Methods of Testing Neuromuscular Transmission in the Intensive Care Unit

François Grand'Maison

ABSTRACT: All disorders of neuromuscular transmission (NMT) may cause ventilatory failure, albeit rarely. Respiratory muscle weakness is occasionally the presenting feature of myasthenia gravis (MG), the Lambert-Eaton myasthenic syndrome (LEMS), hypermagnesemia and botulism. Chronic MG, congenital myasthenic syndromes and LEMS may be acutely exacerbated by various intercurrent conditions and by drugs which interfere with NMT. Finally, in the ICU, difficulty in weaning from the ventilator may be caused by prolonged use of neuromuscular blocking agents. Electrophysiological studies of NMT disorders in the intensive care unit have rarely been reported. Nevertheless, the available data indicates that the electrodiagnosis of severe NMT disorders can be misleading. With severe NMT defects, the electrophysiological distinction between post-synaptic and pre-synaptic disorders is blurred and the differential diagnosis with myopathies may be difficult. A clinically suspected NMT disorder should therefore not be ruled out when electrodiagnosis fails to demonstrate the expected abnormalities.

The electrophysiological evaluation of the neuromuscular junction in the context of ventilatory failure is considered in one of three settings (Table 1): 1) the suspicion of a neuromuscular transmission (NMT) disorder in a patient presenting with respiratory failure; 2) the suspicion of a NMT defect acquired in the ICU; and 3) the evaluation of respiratory failure in a patient with a known NMT disorder. In this last situation, ventilatory insufficiency may result from an exacerbation of the primary condition or from an unrelated process.

NMT disorders can be classified into pre-synaptic and post-synaptic defects (Table 2). The electrodiagnostic features of these two groups of diseases have been well characterized. These characteristics, with emphasis on the difficulties encountered in the ICU, will be reviewed.

Nerve Conduction Studies

The major role of nerve conduction studies in patients with a suspected NMT disorder and respiratory failure is to rule out a neuropathic process, particularly Guillain-Barré syndrome and critical illness polyneuropathy.

Classically, in auto-immune MG, sensory and motor nerve conduction studies are normal. However, compound muscle action potential (CMAP) amplitudes are commonly reduced in patients with severe MG and diaphragmatic weakness. In these subjects, ACh receptor antibody titres may be negative, adding to the diagnostic confusion if the diagnosis had not previously been firmly established.

Respiratory failure may also occur in the rare congenital myasthenic syndromes. In congenital deficiency of acetylcholinesterase and in the slow-channel syndrome, repetitive CMAPs after a single supramaximal stimulus are characteristic. Repetitive CMAPs are caused by prolonged end-plate potentials.
orders. In LEMS, CMAPs in resting muscles are, on average, approximately 6% of patients. Small diaphragmatic potentials are also observed in organophosphate poisoning, because of the inhibition of cholinesterase activity. Organophosphate poisoning is rare in North America but quite common in many Asian countries, where it is a leading cause of chemical intoxication.

CMAP amplitudes are typically reduced in pre-synaptic disorders. In LEMS, CMAPs in resting muscles are, on average, 20-25% of normal values. CMAP amplitude has been correlated with the severity of the clinical condition. Respiratory failure, which may be the presenting feature of LEMS, occurs in approximately 6% of patients. Small diaphragmatic potentials on phrenic nerve stimulation have been reported in these patients. CMAP amplitudes are also small in the other major pre-synaptic NMT disorders, hypermagnesemia and botulism. Hypermagnesemia is a rare condition that may follow excessive therapeutic administration of magnesium sulfate to treat eclampsia. Clinically significant hypermagnesemia may also be caused by oral or rectal administration of magnesium containing products in patients with abnormal renal function. The most common form of botulism in North America is infant botulism, which is reported to have an incidence of 1/100,000 live births in the United States.

**Repetitive Nerve Stimulation**

Abnormalities on repetitive nerve stimulation studies are the hallmark of NMT disorders. These studies are easily performed in the intensive care unit. Classically, in auto-immune MG, a 10% or greater decrement of the CMAP is seen at low frequencies (2-5 Hz). Testing is easier in distal muscles but the diagnostic sensitivity is higher in proximal muscles – a decrement is detected in 80-85% of distal muscles and in 90-95% of proximal muscles in moderately severe generalized MG. Warming the muscle increases the diagnostic yield by reducing the safety margin of NMT. Sources of error include electrode movement and submaximal stimulation. Repetitive stimulation of the phrenic nerves may be very useful but requires considerable experience because of the small size of the response, unstable baseline and the effect of lung volume changes on the amplitude.

Persistent weakness and failure to wean from the ventilator may result from prolonged use (more than two days) of neuromuscular blocking agents, particularly vecuronium. Patients with poor renal function and higher levels of magnesium are at greater risk. Small CMAPs and a decrement on repetitive stimulation are characteristic. Weakness may result from a toxic effect on muscle in addition to the NMT defect. A decremental response at low rate (2-5 Hz) stimulation is found in other disorders of NMT, including LEMS and botulism. However, a decrement is not pathognomonic for primary NMT defects as it may also be seen in rapidly progressive neurogenic disorders such as amyotrophic lateral sclerosis because smaller EPPs are generated in recently reinnervated muscles.

In the intensive care unit, repetitive stimulation studies may be misleading because low rate stimulation may not reveal a decremental response in patients with severe NMT defects

**Needle EMG**

Classically, in MG and LEMS, needle EMG does not reveal abnormal activity in resting muscle. In severe MG and in botulism, fibrillation potentials and positive sharp waves are relatively frequent. In MG, on voluntary activation of muscle, motor unit amplitude and morphology may fluctuate, reflecting intermitting blocking. Easily recruited, short duration, small amplitude, polysynaptic motor unit potentials indicate more severe transmission failure. The differential diagnosis with myopathies may therefore be impossible on the basis of needle EMG alone.

### Table 1: Neuromuscular Transmission Disorders Causing Respiratory Failure.

1. NMT disorders which may present with acute ventilatory failure
   - Myasthenia gravis
   - Lambert-Eaton myasthenic syndrome
   - Botulism
   - Hypermagnesemia
   - Tick paralysis
2. NMT defects acquired in the ICU (difficulty weaning from ventilator)
   - Prolonged effect of neuromuscular blocking agents
   - Hypermagnesemia
3. Factors which may exacerbate previously diagnosed NMT disorders
   - Infections
   - Hypermagnesemia
   - Aminoglycoside antibiotics
   - Calcium channel inhibitors
   - Beta-adrenergic blocking agents
   - Antiarrhythmics

### Table 2: Pre-synaptic and Post-synaptic Disorders.

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(EPPs) which maintain the post-synaptic membrane depolarized beyond threshold after the refractory period of the initial muscle action potential, resulting in the generation of a second, and occasionally a third, action potential. Repetitive CMAPs may also be observed in organophosphate poisoning, because of the inhibition of cholinesterase activity. Organophosphate poisoning is rare in North America but quite common in many Asian countries, where it is a leading cause of chemical intoxication.

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An increment of the CMAP of 100% or more during high frequency (20-50 Hz) repetitive stimulation is characteristic of pre-synaptic disorders, particularly LEMS. A similar result may be obtained following voluntary activation of the muscle if the patient cooperates sufficiently. In severe LEMS, a decrement of one to two seconds may precede the incremental response. In botulism, transmission failure is usually marked and calcium mobilization from high rate stimulation is often insufficient for potentiation. Conversely, incremental responses of up to 200% may be obtained in severe MG.

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Table 3: Electrodiagnostic Abnormalities in Myasthenia Gravis and the Lambert-Eaton Myasthenic Syndrome (Classical vs. Severe).

<table>
<thead>
<tr>
<th>Classical electrodiagnostic abnormalities</th>
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<tr>
<td><strong>CMAP</strong></td>
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<td>Low rate stimulation (2-5 Hz)</td>
<td>Decrement in weak muscles</td>
</tr>
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<tr>
<td></td>
<td>Increment &gt; 100%</td>
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<td><strong>Single fibre EMG</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased jitter and blocking (increase at high rates)</td>
</tr>
<tr>
<td><strong>Needle EMG</strong></td>
<td>Variation in MUP size</td>
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<td></td>
<td>Brief, small, polyphasic units</td>
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MG = myasthenia gravis  
LEMS = Lambert-Eaton myasthenic syndrome  
CMAP = Compound muscle action potential  
MUP = Motor unit potential  
PSWs = positive sharp waves

**Single Fibre EMG**

Single fibre EMG (SFEMG) is the most sensitive electrodiagnostic test to detect NMT disorders.² This technique measures the variability (jitter) of the difference in the EPP rise time in two fibres of the same motor unit. It also serves to quantitate conduction failure (blocking) in a pair of muscle fibres. The value of this test is limited in the ICU because patient cooperation is essential.

Stimulated SFEMG, which does not require cooperation from the patient, may be useful in selected individuals.¹³ The technique consists of stimulating an intramuscular nerve with a needle electrode inserted near the motor point of a muscle. A SFEMG electrode is used to record the activity of a muscle fibre. Jitter with respect to the stimulus artifact and blocking can be measured as in conventional SFEMG. With increasing rates of stimulation, jitter decreases in pre-synaptic disorders and increases in post-synaptic disorders.

When repetitive stimulation testing is equivocal, SFEMG assumes a crucial role for detecting a NMT defect. Although abnormalities on SFEMG are not specific, a normal SFEMG study greatly reduces the possibility of a NMT disorder.

**Additional Investigation**

Various tests may help to distinguish the NMT disorders among themselves and to differentiate them from myopathies and generalized polyneuropathies. A positive edrophonium test strongly supports the diagnosis of post-synaptic NMT disorders. However, false positive results are well-documented. Repair of a decrement on repetitive stimulation following edrophonium has been demonstrated not only in pre-synaptic NMT disorders but also in some peripheral nerve disorders.¹⁴ Elevated CK levels – characteristic of necrotizing myopathies – have been reported in NMT defects induced by neuromuscular blocking agents when associated with thick-filament myopathy.¹⁰ The CK level is usually normal in other NMT conditions causing respiratory failure. Anti-Ach receptor antibodies are detected in approximately 90% of subjects with generalized auto-immune MG and antibodies to voltage-gated calcium channels are present in as many as 92% of patients with LEMS.¹⁵ In selected cases, when the diagnosis remains undetermined, muscle or nerve biopsy may be necessary to establish the underlying pathophysiology. When one of the congenital myasthenic syndromes is suspected, microphysiologic studies of excised intercostal muscle fibres may be performed in specialized centres.

**CONCLUSION**

The electrodiagnosis of NMT disorders initially presenting with respiratory muscle failure may be confusing and quite difficult. With severe NMT defects, repetitive nerve stimulation studies may not reveal the classical abnormalities. In these patients, on the sole basis of electrophysiology, the distinction between post-synaptic and pre-synaptic disorders is blurred and the differential diagnosis with myopathies may be impossible. A clinically suspected NMT disorder should therefore not be ruled out when electrodiagnosis fails to demonstrate the expected abnormalities. Proper diagnosis will rest on serial electrodiagnostic tests, clinical features, associated conditions, serology and other tests.
REFERENCES