Methods of Testing Neuromuscular Transmission in the Intensive Care Unit

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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.

RÉSUMÉ: Méthodes d’évaluation de la transmission neuromusculaire à l’unité de soins intensifs. Tous les désordres de la transmission neuromusculaire (TNM) peuvent entraîner une insuffisance respiratoire. L’insuffisance de la musculature respiratoire est occasionnellement la première manifestation de la myasthénie grave (MG), du syndrome de Lambert-Eaton (SLE), de l’hypermagnésémie et du botulisme. Plusieurs conditions et médicaments provoquent une détérioration aigüe de la MG chronique, du SLE et de certains syndromes myasthéniques congénitaux. Finalement, l’utilisation d’agents curarisants non dépolarisants aux soins intensifs entraîne parfois une difficulté de sevrage du ventilateur. Les études électrophysiologiques de désordres de la TNM aux soins intensifs sont rarement rapportées dans la littérature. Les données disponibles suggèrent que les résultats des tests électrophysiologiques sont occasionnellement trompeurs lorsque le défaut de TNM est important. La distinction entre les blocs jonctionnels présynaptiques et postsynaptiques devient alors incertaine et le diagnostic différentiel avec les myopathies peut être difficile. Aux soins intensifs, un désordre de la TNM ne devrait donc pas être définitivement exclu lorsque les tests électrodiagnostiques ne révèlent pas les anomalies attendues.

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 MG1-3 and diaphragmatic weakness.4 In these subjects, ACh receptor antibody titres may be negative,4 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.5 Repetitive CMAPs are caused by prolonged end-plate potentials...
patients. CMAP amplitudes are also small in the other major
on phrenic nerve stimulation have been reported in these
occasionally a third, action potential. Repetitive CMAPs may
beyond threshold after the refractory period of the initial muscle
approximately 6% of patients. Small diaphragmatic potentials
ed with the severity of the clinical condition. Respiratory fail­
20-25% of normal values. CMAP amplitude has been correlat­
tries, where it is a leading cause of chemical intoxication.
Weakness may result from a toxic effect
greater risk. Small CMAPs and a decrement on repetitive stimu­
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
(Table 3). In these patients, transmission failure may be so
severe that the decline in ACh release resulting from low
frequency stimulation has no effect. Alternatively, a decrement
in very small CMAPs may be difficult to detect.
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.

**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 inter­
mittent blocking. Easily recruited, short duration, small ampli­tude, polyphasic 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 3: Electrodiagnostic Abnormalities in Myasthenia Gravis and the Lambert-Eaton Myasthenic Syndrome (Classical vs. Severe).

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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. 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. 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. Elevated CK levels – characteristic of necrotizing myopathies – have been reported in NMT defects induced by neuromuscular blocking agents when associated with thick-filament myopathy. 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. 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