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 1:1:1 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 in 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.
Exclusion criteria
Patients with known thyroid dysfunction or receiving thyroid 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 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 | 5.00 | 5.00 | 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 | 3.57±1.44     | 3.03±1.4  |
| Control – 1.89±0.75 |          |               |           |
| 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 |

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, Conacher 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| 0.4020          | 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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