

Effect of Antiepileptic Drugs on Thyroid Profile in Patients of Epilepsy

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ABSTRACT

Background: Antiepileptic drug is the main stay of treatment for most patients with epilepsy. These may cause Patients with epilepsy are often required to take antiepileptic drugs (AEDs) for a long period of time. However, prolonged use of AEDs is known to be associated with adverse effects such as metabolic and organ toxicity, endocrine disturbance, negative cognitive effects, and psychiatric problems; particularly with alterations in thyroid function in patients with epilepsy and is thought to correlate with type of AED taken. **Objective:** To study the effect of antiepileptic drugs on serum thyroid profile in epileptic patients and to compare the relationship of change with type of drug intake. **Study Design:** A Case Control Prospective Study. **Methods:** A total number of 80 subjects presenting with epilepsy in the OPD of Medicine of Guru Nanak Dev Hospital, attached to Government Medical College Amritsar, were selected. 40 epileptic patients taking Antiepileptic Drugs for a minimum period of 1 year constituted case group and 40 normal healthy individuals constituted control group. They were again divided according to type of drug intake. **Results:** AEDs causes significant increase in TSH levels and this increase is further related to type of drug intake. **Conclusion:** ?

Keywords: Epilepsy, Thyroid profile.

INTRODUCTION

Epilepsy is the most common, chronic serious neurological disorder and about 65 million people affected worldwide.^[1] In India, epilepsy affects 5 to 10 people out of every 1000 people. It is a disorder of recurrent and spontaneous seizures resulting clinically into permanent alterations of normal function and morphology of neuronal cells and even cell death.^[2] Epilepsy can be idiopathic, (usually genetic), cryptogenic (undiagnosed cause with associated neurological or developmental deficits) or symptomatic (known cause). This aetiological classification also applies to epilepsy syndromes.

Therapy with AEDs remains the mainstay of treatment of patients with epilepsy.^[3] The major groupings of antiepileptic drugs can be defined as: those which facilitate γ -aminobutyric acid (GABA) transmission by various mechanisms; those which block voltage-gated ion channels and thus reduce excitatory transmission and those whose mechanism

of action is still open to debate.^[4]

Most AEDs exert their antiepileptic effects via the Na^+ or the Ca^{2+} channel or via GABAergic transmission. In addition to the major action site, the new AEDs tend to have several minor action sites. In the chronic phase, the incidence of adverse effects with the new AEDs is low, but TPM and PER, drugs that potentiate glutamergic transmission, may elicit behavioural changes and cognition disorders.^[5]

Patients with epilepsy are often required to take antiepileptic drugs (AEDs) for a long period of time. Many studies have shown that AEDs have a negative impact on the endocrine system in both paediatric and adult populations, including thyroid function, fertility, sexuality, and bone health.^[6] However, prolonged use of AEDs is known to be associated with adverse effects such as metabolic and organ toxicity, endocrine disturbance, negative cognitive effects, and psychiatric problems, particularly with alterations in thyroid function in patients with epilepsy.^[7]

Antiepileptic drugs (AED) are widely used in childhood epilepsies and other convulsive conditions. Recently the side effects of antiepileptic drugs to the endocrine system are being reported.

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Effects on the thyroid hormone balance are of primary importance in this regard.^[8]

Certain AEDs such as carbamazepine (CBZ), phenobarbital (PHB), phenytoin (PHT), valproic acid (VPA), and oxcarbazepine (OXC) are known to affect normal thyroid function.

Thyroid hormones are important for maintaining lipid and carbohydrate metabolism, cell growth and development. Hypothyroidism, even in subclinical form, has been associated with an increased risk of coronary heart disease.^[6]

Newer AEDs undergo minimal or no hepatic metabolism and constitute excellent therapeutic choices.⁹ The first study about the effects of antiepileptic drugs on thyroid gland is made in 1961 by Oppenheimer and their team. They found a decrease in iodine bound to serum proteins and a disturbance in thyroxine secretion from thyroxine binding globulin (TBG) in adults taking phenytoin.¹⁰ Since then, several studies have been reported about the toxic effects of antiepileptic drugs on thyroid gland.^[10-13] It's found that some antiepileptic drugs decrease thyroid functions certainly. For example, phenytoin and carbamazepine clearly decrease thyroid functions but do not change the euthyroid state. It has been reported that these drugs decrease the free serum thyroxine concentrations (FT4), but not change the serum free triiodothyronine (FT3) and thyroid stimulating hormone (TSH) levels.^[11-16] The mechanisms of the effects of antiepileptic drugs on thyroid hormones have been studied intensively.

Generally, phenobarbital, phenytoin and carbamazepine are called as "enzyme inducing antiepileptic drugs" because of their activating effects on hepatic microsomal enzyme system.^[10-11] Zimmerman in 1960 showed that an increase in the alanine aminotransferase (ALT) level of >3 times the upper limit of normal, and a total bilirubin level of >2 times the upper limits of normal (especially in the presence of jaundice) is associated with a mortality rate of 10% to 50%.^[17] Therefore, the present study was designed to evaluate the effect of AED's on thyroid profile in Indian population.

MATERIALS AND METHODS

The present study was carried out in the Department of Biochemistry, Government Medical College, Amritsar, in collaboration with Department of Medicine, Guru Nanak Dev Hospital, Amritsar. The study was conducted after obtaining approval from the Institutional ethics committee, Government Medical College, Amritsar. The subjects for the present study were selected from general population of male and females in a rural community.

Study Design

This was a case control prospective study comprising a total of 80 subjects presenting with epilepsy in the O.P.D of Department of Medicine of

Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar.

Selection of Cases

40 epileptic patients taking Antiepileptic drugs for a minimum period of 1 year were considered as study group. These patients must have five or more epileptic attacks. These subjects ages between 20 to 50 years.

Selection of Controls

40 controls were taken which were suffering from any other chronic serious physical illness or an organic brain syndrome due to some cause other than epilepsy.

Biochemical investigations for thyroid profile were done in all Epileptic patients attending outdoor patients of Department of Medicine, Sri Guru Nanak Dev Hospital, Amritsar. A standard proforma was employed in each case and detailed history regarding the disease was accurately recorded and investigations were done. Written informed consent was taken from the cases and controls included in the study.

Inclusion Criteria

Age between 20 to 50 years, thus ensuring a representative sample of the epileptics, which was comparable with the standardization samples of the questionnaire which was used. A minimum period with epilepsy for one year, during which five or more epileptic attacks had occurred. Both new and follow-up patients were taken for the study.

Exclusion criteria

Patients more than 50 years and less than 20 years of age. Patients visited the hospital during the same period, not suffering from epilepsy and were of same age.

Collection and Processing of Blood Samples 5ml of venous blood was taken from all subjects after 12 hour overnight fast in a dry disposable syringe under all aseptic conditions by venepuncture in the anticubital vein in a sterile, dry acid washed vial for biochemical assays.

Preparation of Serum

The blood was allowed to stand for half an hour. After clot formation, the supernatant was centrifuged. All the samples were processed for thyroid hormones, lipid profile, and liver enzymes.

Biochemical assay of Thyroid Profile

1. Triiodothyronine (T3)
1. Thyroxine (T4)
2. Thyroid Stimulating Hormon

1. **Triiodothyronine (T3):** T3 levels were estimated by using the ELISA kit

Methodology: ELISA kit method²⁶ was used for the quantitative determination of T3 levels in human serum.

Principle: The T3 ELISA kit was a solid phase enzyme linked competitive immunoassay for the measurement of T3 in human serum.

The T3 ELISA kit is comprised of two key components:

- 1) Solid microwells pre-coated with T3 analog
- 2) Liquid conjugates containing anti-T3 antibody

During the assay, the test specimen and the anti-T3 antibody-conjugate solution were incubated simultaneously in the coated microwells. T3 present in the patient sample would compete with the T3 analog coated on the microwells for binding with the anti-T3 monoclonal Ab-conjugates. The amount of conjugates that bind to the microwell surface would decrease in proportion to the concentration of T3 in the patient sample.

Unbound conjugates were then removed by washing. The presence of the bound T3 conjugates was shown by a blue colour upon the addition and incubation of the TMB substrate solutions. The reaction was stopped with stop solution, and absorbances were read using a spectrophotometer at 450 nm. The intensity of the colour was inversely proportional to the amount of T3 in the patient sample, within the dynamic range of the assay.

Reagent composition:

Description	Quantity
Microwells coated with T3 analog	1 plate, 96 wells
T3 standards: S1	1ml
S2	1ml
S3	1ml
S4	1ml
S5	1ml
S6	1ml
HRP-anti-T3 Antibody Conjugates	1.2 ml
Enzyme conjugate diluents	2 x 7.5 ml/Each
Wash buffer	25 ml
Substrate	12.0 ml
Stop solution	7.5 ml

Procedure:

- 1) Removed the desired number of coated wells and secured them in the frame. Reseal un-used strips.
- 2) Added 50 µL of T3 standards, controls and patient specimens into the individual test wells.
- 3) Added 100 µL of T3 enzyme conjugates reagent to each well.
- 4) Shaked for 30 seconds to completely mix the liquid within the wells.
- 5) Covered the plate with a lid and incubate the wells for 60 minutes at 37°C.
- 6) Carefully removed the incubation mixture by emptying the solution into a waste container. Fill each well with wash solution and shake gently. Discarded the wash solution completely by emptying the contents into a container.
- 7) Added 100 µL of substrate solution into each well.
- 8) Incubated at room temperature in dark for 20 minutes.
- 9) Stopped the reaction by adding 50 µL of stop solution to each well. Gently mix for 15 seconds.

- 10) Set the microplate reader wavelength at 450 nm and measure the absorbance (OD) of each well within 15 minutes after adding stop solution.

Reference Range: 0.80-2.1 ng/ml

2. **THYROXINE (T4):** T4 levels were estimated by using the ELISA kit.

Methodology: ELISA kit method²⁷ was used for the quantitative determination of T4 levels in human serum.

Principle: The T4 ELISA kit was a solid phase enzyme linked competitive immunoassay for the measurement of T4 in human serum.

The T4 ELISA kit is comprised of two key components:

3. **Solid microwells pre-coated with anti-T4 antibody,** Liquid conjugates comprised of horseradish Peroxidase conjugated with T4 (HRP-T4 conjugates).

During the assay, the test specimen and the HRP-T4 conjugates were added to the anti-T4 antibody coated microwells. T4 present in the patient sample would compete with the T4 conjugates for binding with the anti-T4 antibody that had been pre-coated on the microwell surface. The amount of conjugates that bind to the microwell surface would decrease in proportion to the concentration of T4 in the patient sample.

Unbound conjugates were then removed by washing. The presence of the bound T4 conjugates was shown by a blue color upon the addition of the TMB substrate solutions. The reaction was stopped with stop solution, and absorbances were read using a spectrophotometer at 450/620-690 nm. The intensity of the color reflects the amount of bound enzyme-T4 conjugate and was inversely proportional to the amount of T4 in the patient sample, within the dynamic range of the assay.

Reagent composition:

Description	Quantity
Microwells coated with T4 analog	1 plate, 96 wells
T4 standards: S1	1ml
S2	1ml
S3	1ml
S4	1ml
S5	1ml
S6	1ml
HRP-T4 Conjugates	1.2 ml
Enzyme conjugate diluent	2 x 7.5 ml
Wash buffer	25 ml
Substrate	12.0 ml
Stop solution	7.5 ml

Procedure:

- 1) Removed the desired number of coated wells and secured them in the frame. Reseal un-used strips.
- 2) Added 50 µL of T4 standards, controls and patient specimens into the individual test wells.
- 3) Added 100 µL of T4 enzyme conjugates reagent to each well.

- 4) Shaked for 30 seconds to completely mix the liquid within the wells.
 - 5) Covered the plate with a lid and incubate the wells for 60 minutes at 37°C.
 - 6) Carefully removed the incubation mixture by emptying the solution into a waste container. Fill each well with wash solution and shake gently. Discarded the wash solution completely by emptying the contents into a container.
 - 7) Added 100 µL of substrate solution into each well.
 - 8) Incubated at room temperature in dark for 20 minutes.
 - 9) Stopped the reaction by adding 50 µL of stop solution to each well. Gently mix for 15 seconds.
 - 10) Set the microplate reader wavelength at 450 nm and measure the absorbance (OD) of each well within 15 minutes after adding stop solution.
- Reference Range: 5.0-13.0 µg/dl.

3. **Thyroid Stimulating Hormone (TSH):**T4 levels were estimated by using the ELISA kit.

Methodology: ELISA kit method²⁸ was used for the quantitative determination of TSH levels in human serum.

Principle: The TSH ELISA kit was a solid phase enzyme linked immunosorbent assay based on the principle of antibody sandwich technique for the quantitative determination of TSH in human serum.

The TSH ELISA kit was comprised of two key components:

- 1) Solid microwells pre-coated with monoclonal anti-TSH antibody, specific for β subunit.
- 2) Liquid conjugates composed of monoclonal anti-intact TSH antibody conjugated with horseradish Peroxidase (HRP-anti-TSH conjugates).

During the assay, the test specimen and the HRP-anti-TSH antibody conjugates were incubated simultaneously with the coated microwells. The TSH, if present in the specimen, reacts to the anti-β TSH antibody coated on the microwell surface as well as the HRP-anti-TSH conjugates, forming an antibody sandwich immunocomplex.

Unbound conjugates were then removed by washing. The presence of the conjugate complex was shown by development of a blue color upon additional incubation with substrate. The reaction was stopped with stop solution, and absorbances were read using a spectrophotometer at 450/620-690 nm.

Reagent composition:

Description	Quantity
Anti-TSH Ab Coated Microwells	1 plate, 96 wells
T4 standards: S1	1ml
S2	0.75 ml
S3	0.75 ml
S4	0.75 ml
S5	0.75 ml
S6	0.75 ml
S7	0.75 ml
HRP-anti-TSH Conjugates	6 ml
TMB Substrate	12 ml
Wash buffer	20 ml
Stop solution	13 ml

Procedure:

- 1) Removed the desired number of strips and secured them in the microplate frame. Reseal un-used strips.
 - 2) Added 50 µL of TSH standards, controls and patient specimens into the individual test wells.
 - 3) Added 50 µL of HRP-anti-TSH conjugates into all wells
 - 4) Rock the microplate gently for 30 seconds, and then cover the plate with a microplate sealer.
 - 5) Incubated the wells at 37°C for 60 minutes.
 - 6) Carefully removed the incubation mixture by emptying the solution into a waste container. Fill each well with diluted Wash Buffer and shake gently for 20-30 seconds. Discarded the wash solution completely by emptying the contents into a container.
 - 7) Added 100 µL of TMB Substrate into each well.
 - 8) Incubated at room temperature in dark for 20 minutes.
 - 9) Stopped the reaction by adding 100 µL of stop solution to each well. Gently mix for 30 seconds.
 - 10) Set the microplate reader wavelength at 450 nm and measure the absorbance (OD) of each well within 15 minutes after adding stop solution.
- Reference Range: 0.45-4.12 µIU/ml.

RESULTS

The present study was undertaken with an aim to study the effect of AEDs on serum thyroid profile levels. For this, a total number of 80 subjects were selected, out of which 40 epileptic patients taking Antiepileptic Drugs for a minimum period of 1 year constituted case group and 40 normal healthy individuals constitute control group. The serum samples of both the groups were subjected to biochemical investigations of thyroid profile levels. The subjects were divided into two groups –

Group 1- Epileptic patients taking AEDs for more than 1 year

Group 2- Normal healthy individuals

Group 1 is again divided into 4 groups according to type of drug used

Table 1: Distribution of patients according to type of antiepileptic drug taken

Number of epileptic patients	Antiepileptic drug taken			
	Group 1a Phenytoin	Group 1b Valproic Acid	Group 1c Carbamazepine	Group 1d Levetiracetam
	4	20	11	5
Total number	40			

[Table 1] indicates the distribution of cases according to type of antiepileptic drug taken i.e. Phenytoin, Valproic Acid, Carbamazepine and

Levetiracetam. Out of 40 epileptic patients on AEDs, there were 4 patients taking Phenytoin, 20 patients taking Valproic Acid, 11 patients taking Carbamazepine and 5 patients taking Levetiracetam

Table 2: Comparison of Thyroid Profile in patients and controls

Biochemical Assays	Epileptic patients (Mean \pm SD)	Controls (Mean \pm SD)	P Value
T3 (ng/ml)	1.2 \pm 0.3	1.1 \pm 0.3	0.68*
T4 (μ g/dl)	8.1 \pm 2.0	8.1 \pm 2.0	0.88*
TSH (μ IU/ml)	5.1 \pm 2.1	2.6 \pm 0.8	<0.001**

**highly significant ($p \leq 0.001$); not significant ($p > 0.05$)

[Table 2] indicates the comparison of thyroid profile in patients and controls. Results were highly significant for TSH but not for T3 and T4. The mean serum levels for T3 were 1.2 \pm 0.3ng/ml and 1.1 \pm 0.3ng/ml in patients and controls respectively. On the other hand, the mean serum level of T4 was same (8.1 \pm 2.0 μ g/dl) in both patients and controls. The results were not significant for T3 and T4.

Table 3: Comparison of Thyroid profile in patients taking different antiepileptic drugs

Antiepileptic Drug Taken	T3 (ng/ml)	T4 (μ g/dl)	TSH (μ IU/ml)
Group1a Phenytoin	1.4 \pm 0.4	9.1 \pm 1.6	6.1 \pm 2.8*
Group1b Valproic Acid	1.1 \pm 0.3	7.9 \pm 2.0	4.8 \pm 2.3*
Group1c Carbamazepine	1.1 \pm 0.4	7.8 \pm 2.4	5.4 \pm 1.6*
Group1d Levetiracetam	1.2 \pm 0.4	8.8 \pm 1.7	4.8 \pm 1.8*
Control	1.1 \pm 0.3	8.1 \pm 2.0	2.6 \pm 0.8

[*highly significant ($p \leq 0.001$)]

[Table 3] indicates the comparison of thyroid profile on the basis of drugs taken by patients.

For group 1a patients taking phenytoin, the mean levels were 1.1 \pm 0.4ng/ml of T3, 7.8 \pm 2.4 μ g/dl of T4 and 5.4 \pm 1.6 μ IU/ml of TSH. The results were highly significant in thyroid profile of epileptic patients taking phenytoin.

For group 1b patients taking valproic acid, the mean levels for T3 were 1.2 \pm 0.3 ng/ml, T4 were 7.9 \pm 2.0 μ g/dl and for TSH were 4.8 \pm 2.3 μ IU/ml. The results were also highly significant in patients taking valproic acid.

The group 1c and group1d i.e. patients on carbamazepine and levetiracetam respectively also showed highly significant results in thyroid profile. Hence, the thyroid profile results were statistically different.

DISCUSSION

Epilepsy is one of the most common neurological diseases. It is estimated that approximately 50 million people worldwide suffer from epilepsy. The most common treatment of epilepsy is based on

long-term use of antiepileptic drugs (AEDs). Changes in serum thyroid functions caused by antiepileptic treatment have often been discussed controversially. Many researchers found that long term antiepileptic drug therapy have a significant influence on serum thyroid hormone functions concentrations, while others reported no such effect with some antiepileptic drugs. In the present study, the effect of antiepileptic drugs in epileptic patients has been investigated. The frequency of the most common antiepileptic drugs is rare but the consequences can be very serious leading to death or liver transplantation due to acute liver failure induced by these drugs.^[29] Management of epilepsy depends firstly on the correct diagnosis, with emphasis on considerations of the etiology, seizure type and epilepsy syndrome. Each type of epilepsy differs in its first drug of choice.^[30] VA and carbamazepine are effective antiepileptic drugs for treatment of many types of epilepsies. Although they are well tolerated, many side effects on endocrine function have been reported.^[31] The present case control prospective study comprising of total 80 subjects taken from both rural and urban areas of Punjab state divided into two groups. Group-1 (Study group) comprised of 40 epileptic patients of taking antiepileptic drugs for a minimum period of 1 year must have five or more epileptic attacks. Group-2 (Control group) comprised of 40 normal healthy subjects. The effect of antiepileptic drugs (AED) were analysed according to type of AED intake by observing the changes in serum thyroid profile such as thyroxine (T4), triiodothyronine (T3) & thyroid stimulating hormone (TSH) in both groups and they are discussed as follows.

It is estimated that approximately 50 million people worldwide suffer from epilepsy. The most common treatment of epilepsy is based on long-term use of antiepileptic drugs (AEDs). Changes in serum thyroid functions caused by antiepileptic treatment have often been discussed controversially. Many researchers found that long term antiepileptic drug therapy have a significant influence on total serum thyroid hormone functions while others reported no such effect with some antiepileptic effect with some antiepileptic drugs. In the prese.

In the present study, the TSH values were statistically increased and significant ($p < 0.001$) when compared between these two groups. This shows that thyroid disorders was of subclinical hypothyroidism in which T3, T4 levels were within normal range and TSH levels were higher than the normal range .

The frequency of the most common antiepileptic drugs is rare but the consequences can be very serious

Our study might shed some new light on the pathophysiological role of TSH on lipid in clinical perspective. . Different drugs especially valproic

acid could increase serum TSH by affecting the complex central neuroendocrine control of TSH release that in turn might elevate serum FT4. Valproic acid also inhibits histone deacetylase, so it can modify transcription of many genes.

The pathophysiology of the TSH elevation with increasing age requires further investigation, as does the treatment of the subclinical hypothyroidism in these epileptic patients. Some other authors also have similar observations.^[32]

The effect of AEDs were also recorded in the present study and observed that mean serum T3 levels in patients taking phenytoin were 1.4 ± 0.4 ng/ml, that taking valproic acid was 1.1 ± 0.3 ng/ml, those taking carbamazepine were 1.1 ± 0.4 ng/ml and those taking levetiracetam were 1.2 ± 0.4 ng/ml. The mean serum levels of T4 of patients taking phenytoin were 9.1 ± 1.6 µg/dl, patients taking valproic acid were 7.9 ± 2.0 µg/dl, those taking carbamazepine were 7.8 ± 2.4 µg/dl and those taking levetiracetam were 8.8 ± 1.7 µg/dl. Similarly, the mean serum levels of TSH in patients taking phenytoin were 6.1 ± 2.8 µIU/ml; those taking valproic acid were 4.8 ± 2.3 µIU/ml; those taking carbamazepine were 5.4 ± 1.6 µIU/ml and levetiracetam were 4.8 ± 1.8 µIU/ml. The maximum increase in TSH was with phenytoin and minimum by valproic acid [Table 12].

The abnormalities associated with AEDs results in subclinical hypothyroidism, which is defined as a mild elevation of TSH levels in the presence of normal T3 and T4 levels, and appears to begin with no effect on neuropsychological functions. Different thyroid dysfunctions and subclinical hypothyroidism have been reported in adults.^[33]

Patients with a longer duration of epilepsy are more likely to have a higher seizure burden, which may have a negative impact on thyroid hormone homeostasis, especially through the hypothalamus and thyroid stimulating hormone.

Several mechanisms for AED-induced abnormal thyroid function have been postulated, including competitive binding of TH to thyroxine-binding globulin, increased peripheral conversion of T4 to active T3, and interference with the hypothalamic-pituitary axis.^[11]

Another study conducted on children and adolescents on antiepileptic drugs receiving VPA treatment indicted that subclinical hypothyroidism developed more often in the treatment arm when compared to the control arm.^[34] In adults, an increase in TSH level after long term CBZ treatment was reported only by Tiihonen et al.^[35] These results are similar with our findings.

The major concern with subclinical hypothyroidism has been risk of progression to overt hypothyroidism, hypercholesterolemia and increased risk of cognitive impairment, particularly in elderly individuals.^[18]

CONCLUSION

The present study reveals that epileptic drugs might be responsible for the initiation of subclinical hypothyroidism. Therefore, epileptic patients on different antiepileptic drug treatments might be on risk of suffering from thyroid disorders. Further studies with more sample size are needed to correlate these associations.

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