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Original Research Article

Subclinical hypothyroidism and plasma levels of commonly prescribed anti-seizure medications

Anusha Natarajan[1]*, R. Priyadharsini[1], Suja Xaviar[2], Ramkumar Sugumaran[3]

[1]Department of Pharmacology, JIPMER, Pondicherry, India
[2]Department of Pharmacology, ESIC Medical College and Hospital, Chennai, Tamil Nadu, India
[3]Department of Neurology, JIPMER, Pondicherry, India

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***Correspondence:**
Dr. Anusha Natarajan,
Email: anushanatarajan29@gmail.com

ABSTRACT

Background: Epilepsy remains the most common neurological problem worldwide. Most commonly prescribed antiseizure medications (ASMs) like phenytoin, sodium valproate, and carbamazepine show high inter-individual variability in bioavailability due to genetic and epigenetic factors resulting in either therapeutic failure or toxicity. In our study, we aim to determine the association between subclinical hypothyroidism and the plasma levels of these commonly prescribed ASMs, leading to either therapeutic failure or adverse drug reactions.
Methods: We collected demographic data, details about the antiepileptic medication, and plasma levels of ASMs (phenytoin, carbamazepine, and sodium valproate) from patients on antiseizure medications who came for routine therapeutic drug monitoring (TDM). High-performance liquid chromatography (HPLC) estimated plasma levels of the antiseizure medications as per the TDM laboratory standard operating procedure (SOP) and thyroid function test (TSH) by a standard enzyme-linked immune-sorbent assay (ELISA) kit.
Results: Of the 158 patients who had TDM, 75.31% were taking sodium valproate, 15.18% were on phenytoin, and 9.49% were on carbamazepine monotherapy. In our study, we found that 12 patients (7.59%) had TSH levels between 4 to 10 mIU/l, indicating subclinical hypothyroidism (SCH). The plasma drug levels of all 12 patients who had SCH were found to be below the therapeutic range.
Conclusions: This study has established a significant association between ASMs, particularly sodium valproate, and thyroid dysfunction, specifically SCH, in patients with epilepsy. Our findings suggest that prolonged ASM therapy can lead to thyroid disturbances, warranting careful monitoring of thyroid function in these patients.

Keywords: Antiepileptics, Subclinical hypothyroidism, Plasma levels, TDM

INTRODUCTION

Epilepsy remains the most common neurological problem worldwide.[1] Most commonly prescribed ASMs like phenytoin, sodium valproate, and carbamazepine show high inter-individual variability in bioavailability resulting in either therapeutic failure or toxicity. Genetic and epigenetic factors can explain this variability. Most of the available studies focus on genetic factors that influence the pharmacokinetics of the drugs. Subclinical hypothyroidism (SCH) is defined as a high serum thyroid stimulating hormone (S. TSH) concentration (4 to 10 mIU/l; normal TSH is 0.4–4 mIU/l) with normal serum free thyroxine (FT4) and free triiodothyronine (FT3) concentrations.[2] A study by Desai et al showed that the prevalence of SCH was 32% in the Indian population.[2] Other epidemiological studies in India have shown a prevalence rate between 9% and 26%.[2]

Many studies have shown that antiseizure medications lead to hormonal, metabolic, and vascular disturbances in patients taking these drugs for a long time.[3] One of the

important hormonal abnormalities is SCH.[4,5] SCH is often challenging to diagnose as the classic symptoms of hypothyroidism will be absent.[6] It has been studied that SCH can affect the metabolic process.[7] In regular clinical practice in epilepsy clinics, there are no clear recommendations for monitoring or treating patients with SCH due to ASMs. However, it seems reasonable to monitor and treat patients at high risk for developing SCH (e.g., patients on combined therapy using more than one ASM, those with inadequate serum levels of ASMs, during pregnancy, and patients with an adverse metabolic profile).[1]

The case study by Sarich et al showed that a patient with a decreased level of thyroid hormones presented with phenytoin toxicity.[8] The studies done by Lai et al, Larkin et al, Sui-Qiang et al, and Tiihonen et al, all showed that treatment with ASMs reduced the levels of the thyroid hormones in the patients taking them.[8-11] It is suggested that all patients receiving ASMs should be regularly monitored for thyroid function through physical and laboratory examinations to prevent unintended injuries resulting from hypothyroidism.[9] In such patients, symptoms due to the side effects of their medication may be difficult to distinguish from those due to hypothyroidism. This, therefore, means that long-term monitoring of thyroid function in patients on anticonvulsants is necessary.[11] In our study, we aim to determine the association between the thyroid hormone status and the plasma levels of these commonly prescribed ASMs (phenytoin, carbamazepine, and sodium valproate), which in turn leads to either therapeutic failure or adverse drug reactions of the drugs. This study would find the association between thyroid hormone status and the plasma levels of commonly prescribed ASMs. If found to have an association, this data may guide the treating physician in choosing the appropriate initial dose as well as dose adjustment and also to start thyroid hormones for optimal outcome.

Aim

Aim of the study was to evaluate the association between subclinical hypothyroidism and altered plasma levels of antiseizure medications (phenytoin, carbamazepine, and sodium valproate) in patients on treatment for epilepsy.

Objectives

Objective of the study was to correlate the plasma levels of phenytoin, carbamazepine, and sodium valproate with thyroid function status.

METHODS

In this cross-sectional analytical study, we included adult patients with seizure disorder on antiseizure medications who visited the Department of Pharmacology for routine therapeutic drug monitoring and were willing to give written informed consent.

Inclusion criteria

All patients (≥18 years) of either gender with seizure disorder on antiepileptic drug therapy for at least three months were included.

Exclusion criteria

Patients who are already on treatment with anti-thyroid medications, and participants who previously received any medication that could affect thyroid function (amiodarone, and lithium) were excluded.

The study was conducted between January 2021 to December 2021. The enrolment started after the institute ethics committee clearance. After informed written consent, baseline demographic data, antiseizure medication details, and blood levels (phenytoin, carbamazepine, and sodium valproate) were collected in a predesigned proforma. Plasma levels of the antiseizure medications were estimated by HPLC (Shimadzu-Diode array detector) as per the TDM laboratory SOP. Normal reference plasma levels of the antiseizure medications are phenytoin – 10 to 20 mcg/ml, carbamazepine – 6 to 12 mcg/ml, and sodium valproate – 50 to 100 mcg/ml. Data collection was restricted to those variables necessary to define baseline patient characteristics, relevant study variables, potential confounding factors, and outcomes. We used Five ml of the venous blood sample collected for routine TDM investigation and performed a thyroid function test (TSH) by standard ELISA kit using an ELISA reader.

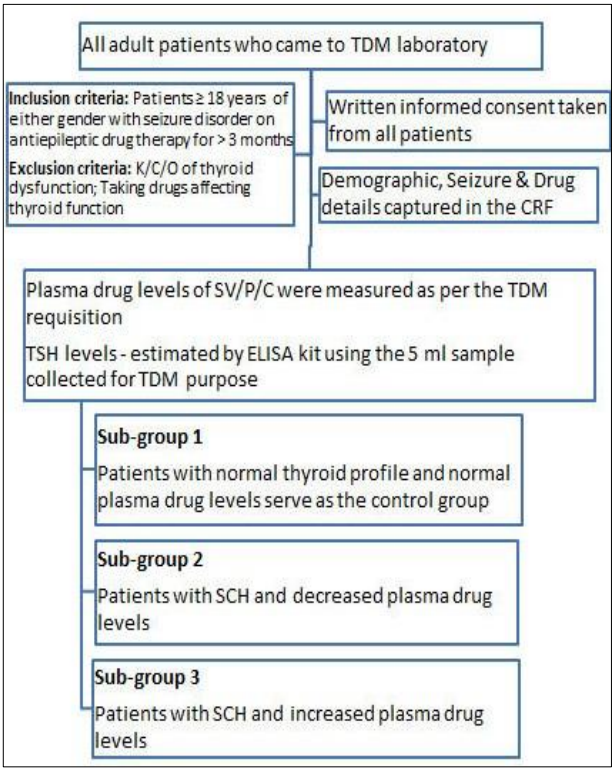

Figure 1: Study flow.

Statistics

Demographics were described using mean, standard deviation (SD), frequency, and percentage. The linear relationship between TSH with age and different drug levels was carried out using correlation analysis. TSH levels vs different antiseizure medications was analysed using one-way analysis of variance (ANOVA). Statistical analysis was performed using statistical package for the social sciences (SPSS) software version 28.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In our study, the total number of study participants was 158, with a mean age of 36.49±12.14 years (mean±SD). Most patients were males (63.29%), followed by females (36.71%). In our study, we found that 75.31% of patients were taking sodium valproate, followed by 15.18% on phenytoin and 9.49% on carbamazepine. 58.23% of patients had plasma drug levels below the therapeutic range, and 10.76% were above the therapeutic range. Subclinical hypothyroidism was present only in 7.59% of patients (Table 1).

Table 1: Baseline characteristics of study participants.

Parameters	Total n=158	Percentage
Age (years)	36.49±12.14 (mean±SD)	
Gender		
Male	100	63.29
Female	58	36.71
Drugs		
Sodium valproate	119	75.31
Phenytoin	24	15.18
Carbamazepine	15	9.49
Plasma drug levels		
Normal	49 (SV)	31.01
Below therapeutic range	92 (SV-58, P-19, C-15)	58.23
Above therapeutic range	17 (SV-12, P-5)	10.76
SCH		
Present	12	7.59
Absent	146	92.41

SV – Sodium valproate, P – phenytoin, C – carbamazepine

Figure 1 shows the comparison of the control group versus altered TSH and plasma drug levels. We found that 27.8% of the patients had normal TSH and normal plasma drug levels, and 7.59% had SCH and decreased plasma drug levels. There was a statistically significant difference between the two groups with a p value of 0.007.

Figure 2 compares the individual antiseizure medications with the TSH levels. We found out that there was a statistically significant association between sodium valproate and TSH levels with p<0.001.

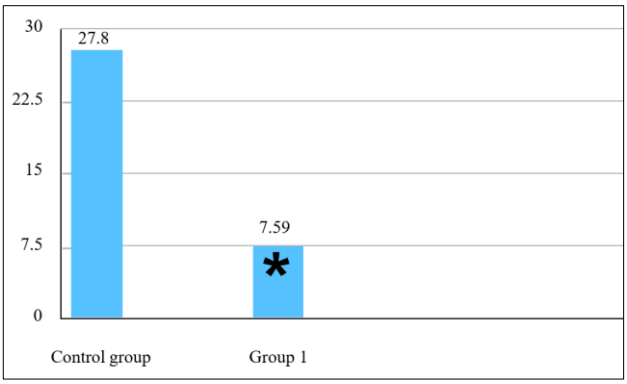

Figure 1: Comparison of control group vs. altered TSH and plasma drug levels (p=0.007).

Control group - normal TSH levels and normal plasma drug levels, group 1 - SCH and decreased plasma drug level
*denotes the p value between the control group and group 1.

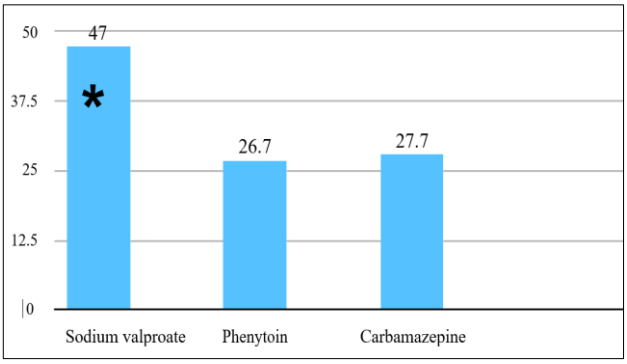

Figure 2: Comparison of TSH levels versus the antiseizure medications (p<0.001).

* denotes the p value

DISCUSSION

Hypothyroidism and epilepsy are two common disorders of their domains. It is estimated that about one percent of the world's population lives with epilepsy.[1] There is also concern about SCH; it is estimated that around 32% of Indians have SCH.[2] Phenytoin, sodium valproate, and carbamazepine are the most commonly used antiseizure medications. These drugs show high inter-individual variability in bioavailability and response in patients with epilepsy. The medicines mentioned above also cause hormonal, metabolic, and vascular disturbances when taken for a long time.[3] Most patients with epilepsy require long-term treatment for at least 2 to 5 years.

In this study, we have assessed the plasma levels of drugs in epilepsy patients and their association with thyroid hormone levels. The previous study by Sarich et al found that subclinical hypothyroidism was associated with phenytoin toxicity.[8] This is concordant with our study, where there is a significant association between plasma drug levels and thyroid hormone levels. Another study by Lai et al showed that people on chronic therapy with ASMs also have concomitant thyroid dysfunction.[9] Similar

studies by Larkin et al and Sui-Quang et al also showed that thyroid dysfunction in epilepsy patients is due to antiseizure medications.[10,11] This is discordant with our study findings, where only a minority of the patients on ASMs had subclinical hypothyroidism. Among the samples analyzed, we found that 58% of the samples collected from patients had sub-therapeutic drug levels. We also found a significant correlation between the drugs and serum TSH levels. But the contrasting evidence is that the drug levels were low in patients with subclinical hypothyroidism rather than in toxic levels reported by Lai et al.[9] Among the samples we assessed, most of the patients were on sodium valproate followed by phenytoin and carbamazepine. According to our study, almost 50% of the participants were on sodium valproate, followed by 75% on phenytoin and carbamazepine. Our study found a significant association between antiepileptic drugs and SCH. Among the patients who had SCH, most of them were on valproate.

Hypothyroidism could range from subclinical to myxoedema when it comes to clinical manifestations. SCH is usually asymptomatic. The mechanisms behind seizures in hypothyroidism are yet to be understood. Some assumed mechanisms include the cerebral edema component involved in worsening seizures.[12] Even though this is not marked in SCH, the chronicity of this condition could result in such a manifestation. Hypothyroidism is also associated with dementia and pericardial effusion due to water retention properties. Hypothyroidism can cause the deposition of glycosaminoglycans in the tissues. Glycosaminoglycans attract water molecules that make them bulkier and oedematous. This mechanism causes non-pitting edema of hypothyroidism, that is, myxedema.[13] One exciting fact that we have noticed here is that most of the patients on ASMs, especially valproate had thyroid dysfunction that manifested as SCH.[14] The possible mechanism behind the development of SCH with sodium valproate is it causes induction of UGT enzyme, thereby increasing thyroid hormone metabolism, which in turn leads to a compensatory increase in TSH levels.[15] With numerous advancements in diagnostics and biomedical research, the mechanism behind the development of seizures is not well known. So, assessing its association with another unknown entity for its clinical relevance is quite challenging.

From the existing knowledge, we could say there is a strong association between thyroid dysfunction and antiepileptic drug intake. As per the study by Sarich et al, ASM levels are above the therapeutic range or toxic range with concomitant thyroid dysfunction.[8] So, our study again emphasizes the fact that ASM therapy can cause thyroid dysfunction, as seen with the participants in our study who were on valproate, which is similar to the study done by Kim-Hee et al.[16]

This study has proven the relationship between plasma levels of first line ASMs and TSH levels, and the effect of other ASMs on thyroid function could not be assessed in the present study.

CONCLUSION

Although we have found a strong association between ASM and thyroid function, the mechanisms are still at the level of assumptions. The intricate details of ASMs affecting the function of the thyroid gland are yet to be clarified. The association is more robust for valproate; one of the commonly used antiepileptic drugs points to the fact that physicians and neurologists who prescribe ASMs should consider thyroid dysfunction. Vigilant monitoring of thyroid function is necessary, as we witness in this study. Even though we have tried to address the lacunae, a lot more has to be addressed, which warrants future research.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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