Original Article

Detection of subclinical hypothyroidism in children with epilepsy on valproate monotherapy in age group of 3-12 years

Sunil Ranga[1], Charanjeet Ahluwalia[2], Harini D[3], I P Choudhry[4], K C Aggarwal[5]

{[1]Consultant, [2]Sr. Specialist, Department of Pathology}, {[4]Sr Specialist, [5]HOD and Consultant, Department of Paediatrics}
VMMC and Safdarjung Hospital, New Delhi, INDIA.
Email: charanjeet.ahluwalia@rediffmail.com

Abstract

Introduction: Sodium valproate is an effective anti-epileptic drug and is commonly used in the treatment of childhood epilepsy .There are conflicting reports in the literature about the influence of valproate on thyroid function. Elevated TSH levels have been demonstrated in a few studies but not all. Therefore, the present study was planned to detect sub clinical hypothyroidism in children in the age group of 3-12 years with epilepsy on valproate monotherapy. **Materials and Methods:** 100 newly diagnosed children with epilepsy aged between 3 to 12 years receiving valproate monotherapy were enrolled in this study. An equal number of age and sex were matched controls were also included in the study. Thyroid Profile was done by Competitive enzyme immunoassay. FT4 and TSH values were compared before starting valproate and after 6 months of receiving the drug. **Results:** A significant difference was observed in mean FT4 values between the epileptic and the control groups On the other hand, TSH values did not show any significant difference between the two groups. A significant increase in TSH values (p value < 0.0001) was observed in patients of epilepsy before (1.98 ± 0.93) and after (4.5 ± 2.81) treatment thus showing that valproate alters the thyroid hormone levels causing subclinical hypothyroidism.

Keywords: subclinical hypothyroidism, epilepsy.

***Address for Correspondence:**
Dr. Charanjeet Ahluwalia, Sr. Specialist and Assistant Professor, Department of Pathology, VMMC and Safdarjung Hospital, New Delhi.
Email: charanjeet.ahluwalia@rediffmail.com
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INTRODUCTION

Subclinical hypothyroidism is defined as an asymptomatic state in which a reduction in thyroid activity has been compensated for by an increased thyroid – stimulating hormone (TSH) output to maintain a euthyroid state. Biochemically, subclinical hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when free thyroxine (FT4) concentration is within its reference range[1]. Although controversial, its presence raises concern of future progression to overt hypothyroidism and effect on development of the child[2]. Therefore, paediatricians should be alerted about conditions with which it may be associated. Sodium valproate is an effective anti-epileptic drug and is commonly used in the treatment of childhood epilepsy. It acts by blocking the voltage gated sodium channels and T-type calcium channels. It also enhances the neurotransmission of GABA by inhibiting GABA transaminase. The dose of sodium valproate is between 10-40mg/kg/day. Twice-a-day dosing is preferred with extended release of preparations, except in syrup (3 times a day). Common side effects are nausea, vomiting, loss of appetite, weight gain, irregular menstruation, alopecia, and somnolence. There are conflicting reports in the literature about the influence of valproate on thyroid function. Elevated TSH levels have been demonstrated in a few studies but not all[3-6]. Both elevated T4 and FT4 level and low T4 and FT4 level have been reported in patients receiving valproate therapy but never associated

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with overt thyroid dysfunction. However, majority of the studies have been performed in adult patients receiving this drug. Therefore, the present study was planned to detect subclinical hypothyroidism in children in the age group of 3-12 years with epilepsy on valproate monotherapy.

AIMS AND OBJECTIVES

To detect subclinical hypothyroidism in children with epilepsy on sodium valproate montherapy in the age group of 3 to 12 years.

MATERIALS AND METHODS

The study was conducted over a period of1 ½ years in the Department of Pediatrics and the Department of Pathology, Vardhman Mahavir Medical College and Safdarjang Hospital. 100 children aged between 3 to 12 years who were newly diagnosed with epilepsy and were receiving valproate monotherapy were enrolled in this study. For Seizure type description, the criteria of International League against Epilepsy was followed. An equal number of normal age and sex matched healthy children were taken as controls. Patients receiving any drug that could alter thyroid function, those with recurrent or refractory seizures, abnormal neurological examination and hydrocephalus or any CNS malformation were excluded from the study. Blood samples were obtained between 8.00am to 9.00am after overnight fasting before giving the morning dose of the drug. Thyroid Profile was done by Competitive enzyme immunoassay. Serum thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels of these children were evaluated before the beginning of anti-epileptic treatement and at 6 months after the start of treatment. The baseline evaluation was performed to document possible previous thyroid dysfunction and to detect if epilepsy itself can cause thyroid dysfunction.

RESULTS

This was a prospective study which included 100 children in the age group of 3-12 years who were receiving valproate monotherapy for treatment of epilepsy. An equal number of age and sex matched controls were also included in the study. The mean age of children in both the groups was 9.3 years and 49% of the patients and controls were males and 51% were females. The mean height of patients with epilepsy was 125.95 cms. (SD=10.25 cms) while mean height of children in the control group was 126.86 cms. (SD=9.61 cms).The mean value of weight among patients with epilepsy was 22.73 kgs. (SD=4.79Kgs.) and in control group it was 22.88kgs. (SD=4.50kgs). Out of all the 100 patients who were given sodium valproate, 5% received a dose of 10mg/kg/day,.24% received a dose of 15mg/kg/day, 56% were given a dose of 20mg/kg/day and 15% received a dose of 25mg/kg/day (Table1).

Table 1: Distribution of subjects in different dosage groups

Dosage(mg/kgday)	Frequency	Percent
10	5	5.0
15	24	24.0
20	56	56.0
25	15	15.0

The serum values of FT4 and TSH were compared in both the groups before starting valproate monotherapy and after 6 months of receiving the drug. Mean FT4 value of patients with epilepsy was 13.45 (SD=1.55) whereas mean T4 value of control group was 12.04 (SD=1.11). The difference of mean T4 value (Table 2) between two groups was statistically significant (p<0.001).

Table 2: Difference in mean FT4 values between the epilepsy and control groups

	FT4	
Groups	**Mean ±SD**	**P value**
With Epilepsy	13.45± 1.55	
Control group	12.04±1.11	<0.001

The serum TSH values were also compared in both the groups before starting valproate monotherapy and after 6 months of receiving the drug (Table3). Mean TSH value of patients with epilepsy was 1.94(SD=0.88) whereas mean TSH value of patients without epilepsy was 1.77 (SD=0.71). The difference of mean TSH value between two groups was not statistically significant, p=0.129.

Table 3: Difference in mean TSH between the epilepsy and control groups.

	TSH	
Groups	**Mean ±SD**	**p value**
With Epilepsy	1.94± 0.88	
Control group	1.77±0.71	0.129

Difference of FT4 and TSH values among the patients with epilepsy before and after the treatment were also assessed (Table 4and 5).The mean FT4 value before treatment was 13.45 (SD=1.55) while after treatment it was 13.67 (SD=1.27). The mean value of change in FT4 was 0.22 (SE=0.07) and it was not statistically significant (p=0.089).

Table 4: Difference of FT4 values between Pre and Post treatment

	FT4	Change in FT4	
Groups	**Mean ±SD**	**Mean ±SE**	**p value**
Pre treatment	13.45± 1.55	0.22± 0.07	0.089
Post	13.67±1.27		

treatment

The mean TSH value before treatment was 1.98 (SD=0.93) whereas after treatment it was 4.5 (SD=2.81). The mean value of change in TSH was 2.53 (SE=0.26). The change in TSH value was statistically significant (p=<0.0001). Table 5

Table 5: Difference of TSH values between Pre and Post treatment

	TSH	Change in TSH	
Groups	**Mean ±SD**	**Mean ±SE**	**p value**
Pre treatment	1.98± 0.93	2.53± 0.26	<0.0001
Post treatment	4.5± 2.81		

There was no statistically significance difference in the pre and post treatment values of FT4 and TSH between males and females. The prevalence of SCH in overall sample was 21% .The prevalence of SCH among male patients was 14.29% and among female was 27.45%.

DISCUSSION

This was a prospective study conducted for detection of subclinical hypothyroidism in children with epilepsy on Valproate monotherapy in age group of 3-12 years. FT4 and TSH values were compared in 100 patients before starting valproate and after 6 months of receiving the drug. A baseline evaluation was done taking the same group of patients before starting the therapy. This base line evaluation was done to find whether epilepsy itself can cause alteration in thyroid status. An equal number of controls were also enrolled who were non-epileptic. The controls were age and sex matched and there was no significant difference in height and weight between the two groups. A significant difference was observed in mean FT4 values (p value < 0.001) between the epileptic and the control groups. Even though the individual values of FT4 were in the normal range for age and sex in the two groups, the mean value of FT4 (13.45 ± 1.55) was slightly higher in patients with epilepsy compared to the control group (12.04 ± 1.11). On the other hand, TSH values did not show any significant difference between the patients with epilepsy (mean 1.95 ± 0.88) and the control group (mean 1.77 ± 0.71). This variation in FT4 levels in patients may be due to the secretion of thyrotropin releasing hormone which stimulates the release of TSH from the pituitary. TSH in turn stimulates thyroxine production during epilepsy[7]. But in our study FT4 was observed to be increased without increase in TSH. This may be due to augmented action of TSH during epilepsy. Studies have also shown that epilepsy itself can stimulate hypothalamic pituitary adrenal axis and also hypothalamic pituitary –gonadal axis. In our study, there was no significant difference between FT4 values before (13.45 ± 1.55) and after (13.67 ± 1.27) treatment with valproate monotherapy (p value 0.089) implying that valproate does not alter FT4 levels. Similar results were obtained by Talebian Ahmad MD.However[8], J. Eiris *et al* observed a decrease in FT4 levels after valproate therapy. They estimated serum FT4 in patients who has been receiving valproate for duration of 12-161 months whereas in our study, FT4 levels were estimated 6months after valproate treatment[4]. A significant increase in TSH values (p value < 0.0001) was observed in patients of epilepsy before (1.98 ± 0.93) and after (4.5 ± 2.81) treatment with valproate monotherapy. This shows valproate alters the thyroid hormone levels causing subclinical hypothyroidism. This study supports the previous studies which have come up with similar results[4,8]. Out of 100 children with epilepsy whose FT4and TSH levels were studied, 21 children showed sub-clinical hypothyroidism, hence prevalence being 21%. Among these 21 children, 7 were males and 14 were females, showing that prevalence of sub clinical hypothyroidism in female children was more than in male children. There was no significant difference between FT4 and TSH in male and female patients before and after therapy. Talebian Ahmad MD recorded sub clinical hypothyroidism in 25.2% of the patients 6 months after valproate therapy and J. Eiris Punal recorded subclinical hypothyroidism in 13 out of 51 children who were taking valproate for 12-161 month. Both these authors did not study the difference in prevalence between male and female children[8,4]. On the other hand, two studies have shown that valproate does not cause sub clinical hypothyroidism. However the sample size of these studies was very less and they studied a combination of 2-3 antiepileptic drugs together[6]. We also studied the association of dosage of the drug and changes in FT4 and TSH. Among all the 100 patients 5% received a dose of 10mg/kg/day, 24% received a dose 15mg/kg/day, 56% were given a dose of 20 and 15% received a dose of 25mg/kg/day. The association between dosage and serum FT4 and TSH levels was not statistically significant.

CONCLUSIONS

Epilepsy itself can alter FT4 levels, possible mechanism being the stimulation of hypothalamic pitutitary thyroid axis. Valproate monotherapy used to treat epilepsy in children causes subclinical hypothyroidism which had a prevalence of 21%. The prevalence of subclinical hypothyroidism is more in female children than in the male children. The dosage of valproate had no association with sub clinical hypothyroidism. The exact mechanism

by which valproate causes subclinical hypothyroidism is not known but the possibility includes the increase in the levels of GABA by stimulating the activity of the GABA synthetic enzyme(glutamic acid decarboxylase)and inhibiting GABA degradative enzyme(GABA transaminase and succinic semialdehyde dehydrogenase). GABA inhibits somatostain .Inhibition of somatostatin releases the inhibition over TSH and thus increases the secretion of TSH. The reason for T4 levels being in normal range is unclear. Thus thyroid profile should be routinely done during the follow up of the patients of epilepsy on valproate monotherapy with female children requiring a more vigilant thyroid profile testing.

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