Key Points in the Differential Diagnosis of Myasthenic Syndromes

Aspectos Fundamentais do Diagnóstico Diferencial dos Síndromas Miasténicos

Sara Machado*,**, Carolina Pires***, Hadil Manji*
1-Hospital Professor Doutor Fernando Fonseca, EPE; 2-Hospital do Divino Espírito Santo de Ponta Delgada, EPE; 3-Institute of Neurology, University College of London; 4-National Hospital for Neurology and Neurosurgery, London; *both authors contributed equally to this manuscript

Abstract
Neuromuscular junction disorders are a heterogeneous group most often caused by immune or genetic abnormalities. They comprise Myasthenia Gravis, Lambert-Eaton Syndrome and Congenital Myasthenic Syndromes. Despite affecting different parts of the synapse, they share clinical and neurophysiological features, posing a diagnostic challenge.

These disorders can be divided in subgroups, according to the causing antibody or genetic defect. However, there are no established clinical criteria and the accurate diagnosis is highly dependent on the recognition of phenotypes. The identification of clues both in the history and examination may be precious to the correct diagnosis.

Treatment depends on the underlying abnormality and the prognosis is generally good. However, more severe forms of Myasthenia Gravis and paraneoplastic Lambert-Eaton Myasthenic Syndrome are recognised.

Resumo
As doenças da placa neuromuscular são um grupo heterogêneo e frequentemente causadas por mecanismos imunológicos ou defeitos genéticos. Deste grupo fazem parte a Miastenia Gravis, o Síndrome de Lambert-Eaton e os Síndromas Miasténicos Congênitos. Apesar de afectarem diferentes constituintes do sinapse, existem características clínicas e neurofisiológicas comuns, o que torna a distinção difícil.

Estas entidades podem ainda ser subdivididas, de acordo com o anticorpo causal ou defeito genético subjacente. Como não existem critérios de diagnóstico estabelecidos, o diagnóstico está dependente do reconhecimento de fenótipos. Assim, a identificação de pistas na anamnese e na observação neurológica podem ser fundamentais.

O tratamento é determinado pela fisiopatologia subjacente e o prognóstico é geralmente favorável. Contudo, formas severas de Miastenia Gravis e de Síndrome miástênico de Lambert-Eaton paraneoplásico são reconhecidas.

Introduction
The neuromuscular junction (NMJ) is a specialized synapse designed to transmit nerve impulses from the motor nerve to the muscle. NMJ disorders comprise a heterogeneous group. Although they affect different parts of the synapse, they share both clinical and neurophysiological features. It is important to correctly diagnose these disorders in order to optimise management strategies and improve the prognosis.

Myasthenia Gravis (MG) is the most common of such disorders, with identifiable pathogenic antibodies. The exact origin of the immune attack remains unknown.

In this review, a discussion of the differential diagnosis of MG, especially with respect to clinical features and investigations, will be addressed.

Background
1. Basic principles
In order to achieve a better understanding of the pathophysiology of NMJ disorders it is important to know its basic anatomy and physiology (vide figure 1). In essence,
the nerve impulse opens the voltage gated calcium channels (VGCC), leading to an influx of calcium and fusion of the acetylcholine (ACh) vesicles to the synaptic membrane.

The binding of ACh to its receptor depolarises the muscle membrane, leading to muscular contraction. The presence of some proteins (such as MuSK – muscle specific tyrosine kinase, Rapsyn and Dok-7) enhances the clustering of ACh receptors (AChR) at the postsynaptic site, improving the efficacy of the neuromuscular transmission. Of note, skeletal muscles express nicotinic type AChR whereas cardiac and smooth muscle express muscarinic type receptors.

The lack of blood-nerve barrier at the NMJ makes it vulnerable to immune attack. As further discussed in the following sections, symptoms may result from a mutation of certain proteins or from the interaction between the immune system (or toxins) and its targets.

2. Myasthenia Gravis and Myasthenic Syndromes

Myasthenia Gravis

MG is a rare disorder, with a prevalence of about 1–2 per 10,000 people and an incidence of 1.7 to 21 per million inhabitants per year. An increased incidence in the elderly and an overall increase in prevalence have also been reported. The incidence has a bimodal distribution, influenced by age and gender; with a female-to-male ratio of 3:1 in young adults (<40 years), whereas the later onset form (especially after 50 years) is more common in men.

The aetiology of the disorder, though not completely understood, is thought to arise out of an immune dysregulation within the thymus, at least in the anti-AChR+ patients subset. Nevertheless, genetic factors may also play a role. Furthermore, MG may be a paraneoplastic disorder with an underlying thymoma in up to 10% of cases.

Although no widely accepted diagnostic criteria exist, there are fundamental clinical features, such as painless fatigable weakness, which often fluctuates during the day or from day to day. In up to 85% of patients the most common presentation is a fluctuating ptosis or diplopia. This occurs because the extraocular muscles are exceedingly vulnerable, possibly due to high blood flow, mitochondrial content and elevated metabolic rate. Ocular weakness is such an important finding that if not demonstrated then the diagnosis of MG should be reconsidered. Another suggestive and related feature is the presence of a "switching ptosis", an unilateral ptosis that changes to the other eyelid. The ocular symptoms typically worsen during trivial activities such as reading and driving, particularly in bright sunlight.

A crano-caudal progression often occurs within 1-2 years, with a progressive involvement of bulbar, limb (any group is potentially affected but proximal muscles are commonly involved) and respiratory muscles. The course of the disease is variable and there are well established precipitants including infections, pregnancy, menstruation, drugs (e.g. aminoglycosides, quinolones, tetracyclines, chloroquine, penicillamine, succinylcholine and botulinum toxin), hypokalaemia and hypophosphataemia, among others. Importantly, in about 15% of patients, bulbar weakness may be the initial symptom, including dysphagia, dysarthria or chewing difficulties.

Apart from ptosis, unilateral frontalis overactivity may be the only clue of weakness. Useful clinical pointers include Cogan's lid twitch sign (this sign may be seen after downgaze, where there is transient unmasking of the increased innervation of the lid from central adaptation, causing the lid to overshoot on upgaze), a complex ophthalmoplegia and a downward droop of the corners of the mouth are other suggestive features.

The aim of the motor examination is to detect fatigability. By definition there is increased weakness after effort (hence, power should be tested before and after exertion). It may be elicited by sustained up-gaze, neck flexion and shoulder abduction. Respiratory weakness is demonstrated by difficulties in chest movement and use of accessory muscles of respiration. At the bedside a forced vital capacity (FVC), lying and standing, may help identify diaphragmatic weakness. The remaining neurological exam is unremarkable, with sparing of sensory modalities as well as myotatic reflexes.

There are two bedside tests easy to perform:

- Ice-pack test: it has a sensitivity of 80% and consists of improvement of ptosis after cooling the eyelid with ice.
- Mary-Sheridan phenomenon: Worsening of the symptoms after exercising the upper arm with an inflated cuff. The mechanism is not clear and it is possibly attributed to lactic acidosis.

There are distinct clinical phenotypes that increase the range of differentials, and influence the treatment and prognosis.

a) AChR+ The AChR+ group comprises three possible clinical pictures: pure ocular involvement, early onset generalized MG and late onset generalized MG.

Early Onset Generalized Myasthenia Gravis and Late Onset Generalized Myasthenia Gravis

The classical form of disease is MG with antibodies against AChR, which accounts for up to 80% of generalised MG patients. These antibodies comprise IgG1 and IgG3 subtypes that activate the complement cascade, resulting in focal destruction of the postsynaptic membrane and AChR itself.

Patients with generalised MG are usually divided in early-onset (EOMG), if the disease onset is before the age of 40 years, and in late-onset disease (LOMG) if it starts later in life. EOMG patients are more often female with a hyperplastic thymus gland and can also have other autoimmune diseases associated, namely thyroid disease. In contrast, LOMG patients are more frequently male with either generalised or ocular weakness and a more severe course. The thymus gland may be normal or atrophic. In this subset, apart from AChR antibodies,
In 10% of patients MG is a paraneoplastic disorder where a thymoma is found, with a peak incidence in the fourth to six decades. In the case of thymoma associated MG, a more severe disease course may also be expected. Pure Ocular MG

Although the first presentation of MG is fluctuating ptosis and diplopia about 15% of the cases, it will commonly generalize in the subsequent months. However, a pure ocular MG (fluctuating ptosis and diplopia) may be diagnosed in about 15-25% of patients. About half of these patients will have anti-ACrR antibodies. If this pattern persists for more than two years, there is a 90% chance that the disease will not generalize.

b) MUSK+

This subgroup accounts for 5-8% of cases and is regarded as a distinct NMJ disease with unique clinical and pathophysiological features. It is caused by IgG4 antibodies against the postsynaptic protein MuSK. It is characterized by an early onset with female preponderance.

In this subgroup, there is preferential involvement of bulbar and respiratory muscles, with relative sparing of ocular and limb muscles, leading to increased susceptibility to myasthenic crisis. Some patients develop marked facial and tongue wasting, which may explain therapeutic failures. In contrast to AChR+ patients, limb weakness tends to be less severe.

Although the management of the condition is out of scope of this review, poor treatment response to the standard drugs used for MG may lead to consideration of this diagnosis. In MuSK+, there is a potential worsening with anticholinesterase drugs (with a higher risk of cholinergic crisis). There is also an unpredictable response to thymectomy (which may be explained by the absence of thymic abnormalities). The prognosis of these patients is worse than in AChR+ patients.

c) Seronegative MG

Seronegative MG does not have any detectable antibodies. Once regarded as responsible for 15% of all generalized MG, it was recently demonstrated that two thirds of patients have a low affinity AChR antibodies, not detectable conventional methods. Thus, its prevalence is probably much lower. Recently, antibodies against a newly identified receptor for agrin – Lipoprotein-related Protein 4 – have been recognized in patients with "seronegative MG", but their pathogenic role remains to be proved. Currently, SN-MG is considered under the spectrum of AChR-MG disorders, given the similar clinical profile and treatment response. However, only a better understanding of the causal antibodies will allow a correct phenotype-antibody correlation.

Congenital Myasthenic Syndromes (CMS)

In contrast to other NMJ disorders, CMS are not immune-mediated but hereditary conditions, caused by mutations in genes critical for a normal NMJ transmission and often following a pattern of autosomal recessive inheritance. The age of onset is usually soon after birth, however they are important to recognize as adult onset cases are well described.

Due to the broad differential, the heterogeneity of possible mutations (causing presynaptic, synaptic and postsynaptic defects) and the variable constellation of symptoms, the diagnosis is can be difficult. However, CMS can have differentiating clinical features such as delayed milestones, apnoeic episodes, arthrogryposis, dysmorphic features, and scoliosis.

One possible way of classification is according to the site of defect in the synapse, either presynaptic, synaptic or postsynaptic. The mutations identified to date affect several proteins, such as AChR, choline acetyltransferase (ChAT), rapsyn, plectin, Nav1.4, MuSK, agrin, B2 laminin, downstream of tyrokinase 7 (Dok-7) and glutamine-fructose-6-phosphate transaminase 1 (GFTP1).

The phenotype may be crucial for an accurate diagnosis. Firstly, ophthalmoplegia is unusual, and even when present it is not accompanied by diplopia. This may occur for two main reasons: on the one hand, many CMS affect presynaptic proteins and the extraocular muscles may be less susceptible to such dysfunction in contrast to the case of postsynaptic defects and on the other hand, ophthalmoplegia may start at birth, leading to central adaptation. As a rule of thumb, patients with presynaptic disorders usually do not have ophthalmoplegia (thus, the same is true for Lambert-Eaton Myasthenic Syndrome). Second, in synaptic and in post-synaptic AChR mutations patients may present, as in MG, with severe ophthalmoplegia.

Other important feature is the presence of limb girdle weakness which has been linked to DOK7 and GFTP1 mutations. Additionally, tongue atrophy and weakness of dorsiflexion of the ankle are common in rapsyn mutations (as well as arthrogryposis, dysmorphic features, scoliosis and epidermolysis bullosa).

Patients have fatigable weakness and neurophysiological abnormalities similar to MG, but antibodies are not detected. Genetic testing may confirm the diagnosis and when no candidate is clearly defined, mutation analysis can be based on the estimated frequency. CMS do not respond to immunosuppressants or thymectomy and there is a variable response to anticholinesterase (AChE) drugs.
### Table 1. Classification of the CMS based on patients investigated at the Mayo Clinic and some associated clues (adapted)

<table>
<thead>
<tr>
<th>DEFECT SITE (N=371 patients)</th>
<th>ASSOCIATED CLINICAL / PHARMACOLOGIC CLUES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presynaptic (6%)</strong></td>
<td></td>
</tr>
<tr>
<td>ChAT deficiency</td>
<td>Recurrent apnoeic episodes</td>
</tr>
<tr>
<td>Paucity of synapse vesicles</td>
<td></td>
</tr>
<tr>
<td>Congenital LEMS like</td>
<td></td>
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<tr>
<td><strong>Synaptic basal lamina (13.7%)</strong></td>
<td></td>
</tr>
<tr>
<td>Endplate AChE deficiency</td>
<td>Symptomatic from birth with delayed milestones</td>
</tr>
<tr>
<td></td>
<td>Facial deformities, progranithism, malacclusion, scoliosis and kyphoscoliosis</td>
</tr>
<tr>
<td></td>
<td>Pupillary light reflex may be delayed</td>
</tr>
<tr>
<td></td>
<td>Satisfactory treatment with ephedrine and albuterol²¹</td>
</tr>
<tr>
<td>B2-laminin deficiency</td>
<td>Pierson Syndrome: nephrotic syndrome + ocular malformations</td>
</tr>
<tr>
<td></td>
<td>Proximal limb muscle weakness</td>
</tr>
<tr>
<td><strong>Postsynaptic (68%)</strong></td>
<td></td>
</tr>
<tr>
<td>Primary AChR kinetic defect</td>
<td></td>
</tr>
<tr>
<td>Primary AChR deficiency</td>
<td></td>
</tr>
<tr>
<td>Rapsyn deficiency</td>
<td>⅛ of patients have multiple joint contractures (such as arthrogryposis)</td>
</tr>
<tr>
<td></td>
<td>Most have ptosis; ⅛ ophthalmoplegia; weakness of ankle dorsiflexion</td>
</tr>
<tr>
<td>Sodium channel myasthenia</td>
<td>Bulbar and respiratory weakness</td>
</tr>
<tr>
<td>Plectin deficiency</td>
<td>Epidermolysis bullosa simplex</td>
</tr>
<tr>
<td><strong>Combined pre and postsynaptic (12.5%)</strong></td>
<td></td>
</tr>
<tr>
<td>Dok-7 myasthenia</td>
<td>Weakness with limb-girdle distribution</td>
</tr>
<tr>
<td></td>
<td>Improvement with ephedrine and albuterol; worsening with pyridostigmine</td>
</tr>
<tr>
<td>CMS in centronuclear myopathy</td>
<td></td>
</tr>
<tr>
<td>Glutamine-fructose-6 phosphate transaminase 1</td>
<td>Weakness with limb-girdle distribution</td>
</tr>
</tbody>
</table>

**Lambert-Eaton Myasthenic Syndrome (LEMS)**

This autoimmune disorder affects the synaptic function not only at the level of the presynaptic nerve terminal but at the autonomic ganglia as well.²² LEMS occurs 20 times less frequently than MG. Voltage-gated calcium channel (VGCC) antibodies are detected in about 90% of cases²² and in approximately 50% an underlying cancer is found (usually small cell lung cancer).²³ It can present in any age group, but paraneoplastic cases usually affect patients over the age of 50 years,⁷ with men and women equally affected.²⁴

Its characteristic triad consists of proximal muscle weakness, dysautonomia and hyporeflexia. Fatigability is not usually prominent. Weakness is explained by an impairment of quantal release of ACh and also by the reduction of the number of VGCC²⁵, leading to skeletal muscle dysfunction.

In contrast to MG, LEMS generally spreads in a caudocranial fashion. It usually starts with proximal weakness of the lower limbs (especially thighs and pelvic girdle) with further involvement of other muscles, and relative sparing of the ocular muscles.

The involvement of parasympathetic and sympathetic neurons results in autonomic symptoms: xerostomia is the most frequent symptom, followed by erectile dysfunction and constipation.²⁶ Myotatic reflexes tend to be reduced (or absent) and paradoxically increased after exercise. Post-exercise facilitation of both power and reflexes may occur in 40% of patients.²¹ Finally, as in MuSK+ patients, AChE inhibitors provide a moderate clinical response.

Paraneoplastic LEMS may be associated with a more rapid progression of symptoms and with paraneoplastic cerebellar degeneration.¹

**Transient neonatal Myasthenia and transient neonatal LEMS**

This is caused by a passive transfer of maternal antibodies (AChR, MuSK and VGCC²⁷,²⁸,²⁹) to the newborn and affects up to 12% of neonates born to MG mothers. The clinical picture is characterized by hypotonia, dyspnoea and sucking difficulties. As there is no active production of antibodies, it is typically self-limiting and should resolve within 12 weeks.

**Weakness Patterns**

![Figure 2. Pattern of evolution of symptoms. In AChR+ there is marked involvement of ocular muscles and the progression is cranio-caudal; In MuSK+ bulbar muscles are preferentially affected and the progression is also cranio-caudal; In CMS it is important to look for tongue atrophy as well as weakness of ankle dorsiflexion; In LEMS the progression is caudo-cranial, usually starting as proximal weakness of the lower limbs (with relative ocular sparing) and there is hyporeflexia and dysautonomia such as xerostomia.](image-url)
3. MG frequent mimickers

Although some of the pitfalls of the diagnosis have already been mentioned, there are also important neurological and systemic conditions that can mimic MG. Their major points of differentiation are summarized in Table 2. It is also worth mentioning that when facing a possible case of ocular myasthenia, entities such as carotid-cavernous fistulae, Tolosa-Hunt syndrome and infiltration must be excluded.

| Table 2: Differential Diagnosis of Myasthenia Gravis, modified after Meriggioli et al., 2009 |
|---------------------------------|---------------------------------|---------------------------------|
| Entity                          | Clinical features               | Clues for Diagnosis             |
| Botulism                        | Rapid descending progression; autonomic involvement | Low amplitude CMAP               |
| Motor Neuron Disease, especially bulbar predominant | Presence of corticobulbar and corticospinal features, fasciculations, wasting | Abnormal single fibre EMG with increased fibre density, loss of motor units and complex motor units |
| Cervical Myelopathy             | Subacute, sensory changes in the upper limbs, urinary retention | MRI scan, CSF                   |
| Mitochondrial Disorders (e.g. Progressive External Ophthalmoplegia) | Gradual onset; no fluctuation; often no diplopia despite severe ophthalmoplegia | Single fibre EMG may be mildly abnormal |
| Myopathies (e.g. Acid Maltase, Oculopharyngeal Muscular Dystrophy) | Proximal weakness, no sensory changes | Raised serum creatine kinase, EMG, muscle biopsy |
| Acute Inflammatory Demyelinating Polyneuropathy Variant Syndromes | No fluctuation in weakness; areflexia; acute onset; some distal sensory symptoms | NCS, blink reflex, CSF          |
| Thyroid Ophthalmopathy          | Proptosis, eyelid retraction, systemic signs of hyperthyroidism | MRI demonstration of enlarged extraocular muscles |
| CNS disorders causing cranial nerve dysfunction (e.g. brainstem tumour/stroke/inflammation) | Sudden onset in vascular lesions; consciousness, coordination and sensation affected; ocular weakness in distribution of individual nerves | CT brain, MRI brain, CSF       |
| Organophosphate Poisoning       | History of pesticide use, chemical warfare, symptoms similar to cholinergic crisis | Red cell acetylcholinesterase levels |
| Cholinergic Crisis              | Salivation, lacrimation, diarrhoea, urinary incontinence, bradycardia, miosis, bronchospasm | Drug history and clinical signs |
| Drug-Induced Myasthenia         | Similar to other autoimmune MG; disappearance of symptoms after drug withdrawal | Drug history, eg. Penicillamine |
| Benign Essential Blepharospasm | Persistent orbicularis oculi spasm, not true ptosis | History                      |
| Sleep Apnoea                    | Daytime somnolence rather than true fatigability | Polysomnography                |
| Chronic Fatigue Syndrome/Depression | Generalised exhaustion, malaise, apathy rather than true fatigability | Normal diagnostic tests        |

4. Investigation

MG is a clinical diagnosis but immunologic and physiologic tests are necessary for its confirmation.

**Immunological and genetic testing**

Several antibodies can confirm the clinical diagnosis, and if present, they are highly specific.

Only AChR and MuSK antibodies are convincingly pathogenic and cases associated with these antibodies are found in more than 90% of cases of MG. Therefore, the first step should be testing for AChR. The antibody test is very specific and sensitive, detecting 85% of patients with generalised and 50% of pure ocular forms. However, a negative result has to be interpreted with caution as it can occur in the beginning of the disease and may also be influenced by immunosuppression. If clinical suspicion is high but antibody testing is negative, it should be repeated as a seroconversion rate of 15.2% as been reported. The second step is to test for MuSK as these are present in up to 70% of patients who are negative for AChR, being that higher prevalence is encountered in equatorial countries.

Antibodies to striated muscle were the first to be discovered in MG (against titin or ryanodine receptors) and
despite having a lower sensitivity, they may be a valuable marker in late onset patients with generalized disease.\textsuperscript{33} They are also useful as a marker of thymoma before the age of 40.\textsuperscript{12} The pathogenic role of anti-voltage-gated K+ channel subfamily A member 4 (KCNA4) and antibodies against low-density lipoprotein receptor-related protein 4 needs further confirmation and its routine testing is not recommended.\textsuperscript{35,36}

In CMS, AchR antibodies are not detected. When no candidate gene is clearly defined, mutation analysis can be based on the estimated frequency.\textsuperscript{22}

If LEMS is suspected, antibodies against VGCC should be requested. They have an extreme sensitivity (85\%\textsuperscript{4} to 100\%).\textsuperscript{36}

Finally, 15\% of cases are still "seronegative" and an intriguing feature is their good response to immunotherapy\textsuperscript{6}, which raises the possibility of undetectable antibodies to undiscovered antigens.

It is still to be determined if seronegative patients should be tested for late-onset CMS, such as due to rapsyn or DOK7 mutations, before initiation of immunosuppressive drug treatment or thymectomy.\textsuperscript{32}

Thyroid function tests and antithyroid antibodies should be performed if a thyroid ophthalmopathy is suspected. Nevertheless, MG and autoimmune thyroid disease may coexist.

**Neurophysiologic tests**

Routine nerve conduction studies (NCS) and electromyography (EMG) are useful to rule out a myopathy or a neuropathy.\textsuperscript{13} Moreover, in LEMS (and in botulism) standard NCS may show a low-amplitude muscle evoked response or repetitive responses in some CMS cases.\textsuperscript{38}

The NMJ can be tested with repetitive nerve stimulation (RNS) and single fibre electromyography (SFEMG). As the NMJ is tested under stress conditions, they can show subtle deficits. The major caveat is their low specificity, as they detect NMJ dysfunction irrespective of the aetiology.\textsuperscript{39}

\textit{a) Repetitive Nerve Stimulation}

RNS involves a repeated electrical stimulation of a motor nerve and measuring the size of the compound muscle action potential (CMAP). The intrinsic hand muscles, anconeus, trapezius, nasalis and orbicularis oculi are the most frequently tested, and the latter two are especially important in the case of ocular myasthenia.\textsuperscript{37} The typical result of the former test in MG patients (with a 3-10Hz frequency) is a decremental response.\textsuperscript{40} It occurs due to a progressive failure in the transmission across the NMJ, leading to activation of fewer muscle fibres. As the result is clearly influenced by AChE drugs, they should be avoided on the day of the exam. Importantly, the RNS sensitivity for diagnosing MG varies according to the pattern of weakness and the muscles tested. For instance, it can reach from 89 to 100\% in the case of generalised presentations (either axial or bulbar), but it is lower in the case of ocular MG.\textsuperscript{19} Depending on the muscles tested, the sensitivity of RNS for diagnosing MG varies from 53 to 100\% in generalised presentations, but it is lower in the case of ocular MG. Importantly, normal results in RNS may also occur in MuSK+ patients, if performed in non affected muscles. The opposite result occurs in LEMS, where an increment in the AChR response takes place at higher frequencies, 50 Hz or post-exercise stimulation (while a decremental response may be seen at lower frequencies).\textsuperscript{26} The underlying immune attack decreases the amount of calcium released into the presynaptic nerve terminal, resulting in insufficient discharge of ACh. When the nerve is stimulated at higher frequencies, recurrent depolarization leads to a high rate of calcium influx, leading to a normal quantity of ACh liberated and a dramatic increase in muscle action potential size.\textsuperscript{30}

RNS may also be helpful in diagnosing a cholinergic crisis, if the patient is overtreated with AChE inhibitors, showing characteristic repetitive nerve discharges. In the case of congenital slow channel myasthenic syndrome a prolonged depolarisation of the end plate is observed, leading to a second peak in the CMAP, very specific of this disorder.\textsuperscript{39}

\textit{b) Single Fiber EMG}

SFEMG can show mild neuromuscular transmission dysfunction, as it measures the instability preceding the neuromuscular block that RNS can record. The decrease in end-plate potential amplitude results in a variability in the time taken to reach the threshold for muscle fibre action potential generation, which is called the neuromuscular jitter. Blocking may also be seen. SFEMG is the most sensitive test of NMJ function available, with a sensitivity of around 95\% if two muscles are studied, and it is especially useful in ocular myasthenia.\textsuperscript{38} However it is less specific, as any cause of NMJ dysfunction (such as recent reinnervation, myopathy or medications) can increase the jitter. Therefore, it is important to perform routine NCS and EMG beforehand.

SFEMG is technically more difficult and it requires the use of a needle electrode as well as a good patient cooperation. A stimulated SFEMG technique was posteriorly developed, which requires no patient cooperation.\textsuperscript{42} Its major limitation is the use of two needles, which can result in a greater source of error as there are more technical pitfalls. Recently, reports on the use of concentric needle electrode for jitter analysis were presented, but larger studies are needed.\textsuperscript{43}

**Erdofionium Chloride Test (Tensilon\textsuperscript{b})**

This is a short-acting acetylcholinesterase inhibitor that may transiently improve muscle strength.\textsuperscript{1} This test has a high sensitivity in generalized MG (71 to 95\%).\textsuperscript{44} Despite being easily performed, it is potentially cardiac arrhythmogenic (being contra-indicated in elderly patients\textsuperscript{5}). It is observer dependent, leading to high percentage of both false negative and false positive results (in conditions such as motor neuron disease, LEMS and botulism\textsuperscript{25}).
Chest Imaging

All patients with a confirmed MG should have a chest image (CT or MRI) in order to exclude a thymoma. A special precaution should be taken regarding the contrast agent and therefore patients should not receive iodine compounds in order to prevent clinical deterioration. In MuSK+ patients there is no associated thymic abnormality.

In LEMS patients, a search for an underlying tumour should be undertaken. Apart from chest CT, bronchoscopy and PET should be considered. Even in the presence of a negative result, the investigation should be periodically repeated, for at least for five years after symptom onset.

5. Key Points

The following table summarises the potential distinguishing features present both in clinical picture and investigations.

<table>
<thead>
<tr>
<th>MG AChR</th>
<th>MG MuSK</th>
<th>CMS</th>
<th>LEMS</th>
<th>BOTULISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranio-caudal progression</td>
<td>Bulbar ++</td>
<td>Early onset</td>
<td>Ascending pattern</td>
<td>Descending paralysis</td>
</tr>
<tr>
<td>Ptosis, Diplopia</td>
<td>Bulbar involvement</td>
<td>Tongue atrophy</td>
<td>or absent myotatic reflexes</td>
<td>Dysautonomia</td>
</tr>
<tr>
<td>Ab: AChR</td>
<td>Ab: MuSK</td>
<td>Different mutations affecting eg DOK7</td>
<td>Ab: VGCC</td>
<td>NS similar to LEMS</td>
</tr>
<tr>
<td>Thymus Hyperplasia</td>
<td>Normal Thymus</td>
<td>None</td>
<td>NS: Increment in RS at higher frequencies; increased jitter</td>
<td>Detection of toxin in serum, stool or food sample</td>
</tr>
<tr>
<td>Favorable response to anticholinesterase drugs and thymectomy. Immunossupression</td>
<td>↑ Sensitivity and ↓ response to anticholinesterase agents; unpredictable to thymectomy</td>
<td>Do not respond to immunosuppressants or thymectomy; Ephedrine or albuterol</td>
<td>Moderate response to AchE inhibitors. Treatment = aminopyridines + immunossuppressors</td>
<td>Catarrhics and enemas</td>
</tr>
</tbody>
</table>

![Figure 3. Key Points. Ab – antibody; NS –Neurophysiology Studies (Nerve conduciton and electromyography); RS – Repetitive stimulation.](image)

Conclusion

MG is a highly variable disease with multiple differentials, making its diagnosis difficult. Additionally, there are no established clinical criteria and the accurate diagnosis is highly dependent on the recognition of phenotypes. However, it is important to obtain an objective confirmation in order to ensure a rapid and appropriate management of the patient.

As weakness and fatigue are symptoms common to several conditions, a good history and neurological examination are crucial to lead the diagnostic workup. When a NMJ disorder is suspected, it is essential to determine the age of onset, pattern of progression, preferentially affected muscles and concomitant symptoms such as dysautonomia. When examining a patient it is crucial to access fatigability, myotatic reflexes and other features such as tongue atrophy and arthropigrosis.

Investigations are usually necessary to confirm the diagnosis or to help in the differential diagnosis. All patients with suspected MG should be tested for anti-AChR antibodies. Initial anti-MuSK testing may be considered in the presence of severe bulbar and facial weakness. The finding of elevated levels of either of these antibodies in the appropriate clinical picture confirms the diagnosis. Neurophysiology studies are also essential ancillary tests. SFEMG is a more sensitive study than RNS, and a negative result usually helps to exclude the diagnosis of MG but is dependent on the neurophysiologist's experience. Nevertheless, it may be also abnormal in myopathies and neuropathies. Finally, one should always consider the limitations of each test and all the results should be interpreted with caution, taking into account the history and examination.
References