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Electrodiagnostic approach to the patient with suspected neuromuscular junction disorder

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The neuromuscular junction (NMJ) is the anatomical site affected by myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), botulism, and congenital myasthenic syndromes [1]. The NMJ is designed for rapid translation of the electrical impulse of the nerve to the muscle using the chemical acetylcholine (Ach). The NMJ is a specialized structure consisting of the motor nerve terminal, the post-synaptic muscle surface, a specialized basal lamina, and an associated Schwann cell. Depolarization of the nerve plasma membrane leads to opening of primarily P/Q-type voltage-gated calcium channels (VGCCs), which initiates a complex machinery of synaptic proteins that ultimately leads to fusion of synaptic vesicles with the nerve terminal's plasma membrane. Each synaptic vesicle releases from 5,000 to 10,000 Ach molecules into the synaptic cleft with an action potential triggering the release of 50 to 300 vesicles. The release sites lie in direct opposition to the tops of the secondary synaptic folds of the postsynaptic muscle membrane, which have high concentrations of AchRs. The concentration of AchRs in the end plate region is 1000-fold higher than other muscle membrane regions. Skeletal muscle sodium channels are concentrated at the depths of the synaptic folds. In the basal lamina of the synaptic cleft, acetylcholinesterase (AchE) is anchored. AchE hydrolyzes most of the

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Ach and prevents repeated binding of Ach to the AchR. Consequently, AchRs are normally activated only once in response to Ach released by a nerve terminal action potential. Inactivation of AchE prolongs the duration of action of Ach and slows the decay of the end plate current.

The electrodiagnostic (EDX) examination in patients with suspected NMJ disorder constitutes the most advanced and complex type of EDX studies. Understanding the anatomy and physiology of neuromuscular transmission is prerequisite for the comprehension and planning of EDX studies in patients with suspected NMJ disorders. In addition to routine nerve conduction studies and conventional needle electromyography (EMG), the EDX studies that are most useful in the diagnosis of NMJ disorders include repetitive nerve stimulation (RNS) and single fiber EMG.

Repetitive nerve stimulation

Basic concepts

The understanding of RNS depends on a few important concepts inherent to the NMJ that dictate the type and frequency of RNS utilized in the accurate diagnosis of NMJ disorders:

- *Quantum.* A quantum is the amount of Ach packaged in a single vesicle. Each quantum (vesicle) released results in an approximate 1 mV change of postsynaptic membrane potential. This occurs spontaneously during rest and forms the basis of the miniature end plate potential (MEPP).
- The number of quanta released after a nerve action potential depends on the number of quanta in the *immediately available (primary) store* and the probability of release, that is, $m = P \times n$, where m = the number of quanta released during each action potential, P = the probability of release (effectively proportional to the concentration of calcium and typically about 0.2, or 20%), and n = the number of quanta in the immediately available store. In normal conditions, the number of quanta released after a single nerve action potential is about 60 vesicles. A single nerve action potential triggers the release of 50–300 vesicles (quanta) with an average equivalent to about 60 quanta (60 vesicles).
- *End plate potential (EPP).* EPP is the potential generated at the postsynaptic membrane following a nerve action potential and neuromuscular transmission. Since each vesicle (quantum) released causes a 1 mV change in the postsynaptic membrane potential, this results in about 60 mV change in the amplitude of the membrane potential.
- *Safety factor.* The safety factor of neuromuscular transmission is simply defined as the difference between the EPP and the threshold potential for initiating an action potential. As long as the threshold potential is achieved, the action potential initiates muscle contraction. In normal conditions, the number of quanta (vesicles) released at the NMJ at

the presynaptic terminal (about 60 vesicles) far exceeds the postsynaptic membrane potential change required to reach the *threshold* needed to generate a postsynaptic muscle action potential (7 to 20 mV). Hence, a nerve action potential results in an EPP that always reaches threshold and results in an all-or-none muscle fiber action potential (MFAP) [2]. Also, the safety factor prevents NMJ failure despite repetitive action potentials. Several factors contribute to the safety factor. Quantal release, AchR conduction properties, AchR density, and AchE activity contribute to the EPP [1]. Postsynaptic folds form a high resistance pathway that focuses end plate current flow on voltage-gated sodium channels concentrated in the depths of the folds. Both these factors reduce the action potential threshold at the end plate and serve to increase the safety factor. Human junctions are smaller and with more extensive folding than other mammals, suggesting an evolutionary pressure towards postsynaptic modifications to enhance safety factor. All disorders of neuromuscular transmission are characterized by a compromise of the safety factor [1].

- *Calcium influx.* Following depolarization of the presynaptic terminal, VGCCs open leading to calcium influx. Through a calcium-dependent intracellular cascade, vesicles are docked into active release sites (called active zones), and releases their Ach molecules. Then, calcium diffuses slowly out of the presynaptic terminal in 100–200 msec. In RNS, the rate at which motor nerves are stimulated dictates whether calcium plays a role in enhancing the release of Ach or not. At slow rate of RNS (more than every 200 msec, or a stimulation rate of <5 Hz), calcium role in Ach release is not enhanced and subsequent nerve action potentials reach the nerve terminal long after calcium has dispersed. In contrast, with rapid RNS (more than every 100 msec, or stimulation rate >10 Hz), calcium influx is greatly enhanced and the probability of release of Ach quanta increases.
- *Acetylcholine storage.* An *immediately available (primary) store* of Ach is placed beneath the pre-synaptic nerve terminal membrane. A *secondary (or mobilization) store* is located toward the axon and starts to replenish the immediately available store after 1–2 seconds of repetitive nerve action potentials. A large *tertiary (or reserve) store* is also available in the axon and cell body [3].
- The *compound muscle action potential (CMAP)* is the summation of all MFAPs generated in a muscle following supramaximal stimulation of all motor axons while recording via surface electrode placed over the belly of a muscle.

Technical aspects

The techniques of RNS should be mastered by electromyographers and technologists to avoid false positive and false negative results, which may

lead to erroneous diagnoses or may miss diagnoses of NMJ disorders. Limb temperature should be maintained at around 33°C, because a CMAP decrement may be masked in a cool limb. The limb tested should be immobilized as best as possible. Patients on AchE inhibitors (such as pyridostigmine) should be asked to withhold their medication for 12–24 hours before RNS, if medically not contraindicated.

RNS often follows a routine motor nerve conduction study (NCS). A good grasp of the techniques of the various motor NCSs is an essential prerequisite to a reliable RNS [3,4]. The stimulator should be as close as possible to the nerve and should not move during RNS. A supramaximal stimulation is secured by delivering a stimulus intensity of 10–20% above the intensity level needed for a maximal response. Long duration and unnecessary high intensity stimuli should be avoided since they are painful and may result in movement artifact. The stimulus rate and number of stimuli are dictated by the clinical problem and the working diagnosis (see below).

Slow repetitive nerve stimulation

After establishing a supramaximal CMAP, slow RNS is usually performed by applying 3–5 stimuli to a mixed or motor nerve at a rate of 2–3 Hz. This rate is low enough to prevent calcium accumulation, but high enough to deplete the quanta in the immediately available store before the mobilization store starts to replenish it. A total of 3–5 stimuli are adequate since the maximal decrease in Ach release occur after the first four stimuli. Exceeding 9–10 stimuli does not add any diagnostic benefit and is painful. Stimulation at rest may be repeated after an interval of one minute to confirm a normal or abnormal response. If there is a reproducible decrement (≥10%), slow RNS should be repeated after the patient exercises for 10 seconds to demonstrate repair of the decrement (''post-exercise facilitation''). If there is no decrement or an equivocal decrement (≤10% decrement) with slow RNS at rest, the patient should perform maximal voluntary exercise for 1 minute (exercise for 30 seconds, rest for 5 seconds and exercise for another 30 seconds). Then, slow RNS should be done immediately and at 1, 2, 3, 4, and 5 minutes after exercise. Since the amount of Ach released with each stimulus is at its minimum 2 to 5 minutes after exercise, slow RNS after exercise provides a higher chance in detecting a defect of transmission at the NMJ by demonstrating a worsening CMAP decrement (''postexercise exhaustion'').

The choice of nerve to be stimulated and muscle to be recorded from depends on the patient's manifestations. Most useful nerves for slow RNS are the median, ulnar, and spinal accessory nerves recoding abductor pollicis brevis, abductor digiti minimi, and upper trapezius respectively [3,4]. The median and ulnar nerves are easily immobilized during RNS, and the stimulations are well tolerated and are accompanied by minimal movement artifacts. However, the recording muscles are distal and may be spared in some

NMJ disorders (such as MG). RNS of the spinal accessory nerve is the most popular RNS of a proximal nerve. It is the least painful and subject to little movement artifact compared to other proximal nerves such as the musculocutaneous or axillary nerves, recording the biceps and deltoid muscles respectively. Facial nerve RNS is indicated in patients with bulbar and ocular weakness when other RNS are normal or equivocal. However, the facial CMAP is low in amplitude and often plagued by large stimulation artifacts. This renders measurements of CMAPs and decrement difficult and subject to error.

Calculation of the decrement with slow RNS, requires comparing the baseline (first) CMAP amplitude to the lowest CMAP amplitude (usually the third or fourth) [3,5]. By the fifth or sixth response, the CMAP decrement plateaus or begins to improve, due to the mobilization store resupplying the immediately available store. The CMAP decrement is expressed as a percentage and calculated as follows:

$$\%\ \text{Decrement} = \frac{\text{Amplitude(1st response)} - \text{Amplitude(3rd/4th response)}}{\text{Amplitude(1st response)}} \times 100$$

For example, if the first CMAP amplitude is 10 mV and the fourth CMAP is the lowest and is 8 mV in amplitude, the decrement is

$$\frac{10 - 8}{10} \times 100 = 20\%$$

In *normal conditions*, slow RNS does not abolish any MFAPs, because neuromuscular transmission at all fibers remains above threshold due to the safety factor (Fig. 1). Although the second to fifth EPPs fall in amplitude, they remain above threshold (due to the normal safety factor), and ensure generation of MFAPs with each stimulation [4]. In addition, the secondary store begins to replace the depleted quanta after the first few seconds with a subsequent rise in the EPP. Thus, with slow RNS, all muscle fibers generate MFAPs, and the CMAP does not change.

In *postsynaptic NMJ disorders* (such as MG), the safety factor is reduced because there are fewer Ach receptors resulting in less binding of Ach. Hence, the baseline EPP is reduced but usually still above threshold. Slow RNS results in the loss of EPPs at many end plates, and as EPPs become subthreshold, there is a decline in the number of MFAPs, leading to a decline in the CMAP (decrement) [4,6,7].

In *presynaptic NMJ disorders* (such as LEMS), the baseline EPP is low, with many end plates often not reaching threshold. Hence, many muscle fibers do not fire, resulting in a low amplitude baseline CMAP. With slow RNS, there is further CMAP decrement, due to the further decline of Ach

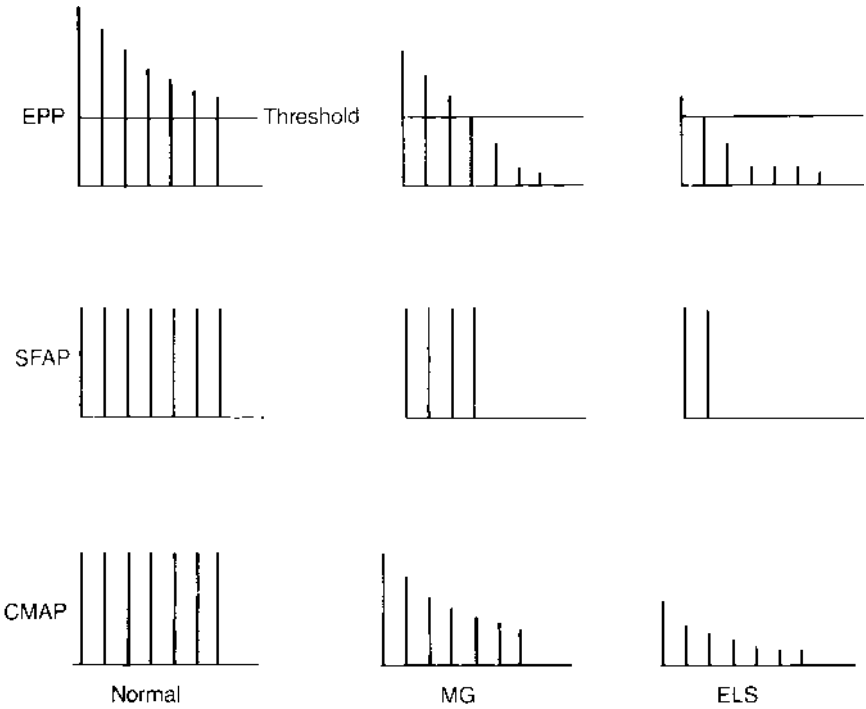

Fig. 1. Slow repetitive nerve stimulation effect on EPP, single fiber action potential (SFAP, referred to in the text as MFAP) and CMAP. In normal, myasthenia gravis (MG) and Lambert Eaton myasthenic syndrome (ELS). *Adapted from* Oh SJ. Electromyography: Neuromuscular Transmission Studies. Baltimore: Williams and Wilkins; 1988, with permission.

release with the subsequent stimuli, resulting in further loss of many EPPs and MFAPs [4].

Rapid repetitive nerve stimulation

Rapid RNS is most useful in patients with suspected presynaptic NMJ disorders such as LEMS or botulism. The optimal frequency is 20–50 Hz for 2–10 seconds. A typical rapid RNS applies 200 stimuli at a rate of 50 Hz (i.e., 50 Hz for 4 seconds). Calculation of CMAP increment after rapid RNS is as follows:

$$\% \text{ Increment} = \frac{\text{Amplitude (highest response)} - \text{Amplitude (1st response)}}{\text{Amplitude (1st response)}} \times 100$$

For example, if the first CMAP amplitude was 4 mV and the highest was 10 mV, then the increment is:

$$\frac{10-4}{4} \times 100 = 250\%$$

A brief (10-second) period of maximal voluntary isometric exercise has the same effect as rapid RNS at 20–50 Hz, is much less painful, and can substitute for rapid RNS in cooperative subjects. Hence, a single supramaximal stimulus is applied to generate a baseline CMAP. Then, the patient performs a 10-second maximal isometric voluntary contraction that is followed by another stimulus and a post-exercise CMAP. In patients who could not exercise (e.g., infants, comatose patients, patients with severe weakness), rapid RNS are necessary. Calculation of CMAP increment after a brief (10-second) voluntary contraction is similar to the calculation of the increment following rapid RNS, as follows:

$$\%\ \text{Increment} = \frac{\text{Amplitude of postexercise response} - \text{Amplitude of preexercise response}}{\text{Amplitude of preexercise}} \times 100$$

For example, if the baseline (pre-exercise) CMAP is 5 mV and the post-exercise CMAP is 15 mV, then the increment is:

$$\frac{15-5}{5} \times 100 = 200\%$$

With rapid RNS or postexercise CMAP evaluation, there are two competing forces that are acting on the nerve terminal:

1. Stimulation tends to deplete the pool of readily-releasable synaptic vesicles. This depletion effect reduces transmitter release by reduction of the number of vesicles that are released in response to a nerve terminal action potential.
2. Repeated stimulation however, causes calcium to accumulate within the nerve terminal, thereby increasing the probability of synaptic vesicle release.

In a *normal nerve terminal*, the effect of depletion of readily releasable synaptic vesicles predominates, so that with rapid RNS, the number of vesicles released decreases; however, the EPP does not fall below threshold due to the safety factor [4]. Hence, the supramaximal stimulus generate MFAPs at all end plates and no decrement of CMAP amplitude occurs (Fig. 2). In fact, rapid RNS or a brief (10-second) exercise in normal subjects often leads to a slight physiological increment of the CMAP which does not

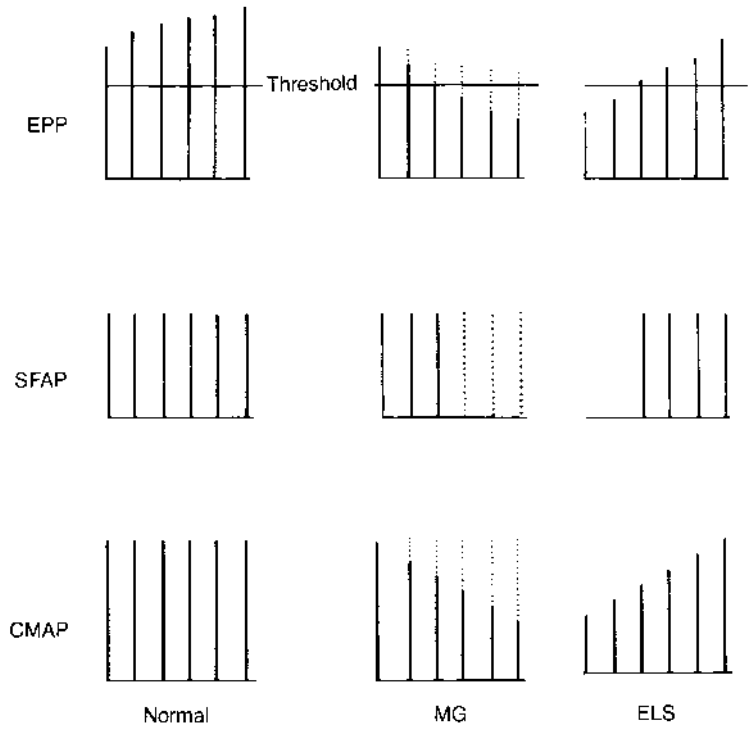

Fig. 2. Rapid repetitive nerve stimulation effect on EPP, single fiber action potential (SFAP, also referred to in text MFAP) and CMAP in normal, MG and Lambert Eaton myasthenic syndrome (ELS). *Adapted from* Oh SJ. Electromyography: Neuromuscular Transmission Studies. Baltimore: Williams and Wilkins; 1988, with permission.

exceed 25% to 40% of the baseline CMAP. This is likely caused by increased synchrony of MFAPs following tetanic stimulation (''post-tetanic pseudofacilitation'').

In a *presynaptic disorder* (such as LEMS), very few vesicles are released so that depletion of vesicles is not a prominent effect. Thus, the baseline CMAPs obtained during routine motor NCSs are low in amplitude since many muscle fibers do not reach threshold due to inadequate release of quanta (vesicles) after a single stimulus. With rapid RNS, the local calcium concentrations in the nerve terminal can rise high enough to stimulate synaptic vesicle fusion for a sufficient number of synaptic vesicles to result in an EPP capable of action potential generation [1,9]. This leads to many muscle fibers reaching threshold required for the generation of MFAPs. Thus, more MFAPs are generated and hence the increment of the CMAP. The increment in LEMS is often higher than 200% [8,10], and is about 30–100% in patients with botulism [11,12,14,26].

In a *postsynaptic disorder* (such as MG), rapid RNS causes no change of CMAP because the depleted stores are compensated by the calcium influx.

In severe postsynaptic blockade (such as during myasthenic crisis), the increased quantal release cannot compensate for the marked NMJ block resulting in a drop in EPP amplitude. Hence, fewer MFAPs are generated along with an associated CMAP decrement.

Nerve conduction studies

Sensory NCSs are normal in all NMJ disorders. Motor NCSs are usually normal in postsynaptic disorders due to the intact safety factor. After a single stimulus, and despite Ach receptors blockade, EPPs reach threshold and generate MFAPs in all fibers, which results in normal CMAP. Occasionally, such as during myasthenic crisis, the CMAPs may be borderline, particularly recording proximal muscles, due to severe postsynaptic neuromuscular blockade. In presynaptic disorders, motor NCSs often show low CMAP amplitudes with normal distal latencies, conduction velocities, and F-wave minimal latencies. The CMAP amplitude (and area) is low because the baseline EPP is low, often not reaching threshold, and many muscle fibers do not fire.

Needle electromyography

Conventional needle EMG is usually normal in NMJ disorders. However, three non-specific changes, that are often observed in other neuromuscular disorders such active myopathies or neurogenic disorders, may be associated with severe NMJ disorders.

1. *Short duration, low amplitude, and polyphasic motor unit action potentials (MUAPs)*. These are similar to the MUAPs seen in myopathies, and are seen primarily in proximal muscles. Such MUAPs are caused by physiological blocking and slowing of neuromuscular transmission at many end plates during voluntary activation. This leads to exclusion of many MFAPs from the MUAP (hence the short duration and low amplitude) and delay of neuromuscular transmission of other fibers (hence the polyphasia).
2. *Moment to moment variation of unstable MUAPs*. In healthy individuals, MUAPs are stable with little, if any, variation in amplitude and configuration [5]. However, in NMJ disorders, individual MUAP amplitude can vary significantly during activation (Fig. 3). Care should be taken not to record from more than a single MUAP at a time, since MUAP overlap may lead to an erroneous assumption of moment-to-moment variation.
3. *Fibrillation potentials*. These potentials are rarely seen in MG or botulism [13,14]. They are usually inconspicuous and present mostly in proximal muscles. Their presence should raise the suspicion of an alternate diagnosis or associated illness. The mechanism of fibrillation potentials in NMJ disorders is likely persistent transmission block, resulting in "effective" denervation of individual muscle fibers.

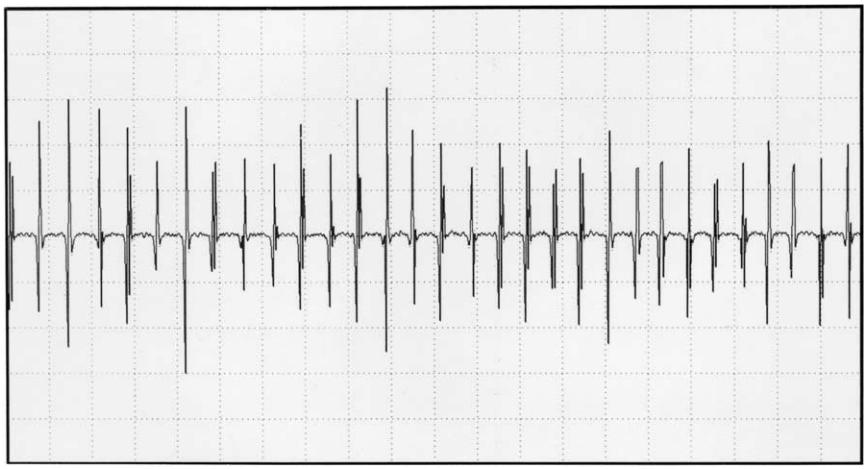

Fig. 3. Moment to moment variation of a single unstable motor unit potential recorded from the deltoid muscle in a patient with generalized MG (sensitivity 0.2 mV/division, Sweep speed 100 ms/division). *Adapted from* Katirji B. Electromyography in Clinical Practice. A Case Study Approach. St Louis: Mosby; 1998, with permission.

Single fiber electromyography

Technical aspects

Single fiber EMG (SFEMG) is the selective recording of a small number of MFAPs (usually two or three) innervated by a single motor unit [15,16]. SFEMG recording requires the following:

1. A concentric single fiber needle electrode with a small recording surface (25 μm) to restricts the number of recordable MFAPs and results in an effective recording area of 300 m^3 (as compared with a concentric conventional needle electrode that records from approximately 1 cm^3).
2. A 500 Hz low frequency filter to attenuate signals from distant fibers (more than 500 μm from the electrode).
3. An amplitude threshold trigger and delay line to allow recording from a single MFAP by triggering on it on a screen with a delay line capability.
4. A computerized equipment with an ability to calculate individual and mean interpotential intervals (IPIs) and jitters (see below).

SFEMG is performed by inserting single fiber concentric needle into a muscle. Filter settings should be set at 500 Hz for the high pass filter, and 10–20 kHz for the low pass filter [3,4]. Selected single MFAPs should have a rise time of 300 seconds and a preferable peak-to-peak amplitude of 200 V or more.

Voluntary single fiber electromyography

Voluntary (conventional or recruitment) SFEMG is the most commonly used method for activating motor units: the patient activates and maintains

the firing rate of the motor unit. This technique is not possible if the patient cannot cooperate (e.g., child, dementia, coma, severe weakness), and is difficult if the patient is unable to maintain a constant firing rate (e.g., tremor, dystonia, spasticity). With minimal voluntary activation, the needle is positioned until two muscle potentials (a pair) from a single motor unit are recognized. When a muscle fiber pair is identified, one fiber triggers the oscilloscope (triggering potential) and the second precedes or follows the first (slave potential). With voluntary activation, fifty consecutive discharges of a single pair is recorded. The interpotential interval (IPI) of the pair is then measured and a mean consecutive difference (MCD or jitter) of that pair is calculated as follows:

$$\mathrm{MCD} = \frac{(\mathrm{IPI1} - \mathrm{IPI2}) + (\mathrm{IPI2} - \mathrm{IPI3}) + \ldots + (\mathrm{IPIN} - 1 - \mathrm{IPIN})}{\mathrm{N} - 1}$$

wherein IPI1 is the interpotential interval of the first discharge, IPI2 of the second discharge, and so forth, and N is the number of discharges recorded. Finally, after analyzing twenty muscle fiber pairs, a mean jitter (MCD) is reported.

Neuromuscular jitter is defined as the random variability of the time interval between two MFAPs innervated by the same motor unit. In normal subjects, there is a slight variability in the amount of acetylcholine released at the synaptic junction from one moment to another. Though, a nerve action potential will result in a MFAP at all times, the rise of EPP is variable, resulting in a small variation of the muscle pair's IPI (Fig. 4). The diagnostic yield of jitter analysis is increased by examining affected muscle(s) performed by an experienced electromyographer on a fully cooperative patient. Though SFEMG may be done on any muscle, the most desired muscles are the extensor digitorum communis, frontalis and orbicularis oculi [4,16]. These muscles are ideal since most patients are able to control and sustain their voluntary activity to a minimum for a long period. Normal values for jitter differ between muscles, and tend to increase with age (Table 1) [17].

Neuromuscular blocking is defined as the intermittent failure of transmission of one potential of the two potentials. This reflects the failure of one of the muscle fibers to transmit an action potential due to the failure of EPP to reach threshold. Blocking represent the most extreme abnormality of the jitter. Blocking is measured as the percentage of discharges of a motor unit in which a single fiber potential does not fire. For example, in an 100 discharges of the pair, if a single potential is missing 30 times, the blocking is 30%. In general, blocking occurs when the jitter values are significantly abnormal.

The results of SFEMG jitter study is expressed by: (1) the mean jitter of all potential pairs, (2) the percentage of pairs with blocking, and (3) the percentage of pairs with normal jitter. Jitter is considered abnormal if (1) the mean jitter value exceeds the upper limit of the normal jitter value for that

Table 1
Reference values for jitter measurements during voluntary muscle activation (μSec): 95% confidence limits for upper limit of mean jitter/95% confidence limits for jitter values of individual fiber pairs (adapted from Gilchrest [17])

Muscle/Age	10 years	20 years	30 years	40 years	50 years	60 years	70 years	80 years	90 years
Frontalis	33.6/49.7	33.9/50.1	34.4/51.3	35.5/53.5	37.3/57.5	40.0/63.9	43.8/74.1		
Orbicularis oculi	39.8/54.6	39.8/54.7	40.0/54.7	40.4/54.8	40.9/55.0	41.8/55.3	43.0/55.8		
Orbicularis oris	34.7/52.5	34.7/52.7	34.9/53.2	35.3/54.1	36.0/55.7	37.0/58.2	38.3/61.8	40.2/67.0	42.5/74.2
Tongue	32.8/48.6	33.0/49.0	33.6/50.2	34.8/52.5	36.8/56.3	39.8/62.0	44.0/70.0		
Sternocleidomastoid	29.1/45.4	29.3/45.8	29.8/46.8	30.8/48.8	32.5/52.4	34.9/58.2	38.4/62.3		
Deltoid	32.9/44.4	32.9/44.5	32.9/44.5	32.9/44.6	33.0/44.8	33.0/45.1	33.1/45.6	33.2/46.1	33.3/46.9
Biceps	29.5/45.2	29.6/45.2	29.6/45.4	29.8/45.7	30.1/46.2	30.5/46.9	31.0/48.0		
Extensor digitorum communis	34.9/50.0	34.9/50.1	35.1/50.5	35.4/51.3	35.9/52.5	36.6/54.4	37.7/57.2	39.1/61.1	40.9/66.5
Abductor digiti minimi	44.4/63.5	44.7/64.0	45.2/65.5	46.4/68.6	48.2/73.9	51.0/82.7	54.8/96.6		
Quadriceps	35.9/47.9	36.0/48.0	36.5/48.2	37.5/48.5	39.0/49.1	41.3/50.0	44.6/51.2		
Tibialis anterior	49.4/80.0	49.3/79.8	49.2/79.3	48.9/78.3	48.5/76.8	47.9/74.5	47.0/71.4	45.8/67.5	44.3/62.9

muscle, (2) more than 10% (more than two pairs) exhibits jitter values above the upper limit of the normal jitter, or (3) there is any neuromuscular blocking.

Jitter analysis is highly sensitive but not specific. Although it is frequently abnormal in MG and other NMJ disorders, it may also be abnormal in a variety of neuromuscular disorders including motor neuron disease, neuropathies, and myopathies. Thus, the value of jitter has to be considered in the contest of the patient's clinical manifestations, nerve conduction studies, and needle EMG findings.

Stimulation single fiber electromyography

Stimulation (axonal-stimulated) SFEMG is an alternative method of motor unit activation. It has the advantage of not requiring patient participation and, thus, may be completed on children, uncooperative or comatose patients. It is performed by inserting another monopolar needle electrode near the intramuscular nerve twigs, and stimulating at a low current and constant rate [15]. This technique is more demanding since the electromyographer has to manipulate two electrodes, a stimulating and recording electrode. The IPI is calculated between a stimulus artifact and a single potential generated by stimulating a motor unit near the end plate zone. In contrast to voluntary SFEMG, where jitter is calculated as the variation in IPIs between two MFAPs (since one potential is time-locked by the trigger, all the variation of both end plates is expressed by the jitter of the other potential), the IPI in stimulated SFEMG is measured as the latency between the stimulation artifact and the single MFAP. As jitter values obtained by stimulation SFEMG are calculated on the basis of one end plate, the normal values are lower than those obtained by voluntary activation. To calculate the normal stimulation jitter value, it is recommended that the reference data for voluntary activation is multiplied by 0.80 [15].

Findings in neuromuscular junction disorders

Myasthenia gravis

MG is an organ-specific autoimmune disease, caused by an antibody-mediated attack primarily on the postsynaptic nicotinic AchRs [18]. The immune-mediated damage of MG leads to a loss of AchR at the NMJ. The primary mechanism involves complement-mediated lysis of the post-synaptic membrane. Antibody cross-linking of AchR leads to their increased internalization, and antibody-binding to the AchR compromises channel function. In addition to the AchR loss of MG, secondary synaptic folds are simplified. This structural feature would be expected to reduce the focus of current on skeletal muscle sodium channels, thereby compromising safety factor further. Finally, skeletal muscle sodium channels are also reduced, in all likelihood, secondary to the loss of post-synaptic membrane. There is no

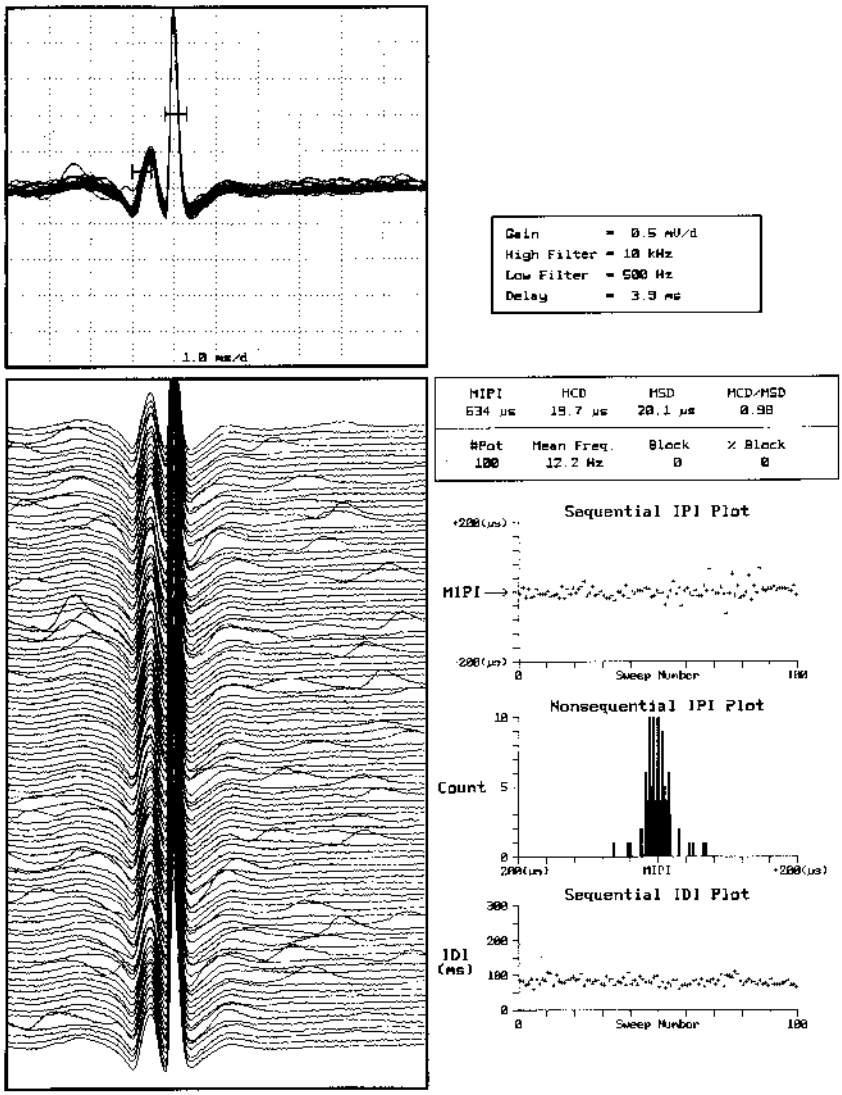

Fig. 4. Normal voluntary jitter analysis of a muscle fiber pair, recording extensor digitorum communis. *Adapted from* Katirji B. Electromyography in Clinical Practice. A Case Study Approach. St Louis: Mosby; 1998, with permission.

evidence of a direct immune attack on the sodium channels, but antibodies against a muscle-specific kinase have been identified among some seronegative patients and may be of pathogenic importance [19].

The manifestations of MG are remarkably varied, though they all center around muscle weakness and fatiguability. The weakness is usually worse

with activity and improves after rest. Generally, patients do much better in the morning than the evening. Fatiguable diplopia or ptosis or both are extremely common symptoms. Bulbar symptoms (dysarthria, dysphagia and chewing difficulties) are also frequent. When generalized, there is usually neck extensor and proximal limb weakness. Rarely, the generalized weakness involves the respiratory muscles resulting in respiratory failure (myasthenic crisis).

Improvement in strength after intravenous injection of *edrophonium* (*Tensilon*®), an AchE inhibitor, helps to confirm the diagnosis. By inhibiting Ach degradation, edrophonium allows the Ach released into the junction, to interact repeatedly with the decreased number of nicotinic receptors. After a test dose of 1–2 mg, a total dose of 10 mg is administered intravenously. A positive response is expected within five minutes. False positive and false negative results are rare. The *ice pack* test may also improve ptosis since cooling improves neuromuscular transmission. Elevated serum *Ach receptor antibodies* occur in about 85–90% of patients with generalized MG, but only in about 50% of patients with ocular myasthenia.

The differential diagnosis of generalized MG includes LEMS, congenital myasthenic syndromes, hyper- and hypothyroidism, glucocorticoid excess, adrenal insufficiency and chronic fatigue syndrome. Ocular myasthenia should be distinguished from thyroid orbitopathy, Kearns Sayre syndrome, congenital myasthenic syndromes, brain stem lesion, and intracranial mass compressing cranial nerves.

The EDX study of patients with suspected MG is often useful and should be tailored to the patient symptomatology. At least one sensory and one motor NCSs should be performed in one lower and one upper extremities, along with a needle EMG emphasizing proximal muscles, to exclude other neuromuscular disorders such as polyneuropathies or myopathies. RNSs are an essential part of the EDX study of patients with suspected MG. They are extremely useful in patients with seronegative disease, negative tensilon test, or equivocal neurological findings. The EDX findings in patients with MG may be summarized as follows:

1. *Baseline CMAP*. The baseline CMAP amplitudes (as well as routine motor nerve conduction studies) are normal in MG. A single supramaximal stimulus to a motor nerve results in Ach release and postsynaptic EPPs which always reach the threshold required to initiate an action potential. Hence, MFAPs are generated in all fibers resulting in a normal CMAP.
2. *Slow repetitive nerve stimulation*. The functional effect of reduced AchRs is a decreased EPP. Depending on the physiological circumstances, the EPP may be adequate; however, if quantal release is lowered, as occurs with slow RNS, the EPP may fall below threshold and the MFAP will not be generated (Fig. 1). In contrast, decreased temperature or inhibition of AchE produces an increase in EPP, which may be adequate to

achieve threshold. In the diagnosis of MG, this property is exploited by the ice pack and Tensilon tests.

Slow RNS results in a progressive decrease in quantal release due to the depletion of the immediate Ach stores. This causes progressive loss of MFAPs since many EPPs do not reach threshold. The end result is a decremental CMAP on slow RNS. The greatest decrease in CMAP amplitude occurs between the first and the second responses but the decrement continues till fourth or fifth responses. Afterwards, the decrement levels off (or sometimes slight improves) due to the mobilization of the secondary stores resulting in no further loss of MFAPs [6,7].

A CMAP decrement of >10% is considered abnormal and eliminates false positive. This should be reproducible and shows the typical decrement described above (maximal at the 3rd to 5th CMAP and plateau after the 5th or 6th CMAP). The diagnostic yield of slow RNS in MG is increased by the following strategy:

a. Obtaining slow RNS following exercise looking for post-exercise exhaustion. After performing slow RNS at rest, patients are asked to contract the tested muscle for one minute. Then, slow RNS is repeated every 30–60 seconds for 3–5 minutes (Fig. 5).) Post-exercise exhaustion usually lasts 3–5 minutes and is particularly useful in patients with suspected MG and equivocal (<10%) CMAP decrement at rest. Tetanic stimulation (30–50 Hz) may be substituted for voluntary contraction, but this is extremely painful and should be reserved to comatose or sedated patients.
b. Recording from clinically weakened muscles. This often includes recording from a proximal muscle (such as trapezius) in generalized MG, or from a facial muscle (such as orbicularis oris or nasalis) in ocular or bulbar MG. The diagnostic sensitivity is clearly higher for slow RNS recording proximal muscles than distal (Figs. 5 and 6) [2].
c. Warming the extremity studied (hand skin temperature should be above 32° C). This decreases false negative results, because cooling improves neuromuscular transmission and may mask the decrement.
d. Discontinuation of AchE inhibitors for 12–24 hours (if clinically possible). This also decreases false negative results of slow RNS.

3. *Rapid repetitive nerve stimulation*. Rapid RNS is not useful in the diagnosis of MG. It is mainly indicated when a presynaptic NMJ disorder (such as LEMS or botulism) is considered in the differential diagnosis and need to be eliminated. With rapid RNS, the depleted stores in MG are usually compensated by the accumulation of calcium resulting in no change of CMAP amplitude [4]. In severe myasthenics, rapid RNS may cause a decrement when the increased Ach release cannot compensate for the marked postsynaptic NMJ blockade. In contrast to MG, rapid RNS results in a CMAP increment in patients with LEMS or botulism (see below).

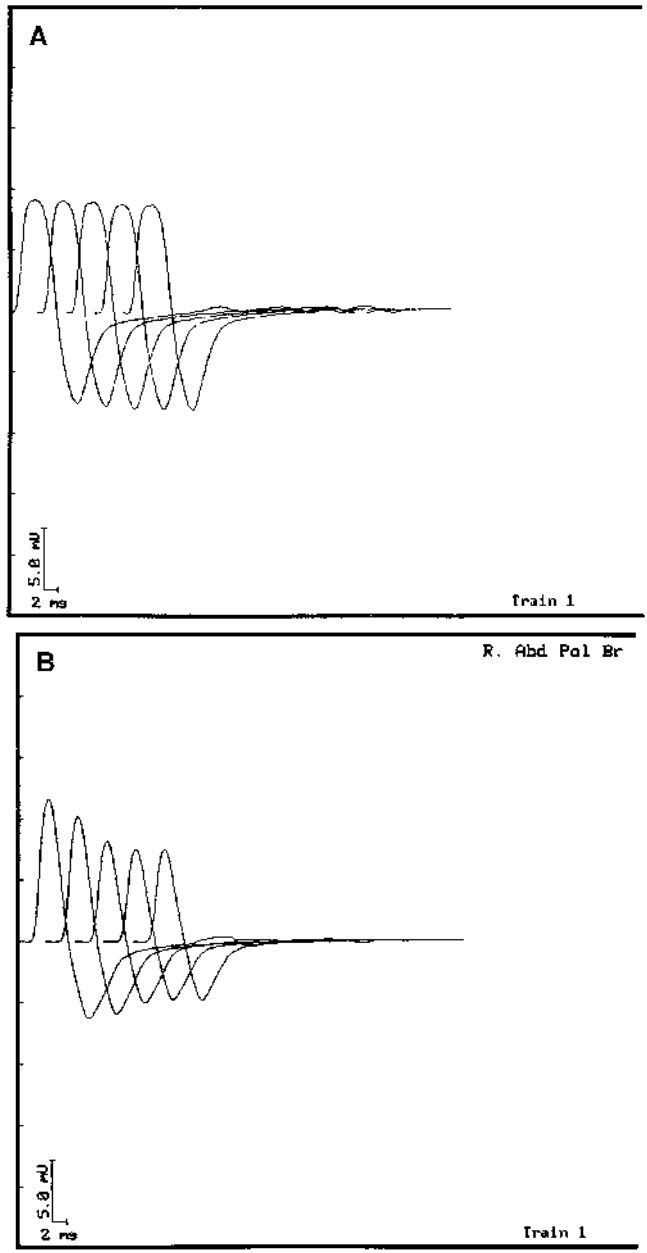

Fig. 5. Slow repetitive nerve stimulation (2 Hz) at rest. (A) Stimulating the median nerve in a normal control. (B) Stimulating the median nerve in a patient with severe myasthenia gravis. Note the significant decrement of CMAP (35% decrement comparing first and fourth CMAP). (C and D) Stimulating the median and spinal accessory nerves in another patient with myasthenia gravis. Note that the decrement stimulating the spinal accessory nerve (D) with 33% decrement comparing first and fourth CMAP) is much more prominent than stimulating the median nerve (C) with 13% decrement comparing first and fourth CMAP). *Adapted from* Katirji B. Electromyography in Clinical Practice. A Case Study Approach. St Louis: Mosby; 1998, with permission.

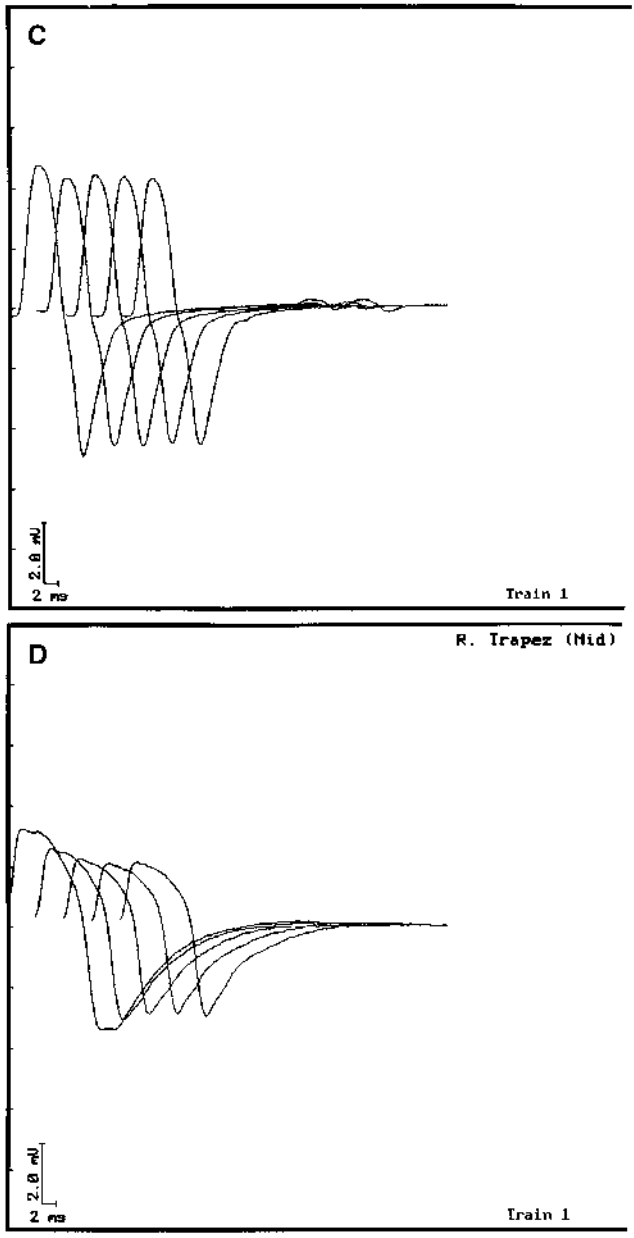

Fig. 5 (*continued*)

4. *Single fiber EMG.* Evaluation of neuromuscular transmission in patients with suspected MG is the most common indication for performing SFEMG. SFEMG is most useful in the diagnosis, but is also helpful in the management, of MG. In patients with MG, abnormal jitter values

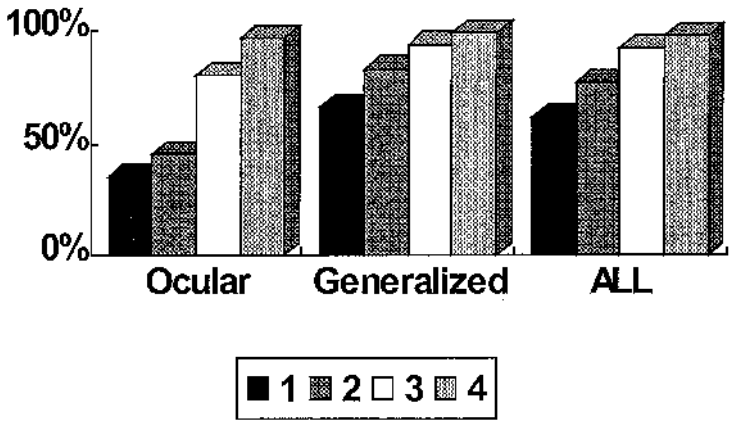

Fig. 6. The diagnostic sensitivity of slow repetitive nerve stimulation and single fiber EMG in the diagnosis of myasthenia gravis [14,20]. *Data compiled from* Oh SH, Kim DE, Kuruoglu R, Bradley RJ, Dwyer D. Diagnostic sensitivity of the laboratory tests in Myasthenia gravis. Muscle Nerve 1992;15:720–4., and from Howard, JF, Sanders DB, and Massey JM. The electrodiagnosis of myasthenia gravis and the lambert-Eaton syndrome. Neurol Clin 1994;12:305–330, with permission.

are common and frequently accompanied by neuromuscular blocking (Fig. 7). Commonly tested muscles in patients with suspected MG are the extensor digitorum communis, orbicularis oculi and frontalis, but it is important to customize the muscle(s) tested depending on patient's symptoms. SFEMG is the most sensitive diagnostic study in MG, with a sensitivity ranging from 90–99% (see Fig. 6) [2,15]. A normal SFEMG jitter study in a weak muscle virtually excludes the diagnosis of MG. In contrast to sensitivity, abnormal jitter is nonspecific since it is often abnormal in a variety of neuromuscular disorders. Hence, SFEMG should always be correlated with the history, examination, and entire EDX study.

5. *Needle EMG.* Conventional needle EMG studies in MG are often normal; however, variation in MUAP configuration with consecutive dischargers (MUAP moment to moment variation) may be apparent (Fig. 3). This is due to intermittent blocking of synaptic transmission of some of the fibers that comprise the MUAP. Similar to SFEMG, however, this finding is nonspecific and is seen with presynaptic NMJ defect (such as LEMS), as well as neurogenic disorders associated with

reinnervation (such as motor neuron disease). Short duration, low amplitude, and polyphasic MUAPs, similar to those encountered in myopathies, may also be seen in MG. Fibrillation potentials are rarely seen in MG, usually in bulbar and paraspinal muscles of patients with late-onset disease [13]; however, when fibrillation potentials are encountered, other neuromuscular diagnoses should be investigated.

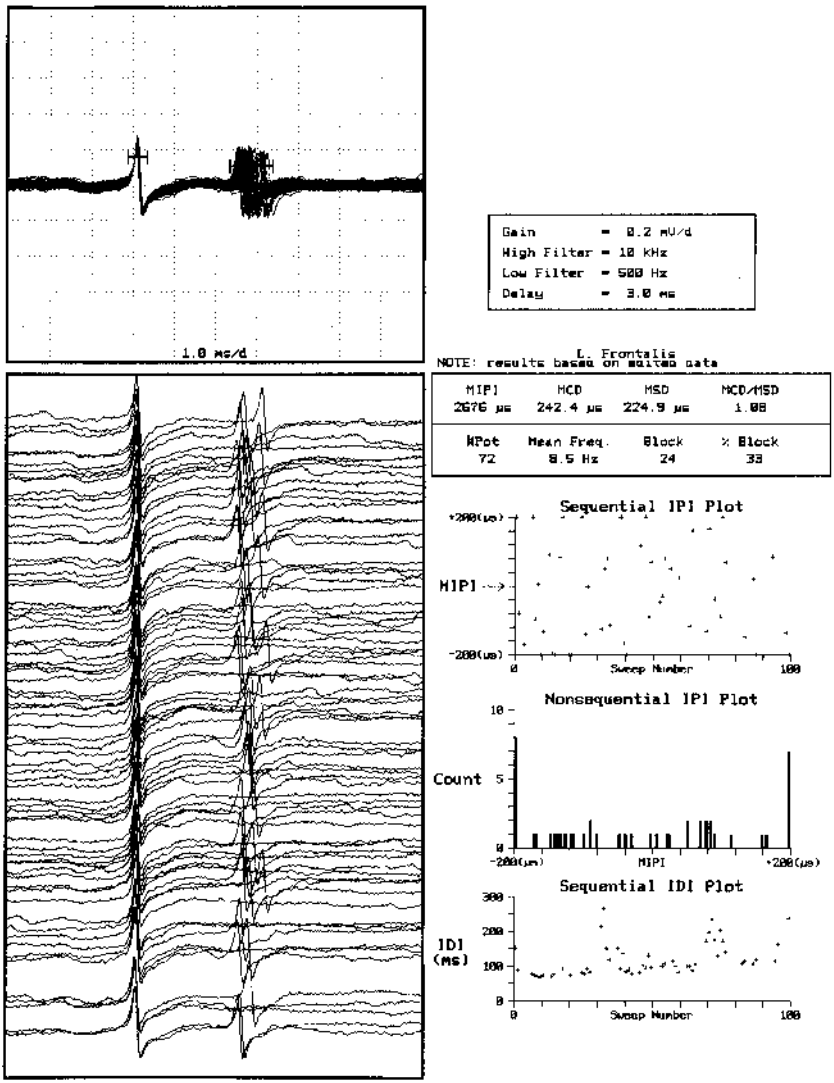

Fig. 7. Abnormal voluntary jitter analysis of a muscle fiber pair with blocking, recording frontalis muscle, in a patient with ocular myasthenia gravis. *Adapted from* Katirji B. Electromyography in Clinical Practice. A Case Study Approach. St Louis: Mosby; 1998, with permission.

Lambert-Eaton myasthenic syndrome

LEMS is an autoimmune disorder caused by a presynaptic NMJ defect. LEMS is a paraneoplastic syndrome in about 60% of cases, often due to a small cell lung carcinoma [8,10]. An autoimmune etiology of LEMS is indicated by the following: (1) the primary autoimmune LEMS responds to corticosteroid treatment, (2) LEMS is associated with other autoimmune disorders, (3) immunosuppressive therapy improves neoplastic and primary autoimmune LEMS, (4) IgG from LEMS patients injected into animals reproduces the electrophysiologic abnormality, (5) patients with LEMS, but not occurring with cancer, have a major histocompatibility locus associated with DRB1 and DQB1, and (6) calcium channel antibodies are found among most LEMS patients [9,20].

Patients usually present with proximal muscle weakness (especially lower extremities), minor ocular and bulbar weakness, and fatiguability. The deep tendon reflexes are characteristically absent or reduced but may be transiently enhanced after brief exercise [9,10]. Autonomic complaints such as dry mouth are common. The diagnosis of LEMS requires a high index of suspicion, particularly in men, smokers, and patients with a known malignancy. At times, LEMS may be confused, clinically and electrophysiologically, with MG (Table 2), and about one fifth of patients with LEMS are originally misdiagnosed as MG [21].

Elevated antibodies towards VGCCs occur in patients with LEMS, and this finding is diagnostic in the appropriate clinical setting. Hence, the

Table 2
Clinical and electrodiagnostic differential diagnosis between generalized myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS)

	Myasthenia gravis	LEMS
Ocular involvement	Prominent	Less prominent
Bulbar involvement	Common, prominent	Uncommon, subtle
Myotatic reflexes	Normal	Absent or depressed
Sensory symptoms	None	Paresthesia is common
Autonomic involvement	None	Dry mouth is common, but also impotence and gastroparesis
Tensilon test	Frequently positive	May be positive
Serum antibodies directed against	Postsynaptic acetylcholine receptors	Presynaptic voltage-gated calcium channels
Baseline CMAPs	Normal	Low in amplitude
Postexercise CMAPs	No change	Significant facilitation
Slow repetitive stimulation	Decrement	Decrement
Rapid repetitive stimulation	No change or decrement	Increment
Single fiber EMG	Increased jitter with blocking	Increased jitter with blocking
Rapid rate simulation jitter	Does not change or worsens jitter	Improves jitter

LEMS = Lambert-Eaton myasthenic syndrome; CMP = compound muscle action potential; EMG = electromyography. (*Adapted from* Katirji B. Electromyography in clinical practice. A case study approach. St. Louis: Mosby; 1998; with permission)

EDX examination is an important diagnostic test in LEMS and constitutes the mainstay of diagnosis. In fact, the electromyographer may be the first to diagnose LEMS in the EMG laboratory by evaluating post-exercise CMAP in patients with universally low CMAP amplitude referred for a variety of reasons (see below). The EDX findings in LEMS are summarized as follows:

1. *Baseline CMAP*. The CMAPs at rest (as well as during routine motor conduction studies) are low in amplitude since many end plates do not reach threshold due to inadequate release of quanta (vesicles) after a single stimulus. Thus, less MFAPs are generated leading to a low amplitude CMAP. This finding occurs in all muscles resulting in diffusely low CMAPs (Table 3).
2. *Rapid repetitive nerve stimulation*. Rapid RNS (usually 20–50 Hz) and postbrief exercise CMAP evaluation enhances calcium influx into the presynaptic terminal, which result in larger releases of quanta and larger EPPs. With many end plates not reaching threshold after the first stimulus, rapid RNS results in many muscle fibers reaching threshold required for the generation of MFAPs (Fig. 2). Thus, more MFAPs are summated with rapid RNS resulting in a CMAP increment (Figs. 8 and 9). The post-tetanic facilitation should exceed 50% and preferably 100% to be diagnostic and specific for a presynaptic defect. This increment is more than 100% in 90% of patients with LEMS, is often more than 200% and may reach as high as 2000% [8,22]. A postbrief exercise CMAP evaluation of at least two motor nerves is a good and sensitive screening test for LEMS [23]. This should be performed also on all patients with universally low (or borderline) CMAPs during routine motor conduction studies, particularly if unexplained. If there is a CMAP increment following a brief exercise, then a rapid RNS should be obtained for confirmation on a single motor nerve.

Table 3
Baseline CMAP and repetitive nerve stimulation findings in common neuromuscular junction disorders

NMJ Disorder	NMJ defect	CMAP amplitude	Slow RNS	Rapid RNS[a]
Myasthenia gravis	Postsynaptic	Normal	Decrement	Normal or decrement
Lambert-Eaton myasthenic syndrome	Presynaptic	Low in all muscles	Decrement	Marked (>200%) increment in all muscles
Botulism	Presynaptic	Low in proximal and weak muscles	Decrement	Modest increment in weak muscles (50–100%)

NMJ = neuromuscular junction; CMAP = compound muscle action potential; RNS = repetitive nerve stimulation ([a] or postexercise CMAP amplitude). (*Adapted from* Katirji B. Electromyography in clinical practice. A case study approach. St Louis: Mosby; 1998; with permission)

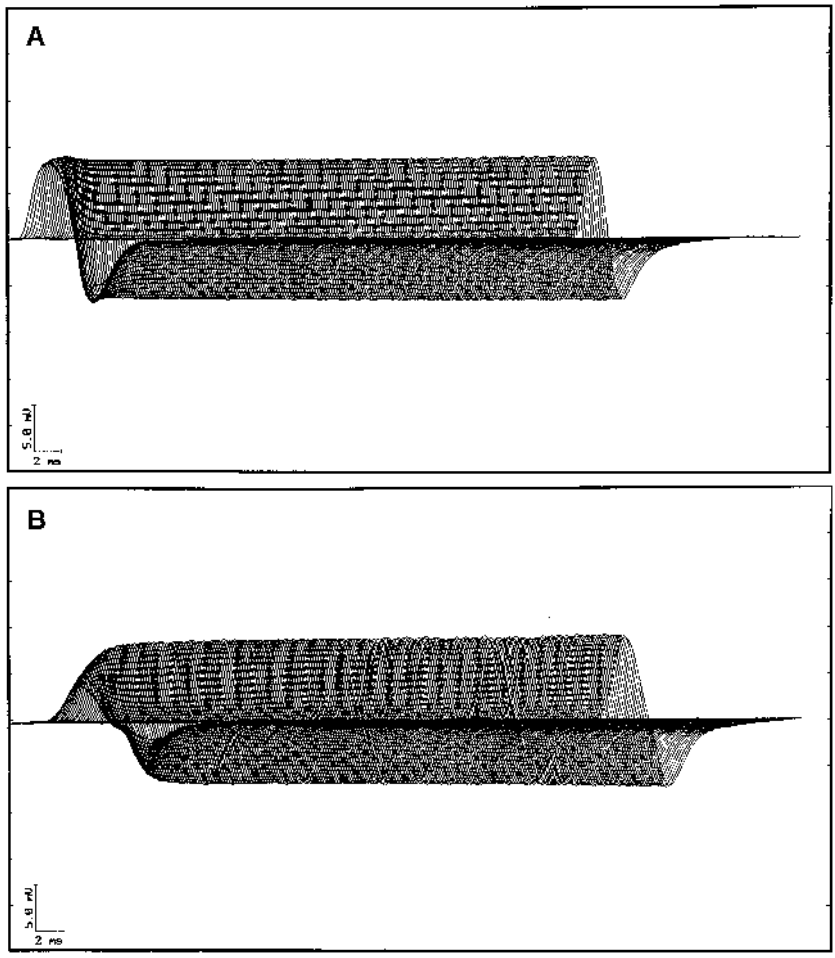

Fig. 8. Rapid repetitive nerve stimulation (50 Hz) of the median nerve. (A) Normal control. (B) Patient with Lambert-Eaton myasthenic myasthenic syndrome. Note the low amplitude first compound muscle action potential (3 mV) and the significant increment (250%) in patient but not in control. *Adapted from* Katirji B. Electromyography in Clinical Practice. A Case Study Approach. St Louis: Mosby; 1998, with permission.

3. *Slow repetitive nerve stimulation*. Slow RNS (usually 2–3 Hz) is not useful in LEMS since it results in decrement of the CMAP, similar to postsynaptic disorders such MG. With slow RNS, ACH release is reduced further because of the depletion of the immediately available stores, and calcium does not accumulate in the presynaptic terminal. The end result is further loss of many MFAPs and a decrement of CAMP amplitude.
4. *Single fiber EMG*. Abnormal jitter and blocking, typical of defective neuromuscular transmission, is seen in all LEMS patients. While this

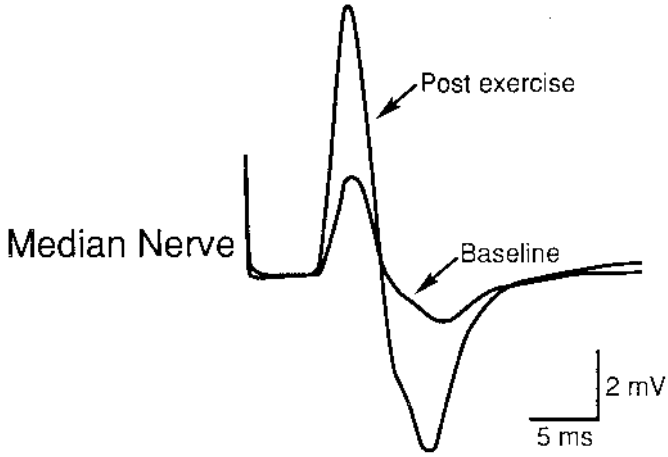

Fig. 9. Baseline (pre-exercise) CMAP with a superimposed CMAP following 10 second of maximal voluntary isometric exercise (post-exercise) in a patient with LEMS. Note the low amplitude baseline CMAP (2.8 mV) and the prominent increment (260%) following exercise. *Adapted from* Katirji B. Electromyography in Clinical Practice. A Case Study Approach. St Louis: Mosby; 1998, with permission.

technique is highly sensitive, it lacks specificity; it is abnormal in MG as well as a variety of other neuromuscular disorders. However, with the stimulation SFEMG technique, the jitter may improve with increasing discharge rate, that is, with rapid rate stimulation (20–50 Hz) compared to the slow rates (2–5 Hz) [23,24]. This finding is caused by the same mechanism as CMAP increment following brief exercise or RNS, that is enhancement of Ach release by the influx of calcium into the presynaptic terminal. Decreased jitter with high rate of stimulation is specific for a presynaptic disorder and is useful in distinguishing LEMS from MG [25].

5. *Needle EMG.* Conventional needle EMG is often normal in patients with LEMS. Short duration, low amplitude and polyphasic MUAPs may be seen occasionally, particular with significant neuromuscular blockade. Similar to postexercise CMAP increment in LEMS, MUAP amplitudes may increase with sustained brief contraction.

Botulism

Botulinum toxins are produced by the anaerobic bacterium Clostridium botulinum. They are extremely potent muscarinic and nicotinic cholinergic presynaptic toxins, with human lethal doses as small as 0.05 to 0.1 micrograms. Botulinum toxins bind to various plasma membrane and vesicle proteins essential for docking of the presynaptic vesicles at the presynaptic active zones of the nerve terminals, resulting in failure of Ach release and ultimate destruction of the presynaptic terminals.

Botulism is rare but may be fatal [11,12,14,26]. Clinically, there are three distinct types of botulism: Food born, infantile and wound botulism. It often presents with a rapid, usually descending, muscular weakness (ocular to bulbar to extremities) with autonomic symptoms (pupillary dilatation, constipation, dry mouth, urinary retention). The differential diagnosis of botulism includes MG, LEMS, Guillain-Barré syndrome (including the Miller-Fisher syndrome), tick paralysis, and diphtheritic polyneuropathy. The diagnosis is confirmed by electrophysiological testing (see below), identification of toxin in serum and stool, or identification of organism in stool cultures (in infantile and wound botulism).

The EDX studies in patients with suspected botulism provides a rapid and readily available method of diagnosis in patients whom bioassay studies for botulinum toxin are pending or stool cultures are negative. The EDX findings are compatible with a presynaptic defect of NMJ but differs from LEMS in that they may vary from day to day, may be normal during the first few days and may be only present in weakened muscles. The findings may summarized as follows:

1. Low CMAP amplitudes is the most consistent finding and is present in 85% of cases, particularly when recording from weak muscles (usually proximal).
2. Rapid RNS, or CMAP following 10 seconds of isometric exercise, results in a CMAP increment consistent with a presynaptic defect (Fig. 10). However, the increment seen in botulism is modest, often ranging between 30 to 100%, when compared to the increment in LEMS which often surpasses 200% (Table 3). This increment may be absent, especially in severe cases such as those caused by type A toxin, presumably due to severe presynaptic blockade.
3. Slow RNS may be normal or reveals a decremental CMAP response; however, this decrement is often mild and does not exceed 8–10%.
4. Needle EMG often reveals increase in the number of small, short polyphasic MUAPs, and occasional fibrillation potentials [14].
5. Increase jitter with blocking on single fiber EMG is a consistent finding. Stimulation SFEMG may improve jitter with a rapid stimulation rate.

Congenital myasthenic syndromes

Congenital myasthenic syndromes are caused by genetic defects of the presynaptic or postsynaptic apparatus [9,27]. Patients have fatigable weakness and ptosis, which may often be traced to birth. Antibodies towards the AchR are not present, and symptoms do not respond to immunosuppressive therapies. Patients may have siblings with a myasthenic disorder, but cases may be sporadic. In newborns, congenital myasthenic syndromes should be differentiated from neonatal MG, which is caused by maternal transfer of anti-ACHR antibodies across the placenta, and may occur in babies of asymptomatic mothers.

Many congenital myasthenic syndromes, regardless of primary etiology, demonstrate a degeneration of the post-synaptic region and simplification of junctional folds often with a concomitant reduction of AchRs. The cause of the membrane damage has been hypothesized to result from the prolonged depolarization of the end plate. The AchR is permeable to calcium, and mechanisms that prolong the time or frequency of channel openings would increase calcium influx. Excess calcium influx could lead to activation of calcium-sensitive proteases and inhibition of mitochondrial respiration. Activation of nitric oxide synthase that is concentrated at the neuromuscular junction could also contribute to free radical damage of the end plate.

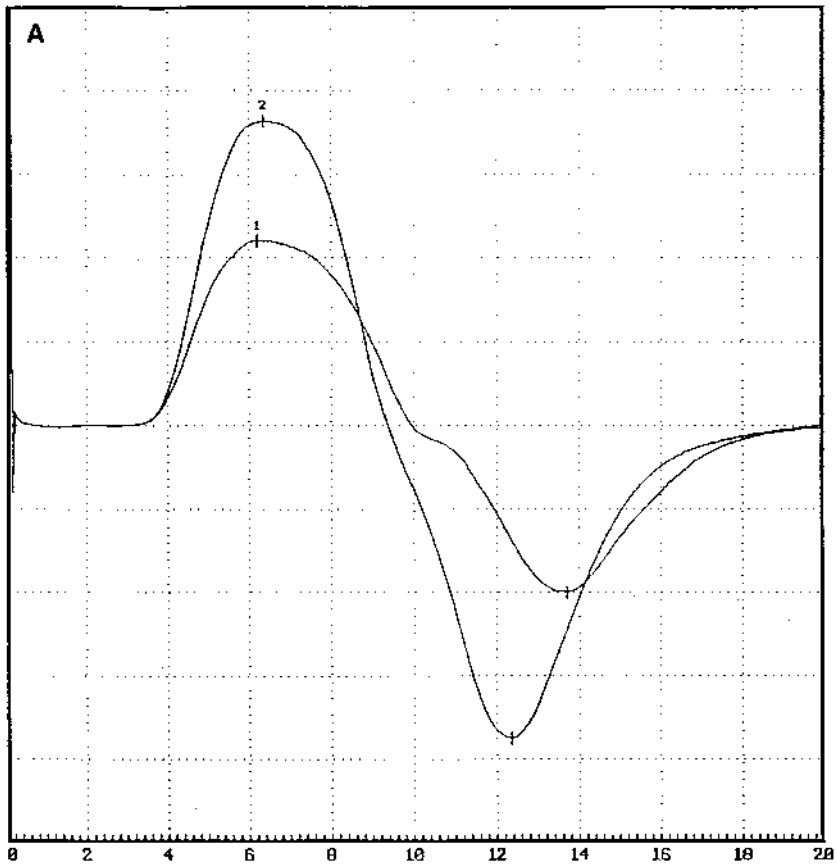

Fig. 10. Increment of CMAP in a patient with food-born botulism. (A) Baseline CMAP (1) and CMAP following 10 seconds of maximal voluntary isometric exercise (2), stimulating the median nerve. Note the 90% CMAP increment following exercise. (B) Following rapid repetitive nerve stimulation (50 Hz) of the spinal accessory nerve. Note the 100% CMAP increment. *Adapted from* Katirji B. Electromyography in Clinical Practice. A Case Study Approach. St Louis: Mosby; 1998, with permission.

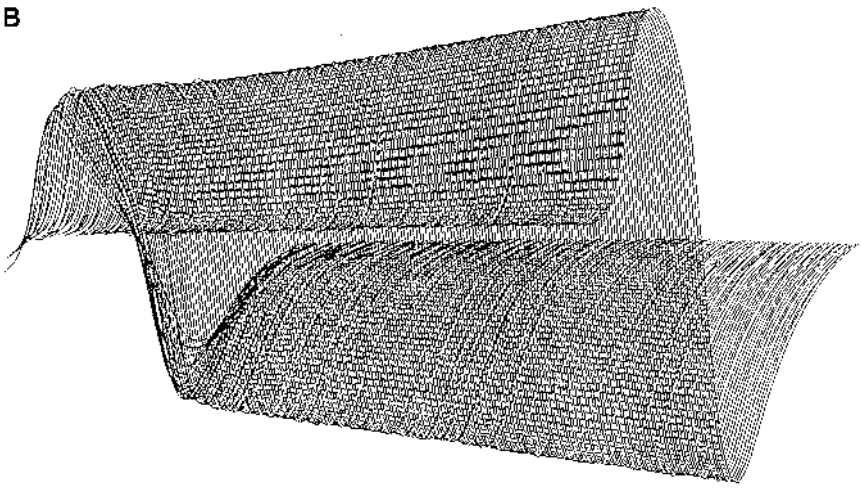

Fig. 10 (*continued*)

Prolonged depolarization of the end plate region may also lead to inactivation of sodium channels that are concentrated in the depths of the junctional folds.

Given the similar anatomic pathology of all the congenital myasthenic syndromes, slow RNS often produces a decremental response. The decrement may be absent during rest and only elicited after several minutes of exercise. In cholinesterase deficiency and slow-channel syndrome, the best characterized of the congenital myasthenic syndromes, a single electrical stimulation leads to repetitive CMAPs. In both these situations, depolarization of the membrane beyond the refractory period for action potential generation would lead to the observed repetitive CMAPs. The repetitive CMAPs is similar to what is seen in organophosphate poisoning and in patients taking AchE inhibitors. Hence, the latter should be discontinued at least 24 hours before testing.

Suggested electrodiagnostic strategy in patients with suspected neuromuscular junction defect

The EDX study of a patient with suspected NMJ disorder should start with a detailed history and comprehensive neurologic examination. Sensory and motor NCSs at least in two limbs (preferably and upper and a lower extremity) should be the initial studies. If the CMAP amplitudes are low, a presynaptic defect should be suspected and ruled out (Fig. 11) [5]. A postsynaptic defect is characterized by normal CMAP amplitudes and, hence, cannot be excluded without the appropriate RNS or SFEMG.

If the diagnosis of LEMS is clinically suspected, baseline and postexercise CMAPs of at least two distal motor nerves is a sufficient screening test [23].

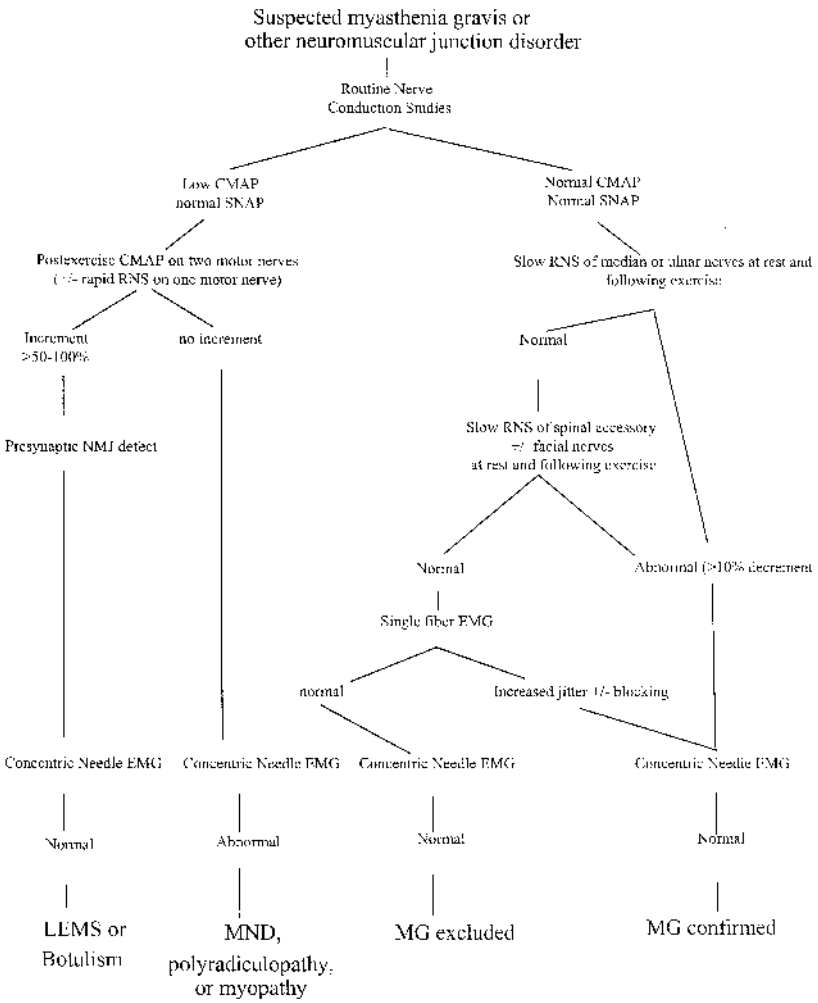

Fig. 11. Diagnostic strategy in patients with suspected myasthenia gravis or other neuromuscular junction disorder (SNAP = sensory nerve action potential; CMAP = compound muscle action potential; RNS = repetitive nerve stimulation; MND = motor neuron disease; LEMS = Lambert-Eaton myasthenic syndrome; MG = myasthenia gravis). *Adapted from* Katirji B. Electromyography in Clinical Practice. A Case Study Approach. St Louis: Mosby; 1998, with permission.

In LEMS, CMAP increment often surpasses 200%. A rapid RNS of one distal nerve, which is extremely painful, should only be done for confirmation if there is a CMAP increment after exercise. If the diagnosis of botulism is considered, the choice of muscle should include weakened, often proximal muscles. In botulism the CMAP increment is usually 30–100%. Also, the study should be repeated in 1–2 days, particularly if the initial evaluation was done during the early phase of the illness.

If the diagnosis of MG is clinically suspected, slow RNS at rest and for 4–5 minutes following a one-minute exercise should be done on at least two motor nerves. The selection of nerves and muscles is dependent on the clinical manifestations with the goal to record from weakened muscles. I suggest performing slow RNS on a distal hand muscle (such as the abductor digiti minimi or abductor pollicis brevis) to start, then moving on to a proximal muscle such as the upper trapezius. Facial RNS should be reserved to patients with oculobulbar symptoms and normal slow RNS recording distal and proximal muscles (see Fig. 11). SFEMG of one or two muscles (such as the frontalis, orbicularis oculi or extensor digitorum communis) should be considered if the diagnosis of MG is still considered despite normal RNS studies (and AchR antibodies).

If the CMAPs obtained on motor NCSs in a patient with suspected MG are low or borderline, postexercise CMAP screening should always be done to exclude LEMS. A misdiagnosis of MG is often made if postexercise CMAP evaluation is not done and a slow RNS shows a CMAP decrement. Similarly, postexercise CMAP screening is recommended for a patient with weakness associated with a malignancy (particularly a small cell lung cancer), or if the clinical situation could not clearly differentiate between LEMS and MG (see Table 2).

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