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THYROID PROFILE IN CHILDREN ON SODIUM VALPROATE MONOTHERAPY

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ABSTRACT

OBJECTIVES:. To study the thyroid profile in children on anticonvulsant sodium valproate monotherapy.
DESIGN: Cross sectional study.
SETTING: Tertiary care teaching hospital.
METHOD: This study was done in 60 children with seizure disorder on sodium valproate monotherapy recruited between Jan 2017 to June 2017 at Institute of Child Health, Chennai. Demographic data including age, sex, type of epilepsy, duration of treatment were recorded and 2ml blood was collected for testing thyroid profile.
RESULTS: Majority belonged to 1-5 years age group. Males (63%) predominated the study. Generalised seizures were the commonest seizure type. 35% had high TSH values and 6.6% had lower thyroid hormone levels. None had clinical symptoms or signs of hypothyroidism.

INTRODUCTION:

Epilepsy is the most common chronic neurological problem that occur in children. Antiepileptic drug therapy is the mainstay of its management. Although these anticonvulsants are well tolerated, many effects on endocrine function have been reported in literature. [1] Among the armamentarium of anticonvulsants, Sodium valproate is one of the broad spectrum drugs that is widely used for the treatment of partial and generalized epilepsy in childhood and adolescence.[2] .The effect of valproate on serum thyroid hormone concentrations has been controversial. Elevated levels of thyroid-stimulating hormone (TSH) have been demonstrated in some studies, [3,4,5] but not in others.[6]. This high levels of TSH could be explained by its GABA stimulating properties.[7]This study was done to assess the impact of sodium valproate on thyroid hormone levels in children on sodium valproate monotherapy.

SUBJECTS AND METHODS:

Study population- The study population comprised of 60 children with seizure disorder on anticonvulsant sodium valproate monotherapy.

Place of study- Children attending Paediatric Neurology Epilepsy outpatient department at Institute of Child Health.

Study period- January 2017- June 2017.

Exclusion criteria - Children with progressive neurological, thyroid or other metabolic disease, those who have received any drug in the past 6 months that could affect thyroid function, family history of thyroid dysfunction or other endocrine problems were excluded.

Study procedure- After getting informed consent from the parents of cases, they were subjected to detailed history and clinical examination and the findings are entered in the proforma. 2ml of blood was collected into test tubes through venipuncture under strict aseptic precautions. Serum is separated from cells by centrifugation. The sample is then subjected to ECLIA (Electro Chemiluminescent Immuno Assay) to measure freeT3,freeT4 and TSH levels. The normal range of thyroid levels are as follows-TSH(micro IU/ml)<1 year-0.72-8.35, 1-6 years-0.73-5.97, 7-12 years-0.60-4.84, freeT3(ng/dl) <1 year-0.89-1.99, 1-6 years-0.96-1.77, 7-12 years-0.97-1.67 and freeT4(pg/ml), <1 year-1.95-5.83, 1-6 years-2.41-5.50, 7-12 years-2.53-5.22.

RESULTS:

Among the 60 children on sodium valproate monotherapy, the distribution among age group were 1-5 years(48%),5-10 years(27%), and 10-12 years(25%). There were 38 males(63%) and 22 females(37%).The distribution of type of seizures were generalised tonic clonic seizures(53%), atypical febrile seizures(33%) and absence seizures(13%). 20% of the children were on the drug for 3-6 months, 45% for 6-12 months and 35% were for 1-5 years. The dose of sodium valproate varied between 10-15mg/kg/day (8.3%), 55% were on 15-20mg/kg/day, 16.6% on 20-25mg/kg/day, and 20% on 25-30mg/kg/day.

21children (35%) had high TSH levels, 4(6.6%) had low free T3 and T4 values. Out of the total 21 children with high TSH levels, 9.5% were on 10-15mg/kg/day,52.4% were on 15-20mg/kg/day,9.5% were on 20-25 mg/kg/day,28.6% were on 25-30 mg/kg/day. None of the children had symptoms of hypothyroidism.

DISCUSSION:

The effect of antiepileptic drugs on thyroid function is known for a long time. Thyroid hormones are important for normal mental and physical growth in children, and hence the study of the effect of antiepileptic drugs on thyroid function is important**.** The influence of anticonvulsants on the thyroid hormonnes has fascinated the clinicians and investigators for more than three decades. It was also found that some antiepileptic drugs decrease thyroid function but does not change the euthyroid state. Various side effects of VPA on endocrine functions have been reported in the literature[6]. Subclinical hypothyroidism with mild or moderately elevated thyroid stimulating hormone (TSH) levels is one of these, which has been demonstrated in some. [3,8], but not in all studies[9]. 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 gammaaminobutyric acid inhibits the release of

somatostatin, and somatostatin inhibits thyroid stimulating hormone secretion[7].

In this study, the commonest age group on sodium valproate was noticed to be 1-5 years followed by 5-10 years. Males predominated the study(63%). Generalised seizures were the common type. Nearly half of the study population were on sodium valproate for 6-12months duration and one third for 1-5 years. Half of them were on the dosage of 15-20 mg/kg/day, one fifth on 20-25mg and 25-30mg/kg/day respectively.

High TSH values were noticed in 21 (35%) of children in our cohort. Eiris-Punal and Vainionpaa et al had found increased serum TSH levels in 26% of children who were on sodium valproate mono therapy. Gulati et al have recorded that there was a significantly high prevalence of subclinical hypothyroidism (26%) in those receiving valproate monotherapy.[10]. Yilmaz et al have noted in their study of 223 children with epilepsy treated with valproate (n=129), the frequency of subclinical hypothyroidism at month 12 was 28% [11]. Elevated serum TSH levels were found in one third of patients on valproate monotherapy[12]. Isojarvi et al have also expressed similar views.[9] This is in contrast to a study conducted by Alberto et al in the university of bologna in which no significant changes in TSH levels were noticed in children on sodium valproate.[1].

In our study we found that 6.6% of the children on sodium valproate monotherapy had lower thyroid hormone levels. Durdane et al reported in their study that freet3 values were abnormal in 4% of the cases[13]. Reem et al have also expressed a similar view[14].Korkmaz et al in their study had also noticed low freet3 levels in children on sodium valproate. However Ihsan et al have noted that the thyroid hormone levels did not change during valproate treatment[15]**.** Yaser et al in their study on twenty children on valproate monotherapy for a minimum of three months and ten apparently normal children concluded that the mean serum levels of thyroid hormones in patients were not statistically significant different from those of the controls.[16].

CONCLUSION:

Thyroid stimulating hormone(TSH) levels are high in nearly one third of epileptic children on sodium valproate monotherapy. It is imperative that thyroid function should be paid attention in children with epilepsy who are on sodium valproate therapy though none of them had clinical symptoms of hypothyroidism.

REFERENCES:

1. Alberto V, Melissa L, Alessandra S, Emilio F, Francesco C. Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate. European Journal of Endocrinology.2009;160:81-86.
2. De Silva M, MacArdle B, McGowan M, Huges E, Stewart J, Neville B G et al Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. Lancet 1996; 347: 709-13.
3. Vainionpaa L K, Mikkonen K, Rattya J, Knip M, Pakarinen A J, Myllyla V V et al Thyroid function in girls with epilepsy with carbamazepine, oxcarrbazepine, or valproat monotherapy and after withdrawal of medication . Epilepsia. 2004; 45: 197-203.
4. Cansu A, Serdaroglu A, Camurdan O, Hirfanoglu T, BideciA, 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;47:1855-59.
5. Hirfanoglu T, Serdaroglu A, Camurdan O, Cansu A, Bideci A, et al . Thyroid function and volume in epileptic children using carbamazepine, oxcarbazepine and valproate.PediatrInt. 2007;49:822-26.
6. Verrotti A, Laus M, Scardapane A, Franzoni E, Chiarelli F. Thyroid hormones in children with epilepsy during long term administration of carbamazepine and valproate . EurJ Endocrinol. 2009; 160: 81-86.
7. Castro-Gago M, Novo-Rodríguez MI, Gómez-LadoC,Rodríguez-García J, Rodríguez-Segade S, Eirís-Puńal J. Evolution of subclinical hypothyroidism in children treated with antiepileptic drugs. PediatrNeurol 2007;37:426-430.
8. Eiris Punal J, Del Rio Garma M, Del Rio Garma M C, Lojo Rocamonde S, NovoRodriguez I, CastroGagoM. Long term ttreatment of children withepilepsy with valproate or carbamazepine may cause subclinical hypothyroidism. Epilepsia. 1999; 40: 1761-66
9. Isojarvi J I, T urkka J, Pakarinen M, Rattya J, MyllylaV V. thyroid function in men taking carbamazepine, oxcarbazepine or valproate for epilepsy. Epilepsia. 2001; 42:.930-34.
10. Sahu J K, Gulati S, Kabra M, Arya R, SharmaR, Gupta N . et al Evaluation of subclinical hypothyroidism in ambulatory children with controlled epilepsy on valproate monotherapy. J Child Neurol. 2012; 27: 594-597.
11. Yilmaz U, Yilmaz T S, Akinci G, Korkmaz H A, Teggul H. The effect of antiepileptic drugs on thyroid function in children. Seizure. 2014 Jan: 23(1): 29-35.
12. Violeta Ilic´ , Dragana Bogicevi , Branislava Miljkovic, Maja Jesi, Marijana Kovacevi, Milica Prostran , Sandra Vezmar Kovacevi . Duration of valproic acid monotherapy correlates with subclinical thyroid dysfunction in children with epilepsy. Epileptic Disord 2016; 18 (2): 181-86.
13. Durdane A, Solmaz V, Çevik B , Pekdaş E, Kurt S Serum Lipids and Thyroid Functions in Young Epileptic Patients Undergoing Monotherapy with Valproate or Levetiracetam. Eur J Gen Med 2015; 12(1):59-63.
14. Reem A. Abdel Aziz, Mostafa A. Abu ELela. Is It Necessary to Measure Thyroid Hormone Levels in Children Receiving Antiepileptic Drugs? J Pediatr Epilepsy DOI: 10.1055/s-0038-1648242.
15. İhsan Kafadar, Kılıç B A, Arapoglu M . Evaluation of Thyroid Hormones in Children Receiving Carbamazepine or Valproate A Prospective Study. J Child Neurol. Volume: 30 issue: 1, page(s): 63-68.
16. Ahmed Y A , Hassan A E A , Hammour A E , Elsayed A E A, Abdel-Meguid A M and Fayed H M. Serum lipids and thyroid hormone level changes in epileptic children on valproate mono therapy: is there a relation? AAMJ, Vol.9, N. 3, September, 2011, Suppl 1.