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Effects of antiepileptic drug on thyroid hormones in patients with epilepsy: A meta-analysis

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ABSTRACT

Purpose: As antiepileptic drugs (AEDs) are known to be associated with alterations in thyroid profiles, we aimed to carry out a meta-analysis to comprehensively assess the effects of AEDs on thyroid hormones in patients with epilepsy.
Methods: We searched the NCBI (PubMed), ISI Web of Science, EMBASE databases, and Cochrane Library to identify studies evaluating the association between AED use and thyroid hormone profiles in patients with epilepsy. Fixed or random effects meta-analysis was used to pool results across studies.
Results: In all, 35 studies were included in our analysis. Out of a total of 997 patients in these studies, epileptic patients receiving AEDs showed an overall significant decrease in thyroxin (T4) and free T4 (fT4) and higher levels of thyroid stimulating hormone (TSH) than the controls (T4: standardized mean difference [SMD] = −1.839, 95% confidence interval [CI], −2.063 to −1.614; fT4: SMD = −1.190, 95% CI, −1.687 to −0.692; TSH: SMD = 0.445, 95% CI, 0.031–0.858). Notably, the use of carbamazepine (CBZ) suggested a significant decrease in triiodothyronine (T3), T4, and fT4; phenytoin (PHT) use showed a decrease in T4 and fT4; and valproic acid (VPA) use was associated with decreased T4 and increased TSH.
Conclusion: Our study suggests that use of AEDs such as CBZ, PHT, and VPA, was associated with alteration of thyroid hormones among patients with epilepsy.

1. Introduction

Epilepsy is one of the most common neurological conditions, with about 65 million people affected worldwide [1]. It is a chronic medical problem that requires long-term or lifelong therapy with antiepileptic drugs (AEDs), particularly for those patients with refractory epilepsy [2]. However, prolonged use of AEDs is known to be associated with adverse effects such as metabolic and organ toxicity, endocrine disturbance, negative cognitive effects, and psychiatric problems [3–6], particularly with alterations in thyroid function in patients with epilepsy [7].

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 and adversely affect endocrine hemostasis in adults [2]. Oppenheimer and McPherson [8] first recognized the alteration of thyroid hormones levels in epileptic patients taking phenytoin (PHT). Thereafter, a number of studies were performed to evaluate the thyroid profiles in patients with epilepsy, but with inconsistent results. Several studies suggested there was no change in the thyroid hormone profile among patients taking AEDs [9–11], while others revealed AEDs might be significantly associated with alteration of thyroid hormones [7,12–15]. With this background, we aimed to conduct a meta-analysis to study the association between AED use and thyroid hormones in patients with epilepsy.

2. Methods

2.1. Study selection

A systematic computerized search was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [16]. Three authors (YXZ, CHS, and QLL) independently screened the NCBI (PubMed), ISI Web of Science, and EMBASE databases and the Cochrane Library for the period

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between January 1980 and April 2015. Only English language articles were considered. The search terms included "anticonvulsants," "epilepsy," "antiepileptic drugs," "oxcarbazepine (OXC)," "PHT," "carbamazepine (CBZ)," "phenobarbital (PB)," "lamotrigine (LTG)," "gabapentin (GBP)," "topiramate (TPM)," "valproic acid (VPA)," "levetiracetam (LEV)," "thyroid hormones," "triiodothyronine (T3)," "free triiodothyronine (fT3)," "thyroxine (T4)," "free thyroxine (fT4)," and "thyrotropin (TSH)." The above listed AEDs are the most commonly prescribed and widely used drugs to treat epilepsy. We retrieved all relevant articles and searched reference lists to identify as many studies as possible.

2.2. Eligibility criteria

Studies were included if they met the following criteria: (i) original data from epidemiologic reports with healthy controls; (ii) cross-sectional, case-control, or cohort studies that evaluated the association between AEDs and thyroid hormones in patients with epilepsy; (iii) the exposure was AEDs; (iv) measured thyroid hormones and expressed the data as means with standard deviations (SDs); (v) met at least six Newcastle-Ottawa Scale (NOS) criteria [17]-an eight-item tool with up to nine possible points, which was developed to assess the quality of observational studies to be included in systematic reviews and meta-analysis.

2.3. Data extraction

Two authors (ZYX and CHS) evaluated the studies and abstracted all relevant information independently using a unified data form. Divergences were discussed and resolved by a third author (QLL). The following data were collected from each study: author, year, country, study design, population, age, gender, AEDs, exposure duration and measurements of thyroid hormones (T3, fT3, T4, fT4, and TSH) in patients with epilepsy and healthy controls.

2.4. Data analysis

Considering the different assays in different studies, values of thyroid hormones were expressed as standardized mean difference (SMD). Statistical heterogeneity was examined using the I^2 statistic; $P < 0.10$ was considered significant. A value of 0% suggests no observed heterogeneity, whereas large values indicate increasing heterogeneity. Thus, $P < 0.10$ and I^2 value >50% indicate significant heterogeneity. When substantial heterogeneity was detected, we performed the summary estimate on the random effect model using the DerSimonian and Laird method. Otherwise, the fixed effect model using the Mantel and Haenszel method was used. To assess the influence of individual results on the pooled estimate, we conducted sensitivity analysis by excluding each study one by one, and recalculating the combined estimates for the remaining studies. According to the definition of children as per The United Nations Convention on the Rights of the Child, the population was stratified into child group (<18 years old) and adult group (>18 years old); subgroup analysis was thus performed by age.

We carried out Egger's test and Begg's test to examine publication bias, $P < 0.05$ was considered to represent significant publication bias. All data analysis was performed using STATA/SE12.0 (Stata, TX, College Station, USA).

3. Results

3.1. Study characteristics

As shown in Fig. 1, our search identified 35 studies about AEDs and thyroid hormones [9,10,15,18–49]. The study details are described in Table 1. Twelve studies [10,20,23,25,27,33,35,38,39,41,42,44] with a total of 997 participants described the association between various AEDs and thyroid hormones; of these, 11 were cross-sectional studies [10,20,23,27,33,35,38,39,41,42,44], and one was a case-control study [25]. Four of 12 studies [25,27,33,38] included only pediatric patients, 3 included only adults [20,23,42], and 5 had a mixed patient population. Moreover, 25 studies [9,10,15,18,19,21–24,26–34,36–40,43,45] focused on specific AEDs, including 17 studies on VPA, 19 on CBZ, and 6 on PHT.

3.2. Use of AEDs and thyroid hormones

Overall, compared to controls, patients with epilepsy receiving AEDs showed a significant decrease in T4 and fT4, but higher TSH levels (T4: standardized mean difference [SMD] = −1.839; 95% confidence interval [CI], −2.063 to −1.614; p_heterogeneity = 0.189, I^2 = 28.8%; fT4: SMD = −1.190; 1.190; 95% CI, −1.687 to −0.692; p_heterogeneity < 0.001, I^2 = 81.0%; and TSH: SMD = 0.445; 95% CI, 0.031–0.858; p_heterogeneity < 0.001, I^2 = 83%) (Tables 2–4, Figs. 2–4). The T3 and fT3 levels showed no significant differences between patients and controls. Furthermore, both the Begg's and Egger's tests showed no publication biases; Begg's test *P* values for T3, fT3, T4, fT4, and TSH were 0.592, 0.734, 0.466, 0.175, and 0.161, respectively, and Egger's test *P* values for and T3, fT3, T4, fT4, and TSH were 0.428, 0.577, 0.247, 0.081, and 0.131, respectively. The shape of the Begg's funnel plot was symmetrical (Fig. 5).

For the sensitivity analysis, we recalculated the combined results by excluding one study per iteration; the results obtained were similar without significant fluctuations. For T4, the study-specific SMD ranged from a low value of −1.927 (95% CI, −2.172 to −1.681) by omission of the study by Rozza et al. [42] to a high value of −1.786 (95% CI, −2.051 to −1.521) by omission of the study by Tiihonen et al. [35]. For fT4, the study-specific SMD ranged from a low value of −1.344 (95% CI, −1.670 to −1.019) by omission of the study by Hamed et al. [20] to a high value of −1.111 (95% CI, −1.627 to −0.594) by omission of the study by Verrotti et al. [33]. For TSH, the study-specific SMD ranged from a low value of 0.338 (95% CI, −0.060 to 0.736) by omission of the study by Rozza et al. [42] to a high value of 0.579 (95% CI, 0.297–0.860) by omission of the study by Rao et al. [41].

Subgroup analysis by age (<18 vs. >18 years) showed significant SMDs were found in the child group (T4: SMD = −1.934; 1.934; 95% CI, −2.379 to −1.490; fT4: SMD = −1.450; 95% CI, −1.899 to −1.002; TSH: SMD = 0.635; 95% CI, 0.088–1.182).

3.3. Some specific AEDs and thyroid hormones

When evaluating the association between CBZ and thyroid hormones, a significant decrease in T3, T4, and fT4 was observed among patients on CBZ monotherapy (T3: SMD = −0.411; 95% CI, −0.686 to −0.136; T4: SMD = −1.505; 95% CI, −1.852 to −1.158; fT4: SMD = −1.198; 95% CI, −1.472 to −0.925). However, the SMDs for fT3 and TSH were insignificant. Subgroup analysis by age showed significant SMDs for T3, T4, and fT4 in the adult group and a significant decrease in T4 and fT4 in the child group.

Likewise, for patients receiving PHT monotherapy, T4 and fT4 were significantly decreased among epileptic patients (T4: SMD = −1.344; 95% CI, −1.838 to −0.850; fT4: SMD = −0.976; 95% CI, −1.295 to −0.658).

The present study showed a significant effect of VPA on serum T4 and TSH. T4 was significantly decreased whereas TSH levels were increased. (T4: SMD = −0.384; 95% CI, −0.589 to −0.179; TSH: SMD = 0.942; 95% CI, 0.664–1.220).