

**PRACTICE PARAMETER FOR REPETITIVE NERVE STIMULATION AND SINGLE FIBER
EMG EVALUATION OF ADULTS WITH SUSPECTED MYASTHENIA GRAVIS OR
LAMBERT-EATON MYASTHENIC SYNDROME:
SUMMARY STATEMENT**

American Association of Electrodiagnostic Medicine

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Key words: Lambert-Eaton myasthenic syndrome; single fiber electromyography; myasthenia gravis; neuromuscular junction; repetitive nerve stimulation

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INTRODUCTION

Myasthenia gravis is an autoimmune disorder that affects approximately 3 out of 10,000 people. Myasthenia gravis affects the neuromuscular junction (NMJ) and produces weakness of voluntary muscles. In some cases, it may be associated with tumors of the thymus (a tissue of the immune system). It also may be associated with thyrotoxicosis, rheumatoid arthritis, systemic lupus erythematosus, and other immune system disorders. In many cases, no other disorder is identified. Myasthenia gravis (MG) is most common in adult women. The exception to this is when MG is associated with thymus tumor, which is most common in elderly men.

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disorder of neuromuscular transmission. Unlike MG, where the neurotransmitter (the chemical that transmits impulses) is blocked because of antibodies, LEMS is caused by an insufficient release of neurotransmitter by the nerve cell. The typical symptoms in LEMS are very similar to the generalized symptoms of MG but there are some important differences in disease progression. LEMS may initially be misdiagnosed as MG because of the similarities.

LEMS was first described in association with lung cancer. The true incidence of LEMS in the United States is unknown. It is estimated that approximately 3% of patients with small cell lung cancer are affected, or approximately 4 per 1 million people in the United States. This estimate does not consider the number of patients with LEMS who do not have small cell lung carcinoma or any identifiable malignancy. Unlike MG, which affects mostly women, LEMS primarily affects men over the age of 40.

Electrodiagnostic studies are used in the diagnosis of MG and LEMS. This article defines the standards, guidelines, and options for electrodiagnostic studies in these diseases.

LITERATURE REVIEW

A Medline search was conducted for literature in English retrospectively through July 1998, under the Medical Subject Headings (MeSH) (1) neuromuscular junction, (2) neuromuscular transmission, (3) myasthenia gravis, (4) Lambert-Eaton, (5) myasthenic, and (6) botulism with electromyography (EMG) or nerve conduction study (NCS). There were 545 articles identified, of which 13 articles met at least 3 of 6 criteria set previously by the American Association of Electrodiagnostic Medicine (AAEM). An additional 21 articles were identified from review articles or the references of these first 13 articles, leading to a total of 34 articles.

LITERATURE CLASSIFICATION CRITERIA

1. Prospective study.
2. Diagnosis in patient population based on clinical criteria independent of the electrodiagnostic procedure under evaluation.
3. Electrodiagnostic procedure described in sufficient detail to permit duplication of the procedure.
4. Limb temperature monitored.
5. Reference values for the electrodiagnostic test obtained with either (a) concomitant studies of a reference population or (b) previous studies of a reference population in the same laboratory.

6. Criteria for abnormal findings clearly stated and, if the measurement is a quantitative one, the criteria for an abnormal value defined in statistically computed terms (e.g., range or mean \pm 2 standard deviations) from data derived from the reference population.

DEFINITIONS FOR CLASSIFICATION OF EVIDENCE

1. Class A evidence: studies that meet all 6 literature classification criteria.
2. Class B evidence: studies that meet 4 or 5 literature classification criteria.
3. Class C evidence: studies that meet 3 or fewer literature classification criteria.

DEFINITIONS FOR PRACTICE RECOMMENDATION STRENGTHS

1. **Practice standards:** Generally accepted principles for patient management which reflect a high degree of clinical certainty (Class A evidence).
2. **Practice guidelines:** Recommendations for patient management that reflect moderate clinical certainty (Class B evidence).
3. **Practice options/advisories:** Other strategies for patient management for which the clinical utility is uncertain (Class C evidence).

PRACTICE RECOMMENDATIONS

The following recommendations are made regarding electrodiagnostic studies when laboratory confirmation of a NMJ disorder is desired.

The practice parameters are based on an extensive review of the scientific literature supporting the use of NCSs and needle EMG in the evaluation of NMJ disorders. The strength of a recommendation is based on the quality and consistency of supporting evidence as well as the magnitude of benefits, risks, and costs. Each recommendation is classified as a **Guideline** or **Option** according to the definitions provided above.

1. **Guideline:** Repetitive nerve stimulation (RNS) of a nerve supplying a symptomatic muscle should be performed. Abnormality in MG is considered to be a reproducible 10% decrement in amplitude when comparing the first stimulus to the fourth or fifth, which is found in at least 1 muscle. Abnormality in LEMS is considered to be a reproducible postexercise increase in amplitude of at least 100% as compared to preexercise baseline value.

The conditions recommended for RNS testing are as follows:

- a. Anticholinesterase medications withheld 12 h prior to testing, if this can be done safely.
- b. Immobilization of limb when possible.
- c. Frequency of stimulation between 2 to 5 Hz.
- d. Baseline and immediate postexercise or posttetanic 2 to 5 Hz nerve stimulation followed by stimulation at regular intervals of 30 s to 1 min, and continuing to 5 min.

e. Skin temperature over the recording site should be maintained as close to 35°C as possible.

2. **Guideline:** If RNS is normal and there is high suspicion for a NMJ disorder, single fiber EMG (SFEMG) of at least 1 symptomatic muscle should be performed. If SFEMG of 1 muscle is normal and clinical suspicion for a NMJ disorder is high, a second muscle should be studied.

The conditions recommended for SFEMG testing are as follows:

- a. Acceptable muscle fiber potential pairs must have an amplitude greater than 200 μ V and a rise time less than 300 μ s.
- b. Jitter is accurately calculated as mean consecutive difference (MCD) using the formula:

$$\text{MCD} = [\text{IPI}_1 - \text{IPI}_2] + \dots + [\text{IPI}_{n-1} - \text{IPI}_n]/n-1$$

where IPI is the interpotential interval.

- c. A study should be considered abnormal if greater than 10% of fiber potential pairs exceed normal jitter or have impulse blockade, and/or mean jitter exceeds normal limits.

3. **Option:** If the patient has very mild or solely ocular symptoms and it is believed the RNS will be normal, or if the discomfort associated with RNS prevents completion of RNS, SFEMG testing may be performed in place of RNS as the initial NMJ test. In laboratories with SFEMG capability, SFEMG may be performed as the initial test for disorders of neuromuscular transmission as it is more sensitive than RNS. Routine needle EMG and NCSs may be necessary to exclude disorders other than MG or LEMS.

RECOMMENDATIONS FOR FUTURE RESEARCH

It is recommended that future research evaluating electrodiagnostic studies in NMJ disorders be designed to:

1. Meet all 6 literature criteria recommended by the AAEM.
2. Report specific clinical criteria and severity used for the diagnosis of MG or LEMS.
3. Include calculation of sensitivity and specificity of the test results.
4. Use prospective study design rather than case series presentations in patients with presynaptic NMJ disorders.

RECOMMENDATIONS FOR FUTURE RESEARCH REGARDING SINGLE FIBER ELECTROMYOGRAPHY STUDIES

It is recommended that future research utilizing SFEMG studies be designed to:

1. Clearly state of whether jitter values of individual fiber pairs or mean jitter of all pairs is being reported.
2. Utilize prospective SFEMG studies of LEMS.

DISCLAIMER

This statement is provided as an educational service of the AAEM. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAEM recognizes that specific patient care decisions are the prerogative of the patient and his/her physician and are based on all of the circumstances involved.

**LITERATURE REVIEW OF THE USEFULNESS OF REPETITIVE NERVE STIMULATION
AND SINGLE FIBER EMG IN THE ELECTRODIAGNOSTIC EVALUATION OF PATIENTS
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ABSTRACT

A retrospective literature review of the electrodiagnosis of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) through July 1998 was performed for the purpose of generating evidence-

based practice parameters. There were 545 articles identified, of which 13 articles met at least 3 of the 6 criteria set previously by the American Association of Electrodiagnostic Medicine (AAEM). An additional 21 articles were identified from review articles or the references of these first 13 articles leading to a total of 34 articles. Results of studies utilizing repetitive nerve stimulation (RNS) showed that a 10% decrement in amplitude from the first to fourth or fifth intravolley waveform while stimulating at 2 - 5 Hz is valid for the diagnosis of MG. The degree of increment needed for the diagnosis of LEMS is at least 25% but most accurate when greater than 100%. Abnormal jitter or impulse blocking are the appropriate criteria for diagnosis of neuromuscular junction (NMJ) disorders when using single fiber electromyography (SFEMG). SFEMG is more sensitive than RNS for the diagnosis of disorders of neuromuscular transmission but may be less specific and may not be available. Therefore, RNS remains the preferred initial test for MG and LEMS.

OVERVIEW

The Quality Assurance (QA) Committee of the AAEM is charged to develop practice guidelines for the use of electrodiagnostic (EDX) studies for the evaluation and management of clinical problems.

REVIEW PROCESS

A literature review was performed using the following key words: neuromuscular junction, neuromuscular transmission, myasthenia gravis, Lambert-Eaton, myasthenic, and botulism with electromyography (EMG) or nerve conduction study (NCS). There were 545 references located. Of these reference sources, 13 articles were found to meet at least 3 of the 6 criteria defined by the AAEM QA Committee.¹⁴

The six literature classification criteria are:

1. Prospective study – A prospective study design permits uniformity and objectivity.
2. Diagnosis in patient population based on clinical criteria independent of the EDX procedure under evaluation. The diagnosis on myasthenia gravis or LEMS independent of EDX findings permits the identification of a patient population suitable for the evaluation of sensitivity and specificity of the EDX procedure.
3. EDX procedure described in sufficient detail to permit duplication of the procedure. A detailed description of the procedure or a reference to established techniques in the literature is necessary for validation of the study methodology and permits duplication of the procedure for subsequent use in the EDX laboratory.
4. Limb temperature monitored. It is important that limb temperature be monitored because sensory and motor nerve conduction are temperature dependent.
5. Reference values. Use of reference values in control subjects assists in the determination of whether patients have suspected MG or LEMS.
6. Criteria for abnormal findings. Use of standard statistical terms permits computation of the sensitivity and specificity of the EDX procedure and comparison of the procedure to other EDX and non EDX tests for MG or LEMS.

Bibliographies of the 13 articles were examined along with the review articles and an additional 21 articles were identified, bringing the total to 34 articles (Table 1).

REVIEW OF ELECTRODIAGNOSTIC LITERATURE

Repetitive Nerve Stimulation

Repetitive Nerve Stimulation in Nonspecified Neurologic Disorders

In 1941 Harvey and Masland¹² reported a method of repetitively stimulating the ulnar nerve supramaximally while recording at the abductor digiti quinti (ADQ) in order to determine the difference in response for 20 patients with various neurological abnormalities as compared to 10 healthy subjects. The article described the importance of immobilization. Measurements of compound motor action potential (CMAP) amplitudes were made during stimulation at 20 or 30 Hz.

Repetitive Nerve Stimulation in Myasthenia Gravis

Harvey and Masland¹³ also reported in 1941 RNS testing of the ulnar nerve recording from the ADQ in 3 patients with MG. They noted that at slower rates of stimulation (13 Hz) the amount of intravolley decrement was greater than at faster rates (60 Hz).

In 1952, Botelho and colleagues⁴ studied 21 patients with MG and 12 normal subjects. Diagnoses of the MG patients were based on clinical observations and reversibility of symptoms with neostigmine. Supramaximal stimuli were delivered at 3, 10, and 25 Hz with a stimulus duration of 0.5 ms or less and a 2 min rest period between volleys while recording at the ADQ, abductor pollicis brevis (APB), or orbicularis oculi. They were the first investigators to note that the greatest decrement occurred by approximately the fifth waveform. The baseline-to-peak amplitudes of the CMAPs were recorded. The 5:1 ratio was calculated to compare the amplitude of the fifth potential to the first. In normal subjects, the ratio was 1.01 at a stimulus rate of 3 Hz and 10 Hz, and 1.08 at 25 Hz. In patients with MG, the 5:1 ratio was 0.82 at a

stimulus rate of 3 Hz, 0.87 at 10 Hz, and 0.85 at 25 Hz. Twelve of 21 patients demonstrated significant decrement with stimulation at 3 Hz, and an additional 3 patients showed decrement with stimulation at 25 Hz. The investigators concluded that recordings should be made at low and high frequencies of stimulation to enhance accuracy.

In 1968, Slomic and colleagues²⁸ examined 30 healthy subjects and 23 MG patients. These investigators used stimulation frequencies of 2 to 50 Hz and measured volleys each 1 to 2 min after exercise. Patients with MG were given edrophonium intravenously 5 to 10 min before RNS. The ulnar nerve was stimulated at the wrist. Recordings were made from the hypothenar eminence. In normal subjects they found an increase in the muscle twitch force with higher rates of stimulation. This was found to be less with slower rates of stimulation. In MG patients, the peak-to-peak amplitude of the action potential decreased by 20% to 40% with 1 to 3 Hz trains. After full voluntary exercise, there was no difference between the first and last response in normal subjects, whereas in patients with severe MG it decreased by more than 40%, and in patients with moderate MG it decreased 20% to 30%.

In 1971, Odzemir and Young²¹ compared 30 patients with MG to 30 normal subjects. CMAPs were recorded from the abductor digiti minimi, flexor carpi radialis, and deltoid muscles. Stimulation rates ranged from 1 to 25 Hz. The postexercise stimulation rates used were 3, 5, and 8 Hz. Testing was repeated every 30 s for 5 min. Decremental response was noted in only 2 normal subjects and was always less than 10%. In 28 of 30 normal subjects increment was noted. The investigators concluded that a greater than 10% decrement should be defined as abnormal with this technique. Twenty-six out of 30 MG patients met this criteria for abnormality in at least 1 muscle. The deltoid muscle had the highest incidence of abnormality (76%). It was also found that the maximum decrement occurred by the fourth or fifth stimulus. They further noted that increment occurred with faster rates; therefore, slower rates were recommended. Testing after exercise was also recommended to increase the percentage of positive results.

Mayer and Williams¹⁸ confirmed in 1974 that a 10% decrement was abnormal and supported the diagnosis of MG. They stimulated the median nerve and recorded potentials from the APB. After examining responses at 3 and 50 Hz, they concluded that 3 Hz should be the standard stimulation frequency. In 1977, Desmedt and Borenstein⁵ confirmed observations made by others previously and combined the RNS test of the ulnar nerve with ischemia creating the double-step nerve stimulation test. The muscles they recorded from were the ADQ, flexor carpi ulnaris (FCU), adductor pollicis, and first dorsal interosseus (FDI). The first step involved supramaximal stimulation at 3 Hz for 4 min. The second step was the same protocol under ischemia. They considered a decrement of greater than 10% abnormal in the ulnar muscle of women and a decrement of greater than 25% abnormal in men. This was due to the occasional appearance of 23% decrement in muscles of normal male subjects. This test was reported to increase the diagnostic yield in patients with ocular MG.

In 1974, Borenstein and Desmedt³ examined the effect of temperature on 30 patients with MG. They cited the example of a patient with an 11% percent decrement of the adductor pollicis muscle using 3 Hz RNS at 31°C. The decrement increased to 44% at 36°C. When they performed RNS of the ADQ at 31°C, there was a 10% decrement in amplitude. The decrement increased to a 64% decrement when warmed to 36°C. The opposite effect occurred with cooling. At 34.2°C, RNS of the facial nerve demonstrated a decrement of 25%. It decreased to normal limits (4%) when cooled by 5°C to 29.2°C. In 1975, Borenstein and Desmedt² then examined the effect of local cooling in MG on RNS. They found that a reduction of the intramuscular temperature from 35°C to 28°C increased the CMAP size of the ADQ, twitch force, and tetany force at 10 and 20 Hz. They suggested that false negatives in RNS testing of MG may be due to insufficient warming of muscles.

In 1977, Ricker and colleagues²² also examined the effect of local cooling in 28 patients with MG. It was found that the amplitude of the adductor pollicis motor action potential increased in size at lower

intramuscular temperatures. The ulnar nerve was stimulated at 3 Hz for 2 s, then 50 Hz for 1.5 s. With mild cooling, there was an increase in tetanic force. With severe intramuscular cooling to 18°C to 22°C, the tetanic force was lower.

Krarup¹⁶ compared RNS in a proximal muscle (platysma) to a distal muscle (adductor pollicis) in 24 patients with MG. He found that the decrement in the platysma with RNS was 2 to 3 times greater than in the adductor pollicis. In addition, 6 of the patients showed abnormality only in the platysma, and 10 displayed more decrement in the platysma than the adductor pollicis.

In 1982, Oh and colleagues¹⁹ noted that anticholinesterase medications should be withheld for at least 12 h before testing. A clear distinction was seen in sensitivity of RNS between ocular and generalized MG. RNS was abnormal in only 17% of ocular MG but was abnormal in 85% of generalized MG, a pattern also seen by Botelho and colleagues⁴ and Slomic and colleagues.²⁸ Oh and colleagues also noted that when stimulating the ulnar nerve at 5 Hz an incremental response of up to 42% could be seen in MG and therefore was not specific for LEMS. Oh and colleagues²⁰ later performed RNS of the ADQ, FCU, orbicularis oculi, trapezius, and deltoid muscles, SFEMG of the extensor digitorum communis (EDC), and acetylcholine antibody (ACh Ab) testing on 120 patients. They found SFEMG was the most sensitive test for detecting MG at 92%, with RNS at 77%, and ACh Ab at 73%. Both SFEMG and RNS became more sensitive with increasing severity of MG.

In 1987, Gilchrist and Sanders¹⁰ compared 10 normal subjects with 10 patients who had symptoms of MG. The double-step stimulation technique of the ulnar nerve was compared to RNS of a proximal muscle or SFEMG of the ADQ. The 10 patients were selected because they had normal RNS of the ADQ. Temperature was maintained at 35°C or greater. A 3 Hz train of 10 stimuli was delivered to the ulnar nerve while recording from the ADQ. Four minutes of stimuli at 3 Hz was then given, followed by further train

recordings at 0.5, 1, 2, 3, and 5 min. This was repeated using a sphygmomanometer on the arm inflated to 50 mm Hg above systolic. A 10% decrement was accepted as the upper limit of normal, and 60 μ s was the upper limit of normal jitter. They found that double-step ulnar RNS and RNS in a proximal muscle (trapezius) were comparable in sensitivity; that is both were substantially better than RNS of a distal muscle but only 60% as sensitive as SFEMG.

Repetitive Nerve Stimulation in Lambert-Eaton Myasthenic Syndrome

Lambert and Elmqvist described their work over 10 years involving case reports of patients with LEMS.¹⁷ In this study, they examined 12 patients with LEMS. Four had small cell carcinoma of the lung. They studied biopsies of intercostal muscles in vitro and found defects in neuromuscular transmission, including a normal miniature end plate potential (MEPP) size and decreased end plate potential (EPP) amplitude. This was in contrast to MG, which displayed a decrease in MEPP and EPP amplitude. RNS in vitro demonstrated increased EPP amplitude at fast stimulation rates (40 Hz).

Mayer and Williams¹⁸ studied 22 patients with MG. They performed RNS of the median nerve at 3, 10, 30, 40, and 50 Hz. They observed that while all the patients demonstrated the characteristic decrementing response of greater than 10% in amplitude, 8 patients occasionally demonstrated incrementing responses. This incremental response was most easily observed at 10 Hz stimulation rates. In comparison to a case series described by Eaton and Lambert,⁶ they noted the incremental responses in LEMS were usually greater than those recorded in MG, but did not specify exact percentages for each disease.

Kennett and Fawcett¹⁵ examined 61 patients with neuromuscular transmission problems and 22 normal subjects using RNS of the anconeus muscle. Decrement was defined as reduction in the peak-to-peak amplitude of the fifth response to the first, stimulating at 3 Hz. LEMS was diagnosed in 4 patients by postactivation potentiation of greater than 25%.

In 1994, Tim and Sanders³² compared RNS in the ADQ or APB muscle of 25 patients with LEMS, 18 patients with MG, and 22 healthy subjects. The conditions for testing were as follows: temperature of 35°C, 3 Hz stimulation, a 9 stimulus train, and 10 to 15 s of maximum contraction for the LEMS patients or 30 s of exercise for the MG patients and the healthy subjects. Only patients with LEMS had increments greater than 100% (13 of 16), but patients with MG could show increments as high as 92%. This study found voluntary contraction to be preferable to 20 Hz RNS in LEMS. Measuring change in CMAP area was found to provide no better information than measuring the change in amplitude, and the lack of abnormal increment in a single hand muscle did not exclude LEMS.

In 1998, Tim and colleagues³² prospectively examined 59 patients with LEMS with 3 Hz RNS of the APB, ADQ, and extensor digitorum brevis (EDB). The study found 98% of the patients had a decrement with 3 Hz stimulation, 88% had CMAP potentiation greater than 100% in at least 1 muscle, but only 39% had potentiation greater than 100% in all 3 muscles. Specifically, they found the APB muscle had a low CMAP amplitude 86% of the time, abnormal decrement 98% of the time, and postmaximum voluntary contraction potentiation of greater than 100% occurring 63% of the time. For the ADQ, the percentages were 94%, 98%, and 78% for the same measures, respectively. The EDB displayed low CMAP amplitude in 80%, abnormal decrement in 82%, and postmaximum voluntary contraction potentiation of greater than 100% in 59%. They also tested the trapezius muscle which showed 62%, 90%, and 24% of patients with abnormalities of the same measures, respectively. These investigators noted that 12% of LEMS patients had no muscles with increment greater than 100%, and that the diagnosis of LEMS should be based on clinical criteria and voltage-gated calcium channel antibody levels as well as CMAP potentiation.

In summary, all studies recommended basing results of RNS testing on measurements of CMAP amplitude. Some studies measured baseline-to-peak amplitude, whereas others measured peak-to-peak amplitude. It should be noted that the technology for measuring CMAP area may not have been in existence when many

of the studies were performed. There was general acceptance of the 10% decrement requirement for diagnosis of MG. There was no agreement on the minimum degree of increment needed for making the diagnosis of LEMS, but it was evident that 100% increment or greater was specific for LEMS. The frequency of stimulation varied from 2 to 50 Hz; however, a rate of 2 to 5 Hz was recommended for volleys that evaluate decrement. Exercise, fast rates of stimulation, or slow rates of stimulation sustained over minutes were used to fatigue muscles and to observe incremental responses. The percentage of change from the first response compared to the fourth or fifth was generally regarded as the point from which decrement was measured. In many studies, however, more than 5 stimuli were given within each volley. The longer trains were usually performed to demonstrate whether the volley followed a characteristic “u-shape” of decrement and partial recovery. Postexercise volleys were spaced 30 s to 2 min apart.

Single Fiber Electromyography

Single Fiber Electromyography in Healthy Subjects

In 1964 Ekstedt⁷ described a new method to record single muscle fiber action potentials. The original SFEMG needle had 14 openings and was called a “multielectrode.” Ekstedt defined the criteria for single muscle fiber recordings. The waves should be smooth, biphasic in shape, and identical for consecutive action potentials. He also noted that “variations were seen as an apparent movement of a part of the display in a restless, nervous manner; hence called the jitter phenomenon.” Jitter can be described as the variation in time between consecutive electrical discharges.

Stålberg²⁹ used the multielectrode developed by Ekstedt and measured propagation time of the potential. He also performed stimulation SFEMG in animal models and made initial calculations of jitter. He noted that temperature changed propagation velocity. He also found that velocities were different for different muscles. Finally, he noted a low propagation velocity in a patient with disuse atrophy.

In 1971 Stålberg and colleagues³⁰ described measurements of EMG jitter in normal muscles, based on the earlier work of Stålberg²⁹ and Ekstedt.⁷ The EDC, biceps brachii (BB), tibialis anterior (TA), and frontalis muscles were tested. Twenty-seven healthy subjects were examined. The intramuscular temperature was maintained at 35°C. A decrease of the intramuscular temperature caused an increase in jitter by 1 to 3 $\mu\text{s}/^\circ\text{C}$. Several methods are now available to calculate jitter. None of them have been compared in a study that met the criteria for selection defined in this study. The method of choice (and the method incorporated in essentially all electrodiagnostic machines) is the mean consecutive difference (MCD) as described by Stålberg.²⁹ The upper limits of normal mean jitter in various muscles as measured by MCD was 15.7 ± 5.5 μs (BB) to 31.5 μs (TA). They considered the study abnormal if: (1) the jitter in any fiber pair had a MCD greater than 55 μs ; or (2) greater than 10% of fiber pairs were blocked. For this reason, many investigations have used 55 μs as the upper limit of normal jitter. This is the limit for some, but not all muscles (see later).

In 1986, Trontelj and colleagues³⁴ compared SFEMG to stimulated SFEMG in 15 healthy subjects. The advantages of stimulated SFEMG included avoidance of interdischarge interval dependent jitter and possible failure to recognize split muscle fibers, as well as reliable activation. The disadvantages of stimulated SFEMG were potential misinterpretation from subliminal stimulation and underestimation of jitter secondary to direct muscle fiber stimulation.

Trontelj and colleagues³³ also studied stimulated SFEMG of the orbicularis oculi muscle in 19 healthy subjects. They found the upper limit of normal MCD was 30 μs . Trontelj and Stålberg³⁵ then studied 9 healthy adults to determine the magnitude of artifactual jitter due to inadequate stimulus strength in stimulated SFEMG. There was a 5 - μs (range 0 to 13 μs) increase in jitter as the stimulus level decreased to a liminal (perceptible) threshold.

Gilchrist and colleagues⁸ collected retrospective and prospective SFEMG reference values from multiple centers. Criteria for acceptable potential pairs were: (1) amplitude greater than 200 μ V; and (2) rise time less than 300 μ s. At least 20 pairs were requested from control subjects, but only 5 out of 20 pairs were acceptable. Jitter was considered abnormal if 2 of 20 pairs exceeded the normal value for that muscle or if mean MCD (mean jitter) exceeded the ninety-fifth percentile. Graphs depicting 95% upper normal limits of mean MCD or jitter for a given age were plotted for individual muscles. Muscles tested included soleus, biceps, deltoid, frontalis, EDC, TA, quadriceps, and orbicularis oculi.

Grana and colleagues¹¹ found muscle disuse after 1 month of immobilization in a leg cast to be sufficient to increase jitter in healthy subjects. They performed SFEMG of the soleus muscle measuring the mean MCD. This suggested the SFEMG test was very sensitive and could lead to false positives in the diagnosis of NMJ disorders.

Single Fiber Electromyography in Myasthenia Gravis

In 1971, Blom and Ringqvist¹ examined 12 patients with MG and 8 healthy subjects. Anticholinesterase medications were withheld 12 h prior to examination. Normal jitter was considered less than 203 μ s in the ADM muscle. In patients with MG, jitter ranged from 160 to 940 μ s. After administration of anticholinesterase medication, jitter and blocking improved in 4 patients with MG.

In 1975, Schwartz and Stålberg²⁷ performed both supramaximal surface RNS testing with SFEMG in 8 patients with MG and 4 control subjects. They found patients with MG had impulse blocking and facilitation at 2 Hz stimulation that was not present in control subjects. This technique is rarely used.

Sanders and colleagues²⁵ studied 127 patients with MG in 1979, performing SFEMG in the EDC muscle. They found the most sensitive criterion of abnormality of neuromuscular transmission was abnormal jitter.

In 1986, Sanders and Howard²⁴ found abnormal jitter in 85% of patients with MG if 1 muscle was studied (usually the EDC), and in 99% of patients if a second muscle (usually the frontalis) was studied when the first was normal. SFEMG was considered abnormal if the mean jitter exceeded the upper limit of mean for a given muscle (34 μ s for the EDC), or 10% or more of the pairs had jitter that exceeded the upper limit of normal in that muscle (55 μ s for EDC).

In 1990, Trontelj and Stålberg³⁵ studied jitter and blocking using stimulated SFEMG in the EDC muscle of 10 patients with MG. They found there was a variable response to change in stimulation rates. Some of the patients had worsening abnormalities at high stimulation rates (15 and 20 Hz) where as others demonstrated less jitter and blocking. This was in contrast to the response they found in the patient they studied with LEMS (discussed later).

In 1992, Oh and colleagues²⁰, examined the diagnostic sensitivity of the laboratory tests in MG. The results are discussed previously in the subsection on RNS.

Gilchrist and colleagues⁹ performed SFEMG and RNS of the same muscle in 46 patients with MG. The muscles tested were the ADM, BB, deltoid, and trapezius. They concluded SFEMG was more sensitive in detecting neuromuscular transmission problems than RNS. Decrement on RNS was never seen unless blocking was evident on SFEMG of the same muscle.

In 1995, Rivero and colleagues²³ performed SFEMG in 17 patients with pure ocular MG and 9 healthy subjects. They studied the superior rectus, levator palpebrae, and orbicularis oculi muscles. They found that all the patients had abnormal SFEMG when testing the superior rectus and levator palpebrae muscles as compared to 62% with abnormality in the orbicularis oculi.

Single Fiber Electromyography in Lambert-Eaton Myasthenic Syndrome

In 1990, Trontelj and Stålberg³⁵ studied jitter and blocking in a patient with LEMS using stimulated SFEMG in the EDC muscle. Both jitter and blocking were found. Increasing the stimulation rate from 2 to 15 Hz decreased jitter and blocking in LEMS.

Sanders and Stålberg²⁶ noted that jitter was increased out of proportion to the severity of weakness in patients with LEMS, and there was frequent impulse blocking. Like Trontelj and Stålberg, they also noted an inverse relationship between firing rate compared to jitter and blocking. They were careful to note this pattern was not pathognomonic for LEMS, however, and it is sometimes observed in patients with MG as well.

In summary, jitter was the most sensitive EDX component in the diagnosis of NMJ disorders. Jitter between paired single muscle fiber potentials of greater than 55 μ s in the EDC muscle was considered abnormal, and it was recommended that the exact values for a given muscle and the age of the patient be taken into account.⁸ If more than 10% of pairs in the tested muscle were found to have increased jitter or blocking, this was considered abnormal. In 2 comparative studies, SFEMG was more sensitive than RNS in diagnosing NMJ disorders. Because SFEMG requires special training and is more likely to demonstrate abnormalities in NMJ disorders other than MG, 1 article recommended that SFEMG be used only when RNS was negative²⁰ or when symptoms were mild and/or limited to ocular findings. In laboratories with SFEMG capability, it may be the preferred test for MG and LEMS as it is more sensitive. Routine EDX studies may be necessary to exclude other disorders such as amyotrophic lateral sclerosis (ALS), axonal neuropathies, or myopathies, which have been associated with decrements on RNS and increased jitter on SFEMG.

Needle Electromyography

Amplitude variability of single motor unit potentials has been well described by Lambert.⁶ Only 1 of the articles that met the criteria for this review mentions variation in motor unit potential size.¹³ Harvey and Masland described the variation in size of the response to be from intermittent blocking of transmission of the nerve impulse across the NMJ.

RESULTS

A total of 34 articles met at least 3 of the 6 literature classification criteria defined by the AAEM.

Repetitive Nerve Stimulation

Twelve of 15 articles mentioned specifically comparing the baseline-to-peak or peak-to-peak amplitude of the first potential to the fourth or fifth waveform within each volley. Two studies discussed measurement of area.^{10,30} Postexercise volleys were measured every 30 s to 2 min in 7 papers. The degree of decrement with a stimulation rate of 2 to 5 Hz was considered significant at 10% in 5 studies. The percent increment considered abnormal in LEMS was 25% or 42% in 2 papers.^{15,19} Due to the fact that up to 92% increment can be seen in MG, 100% increment is considered diagnostic.³¹ The frequency of stimulation for detecting decrement was recommended to be 2 to 5 Hz in 13 publications. High frequencies of stimulation ranging from 10 to 50 Hz were used in 9 studies. Isometric muscle contraction exercise was recommended for activation instead of high frequency stimulation in 3 publications.

Immobilization of the involved limb was specifically mentioned in only 2 studies.^{12,31} Repeating studies for reproducibility was mentioned in 2 studies.^{4,18} Temperature recordings were noted in 9 studies. Withholding anticholinesterase medications was mentioned in 4 studies.^{2,16,19,22} Twelve hours was

recommended as the length of time to withhold the medications.^{16,19} One study did withhold medications from 4 to 18 h.^{16,22}

For LEMS, it was suggested that a screening test be performed to determine if RNS or SFEMG is needed. This involved recording and comparing a single pre- and postexercise supramaximal CMAP for differences in amplitude. If there was any increase in amplitude postexercise, NMJ testing was performed.³¹ For MG, it was suggested that a distal hand muscle be tested first, followed by the trapezius, then facial RNS.²⁰ If the facial RNS was intolerable or normal, SFEMG should be considered.¹⁹ If the patient had only ocular signs and symptoms, one could consider SFEMG first.

The sensitivity of RNS for diagnosing MG ranged from 53% (in anconeus muscle only) to 100% for RNS in generalized MG,⁴ and 60% for double-step RNS (in the ADQ). The sensitivity in ocular myasthenia was lower at 10% to 17%. The sensitivity of RNS for diagnosing LEMS was 98%. The specificity of this test was not discussed.

Single Fiber Electromyography

Jitter was used as the criterion to demonstrate abnormal neuromuscular transmission in all articles. If greater than 10% of pairs in a muscle had increased jitter this was considered abnormal in 3 publications.^{8,11,24} The percentage of blocking considered abnormal was 10% in 2 studies.^{8,9} The average MCD abnormality was considered to be greater than 55 μ s in the EDC in 3 studies, but specific muscles varied slightly.⁸

The suggested muscles to be tested was the EDC if the subject had weakness in oropharyngeal or limb muscles. If the EDC was normal, the frontalis often was tested next, followed by the orbicularis oculi.²⁶ It is important to note that muscle selection should be tailored to the clinical symptoms of the patient. This is

because a normal jitter study in a weak muscle virtually excludes a defect in neuromuscular transmission, whereas a normal study in an asymptomatic muscle neither refutes nor confirms the presence of a defect in neuromuscular transmission.

The sensitivity of SFEMG for diagnosing MG ranged from 82% to 99% in 3 studies with the highest sensitivity when 2 muscles were tested if the first was normal.^{10,20,24,25} A fourth study described 62% sensitivity in the orbicularis oculi muscle compared to 100% when using the superior rectus or levator palpebrae muscles.²² The specificity of the test was not well described.

Needle Electromyography

As discussed earlier, only 1 article meeting the AAEM criteria mentioned motor unit amplitude variability.¹³ None of the remaining selected articles studied this aspect specifically or prospectively. There is no mention of when standard needle EMG should be used in the evaluation of patients with suspected NMJ disorders in these articles with regard to: (1) assistance in deciding whether RNS or SFEMG should be performed; (2) performing it before all RNS/SFEMG testing to screen out other diseases; or (3) determining the degree of motor unit amplitude variability needed to suggest a NMJ disorder. Use of needle EMG has been discussed at length in book chapters and textbooks, and standard needle EMG is recommended to screen out other diseases that could lead to false positive results.

CONCLUSIONS

This literature review has provided scientific evidence that RNS and SFEMG are valid clinical laboratory studies for confirming a clinical diagnosis of MG or LEMS.

SUMMARY OF HARMS, BENEFITS, AND COSTS OF INTERVENTIONS CONSIDERED

The risks of electrodiagnostic testing to the patient include transient discomfort, bruise, hematoma, and infection from the needle insertion required to perform both single fiber and needle EMG. The risks of EMG to the EDX consultant include inadvertent needle puncture of the consultant by the needle used to evaluate the patient and subsequent infection by hepatitis, human immunodeficiency virus (HIV), or other communicable disease. The risks of RNS include transient discomfort and accidental electric shock. The latter is avoided by excluding patients with pacemakers and central lines, as well as avoiding electrical storms and placing dual ground electrodes on the patient. This study has not undertaken a systematic evaluation of the benefits, harms, and costs of electrodiagnostic testing. Such an evaluation would require an outcome study: the present review of the literature did not identify such a study.

DISCLAIMER

This statement is provided as an educational service of the AAEM. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAEM recognizes that specific patient care decisions are the prerogative of the patient and his/her physician and are based on all of the circumstances involved.

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Table 1. Literature classification of electrodiagnostic studies*6 of 6 literature classification criteria met*Gilchrist and Sanders¹⁰*5 of 6 literature classification criteria met*Desmedt and Borenstein⁵Gilchrist and colleagues⁸Gilchrist, Massey, and Sanders⁹Grana, Chiou-Tan, and Jaweed¹¹Kennett and Fawcett¹⁵Oh and colleagues¹⁹Oh and colleagues²⁰Sanders, Howard, and Johns²⁵Slomic, Rosenfalck, and Buchthal²⁸Stålberg, Ekstedt, and Broman³⁰Tim, Massey, and Sanders³¹Tim and Sanders³²*4 of 6 literature classification criteria met*Blom and Rinqvist¹Borenstein and Desmedt²Botelho and colleagues⁴Harvey and Masland¹²

Harvey and Masland¹³

Mayer and Williams¹⁸

Ozdemir and Young²¹

Ricker, Hertel, and Stodieck²²

Rivero and colleagues²³

Sanders and Howard²⁴

Sanders and Stålberg²⁶

Schwartz and Stålberg²⁷

3 of 6 literature classification criteria met

Borenstein and Desmedt³

Ekstedt⁷

Krarup¹⁶

Lambert and Elmquist¹⁷

Stålberg²⁹

Trontelj, Khuriabet, and Mihelin³³

Trontelj and colleagues³⁴

Trontelj and Stålberg³⁵

Trontelj and colleagues³⁶

This guideline is greater than 5 years old. Every five years, an interim literature search is performed and the guideline reviewed. While new studies have been published since this guideline was last reviewed, the Practice Issue Review Panel Committee of the AANEM has determined that these studies are not sufficient to mandate a revision of this guideline at the present time. The information contained in this guideline and the recommendations offered are still relevant to current practice.

Reaffirmation approved by the Practice Issue Review Panel: October, 2015.