

The effects of carbamazepine on thyroid functions in childhood epilepsy

Çocukluk çağı epilepsisinde karbamazepin'in tiroid fonksiyonları üzerine etkisi

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ABSTRACT

Objective: To investigate the effects of carbamazepine therapy on thyroid function tests in children

Methods: The carbamazepine group consisted of 58 children under observation for epilepsy, and the control group of 54 healthy children. Age of onset, length of drug use, drug dosage and laboratory parameters including free triiodothyronine (FT3), free thyroxine (FT4) and thyrotropin (TSH) were recorded. These data were then compared against those from the control group.

Results: In the carbamazepine group, FT3 was 3.86 ± 0.43 pg/mL, FT4 was 1.15 ± 0.18 mg/dL and TSH: 2.58 ± 1.33 ml U/L. In the control group, FT3 was 4.13 ± 0.59 pg/mL, FT4 1.34 ± 0.13 mg/dL and TSH was 2.06 ± 0.89 ml U/L. No statistically significant difference between rates of subclinical hypothyroidism was determined between the two groups ($p=0.196$).

Conclusion: Although, carbamazepine reduces thyroid hormone concentrations, rarely causes hypothyroidism.

Key words: Child, carbamazepine, thyroid function tests

ÖZET

Amaç: Çocuklarda karbamazepin tedavisinin tiroid fonksiyon testleri üzerine etkisini araştırmak

Yöntem: Karbamazepin grubu epilepsi tanısıyla takip edilen elli sekiz çocuktan, kontrol grubu elli dört sağlıklı çocuktan oluşturuldu. Başlangıç yaşı, ilaç kullanım süresi, ilaç dozajı, ve serbest triiyodotironin (FT3), serbest tiroksin (FT4), tirotropin (TSH) parametrelerini içeren laboratuvar parametreleri kaydedildi. Bu veriler kontrol grubuyla karşılaştırıldı.

Bulgular: Karbamazepin grubunda sırasıyla, FT3 $3,86 \pm 0,43$ pg/mL, FT4 $1,15 \pm 0,18$ mg/dL TSH $2,58 \pm 1,33$ ml U/L olarak bulundu. Kontrol grubunda ise FT3 $4,13 \pm 0,59$ pg/mL, FT4 $1,34 \pm 0,13$ mg/dL ve TSH $2,06 \pm 0,89$ ml U/L olarak ölçüldü. İki grup arasında subklinik hipotiroidizm oranı istatistiksel olarak anlamlı değildi ($p=0,196$).

Sonuç: Karbamazepin tiroid hormon konsantrasyonlarını düşürmesine rağmen nadiren hipotiroidizme neden olur.

Anahtar kelimeler: Çocuk, karbamazepin, tiroid fonksiyon testleri

INTRODUCTION

Carbamazepine (CBZ) is one of the classic antiepileptic drugs (AEDs) frequently used for first line monotherapy for complex partial seizures in children [1]. The most important limiting factor in the use of AEDs is their attendant side-effects [2]. Although AEDs are well tolerated, many endocrine side-effects have been reported in the literature [3-5]. The effect of CBZ on serum thyroid hormone concentrations is controversial. CBZ therapy can reduce serum thyroid hormone levels, but serum

thyrotropin-releasing hormone concentrations generally remain normal, except in a small percentage of patients who exhibit increased thyrotropin (TSH) levels [6,7]. CBZ may affect endocrine metabolism by inhibiting or stimulating cytochrome P450 isoenzymes, thereby increasing the peripheral metabolism of thyroid hormones [2,8].

In subclinical hypothyroidism, regarded as the early stage of thyroid dysfunction, serum free thyroxine (FT4) levels are normal and serum TSH levels high [9]. Subclinical hypothyroidism is gener-

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ally asymptomatic, but symptoms are seen in mild thyroid function deficiency in some patients [9,10].

Our scan of the literature revealed only limited data regarding subclinical hypothyroidism in CBZ therapy in childhood epilepsy. This study was intended to investigate subclinical hypothyroidism in children using CBZ.

METHODS

This case-control study was performed at the Ataturk University Faculty of Medicine Pediatric Neurology Division Department of Pediatrics, Turkey. Permission was obtained from the parents of all the children. The study was approved by the local ethical committee.

The study group consisted of 58 ambulatory children under observation for epilepsy and 54 healthy children. All children in the study group were diagnosed with different types of idiopathic epilepsy. Diagnosis of epilepsy was based on electroencephalography and clinical features. None of the patients received any medication other than an antiepileptic drug. CBZ was prescribed at the normal dosages in two daily doses. Children were deemed eligible for inclusion if they were aged 3 to 15 years, had received CBZ monotherapy for 12 or more months, and had been seizure free for 6 months or more.

The patient and healthy groups shared the same parameters. Sex- and age-matched children were selected as controls. The children in the control group were admitted to the pediatric out-patient clinic for reasons other than systemic problems. Controls were similar to patients except for epilepsy and receipt of CBZ therapy. We reviewed the records of all patients and looked at the following details: age at onset, length of drug used, drug dosage and laboratory parameters including free triiodothyronine (FT3), FT4 and TSH.

In accordance with laboratory reference values, normal serum values were determined at 0.35 - 4.94 μ IU/L for TSH, 0.93 - 1.7 ng/dl for FT4 and 1.8 - 4.6 pg/mL for FT3. While TSH was higher than 4.94 μ IU/L in cases with subclinical hypothyroidism, FT4 values remained within normal limits.

Exclusion criteria were use of any medications known to affect hepatic, renal or thyroid functions, thyroid, liver or kidney disease, endocrine disor-

ders, abnormal neurological examination and cerebral computed tomography and/or magnetic resonance imaging scans.

Blood samples were obtained from patients after at least 12 months after start of CBZ therapy, between 8:00 and 10:00 am after 12-h fasting in order to avoid diurnal variations.

All blood samples were stored at - 80°C until analysis. All tests were performed according to the manufacturer's instructions. Serum FT3 (pg/mL), FT4 (μ g/dL) and TSH (μ IU/L) were determined in serum using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, D - 68298, Germany).

Statistical Analysis

Data were subjected to Pearson's chi-square and independent sample T tests using SPSS 18.0 (Armonk, NY, USA) software. Significance was set at $p < 0.05$. Results are expressed as mean \pm standard deviation.

RESULTS

Demographic data for children in the CBZ and control groups are shown in Table 1. In the CBZ group, mean duration of drug use was 28.82 ± 20.7 months and the mean dosage 15.85 ± 5.9 mg/kg.

Table 1. Demographic data for children in the carbamazepine and control groups

	Carbamazepine group	Control group	p
Male, n (%)	34 (58.6)	27 (50)	
Female, n (%)	24 (41.4)	27 (50)	>0.05
Mean age (Years)	9.72 ± 2.78	9.97 ± 2.4	>0.05

Note: Gender was compared between the groups using the Pearson chi square test, and mean age values using the independent sample t test.

Data for FT3, FT4 and TSH levels from the CBZ and control groups are given in Table 2. A statistically significant difference was determined in all three values ($p < 0.05$) (Figure 1).

Length of use of CBZ was significantly negatively correlated with FT3 and FT4 levels ($p < 0.05$, $r = -0.4$). No significant correlation was determined between length of drug use and THS ($p > 0.05$)

Subclinical hypothyroidism was determined in four children in the CBZ group and one in the control group. Rates of subclinical hypothyroidism were not statistically significantly different between the two groups ($p>0.05$).

Table 2. Comparison of the groups' thyroid function test levels

Groups	Carbamazepine group	Control group	p
FT3 (pg/mL)	3.86 ± 0.43	4.13 ± 0.59	0.007
FT4 (mg/dL)	1.15 ± 0.18	1.34 ± 0.13	<0.001
TSH (mIU/L)	2.58 ± 1.33	2.06 ± 0.89	0.018

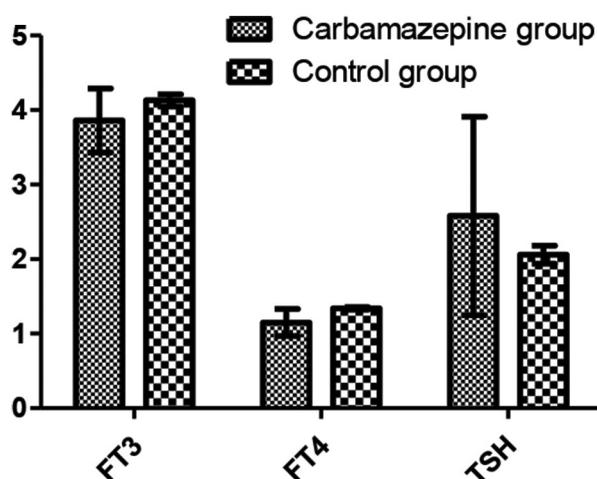


Figure 1. Comparison of thyroid function tests in carbamazepine group versus control group

FT3, free triiodothyroxine (pg/mL); FT4, Free throxine (mg/dL) and TSH, thyroid-stimulating hormone (mIU/L). Results are the means ± Standart error of the mean

DISCUSSION

Several studies have investigated the effects of AEDs on thyroid hormones, and various hypotheses have been suggested. Some authors have suggested that AEDs may have a direct inhibitor effect on hypothalamic and/or anterior pituitary hormones [11, 12]. In contrast, it has also been suggested AEDs directly disrupt thyroid metabolism [13]. In this study, subclinical hypothyroidism levels were not significantly higher in patients using CBZ compared to the control group. FT4 and FT3 levels were within normal levels in both the CBZ and control groups, although closer to the lower limit in subjects using

CBZ. TSH levels were close to the upper limit in the CBZ group.

Decreases in T4 and FT4 concentrations without TSH level changes during CBZ treatment have previously been reported [14]. CBZ interferes with thyroid function without affecting the hypothalamic-pituitary-thyroid axis [15]. Decreases in serum thyroid hormone levels can be detected in early the period after starting CBZ therapy [7]. Reversible hypothyroidism induced by CBZ has been reported in recent studies [16-18]. Early recognition and treatment of hypothyroidism is critical in childhood [19]. The general effect of CBZ is a decrease in the binding of thyroid hormones to their relative proteins via the competitive route [16]. Thyroid hormone catabolism increases through hepatic P450 enzyme system induction [20,21]. One prospective study of the effects of CBZ on thyroid function tests over a 5-year period reported a decrease in FT4 levels 2 months after start of treatment. The authors concluded that induction of cytochrome P450 liver enzymes resulted in a decrease in thyroxin levels [22]. CBZ reduces thyroid hormone concentrations but rarely causes hypothyroidism [23]. The findings of this study were consistent with those in the literature.

There are various limitations to this study; one is that it lacks sufficient impact due to the low patient numbers involved. Our patients were selected from the same geographical region, but could not be completely matched in terms of diet etc. Blood specimens were collected only once because of ethical concerns. No longitudinal studies have been performed concerning the effect of CBZ on thyroid functioning. The inclusion of healthy subjects as the control group was unable to exclude the uncertain effect regarding thyroid functioning in epileptic patients.

In conclusion, CBZ seems to be effective in reducing thyroid hormones, while having no effect on the hypothalamic-pituitary-thyroid axis, through a hepatic enzyme induction mechanism. Precautionary measures, such as intermittent thyroid function test monitoring, should be taken only in at-risk patients. However, further long-term studies involving larger patient numbers are needed. We also think that futher studies should be performed to examine the correlation between subclinical hypothyroidism and CBZ in the treatment of childhood epilepsy.

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