

Vol 45 (3) September , 2021

Print: ISSN 0304 4904
Online: ISSN 2305-820X



PAKISTAN PEDIATRIC JOURNAL



A JOURNAL OF PAKISTAN PEDIATRIC ASSOCIATION

Indexed in EMBASE/Excerpta Medica, Index Medicus WHO

IMEMR & Global Health/CAB Abstracts and UDL-EDGE Products and Services

www.pakpedsjournal.org.pk

<http://www.pakmedinet.com/PPJ>

ORIGINAL ARTICLE

Subclinical Hypothyroidism in Children Treated with Antiepileptic Drugs

MUHAMMAD SAEED, SAEED AL-FADHL, ALI QURESHI, Sanaa Gammaa, Abdul Qadir

Pak Pediatr J 2021; 45(3): 272-76

ABSTRACT

Objective: To study the outcome of valproic acid, carbamazepine, and levetiracetam single drug therapy on thyroid functions.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: Study was done in Department of Pediatrics at King Fahad Armed Forces Hospital Southern Region, Saudi Arabia over three years period starting from March 2017 to February 2020.

Material and Methods: A total of sixty patients, age range of the patients was from 2 years to 14 years, among them 34 (56.66%) were female and 26 (43.33%) were male with newly diagnosed epilepsy treated with valproate (n=24), carbamazepine (n=17), and levetiracetam (n=19) were registered in the study. Serum free thyroxine (f T4), triiodothyronine (f T3) and thyroid stimulating hormone (TSH) were analysed before and six months after starting the treatment.

Results: A baseline thyroid functions were normal in all sixty patients. Two patients in carbamazepine treated group showed abnormal thyroid hormones results. Levetiracetam and valproate treated patients showed no remarkable change in f T3, f T4 and TSH serum levels. The density of subclinical hypothyroidism was only 3.33% overall and 11.76% in carbamazepine group.

Conclusion: In conclusion, carbamazepine has inimical effects on where as levetiracetam and valproate did not affect thyroid function in epileptic patients during the period of 6-month treatment in our study.

Key Words: Carbamazepine, Valproate, Levetiracetam, Children, Epilepsy, Thyroid functions

Correspondence to:

Muhammad Saeed,
Department of Pediatric
Neurology, King Fahad Armed
Forces Hospital Southern Region,
Saudi Arabia

E-mail:

muhammad964@hotmail.com

Received 17th April 2021;
Accepted for publication
15th June 2021

INTRODUCTION

Epilepsy is a chronic disease which needs extended management with anti-seizure drugs. Prolonged use of antiepileptic medications may disturb the cognition, metabolism, and thyroid function as well. It has been described in the literature that antiepileptic drugs may cause changes in the thyroid hormones level by affecting the hypothalamus-pituitary axis endocrine system.¹ The exact prevalence of subclinical

hypothyroidism induced by antiepileptic drugs (AEDs) is not well known, however AEDs may affect the thyroid functions by altering the metabolism, as suggested by a study done by Strandjord et al.²

Little information about the ramification of AEDs is available in the literature on thyroid function in pediatric age group.^{3,4} Valproic acid, carbamazepine, and levetiracetam are commonly prescribed AEDs for the treatment of different types of epilepsies in pediatric age group.^{5,6}

The increased level thyroid-stimulating hormone (TSH) have been mentioned in few studies conducted on patients treated with antiepileptic drugs. Carbamazepine generally decreases blood level of free thyroxine, but has varying impacts on TSH serum concentration. The effect of carbamazepine is similar to those of oxcarbazepine on thyroid function, mentioned in a couple of studies.^{7,8} The treatment of asymptomatic subclinical hypothyroidism in children treated with AEDs remains controversial. However, monitoring of thyroid functions using T4 and TSH serum level should be considered in these patients during anti-convulsive therapy.^{9,10}

MATERIAL AND METHODS

This study was performed in Department of Pediatrics at King Fahad Armed Forces Hospital Southern Region, Saudi Arabia. Confidentiality was maintained throughout the study. Children who were diagnosed with epilepsy based on clinical data and EEGs were included in the study. Children were considered eligible for inclusion if they were not receiving any medication other than antiepileptic drugs and they were in 2 years to 14 years of age range, had received carbamazepine, valproic acid and levetiracetam for 6 months duration and had been well controlled for more than six months. Patients receiving regular medication without any interruption were included in the study. Carbamazepine and valproic acid was advised with standard dosages range: carbamazepine 15 to 30 mg/kg per day and valproate 15 to 30 mg/kg per day respectively. Levetiracetam dosage range was from 30 mg/kg/day to 60 mg/kg/day.

The standard reference values for the serum concentrations of free triiodothyronine was 2 to 4.5 pg/mL, free thyroxine was 0.85 to 2.0 ng/dL, and thyroid-stimulating hormone was 0.6 to 5 mIU/mL.

We collected the information of all the patients which included; age at onset of epilepsy, duration of antiepileptics used and laboratory results including, f T₃ (free triiodothyronine) f T₄ (free thyroxine) and TSH (thyroid-stimulating hormone). All children were developmentally normal. The time of collection for the second sample after six months was between 8.0 am to 10.0 am after 12 hours of fasting in order to avoid diurnal variation.

Children with neurodegenerative disorders associated with epilepsy, symptomatic hypothyroidism due to primary thyroid disorders, metabolic disorders; or patients with poor compliance to AEDs therapy were not included in study.

Statistical analysis: For statistical analysis SPSS soft ware V15.0 was used. Ordinal variables have been mentioned as number and percentage significant set at $p < 0.05$. Chi-square and t-test were used for statistical analysis.

RESULTS

Sixty children with newly diagnosed and different type of epilepsies were enrolled in the study. Age range of the patients was from 2 years to 14 years, among them 34 (56.66%) were female and 26 (43.33%) were male. This study was conducted over three years period from March 2017 to February 2020. Twenty four patients received valproic acid (40%), nineteen patients were treated with levetiracetam (31.66) and seventeen children were given carbamazepine (28.33%). All selected patients in this study were euthyroid. Baseline thyroid profile was normal in all the patients. During follow up thyroid hormones profile was checked after six months after starting the treatment. The patients treated with valproic acid and levetiracetam did not show any significant difference in the serum level of fT₃, fT₄ and TSH. Two patients receiving carbamazepine showed statistically significant decrease in blood level of free T₃ ($p=0.02$) and fT₄ ($p= 0.025$) with elevated level of TSH ($p=0.02$).

TABLE 1: Number of patients according to age (n=60)

Age group (Years)	Number	Percentage
2-5	18	30.0
6-10	28	46.5
11-14	14	23.3
Total	60	100.0

TABLE 2: Study population according to sex (n=60)

Gender	Number	Percentage
Male	26	43.33
Female	34	56.66
Total	60	100.0

Female: Male ratio = 1.3:1

TABLE 3: Patients characteristics treated with antiepileptic drugs

Characteristics	Total n=60	Carbamazepine n=17	Valproate n=24	Levetiracetam n=19	p value
Age of onset, years mean ± SD, range	6±4 (4-14)	F= 7 (41.1%) M= 10 (58.8%)	F=10 (41.6%) M=14 (58.33%)	F=12 (63.15%) M=7 (36.84%)	<0.001
Seizure type Generalized Partial	G=42 (70%) P=18 (30%)	G=3 (17.64%) P=14 (82.35%)	G=20 (83.33%) P=4(16.66%)	G=7 (36.84%) P=12(63.15%)	<0.001
EEG Normal Epileptic	Normal=23 (38.33%) Epileptic=37 (61.66%)	N=5 (29.41%) E=12 (70.58%)	N=10 (41.66%) E=14 (58.33%)	N=8 (42.10%) E=11 (57.89%)	0.133

TABLE 4: TSH (μ IU/ml) serum level (Mean \pm SD) base line and after six months

Time of test	Total (n=60)	Carbamazepine (n=17)	Valproate (n=24)	Levetiracetam (n=19)
Baseline	2.25 \pm 1.9 p<0.015	2.81 \pm 1.12 p<0.020	3.15 \pm 1.33 p<0.010	2.72 \pm 0.95 p<0.021
After six months	3.25 \pm 1.80 p<0.001	3.50 \pm 1.55 p<0.008	2.80 \pm 1.32 p<0.011	2.55 \pm 1.40 p<0.034

DISCUSSION

Antiepileptic drugs have effect on thyroid functions. Different mechanism have been proved by many studies. But exact pathogenic mechanism how these drugs disturb the thyroid function have not been fully elucidated. In some studies, epilepsy is considered as possible potential cause to make the changes in thyroid hormones level by effecting the hypothalamic-hypophysis thyroid axis.¹¹ The purpose of prescribing antiepileptic drugs is to fully control the epilepsy or at least to reduce the frequency of seizures. Most of the studies were done in adult patients and only few studies were conducted in children.¹²

It has been observed in previous studies that asymptomatic hypothyroidism may develop in children during antiepileptic treatment. Although, the children receiving antiepileptics have not shown clinical symptoms of hypothyroidism.^{13,14}

Our study investigated the effects of commonly used antiepileptic drugs, carbamazepine, valproate and levetiracetam, on thyroid hormone level in pediatric patients. In previous studies^{15,16} it has been mentioned that epilepsy itself may affect the thyroid function, although our study is small, but baseline thyroid profile in our patients excluded the possibility of epilepsy as causative factor for subclinical hypothyroidism and we did not find deranged thyroid functions. We therefore, suggest thyroid hormone level disturbances are not due to

epilepsy itself. Couple of researchers described subclinical hypothyroidism in patients on valproate monotherapy whereas, others observed no effects on thyroid function.^{17,18}

It has been proposed that treatment duration of valproate, daily dosage, and serum drug level may have impact on thyroid hormone levels, but the results are controversial.¹⁹

In some studies decrease in thyroid hormone level has been detected in patients receiving carbamazepine as early as 2-3 months after starting the treatment but in most of the researches thyroid hormone level decrease after 6 months of carbamazepine therapy.^{20,21} The decrease serum level of thyroid hormone might be due to competition between thyroid hormone and thyroxin binding protein.²¹ The present study showed a significant increase in the TSH level, and a significant reduction in the FT4 concentrations in two patients treated with carbamazepine.

Our patients who received valproate did not reveal any notable change of thyroid hormones level as compared to control reading. Many earlier studies also did not show effect on thyroid functions.²²⁻²⁴

Study conducted by Verrotti et al showed no abnormalities in pediatric epileptic patients taking valproic acid as single drug therapy.²⁴

In our two subjects who were treated with carbamazepine, there was significant reduction in

T4 & fT4 levels accompanying increased level of TSH. However, our patients who received carbamazepine and had abnormal thyroid hormone levels showed no clinical symptoms or signs of hypothyroidism. This is again similar to results which were found in study conducted by Svalheim et al and Zhang et al.¹⁷

A limited information about the effect of levetiracetam on thyroid is available. In our study, thyroid hormone levels were noticed unchanged in nineteen patients taking levetiracetam. This also, is similar to other studies which did not show effect on fT4 & TSH level in patients receiving levetiracetam.

Limitations: We did not have a comparison group because of social reasons. However, this issue may be resolved by using baseline serum level of thyroid hormones. The small number of patients was the other limitation of the study. Further studies with large sample size are required to make it clear the effects of anti-epileptic drugs on thyroid functions. We also, did not study Thyroid functions in patients who are treated with multiple anticonvulsants.

CONCLUSION

Asymptomatic thyroid hormone deficiency may occur during treatment with AEDs therapy that suggests a need for early and careful monitoring of serum thyroid hormone study in pediatric patients with epilepsy. Clinically and practically, there were no guidelines suggesting to check thyroid functions test on regular basis. However, if there is clinical suspicion about thyroid problem, thyroid functions could be checked. This is observational study which confirms observations of previous findings. Further prospective research may be required to evaluate the mechanisms of thyroid disturbances in children and also thyroid profile should be followed and treatment given if required.

Declaration of conflicting interests funding: Authors declared no conflict of interest.

Financial support: No financial support was received for the research, or publication of this study.

Ethical Approval: This study was approved by King Fahad Hospital ethical committee.

Authors' affiliation

Muhammad Saeed, Saeed Al-Fadhl, Ali Qureshi, Sanaa Gammaa, Abdul Qadir

Department of Pediatric Neurology, King Fahad Armed Forces Hospital Southern Region, Saudi Arabia

REFERENCES

1. Castro-Gago M, Novo-Rodríguez MI, Gomez-Lado C, Rodríguez-García J, Rodríguez-Segade S, Eirís-Punzal J. Evolution of subclinical hypothyroidism in children treated with antiepileptic drugs. *Pediatr Neurol* 2007;37:426–30.
2. Sahu JK, Gulati S, Kabra M, Arya R, Sharma R, Gupta N, et al. Evaluation of subclinical hypothyroidism in ambulatory children with controlled epilepsy on valproate monotherapy. *J Child Neurol* 2012;27:594–7.
3. Epilepsi Hastalarında Antiepileptik İlaç Tedavisinin Tiroid Hormon Düzeylerine Etkisi. Effect of Antiepileptic Drug Treatment on Thyroid Hormone Levels in Epilepsy Patients. *The Medical Bulletin of İstanbul*. March 2019.
4. Shih FY, Chuang YC, Chuang MJ, Lu YT, Tsai WC, Fu TY, Tsai MH. Effects of antiepileptic drugs on thyroid hormone function in epilepsy patients. *Seizure* 2017;48:7-10.
5. Aparicio-Claire AL, Rayo-Mares JD, Nishimura-Meguro E, Herrera-Márquez JR, Muñoz-Montúfar JP, Núñez-Enríquez JC. Prevalence of subclinical hypothyroidism in pediatric patients with drug-resistant epilepsy. *Rev Med Inst Mex Seguro Soc* 2017;55:579-8.
6. Vainionpää LK, Mikkonen K, Rättyä J, et al. Thyroid function in girls with epilepsy with carbamazepine, oxcarbazepine, or valproate monotherapy and after withdrawal of medication. *Epilepsia* 2004;45:197-203.
7. El-Farahaty RM, El-Mitwalli A, Azzam H, Wasel Y, Elrakhawy MM, Hasaneen BM. Atherosclerotic effects of long-term old and new antiepileptic drugs monotherapy: a cross-sectional comparative study. *J Child Neurol* 2015;30(4):451–7.
8. Adhimoolam M, Arulmozhi R. Effect of antiepileptic drug therapy on thyroid hormones among adult epileptic patients: An analytical cross-sectional study. *J Res Pharm Pract* 2016;5:171-4.
9. Jerome M.Hershman, 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;43:135-9.
10. Aygun F, Ekici B, Aydinli N, Aydin BK, Bas F, Tatli B. Thyroid hormones in children on antiepileptic therapy. *Int J Neurosci* 2012; 122(2): 69-73.
 11. Aggarwal A, Rastogi N, Mittal H, Chillar N, Patil R. Thyroid hormone levels in children receiving carbamazepine or valproate. *Pediatr Neurol* 2011; 45(3): 159-62.
 12. Lossius MI, Taubøll E, Mowinckel P, Gjerstad L. Reversible effects of antiepileptic drugs on thyroid hormones in men and women with epilepsy: a prospective randomized double-blind withdrawal study. *Epilepsy Behav.* 2009;16:64-68.
 13. Ihsan Kafadar, MD1, Betül Aydın Kılıç, MD2, Mujde Arapoglu, MD3, Koray Yalçın, MD4, and Nazan Dalgıç, MD. Evaluation of Thyroid Hormones in Children Receiving Carbamazepine or Valproate: A Prospective Study. *Journal of Child Neurology.* 2016;(4):1-6.
 14. Kim SH, Chung HR, Kim SH, et al. Subclinical hypothyroidism during valproic acid therapy in children and adolescents with epilepsy. *Neuropediatrics.* 2012;43:135-139.
 15. Verrotti A, Basciani F, Morrresi S, et al. Thyroid hormones in epileptic children receiving carbamazepine and valproic acid. *Pediatr Neurol.* 2001;25:43-46.
 16. Prasanta Rajak, Mani Kant. A Prospective Study on Thyroid Function in Children with Epilepsy Treated With Sodium Valproate Monotherapy. *Journal of Dental and Medical Sciences.* 2018; 17: 06-11.
 17. Svalheim S, Sveberg L, Mochol M, Tauboll E. Interactions between antiepileptic drugs and hormones. *Seizure* 2015;28:12-7.
 18. Yin-Xi Zhang, Chun-Hong Shen, Qi-Lun Lai, Gao-Li Fang, Wen-Jie Ming, Ru-Yi Lu, Mei-Ping Ding. Effects of antiepileptic drug on thyroid hormones in patients with epilepsy: A meta-analysis. *Seizure.* 2016;35: 72-79.
 19. Unsal Yılmaz, Tuba Sevim Yılmaz, Gu İn Akıncı, Hu seyin Anıl Korkmaz, Hasan Tekgu. The effect of antiepileptic drugs on thyroid function in children. *Seizure.* 2014; 23: 29-35.
 20. Catli G, Abaci A, Büyükgebiz A, Bober E. Subclinical hypothyroidism in childhood and adolescence. *J Pediatr Endocrinol Metab.* 2014;27(11-12):1049-57.
 21. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia.* 2014;55(4):475-82.
 22. Marta Murillo-Vallés, Santiago Martinez, Cristina Aguilar-Riera, et al. Subclinical hypothyroidism in childhood, treatment or only follow-up? *BMC* 2020;(20):282.
 23. Ergin Z, Savaş-Erdeve Ş, Kurnaz E, Çetinkaya S, Ayçan Z. Follow-up in children with non-obese and non-autoimmune subclinical hypothyroidism. *J Pediatr Endocrinol Metab.* 2018 Oct 25;31(10):1133-8.
 24. Gammons S, Presley BK, White PC. Referrals for elevated thyroid stimulating hormone to pediatric endocrinologists. *J Endocr Soc.* 2019 Nov 1;3(11):2032-40.