A direct correlation of QEMG with muscle biopsy findings might help delineate the sensitivity of QEMG in identifying muscle pathology as well as provide information on electrophysiological-histological correlations. In a study of 31 patients with a variety of myopathies we found that the sensitivity of QEMG was between 24 to 69% depending of the specific method of signal analysis. The positive predictive value of abnormal QEMG was more than 90% while its negative predictive value was only about 20%. Amplitude outlier analysis was superior especially in minimally weak muscles (MRC > 4) and was particularly sensitive at detecting increased variability in fiber size and more subtle myopathic changes.

Key words: Quantitative electromyography, muscle biopsy, sensitivity

Introduction

Quantitative electromyographic (QEMG) analysis can be a useful tool in the investigation of muscle disease. It may be used to select a muscle suitable for biopsy and to sample individual muscles periodically to monitor disease activity (1, 2).

The sensitivity and specificity of QEMG in myopathies have been the subject of several studies which have used the clinical diagnoses as the gold (3-7). However, there is only a handful of studies that have directly correlated QEMG with findings on muscle biopsy (8-10). Further knowledge on direct correlations between QEMG and biopsy would help delineate the sensitivity of the former in predicting histological abnormalities.

In the current study we correlate QEMG with biopsy findings in the contralateral muscle in a group of 31 patients referred for neuromuscular evaluation and in which a final clinical diagnosis of myopathy was finally reached.

Methods

Patients

We retrospectively identified 39 patients, referred to the Cyprus Institute of Neurology and Genetics for neuromuscular evaluation between the period 1999 and 2001. During this time period patients suspected of a myopathy had both a QEMG and muscle biopsy as part of their routine work up. An abnormal QEMG was not required for a patient to proceed to biopsy. All patients exhibited proximal weakness and/or hyperCKemia. Twenty two patients had a Medical research council (MRC) > 4 and 17 an MRC ≤ 4 in the muscle in which the QEMG was performed. All patients had symmetrical clinical involvement of the muscles under investigation. In all 39 patients a final clinical diagnosis was reached (Table 1). In 31 the final diagnosis was myopathy.

Electromyography

A Nicolet Viking II was used to record motor unit action potentials via a concentric needle (Medtronic DCN 37mm,0,46mm) using the QMUP mode. MUAPs were manually selected using signal trigger averaging with the patient exerting a weak to moderate effort so as to activate 2 to 5 MUAPs clearly seen on the baseline. Every effort was made to improve sharpness. The filters were set between 2 Hz to 10 kHz; the acquisition sensitivities were set at 100-500 μV/division and 5 ms/division.

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The duration of the MUAPs was determined manually after averaging at 100 μV/division and 5 ms/division. Polyphasic MUAPs, but not satellite potentials, were included in the analyses. MUAPs with amplitude lower than 50μV and rise time longer than 500μsec were rejected. Twenty MUAPs were obtained from each muscle from 4-5 insertion points. The original stored data consisting of 20 averaged MUAPs from each muscle were re-analyzed for the purpose of this study using the mean duration and outlier methods and the results correlated with biopsy findings in the contralateral muscle.

For the mean duration method, the duration of 20 MUAPs from each muscle were averaged and the mean compared with normal values for age (3, 11). A muscle was categorized as neuropathic or myopathic if the mean MUAP duration was 20% above or below the mean normal values for age respectively.

The 20 MUAPs were also analyzed by the outliers method (12). Outliers as defined by Stalberg are the upper or lower MUAP amplitude or duration values beyond which a normal individual has no more than 2 MUAPs. For the outliers method we used the upper and lower limit values of Oh (13). MUAPs less than 6μsecs in duration and/or less than 300μV in amplitude were defined as myopathic, while MUAPs longer than 17msec in duration and/or larger than 3,5mV in amplitude as neuropathic. Muscles with more than 2 MUAPs outside the limits were considered abnormal.

Muscle biopsies

Open muscle biopsies were obtained from 20 vastus lateralis and 19 biceps brachii muscles.

The biopsy was obtained from the contralateral muscle to that examined by QEMG. The selected muscle had a Medical research council (MRC) score more than 3. The pathologist reading the biopsies was not aware of the EMG result.

Muscle biopsy findings were classified for the purpose of the study as myopathic: M1, increased variability in muscle fibre size involving both fibre types, M2, the presence of necrosis and/or regeneration, M3, the presence of endomysial fibrosis indicating chronicity and fibre loss and M4 alterations in the fibre architecture without significant fibre loss or variability in fibre size. Such abnormalities included ragged red and cytochrome c oxidase deficient fibres (Fig. 1). Biopsies were classified as neurogenic if there were angular atrophic fibres of both fibre types and/or the presence of type grouping, indicative of reinnervation (Fig. 1).

![Figure 1](image)

Table 1. Clinical diagnoses and biopsy findings.

| Clinical diagnoses                  | Myopathic findings | Neuropathic findings | Normal findings |
|------------------------------------|--------------------|----------------------|----------------|
|                                    | All M1 M2 M3 M4    |                      |                |
| Inflammatory myopathies (n = 5)    | 5                  | 5                    | 4              | 1              |
| HyperCKemia (n = 2)                |                    |                      |                |
| Muscular dystrophy (n = 5)         | 5                  | 4                    | 1              | 3              |
| Myotonic dystrophy (n = 2)         | 2                  | 2                    | 1              |                |
| Inclusion body myositis (n = 1)    | 1                  | 1                    |                |                |
| Non-specific myopathy (n = 9)      | 7                  | 5                    | 1              | 2              |
| Mitochondrial myopathy (n = 9)     | 9                  | 6                    | 2              | 1              | 5              |
| Motor neuron disease (n = 3)       |                    |                      |                |                | 3              |
| Lumbar canal stenosis (n = 1)      |                    |                      |                |                |                |
| Normal (n = 2)                     |                    |                      |                |                | 1              | 2              |
| Total number                       | 39                 | 29                   | 23             | 7              | 6              | 9              |

Myopathic biopsies could exhibit more than one myopathic feature M1,2,3,4

![Figure 1](image)
Sensitivity

The sensitivity of the QEMG was calculated with reference to the biopsy findings in the contralateral muscle. We calculated the sensitivity of the mean duration and outlier QEMG methods separately. The sensitivity of each QEMG method was also evaluated separately in patients with an MRC > 4 and MRC ≤ 4.

Sensitivity was defined as the proportion of true positives divided by the sum of true positive and false negative results.

Specificity could not be estimated since we did not include any real normal individuals in our study.

Predictive value

The positive predictive value of QEMG, defined as the likelihood of an abnormal QEMG predicting an abnormal biopsy, was calculated.

The negative predictive value of QEMG, defined as the likelihood that a normal QEMG will predict a normal biopsy, was calculated.

Statistical analyses

The sensitivities between the different methods were compared using the nonparametric McNemar test for related samples (14).

Results

Patients

The clinical diagnoses and biopsy findings of the original 39 patients are shown in Table 1. Thirty one patients were diagnosed to have a myopathy. Twenty nine exhibit myopathic features in their biopsy while two had a normal appearance in the biopsy but were weak and had elevated creatine kinase. Two patients were diagnosed to have idiopathic hyperCKemia, four had neurogenic disorders and two were normal. The statistical analyses concern the QEMG-biopsy correlations in the 31 patients with a clinical diagnosis of myopathy.

Sensitivity of QEMG

The sensitivity of QEMG analyses was evaluated against the biopsy findings and is shown in Table 2.

The highest sensitivity (68.9%) in detecting a myopathic biopsy was obtained using the amplitude outlier method (MUP amplitude of < 300μv). The sensitivity of the amplitude outlier method was superior to the duration outlier (p = 0.000) and mean duration methods (p = 0.007).

Sensitivity of QEMG in relation to MRC score

The QEMG data were re-examined according to the MRC score of the muscle in which the QEMG was performed (Table 3).

For MRC > 4 the amplitude outlier method was again significantly more sensitive than the duration outlier method (p = 0.002) and also significantly more sensitive than the mean duration method (p = 0.021). For MRC ≤ 4 there was no significant difference in sensitivity among the three methods.

Predictive values

The positive and negative predictive values for each of the three methods of analyses are shown in Table 4. All three methods of analyses have similar positive and negative predictive values.

Relationship of QEMG to biopsy findings

As can be seen in Table 5 for any given method of analysis there were no significant differences in the sensitivity in detecting the various (M1, M2, M3, M4) histological subdivisions (all p-values > 0.05 based on Chi-squared tests).

In the pure M4 category (the most subtle of the myopathic abnormalities), the amplitude outlier method was significantly more sensitive than the duration outlier (p = 0.000 and p = 0.000 respectively).

Table 2. Sensitivity of Q-EMG methods in detecting abnormal biopsies.

| Method                | Sensitivity |
|-----------------------|-------------|
| Classical Q-EMG       | 31.0%       |
| Amplitude outliers    | 68.9%       |
| Duration outliers     | 24.1%       |

Table 3. Sensitivity of Q-EMG methods according to MRC score.

| Method            | MRC > 4 | MRC ≤ 4 |
|-------------------|---------|---------|
| Sensitivity       | Sensitivity |
| (n = 29)          | (n=16)  | (n=13)  |
| Classical Q-EMG   | 18.7%   | 46.1%   |
| Amplitude outliers| 68.7%   | 69.2%   |
| Duration outliers | 6.2%    | 46.1%   |

Table 4. Predictive values of Q-EMG methods.

| Method            | PPV | NPV |
|-------------------|-----|-----|
| Classical Q-EMG   | 100%| 21% |
| Amplitude outliers| 95% | 33% |
| Duration outliers | 87.5%| 19% |

Positive predictive value; PPV Negative predictive value; NPV
Discussion

The primary aim of the study was to correlate QEMG and pathological findings in the biopsy of the contralateral muscle in patients with muscle disease. Although ideally the correlation should have been done in the same muscle this would not have been pragmatic since current practice is to perform the EMG on one side and do the biopsy on the contralateral muscle to avoid the risk of needle myopathy. We also examined the spectrum of histological abnormalities that are associated with abnormalities on QEMG.

We have found the amplitude outlier method to be the most sensitive in identifying myopathic abnormalities with a sensitivity of 69%. The positive predictive value of QEMG i.e. the likelihood of abnormal biopsy if the QEMG is abnormal is very high (87.5-100%). The number of patients with a normal biopsy is perhaps too small to perhaps give valid negative predictive values.

For the outlier methods of analyses we have arbitrarily used the cut of reference values from Oh which are the values we normally use for qualitative MUAP analysis (13). We are aware that the method we have used to extract MUAP introduces a bias towards low threshold motor units but we made a special effort to vary the window trigger to capture MUAP of various amplitudes as long as the rise time was < 500μsec. The latter requirement ensured that the needle was very close to the firing muscle fiber and the MUAP amplitude greatly influenced by the diameter of the closest fiber.

Although different absolute values for the outliers have been used, derived using the multi-MUAP extraction method other studies have also identified the amplitude outlier analysis as a sensitive method for myopathies. A recent study on facioscapulohumeral muscular dystrophy found that in the milder affected vastus lateralis the amplitude outlier method was 33% sensitive compared to a 10% of the duration outlier method (15). Similarly, in a smaller study of 8 patients with myopathies the amplitude outlier method was 75% sensitive compared to 25% and 37.5% of the duration outlier and mean duration methods (12).

This difference in sensitivity between the various QEMG methods in our study could perhaps be explained by the sequence of histological changes commonly seen in the biopsy of most slowly evolving myopathies. Initially there is increasing variability in fibres size due to round atrophy involving both fibre types (16). As the myopathy becomes more severe there is gradual loss of muscle fibres and replacement with endomysial connective tissue (17). In addition to fibre loss there may be compensatory increase in the diameter of surviving fibres (work hypertrophy) (16). Superimposed on the above changes there may be various amount of necrosis and regeneration.

The amplitude of the MUAP is determined by 5-12 fibres within a 0.5 mm radius of the recording needle tip, while MUAP duration is determined by the number of fibres within a 2.5 mm radius of the recording needle tip (18). As atrophic fibres begin to appear within the 0.5 mm radius of the recording tip this will cause a reduction in MUAP amplitude. As the myopathy progresses and there is random loss of fibres will there be shortening of the MUAP duration.

Our patients were mostly in the early stages of clinical involvement and only 6 out 31 patients exhibited fibre loss as evidenced by the presence of increased endomysial tissue (M3). This perhaps explains the higher sensitivity demonstrated by the amplitude outlier method.

There were no significant differences in detecting the various histological abnormalities (M1, M2, M3, and M4) for any one of the three QEMG methods. Since variability in fiber size (M1) was present in most of the biopsies one can speculate that this histological feature alone drives the sensitivity of each of the method of analysis. Our study is in keeping with the view that EMG can not be reliably correlated with specific features in the muscle biopsy. Previous studies examining QEMG and muscle biopsy have documented a correlation only between long duration motor unit potential and regenerating fibers (9, 10).

No formal morphometry on the biopsies was carried out in our study, such as deriving atrophy or hypertro-

Table 5. Sensitivity of various Q-EMG criteria according to biopsy findings.

| Myopathic findings in muscle biopsy (n = 29) | Sensitivity |
|---------------------------------------------|-------------|
| Classical Q-EMG                            |             |
| All (n = 29)                                | 31.0%       |
| M1 (n = 23)                                | 39.1%       |
| M2 (n = 7)                                 | 28.6%       |
| M3 (n = 6)                                 | 33.3%       |
| M4 (n = 9)                                 | 22.2%       |
| M4 without M1 (n = 5)                      | 0%          |
| Amplitude outliers                          |             |
| All (n = 29)                                | 68.9%       |
| M1 (n = 23)                                | 69.5%       |
| M2 (n = 7)                                 | 71.4%       |
| M3 (n = 6)                                 | 50%         |
| M4 (n = 9)                                 | 77.7%       |
| M4 without M1 (n = 5)                      | 80%         |
| Duration outliers                           |             |
| All (n = 29)                                | 24.1%       |
| M1 (n = 23)                                | 30.4%       |
| M2 (n = 7)                                 | 14.3%       |
| M3 (n = 6)                                 | 33.3%       |
| M4 (n = 9)                                 | 11.1%       |
| M4 without M1 (n = 5)                      | 0%          |
phy factors, since this is not routinely practiced in our laboratory.

There are many other limitations to our study including its retrospective nature and the small numbers of patients. However it was based on material acquired on a pragmatic approach in the investigation of patients. The ideal study would have been prospective and should have included patients in which the QEMG and biopsy are performed sequentially in the same muscle. In addition in interpreting the findings of this study the sampling errors both of QEMG and that of the muscle biopsy need to be kept in mind.

In summary, based on our data, we conclude that the amplitude outlier method of analysis may be the most sensitive method in picking up myopathy at its very earliest stage.

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