Research Article

How common is Hypothyroidism in Children with Epilepsy on Antiepileptic Drugs

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Received on: 21-Apr-2020 Accepted for Publication: 20-May-2020

ABSTRACT:

Background: Epileptic children treated with oral antiepileptic drugs (AEDs) are at risk of hypothyroidism. However, there are still limited data about the influence of AEDs on thyroid function in children.

Aims: To analyze thyroid function of epileptic children.

Methods: A cross-sectional study was conducted during 2015 and 2020 at Dr. Soetomo Hospital Surabaya, Indonesia. Epileptic children treated with AEDs were included. Multiple AEDs were defined as more than one oral AEDs, which consisted of valproic acid, carbamazepine, phenytoin and phenobarbital. Hypothyroid was determined based on the decreased level of free thyroxine (fT4) and an increased level of thyroid stimulating hormone (TSH). Serum fT4 and TSH concentrations were measured in samples from epileptic children with single and multiple AEDs, and were compared using Chi-square and Mann-Whitney test.

Results: Forty-one children were included in the study, with twenty-seven (65.9%) epileptic children were treated with single AED. Thirteen children (31.7%) diagnosed with hypothyroidism, in which 5 children received multiple AEDs. Valproic acid was the most frequent AEDs given to the epileptic children (39 children). Mean level of fT4 and TSH were 1.32±0.25ng/dl and 4.5±4.03mIU/L. There were no significant differences of fT4 and TSH level between single and multiple AEDs (p=0.095, p=0.805). There was no significant difference in thyroid dysfunction between single and multiple AEDs (p=0.734).

Limitations: This is cross sectional study.

Conclusion: More than quarter epileptic children suffer from hypothyroidism.

Keywords: hypothyroid, epileptic children, antiepileptic drugs.

INTRODUCTION

Antiepileptic drugs (AEDs) therapy has been known to have multiple short- and long-term effects. The effects include endocrine disturbances, in particular, an alteration of the thyroid function.[1,2] Many AEDs may alter thyroid hormone homeostasis in biosynthesis, release, transport, metabolism and excretion of thyroid hormones.[3-5]

Several studies reported an increase in thyroid stimulating hormone (TSH) level, but in the vast majority of studies, decrease in thyroxine (T4) level, free thyroxine (fT4) level, triiodothyronine (T3) level, free triiodothyronine (fT3) level; and unchanged TSH levels had been reported in children using carbamazepine (CBZ) and phenobarbital (PB). Another study reported altered thyroid functions while using Valproic acid (VPA), however the results are controversial because there were normal or elevated serum levels of TSH.[4-6]

Single AED has been promoted as an ideal therapy for epilepsy because of its minimal side effects, absence of drug interactions, better compliance, lower cost and improvement of seizure control compared to multiple AEDs.[7] A previous study showed that epileptic patients receiving multiple AEDs had an increase mean level of TSH, resulting symptoms and signs of hypothyroidism, compared to those receiving single AED.[8,9]

Hypothyroidism in children can have harmful effects on the growth, school achievement and pubertal development.[10,11] Pediatricians should be alerted about conditions that may be associated to the children receiving AED. However, there are still limited data about the influence of AEDs on thyroid function in children. Thus, we aimed to analyze thyroid function of epileptic children.

METHODS

This comparative cross-sectional study was conducted during 2015 and 2020 at pediatric neurology outpatient clinic Dr. Soetomo Hospital, Surabaya, Indonesia. Patients who fulfilled inclusion criteria were included in the study.

Inclusion criteria

Children aged less than 18 years who had been diagnosed with epilepsy by clinical examination and EEG and received AEDs for more than 3 months were included.

Exclusion criteria

(i) Any neurological or psychiatric disorder other than epilepsy, thyroid disease, and others chronic diseases;
(ii) Long term medication that could affect thyroid function;
(iii) Thyroid or endocrine dysfunction before the start of treatment

Informed consent was taken from parents before participation.

Anthropometric measurements of age, gender, and weight were recorded. Serum TSH level and serum fT4 level were collected. Hypothyroidism was determined based on the decreased level of fT4 and an increased level of TSH and assessed according to the normal level of the thyroid function test based on the age of the subjects. Multiple AEDs was defined as more than one oral AEDs. In this study, the AEDs were Valproic acid, Carbamazepine, Phenytoin and Phenobarbital.

Calculations were done with the statistical package SPSS for windows, version 12.0 (SPSS Inc., Chicago, IL, USA) through which, descriptive statistics were calculated. Descriptive statistics i.e. mean, standard deviation (SD), median, range and frequency were calculated. The statistical difference of the variable was analyzed by Chi-square and Mann Whitney test. Values of $p<0.05$ (two-tailed) were considered statistically significant.

RESULTS

A total of 41 children with epilepsy on AEDs were screened for eligibility, with 23 (56.1%) subjects were male. Median age of the subjects was 37 (5-168) months old with the median weight of 12 (4.7-55.5) kg. There were 5 (12.2%) children who received AEDs for less than 6 months and 36 (87.8%) children receiving AEDs for more than 6 months. The clinical characteristics of the studied subjects are shown in Table 1.

Median fT4 and TSH level of the children receiving AEDs for less than 6 months was 1.32 ng/dL and 2.48 mIU/L, while those receiving AEDs for more than 6 months had median fT4 and TSH level of 1.30 ng/dL and 3.21 mIU/L. Children on AEDs for more than 6 months showed high incidence of hypothyroidism (13/36) compared to those receiving AEDs for less than 6 months (0/5), but there was no significant difference between groups ($p=0.160$).

There were 61% children receiving valproic acid and 4.9% receiving phenytoin alone. Combination valproic acid and phenytoin; valproic acid and phenobarbital; valproic acid and phenobarbital and phenytoin; valproic acid and carbamazepine were observed in 22%; 4.9%;4.9% and 2.4% patients respectively.

Mean fT4 level of all the subjects was 1.32±0.25 ng/dL, while the mean TSH level was 4.5±4.03 mIU/L. The normal range for children 2-7 years old for FT4 was 1.0-2.1 while TSH 0.7-5.7. The normal range for 8-20 years old for FT4 was 0.8-1.9 while TSH was 0.7-5.7.[12] The comparisons of the mean levels of the thyroid function test between single and multiple AEDs are shown in Table 2. There were no significant differences in fT4 and TSH levels between groups ($p=0.095$, $p=0.805$).

Thirteen (31.7%) epileptic children were diagnosed with hypothyroidism. Hypothyroidism was frequently seen in patients on multiple AEDs compared to single AED (Table 3). There was no significant difference in thyroid dysfunction between single and multiple AEDs ($p=0.734$). From 39 children receiving valproic acid, there were 12 (30.8%) children diagnosed with hypothyroidism. Among 12 children receiving valproic acid, 7 treated with valproic acid alone and 3 valproic acid and phenytoin, 1 valproic acid, phenytoin and phenobarbital, while 1 valproic acid, phenytoin and carbamazepine.

Table 1. Demographic and clinical features of the studied patients.

Variable	N = 41
Gender (%)	
Male	23 (56.1%)
Female	18 (43.9%)
Age, month old	37 (5-168)
Weight, kg	12 (4.7-55.5)
Duration of therapy, months	17 (5-102)
AED	
Single therapy	27 (65.9%)
Multiple therapy	14 (34.1%)
Antiepileptic drugs utilized	
CBZ	1 (2.4%)
VPA	39 (95.1%)
Phenytoin	14 (34.1%)
Phenobarbital	4 (9.7%)
fT4 level, ng/dl	1.32 ± 0.25
TSH level, mIU/L	4.5 ± 4.03

* Data are expressed as n (%) or median (minimum-maximum) or mean ± SD.

Table 2. Comparison of thyroid function test between single and multiple AEDs.

Variable	Single AEDs	Multiple AEDs	*P* Value
fT4 (ng/dl), mean ± SD	1.36 ± 0.26	1.22± 0.22	0.095
TSH (mIU/L), mean ± SD	4.58 ± 4.23	4.37± 3.75	0.805

Table 3. Comparison of thyroid dysfunction between single and multiple AEDs.

AEDs	Hypothyroid		*P* Value
	Yes	No	
Single therapy	8 (29.6%)	19 (70.4%)	0.734
Multiple therapy	5 (35.7%)	9 (64.3%)	

DISCUSSION

In our study, hypothyroid was reported in 13 (31.7%) children receiving AEDs. The disturbances in thyroid hormone homeostasis associated with AEDs were reported for the first time in 1961.[13] Several studies found that epileptic patients receiving AEDs might precipitate hypothyroidism.[9,14,15] Another studies reported abnormal thyroid hormonal levels with enzyme-inducing AEDs (CBZ, phenytoin, PB) and normal thyroid hormonal levels with non-enzyme-inducing AEDs (VPA).[1,2,13]

Valproic acid and carbamazepine therapy are known to affect the thyroid hormone levels by different mechanism. Carbamazepine induces the P-450 enzyme system and its consequent are the increase in the metabolism of thyroid hormones, meanwhile in VPA, inhibition of somatostatin, a potential inhibitor of TSH secretion, via an γ-aminobutyric acidergic effect has been proposed as a basic mechanism.[5,16]

Our study showed that TSH levels in children receiving AEDs (CBZ, VPA, phenytoin, PB) were increased. This result is in accordance with several studies who found that CBZ and phenytoin increased TSH level.[6,14,15] This result is in partial agreement with a previous study who found that CBZ increased TSH level, but VPA had variable effects on TSH level.[17] On the other hand, a previous study reported thyroid dysfunction in men taking AEDs (CBZ and VPA) a decrease in T4 level, but there is no alteration in TSH and T3 levels.[9] Yılmaz et al.[18] reported hypothyroid in 13.9% with CBZ. Another study by Isojarviet al.[9] reported reduced levels

of T4 in 53.3% and fT4 in 28.9% with CBZ. Eirís-Puñalet al.[19] reported increased levels of TSH in 8.2% (versus 3.6% for controls). Valproic acid was used in 39 patients (95.1%) of this study and there were 30.8% with hypothyroidism. This result was in agreement with Mikati et al.[20] that showed from 43 epileptic patients with VPA, 25.2% of them had high TSH serum level.

We found that the number of epileptic children on AEDs who had hypothyroidism increased in multiple AEDs (5 patients out of 14) compared to those receiving single AED (8 patients out of 27). A study showed reduced levels of fT4 in 50-100% of patients on multiple AEDs with CBZ and VPA.[9] Another study showed an increase in the thyroid hormones (including TSH) concentration in epileptic patients receiving AED and these changes were significantly more common in patients undergoing anticonvulsant multiple therapy.[8]

In this study, children on long-term therapy showed high incidence of hypothyroid (13/36), while those receiving short-term therapy showed no evidence of hypothyroid. A study which assessed the thyroid status of patients receiving long-term anticonvulsant therapy found that the mean serum TSH level was slightly increased, thus resulting in the elevation of the clinical score of subclinical hypothyroidism.[21]

Despite the strength of this study, it has some limitations: 1) the recruitment of the study group from a tertiary care center with more severe cases and this explains a high percentage of thyroid hormonal abnormalities. However, it should be kept in mind that hypothyroid is a relatively common condition with the incidence between 3-7% in the general population. Hence probably, such frequency rates for hypothyroid might be increased among the patients with epilepsy, which is also common, and 2) because of its cross-sectional study, it was not possible to know temporal relationship between thyroid dysfunction and AEDs therapy. However, such limitations could only be overcome through a longitudinal and multi-center study design.

CONCLUSION

Hypothyroidism is more frequent, found in more than quarter epileptic children. It might be worthy to measure serum fT4, TSH regularly, especially those on multiple AEDs, regardless of the type of AEDs to avoid development of overt hypothyroidism. This data indicates the importance of monitoring thyroid function in patients with epilepsy and on treatment with AEDs. This data also may have implications suggesting prevention strategies.

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