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Single-fiber EMG in Migraine with or without Aura: Search for Correlations with Disability and Headache Intensity

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ABSTRACT

Background. The idea of a neuromuscular defect in migraine relates to the emergence of mutations in the CACNA1A gene that encodes the subunit of P/Q-type calcium channels in the motor nerve terminals. This study used single-fibre electromyography (SFEMG) to investigate the potential impact of an underlying channelopathy on subclinical neuromuscular transmission at the motor end plate in different types of migraine. Additionally, we sought to validate previous findings, explore the pathophysiology, and examine any potential relationship between neuromuscular dysfunction and disease severity using the Migraine Disability Assessment Scale (MIDAS) and Visual Analog Scale (VAS).

Material and methods. We enrolled 25 healthy volunteers, 30 migraineurs with aura and 30 without aura diagnosed according to the 2018 criteria of the International Headache Society. Voluntary SFEMG was performed on the frontalis muscle. Jitter values were analysed, including the mean individual jitter values of the migraine group, the number of fibers with increased jitter, the mean Mean Consecutive Difference (MCD), and the lowest and highest jitter values, which were then compared with those of the control group. The intensity of the migraine attacks was assessed using the VAS, while disability was evaluated using the MIDAS.

Results. Our findings revealed that the highest jitter values in migraine patients were significantly higher than those observed in the control group. Furthermore, we conducted a subgroup analysis within the migraine group and found that individuals with aura had higher average MCD values compared to those without aura and the control group. Additionally, we examined the association between MIDAS and VAS scores with increased jitter values and neuromuscular transmission abnormalities, but no statistically significant correlation was found ($p = 0.327$).

Conclusions. Our study supports the presence of motor endplate dysfunction in migraines, as indicated by previous literature, particularly in migraines with aura when compared to individuals without aura and controls. This finding aligns with the concept that this dysfunction may stem from a channelopathy associated with a genetic predisposition. Additionally, we found no clinical relationship between the neuromuscular disorder, the severity of the disease, and its disability.

Introduction

Migraine is a common headache disorder characterised by recurrent, unilateral, and throbbing pain, often accompanied by temporary disability. Genetic factors have been implicated in the aetiology of migraine, based on findings from family, twin, and population-based studies, suggesting a multifactorial mechanism [1,2].

Emerging evidence supports the notion of a neuromuscular defect in migraine, primarily linked to mutations in the CACNA1A gene. This gene encodes the pore-forming subunit of P/Q-type calcium channels in motor nerve terminals. The release of acetylcholine, a neurotransmitter, is mediated by these channels and has been associated with familial hemiplegic migraine, a rare hereditary form of migraine [3]. Research indicates that CACNA1A may also be involved in other types of migraine, particularly migraine with a prolonged aura [4]. Apart from their role in the brain, these channels are present at motor nerve endings, where they regulate the release of acetylcholine in response to stimulation. While there is no direct clinical evidence suggesting abnormal neuromuscular transmission in migraine patients, previous studies have reported varying findings. Certain studies using SFEMG have identified subtle subclinical abnormalities in different subgroups of migraine patients [5–8]. Terwindt et al. asserted that single-fiber electromyography (SFEMG) exhibited normal characteristics in familial hemiplegic migraine type 1 (FHM1). Their conclusion was drawn from observing normal mean Mean Consecutive Difference (MCD) values and the absence of fiber blockages. This stands in contrast to findings by Ambrosini et al., primarily because Terwindt et al. did not examine MCD irregularities in individual fibers, a factor found to be abnormal in Ambrosini et al.'s investigations despite also reporting a normal mean MCD [5].

Migraine is currently understood as a polygenetic and multifactorial disorder, yet its pathogenesis remains incompletely elucidated. Neurophysiological tests and analysis of clinical features, genetic factors, and environmental influences hold promise in shedding light on the underlying mechanisms. Detecting neuromuscular transmission disorders through SFEMG could effectively identify specific phenotypes of migraine patients, aiding in selecting candidates for further genetic testing and targeted treatment. Additionally, medications that modulate P/Q-type calcium channels may offer therapeutic benefits for migraine management. This study aims to assess the presence of neuromuscular conduction abnormalities using SFEMG in different types of migraine and investigate potential associations between these findings, pain severity, and disability caused by the disease.

Materials and methods

The study was conducted in the Ankara Yıldırım Beyazıt University, Faculty of Medicine's Hospital between June 2018 and February 2019. The Ethics Committee of Ankara Yıldırım Beyazıt University, Faculty of Medicine, granted ethical approval for the study. All participants provided informed consent before their participation. The study included 85 participants, with 73 females and 12 males. The patient groups consisted of 30 patients with migraine without aura and 30 patients with migraine with aura (visual and sensory). These patients were recruited from the neurology clinic and met the inclusion criteria. The sample comprised female and male patients aged between 18 and 55 years (mean age 32.18 ± 7.92 years), all of whom had a confirmed diagnosis of migraine according to the criteria established by the International Headache Society in 2013 [9]. Additionally, a control group comprised of 25 healthy volunteers matched with the patient group regarding age and gender distribution.

Exclusion criteria for the study included the presence of any other significant health conditions within the past three months, current use of migraine medication, history of chronic migraine, and suspected medication overuse. Patients with diabetes and high HbA1c levels were also excluded, as previous research has shown that SFEMG abnormalities can be observed in individuals with elevated HbA1c levels and diabetic neuropathy [10]. All migraine patients were assessed during the interictal period, defined as one week after their most recent migraine attack. The EMG examiner conducting the assessments was blind to the migraine status of the patients.

To assess the intensity of the migraine attacks, the visual analog scale (VAS) was utilised, while

disability related to migraine was evaluated using the Migraine Disability Assessment Score (MIDAS) questionnaire [11]. The MIDAS questionnaire is a brief, self-administered tool consisting of seven items (with five scored items) that measure headache-related disability. The VAS, commonly used as an outcome measure in such studies, is presented as a 100-mm horizontal line where the patient indicates their pain intensity by marking a point between the two extremes of "no pain at all" and "worst pain imaginable". The VAS is recognised for its simplicity, reliability, validity, and ratio scale properties, making it an optimal tool for assessing pain severity or intensity [12].

Table 1 summarises the demographic data of the patients.

Electrophysiological study

Electrophysiological assessments were conducted at the Electrophysiology Laboratory of the Neurology Clinic at Atatürk Training and Research Hospital, utilising a Dantec-Keypoint electromyography device. SFEMG studies were performed using a concentric needle electrode in both the patient and control groups while the participants voluntarily contracted their frontalis muscles. The device's upper and lower frequency filters were set to 10,000 Hz and 1000 Hz, respectively. For each jitter analysis, a minimum of 100 traces were recorded. In total, 20 different pairs of single-fiber potentials were recorded for

Table 1. Variable distribution table of individuals on a general basis

Variables	Number (percentage) n (%)
Gender	
Women	73 (85.9)
Men	12 (14.1)
Group	
Control	25 (29.4)
Migraine	60 (70.6)
Type of Migraine (patient with migraine only)	
Migraine without aura	30 (50.0)
Migraine with aura	30 (50.0)
Type of Aura (patient with migraine only)	
Visual	24 (80.0)
Sensory	4 (13.3)
Visual and sensory	1 (3.35)
Auditory	1 (3.35)
Relationship with Menstrual cycle (patient with migraine only)	
Not related	29 (51.8)
Related	27 (48.2)
Attack Frequency (patient with migraine only)	
Less than 1 in a month	1 (1.7)
Monthly	5 (8.3)
2–3 in a month	15 (25.0)
Weekly	13 (21.7)
2–3 in a week	19 (31.7)
Daily	7 (11.7)
Jitter interpretation	
Normal	69 (81.2)
Borderline	11 (12.9)
Jitter Impairment	5 (5.9)
Attack length (patient with migraine only)	
Less than 12 hours	9 (15.0)
12 hours – 1 day	2 (3.3)
1 day	21 (35.0)
2 day	16 (26.7)
3 day	12 (20.0)

each participant, resulting in 20 individual jitter values that were subsequently calculated. The MCD was used as the measure of "jitter." Jitter values greater than or equal to 55 microseconds were considered abnormal, while values below 55 microseconds were considered normal.

Motor endplate functions were evaluated based on the recorded fibers and their corresponding jitter values. Normal motor endplate function was determined if all recorded jitter values were within the normal range or if one value exceeded 55 microseconds. Participants with two out of the 20 jitter values surpassing this threshold were considered to have borderline dysfunction at the motor endplate. In comparison, those with three or more values above this limit were classified as having dysfunction at the motor endplate [13, 14].

Statistical Analysis

Descriptive statistics were calculated for the continuous variables, including mean, standard deviation, minimum, and maximum values. To determine if there were statistically significant differences in the lowest and highest jitter values between the control group and the migraine groups, an Independent Sample t-test was conducted. Mean and standard deviation plots were generated for the significant differences.

The MCD values between the control and migraine groups were compared using the non-parametric Mann-Whitney U test to identify any statistically significant differences. Additionally, a One-Way ANOVA was performed to assess whether there were significant differences in the highest and lowest jitter values among the different migraine types and the control group.

An independent sample t-test was employed to examine the potential differences in the highest jitter, average MCD, VAS, and MIDAS scores based on migraine type. The Mann-Whitney U non-parametric test analysed the VAS and MCD values according to migraine type.

All statistical analyses and comparisons were conducted using the IBM SPSS Statistics 21.0 software package (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). A p-value of less than 0.05 was considered statistically significant.

Results

The study comprised 85 participants, 73 females and 12 males, and the mean age was 32.18 ± 7.92 years. The age range of the participants was between 18 and 55 years. The control group comprised 25 participants, while both migraine groups included 60 patients (see **Table 1**). Among the 30 patients in the migraine with aura group, five had impaired neuromuscular transmission, 8 had a borderline impairment, and 17 had normal transmission. In contrast, none of the 30 patients with migraine without aura showed impaired transmission (3 had a borderline impairment, and 27 had normal transmission), and all 25 individuals in the control group had normal transmission (see **Table 2**).

Regarding the interpretation of jitter values, 69 participants had normal neuromuscular junc-

Table 2. Comparison of MCD, lowest jitter, and highest jitter variables based on migraine type and control groups

	Type of Migraine and Control			Test Statistics	
Variables	Migraine without Aura Mean ± SD Median	Mean Migraine with Aura Mean ± SD Median	Control Mean ± SD Median	chi^2	p
MCD	28.30 ± 3.98 27.50	33.26 ± 5.90 33.00	28.96 ± 3.46 29.00	15.401	<0.001*
Lowest jitter	13.60 ± 3.97 12.50	15.00 ± 3.97 15.50 (5.00)	14.64 ± 2.79 15.00 (3.50)	1.090	0.341**
Highest jitter	52.43 ± 8.12 51.00	71.93 ± 35.00 65.00	48.72 ± 4.11 49.00	9.904	<0.001**

* Kruskal Wallis non parametrical test
** One way ANOVA
SD = standard deviation
MCD = Mean Consecutive Difference

tions, 11 had borderline impairment, and 5 had impaired transmission. The highest mean jitter value was 52.43 ± 8.12 in the migraine without aura group, 71.93 ± 35.00 in the migraine with aura group, and 48.72 ± 4.11 in the control group. Statistically significant differences were found in the highest jitter values between the migraine types and the control group ($p < 0.001$). Specifically, differences between the aura and non-aura groups and the control and aura groups ($p < 0.001$ for both comparisons using One-Way ANOVA) were observed. The mean highest jitter values of the migraine patients were higher (see **Table 2**).

We used the Chi-Square test to compare the number of patients with increased jitter values based on the migraine and control groups. The study reported that out of the total participants, 22 subjects who had muscle fibers with increased jitter were in the migraine with aura group. Seven individuals were from the migraine without aura group. On the other hand, none of the subjects in the control group exhibited increased jitter (see **Table 3**).

Regarding disability assessment using the MIDAS questionnaire and attack intensity assessed by the VAS, no statistically significant differences were observed between the migraine groups with and without aura. The mean MIDAS score was 28.5 in the migraine with aura group and 25.5 in the migraine without aura group. The VAS score was 8 for both migraine groups. Furthermore, no statistically significant differences were found when comparing MIDAS and VAS scores with the count of high jitter values and patients with neuromuscular disorders ($p = 0.327$).

Discussion

The study found that the mean MCD values were significantly higher in patients with migraines with aura than those without aura and the healthy control group. Additionally, the migraine patients, regardless of type, had a significantly higher number of fibers with increased jitter compared to the control group.

Previous studies have indicated that a genetic abnormality in the presynaptic P/Q-type calcium channels may be responsible for the neuromuscular transmission disorder observed in migraine [6, 15, 16]. Mutations in the CACNA1A gene on chromosome 19p13 have been associated with familial hemiplegic migraine type 1, episodic ataxia type 2, and spinocerebellar ataxia type 6. Since CACNA1A encodes the neuronal voltage-gated P/Q-type calcium channel responsible for acetylcholine release at the motor nerve terminals, dysfunction in this gene could lead to impaired neuromuscular transmission. Although DNA analysis is required to confirm CACNA1A mutations, SFEMG is considered a valuable diagnostic tool for patients with migraine with aura.

When comparing the findings of similar studies conducted so far, it is important to note that the studies are heterogeneous and direct one-to-one comparisons may not be suitable. In contrast to others, the present study specifically conducted voluntary SFEMG on the frontalis muscle and identified subclinical neuromuscular transmission disorders in patients with migraines with aura. Furthermore, it identified the presence of such transmission defects in heterogeneous migraine subgroups. Demonstrating subclinical defects in neuromuscular transmission using the SFEMG method can improve our understanding of these disorders and potentially lead to the development of new treatment methods for conditions like migraines that significantly impair quality of life during young adulthood.

The widely accepted upper normal limits for stimulated-SFEMG recordings are a mean MCD value of 25 ms and a single fiber with ≤10% of

Table 3. Comparison of fiber presence with increased jitter based on migraine type and control groups

	Type of Migraine and Control			Test Statistics	
Variables	Migraine without Aura n (%)	Migraine with Aura n (%)	Control n (%)	chi^2	p
Muscle Fiber presence with increased jitter					
No	23 (41.1)	8 (14.3)	25 (44.6)	35.024	<0.001*
Yes	7 (24.1)	22 (75.9)	0		

* Chi^2 Comparison test

MCD values above 40 ms. However, these values likely come from control groups that include individuals with migraines or those at genetic risk for migraines. It is essential to establish normal values from strictly selected healthy volunteers [5, 6, 17]. One study considered the SFEMG results abnormal when the mean MCD values of the control subjects were exceeded [7]. Studies using voluntary SFEMG reported a mean MCD value of 33.8 ms and a single-jitter value of 55 ms based on their reference values. The percentage of abnormal single fibers was not considered. In two studies with a voluntary SFEMG design, the test was evaluated as abnormal if an MCD value of ≥15% exceeded 55 ms, and 10% of the MCD values were above such a threshold [18, 19]. In conclusion, the concept of SFEMG may vary between studies that clearly defined the measured parameter and the control population recorded up to the normal values.

In the present study, no increased jitter was identified in any of the fibers analysed in the control group. However, seven fibers analysed in patients with migraine without aura exhibited increased jitter. This piece of information is valuable, as previous studies have built their hypothesis of SFEMG abnormalities in migraine patients on the belief that an inherent channelopathy exists in migraine and that the existing neuromuscular transmission abnormalities would be present mainly in migraine patients with aura. In the present study, the primary SFEMG abnormalities were also distinctive in the group with migraines with aura, which supports the notion that migraines with and without aura are two different entities [20]. On the other hand, the highest jitter values were found to be higher in the patients with migraine without aura than in the control group, which suggests that the neuromuscular transmission disorder and the affected net acetylcholine release may not be influenced only by P/Q-type calcium channel abnormalities, but also by other mechanisms.

One of the advantages of our study is its use of the voluntary SFEMG method. The stimulation may also be used to obtain SFEMG potentials. Still, it is important to acknowledge that the axonal stimulation method carries the risk of producing a threshold more inclined to axonal blocking and increased jitter and may affect the method's objectivity. Moreover, larger axons are stimulated more when the stimulation method is used. This axon type has a higher safety factor, so this technique may cause an existing transmission disorder to remain undetected [21, 22].

A noteworthy finding of the study was that there was no statistically significant relationship between neuromuscular transmission abnormalities, disease severity, and disability as measured by MIDAS and visual pain scores ($p = 0.327$). This suggests that the presence of neuromuscular transmission abnormalities does not directly correlate with the severity or disability of the disease.

Today, there is a general belief that migraine is a polygenetic and multifactorial disease, although its pathogenesis is still not fully understood. Analysing its clinical features and genetic and environmental factors may shed light on the condition and be supported by neurophysiological tests. SFEMG-detected neuromuscular transmission abnormalities could help identify the phenotype of migraine patients who may benefit from further genetic testing and guide treatment strategies. Medications that modify the P/Q-type calcium channel may also benefit migraine treatment.

Another conclusion from the present study is that patients with motor endplate dysfunction detected by SFEMG may not always have a motor endplate disease like myasthenia gravis but rather a headache syndrome such as migraine.

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Conflict of interest statement
The authors declare no conflict of interest.

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