Electrodiagnosis of Disorders of Neuromuscular Transmission

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KEYWORDS
- Neuromuscular transmission • Myasthenia gravis • Lambert-Eaton syndrome
- MuSK • Repetitive nerve stimulation • Single fiber EMG • EMG • RNS

KEY POINTS
- Conventional needle electrode electromyographic (EMG) examinations are necessary in patients suspected of having myasthenia gravis (MG) to exclude diseases that may mimic or coexist with MG such as peripheral neuropathy and inflammatory or ocular myopathies.
- The lack of attention to temperature requirements in repetitive nerve stimulation testing is the most common error made, rendering the study unhelpful. This is most important when considering presynaptic disorders of neuromuscular transmission.
- There is no one muscle that will be more abnormal in every patient with MG in single-fiber EMG. The muscle(s) to be tested must be selected based on the distribution of weakness in the individual patient.
- Single-fiber EMG provides the most useful information particularly when repetitive nerve stimulation studies are normal and is most always abnormal when there is careful selection of involved muscles including those of the paraspinal region.
- Normal jitter in a clinically weak muscle indicates the weakness is not caused by an abnormality of neuromuscular transmission.

INTRODUCTION

The roles of electrodiagnosis in disorders of neuromuscular transmission are to confirm or reject one’s clinical impression regarding the presence or absence of a disorder of neuromuscular transmission (NMT), to determine whether the disorder is either presynaptic or postsynaptic, to exclude other coexisting neuromuscular disorders, and to monitor the disease course in response to its natural history or to treatment.

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Careful clinical and electrodiagnostic evaluation and sometimes genetic, morphologic, and in vitro microphysiologic studies are necessary to achieve an accurate diagnosis. The electrodiagnostic approach is similar to that of any neuromuscular disorder.

The basis of the clinical electrodiagnostic abnormalities in patients with disorders of NMT (eg, myasthenia gravis [MG], Lambert-Eaton syndrome [LES]) is the failure of the muscle fiber to depolarize sufficiently for the end-plate potential (EPP) to reach action potential (AP) threshold (Fig. 1). The resulting impulse blocking accounts for the decremental responses seen on repetitive nerve stimulation (RNS) studies and the impulse blocking seen with single-fiber electromyography (SFEMG). In addition, the time variability of when the EPP reaches AP threshold accounts for the neuromuscular jitter seen in the latter technique. This article will review those electrodiagnostic techniques that are commonly used today and will highlight their specificity, sensitivity, and pitfalls.

**NERVE CONDUCTION STUDIES**

Standard neurographic studies should be performed on all patients suspected of having disease of the neuromuscular junction (NMJ). Conduction velocities, distal latencies, and late responses are typically normal in these patients. Compound muscle AP (CMAP) amplitude or negative peak area to a single stimulus will be

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**Fig. 1.** Sequential raster display of 9 intracellularly recorded APs from an intercostal muscle biopsy specimen from a patient with MG demonstrating neuromuscular jitter and impulse blocking. Note the variation in rise-to-peak of the EPP and the relationship to neuromuscular jitter (short arrows). Impulse blocking occurs (traces 3 and 4, long arrow) when the EPP fails to reach critical threshold to generate an AP. (Copyright JF Howard Jr.)
preserved in postsynaptic disorders (unless the disease is very severe) and typically will be reduced in presynaptic disorders (eg, LES and botulism).

In some congenital myasthenic syndromes, such as the slow channel syndrome and congenital end-plate cholinesterase deficiency, and after exposure to drugs or toxins that inhibit acetylcholinesterase, a single nerve stimulation will evoke more than 1 CMAP response. In this situation, the EPP is abnormally prolonged and remains higher than the AP threshold through the refractory period of the AP. In this situation, each consecutive response is smaller than the previous one and disappears once the EPP amplitude decreases to less than the AP threshold.

**NEEDLE EMG**

Conventional needle electrode EMG examinations are performed in patients suspected of having MG and other disorders of synaptic transmission to exclude diseases that may mimic or coexist with MG (and LES), such as peripheral neuropathy and inflammatory or ocular myopathies. In the absence of other neuromuscular disorders, the EMG examination will demonstrate, in both presynaptic and postsynaptic disorders of NMT, motor unit action potentials (MUAPs) that vary in configuration with consecutive discharges (Fig. 2). This pattern results from intermittent failure of synaptic transmission (impulse blocking) of some of the muscle fibers that comprise the MUAP and is most easily recognized as a variation in amplitude of an isolated MUAP if a slow oscilloscope sweep speed is used. This abnormality may be partially or completely reversed in patients with MG by the administration of edrophonium. This finding may be confused with the abnormality seen in reinnervation in which motor unit instability occurs as a result of immature NMJs. However, patients with reinnervation will have large, prolonged MUAPs. In LES and, to a lesser extent, in botulism, one may see a progressive increase in the EMG envelope amplitude during sustained contraction, as a result of the facilitated release of acetylcholine (ACh) from the nerve terminal.

In rare situations, usually in patients with acute and severe MG, one may find fibrillation potentials, especially in the paraspinal muscles. They may also be seen in patients with severe LES, botulism, and congenital myasthenic syndromes caused by plectin deficiency. Their presence, however, should suggest to the electromyographer that there may be an associated disfigurative process. The interference pattern in patients with MG is typically full, although with sustained contraction one may see a reduction in the envelope amplitude as the muscle fatigues and impulse blocking occurs.

Needle EMG is most important in suspected cases of MG associated with antibodies to muscle-specific protein kinase (MuSK), in which MUAP changes (both myopathic and neuropathic) will be recorded in clinically affected muscles, particularly

![Fig. 2. Concentric needle EMG recordings from the biceps brachii muscle of a patient with MG. Note the marked variation in MUAP amplitude with consecutive discharges caused by intermittent failure of NMT at end-plates within the motor unit. Calibration, 0.1 mV and 200 microseconds per division. (Copyright JF Howard Jr.)](image-url)
those with atrophy. Importantly, patients presenting with isolated neck extensor disease or respiratory failure may have normal electrodiagnostic studies in the limbs. It is therefore important that clinically affected muscles be examined to avoid missing the pertinent abnormalities of this disease.

RNS STUDIES

Repetitive motor nerve stimulation has application to a wide variety of clinical disorders that affect the NMJ and is the most frequently used electrodiagnostic test of NMT. Abnormal results from RNS studies are not diagnostic of specific clinical disorders, and abnormalities may be detected in patients with multiple sclerosis, motor neuron disease, peripheral neuropathy, radiculopathy, or primary muscle membrane disease, in addition to patients with primary disorders of the NMJ such as MG, LES, arthropod envenomation, botulism, congenital myasthenic syndromes, and impaired NMT caused by certain commonly used medications (eg, antibiotics) and toxins (eg, organophosphates).

General Principles

The technique of RNS is similar to that used in conventional neurographic studies, differing only in the application of stimuli trains or paired stimuli, the use of conditioning exercise, and the careful immobilization of the limb to reduce movement artifact (Table 1). The methodology of RNS studies consists of stimulating the peripheral nerve with a supramaximal stimulus (25%–50% greater than the maximum stimulation intensity necessary to activate all the nerve fibers) and recording the CMAP response with an active surface electrode (E1) over the belly of the muscle and a referential electrode (E2) over the tendon of the same muscle. The negative peak amplitude and area of the CMAP response are reflections of the numbers of muscle fibers activated by the nerve stimulus; hence, it is a marker of synaptic efficacy. It is important that measurements of amplitude and area are concordant; a discrepancy implies a technical

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Abbreviations: PAE, postactivation exhaustion; PAF, postactivation facilitation.

Table 1 Comparative features with RNS in presynaptic and postsynaptic disorders
problem. Negative peak area should not be used to assess facilitation as some authors have suggested, because there are many technical factors (eg, variable phase cancellation, repolarization, muscle fiber fatigue, and filter settings) that will impede quality recordings.21

Supramaximal stimulation must be used because failure to do so will result in a false-positive study because of pseudodecrement. Decrement is defined as the percent change comparing the negative peak amplitude or area between the fifth (or fourth or lowest potential) and the first potential. It can be calculated from the formula22–24:

\[
\% \text{Decrement}_n = \left[1 - \left(\frac{\text{Potential}_n}{\text{Potential}_1}\right)\right] \times 100\%
\]

Facilitatory responses are calculated by the formula:

\[
\% \text{Facilitation}_n = \left[\left(\frac{\text{Potential}_n}{\text{Potential}_1}\right) - 1\right] \times 100\%
\]

where \(n\) is the potential number to which the first potential is compared.

The criteria for abnormality will vary to some degree among laboratories.23 Most electromyographers will accept a decrement greater than 10% or a facilitatory response greater than 100% of the initial CMAP response, although the latter is now being reconsidered.25

**Muscle Selection**

Ideally, one would like to test muscles that are involved clinically, although this is sometimes difficult. Larger muscles are, as a group, more difficult to immobilize and therefore are subject to movement artifact from displacement of either the stimulating or recording electrodes. Smaller muscles, such as those in the hand, are easy to immobilize but often are not involved clinically and most often will not show an abnormality unless the muscle is quite weak. The heterogeneous literature of RNS testing precludes drawing specific estimates of sensitivity and specificity and the literature must be interpreted with caution. However, generalizations can be made that will assist the electromyographer in developing a diagnostic strategy.

The abductor digiti quinti muscle is easily examined and is easily immobilized. Studies in this muscle are well tolerated by patients. The abductor pollicis brevis muscle is more difficult to immobilize because of the large moment of movement caused by thenar contraction. Stimulation of deep nerves requires high stimulus intensity, which may be uncomfortable to the patient and not tolerated well. One can reduce the stimulus-induced discomfort by using monopolar needle stimulation electrodes (eg, musculocutaneous nerve stimulation with biceps brachii recording). These techniques often produce movement artifact when large muscles are examined. Stimulation of the brachial plexus will often elicit contraction of several muscles, inducing movement artifact into the recording. Selective stimulation of the accessory nerve with recording over the upper trapezius muscle is often well tolerated and easy to perform, requires low stimulus intensity, and is an excellent choice for a proximal muscle.14,26 This study may be performed with the patient either sitting or lying. Facial muscles (nasalis, orbicularis oculi) studies may tend to be uncomfortable for the patient but offer the advantage of a higher diagnostic yield for bulbar and perhaps ocular disease.27–30 Most investigators begin their evaluation using a distal hand muscle, even though a greater proportion of patients with MG will have abnormalities in proximal muscles, because it allows the patient to experience the procedure with relative comfort. It would be quite unusual to have an abnormality in a distal limb muscle with a normal study in a more proximal location.29

There is a paucity of evidence-based literature regarding the sensitivity and specificity of RNS testing in the diagnosis of MG. There are insufficient data to correlate
abnormalities of specific nerve–muscle combinations with the clinical severity of
disease or the number of nerve–muscle combinations necessary to examine to
achieve the highest diagnostic accuracy.\textsuperscript{27} In general, the specificity of RNS is very
high (~95\%) in both ocular MG and generalized MG, whereas the sensitivity of
RNS in ocular MG is less than 30\% and approaches 80\% in generalized MG when clin-
ically affected muscles are examined.\textsuperscript{27}

**Immobilization**

It is critically important to immobilize not only the muscle being examined but also the
electrodes used to stimulate the nerve. Muscle and electrode movement artifacts are
most often distinguishable by the abrupt change in waveform configuration during
a train of stimuli. Failure to immobilize the tested muscle may also result in a pseudo-
decremental response as a result of submaximal stimulation of the nerve.\textsuperscript{31} Slower
rates of stimulation are less likely to cause movement artifact because the muscle
will return to its relaxation state before the next contraction. Faster rates of stimulation
are more likely to produce movement artifact, primarily because the discomfort
causes the patient to contract the muscle. Tetanic stimulation, in addition to the
induced discomfort, may alter waveform configuration because of a change in the
volume conduction through the muscle produced by change in its shape. Commer-
cially made jigs to restrain movement may be quite useful, but in most instance proper
attention to limb position and fixation of the limb by the examiner will suffice for the
stimulation rates used in most laboratories. Often, the electromyographer only needs
to gently hold the hand in place when recording from hand muscles or, when recording
from the trapezius muscle, have the patient place their fingers under their hip when
supine or to touch the bottom of the chair when sitting.

**Temperature**

Increased temperature is known to aggravate the strength of patients with MG, and
control of intramuscular temperature is important in performing electrodiagnostic tests
of NMT.\textsuperscript{26,32} All patients undergoing RNS studies should have their extremities
warmed to at least 32°C in the leg and to 34°C in the arm. Shoulder and facial muscles
do not need warming in most situations. This may be accomplished by bathing the
limb to be studied in a warm bath or using a heating lamp or a thermostatically
controlled radiant warmer. Failure to warm the limb properly may result in a masking
of the decremental response in patients with disorders of NMT because temperature
changes of only a few degrees Celsius can reverse mild decrements (Fig. 3).\textsuperscript{33,34}
Presynaptic disorders may be misdiagnosed because the CMAP amplitude will be
large and a facilitatory response masked if the muscle is cool (Fig. 4). The mechanism
by which this occurs is not completely understood. Some authors postulate that it
results from an increase in EPP amplitude and prolongation of EPP duration presum-
ably as a result of alteration of the ionic channel conductance.\textsuperscript{34} Others suggest that
cooling potentiates NMT by enhancing transmitter packaging and presentation of
neurotransmitter to the release site of the nerve terminal, by reducing the hydrolysis
of ACh and by increasing ACh receptor sensitivity to ACh.\textsuperscript{35–37}

**Stimulation Rates**

Typically, stimulation rates of 1, 2, 3, or 5 Hz are used. Desmedt found that stimulation
rates between 3 Hz and 5 Hz are most likely to produce a decremental response in MG
because of the depression in quantal release of ACh with a train of stimuli.\textsuperscript{22} We and
others have not found a difference between 2-Hz and 3-Hz stimulation.\textsuperscript{38} Others think
that decremental responses may be missed with stimulation rates less than 7 Hz.\textsuperscript{39}
Stimulation rates in excess of 10 Hz frequently produce artifact and should be avoided except when high-frequency, short-duration stimulation is used to demonstrate the presence of a presynaptic disorder of NMT, such as LES. Excessively fast rates of stimulation or coexisting voluntary muscle contraction may produce an increase in CMAP amplitude with a reduction in the duration of the potential duration but no change in the negative peak area, a phenomenon termed pseudofacilitation. This results from an increase in the synchronization of the propagation velocity of the muscle fibers. In normal individuals, there is no change in the CMAP amplitude with slow rates of stimulation and one may see a minimal increase (pseudofacilitation) of the CMAP amplitude at stimulus rates of 5 Hz or greater. At faster stimulus rates (40–50/sec), there is a mild facilitation of the CMAP amplitude within the first 10 stimuli and then a constant response (Fig. 5). Paired supramaximal stimulations with varying interstimulus intervals have been used in the past to assess NMT. This technique is laborious and does not offer any advantages over RNS.

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**Fig. 3.** Effects of temperature on percent decrement in MG. The change in percent decrement in a patient with generalized MG as the intramuscular temperature is changed from 23°C to 27°C. The percent decrement increases with increasing temperature. (Copyright JF Howard Jr.)

**Fig. 4.** Temperature response in LES. The reduction in abductor digiti quinti CMAP amplitude (7–2 mV) in a patient with LES as the intramuscular temperature is increased from 24°C to 26°C. Normal amplitude is greater than 4.5 mV. An abnormal response is not seen until the intramuscular temperature is 32°C. (Copyright JF Howard Jr.)
Activation Techniques and Provocative Measures

The diagnostic yield of RNS may be increased through several activation techniques or other provocative measures. This is necessary because not all muscles will show the same degree of abnormality. However, these techniques are liable to artifact because many of them require limb movement, rapid rates of stimulation, or noxious procedures.

The most commonly used muscle activation procedure involves having the patient contract the muscle maximally for 10 to 60 seconds or by delivering a high-frequency train of stimuli. Such efforts produce an accumulation of calcium in the nerve terminal, which mobilizes the release of ACh. In a presynaptic disorder, this produces a marked increase in the CMAP amplitude. This phenomenon is termed postactivation facilitation or postexercise facilitation. Following maximum voluntary contraction or tetanic stimulation, there is a depression of end-plate excitability. This response is most often seen 2 to 4 minutes after exercise and is referred to as postactivation exhaustion or postexercise exhaustion. The electrophysiologic accompaniment of this phenomenon is a worsening of the decremental response compared with the preexercise values. In some individuals, particularly those with mild disease, an abnormal decrement may be seen only during the during the exhaustion stage.

Ischemia will enhance the neuromuscular block of presynaptic and postsynaptic disease. Harvey and Masland were the first to describe the effects of ischemia on NMT. The “double-step” RNS test involves prolonged stimulation of a muscle in the hand before and after ischemia of the limb and has been proposed to increase the sensitivity of RNS. In patients with MG, this test was found to be only slightly more sensitive than RNS of the trapezius muscle alone and only 60% as sensitive as SFEMG of a hand muscle. The mechanism that accounts for the worsening decrement is not completely understood. Investigators postulate that ischemia depletes acetyl-coenzyme A, resulting in a failure of ACh synthesis, a depression of vesicle packaging, or vesicular recycling. This technique is not in common use today given the increasing use of SFEMG.
Curare and similar neuromuscular blocking agents will impair synaptic transmission at the NMJ by producing a competitive, nondepolarizing neuromuscular block.\textsuperscript{45} It is our belief that the use of curare should not be used in the diagnosis of MG given the sensitivity of SFEMG. The reader is cautioned that if curare is to be administered to patients with suspected neuromuscular disease, it should be done in a setting where there is appropriate critical care and respiratory support.

**Quality Control in RNS Studies**

As with other electrophysiologic techniques, the issue of quality control is paramount. The electromyographer must be able to review the actual waveform obtained in each train of stimuli to ensure that each is similar to the other. Electrode movement, submaximal stimulation, and muscle contraction will produce unique changes in waveform configuration that may be mistaken for either a decremental or incremental response (Fig. 6). The review of only a stick diagram will not give clues as to any alteration in the waveform, and the sole use of these diagrams must not be relied on for accurate assessment of the study. Acceptable decrements, or increments, are characterized by similar or gradual changes in CMAP amplitude or area with the greatest change occurring between the first and second potentials (Fig. 7). Decrements should be reproducible on repeated testing after appropriate rest periods. The lack of attention to temperature requirements in RNS testing is the most common error made

![Common waveform artifacts during RNS that are mistaken for a true abnormality. (A) The greatest change occurs between potentials 3 and 4 instead of between 1 and 2. (B) There is variable change between successive potentials and the typical envelope pattern is not seen (see Fig. 7). (Copyright JF Howard Jr.)](image-url)
rendering the study unhelpful in this author’s experience. This is most important when considering presynaptic disorders of NMT.

**SFEMG**

SFEMG is a highly selective recording technique in which a concentric needle electrode is used to identify and record extracellular APs from individual muscle fibers. The selectivity of the technique results from the small recording surface (25 μm in diameter) that is exposed at a port on the side of the recording electrode, 3 mm from the tip. The amplitude of signals recorded with this surface decreases rapidly as the distance between the electrode and the signal source increases. Thus, APs from distant muscle fibers are much smaller than those from close fibers. The signals are recorded with a high pass (low frequency) filter of 500 Hz, which heightens the selectivity of the recording because the high-frequency components of EMG signals are attenuated by distance to a much greater degree than are low-frequency components. Thus, filtering the low-frequency components excludes predominantly signals from distant fibers and also helps ensure a stable baseline. The concerns for infectious risk have precluded the use of this reusable electrode in some countries. Investigations are under way to determine the validity of jitter measurements using a concentric needle electrode (see later).

When the SFEMG electrode is positioned to record from 2 or more muscle fibers in 1 voluntarily activated motor unit, variations in the time intervals between pairs of APs from these fibers can be seen. This variation is the neuromuscular jitter, most of which is produced by fluctuations in the time it takes for EPPs at the NMJ to reach the threshold for AP generation (see Fig. 1).

Jitter is the most sensitive clinical electrophysiologic measure of the safety factor of NMT. It is increased whenever the ratio of the AP threshold and the EPP is greater than normal. When NMT is sufficiently impaired, nerve impulses fail to elicit muscle APs and SFEMG demonstrates intermittent impulse blocking. When blocking occurs in many end-plates in a muscle there is clinical weakness. SFEMG can demonstrate abnormal NMT (as increased jitter) in muscles that are clinically normal and have no decrement to RNS. Jitter varies among different end-plates in a muscle, even among several end-plates within one muscle, and from muscle to muscle. To adequately sample the distribution of jitter within a muscle, at least 20 potential pairs should be measured. With increased age, there is a slight increase in jitter in normal subjects.

**Analysis of Neuromuscular Jitter**

Neuromuscular jitter may be measured from SFEMG recordings performed during voluntary activation of the tested muscle or during electrical stimulation of the nerve.
Recordings made during voluntary activation require that the electrode be placed so that APs are recorded from 2 or more muscle fibers in the same motor unit. Jitter is then measured as the variation in the length of the intervals between the 2 APs in the pair (interpotential interval [IPI]). This paired jitter represents the combined jitter in 2 end-plates. Jitter recorded during nerve stimulation is calculated as the variation in the intervals between the stimulus and APs from single muscle fibers. This jitter comes from single end-plates. Jitter values calculated from these 2 different techniques will differ and normal ranges have been developed for each technique (see later).

The variation in intervals can be expressed as the SD of a series of intervals. However, the intervals may slowly increase or decrease as a result of electrode movement, cooling of the muscle, or other factors, in which case the SD is not an accurate measure of NMT. To minimize the effects of such slow trends, one can calculate the mean value of consecutive differences of successive IPIs (MCD) from the following formula:

\[
\text{MCD} = \frac{\sum |IPI_1 - IPI_2| + \ldots + |IPI_{n-1} - IPI_n|}{n - 1}
\]

where \(IPI_i\) is the IPI (or, when nerve stimulation is used, the stimulus-response interval). In the absence of trends and when the data have a Gaussian distribution, \(\text{MCD} = 1.13\) SDs.

In certain situations, the IPI may be influenced by variations in the firing rate. This effect may be minimized by sorting the IPIs in the order of the preceding interdischarge interval and then calculating the mean of consecutive differences in the new sequence. This is called the mean sorted-data difference (MSD). If the ratio MCD/MSD exceeds 1.25, then variations in the firing rate have contributed to the jitter and the MSD should be used to represent the neuromuscular jitter. MCD is used if the ratio is between 0.8 and 1.25. If the MCD/MSD ratio is less than 0.8, there are trends in the data, in which case the MCD is used. The effect of firing rate on jitter is most marked when the IPI is long. If it is not possible to calculate the MSD, this effect can be minimized by having the patient maintain a constant firing rate during voluntary activation, by measuring jitter during nerve stimulation at constant rates, or by excluding from analysis IPIs greater than 4 milliseconds.

Jitter can be calculated most precisely if the IPIs are measured directly with an interval counter or clock. Many commercially available EMG machines now have the capability to measure IPIs and calculate MCD and MSD directly. Most require the electromyographer to set a threshold level to detect the APs of interest and thus to exclude undesired signals. Some systems use a peak-detection algorithm to identify APs for jitter analysis. No system can automatically distinguish spurious triggering potentials from true blocking, however, and the electromyographer should make this distinction and be able to enter this into the record.

The severity of abnormality within a muscle may be quantified by calculating for each muscle tested:

- The mean jitter of all potential pairs tested
- The percentage of potential pairs in which blocking is seen
- The percentage of potential pairs in which jitter is normal

The distribution and severity of jitter and blocking among the potential pairs within a muscle can best be appreciated when the results are displayed graphically (Fig. 8).

Quality Control in SFEMG

To ensure that acceptable signals are being acquired, feedback is provided to the electromyographer in different ways during data acquisition. Some systems electronically store and redisplay the waveforms for review. The electromyographer can select
and exclude those that are not acceptable before final calculations are made. The IPI values can also be displayed graphically by some systems, which permits easy visualization of the distribution of data and any trends. Such a display also makes it easier to detect extreme values that do not follow the expected data distribution. The measurement of jitter cannot be completely automated by any system because the electromyographer selects the signal to be analyzed and determines the quality of that signal. To help ensure that the data obtained are valid, quality control should be exerted by the electromyographer throughout the process.

**Normal Jitter Values**

Normal values for the jitter among potential pairs and the mean jitter of a population of potential pairs within a muscle have been determined for many muscles. To determine if a muscle is normal, jitter should be measured in 20 potential pairs. A study is abnormal if either of the following criteria is met:

a. The mean jitter of all potential pairs recorded exceeds the upper limit of mean jitter for that muscle.

b. Ten percent or more of potential pairs have jitter that exceeds the upper limit of normal for paired jitter in that muscle.

In most abnormal studies, both criteria will be met. For example, in 409 SFEMG studies of the EDC in patients with MG, 78% of the 409 were abnormal by both criteria and only 8% of the 409 were abnormal by only 1 criterion.

In some recordings, the jitter is less than 10 microseconds. This is seen rarely in normal muscles and more often in myopathies. These low values probably represent recordings made from split muscle fibers, both branches of which are activated by a single NMJ. These recordings should not be included in the analysis.

**SFEMG During Axonal Microstimulation**

Single-fiber investigations are most commonly performed during voluntary activation of the muscle. Occasionally it is useful and sometimes it is necessary to use a second
technique termed electrical axonal microstimulation. One advantage of electrical stimulation is that these studies can be performed in uncooperative patients (infants, small children, patients with tremor and unconscious patients) or animals. However, the technical pitfalls of this technique are considerable and, therefore, the electromyographer must be rigorous with his or her technique.

For stimulation, an insulated monopolar needle with a bare tip is inserted in the muscle near the motor end-plate zone. Another needle electrode or surface electrode placed close is used as the anode. The stimulus intensity is adjusted to produce a small visible twitch in a part of the muscle. Usually less than 5 mA is necessary. A stimulation frequency of 2 to 10 Hz is often used. The SFEMG electrode is inserted about 2 cm distally to the cathode into the twitching part of the muscle. With increasing stimulus strength, increasing numbers of single-fiber APs (SFAPs) appear, initially with intermittent blocking and high jitter. This increased jitter is caused by subliminal stimulation. Jitter is measured when further increases in the stimulus intensity no longer decrease the jitter of a particular SFAP. The jitter is measured between the stimulus artifact and the AP.

Jitter measured during axonal stimulation will be less than that measured during voluntary activation of the muscle because only the contribution from single end-plates is being assessed during axonal stimulation. The theoretical relationship between these 2 values is expressed by the formula:

$$\text{Mean MCD}_{\text{axonal stim}} = \frac{\text{Mean MCD}_{\text{vol activation}}}{\sqrt{2}}$$

Normal values for jitter during axonal stimulation determined in the EDC are 40 microseconds (individual muscle fibers) and 25 microseconds (mean of 30 muscle fibers).

**Concentric Needle Jitter Recordings**

There is increasing interest in the use of disposable concentric or monopolar needle EMG electrodes to perform jitter measurements because of the concern for infectious risk when reusing invasive medical devices. The use of a monopolar needle is not feasible because of its large recording surface and because activity is included in the recording as a result of the referential electrode being outside of the recording area. Small concentric electrodes with an elliptical recording surface of 0.019 mm² are currently the most appropriate electrodes to use. The larger recording surface of the concentric electrode predisposes to several technical errors, and much of the literature to date has not taken these into account. The larger recording surface produces a greater shunting effect of the electrical field, and recorded potentials will be smaller than those recorded with the standard SFEMG electrode. Further, the larger recording surface will "see" more SFAPs resulting in a summated signal. This phenomenon is the greatest disadvantage of the technique. The larger recording surface, the recording from multiple SFAPs, and the resulting signal summation produce an underestimation of jitter. Recordings made with concentric electrodes are no different from those made with an SFEMG electrode. However, critical attention must be paid to separation of signals and the absence of shape variation to ensure that SFAPs and not summated signals are being recorded. Details of the technical procedure are described by Stålberg.

Few studies have been published of concentric jitter studies in disease of the NMJ. There are differences in methodology and normative values, and most are fraught with technical errors. There has been no standardization of technique to date. There is limited information available on normative values and that in the literature is for
a very limited number of muscles. In general, all authors demonstrate that concentric jitter is increased in MG. There is only one study in which both techniques were performed on the same muscle; concentric jitter was found to be 5.6 microseconds lower.

**Technical Considerations**

Most adult patients are able to cooperate well enough to permit adequate SFEMG studies. Patient discomfort rarely limits the use of this test, even when several muscles must be examined. The potential complications of SFEMG are those of needle electromyography in general (ie, hemorrhage and infection). Other than an occasional small hematoma, we have had no complications of the procedure.

If the patient has a tremor, it may be impossible to make adequate recordings from distal arm muscles during voluntary activation. In such cases, recordings can usually be made from facial or more proximal arm muscles, especially the biceps brachii. Alternatively, recordings of jitter can be made during nerve stimulation.

Children older than 8 years old can usually cooperate well enough for adequate studies. In uncooperative children or infants, jitter studies can be performed during nerve stimulation, as described, while the child is sedated or under anesthesia.

**EMG FINDINGS IN DISORDERS OF SYNAPTIC TRANSMISSION**

**Autoimmune MG**

Characteristically, in MG the CMAP amplitude is normal, although in severely weak muscles, the amplitude may be slightly reduced. There is a decrementing response to trains of 3- to 7-Hz stimulation. There is partial repair of the decrement after the third or fourth response of the train, producing a “U-shaped” curve (Fig. 9). Postactivation facilitation may be seen after periods of 30 to 60 seconds of activation, but this is usually in the range of 10% to 25% and rarely greater than 50%. Postactivation exhaustion is commonly seen 3 to 4 minutes after 30 seconds to 1 minute of maximum voluntary exercise (see Fig. 9). One is more likely to demonstrate an abnormality in proximal muscles such as the trapezius or in a facial muscle such as the nasalis or orbicularis oculi than in distal hand or foot muscles.

Standard needle EMG recordings will demonstrate beat-to-beat variability in the amplitude of individual MUAPs, and the fullness of the interference pattern may wane with continued contraction in muscles that are moderate to severely weak.

![Fig. 9. RNS paradigm in a patient with MG, demonstrating characteristic electrodiagnostic features of this disorder.](from Howard JF, Sanders DB, Massey JM. The electrodiagnosis of myasthenia gravis and the lambert-eaton myasthenic syndrome. Neurol Clin 1994;12:305–30; with permission.)
The typical SFEMG finding in MG is that within one muscle, there are some end-plates with normal jitter, others with increased jitter, and still others with increased jitter and impulse blocking (Fig. 10). This spectrum of findings may even be seen within the end-plates of a single motor unit. SFEMG demonstrates abnormal jitter in virtually all (98%) patients with MG. One muscle, the EDC, is abnormal in most patients with this disease, but to obtain the maximum diagnostic sensitivity it may be necessary to examine other muscles, especially ones that are more involved clinically. There is no one muscle that will be more abnormal in every patient with MG. The muscle or muscles to be tested must be selected based on the distribution of weakness in the individual patient. In patients with symptoms or signs of weakness in any extremity muscles, the EDC is usually tested first. This muscle is easily activated by most patients and is relatively free of age-dependent changes. Abnormal jitter was found in this muscle in 89% of patients with MG who had weakness in any limb muscle and in 63% of those with weakness restricted to the ocular muscles. If the first muscle studied is normal, another muscle should be examined, selected based on the distribution of clinical weakness. If this is done, increased jitter can be demonstrated in 98% of patients with ocular MG and in 99% of patients with weakness in any limb muscle.

In patients whose symptoms are restricted to the ocular muscles, the frontalis, orbicularis oculi, or orbicularis oris muscle may be examined first. Abnormal jitter can be demonstrated in the EDC in more than 60% of patients with ocular MG, confirming that the physiologic abnormality is more widespread than can be determined by clinical examination alone. In those patients whose forearm study is normal, examination of the frontalis or orbicularis oculi muscles will demonstrate abnormalities in 98% of patients.

We would not consider a jitter study to be normal unless we had tested a clinically affected muscle or, in the case of purely ocular weakness, the orbicularis oculi or

Fig. 10. SFEMG results from the extensor digitorum muscle of the forearm demonstrating 3 muscle fiber APs under the control of the same motor neuron. Potential 1 demonstrates increased jitter and impulse blocking; potential 2 demonstrates increase jitter without impulse blocking; and potential 3 is the triggering potential. The decremental response seen on RNS study is equivalent to potential 1 (impulse blocking). (Copyright JF Howard Jr.)
orbicularis oris muscle. Jitter is more often abnormal in any given muscle in patients with more severe disease. However, there is marked variability of the abnormality within each clinical group, so that no conclusions about disease severity can be drawn from the amount of jitter alone. Jitter is usually increased even in muscles with normal strength but is worse in weak muscles in patients with MG. Jitter is usually worse in facial muscles than in limb muscles but the opposite is true in occasional patients. In most patients with MG, changes in disease severity correlate with changes in jitter measurements. The mean MCD increases by at least 10% in the tested muscle in two-thirds of patients who become worse between SFEMG studies. Conversely, in more than 80% of instances when the mean MCD decreases by at least 10% between 2 studies, there has been definite clinical improvement. Thus, there is a strong correlation between the overall change in clinical status in patients with MG and a change of at least 10% in mean jitter in any muscle. Serial SFEMG studies may be of value in predicting changes in disease severity under certain circumstances. For example, when the jitter values in one muscle have been constant for several months, any subsequent increase in jitter is usually accompanied or followed by clinical deterioration. Although therapeutic decisions should always be based on clinical considerations, jitter measurements may be useful in providing one part of the clinical picture.

It is the opinion of this author that concentric jitter studies must be interpreted with caution and are an underestimation of the severity of the abnormality. Hence, their use in mild or restricted disease is limited.

MG With Antibodies to MuSK

Neurographic studies are typically normal in the limbs of patients with MG with positive MuSK antibodies (MuSK MG) but may demonstrate reduced CMAP amplitudes in axial or facial muscles because of their associated muscle atrophy. Needle EMG is most important in suspected cases of MuSK MG when short-duration, small-amplitude MUAPs will be recorded in clinically affected muscles, particularly those with atrophy. Fibrillation potentials may be seen in some patients. Importantly, patients presenting with isolated neck extensor disease or respiratory failure may have normal electrodiagnostic studies in the limbs. It is therefore necessary that clinically affected muscles be examined to avoid missing the pertinent abnormalities of this disease. The RNS findings of MuSK MG will be reflected by the phenotype of the disease. Studies in the limb will often demonstrate no decrement or a decrement that is disproportionately smaller for the degree of muscle weakness. Studies are abnormal in 52% with examination of multiple muscles compared with 69% of Ach receptor antibody–positive patients. Proximal muscles are more often abnormal, similar to that found in Ach receptor antibody–positive patients with MG, and facial muscles are most often abnormal. SFEMG provides the most useful information, particularly when RNS studies are normal, and is most always abnormal when there is careful selection of involved muscles, including those of the paraspinal region.

Congenital Myasthenic Syndromes

Congenital myasthenic syndromes are a heterogeneous group of genetically determined structural disorders of the presynaptic, synaptic, and postsynaptic elements of the NMJ. Most of these disorders have been elegantly elucidated by Andrew Engel and were recently summarized. The electrophysiologic abnormalities reflect the phenotype of the disorder and, in general, have many of the same characteristics of the prototypical presynaptic and postsynaptic disorders, LES and MG. Specific differentiation of these disorders requires microphysiologic study of synaptic transmission, molecular chemical examination of the membrane proteins, and genetic analysis.
Unique clinical electrodiagnostic features do exist. Prolongation of the EPP, as seen in the slow channel syndrome and congenital acetylcholinesterase deficiency, causes a repetitive CMAP after a single stimulation, because the EPP duration exceeds the refractory period of the AP (Fig. 11). They are usually found in the small muscles of the hand and foot. Afterdischarges are abolished by repetitive stimulation in contrast to artifact, which will persist.

Congenital choline acetyltransferase deficiency demonstrates decremental responses to slow rates of stimulation that worsen with prolonged continuous 5- or 10-Hz stimulation for 5 minutes. Although a similar pattern may be seen in severe auto-immune MG or congenital ACh receptor deficiency, the recovery pattern in congenital choline acetyltransferase is very prolonged, lasting up to 30 minutes. SFEMG is similar to other NMJ disorders. Needle EMG will often demonstrate normal or small varying amplitude MUAPs. Neurographic studies are normal.

**LES**

RNS studies are the most specific test available to confirm the diagnosis of LES. The characteristic electrophysiologic findings on RNS studies in presynaptic disorders of NMT are a reduction in the initial CMAP amplitude, a decremental response to slow stimulation rates (1 Hz through 5 Hz), marked postactivation facilitation following a brief period of maximum voluntary contraction or following a tetanic stimulation, and the absence of significant postactivation exhaustion (Fig. 12). These decrements are most often seen at 3/s stimulation and tend to be less at faster rates of stimulation such as 5/s. Postactivation facilitation is in excess of twice the initial CMAP amplitude and is much more pronounced than that seen in postsynaptic disorders. Care must be taken not to exercise the muscle too long because this will deplete neurotransmitter release and mask the facilitatory response. Unlike postsynaptic disorders in which 30 seconds to 1 minute of maximum exercise is best, 10 seconds is all that is necessary in these disorders. Rapid rates of stimulation will produce a marked facilitatory response in excess of 60% and often much greater (Fig. 13).

SFEMG demonstrates abnormal jitter in virtually all patients with LES. The degree of jitter and blocking for any degree of muscle weakness tends to be greater in these patients compared with those with MG. In presynaptic neuromuscular abnormalities, such as LES and botulism, jitter typically decreases as the firing rate increases. These effects of firing rate are not always seen in these conditions, however, and we have seen jitter and blocking that decreases at high firing rates in some potential pairs in patients with neuropathy or MG. The effects of different firing rates may be assessed by measuring jitter from one pair of potentials while the patient maintains a low activation rate, and again at a higher rate or by using axonal microstimulation techniques.

**Botulism**

The electrodiagnostic abnormalities seen in botulism are very similar to those seen in LES. Neurographic studies are normal other than a reduction in CMAP amplitude. The resting CMAP amplitude is reduced in virtually all cases. Needle EMG recordings will demonstrate fibrillation potentials because there is a functional denervation of muscle. A decremental response is seen with slow stimulation rates, but this may be masked if the CMAP amplitude is markedly reduced. A moderate facilitatory response is seen with rapid stimulation rates or following very brief maximum isometric contraction if the patient is able. This is more likely in children and may be initially absent in the adult form of the disease. In the adult, facilitation may require more prolonged rapid-rate stimulation duration (10–20 seconds) and also lasts longer (5–30 minutes) compared with other presynaptic disorders. The degree of postactivation facilitation is usually
Fig. 11. Repetitive discharges in the abductor digiti quinti muscle in a patient with congenital acetylcholinesterase deficiency. Four consecutive superimposed CMAPs are shown with increasing stimulus rates. Stimulation faster than 0.5 Hz abolishes the repetitive discharge. (From Engel AG. Myasthenia gravis and myasthenic disorders. In Harper CM, editor. Electrodiagnosis of myasthenic disorders. New York: Oxford University Press; 2012. p. 37–59, Figs. 2.1 and 2.10; with permission of Oxford University Press, Inc.)
less than that seen in LES, ranging from 40% to 200%. Postactivation exhaustion is not seen in botulism. SFEMG recordings show increased jitter and impulse blocking disproportionately more severe than in MG and similar to that seen in LES.

**COMPARISON OF DIAGNOSTIC TECHNIQUES IN MG**

RNS studies show an abnormal decrement in a hand or shoulder muscle in approximately 75% of patients with generalized MG and in less than 50% of those with ocular myasthenia. The “double-step” RNS test is only slightly more sensitive than RNS of the trapezius muscle alone and only 60% as sensitive as SFEMG of a hand muscle. SFEMG is the most sensitive test of NMT and is abnormal in up to 95% of patients with MG. SFEMG, because of its high sensitivity, may demonstrate abnormal NMT in diseases other than MG or LES, which must be excluded. It is most valuable in demonstrating abnormal NMT in patients with mild MG or those with purely ocular disease. In addition, it can be helpful in excluding a disorder of NMT; the demonstration of normal jitter in the presence of muscle weakness suggests that the weakness is not caused by a disorder of synaptic transmission. About 25% of patients with MG do not have elevated anti–ACh receptor antibody levels, and SFEMG can be of great value in confirming or excluding the diagnosis of MG in patients in whom these antibodies are not found.

**Fig. 12.** Peak-to-peak amplitudes of all Potentials. Stimulus paradigm in a patient with LES demonstrating the characteristic electrodiagnostic features of this syndrome. Trains of 5 stimuli are administered at stimulus rates of 1, 3, and 5 Hz followed by 10 seconds of activation (maximum voluntary contraction) and subsequent intermittent 5-Hz trains of 5 stimuli maximum for 4.5 minutes. Note the initial low CMAP amplitude (trains 1–3), the decremental response to slow rates of stimulation (train 1–3, 20%, 40%, and 40%, respectively), and the marked postactivation facilitation after 10 seconds of exercise (167%, comparing the initial response of train 4 to the initial response of train 3). Postactivation exhaustion is not easily seen because of the small CMAP responses. Calibration, 0.2 mV per division. (From Howard JF, Sanders DB, Massey JM. The electrodiagnosis of myasthenia gravis and the Lambert-Eaton myasthenic syndrome. Neurol Clin 1994;12:305–30; with permission.)

**Fig. 13.** Responses to a train of 50 stimulations at 50 Hz in a patient with LES. Note the low initial CMAP amplitude (0.3 mV) and the marked facilitation (to 1.5 mV, 400%). Calibration, 0.5 mV and 2 mSec per division. (From Howard JF, Sanders DB, Massey JM. The electrodiagnosis of myasthenia gravis and the Lambert-Eaton myasthenic syndrome. Neurol Clin 1994;12:305–30; with permission.)
SUMMARY

The electrophysiologic examination of a patient suspected of having a disorder of synaptic transmission should be an extension of the physical examination and history. Patients should first undergo standard measures of nerve conduction and needle EMG for the reasons mentioned earlier. The amplitude of the CMAP response to a single shock in an appropriately warmed muscle will give clues as to whether the problem is presynaptic or postsynaptic in origin. Cholinesterase inhibitors should be withdrawn for 72 hours to minimize the risk of masking an abnormality of NMT.

RNS studies should be performed on a clinically involved muscle, typically the trapezius or nasalis muscle, in patients suspected of having MG. A distal hand muscle (eg, abductor digiti quinti) may be used if it is necessary to condition the patient to the procedure. Attention to the caveats previously discussed should be adhered to as careful attention to technique is critical for an optimal study. Should these studies be normal, SFEMG recordings performed initially on the forearm will be abnormal in most cases, and if necessary, a second muscle should be chosen based on the distribution of the clinical weakness. One should not consider a study to be completely normal until a clinically affected muscle or, in the case of suspected ocular MG, the orbicularis oculi muscle has been examined.

Abnormal jitter is also seen in diseases of nerve and muscle; these diseases must be excluded by other electrophysiologic and clinical examinations before diagnosing MG. If neuronal or myopathic disease is present, increased jitter does not indicate that MG is also present. Rarely, MG may be present in the presence of a normal SFEMG study. However, if jitter is normal in a muscle with definite weakness, the weakness is not caused by an abnormality of NMT.

When abnormal NMT has been demonstrated by RNS, the finding of abnormal jitter does not add to the diagnosis, although it may be useful in providing baseline values for comparison with the results of subsequent studies. SFEMG is most valuable clinically in the patient with suspected MG in whom other tests of NMT and anti-ACh receptor antibody titers are normal. Serial measurements of jitter can be useful in following the course of disease and in assessing the effect of treatment, but the results from these studies must always be interpreted in light of the overall clinical picture. It may be necessary to perform SFEMG studies on facial or axial muscles to establish a diagnosis of MuSK MG.

An easy screening test in patients suspected of having LES is to rest an appropriately warmed limb, stimulate the nerve once, and, if the CMAP amplitude is low, voluntarily activate the muscle maximally for 10 seconds before stimulating the nerve a second time. In nearly all cases, there will be a marked facilitation of the CMAP amplitude. More formal studies can then be undertaken to demonstrate the decremental response to slow rates of stimulation and the facilitation following postactivation or tetanic stimulation.

REFERENCES