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PHENYTOIN MONOTHERAPY IN EPILEPSY AND ITS EFFECT ON TSH

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ABSTRACT: Long term administration of antiepileptic drugs has been found associated with development of hypothyroidism. But conflicting reports about effect on thyroid stimulating hormone (TSH) are available in literature and duration required to bring about this effect has also not been reported. Therefore, twenty five newly diagnosed adult patients with epilepsy were subjected to estimation of TSH before starting phenytoin and then at 2 and 6 months of phenytoin therapy. Phenytoin levels were also estimated using high performance liquid chromatography at 2 and 6 months and correlated with levels of TSH. The levels of TSH at 2 months of phenytoin therapy were found to be significantly increased as compared to baseline levels ($p=0.000$) and at 6 months ($p=0.021$) as compared to the levels at 2 months. A significant positive correlation was observed between the levels of phenytoin and TSH at 6 months ($r=0.807$, $p=0.000$) while the correlation was not found to be significant at 2 months duration. Thus, it may be concluded that there is a risk of development of hypothyroidism even at 2 months of phenytoin therapy in patients with epilepsy and should be monitored accordingly.

INTRODUCTION: Phenytoin is used for the treatment of primary or secondary generalized tonic-clonic seizures, partial or complex partial seizures and status epileptics. It is also the most commonly prescribed anticonvulsant drug in our set-up due to its cost-effectiveness and easy availability¹. But long term administration of phenytoin is considered to affect thyroid profile. This is mainly thought to be through increasing clearance from the system by induction of hepatic enzymes². Some authors have linked it with development of autoimmune thyroiditis³.

It becomes hard sometimes to detect the condition as the clinical features of phenytoin toxicity and hypothyroidism are overlapping².

Though effect of phenytoin on thyroid status has been reported by many authors but the reports are contradictory. Some observed no change in thyroid stimulating hormone (TSH) levels^{4,5} while some have reported it to be increased³ and some even have seen a decrease in these levels. There is not much mention of duration of phenytoin administration responsible for bringing out the change in TSH levels. Therefore, this study was planned to assess the effect of phenytoin at 2 and 6 months intake on levels of TSH.

MATERIAL AND METHODS: The present study was conducted on 25 newly diagnosed patients with epilepsy who were put on phenytoin monotherapy (100mg TDS) and 25 age and sex

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matched healthy controls after obtaining informed consent and taking care of all the ethical issues. The diagnosis was made according to the international league against epilepsy classification 2010 and was based on thorough history taking and neurological examination along with electroencephalography and neuroimaging (computerised tomography or magnetic resonance imaging) ⁶. The patients in the pediatric (<14 years) age group, with any history of intake of drugs / supplements affecting thyroid status, pregnant or lactating females and other metabolic or endocrinal diseases were excluded from the study.

The blood samples were collected from all the patients and controls at the beginning of the study and then at 2 and 6 months of commencing the treatment. The sample was collected in the morning just before the next dose of phenytoin was due (trough concentration). The serum was separated immediately and analyzed for TSH the same day and refrigerated (at -40°C) for phenytoin level estimation. Analysis of serum samples for phenytoin levels was done weekly in batches using fast elution HPLC (High performance liquid

chromatography) by Chromsystems, Germany⁷. Quality control was maintained by running three level control sera provided with the kits. TSH was estimated using chemiluminescence technique (Advia Centaur CP, Siemens) ⁸.

RESULTS:

Out of 25 patients, 20 were males and 5 were females. Mean age of the patients was 26.72±11.59 years ranging from 18-65 years. Majority of the patients (53.4%) had partial seizures. No patient was suffering from any neurological or learning disability. TSH levels were found to increase significantly (p=0.000) at 2 months of phenytoin therapy than at diagnosis and at 6 months (p=0.021) as compared to the levels at 2 months. The coefficient of correlation was found to be positive and statistically significant between levels of phenytoin and TSH at 6 months (r=0.807, p=0.000) (**Fig.2**) while the correlation between phenytoin levels and TSH was not statistically significant at 2 months (**Fig.1**). The levels of phenytoin and TSH are shown in **Table 1**.

TABLE 1: COMPARISON OF THE LEVELS OF TSH AND PHENYTOIN IN EPILEPSY PATIENTS

	At diagnosis	2 months	6 months	p Value
Phenytoin (mg/L)	-	15.74±9.49	15.92±5.54	0.000**
TSH(µIU/mL)	3.09±1.02	3.45±0.98	5.73±1.44	0.000*, 0.021**
r Value	-	-0.82 (p=0.697)	0.807 (p=0.000)	

* p Value between the levels at diagnosis and at 2 months

** p Value between the levels at 2 months and at 6 months.

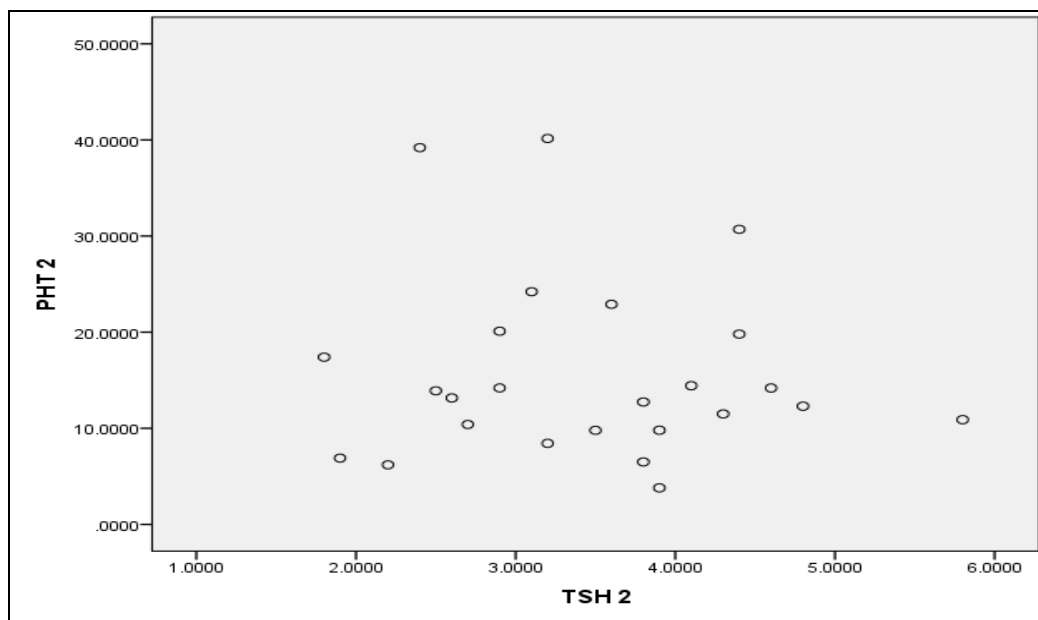


FIG. 1: SCATTER DIAGRAM SHOWING THE CORRELATION BETWEEN PHENYTOIN LEVELS AND TSH AT 2 MONTHS

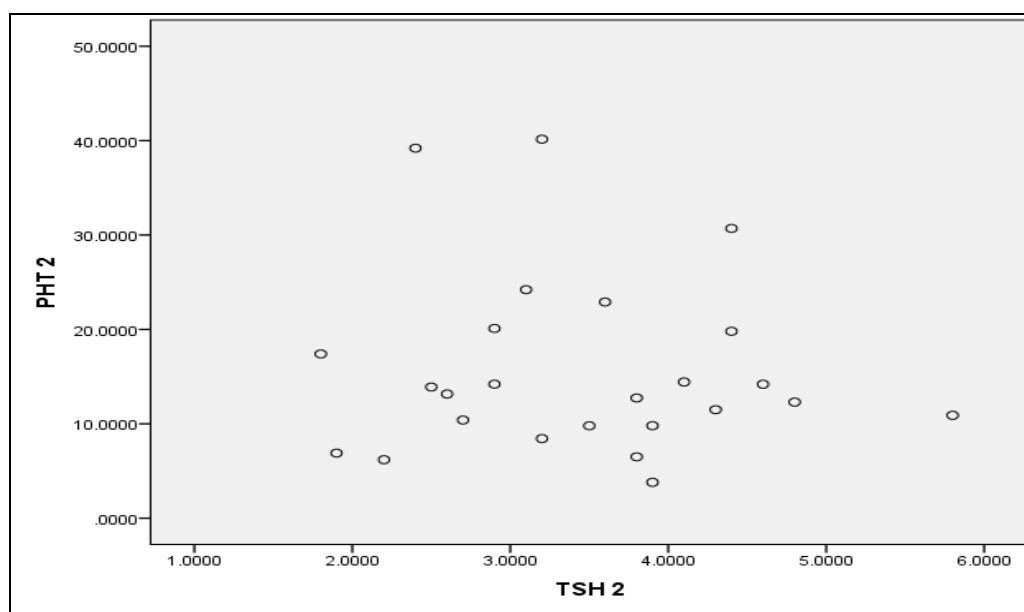


FIG. 2: SCATTER DIAGRAM SHOWING THE CORRELATION BETWEEN PHENYTOIN LEVELS AND TSH AT 6 MONTHS

DISCUSSION: The levels of TSH were found to be increased significantly in patients with epilepsy on phenytoin monotherapy. TSH is the most sensitive parameter to detect any abnormality in the thyroid profile at an early stage. Therapeutic levels of phenytoin displace T4 and T3 from serum binding proteins and may reflect as an increase in free hormone fractions. In drug-treated patients, increased free T4 and T3 fractions offset the significant decrease in serum T4 and T3, resulting in normal free T4 and free T3 concentrations. Therefore, clinicians have been recommended to rely on serum TSH measurements to assess the thyroid status of these patients⁵. The mechanism put forward for alteration in thyroid hormone status includes augmentation of microsomal enzyme function in the liver and inhibition of hypothalamic gland activities and development of autoimmune thyroiditis^{3, 10, 11}.

The reports on levels of TSH are found to be conflicting with some authors reporting no change in TSH levels on intake of phenytoin in patients with epilepsy^{5, 12, 13}, while others have observed an increase in its levels^{14, 15}.

Some authors have suggested a possible inhibitory effect of some antiepileptic drugs on the hypothalamic and/or anterior pituitary hormone levels resulting in non-alteration of the levels of TSH^{16, 17}. The increase in TSH is probably a compensatory mechanism due to the low free

thyroid hormones in serum caused by an increased hepatic degradation of thyroid hormones by phenytoin¹⁴.

Majority of the studies discussed in literature report the effect of phenytoin on long term administration but duration has not been specified. It has been observed that there was a significant rise in TSH ($p=0.000$) on 2 months of phenytoin monotherapy as compared to baseline levels while the correlation between phenytoin and TSH was found to be statistically significant at a duration of 6 months only.

Therefore it may be concluded that there is a risk of developing hypothyroidism in patients with epilepsy on administration of phenytoin for even two months. As the patients require a long term therapy for management of this disease, there is a need for screening and monitoring of patients with epilepsy on phenytoin monotherapy for development of hypothyroidism. Though further studies with larger sample size are required to support these findings.

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CONFLICT OF INTERESTS: None.

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