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Original Research Article

Evaluation of thyroid hormones, prolactin & insulin in children on prolonged valproate monotherapy for epilepsy

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Abstract: Epilepsy is defined as the occurrence of two or more unprovoked seizures. The cumulative life time incidence is 3%, and more than half start in childhood. Antiepileptic valproic acid is used in most of the cases as 1st line therapy. The objective of the study was to evaluate the effect of valproate on thyroid hormone, insulin and prolactin in childhood epilepsy. A hospital-based, analytical cross-sectional study was conducted among the epileptic patients (1-12 years) who used valproic acid uninterruptedly for more than 6 months. Serum thyroid hormone levels including free thyroxine (fT_4) and thyroid stimulating hormone (TSH), insulin and prolactin were analyzed. There was a statistically significant variation of TSH (p value 0.001) among epileptic children receiving valproate monotherapy for more than 6 months. Other hormones fT4 (p value 0.832), prolactin (p value 0.654) and insulin (p value 0.453) did not show any significant variation. It was also shown that significant rise of TSH (p value 0.013) in children receiving valproate for more than 1 year and in children receiving valproate > 40mg/kg/day (p value 0.023) compared to others. The study did not reveal any statistically significant changes in insulin and prolactin level during valproate therapy. The present study showed that valproate causes significant alteration in TSH levels that is on valproate for more than 6 months. We have to check it periodically and also look for any sign or symptom of hypothyroidism appears or not.
Keywords: epilepsy, valproate, thyroid hormones, prolactin, insulin.

INTRODUCTION:

Epilepsy is a brain disorder characterized by its enduring predisposition to generate epileptic seizures and by its neurobiological, cognitive, psychological and social consequences of this condition [1]. The word epilepsy is derived from Greek verb meaning "to seize, possess, afflict" [2]. Around 50 million people in the world have epilepsy [3]. 80% of epileptic patients live in developing countries [4]. Epilepsy has significant economic implications in terms of health-care needs, premature death and lost work productivity. It responds to treatment about 70% of the time [5]. In mid-1800s the first effective anti- seizure medication, bromide, was introduced. Thereafter a wide number of drugs are available for treating epilepsy in children; sodium valproate is one of them. It has a broad spectrum of anticonvulsant activity, being at present anti-epileptic drug of choice for all forms of generalized epilepsy and most of partial seizures [6]. It acts by voltage gated Na^+ and Ca^{2+} channels and also by enhancing GABA-anergic tone by inhibiting GABA transaminase enzyme [7]. Though relatively a safe drug common side effects of valproate are nausea, headache, somnolence, abdominal pain, hepatotoxicity, pancreatitis etc. Weight gain is one of the most common side effects which can lead to hyperinsulinemia, insulin resistance and metabolic syndromes [8, 9]. Few studies have also proved that valproate therapy can change the endocrine status of the body [10-12]. In particular thyroid hormonal change, which can lead to defective neuro skeletal development and prolactin level which has association with PCOD, a common problem in adolescent girls [13-15]. As sodium valproate is widely prescribed drug for epileptic patients, the studies about the hormonal changes caused by valproate become significant. In Indian population not much study has been done in this regard in pediatric patients. Our study is an approach to detect whether any significant endocrine changes occurring in study population. If any significant variation could be detected from the study it can trigger a trend of more judicious clinical use of valproate in epileptic children.

MATERIALS & METHODS:

This observational, descriptive study of cross sectional design was undertaken in the department of Pediatric medicine of R G Kar medical college, Kolkata during 2013-14. Approval was taken from institutional

ethics committee before starting the study. Study population was 50 children of 1-12 years age who was on uninterrupted valproate monotherapy for epilepsy for atleast 6 months. Consent was taken before the study from parents. Children having abnormal liver or kidney function, any endocrinopathies, chromosomal abnormalities, taking drug which can alter insulin, thyroid and prolactin hormone level were excluded from our study. Clinical and socio-demographic parameters were recorded on a predesigned proforma. Blood sample is drawn for estimation of hormones. Sample collected at odd time kept in fridge (2-8^0 c) and sent for investigation on following day. Serum was separated by centrifugation (2000 x g) first, then sample were checked for hormonal levels in Biochemistry lab by using ELISA reader.

Data were entered into Microsoft Excel datasheet and analysed with SPSS-17.0. Number and proportion were calculated for categorical variables. Chi-square test was applied for comparison of these categorical variables. P-value <0.05 was considered statistically significant.

RESULTS:

Total 50 cases were taken of which 23 (46%) were below 6 years and 27 (54%) were of 7-12 years of age. Male were predominant, 30 (60%) in number in our study. Cases were first categorized according to i) duration of treatment (6-12 months and more than 12 months), ii) dosage of valproate (less than or more than 40 mg/kg/day) iii) type of seizure (GTCS, partial seizure with secondary generalization and complex partial seizure), iv) number of seizure (more or less than 5), whether there was history of v) status epilepticus vi) EEG abnormalities vii) family history of epilepsy and viii) patient intelligence quotient.

Then, we measure the distribution of fT4, TSH, insulin and prolactin level according to those parameters. No statistical significance was there between fT4 level and the study variables (Table 1). TSH level, though not related to age, sex, type and number of seizure, status epilepticus, family history, EEG abnormality and IQ of the patient, it had a significant correlation with duration of therapy (those who were taken valproate for >12 months compared to those who had taken for 6-12 months, p-value: 0.013) and dosage of valproate (those taken the drug for >40mg/kg/day with a p-value: 0.023) (Table 2). No statistically significant correlation was found between the study variables and insulin and prolactin hormone level (Table 3 & 4).

Table 1: Distribution of fT4 level

Variables		Min	Max	Mean	SD	p-value
Age	1-3 yrs	0.82	1.99	1.2713	.4470	0.823
	4-6 yrs	.7600	1.9000	1.2507	0.3789	
	7-9 yrs	0.8600	1.9000	1.3721	0.4079	
	10-12 yrs	0.6700	1.8800	1.3562	0.3866	
Sex	Female	0.6700	1.9900	1.3410	0.4547	0.710
	Male	0.8000	1.9000	1.2983	.3503	
Duration of Therapy	6-12 months	0.760	1.9900	1.3048	0.3987	0.810
	>12 months	0.6700	1.9000	1.3326	0.3897	
Dosage of valproate	<40mg/kg	0.670	1.9000	1.2678	0.3789	0.357
	>40 mg/kg	.8200	1.9900	1.3713	0.4070	
Type of seizure	GTCS	.6700	1.9000	1.9000	.3878	0.199
	Partial	1.3400	1.9900	1.9900	.2871	
	complex partial	1.1100	1.8800	1.8800	.5445	
No of seizure	<5	.6700	1.9900	1.2518	.3813	0.198
	>5	.8600	1.9000	1.3964	.3980	
Status epilepticus	no	.6700	1.9000	1.2856	.3808	0.438
	Yes	.8600	1.9900	1.3788	.4188	
EEG abnormality	No	0.6700	1.9900	1.3103	.4000	0.912
	Yes	.8200	1.9000	1.3230	.3885	
Family h/o epilepsy	no	0.6700	1.9900	1.3217	.3929	0.810
	Yes	.7600	1.9000	1.2867	.4073	
Intelligence quotient	Normal	.6700	1.9900	1.3441	.3959	0.163
	Low	.7600	1.6000	1.1050	.3061	

Table 2: Distribution of TSH level

Variables		Min	Max	Mean	SD	p-value
Age	1-3 yrs	2.2000	6.8000	5.7025	1.5938	0.645
	4-6 yrs	3.3000	6.9000	6.0867	1.1047	
	7-9 yrs	3.2000	6.8200	5.6407	1.1171	
	10-12 yrs	2.3000	6.7000	5.4577	1.6060	
Sex	Female	2.2000	6.9000	5.3195	1.6545	0.067
	Male	3.3000	6.9000	6.0150	.9688	
Duration of Therapy	6-12 months	2.2000	6.1000	5.9790	.9986	0.013
	>12 months	3.2000	6.9000	6.3416	1.6721	
Dosage of valproate	<40mg/kg	2.3000	5.9999	5.9100	1.4013	0.023
	>40 mg/kg	3.2000	6.2000	6.2857	1.2253	
Type of seizure	GTCS	.6700	1.9000	1.9000	.3878	0.199
	Partial	1.3400	1.9900	1.9900	.2871	
	complex partial	1.1100	1.8800	1.8800	.5445	
No of seizure	<5	2.3000	6.9000	5.5739	1.3883	0.329
	>5	2.2000	6.9000	5.5941	1.2209	
Status epilepticus	no	2.3000	6.9000	5.7297	1.3042	0.956
	Yes	2.2000	6.9000	5.7519	1.3880	
EEG abnormality	No	2.3000	6.9000	5.7333	1.3544	0.982
	Yes	2.2000	6.9000	5.7420	1.2944	
Family h/o epilepsy	no	2.2000	6.9000	5.5817	1.4026	0.075
	Yes	5.8000	6.9000	6.4433	.3271	
Intelligence quotient	Normal	2.2000	6.8200	5.6198	1.3563	0.089
	Low	5.8000	6.9000	6.5950	.4262	

Table 3: Distribution of prolactin

Variables		Min	Max	Mean	SD	p-value
Age	1-3 yrs	11.5000	34.2000	24.4625	7.8051	0.842
	4-6 yrs	9.4000	36.6000	21.4667	9.7485	
	7-9 yrs	11.2000	41.2000	20.9429	10.6877	
	10-12 yrs	11.1000	38.6000	23.0923	10.3446	
Sex	Female	11.1000	37.1000	20.7100	9.4301	0.898
	Male	9.4000	41.2000	23.2300	9.8989	
Duration of Therapy	6-12 months	10.3000	38.6000	23.4000	10.1797	0.277
	>12 months	9.4000	41.2000	20.3000	8.7733	
Dosage of valproate	<40mg/kg	10.3000	41.2000	20.2926	10.3329	0.128
	>40 mg/kg	9.4000	38.6000	24.4870	8.5626	
Type of seizure	GTCS	9.4000	41.2000	21.5591	9.7162	0.431
	Partial	11.2000	38.1000	26.8000	11.2715	
	complex partial	26.1000	29.2000	27.6500	2.1920	
No of seizure	<5	10.3000	41.2000	20.3893	10.1526	0.133
	>5	9.4000	38.6000	24.5545	8.7578	
Status epilepticus	no	10.3000	41.2000	21.4324	10.0703	0.407
	Yes	9.4000	38.1000	23.9000	8.9244	
EEG abnormality	No	10.3000	38.1000	20.3633	9.8001	0.097
	Yes	9.4000	41.2000	25.0100	9.0703	
Family h/o epilepsy	no	9.4000	38.6000	21.7659	9.5073	0.483
	Yes	10.4000	41.2000	24.3000	10.8657	
Intelligence quotient	Normal	9.4000	41.2000	22.0432	9.8545	0.727
	Low	11.2000	36.6000	23.5333	9.1646	

Table 4: Distribution of insulin

Variables		Min	Max	mean	SD	p-value
Age	1-3 yrs	12.5300	18.5000	14.9038	2.1836	0.1206
	4-6 yrs	9.4000	36.8700	15.4660	6.5422	
	7-9 yrs	3.9700	16.4000	11.9050	3.9979	
	10-12 yrs	3.2000	17.3000	12.1231	3.6827	
Sex	female	3.2000	19.4000	13.3465	3.5631	0.847
	male	3.9700	36.8700	13.6187	5.5554	
Duration of Therapy	6-12 months	3.9700	19.4000	13.2039	3.7240	0.571
	>12 months	3.2000	36.8700	14.0089	6.2957	
Dosage of valproate	<40mg/kg	3.2000	36.8700	12.8281	6.0511	0.282
	>40 mg/kg	8.3000	19.4000	14.3100	2.6785	
Type of seizure	GTCS	3.2000	36.8700	13.4634	5.0391	0.913
	Partial	9.6000	18.5000	14.4000	3.6615	
	complex partial	12.2000	13.3000	12.7500	0.7778	
No of seizure	<5	3.2000	36.8700	12.8175	5.9383	0.255
	>5	8.3000	19.4000	14.3909	2.7126	
Status epilepticus	no	3.2000	36.8700	13.1585	5.5581	0.458
	Yes	8.3000	18.5000	14.2563	2.6402	
EEG abnormality	No	3.2000	36.8700	13.6020	5.6123	0.870
	Yes	4.5000	18.5000	13.3715	3.4263	
Family h/o epilepsy	no	3.2000	36.8700	13.2290	5.2221	0.384
	Yes	12.3000	18.5000	14.7889	1.8818	
Intelligence quotient	normal	3.2000	36.8700	13.5339	5.1168	0.925
	Low	11.2000	15.3000	13.3333	1.4895	

Table 5: Mean with SD of fT4, TSH, Prolactin, Insulin of all patients

	Mean	**SD**	**p-value**
fT4 (ng/dl)	1.32	0.39	0.832
TSH (uIU/ml)	6.40	1.32	0.001
Prolactin (ng/dl)	13.22	9.69	0.654
Insulin (uIU/ml)	11.51	4.81	0.453

Table 5 showed that, in this study statistically significant variation of TSH (mean value 6.40+1.32uIU/ml, p-value 0.001) found among epileptic children receiving valproate monotherapy. Other hormones fT4, Prolactin and Insulin did not show any significant variation.

DISCUSSION:

This is an observational analytical study of cross sectional design focused on effect of prolonged sodium valproate monotherapy on thyroid, insulin and prolactin hormone level in children having epilepsy. In our study we included 50 children receiving sodium valproate monotherapy for more than 6 months. Our study revealed statistically significant elevation of TSH (mean value 6.40+1.32uIU/ml, p value 0.001) among epileptic children. Other hormones fT4 (mean value 1.32 +.39 ng/dl, p value .832), prolactin (mean value 13.22+9.69 ng/dl, p value .654), insulin (mean value 11.57+ 4.81 uIU/ml, p value .453) did not show any significant variation. As fT4 value didn't show any variation, at the same time TSH value elevated our study concluded a significant correlation between sodium valproate therapy and subclinical hypothyroidism. Although the exact mechanism in unknown, it has been postulated in previous studies that thyroid hormone levels alteration can be caused by antiepileptic therapy through several mechanisms. One possible mechanism is attributed to hepatic CYP450 enzyme induction by conventional drugs (phenytoin, carbamazepine, and phenobarbitone) with consequent accelerated thyroid hormone metabolism, thereby decreasing its serum concentration. [16]. another possible mechanism could be due to interference with hypothalamic-pituitary axis regulation of thyroid hormone production [17]. This was supported by Surks *et al*. and Theodoropoulos *et al.;* who showed that drug-induced inhibition of thyrotropin-releasing hormone (TRH) action on TSH release [18, 19].

Sahu JK *et al.;* conducted a cross sectional study in children aged 3-15 years (57 cases and 52 healthy age and sex matched control) with controlled epilepsy receiving valproate monotherapy for atleast 6

months [20]. TSH, fT4, anti-TPO antibody and valproic acid level was measured. There was a significantly high (p=0.12) subclinical hypothyroidism in those receiving valproate monotherapy compared with healthy controls (7.7%). This is supportive to the result of our study. The incidence of subclinical hypothyroidism was significantly higher in patients with valproate therapy than in controls (52.4 vs 16.7; p< 0.001) in a study done by Kim SH *et al.;* [21]. A study in Indian population of 2-12 years age by Aggarwal A *et al.;* revealed increased TSH level with both valproate and carbamazepine compared to control but was statistically significant only with valproate (p< 0.001) [22]. On the contrary, study done by Verrotti A *et al.;* showed that there is no significant changes in thyroid hormone in patients receiving valproate monotherapy, but significant changes in patients on combined therapy of valproate and carbamazepine [23].

We have evaluated correlation of different variables with thyroid hormone changes. Among them duration of therapy and dosage of valproate showed significant correlation with subclinical hypothyroidism. In our study 58% of children were getting sodium valproate for more than 1 year. It showed significant rise of TSH level (mean value 6.3416 + 1.6721 Uiu/ml, p value 0.013) in children received sodium valproate for more than 1 year compared to others who have received valproate for 6-12 months (mean value 5.9790+ .9986 Uiu). fT4 showed no significant variation as such. Findings corroborate with study done by Sahu *et al.;* according to their study, median duration of valproate therapy was significantly higher (p=0.039) in the subclinical hypothyroidism group (21 months) compared with those without subclinical hypothyroidism (14 months). Though study done by Cansu A show that, there is subclinical hypothyroidism in valproate treatment but the hormonal level did not change with short term or long term valproate therapy [24].

We have checked the effect of dosage of valproate on TSH level. In our study 23 children were getting sodium valproate at a dose above 40mg/kg. It showed significant rise of TSH level (mean value 6.2857+1.2253 uiu/ml, p value 0.023) in children received sodium valproate at high doses compared to others. fT4 showed no significant variation. No statistically significant correlation between sex and age group with subclinical hypothyroidism found in our study. No significant changes in thyroid hormone found in patients having more number of seizures (>5), patient having history of status epilepticus, family history of epilepsy and low IQ compared to other group. Kim SH et al in his study analysed the effect of valproic acid on thyroid function, seizure type, duration of treatment, dose and serum level of valproate on thyroid function[21]. It showed significant correlation between subclinical hypothyroidism and dosage of valproate, but no correlation with age and seizure type. Those results are supportive to our study.

Study done by Verrotti A *et al.;* found a statistically significant relationship between severe EEG changes and thyroid dysfunction (p=0.041) [23]. It was concluded that these patients should be followed up closely by thyroid function tests during treatment. But, in our study we didn't get any correlation between EEG changes and thyroid hormone level.

Our study didn't reveal any statistically significant changes in insulin and prolactin level during sodium valproate therapy. A study by Hideaki Kanemura et al contradicts it [25]. There was significant increase (p<0.01) in serum insulin level and insulin/glucose ratio in their population who had gain weight during treatment with valproate for more than 6 months. However, BMI stopped increasing with intensive behavior therapy without discontinuation of valproate. Another study done by A Masala et al evaluated the effect of sodium valproate on the prolactin levels [26]. No significant difference was observed like our study. It is explained by the fact that although sodium valproate may act as anticonvulsant by increasing GABA levels in the central nervous system, a central GABA ergic pathway is probably not involved in the control of prolactin secretion.

There is little limitation in our study. The results would have more reliable if we had conducted a prospective study instead of a cross-sectional one and if we can follow up the children who diagnosed as sub-clinical hypothyroidism on valproate therapy whether they develop sign and symptom of hypothyroidism in future or not. Even though there are lots of children who were on long term valproate therapy getting admitted or followed up in our outpatient department we could not involve all of them due to time constraints, difficulty in blood sample storage and cost of insulin ELISA kits.

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