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Research Article

THE EFFECT OF ANTICONVULSANT DRUGS ON SERUM THYROID-STIMULATING HORMONE

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ABSTRACT

Objective: Antiepileptic (AED) drugs are an integral component of the management of seizure disorder; however, they have a wide spectrum of adverse effects. It is important to be aware of these side effects as they have a major impact on the quality of life and are sometimes partially reversible after drug discontinuation. Among them, the influence of AED on thyroid function is an important one. However, there is only limited data available. The objective of this study is to evaluate the effect of AED on thyroid-stimulating hormone (TSH).

Methods: A cross-sectional study of 1-year duration (march 2017 – march 2018) was conducted among 150 epileptic patients receiving phenytoin, carbamazepine, and sodium valproate for more than 6 months in a tertiary care center in central Kerala. Serum levels of TSH of patients on AED were compared with that of 50 healthy age- and sex-matched control groups. Data regarding the same were analyzed using SPSS version 16 with the Chi-square test, ANOVA, and independent t-test.

Results: A total of 150 epileptic patients with a mean age of 35.54 + 10.72, including 66 males (44%) and 84 females (56%) were enrolled in this study. Fifty adults of mean age 36.5+ 8.4 and male to female ratio 1.10:1 formed the control group. It was found that the mean TSH value of patients on phenytoin (3.97+ 1.47), carbamazepine (3.57+ 1.44), and sodium valproate 3.03 + 1.41 significantly higher than that of the control group (1.91 + 0.72). On comparing the mean serum TSH of the drug group significant difference noted between phenytoin and sodium valproate treated group. Among the 12 patients develop subclinical hypothyroidism 65% taking drugs for more than 5 years.

Conclusion: There is a positive correlation between the use of anticonvulsants and thyroid dysfunction and the association increases with the duration of therapy. The clinicians should be encouraged for regular monitoring of thyroid function test to impart a better quality of life to the patients.

Keywords: Anti-convulsant drugs, Anti-epileptic drugs, Thyroid-stimulating hormone, Hypothyroidism, Epilepsy, Adverse drug reaction, Adverse effects.

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INTRODUCTION

Epilepsy is one of the most common neurological disorders having a significant impact on the quality of life. The incidence of epilepsy is about 0.3–0.5 % in different world population and the prevalence has been estimated at 5–30 persons per 1000 [1].

Standard therapy warrants control of seizure episodes in 80% of patients. The goal of the therapy is to suppress seizure without causing any unwanted effects. Seizure type and the patient's specific needs, especially side effect assessment, are important elements in designing the treatment plan. Conventional antiepileptics (AED) such as phenytoin, carbamazepine, and sodium valproate are generally considered as first-line drugs for most of the seizure disorders in our institution. Phenytoin and carbamazepine are preferred drugs in partial seizure and sodium valproate in the generalized seizure. However, phenytoin causes dose-dependent as well as long-term adverse drug effects. Carbamazepine causes blood dyscrasia and hepatitis, while sodium valproate causes ataxia, tremor, and fulminant hepatitis [2,3].

These conventional AED are well known for their microsomal enzyme induction or inhibition property. Phenytoin and carbamazepine stimulate different cytochrome P450 enzymes, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4 as well as glucuronyl transferases [4,5]. Sodium valproate differs from other conventional drugs in being an enzyme inhibitor [6]. Several studies revealed that enzyme induction is associated with endocrine abnormalities, especially thyroid dysfunction [7]. The first study about this correlation was shown in 1981 by Strandjord *et al*., which demonstrates a significant decrease in serum thyroxine (T4), free T4, and triiodothyronine concentration in anticonvulsant treated patients than controls [8]. Even though extensive studies on endocrine abnormalities have been done, but the literature available is limited. The objective of the study was to estimate the incidence of abnormal thyroid-stimulating hormone (TSH) level in patients on anticonvulsant therapy.

METHODS

A cross-sectional study was conducted among epileptic patients of either sex between the age of 15–55 years on monotherapy with phenytoin, carbamazepine, and sodium valproate for more than 6 months. The study was done at the neurology outpatient department of a tertiary care hospital for 12 months. Patients were recruited after informed consent and institutional review board approval (IRB number - 9/2016). Data were collected using structured pro forma. Pro forma included demographic data, diagnosis, age at onset, treatment details, and lab reports. Anticonvulsant drugs were selected by the neurologist based on the type of seizure. Serum TSH was measured using Beckman Coulter Access 2. Blood samples were taken between 8 AM and 10 AM after overnight fasting and the test was done in the hospital central laboratory. The normal range of TSH was 0.34–5.2 mIU/ml. Using formula, $n = (Z\alpha^2 \times SD^2)/d^2$ [9] Standard Normal Variate ($Z\alpha$) -1.96, Absolute error (d) -0.05, and Standard Deviation (SD)- 2.73.

A sample size of a minimum of 29 in each group was calculated and we took 50 subjects in every four groups. Standard deviation obtained from the study by Yilmaz *et al*. [10].

Statistical analysis

Data were entered into MS Excel and analyzed using SPSS for windows 16 (SPSS Inc, Chicago, USA). Qualitative variables were analyzed using the Chi-square test. Quantitative were analyzed using ANOVA and independent t-test.

Exclusion criteria
Patients with known thyroid dysfunction or receiving thyroxine replacement, anti-thyroid drugs, or any drug affecting thyroid function (such as Lithium and Amiodarone), family history of hypothyroidism, and those who had undergone thyroidectomy were excluded from the study.

RESULTS

A total of 150 epileptic patients with a mean age of 35.54+10.72 years, including 66 males and 84 females, were enrolled in this study. Fifty adults of mean age 36.5+8.4 years (27 males and 23 females) formed the control group. All subjects were included in the study after written informed consent. A total of 121 (60.5%) were on treatment for partial seizure and 29 (14.5%) generalized seizure (Table 1).

The serum TSH value of 14 patients found to be higher than the normal range. Of the 14 patients, six were taking phenytoin, five were on carbamazepine, and three of them on sodium valproate. Hence, the incidence of altered serum TSH among patients on anticonvulsants is 9.33%.

As shown in Table 2, mean serum TSH in phenytoin, carbamazepine, and valproate treated group was higher than the control group. Independent t-test showed that there was a significant difference in the mean TSH value of phenytoin, carbamazepine, and sodium valproate group compared to control.

Multiple comparisons among the drug group (Table 3) revealed that there was a significant difference in mean serum TSH among the groups. F= 5.4, p=0.005. Using *post hoc* analysis, Bonferroni, it was found that phenytoin treated patients have significantly higher serum TSH than the sodium valproate group (p=0.004, CI-0.25–1.64).

Table 1: Clinical profile of epileptic patients

Characteristics	Phenytoin	Carbamazepine	Valproate
Male (n=43), n (%)	20 (40)	23 (46)	23 (46)
Female (n=55), n (%)	30 (60)	27 (54)	27 (54)
Age at onset of the seizure (years)	36.5+8.3	31.2+10.2	28+10.5
Seizure type partial generalized	50.0	50.0	21.29
Mean duration of drug intake (years)	4.62+3.70	3.7+2.38	2.79+1.98

Table 2: Comparison of mean thyroid-stimulating hormone of antiepileptic drugs with the control group

Drug	Phenytoin	Carbamazepine	Valproate
Mean TSH	3.97+1.47 Control – 1.89+0.75	3.57+1.44	3.03+1.4
p	<0.001	<0.001	<0.001
t	8.94	7.34	5.02
CI	1.60–2.52	1.21–2.11	0.68–1.57

TSH: Thyroid-stimulating hormone, CI: Confidence interval

Among the 14 patients with altered serum TSH, 64% (9) of them received the drug for more than 5 years (Odds ratio 9.85, p=0.00). It revealed an important relationship between duration of drug intake and thyroid dysfunction. Patients on long-term AED therapy had more chance of developing thyroid dysfunction.

DISCUSSION

Anticonvulsant drugs and associated thyroid hormone dysfunction are a matter of concern due to subclinical presentation, irregular follow-up, and limited data in our population. Martinez-Juarez *et al*. found that 32% of epileptic patient develop thyroid dysfunction following AED therapy, most relevant were increased TSH in sodium valproate treated patients (Valproate -61.5%, Carbamazepine-47.9%, and Phenytoin-17%) [11]. Subclinical hypothyroidism is more frequently seen, which is defined as a mild elevation in serum TSH levels in the presence of normal thyroid hormone concentrations [12,13]. Patients with subclinical hypothyroidism have an increased incidence of progression to overt hypothyroidism, 4.3% per year if thyroperoxidase antibodies are present [14]. In addition, to progression to hypothyroidism number of complications is associated with hypothyroidism including cardiac dysfunction, neuromuscular dysfunction which can be reversed by levothyroxine treatment, and psychiatric and cognitive dysfunctions [15-17].

The study conducted by Warren *et al*. revealed the importance of serum TSH value. They found that baseline TSH value is a better predictor of hyper or hypothyroidism [18]. The present study demonstrated that there is a significant increase in serum TSH after phenytoin, carbamazepine and sodium valproate monotherapy than the control group and the incidence of altered serum TSH was found to be 9.33%. Although the exact mechanism is unknown, the previous studies postulated several mechanisms which explain the thyroid dysfunction in anticonvulsant treated patients. One possible mechanism is hepatic CYP450 enzyme induction by conventional AED (Phenytoin and Carbamazepine) with resultant accelerated thyroid hormone metabolism, thus decreasing its serum concentration [19]. Another possible mechanism is due to alteration with hypothalamic-pituitary axis regulation of thyroid hormone synthesis [20]. This mechanism was supported by Surks *et al*. who postulated the drug-induced inhibitory response of thyroid releasing hormone on TSH release [21]. Villa and Alexander proposed another mechanism for carbamazepine induced thyroid dysfunction due to the inhibition of iodine uptake by the thyroid gland [22].

In this study, patients receiving phenytoin had significantly high serum TSH as compare to sodium valproate treated group. None of the patients shows the symptoms of hypothyroidism. It is inconsistent with the study conducted by Dhodi *et al*. showed alteration in thyroid status in phenytoin and carbamazepine treated patients, but not in those on valproate therapy [23]. In contrast with the present study, Connacher *et al*. observed that no significant change in mean serum TSH among these drug group. However, they observed a significant decrease in T4 and free-T4 in phenytoin and carbamazepine compared to valproate treated group [24].

The study by Yılmaz *et al*. in 223 children with the new-onset disease treated with AED (phenobarbital, valproate, carbamazepine, oxcarbazepine, and levetiracetam) found the varying degree of thyroid dysfunction for all except levetiracetam, a newer anticonvulsant with

Table 3: ANOVA *Post hoc* analysis

Drug Group 1	Drug Group 2	Mean difference	Significance	95% CI
Phenytoin	Carbamazepine	0.40220	0.495	−0.2957–1.100
Phenytoin	Sodium valproate	0.94360*	0.004	0.2457–1.64
Carbamazepine	Phenytoin	−0.40220	0.495	−1.1001–0.295
Carbamazepine	Sodium valproate	0.54140	0.187	−0.1565–−1.23
Sodium valproate	Phenytoin	−0.94360*	0.004	−1.6415–−0.2457
Sodium valproate	Carbamazepine	−0.54140	0.187	−1.2393–−0 .156

CI: Confidence interval

a better safety profile [10]. The study which investigated the effect of valproate and levetiracetam on thyroid function in young epileptics by Aksoy *et al*. emphasize the advantage of levetiracetam over conventional AED [25].

Epilepsy is a disorder that requires long-term drug therapy which results in more chances of developing adverse drug effects. The present study demonstrated a positive association between thyroid dysfunction and duration of drug intake. Among patients with thyroid dysfunction, 64% took anticonvulsant drugs for more than 5 years.

The limitation of the study includes the short duration of the study and lack of multiple follow-up to check whether those patients with thyroid dysfunction developed symptoms of hypothyroidism. The baseline values of patients could not be obtained as we included patients taking AED for more than 6 months. The whole thyroid function test was not done. Studies with longer duration, checking complete thyroid profile on newly diagnosed epileptic patients need to be conducted.

CONCLUSIONS

Conventional anticonvulsants induce thyroid dysfunction which increases with the duration of treatment. Monitoring of thyroid function should be done routinely to preserve the quality of life in these apparent clinically euthyroid patients as the dysfunction is only partially reversible after untimely drug discontinuation or replacement.

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AUTHORS CONTRIBUTIONS

SYAM S – study idea, study conducting, literature review, manuscript review.

NEETHU T T – study idea, study conducting, literature review, data collection, and analysis, manuscript preparation.

BEENA V – study idea, literature review, data collection, manuscript review.

DHANYA S P – literature review, statistical analysis, manuscript preparation, manuscript review.

CONFLICTS OF INTEREST

No conflicts of interest.

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