Risk Factors for Clinically Overt Hypothyroidism in Unselected Population of Adult Epilepsy Patients

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Cite this article as: Çarkı Bal NÇ, Apaydın Doğan E, Şenol Y. Risk Factors for Clinically Overt Hypothyroidism in Unselected Population of Adult Epilepsy Patients. *Arch Epilepsy.* 2023;29(2):46-49.

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Received: 08.09.2022 **Accepted:** 27.01.2023 **Publication Date:** 09.06.2023

DOI: 10.4274/ArchEpilepsy.2023.221021

Abstract

Objective: This study aimed to investigate the risk factors for hypothyroidism in patients with adult epilepsy patients.

Methods: Hospital charts of 530 patients were reviewed retrospectively. Patients with a definite diagnosis of hypothyroidism with persistent adherence to antiseizure medications (ASM) were included. An age and gender-matched group of 110 patients was selected as the control group.

Results: The rate of hypothyroidism was significantly higher in patients with epilepsy (p=0.01). The patients with epilepsy were separated into two groups-the patients with and without hypothyroidism. The distribution of other neurologic disorders was similar in epilepsy patients with and without hypothyroidism (p=0.46). The comparison of the two groups showed that, independent of the ASM type, receiving any polytherapy regimen was a significant risk factor for hypothyroidism (p=0.02) and epilepsy patients with hypothyroidism had a longer duration of epilepsy (p=0.03). Logistic regression analysis revealed that the only independent risk factor for hypothyroidism was being on a polytherapy regimen (p=0.02).

Conclusion: In this study, we found two major results: i) compared with an age and gender-matched control group, epilepsy is a major risk factor for hypothyroidism, ii) independent of the ASM type, receiving a polytherapy regimen is a predictive risk factor for hypothyroidism.

Keywords: Hypothyroidism, epilepsy, polytherapy

INTRODUCTION

Epilepsy has as an overall incidence of 0.2-4.1% amongst the adult population and causes a significant burden in all age groups.[1] Critically, the negative impact of epilepsy is disproportionate to its prevalence. Persons with epilepsy (PWE) have a lower quality of life compared with other chronically ill individuals.[2,3] When combined with the comorbidities, epilepsy becomes a more complicated disease.

Comorbidity is defined as the simultaneous presence of two or more diseases in the same individual more frequent than the chance expectation derived from an age-matched control cohort of healthy subjects.[4] Comorbidity does not always imply a directional relationship, although diseases may share common genetic or environmental risk factors, recent studies suggest that thyroid dysfunction should be regarded as a comorbidity of epilepsy.[5]

Therefore, in this study, we characterized the relationship between thyroid dysfunction and antiseizure medicines (ASM) in an unselected adult patient population with epilepsy.

METHODS

Patients

Hospital charts of patients aged more than 18 years old who were admitted to the epilepsy outpatient clinic of Akdeniz University between November 2017 and December 2018 were reviewed retrospectively. Patients who were diagnosed with epilepsy and receiving ASMs were included. Patients with the evidence of persistent nonadherence to medications were excluded from the study. An age and sex-matched group of patients those have attended the neurology outpatient clinic for other illnesses other than epilepsy were selected as the control group. Data regarding the seizure type, etiology, and epilepsy syndromes were classified according to the recommendations of the International League Against Epilepsy. Only the patients those have were evaluated by an endocrinologist and diagnosed with hypothyroidism in whom L-thyroxine replacement therapy was initiated were included in the patient group. The study was started with the

permission of the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 17/02/2022 and numbered 7090450.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation and categorical variables as numbers and percentages. Significances of the differences between the groups were tested by the two-sided independent samples t-test for parametric data and by Mann-Whitney U test for non-parametric data. Pearson's chi-square test was used for categorical comparisons of nominal values. A binary logistic regression analysis was performed to identify the predictors of hypothyroidism in patients with epilepsy. A p value less than 0.05 was considered to be statistically significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Data of 530 consecutive patients with epilepsy and an age- and gender-matched group of patients consisting 110 individuals (those were selected as the control group) were reviewed retrospectively. ASMs used by the patients with epilepsy are listed in Table 1. The rate of hypothyroidism was significantly higher in patients with epilepsy (p=0.01) (Table 2). Patients with epilepsy were separated into two groups-patients with and without hypothyroidism. The distribution of other neurologic disorders was similar in epilepsy patients with and without hypothyroidism (p=0.46). A comparison of the two groups showed that the prevalence of polytherapy regimen was higher (p=0.02) and epilepsy duration was longer (p=0.03) in epilepsy patients with hypothyroidism (Table 3). Logistic regression analysis revealed that the only independent risk factor for hypothyroidism was being on a polytherapy regimen (p=0.02) (Table 4).

Table 1. The table shows list of antiseizure medications which were used by the epileptic patient group

Drug names	n (%)
Levetiracetam	261 (49.2%)
Valproate	134 (25.3%)
Lamotrigine	88 (16.6%)
Zonisamide	71 (13.4%)
Carbamazepine	90 (17.0%)
Clonazepam	21 (4.0%)
Lacosamide	55 (10.4%)
Oxcarbazepine	90 (17.0%)
Topiramate	29 (5.5%)
Clobazam	11 (2.1%)
Primidone	3 (0.6%)
Phenytoin	6 (1.1%)
Phenobarbital	3 (0.6%)

*151 (65.7%) of the patients were using 2 ASM drugs, 53 (23.0%) of the patients were using 3 ASM drugs, 23 (10.0%) of the patients were using 4 ASM drugs and 3 (1.3%) of the patients were using 5 ASM drugs.
ASM: Antiseizure medications

MAIN POINTS

- In this study, we characterized the relationship between thyroid dysfunction and antiseizure medicines (ASM) in an unselected adult patient population with epilepsy.
- According to our results, we suggest two main results; a) epilepsy is a risk factor for hypothyroidism, b) receiving any polytherapy regimen is a significant independent risk factor for hypothyroidism in patients with epilepsy.
- The routine evaluation for thyroid dysfunction should be considered part of routine medical care for patients receiving combination therapy and for those receiving any ASM for a long duration.

DISCUSSION

In this study, we found two major results, i) epilepsy is a risk factor for hypothyroidism; when compared with an age and gender-matched control group of patients without epilepsy, the percentage of hypothyroidism was significantly higher in patients with epilepsy, ii) independent of the ASM type, receiving any polytherapy regimen is a significant risk factor for hypothyroidism. In patients with hypothyroidism, the epilepsy duration was found to be longer. However, using binary logistic regression analysis, it was not found to be an independent risk factor for hypothyroidism.

In our study, 7.4% of epilepsy patients had a diagnosis of hypothyroidism and were receiving L-thyroxine treatment. This ratio was significantly higher than that of the control group (p=0.01).

Table 2. Frequency of hypothyroidism amongst patients with and without epilepsy

	Epilepsy patients (n=530)	Control group (n=110)	p value
Age (year±SD)	37.1±16.2	38.1±13.0	0.48
Female gender, n (%)	273 (51.5%)	61 (55.5%)	0.45
Hypothyroidism, n (%)	39 (7.4%)	1 (0.9%)	0.01

SD: Standard deviation

Table 3. Demographics regarding hypothyroidism amongst patients with epilepsy

	Hypothyroidism (+), (n=39)	Hypothyroidism (-), (n=491)	p value
Age (year±SD)	39.6±16.6	36.9±16.2	0.32
Duration of epilepsy (year±SD)	17.5±9.5	13.7±10.4	0.03
Female gender, n (%)	24 (61.5%)	249 (50.7%)	0.20
Other neurological disorders, n (%)	7 (17.9%)	113 (23.0%)	0.46
Polytherapy, n (%)	24 (61.5%)	206 (42.0%)	0.02

SD: Standard deviation

Table 4. Logistic regression analysis revealing the independent risk factor for hypothyroidism

	Odds ratio	Coefficient interval (95%)	p value
Age	1.01	0.99-1.04	0.20
Female gender	0.57	0.29-1.13	0.11
Polytherapy	2.36	1.17-4.76	0.02
Duration of epilepsy (years)	1.02	0.99-1.05	0.11

There is growing evidence regarding serious endocrinological comorbidities in epilepsy. Although the prevalence of thyroid dysfunction and evidence about the interrelation is conflictive, several investigations support the idea that hypothyroidism is more common in PWE than in the general population.[6] ASMs are the mainstay of treatment and postulation about the mechanisms differ, but ASMs affect the thyroid hormone levels.

Carbamazepine is one of the most investigated ASMs for its endocrinological adverse effects. Carbamazepine induces the P-450 enzyme system and increases the metabolism of thyroid hormones, which leads to low thyroid serum concentrations. Thyroid hormonal abnormalities were also reported with phenobarbital, phenytoin, valproate and oxcarbazepine, but not with lamotrigine, levetiracetam, topiramate, tiagabine and vigabatrin.[7]

Amongst several ASMs, significant correlations were reported between thyroid volume and thyroid hormonal abnormalities in adults, particularly those on valproate. The mechanism of valproate on thyroid homeostasis is unclear. One hypothesis suggests that an increase in TSH with valproate therapy results from g-aminobutyric acid-stimulating properties of valproate by inhibiting the release of somatostatin, which in turn inhibits TSH secretion. Another mechanism postulated for hypothyroidism is that valproate leads to zinc and selenium deficiency, which are important enzymes in thyroid hormone synthesis.

Oxcarbazepine, despite its structural resemblance to carbamazepine, does not induce enzyme activity. Even normalization of serum thyroid hormone levels induced by carbamazepine has been shown after replacement of carbamazepine with oxcarbazepine in adults.[8]

According to several studies, it appears that the effect of oxcarbazepine on thyroid function is short-term, transient, and less significant than the effects of carbamazepin. Phenytoin has also been investigated. Phenytoin induces the thyroid hormone metabolism and displaces thyroid hormones from serum-binding proteins, which in turn leads to low serum thyroid levels.

Phenobarbital was found to lower T3 and T4 levels only when it has been used for longer than six years. However, the changes on TSH concentrations were less marked than those in patients treated with valproate. A previous study has shown that the increased TSH concentrations returned to normal values after the withdrawal of phenobarbital. Thus, the effects of phenobarbital on thyroid function appear reversible.[9-11] However, transient TSH alterations leading to subclinical hypothyrodisim should also be regarded as a major health problem mainly in the adult patient population. In recent studies, it is emphasized that unstable TSH levels -even at the euthyroid level- are associated with a higher mortality rate.[12,13]

The second main finding of our study was that being on any polytherapy regimen was a major risk factor for hypothyroidism. The effects of polytherapy on thyroid functions have been investigated in five previous studies. In these studies being on polytherapy has also been proposed as a risk factor for hypothyroidism. The profound risk in patients receiving polytherapy might be explained by the fact that this particular group of patients are more likely to be exposed to a longer duration of ASM treatment and a higher seizure frequency. Higher seizure frequency may interfere with the hypothalamic axis and alter the TSH levels.[14-16]

Another finding of our study was that the duration of epilepsy was longer in epilepsy patients with hypothyroidism. However, according to the logistic regression analysis, this was not an independent risk factor for hypothyroidism. Further studies evaluating the relationship between the duration of treatment and hypothyroidism is warranted.

As a result, considering the current literature and our results, we might suggest that compared with an age and gender-matched population, hypothyroidism is more prevalent in epilepsy patients and should be regarded as a serious comorbidity. Being on a polytherapy regimen is an independent risk factor.

Study Limitations

Because of the retrospective design, there are several limitations of this study. First, baseline thyroid hormone levels were not availabl; therefore, we compared these parameters with an age and gender-matched control group to eliminate this bias.

The abscence of description of the comorbiditiesand other systemic and neurological disorders of the patients with epilepsy was another limitation. Our data regarding drugs other than ASMs were also lacking. Therefore, the potential negative endocrinological effects of these circumstances could not be clarified. Hence, the possible interaction of these parameters with the results of our study could not be eliminated.

Another limitation was the lack of body mass index of both the patient and the control group as obesity is closely related to altered serum thyroid levels; anthropometric values would add value to the findings of our study. To come over these limitations, we used multiple logistic regression analyses to correct these variables. Prospectively designed large-scaled studies are warranted.

CONCLUSION

In conclusion, epilepsy is a risk factor for hypothyroidism and irrespective from the ASM type, receiving a polytherapy regimen is an independent risk factor. Further studies are needed in this field, before a definite recommendation can be given, as hypothyroidism is a serious health problem that may result in increased cardiovascular morbidity and mortality.

Ethics

Ethics Committee Approval: The study was started with the permission of the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 17/02/2022 and numbered 7090450.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.A.D., Design: E.A.D., Data Collection or Processing: Y.Ş., Analysis or Interpretation: N.Ç.Ç.B., Y.Ş., Literature Search: N.Ç.Ç.B., E.A.D., Writing: N.Ç.Ç.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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