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Full Length Research Paper

Volitional single fiber electromyography of the masseter muscle; normative values and in myasthenia gravis

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This study was aimed at establishing normative values for volitional single fiber electromyography (SFEMG) of the masseter muscle in Egyptians and evaluating the sensitivity of this test in the diagnosis of generalized myasthenia gravis. Twenty two patients with myasthenia gravis (mean age of 37.72 years; range, 20 to 59; mean duration of illness, 4 years; range, 1 months to 16 years) where enrolled in the study to assess for SFEMG of the masseter muscle and of the extensor digitorum communis (EDC) muscle. Twenty normal individuals (mean age 34.3; range 22 to 55 years) where similarly studied to determine the normative values of SFEMG of the masseter muscle. The mean jitter of the masseter in the patients' group was 63.4 ± 9.98 us, compared to 21.3 ± 4.9 us in the control group. Examination of the masseter muscle yielded 100% sensitivity in this study, compared to 90% sensitivity for EDC. We suggested a normal upper limit of masseter's mean jitter of 26 microsecond/ study (mean +/- 1 SD) and 28 us / individual fiber pair (The 95th upper percentile was 27.51 us). Volitional SFEMG of the masseter muscle is highly sensitive test to diagnose generalized MG that is not related to weakness of this particular muscle but correlated to the degree of the disease's severity.

Key words: Single fiber electromyography (SFEMG), masseter muscle, extensor digitorum communis, myasthenia gravis, repetitive nerve stimulation, neostigmine test.

INTRODUCTION

Myasthenia gravis (MG) remains one of the most challenging medical diagnoses due to its fluctuating character and to the similarity of its symptoms to those of other disorders. Although a formal clinical classification system and research standards have been established for MG there are no widely accepted formal diagnostic criteria (Jaretzki et al., 2000). The most important element of diagnosis are clinical history and examination findings of fluctuating and fatigable weakness, particularly involving extraocular and bulbar muscles. Clinical diagnosis may be confirmed by edrophonium chloride testing, repetitive nerve stimulation (RNS), SFEMG, and/or serological demonstration of acetylcholine receptor antibodies or muscle-specific tyrosine kinase (MuSK) antibodies (Juel and Massey, 2007).

Single fiber EMG is used to measure the relative firing of adjacent single muscle fibers from the same motor unit and can detect both prolonged jitter and blocking. Whereas the clinical correlate of blocking is muscle weakness, there is no clinical correlate for increased jitter. Thus, the main advantage of SFEMG over RNS is that SFEMG can be abnormal, showing increased jitter, even in patients without overt clinical weakness, whereas for RNS to be abnormal the neuromuscular junction disorder must be sufficiently severe that blocking also occurs, leading to a decremental response (Preston and Shapiro, 2005).

The masseter muscle was found to be clinically weak

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early in the course of myasthenia gravis in about 6% of patients, and becomes involved later as one of the mastication muscles in most patients (Rousseff et al., 2007). It is thought to be suitable for SFEMG for the following reasons; it is a superficial and easily accessible muscle and frequently involved in MG. It is thought to be more susceptible for weakness than facial muscles in MG (Khuraibet et al., 2008). Moreover, the motor portion of the mandibular nerve is rarely affected by neuropathies, so the masseter is unlikely to yield false-positive results (Rousseff et al., 2007).

Aim of work

This study was aimed at establishing normative values for volitional SFEMG of the masseter muscle in normal Egyptian subjects and evaluating the sensitivity of this test in the diagnosis of generalized myasthenia gravis.

Subjects

22 Patients with generalized myasthenia gravis by clinical presentation of fluctuating excessive muscle fatigability with the age between 20 to 60 years old were included. Patients in myasthenic crisis or had other neurological symptoms or signs were excluded from the study.
Twenty normal (neuropathic or muscle disorders excluded by NCS and EMG) age, sex matched subjects were studied for single-fiber examination of the masseter muscle to serve as a normal control group.

METHODS

All enrolled patients had thorough clinical history taking, thorough general and neurological examination. The degree of weakness is assessed according to the Myasthenia Gravis Foundation of America (MGFA) (Jaretzki et al., 2000).

Pharmacological testing with neostigmine were done for patients only. All anticholinestrase drugs are discontinued 8 h before performing this test. Atropine sulphate IM (0.011 mg/Kg) was administered 30 min before administering 1.5 mg neostigmine methylsulfate to prevent adverse muscarinic effects. Placebo response was determined by measuring muscle strength in cranial muscles before and after atropine sulfate administration. The patient was re-assessed for improvement after 20 to 30 min. (Gunn and Nechyba, 2002)

An electro-diagnosis tests was done using a Nihon Kohden; Neuropak MEB-9200G/K EP/EMG measuring system (Neuropak M1)- 4 channels-version 08.11 was used for EMG, NCS, RNS, and SFEMG in the Clinical Neurophysiology Unit, Kasr Al Ainy Hospital, Cairo University, Egypt.

Motor and sensory nerve conduction studies were carried out for upper limbs (left ulnar and right median) and lower limbs (left common peroneal and right tibial) nerves to exclude the presence of any neuropathies and to insure the nerves that will be examined by RNS were intact. EMG was similarly performed to exclude muscle diseases.

The left ulnar, facial and spinal accessory nerves were examined for decrement. The patient was asked to stop taking acetylcholine esterase inhibitors for 12 to 24 h before the test. Slow rate repetitive stimulation (3Hz) was given for a train of 10 responses. RNS was considered positive when there was an amplitude decrement exceeding 10% between the first and forth responses for ulnar and spinal accessory nerves and 20% for the facial nerve.

If significant decrement was observed in the muscle at rest, the patient was asked to perform 10 s of voluntary exercise to look for repair of the decrement (post-exercise facilitation). If no decrement was observed at rest, the patient was asked to perform 1 min of voluntary exercise of the muscle. The repetitive stimulus train was repeated at 1, 2, 3 and 4 min post exercise (post-exercise exhaustion). After demonstrating decrement, the patient was asked to perform maximal exercise for another 10 s. A repair of the decrement should be seen, demonstrating post-exercise facilitation, not exceeding 40% of the CMAP amplitude.

Volitional Single fiber EMG examination of the masseter muscle and the extensor digitorum communis muscle.

The gain was initially set at 0.05 mV per division. Sweep time was 1.0 msec per division. The bandpass was 10 to 500 Hz. The recording SFEMG needle was inserted into the masseter muscle, 2.5 cm above the angle of the mandible on a line that connects it to the outer canthus of the eye, at a depth of 0.5 to 1.0 cm (Figure 1). For the extensor digitorum communis muscle, SFEMG needle was inserted 3 to 4 fingerbreadths distal to the olecranon with the patient's forearm pronated.

The ground electrode was a surface electrode placed on the back of the patient's hand and forehead, during examination of the EDC and the masseter respectively.

The patient was asked to contract the muscle minimally and maintain that contraction.

5 to 6 insertions were made to record 10 to 20 pairs of single muscle fibers. The needle was moved until a single muscle fiber potential was located. With this single muscle fiber potential triggered on a delay line, the needle was slightly and carefully moved or rotated to look for a second potential that was time locked to the first potential, signifying that it was from the same motor unit. Multiple, consecutive firings of the muscle fiber potential pairs were then recorded. The mean consecutive difference (MCD) for each fiber pair was calculated as well as the mean MCD of all fiber pairs, the presence of blocking of the second potential was also looked for.

Normative values for the SFEMG of the EDC muscles were taken according to a previous study performed at our lab (Mostafa et al., 2005).

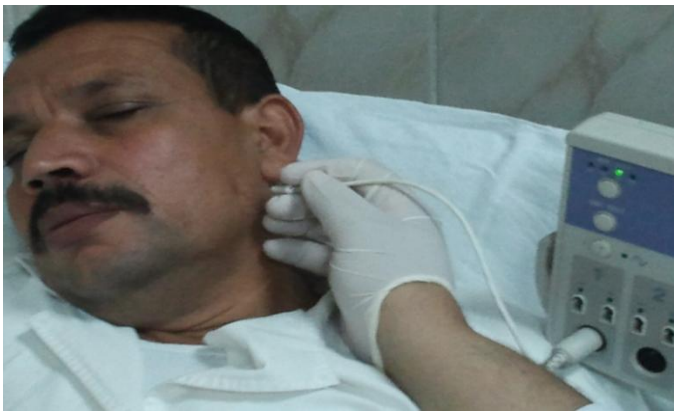

Figure 1. Site of needle insertion for masseter muscle examination.

Statistical evaluation

Computer software package SPSS 15.0 was used for quantitative and qualitative variable analysis. For quantitative variables mean/median (as a measure of central tendency) standard deviation/ range, minimum and maximum (as a measure of variability) were presented. Frequencies were performed for qualitative variables. T and Mann-Whitney tests were used to estimate differences in quantitative variables. Speaman correlation to estimate association between quantitative variables was presented in the form of correlation coefficient and its significance. P-value < 0.05 was considered significant.

RESULTS

Patient group

Their age ranged from 20 to 59 years with a mean age of 37 ± 12.37 years. 10 males (45%) with a mean age of 41.6 years and 12 females (55%) with a mean age of 33.1years

The duration of illness ranged from 1 month to 16 years with a mean of 4.02 ± 5.37 years and a median of 1 year (Table 1).

Control group

10 males (50%) and 10 females (50%), their age ranged from 22 to 55 years with a mean age of 34.3 ± 10.32 years.

Clinical classification

According to MGFA clinical classification patients were classified into: Class II comprised of 10 patients: Group (II a) included 2 patients who had predominant weakness involving limb (predominantly proximal) muscles. Group (II b) six patients had predominant oropharyngeal muscle weakness in the form of nasal tonation, nasal regurgitation, difficulty in swallowing and mastication and, in 4 of them, milder limb weakness. Class III included 8 patients, all were classified as class (III a) and suffered from ptosis and moderate limb weakness. Two also complained of difficulty of mastication. Class IV included 4 patients, all classified as class (IV a) and suffered from severe generalized weakness, as well as moderate respiratory muscle weakness, moderate ptosis and diplopia (Table 1).

Neostegmine test was positive in 16 patients (72.7%), 12 males and 4 females. Six of them were class II, another six were class III and four were class IV (Table1).

SFEMG results

1. SFEMG of the masseter muscle in the control group: The mean consecutive difference had a minimum value of 14.9 us (microsecond) and a maximum of 27.9 us. The mean MCD of all fiber pairs was 21.99 ± 4.96 while its median value was 21.3 us. The 95th percentile for an individual fiber pairs was 27.51 us. The percentage of abnormal pairs was 3.75 ±3.69 and 0% blocking. (Table 2, Figure 2)
2. SFEMG results of the EDC muscle in the patient group: 20 out of 22 (90.9%) patients showed abnormal mean MCD and percentage of abnormal pairs. Blocking was found in 6 patients only (27.3%). (Table 2)
3. SFEMG results of the masseter muscle in the patient group: All the patients (100%) showed abnormal mean MCD. 20 patients (90.9%) showed a significant (Table 2, Figure 3)

percentage of abnormal pairs and 8 patients (36.4%) showed blocking.

4. Comparison between SFEMG results of the masseter muscle in the patient group and normal control group.

There was a highly statistically significant difference

Table 1. Demographic data, clinical classification, neostigmine test and repetitive nerve stimulation of the patients' group.

Variables	Mean + SD
Age (years)	37 ± 12.37
Sex	45% Males, 55% Female
Duration of illness (years)	4.02 ± 5.37
Clinical classification MGFAClass II	10 (45%) patients
Class III	8 (36.4%) patients
Class IV	4 (18%) patients
Neostigmine test	+ve in 73%, -ve in 27%
RNS: -ve	8 patients (36%)
+ve in one nerve only	2 patients (9%)
+ve in two nerves	8 patients (36%)
+ve in all three nerves	4 patients (18%)

Table 2. SFEMG parameters of the masseter muscle and EDC in control group and patient group.

SFEMG parameter	Control group masseter	Patient group masseter	Patient group EDC
Median MCD (us)	21.3	68.8	72.8
Mean MCD (us)	21.99±4.96	63.38±9.98	70.55±12.72
% abnormal pairs	3.75±3.69	68.89±27.43	55.38±25.09
% blocking	0	37.5	27.0

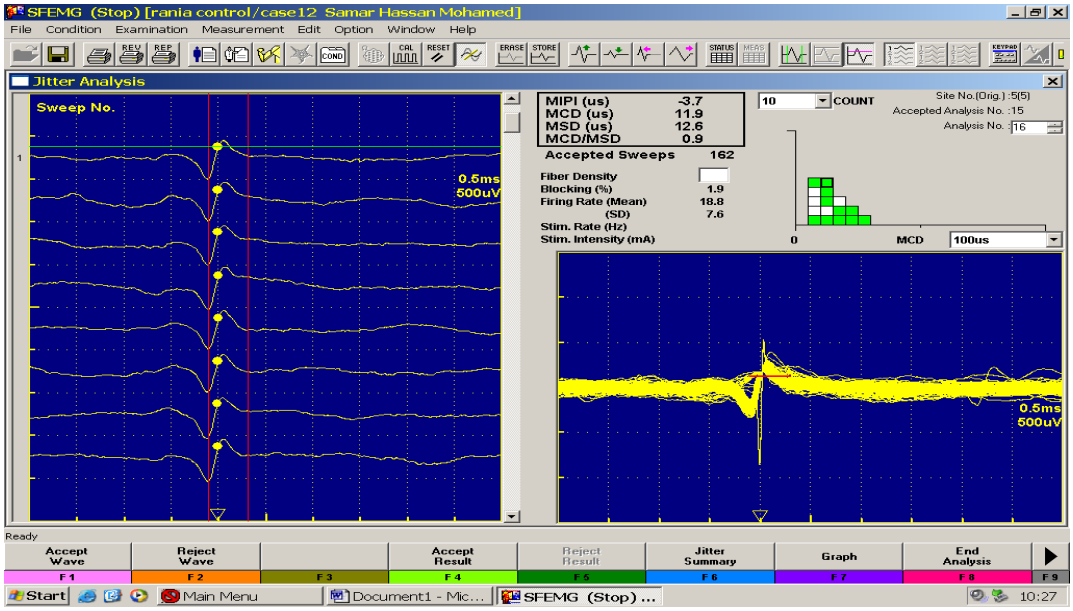

Figure 2. Normal SFEMG of the masseter muscle.

between the normal control group and the patient group as regarding the mean MCD (P-value = 0.0001), the percentage of abnormal pairs (P-value= 0.0001) and the percentage of blocking (P-value = 0.02).

5. Comparison between SFEMG results of the masseter muscle and those of the EDC in the patient group.

There was no statistically significant difference between the EDC (55.4%) and the masseter muscle (68.9%) as

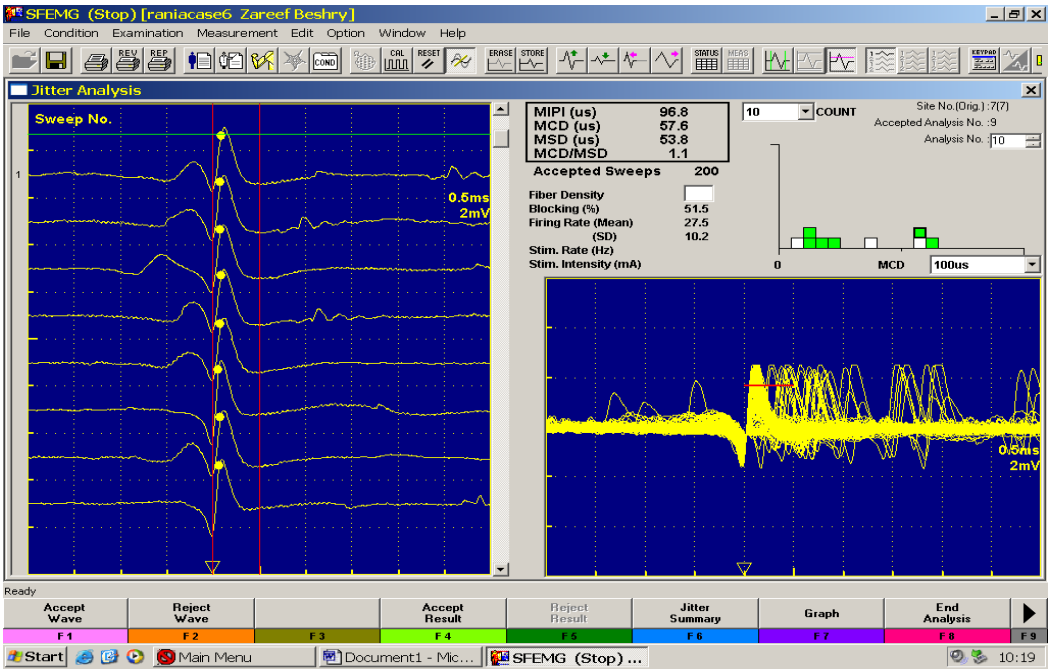

Figure 3. Abnormal volitional SFEMG of the masseter muscle showed increased jitter.

Table 3. Effects of duration of illness and degree of weakness on SFEMG results of the masseter muscle (P-value).

SFEMG masseter	Mean MCD	% abnormal pairs	% of blocking
Duration of illness	0.38	0.61	0.16
Degree of weakness	0.004**	0.04*	0.13

*Significant, ** highly significant.

regarding the percentage of abnormal pairs (P = 0.175) on the other hand there was a highly statistically significant difference as regards the percentage of blocking which was 27.0% in EDC and 37.5% in masseter muscle. (P = 0.001).

6. Clinical factors affecting SFEMG parameters of the masseter muscle were summarized in Table 3.

7. The sensitivity of the mean MCD of the masseter muscle was 100%, while that of the EDC was 90%. Repetitive nerve stimulation showed a sensitivity of 66%. Neostigmine test was 72.7% sensitive.

DISCUSSION

Although SFEMG examination of the masseter muscles seems to be easier as it is superficial with a simple surface anatomy, it faces some difficulties. Most of the patients were afraid from needle electrode insertion in their face. Maintaining a minimal voluntary contraction in this powerful muscle of mastication was another challenge.

Roussseff et al. (2007) studies the normative values of stimulated jitter of the masseter muscle and they recommended an upper normal limit for mean MCD per study of 21 microseconds and upper normal limit of MCD for individual fibers of 30 us. Stimulated jitter is particularly useful in uncooperative, severely weaker patients, those with tremors but on the other hand needs sophisticated techniques to stimulate the individual motor branch of the mandibular nerve, a technique which could not be available in many centers. In our study we can recommend longer value (26 us, mean+/- 1SD) for the study but less one (28 us) for individual fibers and the difference between them is much less.

The normative values for other facial muscles were reported by many authors; Valls-Canals et al. (2003) calculated 14.6 ± 6.8 us in frontalis and 12.68 ± 6.10 us in orbicularis oculi after stimulated SFEMG. Balci et al. (2005) was calculated the normal limit of jitter of the frontalis muscle as 40.4 micros for healthy subjects between 70 and 79 years old and 43.7 micros for healthy subjects older than 80 years while Kokubun et

al. (2012) suggested 56.8µs for voluntary SFEMG and 51.0µs for stimulated SFEMG for frontalis.

These marked difference in mean MCD according to the technique used, the selection of muscle tested and/ or the age of the subjects' means that each lab must has its own reference values for better diagnosis of abnormalities.

The MG's patients in this study, showed a slight female preponderance that agrees with the sex distribution of MG. The younger mean age of the female subjects is in agreeing with the earlier peak incidence of MG in females (Shah, 2006).

The diagnostic sensitivity of SFEMG of the EDC was 90% in this study, comparing to a sensitivity of 96.4% in a study conducted by Ptolemaios et al. (2006) 99% by Srivastava et al. (2007) and 74% by Mostafa et al. (2005) all for generalized MG cases. The difference in sensitivities may be related to the number of patients who did not suffer weakness of this muscle at the time of testing in each study (Ptolemaios et al., 2006). In this study the only subject who had normal SFEMG values for the EDC did not have weakness of the examined muscle.

The examination of the masseter muscle yielded 100% sensitivity in this study, as well as in all generalized cases studied by Khuraibet et al. (2008) with an overall sensitivity of 90% when they combined ocular and generalized cases. In addition, in our study sixteen out of the twenty two patients had normal masseter power upon examination, while the remaining six patients had mild to moderate masseter weakness. Such results reinforce the hypothesis demonstrating that SFEMG of the masseter muscle is a highly sensitive diagnostic tool in MG, even in the absence of any clinical weakness of the muscle. The high sensitivity of masseter SFEMG in MG is consistent with findings in other craniofacial muscles studied by the volitional method, frontalis by Katzberg and Bril (2005) and orbicularis oculi by Witoonpanich et al. (2011). However, it should be emphasized that the masseter is not simply a "replica" of facial muscles. Facial muscles consist of 80 to 90% type II fibers, whereas the masseter is composed predominantly (>70%) of type I fibers, which have a significantly lower safety factor than type II fibers, and therefore may exhibit a synaptic defect earlier (Khuraibet et al., 2008). Masseter muscle also showed a significant percentage of blocking rather than EDC due to its low safety factor.

A correlation between masseter SFEMG abnormality and clinical severity was also demonstrated.

Conclusion

We suggested a normal limit of masseter's mean MCD of 26 microsecond/ study (mean +/- 1SD) and 28 us / individual fiber pair (The 95th upper percentile was 27.51 us). Volitional SFEMG of the masseter muscle is highly sensitive test to diagnose generalized MG that is not related to weakness of this particular muscle but correlated to the degree of the disease's severity.

We recommended to extent this work to only recently diagnosed and/or suspected cases of generalized myasthenia gravis for better evaluation of its sensitivity.

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