16. Neurophysiological assessment of muscular disease

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Abstract. Electromyoneurography (EMNG) is a unique method for testing muscle and nerve function and is, therefore, of crucial significance in the assessment of various diseases of the peripheral nervous system. In clinical practice, neurophysiologic examination is most frequently the initial step in the assessment of patients suspected of having muscle weakness of peripheral origin. The EMNG studies not only play an important role in establishing the diagnosis, but significantly contribute to our understanding of the underlying pathogenetic mechanisms of these diseases. It is important to stress that, in addition to EMNG studies, other diagnostic procedures provide valuable information on muscle structural and functional integrity. The EMNG is a diagnostic method consisting of sensory and motor nerve conduction studies (measurement of sensory and motor evoked potential amplitudes and nerve conduction velocities), repetitive nerve stimulation and single fiber electromyography - SFEMG, needle electromyography (EMG), and specific tests such as macro EMG, surface EMG and quantitative EMG. The aim of this review is to present the role of modern neurophysiology in the diagnosis of muscle diseases.

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Electromyoneurography (EMNG) is a unique method for testing muscle and nerve function and is, therefore, of crucial significance in the assessment of various diseases of the peripheral nervous system. In clinical practice, neurophysiologic examination is most frequently the initial step in the assessment of patients suspected of having muscle weakness of peripheral origin. Possible causes include peripheral motor neuron disease, peripheral nerve disorders, pre- or postsynaptic neuromuscular junction disorders, or muscle disease (1). In such cases EMNG studies not only play an important role in establishing the diagnosis, but significantly contribute to our understanding of the underlying pathogenetic mechanisms of these diseases (2). It is important to stress that, in addition to EMNG studies, other diagnostic procedures provide valuable information on muscle structural and functional integrity.

The initial step in the evaluation of each patient suspected of having a muscle disease is to obtain a thorough patient’s history. The time of onset of first symptoms, details on the evolution of the disease (acute, subacute or gradual, over a longer time period), the degree and distribution of muscle weakness, daily fluctuation of symptoms, and possible occurrence of similar symptoms in close relatives should be noted. After obtaining a detailed patient’s history, a careful neurological examination should be performed. This examination is the most important step in the diagnostic procedure since it provides crucial information for establishing a clinical diagnosis. On the other hand, a clinical diagnosis should always be confirmed by additional paraclinical tests, even when a clinical diagnosis is highly probable. The most common additional tests in clinical practice are biochemical blood analyses (levels of creatine phosphokinase, lactate dehydrogenase, myoglobin, lactate and piruvate and other specific enzymes). However, the most useful information is obtained by performing a detailed electromyoneurographic examination which is often sufficient to confirm a clinical diagnosis. Nevertheless, other additional examinations such as CT or MRI muscle imaging, genetic testing and muscle biopsy are frequently performed.

The aim of this review is to present the role of modern neurophysiology in the diagnosis of muscle diseases.

Electromyoneurography (EMNG) is a diagnostic method consisting of sensory and motor nerve conduction studies (measurement of sensory and motor evoked potential amplitudes and nerve conduction velocities), repetitive nerve stimulation and single fiber electromyography - SFEMG, needle electromyography (EMG), and specific tests such as macro EMG, surface EMG and quantitative EMG (3).
Sensory and motor nerve conduction studies

Initial sensitive and motor nerve conduction studies in the evaluation of patients with suspected muscle disease are expected to reveal normal sensory and motor nerve conduction velocities, and thus rule out peripheral nerve lesions. However, in some conditions with both muscle and nerve involvement (mitochondrial disease, paraneoplastic and/or immune mediated systemic diseases and associated neuropathy in some genetically determined myopathies such as myotonic dystrophy type I) reduced amplitudes of sensory and motor evoked potentials and reduced conduction velocities may be found.

Evaluation of neuromuscular transmission

Electrophysiological evaluation of neuromuscular junction disturbances consists of standard repetitive nerve stimulation and single fiber EMG in selected cases. Standard repetitive nerve stimulation may be performed on any muscle and is most reliable when performed on clinically affected muscles. Low frequency stimulation (2-3 Hz) of the appropriate nerve is applied. The most commonly tested muscles are facial muscles (nasalis), proximal upper limb muscles (deltoid, trapezius), anconeus and abductor digiti minimi. This test is exceptionally significant in patients with suspected myasthenia gravis (MG). A reproducible 10% or greater decrement in amplitude when comparing the first stimulus to the fourth or fifth, found in at least one muscle is considered to indicate impairment of neuromuscular transmission and supports the diagnosis of MG (Figure 1).

Figure 1. Positive decremental response in MG
Repetitive nerve stimulation is abnormal in approximately 50% of patients with pure ocular MG, and in approximately 80% of patients with generalized MG (4).

Repetitive nerve stimulation is used in the evaluation of patients with other suspected disturbances of neuromuscular transmission such as congenital myasthenic pre- or postsynaptic syndromes, presynaptic Eaton-Lambert myasthenic syndrome, botulism, neuromuscular transmission defects caused by organophosphate poisoning or other toxic and infective agents (5). In Lambert-Eaton myasthenic syndrome (ELS), which can be paraneoplastic (most commonly associated with oat cell lung cancer) or an autoimmune disease, repetitive nerve stimulation reveals an increment in amplitude, typically greater than 100%. A characteristic finding in ELS is a very low amplitude of the first response with a significant postexercise increment (greater than 100% as a rule, in some cases greater than 400%). The physiologic basis of the response to repetitive nerve stimulation in ELS is a presynaptic neuromuscular junction defect with a very low amplitude of the initial response due to reduced acetylcholine (ACh) release at the presynaptic nerve terminal and a substantial postexercise increment as a consequence of calcium facilitation of available ACh release at rapid rates of stimulation.

**Single fiber electromyography (SFEMG)**

Single fiber EMG (SFEMG) is a technique which evaluates the microphysiology of motor units and motor end-plates. It provides a tool for the quantification of neuromuscular transmission and is helpful in studying the topography of motor units. Neuromuscular transmission is assessed by recording action potentials from individual muscle fibers belonging to the same motor unit. When the SFEMG electrode is positioned to record from two or more muscle fibers in one activated motor unit, variations in time intervals between pairs of action potentials, the “neuromuscular jitter” can be observed and calculated. When neuromuscular transmission is sufficiently impaired, nerve impulses frequently fail to elicit action potentials and SFEMG shows intermittent “blocking”. In addition, fiber density measurements provide information on the topography of motor units.

Jitter analysis is an exceptionally sensitive method for detecting disturbances of neuromuscular transmission (almost 100%) and is indispensable in patients suspected of having MG or other neuromuscular transmission defects, especially when repetitive nerve stimulation shows normal findings. However, jitter analysis lacks specificity and increased jitter can be found in most neuromuscular disorders. Therefore, the obtained results must be interpreted in context of clinical data and other electrophysiological findings (6).
Typical SFEMG findings (increased jitter and blocking) in a patient with MG (Figure 2).

**Figure 2.** SFEMG recordings from extensor digitorum communis muscle (10 superimposed traces). The oscilloscope is triggered by the rising phase of the first action potential. A. Normal jitter (39 μs), B. The second potential shows increased jitter (95 μs) without blocking, C. The second shows increased jitter (59 μs) and the third shows markedly increased jitter (98 μs) and blocking.

**Standard (conventional) (EMG)**

Conventional needle EMG provides insight into motor neuron, nerve root, peripheral nerve and muscle structure and function. Conventional EMG is dependent on the subjective assessment of all observed phenomena by the investigator. Therefore, this examination should be performed by an experienced neurologist familiar with neuromuscular diseases. The EMG examination is performed with concentric or monopolar needle electrodes and is an invasive procedure. Patients should be thoroughly informed about the procedure prior to the examination and should give their consent (7). In a conventional EMG examination motor unit potentials (MUPs) are recorded and their electrophysiological characteristics are assessed – the shape, amplitude, duration, number of phases, stability and frequency. A motor unit consists of all muscle fibers innervated by one motor neuron. A motor unit is defined as one motor neuron, its axon and all of the muscle fibers it innervates. The innervation ratio represents the number of muscle fibers per axon and varies among muscles (8).

Needle EMG provides information on the structure and function of entire motor units. A detailed EMG examination can localize lesions from motor neuron to muscle and is helpful in determining the nature of the underlying pathological process.
In order to adequately assess each patient suspected of having a primary muscle disease, four basic steps of EMG examination have been defined: inspection of insertional activity, recording of spontaneous activity with the muscle at rest, analysis of characteristics of motor unit potentials during mild to moderate muscle contraction and analysis of recruitment and interference pattern during progressively increasing levels of contraction to a maximal level (9). Needle EMG detects the type and degree of lesions in the examined muscles and is helpful in determining which muscles are most suitable for muscle biopsy if it is important for a definite diagnosis.

Insertional activity is caused by movement of a needle electrode in the muscle. Insertion of the needle electrode into a normal or dystrophic muscle usually gives rise to short bursts of electrical activity (lasting less than 300 ms). In a denervated muscle or in inflammatory myopathy such as polymyositis, the insertional activity lasts longer. Insertional activity most commonly appears as positive or negative high-frequency spikes in a cluster lasting in average a few hundred milliseconds, as a result of mechanical stimulation or injury of muscle fibers ("injury potentials"). Reduced or absent insertional activity is seen in atrophic muscles with fibrosis and in functionally inexcitable muscles as in patients with familial periodic paralysis. Conversely, prolonged insertional activity indicates instability of muscle fiber membranes as in patients with myotonic disorders and myositis. Insertional positive sharp waves appearing with a frequency of 3 to 30 Hz, lasting from a few seconds to one minute are seen in acute or chronic denervation and in conditions with rapidly progressive degeneration of muscle fibers (10).

There is no spontaneous activity in a normal muscle and this phenomenon is known as “electrical silence”. In contrast, any forms of spontaneous activity such as fibrillation potentials, positive sharp waves, myotonic or pseudomyotonic discharges, myokimia and/or cramps recorded in a relaxed muscle unequivocally indicate a pathological process (see table below). However, it is important to note that some forms of spontaneous activity can be registered in normal muscle at the end-plate region. End-plate activity consists of two components: end-plate noise and end-plate spikes and this type of spontaneous activity can resemble denervation activity. Endplate noise is caused by spontaneous quantal release of acetylcholine and consists of irregular negative potentials 10 to 50 μV in amplitude and 1 to 2 ms in duration. End-plate spikes are 100 to 200 μV in amplitude and fire irregularly at 5 to 50 per minute. These potentials should not be mistaken for a pathological finding (11).

Fibrillation potentials range from 20 to 200 μV in amplitude and 1 to 5 ms in duration, and fire with a frequency of 1 to 30 Hz. They usually show
diphasic or triphasic waveforms with an initial positivity. Fibrillations are seen in some muscular dystrophies and in inflammatory myopathies.

Complex repetitive discharges arise as a result of almost simultaneous firing of a group of muscle fibers. They range from 50 μV to 1 mV in amplitude and from 50 do 100 ms in duration. Complex repetitive discharges are encountered in Duchenne muscular dystrophy and chronic myopathies.

Neuromyotonia results from continuous, irregularly occurring, repetitive, single or multiplet muscle fiber or motor unit discharges, firing at a high intraburst frequency (30 do 300 Hz).

Muscle cramps are painful, involuntary muscle contractions. Electrically, muscle cramps consist of high-frequency (40 to 60 Hz) irregular motor unit discharges which typically begin and cease suddenly.

Myotonia represents repetitive discharges firing at rates of 50 to 100 Hz and ranging in amplitude from 10 μV to 1 mV. Myotonic discharges are of two different types: biphasic spike potentials with a small initial positivity, less than 5 ms in duration resembling fibrillation potentials and positive waves of 5 to 20 ms in duration resembling positive sharp waves. The amplitude and frequency of the potentials must both wax and wane to be identified as myotonic discharges (12).

One of the most important parts of the EMG examination is the analysis of muscle activity during voluntary contraction, following evaluation of insertional and spontaneous activities. Voluntary activity is analyzed at the beginning of the contraction, at submaximal and full muscle contraction and, finally, during gradual relaxation (13). Initially, motor unit characteristics are noted during mild muscle contraction—the shape, duration, rise time, phases and stability. The following part of the examination consists of MUP
amplitude, recruitment pattern and interference pattern estimation during gradually increasing contraction to a maximal level. The recorded amplitude varies from a few hundred μV to a few mV and reflects the number of firing muscle fibers at the tip of the electrode, i.e. muscle fiber density. The amplitude depends on the distance of the tip of the needle electrode from the discharging muscle fibers. The rise time (time from the initial positive peak to the next negative peak) of APs is also determined by this distance. The duration of motor units is 5 to 15 ms and reflects the activity of the majority of muscle fibers of individuals motor units. Duration also varies in relation to age. The number of phases defines the shape of motor units. The phases consist of positive and negative deflections from the baseline and normal motor units have less than four or four phases. Only 5 to 15% motor units in a normal muscle consist of five or more phases. An increased number of phases indicates temporal dispersion of muscle fiber potentials within a motor unit due to differences in conduction time along nerve terminal branches or over the muscle fiber membranes.

The interference pattern (IP) is recorded during maximal muscle contraction and can be obtained using a needle or surface electrode. IP represents a simultaneous activation of many, rapidly firing motor units. Motor units are activated gradually according to the size principle (earlier activation of small type IA muscle fibers during mild contraction and later activation of large type II muscle fibers during strong voluntary contraction). This phenomenon is known as the "recruitment pattern" (14). Muscle force is increased not only by recruiting previously inactive motor units, but with more rapid firing of already active units.

Analysis of IP comprises the analysis of amplitude and density (fullness) of the EMG trace at full muscle contraction.

In primary and secondary muscle diseases (myopathies) characteristic electromyographic features of myopathy are found. As the number of muscle fibers is reduced in these conditions, low-amplitude and short-duration motor unit potentials are a regular finding (15). In addition, due to significant desynchronization of depolarisation of muscle fibers within a motor unit, the motor units in myopathy are markedly polyphasic (Figure 3).

Therefore, a characteristic myopathic pattern consists of low-amplitude, short-duration MUPs and a full interference pattern during weak muscle contractions. In advanced stages of myopathy the interference pattern becomes incomplete and can sometimes be confused with a reduced IP in neurogenic lesions.

In conclusion, EMNG studies play a crucial role in the investigation of muscle diseases and are indispensable in the assessment of patients with myopathies. EMG findings enable clinicians to diagnose myopathies with high
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Figure 3. Myopathic pattern of EMG (low amplitude and short duration action potentials and reduced interference pattern).

certainty and provide additional useful data concerning the underlying pathophysiological process. EMG evaluation is also helpful in distinguishing primary from secondary myopathies, slowly progressive from rapidly deteriorating muscle diseases, in diagnosing inflammatory myopathies and channelopathies.

Acknowledgment

The author thank Sanja Pavlovic for her help in editing this chapter.

References


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