RESEARCH ARTICLE

Thyroid Function in Epileptic Children who Receive Carbamazepine, Primidone, Phenobarbital and Valproic Acid

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Abstract

Objective

In this study, we investigated the changes of the serum levels of thyroid hormones including Thyroxine (T4), Triiodothyronine (T3), T3 resin uptake and Thyroid stimulating hormone (TSH) in epileptic children during treatment with anti-epileptic drugs (AEDs) including carbamazepine (CBZ), primidone (PRM), phenobarbital and valproic acid (VPA).

Materials and Methods

This study consisted of four case-series comparisons, was conducted on 115 epileptic children (37 girls and 78 boys with an age range between 2 months and 15 years, mean: 62.06 ± 44.97 months). These children were divided into 4 groups who took either phenobarbital (n=29), PRM (n=28), CBZ (n=29), or VPA (n=29) for 3 months. Thyroid hormone levels (T3, T3 resin uptake, T4 and TSH) were measured at the beginning and three months after starting the study.

Results

At first, all patients were euthyroid and there were no clinical or laboratory findings suggestive of hypothyroidism. Regarding thyroid hormones before and after the administration of phenobarbital, carbamazepine, valproic acid and primidone, there were no significant changes in serum T3, T4, T3 resin uptake and TSH levels.

Conclusions

Our findings showed that short term therapy with phenobarbital, carbamazepine, valproic acid and primidone had no effect on thyroid function tests.

Key words: Anti-epileptic drugs; Thyroid hormones; Epileptic children.

Introduction

Epilepsy describes a state in which a person has revolving seizures due to a chronic-underlying process. The prevalence of epilepsy has been estimated at 5–10 patient 1000 (1). Older antiepileptic drugs (AEDs) such as phenytoin, valproic acid, carbamazepine, phenobarbital and ethosuximide are generally used as the first-line therapy for most seizure disorders (2). Effects on the thyroid hormone balance are of early importance in the side effects of AEDs on the endocrine system (3).

The prime study around the effects of AEDs on thyroid gland was made in 1961 by Oppenheimer et al who met a downfall in iodine bound to serum proteins and a disorder in T4 secretion from thyroxin binding globulin (TBG) in adults taking phenytoin (4). AEDs with an enzyme-inducing activity and distinct protein binding activity, such as diphenylhydantoin, carbamazepine (5), and oxcarbazepine,

typically induce diminished levels of thyroxin and free thyroxin, but have transitive effects on levels of TSH, T3, free T3 and TBG (6-9). Among studies seeking the consequences of AEDs on thyroid hormones, the best and most diverse results are obtained with valproate which does not alter the thyroid hormone levels; however, later studies showed that valproate could cause subclinical hypothyroidism (10-14).

Liewendahl et al (15), first reported a reduction in free thyroxin (FT4)and T4 concentrations, with TSH levels, remained unchanged with Carbamazepine (CBZ) treatment. From this study, multiple reports with the goal to assess serum thyroid hormone balance in children receiving long-term therapy with Carbamazepine were suggested (16-18). Isojarvi et al (19) and Eiris-Punal et al (20) recommended that CBZ may induce subclinical hypothyroidism. A distinct downfall in thyroid hormone serum levels is present in all patients who receive Phenytoin (PHT) (7, 20).

There are few reports regarding the relationship between barbiturates and thyroid hormones levels (21). Cavlieri et al (22) declared that in hyperthyroid patients with Graves disease on phenobarbital (PB) treatment, , the fact that TSH does not increase shows that the average effect of therapeutic levels of PB on thyroid hormone metabolism is fairly gentle (21).

Lots of studies have reported altered thyroid function (especially low FT4) in patients with epilepsy during treatment with Valproic Acid (VPA), but the outcomes were controversial: normal or increased serum levels of thyroid hormones and TSH have been announced (23).

In this study, we investigated the changes of serum levels of Free T4 , T3, T3 resin uptake (T3RU) and TSH in epileptic children during treatment with carbamazepine, Primidone, phenobarbital and valproate, before and 3 months after prescription.

The aim of this study was to investigate the effects of four AEDs on thyroid function tests.

Materials and Methods

This analytical cross sectional study was performed between Sep 2008 and Sep 2009 in pediatric neurology outpatient clinic of Baqyiatallah Hospital. A total of 115 children with epilepsy were consecutively divided into four groups who were taking either phenobarbital, PRM, CBZ, or VPA because of generalized or partial epilepsy. They included 37 girls and 78 boys with an age range of 2 months to 15 years with a mean age of 62.06 ± 44.97 months. The exclusion criteria were as follows: abnormal neurologic examination, malformed cerebral computed tomography (CT) and/or magnetic resonance imaging (MRI), liver or kidney disease, thyroid disease or endocrinopathies, using contraindicated remedies and genetic or chromosomal abnormalities. The patients with uncontrolled seizures, those who received a multi-drug treatment regimen and /or those with chronic diseases known to disturb thyroid function were excluded as well. Twenty-nine children were treated with VPA, 29 with CBZ, 29 with Phenobarbital and 28 with PRM. The type of epilepsy was classified as stated by the proposals of the International League Against Epilepsy (25). The AEDs were chosen by a pediatric neurologist depending on the age of the patients and the type of epilepsy; CBZ was preferred for the therapy of patients with partial seizures with or without generalization, VPA was preferred for patients with primary generalized seizures (including absence and myoclonic seizures), Phenobarbital and PRM were preferred for children with generalized or partial seizures under age 3 due to better serum levels and lower side effects. Prescribed doses of CBZ and VPA were within therapeutic limits: 20-30 mg/kg/day(200-600 mg/day). Prescribed doses of Phenobarbital and PRM were within the therapeutic range: 3-5 mg/kg/day and 20 mg/kg/day, respectively. No other medications known to disturb thyroid function were prescribed.

Serum thyroxine (T4), triiodothyronine (T3), T3 resin uptake and thyroid-stimulating hormone concentrations were measured in all patients before and 3 months after the treatment commenced with antiepileptic drugs. The results of computations were inspected by an endocrinologist to evaluate thyroid function status.

Data with a normal distribution were reported as mean ± SD, whereas data with a non-normal distribution were summarized as median and range. For statistical analysis of variables indicating a normal distribution, we used analysis of variance, with the Student t test for subsequent pair wise comparisons. For statistical analysis of variables indicating a non-normal distribution, we used the Mann-Whitney U test and Pearson and Spearman

rank correlations as well. Data was analyzed with SPSS software edition 14. Estimated thyroid dysfunction was based on chi-Score test. P< 0.05 and CI: 95 % were considered significant. This study was approved by the Ethics Committee of Baqyiatallah University of Medical Sciences. A written informed consent was obtained from all parents prior to initiation of the study.

Limitations of study: Few patients were excluded from the study due to their need for multiple AEDs. Five patients were excluded from the study due to thyroid dysfunction before starting the AEDs.

Results

At the beginning of the study, all 115 patients were clinically and paraclinically euthyroid. Twenty nine patients, 55.2% male and 44.1 %females, (mean age: 86.75 ± 42.07 months) received VPA. There was no significant difference in serum T3, T4, T3RU and TSH before and after prescription (p>0.05) but T3, T4, T3RU levels mildly decreased 3 months after starting VPA. Age of these patients was significantly higher than PRM and PB groups (p<0.05).

There were 29 patients in the carbamazepine group (75.9% male and 24.1% female, mean age: 78.27 ± 45.38 months). Patients receiving carbamazepine showed no significant difference in serum T3, T4, T3RU and TSH levels before and after prescription (P>0.05), but their ages were remarkably higher than PRM and PB groups (p<0.05). This was predictable because PB & PRM are administered more for children below 3 years of age but CBZ & VPA are mostly administered for children above the age of 3 years.

Twenty-nine cases received Phenobarbital (75.9% male and 24.1% female, mean age: 38 ± 28.75 months). Patients receiving Phenobarbital showed no significant variation in serum T3, T4, T3RU and TSH level before and 3 months after prescription (P>0.05). Their ages were remarkably lower than CBZ and VPA groups.

Twenty-eight cases (64.3% male and 35.7% female, mean age 35.37 ± 31.85 months) received Primidone. They had a notably lower mean age than CBZ and VPA groups (p<0.05), but there were no significant differences in serum T3, T4, T3Ru and TSH levels before and 3 months after prescription (p>0.05).

Number and age of the patients receiving PB, PRM, CBZ, and VPA are presented in Table 1.

Serum T3, T4, T3RU and TSH values before and after the medication are shown in Table 2 and 3, respectively.

Discussion

In this study, we evaluated the impressions of single-drug therapy with 4 widely used conventional antiepileptic drugs (carbamazepine, pirimidon, phenobarbital, and valproate) on the thyroid function of epileptic children.

The effects of AEDs on thyroid functions are recognized for a long time; however, a general finding does not exist yet. In humans, only free forms of thyroid hormones are functional, FT4, FT3, T3 RU and TSH levels are used by most of the investigators (9, 26, 28). Among investigations on the effects of AEDs on thyroid hormones, the most incoherent results are obtained with Valproate. It has been suggested in some researches that valproate does not alter thyroid hormone levels because it is not an inducing drug (19,27).

Phenobarbital is one of the drugs inducing the hepatic microsomal enzyme system. Phenobarbital effects on thyroid functions are similar to phenytoin and carbamazepine. There is no agreement among the researchers on how phenobarbital affects the thyroid (4,7,12), Haidukewitych and Rodin (27) observed a notably low serum T4 and FT4 index in 58 cases receiving Phenobarbital but reported that patients maintained their euthyroid state. Rousso et al (29) assessed serum T4, FT4 index (T3 uptake × total T4) and TSH levels in 110 children on long-term Phenobarbital, carbamazepine and phenytoin therapy and noted low serum T4 levels and FT4 index but no change in TSH concentrations in Phenobarbital receiving patients. They also reported significantly high serum TSH levels but significantly low serum T4 and FT4 in children receiving carbamazepine. Yüksel et a (30) reported a significant reduction in serum FT4 and FT3 levels in ten children receiving Phenobarbital compared to the control group; they also reported a significant decline in serum FT4 and FT3 levels in 11 children receiving carbamazepine compared to the control group. Deda et al (26) conducted a study on 20 pediatric cases receiving Phenobarbital and 15 children on Phenytoin but found no significant difference in serum FT4, FT3 and TSH levels when compared to the control group.

Isojarvi et al (19) evaluated cases who were receiving carbamazepine and phenytoin, and reported a significant reduction in T4 and FT4 but no alteration in T3 and TSH levels. They also described 24 carbamazepine receiving cases with a significant reduction of T4 and FT4 but unchanged T3 and TSH levels in 1992; they reported that there was no significant difference between valproate users and the control groups (19). Ericsson et al. (31) reported normal TSH but elevated serum T3 and T4 levels. There are no contradictions regarding thyroid hormones in other studies (27,30).

Strandjord et al (32) reported that in 42 cases, serum T3, T4 and FT4 levels significantly diminished after receiving carbamazepine for 8-24 months compared to the control group. They also pursued 12 cases for 1-5 months and found that their serum T3 and TSH concentrations did not change, but their serum T4 concentrations notably diminished in comparison with the pre-treatment levels. Tiihonen et al (33), as well as Rootwelt et al (34), found that in the first 4-20 days of treatment, TSH levels increased and then decreased quickly to normal levels.

Castro-Gago et al (2) investigated 23 cases with a mean age of 7.5 years who received carbamazepine for a mean duration of 17.82 months and found no significant difference in serum FT3 and TSH levels but significant low serum FT4 levels compared to the control group. They also found no difference in thyroid hormone levels in patients receiving valproate as compared to the control group.

In our study on 115 cases with a mean age of 62.06±44.97 months who received AED for 3 months, we noted no significant changes in thyroid hormones but mild alterations in some variants.

In conclusion, short term administration of these AEDs by children does not appear to increase the risk of thyroid dysfunction. We suggest investigators to re-conduct this study with more patients and a longer follow-up period.

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Table 1: Patients mean age in different groups

Medication	Phenobarbital	Primidone	Valproate	Carbamazepine
Number	29	28	29	29
Mean age (months)	38 ± 28.55	35.37 ± 31.85	86.75± 42.07	87.27±45.28

Table 2: Thyroid hormones levels before AED prescription.
TSH (micIU/ml), T3 (ng/ml), T4 (ng/ml), T3RU (%)

	Valproate	Carbamazepine	Primidone	Phenobarbital
TSH	2.71±1.42	2.78 ± 0.29	2.26 ± 1.09	2.48 ± 1.15
T3	1.47±0.30	1.79±0.21	1.64± 0.28	1. 53± 0.16
T4	8.14±1.91	9.02 ± 2.54	9.15± 2.17	8.57 ± 1.71
T3RU	30.01±1.83	30.01± 1.13	29.22±1.34	31.8±1.26

Table 3. Thyroid hormones levels after AED prescription.
TSH (micIU/ml), T3 (ng/ml), T4 (ng/ml), T3RU (%)

	Valproate	Carbamazepine	Primidone	Phenobarbital
TSH	2.97±1.63	2.97 ± 1.23	2.18 ± 1.3	2.72 ± 1.68
T3	1.23±0.42	1.47±0.38	1.71± 0.27	1. 4± 0.54
T4	7.88±1.81	8.24 ± 2.7	8.67± 2.06	8.3 ± 2.65
T3RU	28.95±1.35	30.28± 2.04	30.15±2.49	31.8±1.26

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