**Effect Of Valproate On Thyroid Gland Function In Children With Epilepsy**

**Dr. Eman Sh. AL- Obeidy\* Ph.D**

**ABSTRACT**

**Background**

Epilepsy is the fourth most common neurologic disease, following migraine, stroke, and Alzheimer-related dementia. the primary treatment is the use of anticonvulsant drugs , valproate is an effective anticonvulsant that is widely used for the management of focal and generalized epilepsy. It was approved for use in 1978 , although it is well tolerated many side effect have been reported .

**Aim of the study**

To study the effect of valproate drug on thyroid function in epileptic children.

**Patients and methods**

This cross sectional study looking for thyroid function status in two cross section , one is the valproate group (epileptic children used valproate ) and a second healthy group age and sex matched (not used valproate and not having epilepsy ).

The study was conducted and included seventy two children , among them 36 were epileptic children treated with valproate (valproate group) and 36 were healthy children ( healthy group ) , who met the

inclusion criteria , who were interviewed using questionnaire, during first of January till the first of December 2018 , in ( Epileptic Clinic in Baghdad Teaching Hospital) , ( Pediatric Neurology Clinic and Ward in Children Welfare Teaching Hospital ) and ( General Pediatric Clinic in Children Welfare Teaching Hospital) in Medical City Directorate , We compared the two group (valproate group and healthy group) by

some variables studied include thyroid stimulating hormone , Thyroxine and triiodothyronine .

Then we did compared in valproate group according to the change of result in thyroid function test by following variables age , sex , type of epilepsy (focal or generalized ) , duration of valproate , dose of

valproate .

**Result**

This study has enrolled 36 children known to have epilepsy on valproate treatment and age and sex matched 36 healthy children as a healthy group. According to thyroid function test there's significant increase in thyroid stimulating hormone in valproate group while none of healthy

group was having elevated thyroid stimulating hormone . Thyroxine and triiodothyronine stay within normal reference for both groups . Duration of treatment with valproate more than 24 months have a

significant value in increase thyroid stimulating hormone in valproate group , while other variables age , sex , type of epilepsy and dose of valproate didn’t have significant value in increase thyroid stimulating

hormone in valproate group.

**Conclusion**

Subclinical hypothyroidism can occur in epileptic children treated with valproate for long duration more than 24 months .

**\*Virology Lab-dialysis Center-Medical City-Baghdad**

**Introduction**

Epilepsy is the fourth most common neurologic disease, following migraine, stroke, and Alzheimer-related dementia (1) , its defined as a disorder of the brain characterized by any of the following conditions:

(1) At least two unprovoked (or reflex) seizures occurring >24 hour apart.

(2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

(3) Diagnosis of an epilepsy syndrome. (2,3)

A seizure on the other hands,is defined as an excessive burst of abnormal synchronized neuronal activity affecting small or large neuronal networks that results in clinical manifestations that are sudden, transient and usually brief(2).

The cumulative life time incidence of epilepsy is 3% and more than

half of cases start in childhood.

Developing countries have higher prevalence due to the poorer perinatal care, standards of nutrition , public hygiene and the greater risk of brain injury, cerebral infection. Incidence of seizures is age dependent(4).

The highest incidence rate (100 per 100,000) is observed in the first year of life, declining to approximately 20 cases per 100,000 per year in adolescence . (5,6). Many drugs are used for treatment of this disease valproate is among them which is an effective anticonvulsant drug that is widely used for the management of focal and generalized epilepsy.(7,8)

It was approved for use in 1978.(9). There action depend on the enhance GABA transmission, inhibit voltage- dependent sodium channels andinhibit voltage dependent T-type calcium channels but unfortunately many studies searching about the effect of sodium valproate on thyroid gland, in epileptic children treated with sodium valproate as a monothearpy .

In some studies no alteration have been determined in thyroid hormone function in patients treated with sodium valproate . Other studies have determined alteration in thyroid hormone function , the underling mechanisms remained unclear .

Sodium valproate may interfere with secretion , metabolism and feedback regulator of thyroid stimulating hormone via its gamma aminobutiric acid properties . (9,10)

Another possible mechanism may be due to difference of serum trace elements in epileptic children treated with sodium valproate .(10) Therefor our study aimed to shed light on the effect of valproate on thyroid function in epileptic children.

**PATIENTS AND METHODS**

This cross sectional study looking for thyroid function status in two cross section, one is the valproate group (epileptic children used valproate) and a second healthy group age and sex matched (not used valproate and not having epilepsy).

First part of the analysis evaluated thyroid function status between the two study group and the second part of the analysis looking for variables associated with thyroid dysfunction within valproate group.

This study was conducted in ( Epileptic Clinic in Baghdad Teaching Hospital) , ( Pediatric Neurology Clinic and Ward in ChildrenWelfare Teaching Hospital ) and ( General Pediatric Clinic in Children Welfare Teaching Hospital) in Medical City Directorate , Baghdad , Iraq , from first of January 2018 to first of December 2018 .

The total number of children enrolled in the current study was seventy two , among them 36 were epileptic child (valproate group) who meet the inclusion criteria and 36 were healthy child ( healthy group ) . For healthy group , they studied thirty sex (36) age- and sexmatched , healthy children , including the children with simple cases (like upper respiratory tract infection , mild headache ) attended to the out patient clinic in Welfare Child Teaching Hospital during the same period.

The sample of blood ( 2 ml ) send to Medical City Teaching Laboratories/ Hormonal Assay to measure thyroid function test ( TSH , T3, T4 ) by IMMULITE analyzer / SIEMENS , competitive chemiluminescent enzyme immunoassay.

Then we compared the two group (valproate group and healthy group) by some variables studied include TSH , T3 and T4 . Then we did compared in valproate group according to the change of result in thyroid function test by following variables age , sex , type of epilepsy (focal or generalized ) , duration of valproate , dose of valproate

in mg/kg/day . Dose of valproate was calculated by dividing the total dose per

day (mg) on child weight(kg). Epilepsy type was classified to focal and generalized according to 2010 ILAE(international league against epilepsy) .

**Statistical Analysis:**

Data were first entered in an excel file, transported later into statistical package for social sciences file version 24 (SPSS v24) for data analysis. Continuous variables presented as means and disdiscrete variables presented as numbers and percentages. Chi-square test for independence used to test the significance of association between discrete variables.

Level of significance was set at P value equal or less than 0.05.

**RESULTS**

This study has enrolled 36 children known to have epilepsy on Valproate treatment (Valproate group) and age and sex matched 36 healthy children as a comparison group (Healthy group).

Age varied in Valproate group from 2.2 to 15.2 years with a mean age of 8.3±4.0 years. In healthy group, age varied from 2.1 to 14.5 years with a mean age of 7.6±3.3 years.

Most frequent age group was the age group >5 to 10 years (table 1).

Males contributed to 55.6% of sampled children (table 1).

Table 1: Characteristics of children according to study group:

|  |  |  |
| --- | --- | --- |
| **Healthy group N=36** | **Valproate group**  **N=36** | **Variables** |
| 10(27.8)  15(41.7)  11(30.6) | 10(27.8)  15(41.7)  11(30.6) | **Age Group**  2 - 5 y n(%)  >5 - 10 y n(%)  > 10 y n(%) |
| 20(55.6)  16(44.4) | 20(55.6)  16(44.4) | **Sex**  Male n(%)  Female n(%) |

T 3 level varied from 1.32 to 2.58 nmol/L with a mean of 1.82±0.35 nmol/L in Valproate group, and in healthy group it varied from 1.34 to 2.61 with a mean of 1.89±0.33 nmol/L. this variation in means was found not significant (P > 0.05, table 2).

T 4 level varied from 60 to 151 nmol/L with a mean of 96.68±22.59 nmol/L in Valproate group, and in healthy group it varied from 68 to 152 with a mean level of 100.78±21.67 nmol/L. This variation in means found not significant (P > 0.05, table 3).

TSH level varied from 0.87 to 8.23 ulu/L with a mean of 3.52±2.15 ulu/L in Valproate group, and in healthy group it varied from 0.55 to 3.46 ulu/L with a mean of 2.18±0.92 ulu/L. Higher mean for TSH level in Valproate group compared to halthy group was found significant (P < 0.05, table 3). Seven children (20.6%) of Valproate group were having elevated TSH while none of comparison group was having elevated TSH.

Table 2: Thyroid function results for study group:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Statistic** | **Valproate Group**  **N=36** | **Healthy Group**    **N=36** | **P value** |
| **T3 level nmol/L** | Min- Max  Mean± SD | 1.32-2.58  1.82-0.35 | 1.34-2.61  1.89-0.33 | **0.402** |
| **T4 level nmol/L** | Min- Max  Mean± SD | 60.00-151.00  96.68±22.59 | 96.68±22.59  100.78±21.67 | **0.434** |
| **TSH level ulU/mL** | Min- Max  Mean± SD | 0.87-8.23  **3.52±2.15** | 0.55-3.46  **2.18±0.92** | **0.001** |

**Figure 1: Distribution of enrolled children according to study group and to**



Within Valproate group, seven (20.6%) children found having elevated TSH level, and remaining children were having normal TSH level (figure 1).

Each of age, sex and type of epilepsy did not significantly associated with TSH status in Valproate group (P > 0.05, table 4). Duration of Valproate use varied from 13 to 33 months in those with elevated TSH with a mean duration of use of 24.4±6.7 months. Children on Valproate with normal TSH gave history of Valproate treatment duration

varying from 6.5 to 28.0 months with a shorter mean duration (13.7±6.4 months).

There is a significant association between duration of Valproate treatment and TSH elevation, that majority (71.4%) of those with elevated TSH are on Valproate treatment for more than 24 months and majority (86.2%) of those with normal TSH did not cross the period of 24 months of treatment with Valproate (P < 0.05, table 3, figure 2). Taking into consideration that none of studied children in their first 6 months of Valproate treatment was having elevated TSH level.

Dose of Valproate in mg per Kg per day given to Valproate group varied from 21.7 to 43.0 with a mean dose of 27.9. This study did not found children with elevated TSH significantly having higher dose (in mg/kg/day) of Valproate treatment (31.4±6.8) compared to (27.0±4.7) in children with non-elevated TSH (P > 0.05, table 3).

Table 3: Characteristics of valproate group according to status of TSH level:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable Statistic TSH status in Valproate Group P-value | | | | | |
| All Elevated Normal | | | | | |
| **Age Group**  2 - 5 y  >5 - 10 y  > 10 y | n(%)  n(%)  n(%) | 10(27.8)  15(41.7)  11(30.6) | 3(42.9)  2(28.6)  2(28.6) | 7(24.1)  13(44.8)  9(31.1) | 0.583 |
| **Sex**  Male  Female | n(%)  n(%) | 20(55.6)  16(44.4) | 4(57.1)  3(42.9) | 16(55.2)  13(44.8) | 0.925 |
| Type of epilepsy  Generalized  Focal n(%) | n(%)  n(%) | 26(72.2)  10(27.8) | 5(71.4)  2(28.6) | 21(72.4)  8(27.6) | 0.958 |
| **Duration on Valproate**  6-12 m  >12-24 m  >24 m | n(%)  n(%)  n(%) | 15(41.7)  12(33.3)  9(25.0) | **0(0.0)**  **2(28.6)**  **5(71.4)** | **15(51.7)**  **10(34.5)**  **4(13.8)** | **0.004** |
| **Dose of Valproate/kg/day (mg)** | Min- Max  Mean± SD | 21.7-43.0  27.9±5.3 | 22.0-43.0  31.4±6.9 | 21.7-41.0  27.0±4.7 | 0.051 |



**Figure 2: Distribution of children in Valproate group according to status of TSH level and to duration of treatment with Valproate.**

**Figure 3: Mean Valproate dose of children in Valproate group according to status of TSH level.**

**DISCUSSION**

The goal of anti-seizure drugs is to control seizure or at least to reduce their number, but the side effect of anti- seizure drugs is also important.

The current study has been found that seven out of thirty six children (valproate group) have increased the serum thyroid stimulating hormone more than normal reference , but serum T3 and serum T4 didn’t increased or decreased more than normal reference , while in the healthy group serum TSH , T4 and T3 were not affected and remained within their normal reference , and this was statistically significant , therefore the current study showed that valproate has an effect on thyroid gland increased serum TSH and normal serum T3 , T4 ( subclinical hypothyroidism ) and this result consistent with Serbia study by Violeta , et al.(11) , Republic of Korea study by Kim , et al . (12) In which valproate

cause subclinical hypothyroidism , while inconsistent with Egypt studyby Ahmed , et al .(13) , Iran study by Susan , et al . (14) .and Italy study byAlberto et al.(15) in which all of them no determined any effect ofvalproate on thyroid function ( TSH , T3 and T4) , this may be due tosmall sample effect on result in Ahmed , et al .(13) (valproate group 20 ,healthy group 10) , Alberto ,et al (15) (valproate group 14) and may be dueto short duration of treatment with valproate ( three months ) effect on result in Susan , et al.(14)

In this study we found that the age was not significant risk factor for developed subclinical hypothyroidism in valproate group and this result agree with Serbia study by Violeta , et al.(11) , Republic of Korea study by Kim , et al . (12), India study by Sahu. et al . (16) but disagree with Lebanon study by Mikati ,et al. (17) which showed younger age less than 4 years have increased risk to developed subclinical hypothyroidism , may be due to Mikati , et al .(17) study included patients treated with valproate as poly therapy , as well as patients with diseases other than epilepsy , so these reasons may have influenced the results. In the current study the gender was not important risk factor for

developed subclinical hypothyroidism in valproate group and this result

was consistent with other studies (11,12,17) .

Epilepsy type in our study was not influenced the developed of subclinical hypothyroidism in epileptic children treated with valproate this may be need larger sample and longer duration to evaluate this factor more precisely , this result consistent with other broad studies (11,12,16)

In the current study duration of valproate associated with subclinical hypothyroidism by Mean ±SD was 24.4 ±6.7 months while in normal thyroid function test was 13.7±6.4 months and this was statistically significant P value ( 0.004 ) , this means increase in duration associated with increase in subclinical hypothyroidism ( 6\_12 months

SCH was 0% , >12\_24 months SCH was 28.6% , > 24 months SCH was

71%) , this consistent with India study by Sahu. et al.(16) which also

revealed duration of valproate more than 24 months as a risk factor for

subclinical hypothyroidism , while in Lebanon study by Mikati ,et al. (17)

revealed duration from ( 6 months\_ 24 months )as a risk factor for

subclinical hypothyroidism.

The dose of valproate in epileptic children associated with subclinical hypothyroidism was by Mean ±SD was 31.4±6.8 mg/Kg/day , while in epileptic children associated with normal thyroid function was 27.2±4.8 mg/Kg/day , and this was statistically not significant P value (0.051), and this agree with Serbia study by Violeta , et al.(11) , Lebanon study by Mikati ,et al (17) India study by Sahu. et al.(16) , but disagree with

Republic of Korea study by Kim , et al (12) which revealed dose of valproate as a risk factor for subclinical hypothyroidism , this may be due to in Korea study included large sample 61 patients treated with valproate compared to our study (36 patients ) , also Korea study showed that 52.4% of patients with epilepsy had subclinical hypothyroidism during valproate treatment while in our study only 20.6% of epileptic group showed subclinical hypothyroidism and this different may effect on result.

**REFERENCE**

1. Swaiman KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, Pearl PL, Shevell M. Swaiman's Pediatric Neurology E-Book: Principles and Practice. Elsevier Health Sciences; 2017 Sep 21: p 497\_500.

2. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel Jr J, Forsgren L, French JA, Glynn M, Hesdorffer DC. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82.

3. Tamber MS, Mountz JM. Advances in the diagnosis and treatment of epilepsy. InSeminars in nuclear medicine 2012 Nov 1 (Vol. 42, No. 6, pp. 371-386).

4. Bourgeois BF, Dodson E. Pellock, J.M .Pediatric epilepsy: diagnosis and therapy. Demos Medical Publishing; 2007 Dec 16.p147\_162.

5. Sharma A. Seizures and epilepsy in children. The Indian Journal of Pediatrics. 2013 Nov 1;80(11):925-35.

6. Cross JH, Kluger G, Lagae L. Advancing the management of childhood epilepsies. european journal of paediatric neurology. 2013 Jul 1;17(4):334-47.

7. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshé SL. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010 Apr;51(4):676-85.

8. Abaci A, Saygi M, Yis U, Demir K, Dirik E, Bober E. Metabolic alterations during valproic acid treatment: a prospective study. Pediatric neurology. 2009 Dec 1;41(6):435-9.

9. McNamara JO. Drugs effective in the therapy of the epilepsies. Goodman & Gilman's The pharmacological basis of therapeutics. 10th ed.:Appleton and lange. 2001:461-86.

10. Doneray H, Kara IS, Karakoc A, Tan H, Orbak Z. Serum thyroid hormone profile and trace elements in children receiving valproic acid therapy: a longitudinal and controlled study. Journal of Trace Elements in Medicine and Biology. 2012 Oct 1;26(4):243-7.

11. 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(03):135-9.

12. Ahmed YA, Hassan AE, Hammour AE, Elsayed AE, Abdel-Meguid MM, Fayed HM. SERUM LIPIDS AND THYROID HORMONE LEVEL CHANGES IN EPILEPTIC CHILDREN ON VALPROATE MONO THERAPY: IS THERE A RELATION?. AAMJ. 2011 Sep;9(3):1.

13. Sahu JK, Gulati S, Kabra M, Arya R, Sharma R, Gupta N, Kaleekal T, Reeta K, Gupta YK. Evaluation of subclinical hypothyroidism in ambulatory children with controlled epilepsy on valproate monotherapy. Journal of child neurology. 2012 May;27(5):594-7.

14. Ilić Violeta , Bogićević D, Miljković B, Ješić M, Kovačević M, Prostran M, Kovačević SV. Duration of valproic acid monotherapy correlates with subclinical thyroid dysfunction in children with epilepsy. Epileptic Disorders. 2016 Jun;18(2):181-6.

15. AMIRSALARI SUSAN , DOST ZT, KAVEMANESH Z, TORKAMAN M, BEIRAGHDAR F, AFSHARPAYMAN S, TEIMOORI M, SABOURI A, ARANI AM, GHAZAVi Y. Thyroid function in epileptic children who receive carbamazepine, primidone, phenobarbital and valproic acid. Iranian Journal of Child Neurology. 2011 May 23;5(2):17-22.

16. Verrotti Alberto , Laus M, Scardapane A, Franzoni E, Chiarelli F. Thyroid hormones in children with epilepsy during long-term administration of carbamazepine and valproate. European journal of endocrinology. 2009 Jan 1;160(1):81-6.

17. Mikati MA, Tarabay H, Khalil A, Rahi AC, El Banna D, Najjar S. Risk factors for development of subclinical hypothyroidism during valproic acid therapy. The Journal of pediatrics. 2007 Aug 1;151(2):178-81.