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A Prospective Study on Thyroid Function in Children with Epilepsy Treated With Sodium Valproate Monotherapy

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Abstract: ***Objective****: To study the effect of sodium valproate on thyroid function in children with epilepsy.*
Method*: This was a prospective study evaluated 50 children with first attack of epilepsy treated with valproic acid. Thyroid fuction test was done before starting treatment and thereafter every 3montly for 1 year.*
Result*: Serum level of TSH significantly increased after 3 months (p=0.0045), 6 months (p=0.0026), and 9 months (p=0.0414), whereas serum FT_4 value significantly decreased after 3months (p=0.009), 6months (p=0.0026), and 9 months (p=0.0011) of valproate therapy.*
Conclusion*: VPA monotherapy in children may cause early and persistent alterations in thyroid function, which suggests a need for early and careful monitoring of serum thyroid hormone concentrations in epileptic children who receive VPA.*
Key words*: Epilepsy ,thyroid function, VPA(valproic acid).*

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I. Introduction

Epilepsy is recognized as a collection of heterogeneous syndromes characterized by additional conditions that coexist with seizures and impacts over 50 million people worldwide(1).

Seizures are typically divided into two main categories: partial (focal) and generalized. Generalized seizures affect both cerebral hemispheres from the onset of seizure.

Seizures produce loss of consciousness, either for long periods of time or temporarily, and are sub-categorized into generalized tonic-clonic, myoclonic, absence, or atonic sub-types (2).

In the treatment of epilepsy, no anti-epileptic drug (AED) has been shown to be the most effective, and all AEDs have published side effects. AEDs are selected following consideration of side effects, ease of use, cost, and physician knowledge. Patients with newly diagnosed epilepsy who require treatment can be started on standard, first-line AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital.

Alternatively, newer AEDs introduced in the past decade may be used. These include gabapentin, lamotrigine, oxcarbazepine or topiramate(3).

Sodium valproate or the valproic acid is an anti epileptic drug used in prophylactic management of complex partial seizure, primary generalized tonic clonic seizure, childhood absence seizure, juvenile myoclonic epilepsy, etc. Valproate monotherapy may cause significant alteration in thyroid profile in children with epilepsy occurring early in the course of treatment and persisting as long as valproic acid is continued(4).

A baseline evaluation is required to document possible previous thyroid dysfunctions and to detect if epilepsy itself can cause thyroid dysfunction.

The effects of VPA on serum thyroid hormone and TSH levels may be mediated by effects on TSH secretion and on the protein binding of thyroid hormones (5).

Therefore, it may be useful to measure serum thyroid hormone concentrations routinely in children with epilepsy taking VPA.

II. Materials & Methods

A) STUDY AREA: Neurology clinic of department of pediatric Medicine, OPD, Pediatric Medicine, Inpatient Department of pediatric Medicine, Calcutta National Medical College &Hospital, Kolkata.
B) STUDY POPULATION: 50 patients of childhood epilepsy (valproic acid indicated) attending Pediatric Neurology Clinic, OPD Pediatric Medicine, IPD Pediatric Medicine, Calcutta National Medical College & Hospital, treated with Sodium Valproate.
C) STUDY PERIOD: June 2013 to May 2014.

D) SAMPLE SIZE: As approximately 150 epileptic patients are admitted or visit OPD in a period of one year, so approximately 30% of that i.e. 50 patients meeting the inclusion criteria were taken as sample size, due to time constraints and feasibility of patients.

E)SAMPLE DESIGN:

Baseline evaluation of thyroid profile (FT_3,FT_4,TSH) and anti-TPO measured before initiation of valproic acid treatment. Then Thyroid profile ($FT_{3F,}$ $FT_{4,}$ TSH) evaluated at 3 month, 6month,and 9 month of treatment. Valproic acid was started @10-15mg./kg. body wt. and gradually increased till therapeutic response obtained (max.-60mg./kg Body wt.) or adverse effect prevent increasing dosage.

F) INCLUSION CRITERIA:

a.)Children with epilepsy where valproic acid was indicated.
b.)Normal thyroid profile at presentation.

G) **EXCLUSION CRITERIA**:

a.)Patients with deranged thyroid profile ($T_{3,}T_{4,}$ TSH) in baseline evaluation.
b.)Patients with abnormally increased anti-TPO antibody.

H) STUDY DESIGN: Prospective Observational longitudinal hospital based study.

I)PARAMETERS TO BE STUDIED:

Detail history and clinical examination (general survey & systemic examination).
Blood for serum FT_3, FT_4, TSH.
Blood for anti-TPO antibody.

J) STUDY TECHNIQUE:

A baseline thyroid profile (FT_3,FT_4,TSH) with serum anti-TPO was measured in patients with epilepsy, planned to be treated with sodium valproate. Patients were asked to attend neurology clinic for regular follow up, Their thyroid profile was checked serially at 3month, 6month and 9 month. Then the values were recorded in a predesigned proforma. Results of thyroid hormones were evaluated in respect of severity of derangement and percentage of patients having deranged serum thyroid profile with time.

Normal values of serum thyroid hormones(ref.-Pediatric Endocrinology, 3rd. edition, by Sperling.)

Parameters:	**Normal value:**
FT_3	2.8-5.2pg./ml.
FT_4	0.8-2ng./ml.
TSH	0.6-6.3µIU/ml.
Anti-TPO Ab.	<9IU/ml.

III. Results

TABLE NO.-1

Distribution of study population according to age(n=50).

Age group(Yr.)	No.	%
2-4yrs.	22	44
5-7yrs.	18	36
8-10yrs.	8	16
>11yrs.	2	4
Total	50	100

Mean age ±SD = 5.44±2.314

The above table shows that of Epilepsy is more among age group 2-4yrs.(44%), and decrease with increasing age.

TABLE NO.-2

Distribution of study population according to sex (n=50).

GENDER	NO.	%
Male	30	60
Female	20	40
Total	50	100

M:F ratio-1.5:1

The above table shows that males (60%) are more affected than females.

TABLE NO.-3
Serum TSH values after 3rd month of follow up.

TSH values(µIU/ml.)	No.	%
Normal(0.6-6.3)	44	88
Above normal(>6.3)	6	12
Total	50	100

The above table shows that Blood TSH value is above normal range (0.6-6.3µIU/ml.) in 12% of children, after 3month of sodium valproate therapy.

TABLE NO.-4
Serum TSH values after 6th month of follow-up.

TSH value (µIU/ml.)	No .	%
Normal (0.6-6.3)	38	76
Above normal (>6.3)	12	24
Total	50	100

The above table shows that after 6month of valproate therapy among epileptic children, 24% children are having blood TSH level more than normal range (0.6-6.3µIU/ml.).

TABLE NO.-5
Serum TSH values after 9th Month of follow up.

TSH value(µIU/ml.)	No.	%
Normal (0.6-6.3)	32	64
Above normal (>6.3)	18	36
Total	50	100

After 9 months of valproate therapy 36% children having raised blood TSH level. The percentage of children having increased TSH level is gradually increasing with duration of therapy.

TABLE NO.-6
Serum FT4 values after 3rd month of follow up.

FT4 values(ng/ml.)	No.	%
Normal (0.8-2)	49	98
Below normal (<0.8)	1	2
Total	50	100

The above table shows that only 2% of children have blood FT_4 value below the normal range (<0.8ng/ml.)

TABLE NO.-7
Serum FT_4 values after 6th Month of follow up.

FT4 values (ng/ml.)	No.	%
Normal (0.8-2)	45	90
Below normal (<0.8)	5	10
Total	50	100

The above table shows that after 6month of valproate therapy, 10% children have below normal range blood FT_4 value, which is more than what was after 3month therapy (2%).

TABLE NO.-8
Serum FT_4 values after 9th Month of follow up.

Blood FT4 value(ng/ml.)	No.	%
Normal (0.8-2)	36	72
Abnormal (<0.8)	14	28
Total	50	100

After 9month of valproate therapy , 28% children have FT_4 below normal range, and it is evident that with increasing duration of therapy percentage of children having below normal FT_4 is also increasing.

TABLE NO.-9
Serum FT_3 values after 3m, 6m, and 9months of therapy.

FT_3 values(pg./ml.)	3month.		6month.		9month.	
	No .	%	No.	%	No.	%
Normal (2.8-5.2)	50	100	49	98	41	82
Below normal(<2.8)	-	-	1	2	9	18
Total	50	100	50	100	50	100

The above table shows that all children have FT_3 value within normal range after 3month of valproate therapy.
The above table shows that only 2% children has blood FT_3 level below normal range after 6month therapy.
From the above it is evident that 18% children has FT_3 value below the normal range after 9month of therapy and the percentage is increasing with duration of valproate therapy.

TABLE NO.-10

FT_3(O MONTHS)	3.88±0.6518(MEAN±S.D)	Z=4.2175,p=0.0001
FT_4(9 M0NTHS)	3.29±0.7441(MEAN±S.D)	

The above Table shows that serum FT3 value is significantly decreased below normal after 9month of therapy (p=0.0001).

TABLE NO.-11

Thyroid function tests.	Duration of therapy			
	0.month Mean ±SD	3rd.month Mean±SD	6th.month Mean±SD	9th.month Mean±SD
FT_3	3.88±0.651	3.897±0.707	3.672±0.629	3.290±1.790
FT_4	1.375±0.334	1.610±0.373	1.382±0.383	1.109±0.451
TSH	2.723±2.502	3.946±1.725	5.005±1.790	5.861±2.367

Serum TSH (0mo.-3mo.) = p value 0.0045
Serum TSH (3mo.-6mo.) =p value 0.0026
Serum TSH (6mo.-9mo.) = p value 0.0414
Serum FT_4 (0mo.-3mo.) =p value 0.009
Serum FT_4 (3mo.-6mo.) = p value 0.0026
Serum FT_4 (6mo.-9mo.) = p value 0.0011

Table no.-11, shows, Serum level of TSH significantly increased after 3 months (p=0.0045), 6 months (p=0.0026), and 9 months (p=0.0414), whereas serum FT_4 value significantly decreased after 3months (p=0.009), 6months (p=0.0026), and 9 months (p=0.0011) of valproate therapy.

IV. Discussion

Epilepsy is recognized as a collection of heterogeneous syndromes characterized by additional conditions that coexist with seizures. Cognitive, emotional, and behavioral comorbidities are common. In the treatment of epilepsy, no one anti-epileptic drug (AED) has been shown to be the most effective, and all AEDs have published side effects.

Valproic acid (VPA) is one of the most effective broad-spectrum and extensively used antiepileptic drugs available for treatment of both generalized and partial epilepsies in children.

The most recognized adverse reactions encountered in VPA therapy are hepatotoxicity, thrombocytopenia and other hematological abnormalities as well as weight gain.

Despite being a widely used and already extensively studied antiepileptic drug, the increasingly positive correlations between VPA therapy in children with epilepsy and induction of subclinical hypothyroidism, as well as the relatively scarce information on the mechanisms involved, suggest that more attention should be paid to implementation of standard thyroid tests to aid in prospective studies.

This study entitled ¨**A PROSPECTIVE STUDY ON THYROID FUNCTION IN CHILDREN WITH EPILEPSY TREATED WITH SODIUM VALPROATE MONOTHERAPY"** is a sincere effort to evaluate the effect of valproic acid, used in treatment of childhood epilepsy, on thyroid hormone profile.

We performed a baseline evaluation and a long-term follow-up.

Previous studies [6,7] have reported some endocrine abnormalities linked to epilepsy, but our baseline evaluation allowed us to exclude the possibility that thyroid abnormalities can be the result of the convulsive disorder itself (or from other situations like congenital thyroid diseases).

A baseline thyroid profile (FT_3, FT_4 ,TSH), with serum anti-TPO-antibody was measured in patients with epilepsy , planned to be treated with sodium valproate. Patients were asked to attend neurology clinic for regular follow up. Then thyroid profile was checked serially at 3 month, 6month and 9months. Anti-TPO antibody checked at 9month of valproate therapy to exclude any auto-immune thyroid disease which may rarely occur after valproate therapy.

Our follow-up study demonstrates that in valproate-treated children, serum FT_4 concentrations were lower, whereas TSH were above normal in significant number of patients and serum anti-TPO antibody remained unchanged at the end of the study and there was a late alteration in serum FT_3 level.

Distribution of study population according to age is depicted in Table No.-1. It shows that Epilepsy is more among age group 2-4yrs.(44%), and it decreases with increasing age. A study by *MB Duggan, Epilepsy in rural Ugandan children: seizure pattern, age of onset and associated findings shows that* Half (212 or 50.2%) had presented during infancy(8).

Sex prevalence of seizure in Table-2 concludes that there is male preponderance (1.5:1). *Wong et al* determined a M/F ratio of 1.22:1, while Karabiber et al, determined a ratio of 1.42:1 in a study of children aged 1-12yrs. in Malatya, Turkey**,** which is similar to our study.

Table-3, Table-4, and Table-5 shows that percentage of children having above normal value of blood TSH hormone level (>6.63µIU/ml.), is progressively increased with increasing duration of therapy, and this is also statistically significant ($p<0.05$). Blood TSH value was also significantly increased between 0month to 3month, 3month to 6 month and 6moth to 9 month, and this is also statistically significant.

Serum TSH (0mo.-3mo.) = p value 0.0045

Serum TSH (3mo.-6mo.) =p value 0.0026

Serum TSH (6mo.-9mo.) = p value 0.0414.

The finding of low serum fT_4 concentrations and higher TSH concentration in epileptic patients receiving VPA is coherent with earlier study by *Achilleas et al,* showed that Serum levels of thyroxin and free thyroxin were significantly decreased after 6 (*P* =.000 and .000, respectively), 12 (*P* =.000 and .015, respectively),and 24 (*P*=.000 and .003, respectively) months of treatment with VPA, whereas serum levels of triiodothyronine were significantly decreased only after 24 months of treatment (*P* =.043). Serum levels of thyrotropin were significantly increased after 6 (*P*=.000), 12 (*P*= .000), and 24 (*P* =.000) months of treatment with VPA. Thirteen children (43.3%) had thyrotropin values higher than the normal-range maximum after 6, 12, and 24 months of VPA monotherapy.

They concluded that VPA monotherapy in childhood may cause early and persistent alterations in thyroid function, which suggests a need for early and careful monitoring of serum thyroid hormone concentrations in epileptic children who receive VPA.

Jerome M.Hershman et al, studied 61 ambulatory children with epilepsy who had taken valproic acid (VPA) for more than 6 months showed that mean TSH in the VPA group was higher than that in the control group. FT_4 was slightly higher and FT_3 slightly lower in the VPA group as compared with the controls. None of the children had positive anti-TPO.

The high levels of serum basal TSH observed in VPA monotherapy patients may be due to the γ-aminobutyric acid (GABA) ergic properties of VPA (9), because GABA inhibits somatostatin release, and somatostatin inhibits TSH secretion(10).

They concluded, Subclinical hypothyroidism is prevalent among children with epilepsy on VPA therapy. This seems to justify screening for thyroid dysfunction during VPA therapy, especially when a high dose of VPA is used.

Table 6, table 7, and table 8, shows that serum FT_4 value is below normal in more and more children with increased duration of treatment ,3month(2%), 6month(10%), and 28% after 9month of therapy and which is also statistically significant((0mo.-3mo.) =p value 0.009, (3mo.-6mo.) = p value 0.0026, (6mo.-9mo.) = p value 0.0011.

Study from Ghaziabad UP, India by Mishra Harsh et al; Serum level of T_3, T_4 and TSH were determined in 40 epileptic patients of valproate monotherapy by EIA method. Epileptic patientshad significantly decreased T_3, T_4 whereas TSH level was significantly increased on valproate monotherapy.

VPA is metabolized in the liver via glucuronide conjugation and oxidation, as are, to a small extent, FT_3 and FT_4. However, there are contrasting results in clinical trials carried, in different conditions (11).

Doneray H et al .prospectively investigated this relationship in children receiving VPA monotherapy for a period up to 6 months. Serum TSH level was significantly increased in the patient group whereas FT_4 was significantly decreased, which is similar to our study result. The mean Cu concentration in the 6th months of VPA therapy was significantly lower than that of the control group. This study suggests that the alteration in the serum thyroid hormone profile during VPA therapy may result from the reduction in serum Cu levels, but in our study we did not measure serum Cu level, which need further study (7).

Although valproic acid has been used for the treatment of epilepsy for over 40 years, its mechanism of action is still unclear; this is also the situation with regard to the basis for the elevation of serum TSH. Valproic acid could increase serum TSH by affecting the complex central neuroendocrine control of TSH release that in turn might elevate serum FT_4.

Valproic acid also inhibits histone deacetylase, so it can modify transcription of many genes. The pathophysiology of the TSH elevation requires further investigation, as does the treatment of the subclinical hypothyroidism in these children (12).

J. Eiris-Pufial et al, studied 141 children to evaluate serum thyroid hormone balance in children receiving long-term therapy with carbamazepine (CBZ), valproate (VPA), and Phenobarbitone(PB).

The causal relation between VPA and increased TSH levels was clearly demonstrated by the recovery of normal TSH levels after the switch from VPA to ESM (ethosuximide) in one case. Increased TSH levels in patients treated with VPA alone have been reported in only three previous studies [13,14,15].

Table -9, shows that there is no alteration in the serum FT_3 value after 3month (0%), or 6month (2%) of therapy, but after 9 month , 18% children have below normal value which is statistically significant($p<0.0001$) (*shown in Table No.-10*) and our observation is supported by study made by *Achilleas Attilakos et al*, serum levels of triiodothyronine were significantly decreased only after 24 months of treatment (P =.043). It emphasize the need for follow up study for more duration.

V. Conclusion

VPA monotherapy in children may cause early and persistent alterations in thyroid function, which suggests a need for early and careful monitoring of serum thyroid hormone concentrations in epileptic children who receive VPA.

Further prospective studies are required to determine the mechanisms and risk factors for development of thyroid disturbances in children treated with VPA monotherapy and also need for follow up thyroid profile and treatment if required so.

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