DOI: 10.14744/DAJPNS.2023.00222
Dusunen Adam J Psychiatr Neurol Sci
2023;36:189-194

RESEARCH ARTICLE

# Single fiber electromyography of the frontalis muscle: A view from the electromyography laboratory perspective

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**ABSTRACT**

**Objective:** The present study reports single fiber electromyography (SFEMG) findings in patients with ocular symptoms referred to the electromyography (EMG) laboratory with a presumed diagnosis of myasthenia gravis (MG). This study also examines repetitive nerve stimulation and serologic and clinical findings.

**Method:** We reviewed the medical records of 45 consecutive patients from January 2019 to September 2021 retrospectively. SFEMG was performed on the frontalis muscle (Front) during voluntary contraction using a disposable concentric needle electrode (CNE) (25 mm, 30 G). The number of single fiber-like action potential (SFLAP) pairs, the mean consecutive difference (MCD), the mean sorted difference (MSD), and the percentage of abnormally high individual jitters were noted.

**Results:** SFEMG results were normal for 16 patients, abnormal for 15, and borderline for 14. The mean jitters for the normal, borderline, and abnormal SFEMG groups were 19.75±3.84 µs, 27.21±4.89 µs, and 74.4±38.74 µs, respectively. A minimum of 20 SFLAP pairs were acquired in the normal or borderline SFEMG groups, whereas an analysis of fewer than 20 SFLAP pairs sufficed for 53% of the patients in the abnormal SFEMG group ($p=0.001$). SFEMG revealed diagnostic high jitter in 79% of patients with MG. The acetylcholine receptor (AchR) antibody titer correlated positively with mean MCD and MSD ($p<0.01$) but not with the percentage of high jitter.

**Conclusion:** CNE SFEMG of the Front is beneficial for diagnosing ocular and mild MG. The correlation of absolute AChR antibody titers with mean MCD and MSD, but not with the percentage of high jitter, is notable.

**Keywords:** Single fiber electromyography, concentric needle electrode, myasthenia gravis, repetitive nerve stimulation, anti-acetylcholine receptor antibody, frontalis muscle

## INTRODUCTION

Diagnosing diseases with neuromuscular transmission defects in electromyography (EMG) laboratories is challenging. Two distinct methods, namely repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG), are typically employed for these investigations. While RNS is more specific for the disease type and identifies the affected side of the neuromuscular junction (NMJ) as either pre- or post-synaptic, SFEMG is much more sensitive (1).

During a slight voluntary contraction of the muscle under investigation, one can measure changes in neuromuscular transmission time. This measurement

**How to cite this article:** Alpaydin Baslo S, Atakli D, Soysal A. Single fiber electromyography of the frontalis muscle: A view from the electromyography laboratory perspective. Dusunen Adam J Psychiatr Neurol Sci 2023;36:189-194.

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**Received:** August 10, 2023; **Revised:** August 20, 2023; **Accepted:** September 03, 2023

reflects the function of two junctions that produce two distinct, yet time-locked, single fiber action potentials (SFAP) belonging to the same motor unit. This is achieved using a trigger-delay line (2). Although the original method described by Ekstedt and Stålberg required a specially designed needle electrode or single fiber electrode (SFE) (3), today a disposable concentric needle electrode (CNE) with the smallest recording surface is preferred, especially for recording at 1-kHz low-cut filtering (4,5). The mean value of consecutive differences between interpotential intervals of two single fiber-like action potentials (SFLAP) yields what is called jitter. This physiological phenomenon mirrors the fluctuating amplitude of the endplate potentials, which is influenced by the variability of the safety factor. In NMJ diseases, this fluctuation is more pronounced, leading to higher jitter values, which are diagnostic. If the endplate potential fails to reach the threshold needed to trigger an SFLAP, this neuromuscular blocking is evident in consecutive traces; one of the SFLAPs – other than the triggering one – is absent.

When neuromuscular blocking is both frequent and widespread across many junctions, the amplitude of the compound muscle action potential (CMAP) decreases following low rates of repetitive nerve stimulation (2–5 Hz), known as decrement (6). A certain degree (more than 8–10%) of consistent decrement is significant and diagnostic, as is high jitter, with or without blocking. Along with the specific types of decrement, which manifests as "U" or "L" shaped in myasthenia gravis (MG), RNS achieves its highest specificity (7,8).

The objective of this study is to present the SFEMG findings of the frontalis muscle (Front) in patients referred to the EMG laboratory of a tertiary center. These patients have a suspected diagnosis of MG, supported by RNS, serologic, and clinical findings. This research also seeks to explore the sensitivity of CNE jitter of the Front when voluntarily activated, particularly in diagnosing ocular and mild MG. Moreover, it aims to investigate potential correlations between electrophysiological and clinical parameters.

## METHOD

We retrospectively reviewed the medical records of consecutive patients referred to the EMG laboratory for SFEMG between January 2019 and September 2021. These patients presented with ocular symptoms and exhibited isolated ocular muscle weakness (like ptosis, diplopia, and/or internuclear ophtalmoplegia) +/– mild generalized weakness in their neurological examinations. Records of patients under the age of 18 or those who had received botulinum toxin injections were excluded. Neuropathic or myopathic abnormalities were ruled out using conventional electrodiagnostic test results. All patients were off cholinesterase inhibitors for at least 12 hours before SFEMG testing. We noted their demographic features, SFEMG and RNS results, antibody profiles, and the presence of thymus pathology.

SFEMG was performed on the Front during mild-to-moderate voluntary contraction by the same physician (S.A.B.). A disposable facial CNE (25 mm, 30 G) was used. Two to three different insertions were made to collect the potential pairs. Bandpass filtering was set from 1 kHz to 10 kHz. SFLAPs with stable shapes, without notches, with amplitudes greater than 200 µV, and rising times shorter than 0.3 ms were included (4,9). A Medelec Synergy EMG device (Natus Medical Inc., Middleton, WI, USA) was used for recording and analysis. At least 60 consecutive traces containing two time-locked SFLAPs were acquired (10). MCD was recognized as jitter. The mean of the mean consecutive difference (MCD) and mean sorted difference (MSD) for each patient were calculated. The upper limit of normal for individual and mean jitter values was set at 38 µs and 28 µs, respectively (11). The percentage of abnormally high individual jitters and mean jitter values were provided. The study result was defined as abnormal when the mean jitter exceeded the upper limit of normal or the percentage of high jitter was over 10%, normal when both the mean jitter was within normal range and the percentage of high jitter was below 10%, and borderline when the mean jitter was normal but the percentage of high jitter was 10%.

For RNS, orbicularis oculi and nasalis muscles were chosen for recording. The corresponding facial nerve was stimulated at frequencies of 2, 3, and 5 Hz at rest, immediately after 20 seconds of maximal contraction, and thrice each minute post-maximal contraction, consecutively. A reproducible decrement exceeding 10% was deemed abnormal.

The study received approval from the local ethics committee at Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery (IRB Approval Date: 03.09.2019; No: 2019/348). Informed consent was not required, as the researchers obtained retrospective data from individuals in an anonymous manner, with no recording of identifiable personal information.

### Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc., Chicago, IL, USA)

**Table 1: Demographics, SFEMG, RNS features, antibody profile, and presence of thymus pathology in patients with normal, borderline, and abnormal SFEMG results**

| NMT | Age (years) | Sex (F:M) | SFLAP pair # | Mean MCD (µs) | Mean MSD (µs) | Percentage of high jitter (%) | RNS (N:P) | AchRAb (Ne:Po) | Thymus (N:P) |
|---|---|---|---|---|---|---|---|---|---|
| Normal (n=16) | 41.4±18.7 (16–85) | 6:10 | 24.81±2.43 (21–28) | 19.75±3.84 (14–27) | 21.63±3.67 (16–29) | 4.44±0.14 (4.35-4.55) | 12:0 | 10:2 | 8:1 |
| Borderline (n=14) | 48.1±13.9 (23–71) | 10:4 | 23.79±2.45 (20–27) | 27.21±4.89 (18–34) | 31±6.88 (21–45) | 5.85±2.97 (3.70–14.29) | 13:0 | 14:0 | 9:1 |
| Abnormal (n=15) | 52.3±17.1 (22–74) | 7:8 | 17.6±6.24 (7–28) | 74.40±38.74 (38–175) | 74.4±35.4 (43–174) | 49.39±27.05 (17.86–94.12) | 9:3 | 3:9 | 9:4 |
| p[a,b] | 0.131[a] | 0.164[b] | **0.001[a]** | **<0.001[a]** | **<0.001[a]** | **<0.001[a]** | 0.077[b] | **0.006[b]** | 0.308[b] |

[a]: Kruskal-Wallis Test, [b]: Chi-square. Data are presented as mean±SD (minimum-maximum). P<0.05 statistically significant (bold values). SFEMG: Single fiber electromyography; RNS: Repetitive nerve stimulation; NMT: Neuromuscular transmission; SFLAP: Single fiber-like action potential; MCD: Mean consecutive difference; MSD: Mean sorted difference; AchRAb: Anti-acetylcholine receptor antibody; F: Female; M: Male; N: Normal; P: Pathologic; Ne: Negative; Po: Positive.

was used for statistical analysis. Descriptive statistics are displayed as mean and standard deviation (SD) for data with normal distribution. For comparing two groups, the Mann-Whitney U test was used for non-parametric variables. The Chi-square test was used to compare categorical variables. Correlation analysis was performed using Spearman's rank correlation for non-normally distributed variables. A p-value less than 0.05 was considered statistically significant.

## RESULTS

In total, 45 consecutive patients (23 females, 22 males) with ocular symptoms were referred to the EMG laboratory and enrolled. The mean age was 47.04±16.9 (range, 16–85) years. The anti-acetylcholine receptor (AChR) antibody was tested in 39 patients, with 11 (28%) testing positive, while the anti-muscle specific tyrosine kinase (MuSK) antibody was tested in ten patients, with one (10%) testing positive.

SFEMG results were normal for 16 (35.6%), abnormal for 15 (33.3%), and borderline for 14 (31.1%) patients. No age or sex differences were observed between the normal, abnormal, and borderline SFEMG groups. The mean jitters for the normal, borderline, and abnormal SFEMG groups were 19.75±3.84 µs, 27.21±4.89 µs, and 74.4±38.74 µs, respectively (p<0.001). The mean MSD for the normal, borderline, and abnormal SFEMG groups were 21.63±3.67 µs, 31±6.88 µs, and 74±35.44 µs, respectively (p<0.001). The percentage of high jitter for the normal, borderline, and abnormal SFEMG groups was 4.44±0.14, 5.85±2.97, and 49.39±27.05, respectively (p<0.001). At least 20 SFLAP pairs were collected from the normal or borderline SFEMG groups, but fewer than 20 SFLAP pairs sufficed for diagnosing 53% of the patients in the abnormal SFEMG group (p=0.001) (Table 1).

Twelve of the 15 patients with abnormal SFEMG underwent RNS, with only three (25%) showing a significant decrement; nine (75%) were normal. RNS was conducted on 12 of the 16 patients with normal SFEMG and 13 of the 14 with borderline SFEMG. All RNS tests for the normal and borderline SFEMG groups were normal (Table 1).

In the abnormal SFEMG group, 13 were tested for antibody positivity. Among them, nine (69%) tested positive for the AChR antibody, one (8%) for the MuSK antibody, and three (23%) were seronegative (Table 1). In the borderline SFEMG group, all 14 patients were seronegative for the AChR antibody (100%). In the normal SFEMG group, 12 were tested for the presence of AChR antibodies. Of them, ten (83%) were negative, and two (17%) were positive and had low titers. The abnormal SFEMG group had a higher percentage of abnormal antibody results (66.7%) compared to the borderline and normal SFEMG groups (6.7%) (p<0.001).

Computed tomography identified thymus pathologies in six (19%) of 32 patients. Among these, four had abnormal SFEMG, one was borderline, and one was normal.

Fourteen patients were diagnosed with MG either through antibody positivity or treatment response. Of these, ten patients (71%) exhibited isolated ocular muscle weakness and, according to the Myasthenia Gravis Foundation of America (MGFA), were classified as MGFA1. The remaining four patients were classified as MGFA2. Of the 14 MG patients, RNS indicated a diagnostic decrement in 23% (3/13), while SFEMG identified diagnostic high jitter in 79% (11/14). Six patients did not receive an MG diagnosis but were given other diagnoses such as diabetic cranial neuropathy, toxic cranial neuropathy, pseudotumor cerebri, and immune-mediated neuropathy. Among these six patients, one with immune-mediated neuropathy

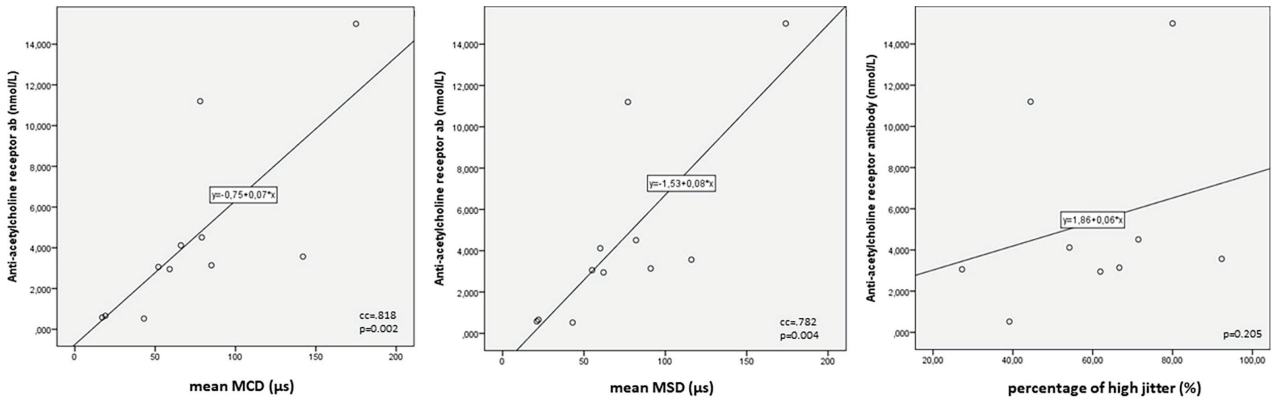


**Figure 1.** The correlation of anti-acetylcholine receptor antibody titer and mean MCD, MSD, and percentage of high jitter.
MCD: Mean consecutive difference; MSD: Mean sorted difference.

had borderline SFEMG results (mean MCD=33 µs, high jitter ratio=2/24), while the remaining five, including the one diagnosed with diabetic cranial neuropathy, had normal SFEMG (mean MCD=27 µs, high jitter ratio=1/23). RNS results for these six patients were all normal. A final diagnosis for 25 patients remained elusive. The AChR antibody titer correlated positively with both mean MCD (p=0.002, rho: 0.818) and mean MSD (p=0.004, rho: 0.782) but not with the percentage of high jitter (p=0.205) (Fig. 1).

## DISCUSSION

The present study provides a sensitivity value of CNE jitter of the Front with voluntary activation in patients with ocular and mild MG, a topic for which reported data is limited thus far. Additionally, it introduces a new correlation between the AChR antibody titer and the mean MCD and MSD, which may offer insights into the antibody-associated pathophysiology of the disease from an electrophysiological standpoint.

The sensitivity of SFEMG varies based on the muscle studied (extensor digitorum (ED), Front, orbicularis oculi (OO)), the needle used (SFE, CNE), the activation method (stimulated, voluntary), the MG diagnostic criteria used as the gold standard (antibody positivity, response to treatment), and the MG clinical classification (ocular or generalized, mild, moderate or severe, being treated or untreated) (4). In 1986, Sanders and Howard reported increased SFE jitter in at least one muscle in up to 99% of patients with MG if three muscles were examined (12). When jitter was normal in the ED, testing the Front detected abnormalities in 85% of patients with MG. When both were normal, testing the third muscle, the OO, showed increased SFE jitter in all patients (13).

Literature on the sensitivity of CNE jitter studies in ocular MG using voluntary activation of the Front remains scant. Benatar et al. (14) studied 21 patients with MG diagnosed through positive AChR antibodies or response to treatment and 30 non-MG participants, reporting the sensitivity of CNE jitter with voluntary activation of the Front as 62% in patients with ocular MG. Sirin et al. (15) examined 30 untreated patients with MG diagnosed through positive AChR or MuSK antibodies or clinical response to cholinesterase inhibitors. They reported the CNE jitter with voluntary activation of the ED or Front as 93% in patients with ocular MG. In our study, we identified abnormal CNE jitter at the Front in 11 of 14 MG patients, predominantly presenting with isolated ocular muscle weakness (MGFA1 n=10, and MGFA2 n=4) who were diagnosed through AChR or MuSK antibody positivity or response to treatment. Therefore, in this small retrospective study, the sensitivity of CNE jitter of the Front with voluntary activation was 79% in patients with ocular and mild MG.

A significant finding in our study was the correlation of the AChR antibody titer with mean MCD and MSD, rather than the percentage of high jitter. AChR antibodies, which are highly specific and diagnostic for MG, are positive in up to 90% of patients with generalized MG and in more than 50% of those with ocular MG (16). The relationship between circulating antibodies and disease severity in MG patients is highly complex (17). Various studies have assessed the use of the AChR antibody titer as a disease biomarker, with conclusions remaining contested. Sanders et al. (18) observed a decline in AChR antibody titers in 92% of improving MG patients, and in 63% who did not improve. Kojima et al. (19) reassessed AChR antibody levels within 100 days of initiating immunosuppressive treatment in 53

MG patients who were AchR antibody-positive, noting early achievement of minimal manifestation in those with high AChR antibody level reduction rates. Some studies have reported decreased antibody titers and significant clinical improvement following plasma exchange in MG patients (20,21).

Although debated, certain studies suggest that variations in serum AchR antibody titers may indicate clinical progress and/or response to treatment modalities. These studies mainly focused on the rate of antibody reduction over time, not the absolute antibody titer. The absolute AChR antibody titer value was proposed to reflect the affinity of AChR antibodies rather than the serum antibody pool (17). The correlation of the AChR antibody titer with mean MCD and MSD, and not the percentage of high jitter, could be inferred as reflecting the stronger affinity of antibodies to receptors, resulting in higher individual jitter values. In this study, jitter values exceeding 150 µs and those with blocking were not calculated separately. Hence, an elevated individual jitter value, surpassing 150 µs, could influence mean MCD more than the percentage of high jitter. Sanders et al. (22) analyzed SFE jitter and clinical outcomes in MG patients with at least two SFEMG results in ED or the Front. They found that changes in mean jitter were more precise than changes in the proportion of fibers with blocking or normal jitter in forecasting clinical changes.

The present study has several limitations. First, its retrospective design may affect the results due to the potential of selection bias, and some data could not be retrieved. Second, the number of enrolled patients was small since the study was conducted at a single institution, and SFEMG was performed by one investigator. Lastly, there are no follow-up data, so the outcomes for some patients remain unknown, given that the study was approached cross-sectionally from a laboratory perspective in a retrospective manner.

## CONCLUSION

In conclusion, this study offers insights into the SFEMG experience with CNE at the Front in patients exhibiting ocular symptoms, as observed from an EMG laboratory standpoint. The sensitivity of CNE jitter of the Front with voluntary activation stood at 79% in cases of ocular and mild MG. The correlation of the absolute AChR antibody titers with mean MCD and MSD, but not with the percentage of high jitter, was notable. It would be interesting to study the changes in MG clinical scales, antibody titers, and CNE jitter values over time in a prospective follow-up study in the future.

| Contribution Categories | | Author Initials |
|---|---|---|
| Category 1 | Concept/Design | S.A.B., D.A., A.S. |
| | Literature review | S.A.B., D.A., A.S. |
| | Data analysis/Interpretation | S.A.B., D.A., A.S. |
| Category 2 | Drafting manuscript | S.A.B., D.A., A.S. |
| | Critical revision of manuscript | S.A.B., D.A., A.S. |
| Category 3 | Final approval and accountability | S.A.B., D.A., A.S. |

**Ethical Approval:** The Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery Ethics Committee granted approval for this study (date: 03.09.2019, number: 2019/348).

**Informed Consent:** Informed consent was not applicable since the researchers retrieved retrospective data from individuals anonymously without recording any accessible personal identifying information.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Financial Disclosure:** The authors declare that they have no financial support.

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