Investigation of Motor End Plate Functions in Individuals with Incidentally Detected Thymoma

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ABSTRACT

Purpose: Thymoma is a mediastinal tumor that is frequently associated with Myasthenia Graves (MG) and develops from thymic epithelial cells. In our study, we aimed to determine whether there is a neuromuscular transmission defect in individuals with incidentally detected thymoma and to show whether these individuals have subclinical involvement without any clinical findings.

Materials and Methods: Single fiber electromyography (SFEMG) records made between March 2019 and January 2024 were examined, individuals who underwent SFEMG due to thymoma and structural ptosis were identified and detailed file record information of the patients was accessed. Individuals with any other disease or neurological complaint were excluded from the study. Asymptomatic individuals who underwent SFEMG were divided into two groups: individuals with thymoma and individuals with structural ptosis, and the demographic information and SFEMG findings of the two groups were compared with each other.

Results: Maximum jitter mean, minimum jitter mean and mean consecutive difference (MCD) values were found to be significantly higher in asymptomatic individuals with incidentally detected thymoma compared to patients with structural ptosis.

Discussion: Patients with thymoma may have subclinical neuromuscular transmission abnormalities even when they are asymptomatic in terms of MG. This is important for early diagnosis of MG and understanding the pathological processes in thymoma.

Keywords
Thymoma, Myasthenia graves, Single fiber electromyography.

Introduction
Dysfunction at the neuromuscular junction underlies a variety of disorders characterized by skeletal muscle weakness, often affecting some but not all muscle groups. Myasthenia gravis (MG) constitutes the largest disease group of neuromuscular junction disorders and is caused by pathogenic autoantibodies against postsynaptic muscle end plate components. MG is a disease characterized by clinical findings caused by local or generalized muscle fatigue resulting from a defect in neuromuscular transmission. MG associated with thymoma is a paraneoplastic disease. MG is by far the most commonly reported autoimmune disease associated with thymoma [1-3]. Thymomas are rare tumors located in the mediastinal region and developing from thymic epithelial cells. Approximately 50% of patients with thymoma develop MG, while thymoma is detected in 10-15%
of patients with MG [4,5]. Epithelial cells have the capacity to express epitopes cross-reactive with skeletal muscle proteins such as acetylcholine receptor (AChR), titin, and ryanodine receptor (RyR) [6,7]. Muscle-like epitopes are presented to T cells together with costimulatory molecules [7]. Autoreactive T cells specific for AChR and titin are found both in thymoma and in the serum of patients with coexistence of thymoma and MG [8]. Therefore, some of the mechanisms related to the responsible pathogenesis in patients with MG can be detected in patients with thymoma but without developing clinical findings of MG. In fact, detecting these findings in advance may be important in terms of being a predictor of the disease before the disease develops for MG.

Single fiber electromyography (SFEMG) is an electrophysiological method with very high sensitivity in detecting neuromuscular junction pathologies. SFEMG also has remarkable sensitivity in detecting subclinical neuromuscular conduction disorders. In some studies, neuromuscular junction dysfunction was detected electrophysiologically in the SFEMG studied in extensor digitorum communis muscle in patients with isolated ocular MG, even though this muscle was not symptomatically involved [9,10]. Based on this information, we aimed to determine whether there is an abnormality in neuromuscular conduction in patients with incidentally detected thymoma, although no clinical findings of MG were observed.

Material and Methods
This study included 62 patients who were referred to our hospital's clinical neurophysiology laboratory for SFEMG between March 2019 and January 2024, whose thymoma was detected on thorax computed tomography (CT) taken for another indication and who were asymptomatic in terms of MG, and 36 individuals who underwent SFEMG due to structural ptosis. The demographic, clinical, laboratory, radiological and electrophysiological parameters of the individuals in both groups were accessed by retrospectively examining the records of patients who underwent SFEMG between March 2019 and January 2024. Individuals with insufficient data on SFEMG or with another known disease were excluded from the study. Neurological examinations and SFEMGs of the patients were performed by the researchers in the laboratory environment. This research was approved by the local ethics committee (03.13.2024/ TABED 1-24-76).

SFEMG electrode (diameter for recording 2.5 μm) and a counterpoint EMG instrument (Keypoint. 4ch, Medtronic, Denmark) were used for minimum voluntary contraction SFEMG test. Jitter was calculated as mean consecutive difference (MCD). The criteria for acceptable potential pairs were: Amplitude >200 μV; and rise time 50 μs. Pathological increase in jitter was accepted as MCD>55 μs.

Statistical Method
The data were evaluated in the statistical package program IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were given as number of units (n), percentage (%), mean ± standard deviation (SD), median (M), minimum (min) and maximum (max) values. Normal distribution of the data of numerical variables was evaluated with the Shapiro Wilk normality test. When comparisons between groups were evaluated, the Independent two-sample t test was used when the data met the parametric test prerequisites, and the Mann-Whitney U test was used when the data did not meet the parametric test prerequisites. Pearson chi-square test was used to compare categorical variables with each other. A value of p<0.05 was considered statistically significant.

Results
98 patients who were asymptomatic in terms of MG, who were incidentally diagnosed with thymoma, or who were sent to the clinical neurophysiology laboratory for SFEMG due to structural ptosis, were included in the study. These patients were divided into 2 groups. The patients in Group 1 consisted of 62 patients who had a thymoma on thorax CT taken for another reason and did not have any neurological symptoms. The patients in Group 2 consisted of 36 patients who did not have any neurological complaints and had structural ptosis. While the average age of the patients in Group 1 was 41.62±12.62, the average age of the patients in Group 2 was 52.80±16.41. 38.7% of the patients in Group 1 were female and 61.3% were male. Of the patients in Group 2, 44.4% were female and 55.6% were male. Although there was a significant difference between the two groups in terms of age, there was no difference between the groups in terms of gender.

When the SFEMG parameters were examined, the mean minimum jitter value of the patients in Group 1 was 14.62±3.77, while the mean minimum jitter value of the patients in Group 2 was found to be 11.25±2.81. While the mean maximum jitter value of the patients in Group 1 was 53.0±14.47, the mean maximum jitter value of the patients in Group 2 was 43.55±14.61. While the average MCD of the patients in Group 1 was 28.59±4.18, the average MCD of the patients in Group 2 was 23.41±4.79. When Group 1 and Group 2 were compared, the minimum jitter, maximum jitter and average MCD values in the individuals in Group 1 were found to be significantly higher than those in the individuals in Group 2 (p<0.001).

A pathological increase in jitter was detected in 1 fiber in 17.7% of the individuals in Group 1, and a pathological increase in jitter was detected in 2 fibers in 3.2%. In Group 2, a pathological increase in jitter was found in 1 fiber in 5.6% of the individuals, and a pathological increase in jitter was found in 2 fibers in 2.8% of the individuals (p=0.248).

Discussion
In our study, we found that the minimum jitter, maximum jitter and mean MCD values of individuals with no symptoms and incidentally diagnosed thymoma were significantly higher than those of patients who had no neurological complaints and underwent SFEMG due to structural ptosis. In addition, the percentage of fibers with pathologically increased jitter in individuals with incidentally detected thymoma was found to be higher than in individuals without thymoma. These findings show...
that individuals who are asymptomatic for MG but have thymoma have a significantly impaired neuromuscular transmission at the neuromuscular junction.

Histologically, thymomas are epithelial neoplastic cells surrounded by maturing T cells. There are a few case reports that detected elevated antibodies in patients with thymoma even when MG did not develop [8,11]. However, there is no study in the literature to date that evaluates neuromuscular transmission in patients with thymoma who are asymptomatic in terms of MG. In this study, we determined that there is dysfunction in neuromuscular transmission in individuals with thymoma, even in the asymptomatic period. In this respect, our study is the first and provides important information to the literature in this context. The relationship between thymoma and MG can be explained by the function of thymic tissues and the connection in the pathogenesis of MG. Immunological maturation occurs when T cells interact with cell surface proteins on thymic tissue cells to distinguish between self and non-self antigens. In the case of thymoma-associated MG, thymomas are hypothesized to retain epitopes that can cross-react with certain skeletal muscle proteins. These epitopes are ryanodine receptor (RyR), titin and acetylcholine receptor [12]. The genetic profile of the patient and the ability of the thymus to export autoreactive T cells are equally important in the development of MG [13]. The neuromuscular conduction abnormalities we found in our study are probably related to the onset of subclinical involvements even when MG has not yet developed, and to the fact that these involvements only produce clinical findings if they exceed a certain threshold point.

MG is a neuromuscular junction disease characterized by muscle weakness and fatigue, caused by AChR antibodies in 85% of cases [14]. When MG occurs with a thymoma, MG is a paraneoplastic disease caused by the presence of a thymoma. MG with thymoma accounts for approximately 15% of all MG cases [15]. The immune response against an epitope expressed in thymoma cells spreads to components of the neuromuscular junction that share the same epitope [16]. Therefore, thymoma is a tumor with a very high risk for the development of MG. In the 1970s, Ekstedt and Stalberg [17,18] introduced SFEMG as an important method for evaluating neuromuscular conduction defects. Since then, its diagnostic value in MG has been evaluated in many studies in both extraocular muscles and extremity muscles [19-21]. Therefore, SFEMG has a very high sensitivity in detecting neuromuscular conduction disorder in MG. Based on this information, in our study, we investigated whether SFEMG could detect subclinical involvements in patients with thymoma but no MG symptoms. There was no study on this subject in the literature. In our study, the high mean, minimum, maximum jitter and MCD values in patients with thymoma supported the existence of subclinical neuromuscular junction dysfunction, although MG did not develop in patients with thymoma. SFEMG abnormalities studied from the extremity muscles of patients with pure ocular MG, previously reported in the literature, also support this hypothesis [9,10,22,23].

Our study is important because it is the first study to show subclinical neuromuscular conduction abnormalities in patients with thymoma, even when they are asymptomatic in terms of MG. One of the limitations of our study is its retrospective design. Another limitation is that it did not follow up this patient group to confirm this information and evaluate whether they would develop MG and which patients would convert to MG. Prospective randomized controlled studies are needed on this subject.

References


