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Original Article

Effect of antiepileptic drug therapy on thyroid hormones among adult epileptic patients: An analytical cross-sectional study

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ABSTRACT

Objective: The objective of the study was to evaluate and compare the effect of conventional and newer antiepileptic drugs (AEDs) on thyroid hormone levels in adult epileptic patients.

Methods: A hospital-based, analytical cross-sectional study was conducted among the adult epileptic patients receiving conventional AEDs (Group 2) or newer AEDs (Group 3) for more than 6 months. Serum thyroid hormone levels including free triiodothyronine (fT_3), free thyroxine (fT_4), and thyroid stimulating hormone (TSH) were analyzed and the hormonal status was compared with healthy control subjects (Group 1).

Findings: Sodium valproate and phenytoin were commonly used conventional AEDs; levetiracetam and topiramate were common among the newer drugs. There was a statistically significant decrease in serum fT_4 and increase in serum TSH levels ($P < 0.0001$) in patients on long-term therapy with conventional antiepileptic agents than in the control group. No significant change in thyroid hormone levels (fT_3, fT_4, and TSH; $P = 0.68$, 0.37, and 0.90, respectively) was observed with newer antiepileptics-treated patients when compared to control group. One-way analysis of variance followed by *post hoc* Dunnett's test was performed using SPSS version 17.0 software package.

Conclusion: The present study showed that conventional AEDs have significant alteration in the thyroid hormone levels than the newer antiepileptics in adult epileptic patients.

Keywords: Antiepileptic drugs; conventional drugs; epileptic patients; thyroid hormones

INTRODUCTION

Epilepsy is the common neurological disorder which imposes economic burden on health care system in India. It is estimated that epileptic patients in India are 5,500,000 whereas in the USA are 2,000,000 patients and in the UK are 300,000 patients.[1] The purpose of therapy is to control rapid firing of population of neurons with antiepileptic drugs (AEDs) either as monotherapy or as combination therapy.[2] Conventional AEDs such as phenytoin, phenobarbitone, carbamazepine, and valproate (VPA) are commonly used drugs, and newer drugs such as lamotrigine, gabapentin, levetiracetam, and topiramate were also used as alternative or add-on therapy. Long-term treatment with AEDs is associated with cognitive impairment, idiosyncratic effects,

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chronic effects such as weight gain, increased risk of teratogenicity, and endocrine effects on reproductive, adrenal, and thyroid systems.[3] In particular, there is growing support that chronic therapy with AEDs is associated with changes in homeostasis of thyroid hormones. These changes are accompanied by remarkable alteration in the metabolic, cardiovascular, central nervous, musculoskeletal, hematological, reproductive, dermatological, and gastrointestinal system activity.[4] With various studies, different results have been achieved based on the effect of antiepileptic medications on thyroid function tests.[5-7] One study reported significant reduction in free thyroxine (fT_4) without alteration in free triiodothyronine (fT_3) and thyroid stimulating hormone (TSH) with carbamazepine, phenytoin, phenobarbital, and clonazepam therapy, with no change in hormone levels in VPA therapy. VPA therapy causing subclinical increase in TSH levels was also reported.[8,9] In addition, one study demonstrated that levetiracetam had no effects on thyroid hormone levels than compared to other conventional antiepileptics.[10] Although studies suggest that patients treated with conventional AEDs have an increased risk of thyroid hormone changes, studies associated with long-term effects of newer AED treatment are less reported. Hence, this present study was undertaken to evaluate and compare the effect of conventional and newer AEDs on thyroid hormone levels in South Indian adult epileptic patients.

METHODS

This was a hospital-based, analytical cross-sectional study carried out by the Department of Pharmacology in Collaboration with Neurology department at a Tertiary Care Teaching Hospital. After getting written informed consent from patients and permission from the Institutional Ethics Committee, the study was commenced (IEC–SMVMCH-EC/DAO/AL/558/2015). Confidentiality was maintained throughout the study. Adult epileptic patients of both genders, age 20–60 years, taking AEDs for more than 6 months, and patients receiving regular medication were included in the study. Patients with secondary epilepsy, receiving more than one AED, patients on irregular medication, receiving thyroxine replacement and anti-thyroid drugs, and pregnant females were excluded from the study. Patients with other systemic diseases such as diabetes, hypertension, ischemic heart disease IHD, stroke, or other chronic medical disorders were also excluded from the study. This study was conducted over 2 months. Sample size was calculated based on the prevalence of epilepsy in India as 5.59 and meta-analyses studies published in India. Considering the allowable error as 5, the sample size calculated was 84.[11] The patients and control subjects were grouped as Group 1: adult healthy nonepileptic control subjects (n = 28); Group 2: epileptic patients receiving conventional AEDs including phenytoin, carbamazepine, and valproic acid (n = 28); and Group 3: epileptic patients receiving newer AEDs such as levetiracetam and topiramate (n = 28). Age- and sex-matched control subjects were selected from patient's relative volunteer.

A specially designed case study form was used. Patient's demographic data including age, sex, diagnosis, duration of treatment, other medications, and serum fT_3, fT_4, and TSH levels were monitored. Fasting venous blood sample of 5 ml was collected from the patients and control subjects. Then, the blood was centrifuged and serum obtained was subjected to chemiluminescence autoanalyzer for assessing serum fT_3, fT_4, and TSH levels (Immulite-Siemens). The normal range of serum fT_3 is 1.5–4.1 pg/ml, serum fT_4 is 0.8–2.0 ng/dl, and serum TSH is 0.4–4 mIU/ml.

Data were entered and analyzed using (Statistics for Windows, Version 17.0. Chicago: SPSS Inc., IL, USA). Values were expressed as mean ± standard deviation (SD). One-way analysis of variances followed by *post hoc* Dunnett's test was performed to study the significance among the groups. $P < 0.05$ was considered statistically significant.

RESULTS

The results of the present study showed that there were 47 (56%) males and 37 (44%) females. Age distribution (mean ± SD) of the study population was 39.9 ± 13.5 years in Group 1, about 37.1 ± 8.7 years in Group 2, and 36.2 ± 12.0 in Group 3 (n = 28, in each group). The distribution of drugs used by the patients is showed in Figure 1. Sodium VPA and phenytoin were commonly used conventional AEDs, whereas levetiracetam and topiramate were common among the newer drugs.

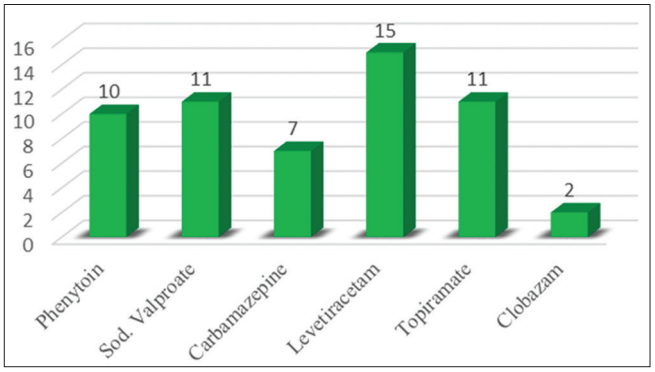

Figure 1: Percent of antiepileptic drugs utilized by the patients

Duration of therapy was about 3.35 ± 1.84 years in Group 2 and 4.01 ± 1.68 years in Group 3. Mean duration of drug therapy is about 3–4 years. As depicted in Table 1, estimation of fT_3, fT_4, and TSH levels showed that there was a statistically significant decrease in fT_4 (0.82 ± 0.14) and increase in TSH levels (3.92 ± 1.59) in the conventional drugs-treated patients (Group 2) than compared to control group (fT_4: 0.97 ± 0.09; TSH: 2.12 ± 0.93) ($P < 0.0001$). Our results also showed that there was no statistically significant changes in the fT_3 (2.70 ± 0.33), fT_4 (1.05 ± 0.26), and TSH (2.20 ± 0.29) levels in the patients treated with newer drugs (Group 3) than compared to control group (P = 0.68, 0.37, and 0.92, respectively). Difference between Groups 2 and 3 was also statistically significant for fT_4 and TSH ($P < 0.001$).

DISCUSSION

Disturbances in thyroid hormone function have been reported with some AEDs. In the present study, it was observed statistically significant decrease in serum fT_4 and increase in serum TSH levels ($P < 0.0001$) in the epileptic patients on long-term therapy with conventional antiepileptic agents than in the control group. However, serum fT_3 appeared unaffected by anticonvulsant administration (P = 0.20). In addition, none of the patients developed overt symptoms of hypothyroidism and all were clinically euthyroid. This was similar to a study done by Yehia *et al*., who demonstrated significant decrease in fT_4 and increase in TSH levels in his study.[12] Decrease in fT_4 and increase in TSH levels were also shown in yet another study done by Yilmaz *et al*. with carbamazepine, oxcarbazepine, VPA, and phenobarbitone but not with levetiracetam.[10] Newer drugs such as levetiracetam, topiramate, gabapentin, clobazam, lamotrigine, and tiagabine were also used as monotherapy and add-on therapy in epilepsy. Only levetiracetam, topiramate, and clobazam were commonly used by the patients in our study group. Moreover, with these three drugs, no significant change in thyroid hormone levels (fT_3, fT_4, and TSH; P = 0.68, 0.37, and 0.9, respectively) was observed in epileptic patients when compared to control group. Studies reported by Yilmaz *et al*. and Leskiewicz *et al*. showed similar effects with newer drugs.[10,13] 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.[14] Another possible mechanism could be due to interference with hypothalamic-pituitary axis regulation of thyroid hormone production.[15] 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.[16,17] In addition, study done by Villa and Alexander also suggested that iodine uptake inhibition by the thyroid gland might be one of the other mechanism by which carbamazepine can induce thyroid dysfunction.[18] Although mechanistic approach based study was not conducted, the present study showed screening for thyroid hormones is recommended for patients periodically taking long-term conventional AEDs than for the newer drugs, thereby thyroid dysfunction induced complications can be prevented in the epileptic patients. The small sample size was the limitation in our study; therefore, further prospective studies are required to be mediated on a larger scale of adult epileptic patients to confirm our results.

Table 1: Serum free triiodothyronine, free thyroxine, and thyroid stimulating hormone levels of study population

Serum hormone levels	Group 1	Group 2	Group 3
fT_3 (pg/ml)	2.82±0.35	2.50±0.80	2.70±0.33
P		0.20	0.68
fT_4 (ng/dl)	0.97±0.09	0.82±0.14	1.01±0.26
P		<0.001*	0.37
TSH (mIU/ml)	2.12±0.91	3.91±1.50	2.20±0.29
P		<0.001*	0.92

*P<0.001 as compared with Group 1. Values are expressed as mean±SD for all variables. Comparison was done by one-way ANOVA followed by *post hoc* Dunnett's test. Groups 2 and 3 were compared to Group 1. SD=Standard deviation, fT_3=Free triiodothyronine, fT_4=Free thyroxine, TSH=Thyroid stimulating hormone, ANOVA=Analysis of variance

The current study showed that conventional AEDs have significant alteration in the thyroid hormone levels than with the newer antiepileptics. Although these drugs therapy was not associated with clinical hypothyroidism, it is suggested that evaluation of thyroid hormone levels is needed. Further large-scale prospective clinical studies in epileptic patients are required to support our results.

AUTHORS' CONTRIBUTION

Mangaiarkkarasi Adhimoolam contributed in the idea of research, study design, data collection, data analysis and manuscript preparation with literature analysis. Ranjitha Arulmozhi contributed in study design, data gathering, data analysis and preparing first draft of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sridharan R. Epidemiology of epilepsy. Curr Sci 2002;82:664-70.
2. McNamara JO. Pharmacotherapy of the epilepsies. In: Brunton LL, Chabner BA, Knollman BC, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2011. p. 583-607.
3. Pack A. Effects of treatment on endocrine function in patients with epilepsy. Curr Treat Options Neurol 2005;7:273-280.
4. Toft A. Hypothyroidism. Med J Aust 1989;8:2596-60.
5. Isojärvi JI, Turkka J, Pakarinen AJ, Kotila M, Rättyä J, Myllylä VV. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. Epilepsia 2001;42:930-4.
6. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 2006;61:246-55.
7. Naithani M, Chopra S, Somani BL, Singh RK. Studies on adverse metabolic effects of antiepileptics and their correlation with blood components. Curr Neurobiol 2010;1:117-20.
8. Kirimi E, Karasalihoğlus T, Boz A. Thyroid function in children under long-term administration of antiepileptic drugs. East J Med 1999;4:25-6.
9. Mikati MA, Tarabay H, Khalil A, Rahi AC, El Banna D, Najjar S. Risk factors for development of subclinical hypothyroidism during valproic acid therapy. J Pediatr 2007;151:178-81.
10. Yilmaz U, Yilmaz TS, Akinci G, Korkmaz HA, Tekgül H. The effect of antiepileptic drugs on thyroid function in children. Seizure 2014;23:29-35.
11. Bharucha NE. Epidemiology and treatment gap of epilepsy in India. Ann Indian Acad Neurol 2012;15:352-3.
12. Yehia MA, Ahmad SF, El-Bakey A, Omar AE, Helmy AK, Zanaty ES, *et al*. Antiepileptic drugs and risk of subclinical hypothyroidism. Egypt J Neurol Psychiatry Neurosurg 2012;49:131-6.
13. Leskiewicz M, Budziszewska B, Lason W. Endocrine effects of antiepileptic drugs. Przegl Lek 2008;65:795-8.
14. Benedetti MS, Whomsley R, Baltes E, Tonner F. Alteration of thyroid hormone homeostasis by antiepileptic drugs in humans: Involvement of glucuronosyltransferase induction. Eur J Clin Pharmacol 2005;61:863-72.
15. Verrotti A, Scardapane A, Manco R, Chiarelli F. Antiepileptic drugs and thyroid function. J Pediatr Endocrinol Metab 2008;21:401-8.
16. Surks MI, Ordene KW, Mann DN, Kumara-Siri MH. Diphenylhydantoin inhibits the thyrotropin response to thyrotropin-releasing hormone in man and rat. J Clin Endocrinol Metab 1983;56:940-5.
17. Theodoropoulos T, Fang SL, Azizi F, Ingbar SH, Vagenakis AG, Braverman LE. Effect of diphenylhydantoin on hypothalamic-pituitary-thyroid function in the rat. Am J Physiol 1980;239:E468-73.
18. Villa SM, Alexander NM. Carbamazepine (Tegretol) inhibits *in vivo* iodide uptake and hormone synthesis in rat thyroid glands. Endocr Res 1987;13:385-97.