Research Article / Araştırma Makalesi
doi: 10.18678/dtfd.1068664

Duzce Med J, 2022;24(2):142-146
Düzce Tıp Fak Derg, 2022;24(2):142-146

The Relationship of Thyroid Hormone Levels and Motor Symptoms in Parkinson's Disease

Parkinson Hastalığında Motor Semptomların Tiroid Hormon Seviyeleri ile İlişkisi

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Received / Geliş Tarihi : 05.02.2022
Accepted / Kabul Tarihi : 12.06.2022
Available Online / Çevrimiçi Yayın Tarihi : 20.07.2022

ABSTRACT

Aim: This study aimed to investigate the relationship between thyroid hormone levels and the motor symptoms of Parkinson's patients.
Material and Methods: Neurology clinic logs of the patients diagnosed with Parkinson's disease and whose thyroid function tests were measured between 01.01.2018 and 01.04.2021 were selected. Those with primary thyroid hormone disorder were excluded. Motor symptom stages were determined according to the modified Hoehn and Yahr scale (mHYS) by records. According to the thyroid function test results, whether there was a difference in motor symptoms, duration of the disease, and effects of the drugs were examined.
Results: Of the 93 patients included in the study, 53 (57.0%) were male and 40 (43.0%) were female. The median age of the patients was 71 years. The motor symptoms of the patients were classified as stage 1 in 21 (22.6%), stage 1.5 in 18 (19.4%), stage 2 in 29 (31.2%), stage 2.5 in 13 (14.0%), stage 3 in 4 (4.3%), stage 4 in 6 (6.5%), and stage 5 in 2 (2.2%) patients. The median levels of TSH, fT3, and fT4 were 2.075 uIU/ml, 2.925 ng/dl, and 1.235 ng/dl, respectively. There was no significant correlation between the mHYS stages of the patients and TSH (r=-0.148, p=0.164), fT3 (r=-0.073, p=0.623), and fT4 levels (r=0.075, p=0.491).
Conclusion: There was no relationship between the severity of motor symptoms and hormone levels in patients with normal thyroid functions. Thyroid dysfunction may mimic many motor findings, but they do not affect the severity of motor findings in Parkinson's patients.
Keywords: Parkinson's disease; motor symptoms; thyroid functions.

ÖZ

Amaç: Bu çalışmanın amacı Parkinson hastalarının tiroid hormon seviyeleri ile motor semptomları arasındaki ilişkisinin araştırılmasıdır.
Gereç ve Yöntemler: 01.01.2018 ve 01.04.2021 tarihleri arasında Parkinson hastalığı tanısı almış olan ve tiroid fonksiyon testleri ölçülmüş olan hastaların nöroloji kliniği kayıtları seçildi. Primer tiroid hormon bozukluğu tanısı olanlar dışlandı. Kayıtlar incelenerek modifiye Hoehn ve Yahr ölçeğine (modified Hoehn and Yahr scale, mHYS) göre motor semptom evreleri belirlendi. Tiroid fonksiyon test sonuçlarına göre motor semptomlarda fark olup olmadığı, hastalık süresi ve ilaçların etkileri incelendi.
Bulgular: Çalışmaya dahil edilen 93 hastanın 53'ü (%57,0) erkek ve 40'ı (%43,0) kadın idi. Hastaların medyan yaşı 71 yıl idi. Hastaların motor semptomları 21 (%22,6) hastada evre 1, 18 (%19,4) hastada evre 1.5, 29 (%31,2) hastada evre 2, 13 (%14,0) hastada evre 2.5, 4 (%4,3) hastada evre 3, 6 (%6,5) hastada evre 4 ve 2 (%2,2) hastada evre 5 olarak sınıflandırıldı. Medyan TSH, fT3 ve fT4 düzeyleri sırasıyla 2,075 uIU/ml, 2,925 ng/dl ve 1,235 ng/dl idi. Hastaların mHYS evreleri ile TSH (r=-0,148; p=0,164), fT3 (r=-0,073; p=0,623) ve fT4 (r=0,075; p=0,491) düzeyleri arasında anlamlı bir korelasyon yoktu.
Sonuç: Tiroid fonksiyonları normal olan hastalarda motor semptomların şiddeti ve hormon seviyeleri arasında bir ilişki yoktur. Tiroid fonksiyon bozuklukları Parkinson hastalarındaki birçok motor bulguyu taklit edebilir, fakat motor bulgularının şiddetini etkilememektedir.
Anahtar kelimeler: Parkinson hastalığı; motor semptomlar; tiroid fonksiyonları.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative and progressive disease characterized clinically by bradykinesia, resting tremor, impaired postural reflexes, and rigidity (1). The essential criteria were determined by the Movement Disorders Association as bradykinesia with at least one of rigidity or resting tremor (2).

PD significantly impairs quality of life and prevents activities of daily living. The differential diagnosis of the disease involves some difficulties. These markers are easily accessible parameters and may be effective in differential diagnosis and in changing the severity of motor symptoms.

Thyroid hormones (TH) are formed by the binding of iodine to the amino acid tyrosine. The most synthesized hormone of the gland is thyroxine (T4), and the most active hormone is triiodothyronine (T3). For the continuity of metabolic events in the body, TH must be secreted continuously in a controlled manner (3). The efficacy of thyroxine is very doubtful and according to many researchers, it is seen as a precursor of T3. The main TH secreted by the thyroid gland is T4. Only 20% of the total plasma T3 is secreted by the thyroid gland, and the remaining 80% is formed as a result of deiodination of T4 in the periphery. Most of the T3 and T4 in plasma circulate bound to proteins. A smaller portion is free. They are the only free fractions that enter the cell and show bioactivity. Mutual adjustment with thyroid stimulating hormone (TSH) is also carried out by these free hormones (3).

Findings such as rigidity, bradykinesia, hypomemia, hypophonia, swallowing disorders, peripheral edema, respiratory problems, dementia symptoms, depression, sleep disorders, fatigue, weakness, constipation, orthostatic hypotension, sexual dysfunction seen in PD may also occur due to hypothyroidism. Tremor, anxiety disorders, panic disorder, excessive sweating, cramps, and paresthesia symptoms seen in PD are signs and symptoms that can also be seen in hyperthyroidism (4). Therefore, thyroid dysfunctions detected in the early period in PD patients will enable to distinguish similar signs and symptoms encountered in the clinic.

Although the relationship between PD and TH has been scientifically interesting and researched, studies have generally focused on the common features of diseases and the evaluation of impaired hormone levels, and the effect of TH levels on symptoms of PD has not been studied at a level to reach definitive conclusions (5).

In this study, we aimed to investigate whether TH levels are effective on motor symptoms in PD patients and to comment on whether the evaluation of thyroid function tests is necessary in the follow-up of PD.

MATERIAL AND METHODS

The study was carried out on the patient registration system data of Çanakkale Onsekiz Mart University Hospital. Ethics committee approval was obtained for the study from Çanakkale Onsekiz Mart University Ethics Committee for Clinical Studies with the decision number 08-02, dated November 03, 2021. The study population consisted of the patients included in the hospital registration system, and all existing records included.

Thyroid function test levels of those who were diagnosed with PD in the Neurology Clinic of Çanakkale Onsekiz Mart University Hospital between 01/01/2018 and 01/04/2021 were collected from the patient registry system. Those with a diagnosis of primary TH disorder were excluded. The oldest date was taken if thyroid function tests were measured more than once. Information on patients' motor symptom status, duration of illness, and medications were also collected from the hospital registry system.

Within the specified date range, 125 records matching the diagnostic features and thyroid function tests were examined. Thirty-two of the records (1 due to a past thyroid operation, 10 due to mismatch of diagnosis (3 secondary Parkinsonism (medication-induced), 1 vascular Parkinsonism, 6 Parkinson-plus syndromes), and 21 due to missing and inconsistent data were excluded from the study set. A total of 93 records were included in the study.

The modified Hoehn and Yahr scale (mHYS) is a widely used clinical rating scale for the coarse assessment of motor functions in PD. The scale provides a simple staging of the severity of bilateral motor involvement and the impairment of gait and balance. The scale was modified to include stages on the bilaterality of dysfunctions (6). Simple and easy to apply, it detects typical progressive motor deterioration patterns independent of patients' treatment. Progression in stages is associated with motor decline, deterioration in quality of life, and dopaminergic loss. It does not provide information on specific aspects of motor deficiency as well as non-motor aspects of PD (6). By examining the records of the patients, motor symptom stages were determined according to the mHYS.

Thyroid function tests of all patients were measured in the biochemistry laboratory of the hospital by electrochemiluminescence immunoassay (ECLIA) method on Roche Cobas 6000 (Roche Diagnostics, Mannheim, Germany) with the same brand kits. Laboratory normal standards are 0.27-4.20 uIU/ml for TSH, 2.00-4.40 ng/dl for free T3 (fT3), and 0.93-1.70 ng/dl for free T4 (fT4).

Statistical Analysis

The statistical analyses were performed with IBM SPSS Statistics for Windows, version 22. Assumptions of normality were controlled with the Kolmogorov-Smirnov test and non-parametric tests were used since none of the variables fit the normal distribution. Descriptive statistics were presented as the frequencies and percentages for categorical data, and with median, interquartile range, and minimum-maximum for numerical data. Mann-Whitney U and Spearman correlation tests were used for analyses. $p<0.05$ was accepted as the significance level.

RESULTS

Of the 93 patients included in the study, 53 (57.0%) were male and 40 (43.0%) were female. The median age of the patients was 71 (range, 39-89) years. Descriptive characteristics of the patients were given in Table 1. The median age of males was not significantly different from that of females (72 vs. 70, U=1559.0, p=0.052).

The median disease duration of the 93 patients included in the study was 4 (range, 1.5-22) years. The number of drugs used by patients was (minimum 1, maximum 4), one for 35 (37.6%) of them, two for 41 (44.1%) of them, three for 14 (15.1%) of them, and four drugs for 3 (3.2%) of them.

Fifty-seven (61.3%) of the patients were receiving levodopa treatment. There was no significant difference between the genders in terms of disease duration and the number of drugs (U=1048.5, p=0.496, and U=970.0, p=0.339, respectively). There was no significant correlation between the age of the patients, the duration of the disease, and the number of drugs they used (r=-0.056, p=0.588 and r=-0.057, p=0.587, respectively). There was a moderate positive correlation between the duration of the disease and the number of drugs used (r=0.316, p=0.002).
The motor symptoms were classified as stage 1 in 21 (22.6%), stage 1.5 in 18 (19.4%), stage 2 in 29 (31.2%), stage 2.5 in 13 (14.0%), stage 3 in 4 (4.3%), stage 4 in 6 (6.5%), and stage 5 in 2 (2.2%) patients according to the mHYS. There was no significant difference between the genders in terms of disease motor symptom stage (U=988.5, p=0.569). There was no significant correlation between the ages of the patients and the stage of motor symptoms (r=0.042, p=0.688). The motor symptom stage has a moderate positive correlation with the disease duration (r=0.430, p<0.001) and a weak positive correlation with the number of drugs used (r=0.242, p=0.019). Motor symptom stages were significantly higher in patients using Levopoda (U=630.0, p=0.001).
The descriptive statistics of TSH, fT3, and fT4 levels according to the patient records examined were given in Table 2. There was no significant difference between the genders in terms of TSH, fT3, and fT4 levels (U=1649.5, p=0.522, U=303.5, p=0.051, and U=1709.0, p=0.991, respectively). There was no significant correlation between the ages of the patients and their TSH and fT4 levels (r=-0.017, p=0.855, and r=0.016, p=0.861, respectively), while fT3 has a weak negative correlation with the age of patients (r=-0.272, p=0.037). There was no significant correlation between disease duration and TSH, fT3, and fT4 levels (r=-0.006, p=0.953, r=0.064, p=0.664, and r=0.096, p=0.374, respectively).
There was no significant correlation between the number of drugs used and TSH, fT3 and fT4 levels (r=-0.079, p=0.464, r=0.274, p=0.066, and r=0.051, p=0.643, respectively). Mean TSH, fT3 and fT4 levels were not significantly different between patients using and not using levodopa (U=873.5, p=0.645, U=209.5, p=0.242, and t=752.5, p=0.341, respectively).
The TSH values of the patients according to the mHYS motor symptom stages are given in Figure 1. There was no significant correlation between motor symptom stages and TSH, fT3, and fT4 levels (r=-0.148, p=0.164, r=-0.073, p=0.623, and r=0.075, p=0.491, respectively).

DISCUSSION

PD is usually observed in middle and advanced age and starts at the age of 50-60 on average and progresses over a period of 10-20 years. The annual incidence of PD is between 4.5-21/100000 (7). The diagnosis is principally clinical (2). The heterogeneous clinical picture includes motor subtypes as 'tremor dominant', 'postural instability and gait difficulty', or 'indeterminate'. The main clinical features of the disease can be listed as rigidity, flexion posture, loss of postural reflexes, resting tremor, bradykinesia, and the phenomenon of freezing (2).
Neuronal cell loss and appearance of Lewy bodies in substantia nigra are known as pathological determinants of sporadic PD. Nigrostriatal dopaminergic loss has been shown to be closely related to the severity of the classical motor findings especially bradykinesia and rigidity (9). The etiopathogenesis of selective loss of dopamine neurons in PD is still unclear. However, growing evidence suggests that oxidative stress and inflammation play an important role in the degeneration of dopaminergic neurons in PD (10). Possible mechanisms are associated with vascular risk factors, mitochondrial dysfunction, genetic, environmental factors, apoptosis, and oxidative stress (11). Non-motor symptoms observed in IPD are anxiety, sexual dysfunction, sleep disorders, cognitive dysfunction, apathy, depression, and psychosis, and sometimes they may cause more problems than non-motor symptoms (12).
Thyroid diseases are the most common endocrine disorders associated with PD. Bradykinesia and hypomimia, which are also observed in Parkinson's patients, may mask hypothyroid symptoms. Hyperthyroidism may worsen tremor and mask the levodopa response. It has been reported that both subclinical and clinical hypo- and hyperthyroidism occur

Table 1. Descriptive characteristics of the patients

Gender, n (%)	
Male	53 (57.0%)
Female	40 (43.0%)
Age (years)	71 (66-78) [39-89]
Disease duration (years)	4 (3-6) [1.5-22]
Number of drugs, n (%)	
1 drug	35 (37.6%)
2 drugs	41 (44.1%)
3 drugs	14 (15.1%)
4 drugs	3 (3.2%)
Levodopa treatment, n (%)	57 (61.3%)

Descriptive statistics were presented as median (25^{th}-75^{th} percentile) [min-max]

Table 2. Descriptive statistics of TSH, fT3, and fT4 levels

	Median	Q1-Q3	min-max
TSH (uIU/ml), (n=92)	2.075	1.21-2.69	0.218-7.99
fT3 (ng/dl), (n=46)	2.925	2.51-3.17	1.75-4.18
fT4 (ng/dl), (n=85)	1.235	1.12-1.39	0.798-1.79

TSH: thyroid stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, Q1-Q3: 25^{th}-75^{th} percentile

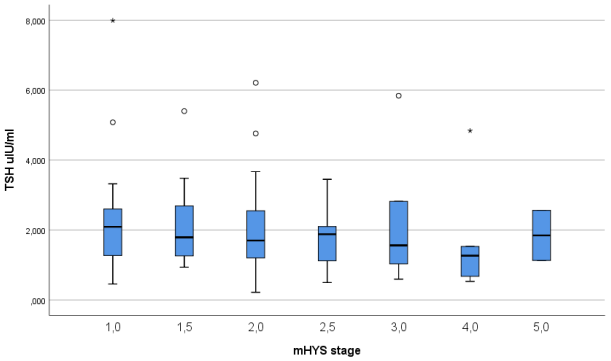

Figure 1. The TSH values of the patients according to the mHYS motor symptom stages
TSH: thyroid stimulating hormone, mHYS: modified Hoehn and Yahr scale

with PD. Thyroid hormones are important in the development and functioning of many organ systems, including the central nervous system. Thyroid function in advanced ages has been associated with the neurodegeneration process (13). High TH levels can cause oxidative stress by increasing basal metabolism and oxygen consumption. These effects are most pronounced in metabolically active organs such as the brain and have adverse effects on neuronal integrity (14).

Oxidative stress is important in the apoptosis of dopaminergic neurons and in the pathogenesis of PD. Increased oxidative stress is a risk factor for dopaminergic neuron degeneration in the early stages of PD (15). There is a mutual interaction between dopamine and thyrotropic hormone levels. Central dopamine deficiency in PD directly or indirectly leads to hormonal secretion disorders in the hypothalamo-pituitary pathway. Under normal conditions, dopamine modulates the hypothalamo-pituitary axis, increasing growth hormone secretion and decreasing prolactin secretion. Decreased prolactin levels also cause changes in TSH secretions (16). It has been reported that TSH levels can be decreased after levodopa treatment in Parkinson's patients, and low TSH levels detected in some PD patients were thought to be secondary to levodopa treatment (17). Even with significant fluctuations in circulation, brain T4 and T3 concentrations remain within a narrow range. This suggests that even slight changes in T4 may have consequences on CNS function (18).

The most common endocrine disorder associated with PD is thyroid disease. In addition to the fact that both hyperthyroidism and hypothyroidism are reported more frequently in PD patients than in healthy individuals, slightly increased fT4 levels are also observed in the early stages of the disease. The negative correlation between fT3 level and PD disease severity has been interpreted as patients with low fT3 levels may have a higher risk of developing serious disease. No results have been reported regarding the relationship of thyroid function to PH severity and motor symptoms in euthyroid patients (19).

Hypothyroidism is associated with PD motor symptom severity. fT3 levels have been shown to be lower in patients with the akinetic-rigid motor subtype than in patients with the tremor-predominant or mixed subtype. Patients with low thyroid hormone levels have symptoms of PD such as rigidity, hypokinesia, facial hypommia, and voice abnormalities. Hyperthyroidism exhibits clinical signs such as tremor, sweating, and weight loss experienced by many Parkinson's patients while exacerbating symptoms such as tremor and dyskinesia (20).

In this study, it was found that TH level did not affect the severity of motor findings in Parkinson's patients. This study gave us the opportunity to evaluate the effect of thyroid functions on PD motor symptoms from a different perspective. In many previous studies, the effects of thyroid dysfunctions on PD clinical findings were investigated and significant findings were obtained. In this study, the relationship between motor findings and thyroid function values in patients with normal thyroid function was investigated and it was found that it was not clinically related.

The main limitation of the study is that it was conducted in a cross-sectional design based on a single measurement. Therefore, the results do not reflect any changes that patients will experience throughout their disease process. Since the data belong to a single clinical center and representative power is not certain, care should be taken in generalizing the results. The study was carried out retrospectively using the available data from the hospital registry system. In this way, it was possible to evaluate the natural clinical course of the disease in the general clinical setting.

CONCLUSION

Although thyroid dysfunction is observed in more than 10% of Parkinson's patients, this rate was not different from the general population. Studies have generally focused on whether the frequency of thyroid dysfunction is different between Parkinson's patients and control groups. In this study, the relationship between normal differences in thyroid functions and motor functions in Parkinson's patients was investigated. Although thyroid dysfunctions and Parkinson's disease have similarities in the pathogenic mechanisms, causing difficulties in the clinical presentation and differential diagnosis, our results have shown that the differences in thyroid hormone levels that do not reach the level of disorder do not have a counterpart in the Parkinson's disease clinic. The main difference of this study from previous studies on this subject is that patients with normal thyroid hormone function were evaluated. These results revealed that when there is no clinical symptom in the follow-up of PD, control of thyroid hormone levels has no clinical benefit and the importance of hormone disorder is limited in the diagnostic work-up.

Ethics Committee Approval: The study was approved by the Clinical Researches Ethics Committee of Çanakkale Onsekiz Mart University (03.11.2021, 08/02).

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: Idea/Concept: ÖO, EMŞ, MÇ; Design: ÖO, EMŞ, MÇ; Data Collection/Processing: ÖO, EMŞ, MÇ; Analysis/Interpretation: ÖO, EMŞ, MÇ; Literature Review: ÖO, EMŞ, MÇ; Drafting/Writing: ÖO, EMŞ, MÇ; Critical Review: ÖO, EMŞ, MÇ.

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