

COMPARISON OF INCIDENCE OF HYPOTHYROIDISM SECONDARY TO PHENOBARBITONE VERSUS VALPROATE VERSUS CARBAMAZEPINE VERSUS PHENYTOIN IN 1 MONTH TO 12-YEAR-OLD CHILDREN

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Abstract

Background: Seizures are commonest neurological problem that occur in children. It is defined as a transient occurrence of signs and symptoms that occurs due to abnormal excessive or synchronous neuronal activity in the brain. It is associated with high degree of mortality and morbidity. **Objective:** To study the comparison of incidence of hypothyroidism secondary to phenobarbitone versus valproate versus carbamazepine versus phenytoin in 1 month to 12-year-old children. **Materials and Methods:** This Prospective observational study was conducted among the children between 1mo to 12 yrs of age visiting to Department of Paediatrics and Department of Neurology JSS Hospital for a period of 18 months. **Result:** Thyroid profile was altered in the children on AED'S. Only 1.7% had signs and symptoms of hypothyroidism. Incidence of hypothyroidism was 0% in our study. In this study subclinical hypothyroidism was noted in subjects on phenytoin, valproate, carbamazepine. **Conclusion:** Significant alteration of TSH values were noted in children on phenytoin, valproate and carbamazepine with normal T3 and T4 levels.

INTRODUCTION

Four to ten percent of children develop seizure in first 16 years of life. Highest incidence of seizures was noted in children less than 3 years of age with reduced incidence with increasing age.^[1]

Febrile seizures is commonest form of seizures in pediatrics population. The risk of developing epilepsy after one episode of afebrile seizure is around 30% and the incidence decreases to 20% if neurological examination and EEG and imaging are normal.

Epilepsy, by definition is disorder of brain characterized by enduring predisposition to generate seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. At least one unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly demonstrate an enduring predisposition to develop recurrences is required for diagnosis of epilepsy.

Seizure disorder is a general term that is used to include febrile seizures, epilepsy, single seizures and symptomatic seizures secondary to infections, metabolic and other aetiologies. Epileptic syndrome is a disorder that manifests as one or more

specific seizure with complex of signs and symptoms that define a unique epilepsy condition.

Epileptic encephalopathy is a syndrome associated with severe EEG abnormalities that causes cognitive impairment in affected individual. Developmental encephalopathy denotes a disorder in which the underlying etiology (e.g., a specific gene mutation) contributes to a developmental delay independently of the patient's seizure burden and/or EEG abnormalities. Seizures can be either provoked or unprovoked seizures. Provoked seizures also called as acute symptomatic seizures, may result from electrolyte disorders, head injury, toxins, vascular anomalies, infections, tumours or other mass lesions, and many other causes. Primary generalized seizures develop from abnormal electrical discharge from both hemispheres simultaneously and involve reciprocal thalamocortical connections. Classification is important in the diagnosis, treatment, and understanding of seizures and epilepsies, including epilepsy incidence. A detailed history and clinical examination is required to determine the type of seizure. Starting antiepileptic drug also depends on several other characteristics such as age of child, compliance, side effects.^[2]

Thyroid hormones play an important role in growth and development especially in children, so the effect of

AED'S on thyroid hormones needs to be evaluated as early detection of hypothyroidism and treatment can prevent growth and developmental delay.

The affect of antiepileptic drugs on many of the endocrine functions have been reported especially the long term effect on thyroid hormones. Through several mechanisms AED'S affect thyroid hormone's. Some of them increase hepatic microsomal enzyme, leading to accelerated metabolism of thyroid hormone. Some of them hinder with the hypothalamic-pituitary axis.

Thyroid hormones play an important in growth and development especially in children, so the effect of AED'S on thyroid hormones needs to be evaluated as early detection of hypothyroidism and treatment can prevent growth and developmental delay.

Hence this study was conducted to study the comparison of incidence of hypothyroidism secondary to phenobarbitone versus valproate versus carbamazepine versus phenytoin in 1 month to 12-year-old children.

MATERIALS AND METHODS

This Prospective observational study was conducted among the children between 1mo to 12 yrs of age visiting to Department of Paediatrics and Department of Neurology JSS Hospital for a period of 18 months. Children between 1 month to 12 years of age with newly diagnosed seizure disorder starting on 1st line anti epileptics (Phenytoin, Phenobarbitone, Carbamazepine, Valproate) will be chosen to be included in the study. Purposive sampling was used. All cases fulfilling inclusion criteria from November 2020 to April 2022.

Children between 1 month to 12 years of age with newly diagnosed seizure disorder starting on 1st line anti epileptics (Phenytoin, Phenobarbitone, Carbamazepine, Valproate) will be chosen to be included in the study. Written and informed consent will be taken from the parents of the children chosen for the study.

Inclusion Criteria

- Children between 1 month to 12 years of age.
- Newly diagnosed seizure disorder, going to start on 1st line antiepileptic drugs (Phenytoin, phenobarbitone, carbamazepine, valproate).
- Child should be in euthyroid state at entry level.

Exclusion Criteria

- Child is on polytherapy.
- Child who received any drugs that effect thyroid function in the past 6 months.
- Hypothyroidism in the family or other endocrine problems

Full history taking and detailed clinical examination, in particular CNS examination was done. TSH, Total T3, Total T4 will be analysed using ECLIA (Electrochemiluminescence immunoassay analyser) in the fully automated hormone analyser Cobas E601E4

These children will be followed up for thyroid profile status at 3 months and 6 months after starting of anti-epileptics.

If child is in euthyroid state at 3rd month, child will be followed up at 6th month. If child is diagnosed with hypothyroidism during follow up at 3rd or 6th month, child will be treated for hypothyroidism as per unit protocol.

Statistical Analysis

The resulting variables will be categorized as normal or abnormal (low) or (high). Their incidence will be expressed as percentage and p values of <0.05 will be taken significant.

RESULTS

Age distribution among the subjects were 33.3% were between 4- 6 years, 31.7% were between 1- 3 years, 11.7% were between 7 and 9 years, 8.3% each were between 6 months and 1 year and 10- 12 years respectively and 6.7% were below 6 months. The mean age in the study was 4.16 ± 3.25 years. The study consisted of 37 males and 23 females with the sex ratio being 1.6: 1 [M: F].

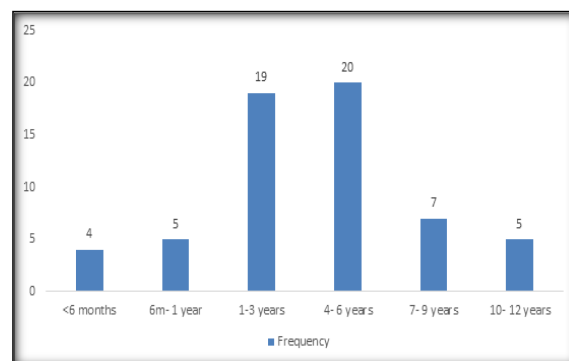


Figure 1: Column chart showing age

In the study 15% of the children had developmental delay and the remaining 85% had normal development. Family history was present in 3.3% (2 subjects) and the remaining 96.7% had no relevant family history.

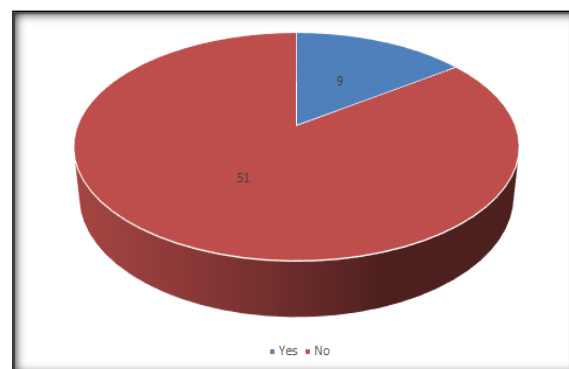


Figure 2: Pie chart showing developmental delay

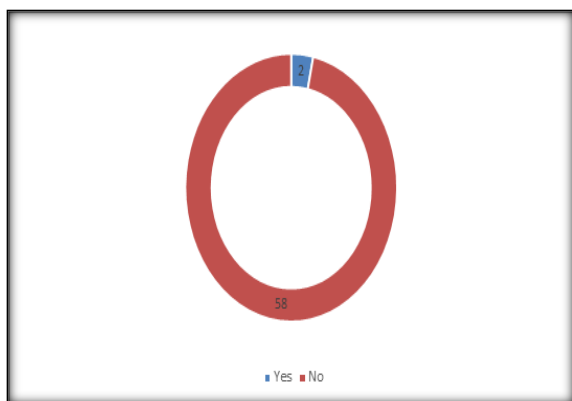


Figure 3: Pie chart showing family history

Microcephaly was present in 16.7% of the subjects and the remaining 83.3% had no microcephaly.

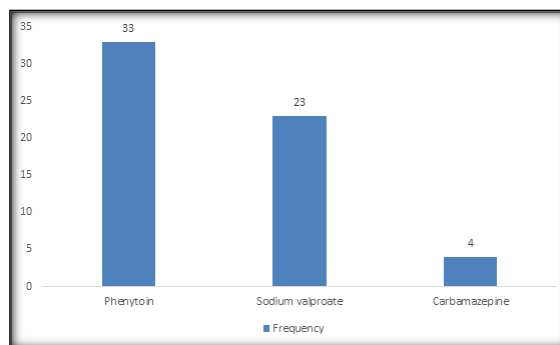


Figure 4: Column chart showing anti-epileptic drugs

The various drugs used in the study, where 55% were given phenytoin, 38.3% were given sodium valproate and 6.7% were given carbamazepine. The clinical signs and symptoms of hypothyroidism was present only in one 1 subject (1.7%) and none of the remaining 59 had any signs and symptoms of hypothyroidism.

Table 1: Distribution according to microcephaly

Microcephaly	Frequency	Percent
Present	10	16.7%
Absent	50	83.3%
Total	60	100%

Table 2: Thyroid profile of the subjects

Thyroid profile	At admission	3 months follow up	6 months follow up	p-value
Mean T ₃ nmol/L	1.65± 0.28	1.83± 0.39	2.19± 0.58	<0.001*
Mean T ₄ ng/dl	7.54± 2.12	8.54± 1.97	9.6± 1.98	<0.001*
Mean TSH mIU/L	1.62± 1.17	2.2± 1.38	2.82± 1.49	<0.001*

*Level of significance: p<0.05

The mean T3 level at admission was 1.65± 0.28, at 3rd month of follow up the mean was 1.83± 0.39 and the at 6th month of follow up mean was 2.19± 0.58 nmol/L. The mean T4 level at admission was 7.54± 2.12, at 3rd month of follow up the mean was 8.54± 1.97 and at 6th month of the follow up the mean was 9.6± 1.98 nmol/L. The mean TSH level at admission was 1.62± 1.17, at 3rd month of the follow up the mean was 2.2± 1.38 and at 6th month of the follow up mean was 2.78± 1.49 mIU/L as shown in table 9. A gradual increase in the levels at follow up was statistically significant (p<0.001).

Table 3: Incidence of sub clinical hypothyroidism among the subjects started using first line anti-epileptic drugs

Thyroid profile	Phenytoin (n=33)	Sodium valproate (n=23)	Carbamazepine (n=4)
T3	0	0	0
T4	0	0	0
TSH	2	2	1
Total	2 (6.06%)	2(8.6%)	1(25%)

The incidence of subclinical hypothyroidism among the phenytoin group (n= 33) was 6.06%, among the sodium valproate group (n= 23) the incidence was 8.6% and among the carbamazepine group (n=4) the incidence was 25% as seen in [Table 3].

DISCUSSION

In the present study, the mean age of the study population was 4.16± 3.25 years. In this study 61.7% were males and 38.3% were females with the sex ratio being 1.6: 1 [M: F]. In this study 15% of the children had developmental delay and the remaining 85% had normal development.

In the present study, 55% were given phenytoin, 38.3% were given sodium valproate and 6.7% were given carbamazepine. In the present study, the mean

T3 level at enrolment was 1.35± 0.57, at 3rd month of the follow up the mean was 1.59± 0.57 and at 6th month of the follow up the mean was 1.91± 0.69 nmol/L. The mean T4 level at admission was 7.43± 2.35, at 3rd month of the follow up the mean was 8.42± 2.16 and at 6th month of the follow up the mean was 9.41± 2.28 nmol/L. The mean TSH level at admission was 1.65± 1.25, at 3rd month of follow up the mean was 2.2± 1.38 and at 6th month of the follow up the mean was 2.82± 1.5 mIU/L. We found a significant increase in TSH values from baseline

to 3 months and later at 6 months.(p value <0.001%).

A study conducted by Dhodi DK, a cross sectional,non-randomized study of thyroid study patients on phenytoin, valproate and carbamazepine monotherapy was conducted over a period of 12 months in department of neurology from November 2012 to October.90 subjects were enrolled in the study. 56 were males and 34 were female. Alteration of thyroid profile status were seen in patients treated with phenytoin and carbamazepine group. No alteration of thyroid profile status was noted in valproate group.³

The present study findings concurred with a study by Dhodi DK et al in which mean TSH levels before treatment were 1.93 ± 0.19 , 1.66 ± 0.27 and 1.32 ± 0.16 U/ml in phenytoin, carbamazepine and valproate group respectively. Mean T3 levels before treatment were 3.25 ± 0.31 , 3.2 ± 0.22 and 3.47 ± 0.29 pg/ml in phenytoin, carbamazepine and valproate group respectively. Mean T4 levels before treatment were 1.8 ± 0.1 , 1.89 ± 0.13 and 2.25 ± 0.11 ng/ml in phenytoin, carbamazepine and valproate group respectively.^[3]

The present study findings concurred with a study by Dhodi DK et al in which mean TSH levels after treatment were 3.55 ± 1.40 , 1.7 ± 0.68 and 1.22 ± 0.61 U/ml in phenytoin, carbamazepine and valproate group respectively. Mean T3 levels after treatment were 3.12 ± 0.4 , 1.9 ± 0.69 and 3.54 ± 0.44 pg/ml in phenytoin, carbamazepine and valproate group respectively. Mean T4 levels after treatment were 1.66 ± 0.2 , 0.72 ± 0.26 and 2.22 ± 0.58 ng/ml in phenytoin, carbamazepine and valproate group respectively.^[3]

A study conducted by Kim SH was aimed to estimate the incidence of thyroid dysfunction on valproic acid monotherapy among children and adolescents between age range of 1 to 18 years at Department of Paediatric Neurology outpatient clinic of Seoul National University. Thyroid function tests were evaluated. They concluded that incidence of the subclinical hypothyroidism was significantly high in patients treated with valproate compared to controls.^[4]

In our study, the incidence of subclinical hypothyroidism in the phenytoin group (n= 33) was 6.06%, among the sodium valproate group (n= 23) was 8.6% and 25% among the carbamazepine group with T3 and T4 values being normal. The present study findings concurred with a study by Kim SH et al in which incidence of subclinical hypothyroidism among patients on treatment with Valproic acid drug was 52.4%.^[4]

A study conducted by Yilmaz U et al was aimed to study the effect of phenobarbitone, carbamazepine, oxcarbamazepine, levetiracetam monotherapy on the thyroid functions during a period of 12 months at Department of Paediatric Neurology, at Dr.Behcet Uz Hospital, turkey. A total of 223 children with new onset seizures were enrolled in the study. Out of which 103 were females and 120 were males. They were treated with valproate, phenobarbital, carbamazepine, oxcarbazepine, levetiracetam monotherapy. Thyroid function tests were measured at first, Sixth and twelfth months of therapy. Frequency of subclinical hypothyroidism was noted to be 28% at month 12 in subjects on valproate, 21.4% in subjects on oxcarbazepine, 18.2% in subjects on phenobarbital, 13.9% in subjects on carbamazepine, and 0% in levetiracetam groups.^[5] The present study findings were comparable to a study by Yilmaz U et al in which frequency of the subclinical hypothyroidism was noted to be 28% in valproate, 18.2% in phenobarbital and 13.9% in carbamazepine.^[5]

CONCLUSION

Thyroid profile was altered in the children on AED'S. Significant alteration of TSH values were noted in children on phenytoin, valproate and carbamazepine with normal T3 and T4 levels. Only 1.7% had signs and symptoms of hypothyroidism. Incidence of hypothyroidism was 0% in our study. In this study subclinical hypothyroidism was noted in subjects on phenytoin, valproate, carbamazepine. S. ignificant alteration of TSH values were noted in children on phenytoin, valproate and carbamazepine with normal T3 and T4 levels.

REFERENCES

1. Friedman MJ, Sharieff GQ. Seizures in children. *Pediatr Clin North Am.* 2006 Apr;53(2):257-77.
2. Falco-Walter JJ, Scheffer IE, Fisher RS. The new definition and classification of seizures and epilepsy. *Epilepsy Res.* 2018 Jan;139:73-9.
3. Dhodi DK, Bhagat SB, Patil KC. A comparative study of thyroid status of patients on phenytoin, carbamazepine and valproate monotherapy. *Int J Basic Clin Pharmacol.* 2016;5:362-5.
4. Kim SH, Chung HR, Kim SH, Kim H, Lim BC, Chae JH, et al. Subclinical hypothyroidism during valproic acid therapy in children and adolescents with epilepsy. *Neuropediatrics.* 2012;43(3):135-9.
5. Yilmaz U, Yilmaz TS, Akıncı G, Korkmaz HA, Tekgöl H. The effect of antiepileptic drugs on thyroid function in children. *Seizure* 2014;23(1):29-35.