ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 11 | November - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"TO STUDY THE THYROID FUNCTION TESTS ABNORMALITY AMONGST CHILDREN WITH EPILEPSY TAKING SODIUM VALPROATE MONOTHERAPY AT A TERTIARY CARE HOSPITAL".

Paediatrics

Dr Shivani Mathur* Post graduate 3rd year, Dept. of Pediatrics, Jhalawar Medical College, Jhalawar. *Corresponding Author

Dr Deepak Kumar Pareek Senior Resident, Dept. of Pediatrics, MAMC Agroha.

Dr Jeengar Sudha Rani Post graduate 3rd year, Dept. of Pediatrics, Jhalawar Medical College, Jhalawar.

Dr Rajendra Gupta Senior Professor and Head Dept. of Pediatrics, Jhalawar Medical College, Jhalawar.

ABSTRACT

BACKGROUND: Long-term administration of valproic acid (VPA) has side effects, including thyroid dysfunction. This study is conducted to study the thyroid profile in children of epilepsy on Sodium Valproate monotherapy and to determine if there is a relationship between dose and duration of sodium valproate used and its effect on thyroid function tests.

METHOD: This is a prospective observational Study conducted at SHKBM Hospital, Jhalawar Medical College, Jhalawar over a period of 3 months. Subjects were children who were diagnosed with epilepsy and were on sodium valproate monotherapy for a minimum duration of 6 months. Blood specimens were taken to evaluate serum T3, T4, and TSH levels in all subjects. Data was analysed using bivariate and multivariate analyses.

RESULTS: A total of 110 subjects were included in the study. Out of which 33.6% had elevated TSH (P value-0.001) which is significant. Duration of treatment for >5 years was found to be significantly associated with TSH elevation (p value :0.01)

CONCLUSION: Subclinical hypothyroidism occurs in patients on sodium valproate monotherapy for a minimum duration of 6 months. Thus, periodic monitoring of TSH values may be needed in children on sodium valproate for timely intervention.

KEYWORDS

Sodium Valproate, Epilepsy, TSH, T4, T3

INTRODUCTION:

Epilepsy affects 0.5 to 1% of children and is the most frequent chronic neurologic condition in childhood. It is a disorder characterised by a predisposition to generate seizures and by the neurobiological, cognitive, psychologic and social consequences of the condition. The main treatments for epilepsy are anti-epileptic drugs (AEDs), chosen in accordance with the frequency of seizures .Antiepileptic drugs change circulating hormones concentration and also pituitary responsiveness to various stimuli[1]. The level at which the antiepileptic drugs affect the endocrine system is not certain. It was found that some antiepileptic drugs decrease thyroid function but does not change the euthyroid state[2].Another hypothesis is that at therapeutic concentrations these drugs displace thyroid hormone from their serum binding protein[3].The high levels of serum basal thyroid-stimulating hormone observed in patients receiving valproate monotherapy may be because of the GABA stimulating properties of valproate, because gamma aminobutyric acid inhibits the release of somatostatin, and somatostatin inhibits thyroid stimulating hormone secretion[4]. Several possible risk factors for thyroid function disorders are the age at initiation of VPA, duration of VPA use, dose of VPA and concomitant use of VPA with other AEDs, like carbamazepine. The aim of our study was to evaluate for possible associations between thyroid dysfunction with daily dose and duration Of VPA use.

METHOD:

It is a Prospective Observational Study conducted on pediatric patients attending outpatient department and admitted in the medical wards at SHKBM Hospital, Jhalawar Medical College, Jhalawar from September 2021 November 2021. Inclusion criteria were children of 1-18 yr who were diagnosed cases of epilepsy attending opd and admitted in medical wards and were on sodium valproate monotherapy for a minimum duration of 6 months. We excluded children with progressive neurological, thyroid or other metabolic disease, those who have received any drug in the past 6 months that could effect thyroid function, family history of thyroid dysfunction or other endocrine problems and had poor compliance to medications.

History of some clinical manifestation of hypothyroidism such as short stature, alteration of the school yield, skin dries, fragile hair, and muscle pain was taken from parents and subjects. Blood specimens (2 mL) were obtained from the peripheral vein, without anticoagulant, using a 2 mL syringe. Serum is separated from cells by centrifugation. The sample is then subjected to Electro Chemiluminescent Immunoassay to measure freeT3,freeT4 and TSH levels.

All analyses were conducted using SPSS 25 Version. Statistical analyses used was Chi- square with significance at $P < 0.05$.

RESULTS:

Out of 110 children included in the study,72 were male and 38 were female. the highest prevalence was reported among 5-10 year age group(42%).

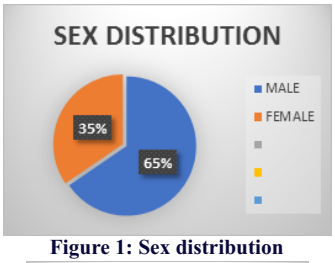

Figure 1: Sex distribution

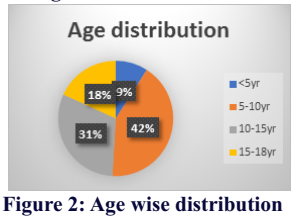

Figure 2: Age wise distribution

In this study none of the children had symptoms of hypothyroidism and 1.8% had signs of hypothyroidism.

TSH values were normal in 66.3% cases and increased in 33.6% cases. Among the cases 94.54% had normal T3 and T4 values and 5.4% had low values.

On comparing the effect of daily dose of VPA on TSH, it is found that

TSH is elevated in 21%, 39% and 19.4% in <20mg/kg, 20-40mg/kg and >40mg/kg group respectively which is found to be non significant as p value is >0.05.

T3 and T4 is low in 5.2%, 5.6% and 5.2% in <20mg/kg, 20-40mg/kg and >40mg/kg respectively. It is non significant.

On comparing the effects of duration of treatment with VPA on TSH, it is elevated in 16.2%,39.3% and 58.3% in <20mg/kg, 20-40mg/kg and >40mg/kg group respectively which is found to be significant as p value is <0.05.

T3 is low in 2.7%, 4.9% and 16.6% while T4 is low in 5.4%, 4.9% and 8.3% in 21%,39% and 19.4% in <20mg/kg, 20-40mg/kg and >40mg/kg group respectively which is found to be non significant as p value is >0.05.

Table 1: Effect of daily dose OF VPA on TSH, T3 and T4-

S.NO.	DOSE	TSH		χ^2, p value	T3		χ^2, p value	T4		χ^2, p value
		NORMAL	HIGH	4.157, 0.125	NORMAL	LOW	0.008, 0.99	NORMAL	LOW	0.255, 0.87
1.	<20mg/kg	30	8		36	2		36	2	
2.	20-40mg/kg	32	21		50	3		50	3	
3.	>40mg/kg	11	8		18	1		18	1	

The result is not significant for TSH, T3 AND T4 As p value is>0.05.

Table 2: Effect of duration of treatment of VPA on TSH, T3 AND T4-

S.NO.	DURATION	TSH		χ^2, p value	T3		χ^2, p value	T4		χ^2, p value
		NORMAL	HIGH	9.199, 0.010	NORMAL	LOW	3.576, 0.167	NORMAL	LOW	0.161, 0.922
1.	6mo-12mo	31	6		36	1		35	2	
2.	1yr-5yr	37	24		58	3		58	3	
3.	>5yr	5	7		10	2		11	1	

The result is significant for TSH AS P VALUE IS <0.05 , but not significant for T3 AND T4.

DISCUSSION:

Subclinical hypothyroidism can lead to clinical symptoms, such as growth failure and cognitive impairment, when the patient falls into a state of overt hypothyroidism. Monitoring of thyroid hormone levels is imperative so that therapy can be administered immediately, especially in high-risk groups, namely under the age of two years. In our study, subjects had no clinical manifestations of hypothyroidism.

A study conducted by Eiris Pufial in Spain founded that 26% of children treated with sodium valproate had an elevated TSH, and the incidence of subclinical hypothyroidism was higher in patients on sodium valproate therapy when compared with other antiepileptic drugs.

Manuel et all studied the evolution of subclinical hypothyroidism in children on anticonvulsants and observed subclinical hypothyroidism in the children receiving sodium valproate and carbamazepine group and there was a complete return to baseline was observed after a period of three months of drug discontinuation attributing the alterations in thyroid hormone levels to the anticonvulsants.

Achilleas Attilakos [5] et al studied **t**hyroid function in children with epilepsy treated with sodium valproate monotherapy and concluded that 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 VPA is initiated.

Se Hee Kim [6] et al studied Subclinical hypothyroidism during valproic acid therapy in children and adolescents with epilepsy and concluded that Serum VPA level and daily dose of VPA were correlated with TSH level. Subclinical hypothyroidism developed frequently in children and adolescents during VPA therapy.

an Italian study [7] in 2006 found that serum T4, fT4, T3, fT3 and rT3 levels decreased in the third and sixth month while on oxcarbazepine, whereas those using VPA had serum T4, fT4, T3, FT3, and RT3 levels almost equal to the base value, but increased mean serum TSH level, especially after 6 months of use. Those who used oxcarbazepine did not experience a significant change in serum TSH. This finding suggests that thyroid dysfunction may occur after 6 months of VPA use.

Several studies have shown that treatment of subclinical hypothyroidism can reduce the risk of overt hypothyroidism [8,9] Currently, there is no consensus on management of subclinical hypothyroidism in patients using VPA. Regular monitoring of serum thyroid levels every six months should be performed [8.] For the treatment of subclinical hypothyroidism in patients with manifestations, administration of L-thyroxine can be considered, as it may prevent atherosclerosis and intellectual impairment [9.]

To our knowledge, this study access the risk factors for thyroid dysfunction in patients with epilepsy using VPA monotherapy as an AED. Moreover, this study focused on the use of VPA as the antiepileptic drug. Our results show that despite relative safety and stability, the use of VPA monotherapy may increase the risk of thyroid.

CONCLUSION:

In this study TSH elevation in children on VPA is significant while decrease in T3 and T4 is non significant which goes in favour of subclinical hypothyroidism and none of them have any symptoms while 1.8% have few signs in favour of subclinical hypothyroidism.

In this study duration of treatment >5 years is significantly associated with subclinical hypothyroidism no association was found between drug dosage with thyroid dysfunction. Further studies should be done with a larger sample size scale and prospective cohort design.

Subclinical hypothyroidism has been found to affect cognition and growth of children. Thus, periodic monitoring of TSH values may be needed in children on sodium valproate for timely intervention.

CONFLICT OF INTEREST- NONE

FUNDING ACKNOWLEDGMENT-

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES:

1. Fichsel H, Knopfle G. Effect of anticonvulsants drugs on thyroid hormones in epileptic children. Epilepsia 1978; 19; 323-36.
2. Luhdorf K, chiristiansen P, Hansen JM, Lund M. The influence of Phenytion and carbamazepine on endocrine function: preliminary results. In Penry J K ed.Epilepsy:The 8th international symposium NewYork, WY: Raven Press, 1997 : 209 – 213
3. Oppenheimer JH, Fisher LV, Nelson KM, Jailer JW.Depression of the serum protein bound iodine in level by diphenylhydantoin. J Clin Endocrinal Metab 1961; 21: 252 -62.
4. Castro-Gago M, Novo-Rodríguez MI, Gómez-LadoC,Rodríguez-García J, Rodríguez-Segade S, Eirís-PuñalJ.Evolution of subclinical hypothyroidism in children treated with antiepileptic drugs. PediatrNeurol 2007;37:426- 430
5. Attilakos A, Katsarou E, Prassouli A, Mastroyianni S, Voudris K, Fotinou A, Garoufi A. Thyroid function in children with epilepsy treated with sodium valproate monotherapy: a prospective study. Clin Neuropharmacol. 2009 Jan-Feb;32(1):32-4. doi: 10.1097/WNF.0B013E318166CBCD. PMID: 18978499.
6. Kim SH, Chung HR, Kim SH, Kim H, Lim BC, Chae JH, Kim KJ, Hwang YS, Hwang H. Subclinical hypothyroidism during valproic acid therapy in children and adolescents with epilepsy. Neuropediatrics. 2012 Jun;43(3):135-9. doi: 10.1055/s-0032-1313913. Epub 2012 May 22. PMID: 22618302.
7. Cansu A, Serdaroglu AG, Camurdan O, Hırfanoglu T, Bideci A, Gucuyener K. The evaluation of thyroid functions, thyroid antibodies, and thyroid volumes in children with epilepsy during short-term administration of oxcarbazepine and valproate. Epilepsia. 2006;47:1855-9.
8. Adlin V. Subclinical hypothyroidism: deciding when to treat. Am Fam Physician. 1998;57:776-80.
9. Kaplowitz PB. Subclinical hypothyroidism in children: normal variation or sign of a failing thyroid gland? Int J Pediatr Endocrinol. 2010;2010:281453.