International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (2): 1137-1146
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Biological Sciences | Open Access | MCI Approved
UGC Approved Journal

The Long-Term Effect of Anticonvulsant Therapy on Thyroid Profile in Children

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Received: 10 Jan 2019 / Accepted: 9 Mar 2019 / Published online: 1 Apr 2019
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Abstract
Background: Inadequate and contradictory data exist for the effect of anticonvulsant drugs on thyroid profile in children. Objectives: To investigate the effect long term monotherapy of phenytoin, valproate, and carbamazepine on thyroid profile. Method: A total of 66 children were included in the study. Of the total, 24.2% received carbamazepine (n=16), 25.8% received phenytoin (n=17), and 50% received valproate (n=33). Only children on anticonvulsant therapy for at least one year were included in this study. TSH, T4 and T3 by Electro-chemiluminescence immune assay (ELICA) were evaluated for each child. Children on treatment with carbamazepine and phenytoin presented with decrease in T4 and only a slight change in TSH, Children on valproate presented with change in both TSH and T4. The frequency of subclinical hypothyroidism is 25% with carbamazepine, 5.9% with phenytoin and 18.2% with valproate. A total of 16.7% children presented with subclincal hypothyroidism. A 'p' value of less than 0.05 is taken as significant. Conclusion: The p value for TSH is 0.001 ($p<0.05$) which shows that subclinical hypothyroidism is prevalent in all three drug therapies. Therefore, thyroid profile should be done before prescribing anticonvulsant therapy and should be checked periodically

Keywords
Anti-convulsant Therapy, Carbamazepine.

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INTRODUCTION:
Epilepsy is a chronic disorder which requires long term therapy with anticonvulsant drugs. The incidence rate of epilepsy is 0.5-1% of children worldwide.[1]The prevalence of subclinical hypothyroidism in children is 2%.[2] In India, the incidence rate of epilepsy in children is 3.74 out of 1000 male children and 3.17 out of 1000 female children.[3] It has been established that the drugs used for epilepsy may disturb the thyroid function in adults but it has not been confirmed in children.
The main drugs used in the outpatient department for paediatric epilepsy are phenytoin, carbamazepine and valproate. Hence our study is to investigate the thyroid levels in children who are using these anti-epileptic drugs.
Oppenheimer et al. (1961) first reported changes in serum thyroid hormone levels in phenytoin (PHT)-treated epilepsy patients.[4] Thyroid hormones are

essential for the development and regulation of the metabolic state of many tissues; thus, disturbances of thyroid function may impede growth and development in children.[5] Serum thyroxine (T4) and free thyroxine (FT4) concentrations appear to decrease during phenytoin or carbamazepine (CBZ) treatment, but thyrotropin (TSH) levels appear to be increased.[5] Published reports on the effects of valproate (VPA) on serum thyroid hormone levels are inconclusive.[5]

Children on anticonvulsants are subjected to subclinical hypothyroidism.[6]It is a benign and remitting disease with less chances of becoming overt hypothyroidism. The normal TSH value in children is 0.6-5.0 mIU/ml. Replacement therapy for the treatment of subclinical hypothyroidism is not indicated in children with TSH of 5-10 mIU/ml, when there was no goiter and no antithyroid antibodies.[6]

The results so far have been controversial. The studies so far have seen a subclinical hypothyroidism in 12% of children on valproate therapy and 13.9% on carbamazepine therapy.[7]

Review of Literature:

Overview

Hypothyroidism is a preventable cause of mental retardation in children. Inadequacy of existing data of incidence and prevalence of hypothyroidism and hyperthyroidism in neonates, children and adolescents leads to many undetected cases. Nowadays routine neonatal thyroid screening is being carried out to substantiate the incidence levels of subclinical hypothyroidism in children and for early detection.

Most common cause of hypothyroidism is autoimmune thyroid disease. McLeod and Cooper et al study confirms that the prevalence of autoimmune thyroid disease is 4.3% in males and 16.2% in females.[8]Previous radioiodine therapy, thyroid surgery, and external radiation therapy can also result in subclinical hypothyroidism. Patients with subclinical hypothyroidism may progress to overt hypothyroidism. This may lead to cardiac dysfunction, mental retardation, systemic hypothyroidism symptoms and hypercholestrolemia. The major cause of hyperthyroidism is grave's disease, thyroid adenoma, multinodular goiter, and thyroiditis.

Lancet et al study shows that about 1 in 3000-4000 infants are reported to have congenital hypothyroidism when screened in infancy.[9] Glorieux J, Dussault JH, Morissette J, Desjardins M, Letarte J, Guyda H et al study expresses that infants with congenital hypothyroidism have normal developmental quotients at 6-7 years of age if they are treated promptly after birth and monitored closely in their early years.[10,11] Fernhoff, Brown and Elsas et al study shows that since the thyroid gland develops simultaneously with several other organs, and since thyroid hormone affects cellular metabolism, it is likely that infants with congenital hypothyroidism would be at high risk of congenital malformations.[12] Virtanen et al confirms that in history the complaints in a child with congenital hypothyroidism are usually feeding difficulties, drowsiness, flaccidity and hypothermia. On examination, increased irritability, abnormal muscle reflexes, hypothermia. Other findings are large tongue, dry skin, umbilical hernia, rough hair, abdominal distension, cold and mottled skin.[13]

In case-finding, testing for thyroid dysfunction is performed among patients who come to their clinicians for unrelated reasons. When the test is abnormal, the patient is called back for a detailed thyroid-directed history and confirmatory testing. Subclinical hypothyroidism is diagnosed if the TSH remains elevated and the free T4 remains normal for a period of 3-6 months. While hypothyroidism and hyperthyroidism are distinctly different disorders, with different symptoms and potential complications, screening for both subclinical hypo- and hyperthyroidism is accomplished through testing of serum TSH, with testing of serum free T4 if the TSH is high, and of T3 as well as free T4 if the TSH falls below the normal range.

History:

Werner et al study states that in 1896, Bauman discovered high iodine concentration within the gland. The work of Oswald with thyroglobulin gave a firm basis to a relation between iodine and the thyroid. Gross and Pitt-Rivers found Triiodothyronine (T3), a more potent and more rapid in onset of action than T4 and was clinically effective in myxedema. Paracelsus in Salzburg described endemic cretinism. Faggie described sporadic cretinism in 1871. In 1874, Sir William W. Gull, MD, published his observations in five women suffering from hypothyroidism, which he called myxedema associated with a "cretinoid state." Thyrotoxicosis was first described in 1786 by C H Parry but was reported in 1825. R J Graves described exophthalmic goiter and the disease named after him.[15] Perrier and Boger et al study states that Magnus-Levy described the characteristic elevation of basal metabolic rate in this disorder.[14] Plummer in 1913 distinguished toxic adenomatous goiter from exophthalmic goiter and so the disease was named after him.

Surveillance:

Lancet et al study confirms that the incidence of congenital hypothyroidism from neonatal thyroid screening programs is 1:3000 to 1:4000 worldwide.[9] Hunter et al study expresses that the overall prevalence of hypothyroidism in young people less than 22 years of age is 0.135%, and in the group aged 11-18 years it is 0.113%.[16]

Etiology:

Almandoz et al study shows that hypothyroidism can arise as primary from the thyroid gland, when there is a defect in thyroid hormone synthesis and release or centrally from the hypothalamic-pituitary thyroid axis, when there is a defect in either TRH or TSH signaling to the thyroid. Hypothyroidism is of two types-primary and secondary.

Primary hypothyroidism could be due to medications, autoimmune, iatrogenic, diet deficient in iodine, thyroid agenesis, radiation exposure, defective hormone synthesis or thyroid hormone resistance.

Secondary hypothyroidism could be due to tumours, infarction, trauma, infiltrative disorders, infection, medications or lymphocytic hypophysitis.[17]

Studies have proven that children with normal thyroid profile on long term anticonvulsant therapy present with subclinical hypothyroidism. Yilmaz et al study shows that the incidence of subclinical hypothyroidism is 12% in children on valproate therapy and 13.9% on carbamazepine therapy.[7]The results are still controversial. Children on anticonvulsant therapy may have a higher frequency of developing subclinical hypothyroidism.

Recent Trends:

McAninch and Bianco et al study shows that recently the Thr92AlaD2 protein been found to have a longer half-life, ectopically localize in the Golgi apparatus, and significantly alter the genetic fingerprint in cultured cells and in the temporal pole of the human brain without evidence of reduced thyroid hormone signaling. Thr92Ala polymorphism in the type 2 deiodinase gene (*DIO2*), seen in a subpopulation of patients has improved well-being and preference for combination therapy.[18]

Epidemiology:

Desai PM et al study from Mumbai have suggested that congenital hypothyroidism is common in India, the disease occurring in 1 out of 2640 neonates, when compared with the worldwide average value of 1 in 3800 subjects. In a clinic-based study from Mumbai, out of 800 children with thyroid disease, 79% had hypothyroidism. Common causes of hypothyroidism in these children were thyroid dysgenesis, dyshormonogenesis, and thyroiditis.[19]

Usha Menon et al study shows that in a population-based study done in Cochin on 971 adult subjects, the prevalence of hypothyroidism was 3.9%. The prevalence of subclinical hypothyroidism was also high in this study, the value being 9.4%. In women, the prevalence was higher, at 11.4%, when compared with men, in whom the prevalence was 6.2%.[20]

Vanderpump, Braverman, Utiger et al study shows that in iodine-replete communities in the United States, the prevalence of spontaneous hypothyroidism is between 1 and 2%, and it is more common in older women and 10 times more common in women than in men. Studies in Northern Europe, Japan and the USA have found the prevalence to range between 0.6 and 12 per 1000 women and between 1.3 and 4.0 per 1000 in men investigated.[21]

Prevention:

The National Goitre Control Programme was initiated in1992 and was renamed to National Iodine Defeciency Disorder Control Programme. This programme aims to provide iodated salt to all communities of India.

Aims and Objectives

1. To assess the thyroid levels of children on anticonvulsant drugs
2. To establish the incidence of hypothyroidism in children on anticonvulsant drugs

MATERIALS AND METHODS:

Patient:

Sixty-six epileptic children who were treated for at least one year with anticonvulsants with carbamazepine, valproate or phenytoin monotherapy were included in this study. 17 received carbamazepine, 16 received phenytoin and 33 received valproate. All children suffered from generalized epilepsy and were followed up in a tertiary care hospital.

The main exclusion criteria of the study are known case of thyroid dysfunction, family history of thyroid disease, family history of chromosomal abnormalities, metabolic abnormalities and patients who are not willing to participate in the study.

Serum thyroxine, triiodothyronine and thyroid stimulating hormone were assessed by Electro-chemiluminescence immunoassay (ELICA) for all of the sixty-six children

Study Design: Cross-sectional study

Study Population: All patients between the ages of 2-16 years of age on anticonvulsant drugs in both the medical and neurological wards of a tertiary care hospital

Expected sample size: 66 cases derived from the number of cases seen in the follow up and review cases from the outpatient department.

N= (P x Q) [1.96/D]^2

P- Prevalence rate of seizures among children
Q- Non-Prevalence
D- Expected difference in the population

Inclusion Criteria:

1. Children between the age of 2 to 16 years
2. Children with onset of epilepsy
3. Children on antiepileptic therapy for more than 6 months
4. Patients willing to participate in the study

Exclusion Criteria:

1. Children with known case of thyroid dysfunction
2. Children with family history of thyroid dysfunction.
3. Children who has family history of chromosomal abnormalities
4. Those with metabolic abnormalities
5. Patients unwilling to participate in the study

Data Collection: The following will be collected from the patient:

Informed Consent, Patient's identification details, Patient's age and gender, Duration of intake of antiepileptic drugs, type of seizure, dose and frequency of antiepileptic drugs, personal and clinical history, family history of thyroid dysfunction, both general and neurological examination, lab investigations.

Instruments/Facilities available in the hospital: Serum T3, T4, and TSH will be measured by Electro-chemiluminescence immunoassay (ELICA) which has a functional sensitivity of 0.014µIU/ml for TSH, 4.61pmol/ml for T3 and 0.974ng/dl for T4

Statistical Analysis:

Statistical analysis was performed using analysis of variance (ANOVA) and Pearson's correlation coefficient was calculated. A 'p' value less than 0.05 was considered significant.

RESULTS AND DISCUSSION:

A total of 66 children between the ages of 2 and 16 consisting of 43 males (65.2%) and 23 females (34.8%) were enrolled in the study. Of the 66 children, 17 (24.2%) were receiving carbamazepine, 16 (25.8%) were receiving phenytoin and 33 (50.0%) were receiving valproate. Out of the 66 children, 11 were found to be hypothyroid and 55 were found to be normal.

Subclinical hypothyroidism is a preventable and manageable cause for mental retardation in school going children. It has been confirmed that anticonvulsants cause subclinical hypothyroidism in children, but the information is still in adequate. It has now become routine to screen neonates and pregnant women for hypothyroidism.

Verotti, Scardapane, Manco, Chiarelli et al concluded that antiepileptic drugs have been proved to alter thyroid hormone levels in both adults and children. Subclinical hypothyroidism and alterations in thyroid hormone serum levels are reported in the literature. Phenytoin, valproate and carbamazepine, in particular, seem to be involved in these alterations.[24] This study investigated the effect of widely used antiepileptic drugs such as phenytoin, valproate and carbamazepine on thyroid function in children on therapy for at least 1 year.

In our study, out of 66 children, 65.2% were male and 34.8% were female. 19.7% of children were below the age of 5, 30.3% were between the ages 5 and 10 and 50% were above the age of 10. Out of the total, 16.7% presented with subclinical hypothyroidism and 83.3% presented normal. Subclinical hypothyroidism is more predominant in female children than male children. Of the total, 24.2% received carbamazepine, 25.8% received phenytoin and 50% received valproate (Table 1). The p value is 0.001 ($p<0.05$) for TSH which is considered significant (Table 2). The mean value for TSH is higher in the age group of less than 5 (Graph 7). TSH values are significantly increased in carbamazepine therapy as compared to phenytoin and valproate (Graph 8). Our study also shows that children on therapy with carbamazepine have higher risk of developing subclinical hypothyroidism (Table 4).

In our study, there is a female predominance over male. In females there is a prevalence of subclinical hypothyroidism of 21.05% and in males it is 19.4%. There is a higher prevalence of subclinical hypothyroidism in females on long term anticonvulsant therapy. This result is consistent with other studies.[7, 25, 26]

Of the children taking carbamazepine therapy, 25% of the children presented with subclinical hypothyroidism. Vanionpaa et al stated that carbamazepine causes altered thyroid hormone levels due to the ability to induce hepatic p450 enzyme system that leads to an increase in the metabolism of the hormone.[25]The outcome of this study for carbamazepine is similar to other studies. There is a significant decrease in T4, and some patients had a slight decrease in T3 but no virtual change in TSH in many cases. Children on therapy with carbamazepine have a higher frequency of developing subclinical hypothyroidism compared to the other drugs.[6, 7,25,26,27]

Of the children taking phenytoin therapy, 5.9% of children presented with subclinical hypothyroidism. Connacher and Verotti et al prove that phenytoin has similar effect as carbamazepine on thyroid profile. [26, 27]

Of the chidren on valproate therapy, 18.2% presented with subclinical hypothyroidism. Previous studies express no conclusive information on the effect caused by valproate on thyroid profile. Few studies mention that there is no change in the thyroid levels after long term anticonvulsant therapy.[4, 6, 25] On the contrary, some other studies state that there was a change found in the thyroid profile which was inconsistent in nature.[7, 26] The outcome of this study shows a slight increase in TSH and in some patients a decrease in T4.

Table 1: (n=66)

		No.%	
Gender	**Male**	43	65.2
	Female	23	34.8
Age	**< 5 Years**	13	19.7
	5 - 10	20	30.3
	> 10 Years	33	50.0
Result	**Normal**	55	83.3
	Hypothyroidism	11	16.7
Drug	**Carbamazepine**	16	24.2
	Phenytoin	17	25.8
	Valproate	33	50.0

Table 2: Comparison of means of thyroid profile between normal and hypothyroid (n=66)

Thyroid profile		Values		't'* value	p value
		Mean	S.D.		
T3	Normal	3.04	1.01	-1.319	0.192
	Hypothyroidism	3.50	1.27		
T4	Normal	1.02	0.28	-1.353	0.181
	Hypothyroidism	1.15	0.28		
TSH	Normal	2.59	1.27	-10.904	**<0.001**
	Hypothyroidism	**7.13**	1.20		

*'t' value: Independent sample 't' test

Table 3: Comparison of means of thyroid profile between age groups (n=66)

Thyroid profile	Age group	Values		F* value	p value
		Mean	S.D.		
TSH	< 5 years	4.24	2.75	1.556	0.219
	5 – 10 years	3.28	1.96		
	> 10 years	3.03	1.89		
T3	< 5 years	4.37	1.36		
	5 – 10 years	3.17	0.53		
	> 10 years	2.59	0.70	21.576	<0.001**
T4	< 5 years	1.11	0.19		
	5 – 10 years	1.08	0.25		
	> 10 years	1.00	0.33	0.825	0.443

***F value- One-way ANOVA**

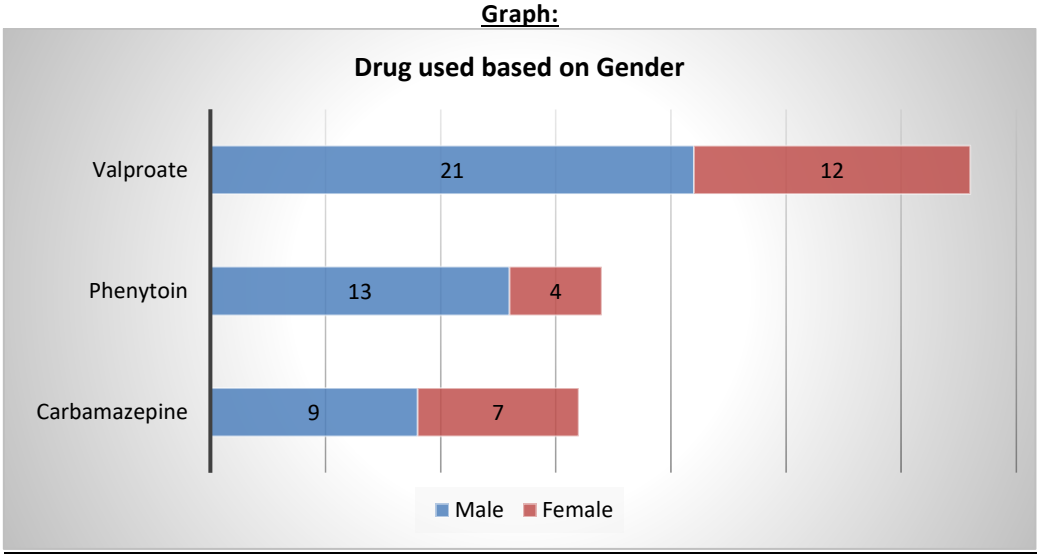
****p value shows a significant difference of means between the age groups for T3**

Table 4: Association of thyroid status in children with type of anticonvulsant therapy

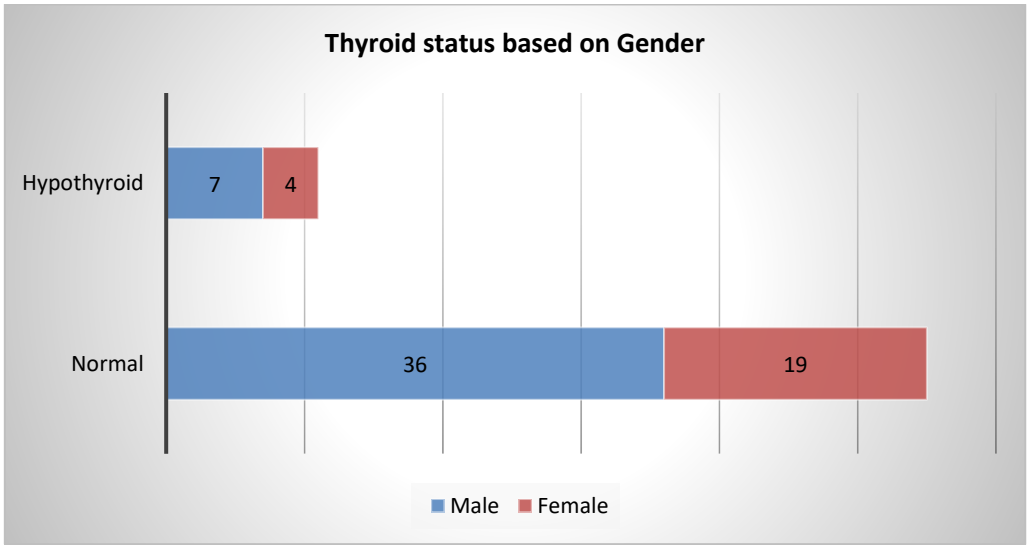
Anticonvulsant Used	Thyroid status		Total	Chisquare Value*	p value
	Normal N (%)	Hypothyroidism N (%)			
Carbamazepine	12 (75.0)	4 (25.0)	16 (24.2 %)	2.278	0.320
Phenytoin	16 (94.1)	1 (5.9)	17 (25.8)		
Valproate	27 (81.8)	6 (18.2)	33 (50.0)		
Total	55 (83.3)	11 (16.7)	66		

***Pearson's Chisquare test**

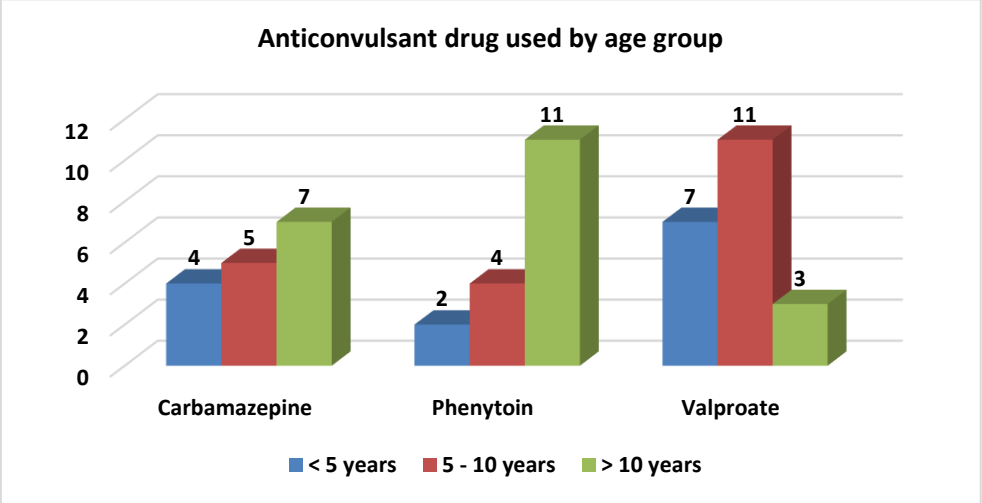
Graph:



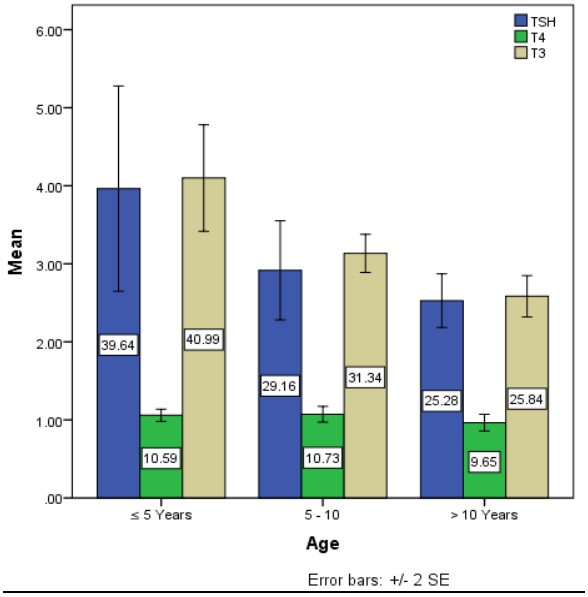
Graph 1: Bar Graph representing the drug used based on gender, (n=66)



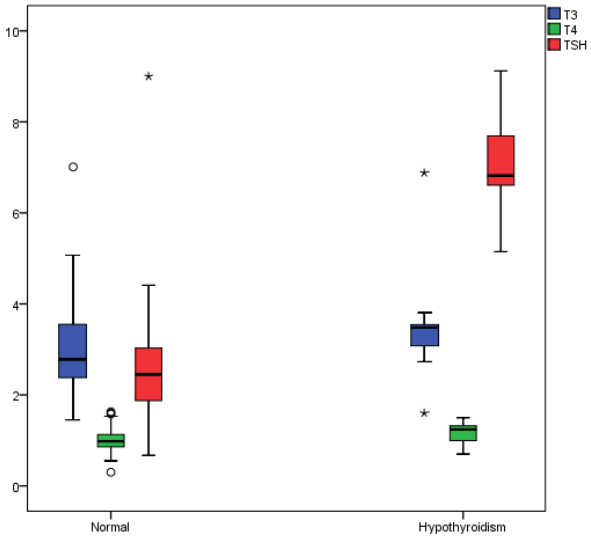
Graph 2: Bar graph representing the thyroid status based on the gender (n=66)



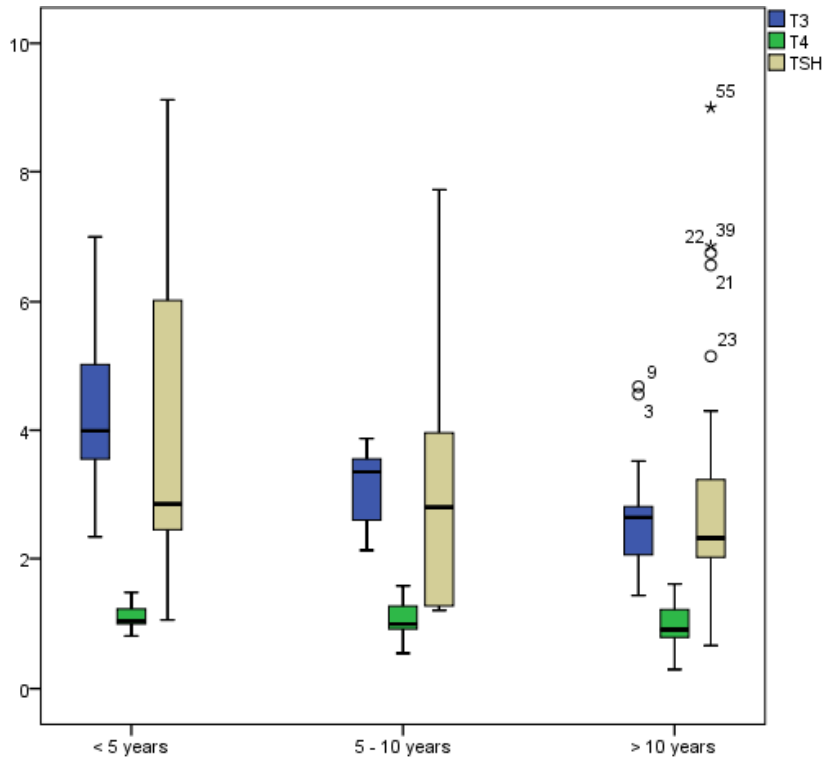
Graph 3: Bar graph representing anticonvulsant drug used by age group (n=66)



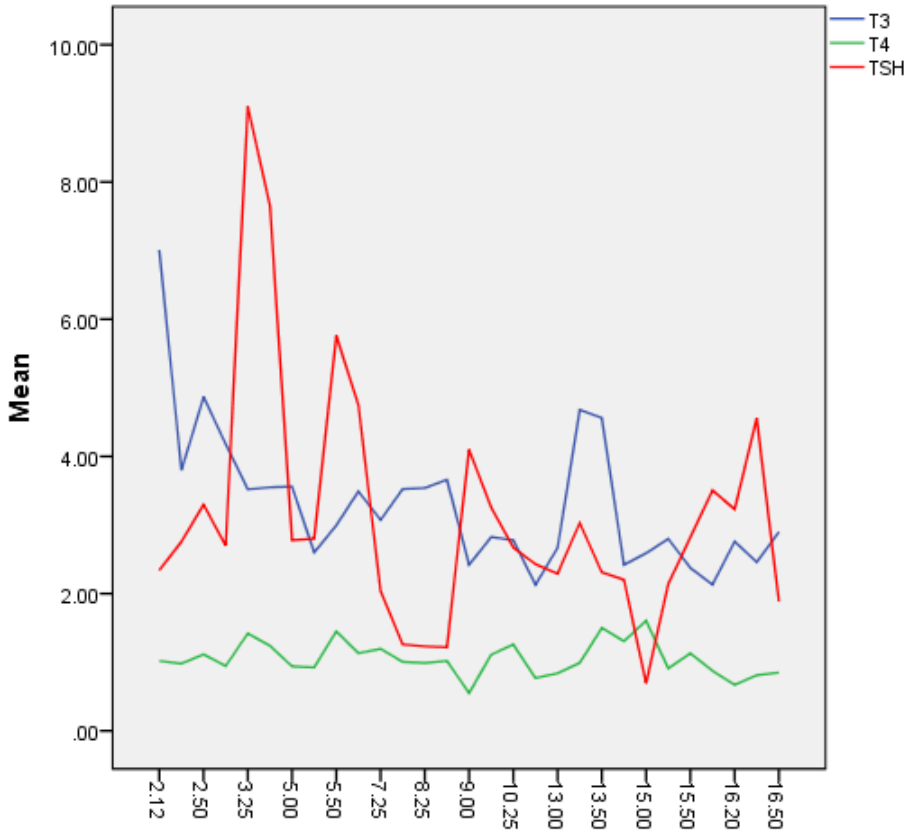
Graph 4: Error plot to show the mean thyroid profile in different age groups



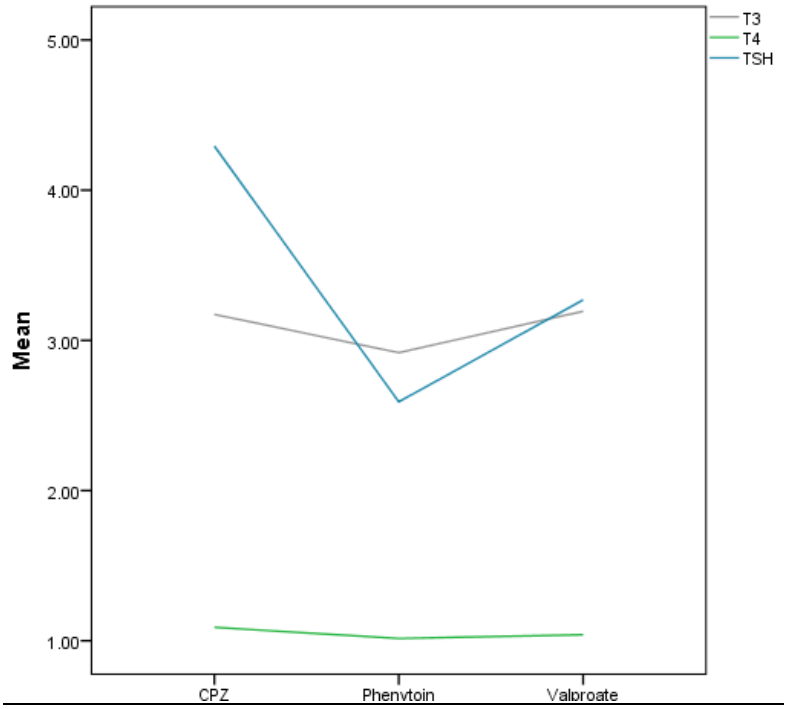
Graph 5: Box and Whisker plot to show the thyroid values in euthyroid and hypothyroid



Graph 6: Box and Whisker plot to show thyroid values in all age groups



Graph 7: Line graph to show the trend of thyroid values with age



Graph 8: Line graph to show the thyroid status according to the Anticonvulsant used

CONCLUSION

In conclusion, subclinical hypothyroidism is prevalent in all three drug therapies and is statistically significant. Therefore, thyroid profile should be done before prescribing anticonvulsant therapy and should be checked periodically. If any child presents with persistently high TSH levels or with deteriorating scholastic performance, the hypothyroidism should be treated or the anticonvulsant causing this effect should be withdrawn.

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