Effect of valproic acid monotherapy on thyroid function on short-term follow-up in children with newly diagnosed epilepsy

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ABSTRACT

Background: The effect of valproic acid (VPA) monotherapy on thyroid function test is controversial. **Objective:** The aim of this study is to assess the effect of VPA monotherapy on thyroid function on short-term follow-up in children with newly diagnosed epilepsy. **Methods**: In this prospective case–control study, conducted at the suburban tertiary care hospital in Pune, India, 55 cases of newly diagnosed epilepsy on valproate monotherapy were enrolled. 55 age- and sex-matched children were taken in the control group. Thyroid function tests were done during enrollment, at 3 months, and 6 months in case group and baseline and 6 months in the control group, and their association with serum valproate levels was correlated. **Results:** Thyroid functions tests were normal in all the children before the initiation of VPA therapy. On follow-up at 6 months, 12 of 55 children (21.8%) showed increasing trend of mean thyroid-stimulating hormone value which was statistically significant (p=0.003) with normal T3 and T4 levels. No statistically significant correlation was seen between serum VPA levels and thyroid function. **Conclusion:** Our data suggest a positive correlation between subclinical hypothyroidism and VPA monotherapy which can occur in the early course of the treatment. Therefore, it would be prudent to measure serum thyroid hormones routinely in children treated with VPA.

Key words: *Children, Epilepsy, Subclinical hypothyroidism, Thyroid function tests, Valproic acid*

Epilepsy is the most common neurological disorder in childhood which often requires long-term or sometimes lifelong treatment. Sodium valproate or valproic acid (VPA) is a broad-spectrum antiepileptic drug and one of the most commonly used antiepileptics in childhood. As VPA is used for prolonged periods in the management of seizures, it is important to monitor patients in terms of its potential adverse effects. Many antiepileptic drugs such as carbamazepine, phenytoin, and phenobarbitone have been associated with thyroid dysfunction, but the association with VPA is controversial.

There are conflicting results in clinical trials on the possible role of VPA in affecting the thyroid function in children [1-7]. Moreover, the age of the child, total daily dose, duration of VPA treatment, and serum levels of drug have been implicated as potential risk factors for the development of subclinical hypothyroidism [5,7]. Undiagnosed and untreated hypothyroidism in children can have harmful effects on the growth, school performance, and the pubertal development [8]. Therefore, the main objective of our study was to assess the effect of VPA monotherapy on thyroid function on short-term follow-up in children with newly diagnosed epilepsy.

METHODS

This was a prospective case–control study conducted at a tertiary care teaching institute from Western Maharashtra, India, during the period of June 2014–May 2016. Ethical committee clearance was taken before the commencement of the study. Children were recruited after obtaining a written consent from the parents. Inclusion criteria were children aged 1–12 years with newly diagnosed epilepsy who were started on VPA monotherapy, not on any other antiepileptics before the enrollment, with normal development, normal neurological examination, and normal thyroid function. Children with clinical suspicion of thyroid dysfunction or with family history of thyroid illness, children with congenital anomalies, and those on polytherapy for epilepsy were excluded from the study. Based on the number of patients with new onset epilepsy seen in our pediatric neurology OPD over a period of the past 1 year and considering the dropout rate of 5%, the sample size was calculated as 55 using the formula n=Z2pq/d2.

The control group consisted children with similar age and sex with normal development and no seizures. The control group was selected from the children visiting the pediatric outpatient department for any other complaints belonging to the same geographic area and similar lifestyle patterns as compared to the children in the study group. The sociodemographic details along with detailed seizure history were documented as per structured clinical pro forma. Standard charts and screening tools such as Trivandrum Development Screening tool and Vineland Adaptive Behavioral scales were used for the assessment of development and neurological examination. Seizure was classified as per the ILAE 2010 classification. New onset epilepsy was defined as

two or more unprovoked seizures more than 24 h apart. Detailed clinical examination of all children was done to rule out any abnormal neurological findings and to rule of any signs and symptoms of thyroid dysfunction. The same pediatric neurologist was involved in the initial assessment, follow-up, and the interpretation of electroencephalography (EEG).

EEG was done for all the subjects in the case group in the same institute and neuroimaging as indicated. A baseline thyroid function was done in all the children - both cases and controls. Once the diagnosis of epilepsy was established, based on the clinical history and EEG findings, oral VPA therapy was started in a dosage of 15–20 mg/kg/day in two divided doses. The serum VPA levels were estimated at 72 h and 6 months of the initiation of therapy. The therapeutic blood level of VPA was considered as 50–125 µg/mL. Repeat clinical examination for the signs of thyroid dysfunction was done at 3 months and 6 months of follow-up.

Thyroid function - serum T3, T4, and thyroid-stimulating hormone (TSH) - was done in all children during enrollment, then at 3 months, and 6 months in case group and at 6 months in control group. The blood samples for thyroid function test were collected in the fasting state between 8 am and 10 am and were assessed using Chemi-Lumina illumination method at the Central Clinical Laboratory. Normal levels of thyroid hormones (reference ranges of serum T3 - 0.87–1.78 ng/ml, serum T4 - 6.09–12.23 ug/dL, and serum TSH - 0.35–5.5 µIU/mL) were used from our laboratory. Subclinical hypothyroidism was defined as the presence of an elevated level of TSH (>5.5 µIU/mL), with normal concentrations of serum T4 and T3. Overt hypothyroidism was defined as having an elevated TSH level of >10 µIU/mL and decreased T4 and T3 levels. Baseline hemogram and liver function test were done in all children started on valproate.

Data were expressed as mean±standard deviation values. Statistical analysis was done using the Statistical Package for the Social Science Version 17, and repeated measure test (ANOVA) was used as a test for statistical significance; $p<0.05$ was considered as statistically significant.

RESULTS

Sixty-two children with new onset epilepsy attending the pediatric neurology OPD were approached, of which three parents declined the consent, and four children needed to start on other AEDs before they could get enrolled in the study. Therefore, 55 children, who fulfilled the inclusion criteria, were finally enrolled in the study group. The control group consisted of 55 age- and sex-matched children with normal development and no seizures. The characteristics of the subjects in both study and control group are summarized in Table 1. Of 55 children with epilepsy, 27 (49%) children were in the age group of 1–3 years. Most of the children (45.5%) had the onset of seizures in the same age group (1–3 years). Only two children had a family history of epilepsy. The mean serum VPA levels were 57.0±13.01 µg/ml at baseline and 80.92±17.44 µg/ml at 6 months that showed increasing trend but were within in therapeutic reference range during the study period. The most common type of seizure was generalized (51 cases), of which 46 children had generalized tonic-clonic convulsions.

Table 2 summarizes the thyroid function tests done at baseline and follow-up values in both groups. Baseline thyroid function test was comparable in both the groups. On follow-up at 6 months, 12 of 55 children (21.8%) showed subclinical hypothyroidism with elevated TSH levels, which was statistically significant (p=0.003) and normal T3 and T4 levels. The control group did not show any significant change in thyroid hormone levels at 6 months of follow-up compared to baseline levels.

Table 3 demonstrates the comparison of thyroid function test between VPA group and control group. T3 levels in VPA group showed higher levels compared to control group, but levels were within normal range. TSH levels showed a significant increase in VPA group compared to control group (p=0.015).

There was no statistically significant correlation between the serum VPA levels and the thyroid function at 6 months of follow-up (Spearman's rho value 0.114; p=0.20).

DISCUSSION

Adverse effects of antiepileptic drugs are common, and the profile includes cognitive impairment, coordination difficulties, sedation, behavioral abnormalities, and endocrine dysfunction. Derangement in thyroid function has been demonstrated with carbamazepine, oxcarbazepine, and phenobarbital by various studies [3,4,6,9-11], but the association with VPA remains

Table 1: Characteristics of subjects

Parameters	Cases	Control
Mean age	4.78±3.3	4.84±3.18
1–3 years	27 (49)	24 (43.63)
4–6 years	16 (29)	18 (32.7)
7–9 years	4 (7.2)	6 (10.9)
10–12 years	8 (7.27)	7 (12.7)
Gender		
Males	27 (49.1)	29 (52.7)
Females	28 (50.9)	26 (42.2)
Age of onset of seizures		
≤1 year	12 (21.8)	-
1.1–3 year	25 (45.45)	-
3.1–6	8 (14.55)	-
>6	10 (18.18)	-
Serum valproate acid levels (µg/ml)		
Baseline	57.0±13.01	
6 months	80.92±17.44	
Type of seizures		
Generalized	51 (92.7)	-
GTCS	46 (83.63)	-
Myoclonic	4 (7.27)	-
Absence	1 (1.82)	-
Focal	4 (7.27)	-

GTCS: Generalized tonic-clonic seizure

Table 2: Comparison of thyroid function test

Study Population	Thyroid function	Baseline (n=55)		At 3 months (n=55)		At 6 months (n=55)		t value	p value
		Mean	SD	Mean	SD	Mean	SD		
VPA group	T3 (ng/ml)	1.25	0.43	1.22	0.64	1.22	0.33	0.64	0.53
	T4 (µg/dl)	8.54	2.37	7.83	1.98	8.41	1.97	0.49	0.62
	TSH (mIU/ml)	3.21	1.80	3.12	1.53	4.13	2.03	3.10	0.003
Control group	T3 (ng/ml)	1.07	0.26	-	-	1.07	0.26	1.16	0.25
	T4 (µg/dl)	7.99	2.19	-	-	8.31	2.02	1.41	0.16
	TSH (mIU/ml)	3.31	1.29	-	-	3.32	1.32	0.07	0.95

VPA: Valproic acid, TSH: Thyroid-stimulating hormone

Table 3: Comparison of thyroid function test between cases and controls

Thyroid function	Case	Control	p value
T3			
Baseline	1.25±0.43	1.03±0.25	0.001
6 months	1.22±0.33	1.07±0.26	0.011
T4			
Baseline	8.54±2.37	7.99±2.19	0.22
6 months	8.41±1.97	8.31±2.02	0.78
TSH			
Baseline	3.21±1.80	3.31±1.29	0.72
6 months	4.13±2.03	3.32±1.32	0.015

TSH: Thyroid-stimulating hormone

controversial [12,13]. It has been demonstrated that even subclinical hypothyroidism during childhood may cause growth and developmental disorders, cognitive impairment, and subtle neuromuscular abnormalities [14-16]. VPA is well known for its broad-spectrum antiepileptic activity, excellent tolerance, absence of sedative action, and no effect on cognition [8]. Therefore, it is widely used for control of many types of epilepsies and epileptic syndromes in children.

The present study showed the trend of rising TSH levels on VPA monotherapy at 6 months of follow-up that was statistically significant ($p<0.05$). Similar results were obtained by previous studies [1-3,5,7,8,17-20] but not in all studies [12,13]. All the subjects remained asymptomatic during the follow-up period. Measurement of serum TSH level is considered as the most reliable in evaluating the true thyroidal state of patients taking antiepileptic drugs [1,17]. Of 55 children, 12 out of 55 (21.8 %) subjects showed subclinical hypothyroidism. The incidence of subclinical hypothyroidism in our study seems to be low (21.8% - 12/55) as compared to Kim *et al.* [5] (52.4% - 32/61), Eris – Punal [2] (25.5% - 13/51), and Mikati [7] (25.1% - 36/143).

Several well-conducted studies have identified various risk factors for subclinical hypothyroidism in VPA monotherapy patients including younger age, duration of treatment between 6 months and 24 months, VPA levels [5], and polytherapy [7]. Our study group showed more incidence of subclinical hypothyroidism in younger age group (1–3 years) which was consistent with the study by Mikati *et al*. and Cansu *et al.* [3,7]. Furthermore, few authors have reported no significant impact of age on subclinical hypothyroidism in patients with VPA monotherapy [5,18,20,21].

We found the onset of subclinical hypothyroidism at 6 months of duration of treatment, which was in agreement with the majority of studies that have demonstrated onset of subclinical hypothyroidism at 1 month [19], 6 months, 12 months, and 24 months [1,3,7,10,22]. In contrast, some authors have shown no effect on length of the treatment on TSH levels [5,9]. The effect of VPA on thyroid hormone may be transient and lasts as long as drug is continued. Attilakos *et al.* [1] and Vainionpaa *et al.* [17] have demonstrated restoration of thyroid function after VPA discontinuation.

The seizures were well controlled during the study period in all the subjects, and even though dose adjustment was done, up to 40 mg/kg/day in few patients, serum VPA levels were maintained in therapeutic range only. We found no correlation between VPA serum levels and subclinical hypothyroidism ($p=0.20$) which was in congruent with many of the studies [1,7,9,18,20]. To the best of our knowledge, there is only one study which identified a positive correlation between VPA levels and subclinical hypothyroidism [5]. Kim *et al.* [5] demonstrated that 32 children with subclinical hypothyroidism had elevated serum VPA levels.

The current understanding of the pathogenesis of subclinical hypothyroidism and VPA monotherapy is unclear. The possible mechanisms suggested are interference with the secretion, metabolism, or feedback regulation of TSH through its GABAergic properties [23] and deficiencies of zinc and selenium which could contribute to subclinical hypothyroidism [24,25].

Limitations of our study are small sample size and short duration of follow-up. It was difficult to have a control group of children with epilepsy without treatment with obvious ethical reasons. There is evidence that body mass index can influence thyroid function test which we have not evaluated. However, this study has highlighted the trend toward rising TSH levels in valproate monotherapy at 6 months.

CONCLUSION

We found a positive correlation between subclinical hypothyroidism and VPA monotherapy which can occur early in the course of treatment. Therefore, it would be prudent to measure serum thyroid hormones routinely in children treated with VPA. Although there is no consensus on frequency of measurement of thyroid function while on VPA treatment, based

on few good clinical studies, it can be advocated to do at every 3 month. Further, prospective studies are needed to demonstrate the association between daily dose, VPA serum concentration, age and subclinical hypothyroidism, as well as possible role of ethnicity and geography.

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