvi *et al*. This group of investigators have suggested that these cyclic abnormalities are related to a specific antiepileptic drug, valproate, rather than to the brain disorder itself [12,13]. Some authors have suggested that VAL therapy in WWE induces hyperandrogenism and a metabolic syndrome with centripetal obesity, hyperinsulinemia, lipid abnormities and polycystic appearing ovaries and that, therefore, VAL treatment in young women is relatively contraindicated [9]. Other investigators have concluded that the prevalence of PCOS is increased in epilepsy independent of antiepileptic drug treatment, or they contest the association between epilepsy and PCOS [14, 15, 16]. Murialdo *et al* reported the results of a cross-sectional study in 65 WWE on AED monotherapy (21 treated with valproate, 21 with phenobarbital and 23 with CBZ). They found no significant difference among the treatment groups in the incidence of hirsutism or PCO(10, 10 and 18%, respectively) [17]. The present study did not show a difference among the treatment groups, similar to findings by Murialdo *et al*. In the present study, PCOS was similarly common in patients without AED and in those treated with DPH, VAL or CBZ monotherapy. There was no significant difference in the occurrence of PCOS in WWE among DPH, VAL, and CBZ monotherapy, despite obesity in the VAL and CBZ groups.

Indian data on the prevalence of PCOS in WWE on AED done previously by Sahota *et al*[1] showed a significantly higher prevalence of PCOS in the valproate (11.8%) group as compared with that of 4.5% in women treated with CBZ. In the present study, despite a higher occurrence of obesity in the VAL and CBZ groups, the frequency of PCOS did not increase. The reasons could be the small sample size and our inability to assess the change in BMI. Although obesity appears to be closely associated with PCOS, it is unclear whether the increase in obesity altered the prevalence of PCOS or whether the presence of obesity in PCOS simply reflects the populational prevalence of obesity. Yildiz *et al*, in their study observed that the role of obesity in altering the development or prevalence of PCOS is modest [18], stressing the fact that PCOS is likely due to inherited or intrinsic factors, with only a limited role played and not primarily the result of environmental factors.

Bilo *et al* reported a high frequency (26%) of PCOS in WWE, which was independent of seizure type and antiepileptic medications [14]. The Indian study by Sahota *et al* reported a PCOS prevalence of 19.4%, where PCOS is diagnosed using the criteria laid down at the NIH conference in 1992 [19].The frequency of PCOS in WWE in the present study using the Rotterdam criteria is 20% in contrast to controls, where the frequency is 15%. These results again do not show increased occurrence of PCOS in the WWE group as compared with healthy controls. In the present study, the frequency of PCOS is 30% in VAL, 20% in CBZ and10% in DPH. In the study by Bilo *et al*, PCOS occurred in 23.1% of VAL users and 23.8% of those receiving other AEDs [14]. Similar to this report, our study shows no difference in the prevalence of PCOS among the three drugs. The study by Sahota *et al* revealed that 11.8% of Valproate - treated women had PCOS. The reasons for the differing frequency of PCOS occurrence in the various studies could be the criteria adopted by the earlier two studies. The earlier studies adopted the NIH criteria for diagnosis of PCOS while the present study used the Rotterdam criteria. There is some evidence that suggest that PCOS prevalence could effectively double under the Rotterdam criteria [20, 21]. March *et al* in their study found that the prevalence of PCOS using the more expansive Rotterdam criteria was over twice the NIH criteria prevalence studies [22].

In the present study, the valproate group showed elevation of TSH with normal T3 and T4 levels, and they were clinically euthyroid. Serum TSH levels were increased in girls using Valproate in earlier studies, which was reported earlier by Vainionpaa *et al* and De Vries *et al* [23, 24]. The effects of anticonvulsant medicines on the thyroid are complex. Effects include elevated degradation of thyroid hormone, elevated conversion of T4 to T3 and reduced binding of thyroid hormone to TBG. All these changes may lead to lowered levels of free T4 and elevation of TSH. This is especially observed with Valproate, and the exact mechanism and significance of these alterations is unknown. Verroti et al did not find changes in thyroid hormone metabolism, and the TSH response to TRH was normal [25].

Patients treated with VPA have significant weight gain that is often associated with increased serum leptin levels. Increased serum leptin levels are associated with human obesity, and obesity is a state of leptin resistance [26,27]. A recent report demonstrates that VAL decreases leptin secretion and mRNA levels in adipocytes *in vitro*, suggesting that VAL therapy may be associated with altered leptin homeostasis contributing to weight gain *in vivo* [28]. Leptin is also an important neuroendocrine regulator of the hypothalamic-pituitary-thyroid axis by regulation of TRH gene expression in the paraventricular nucleus, and TSH in turn will stimulate leptin secretion by human adipose tissue. Leptin, has been experimentally shown to stimulate pituitary TSH secretion[29]. All the foregoing data support the concept of a complex relationship between thyroid hormone and leptin. Whether valproate increased TSH through leptin needs to be studied.

The study does have limitations – a small number, cross - sectional study and non- availability of biochemical testing for anticonvulsant drug levels, and further testing for thyroid dysfunction. We need a multicenter, prospective study with larger number of patients and further biochemical testing for serum anticonvulsant concentrations and thyroid antibodies estimation to have definite evidence.

In conclusion, our data suggest that effects on body weight are observed in WWE in VAL and CBZ users compared with DPH. Despite weight gain, there was no difference in the incidence of PCOS among the users of VAL, CBZ and DPH. As compared with healthy controls, more WWE on drug therapy had significantly elevated TSH. The TSH elevation was significant in the VAL group when compared with the DPH and CBZ groups. Further studies are needed to confirm the elevation of TSH in WWE on Valproate therapy.

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