Diagnostic challenges in myasthenia gravis: a clinical approach

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ABSTRACT

The development of antibody tests and neurophysiological techniques have aided in confirming the diagnosis of myasthenia gravis (MG) over the years. However, there still remains an unmet diagnostic need in the subgroup of MG patients with weakness restricted to ocular muscles (OMG) as routine diagnostic tests are less sensitive in this group: around 50% of these patients have no positive antibody test and around 71% have no significant decrement with repetitive stimulation EMG. Moreover, virtually all disorders that can cause a pupil-sparing ptosis or diplopia have been reported to be confused with OMG. Among the most mentioned mimics for OMG are Graves ophthalmopathy, cranial nerve palsies, ocular tendinomuscular deficits (such as levator dehiscence), myopathy, demyelinating disease and stroke. Diagnostic delay and confusion of OMG with mimicking disorders might lead to a worse prognosis due to a possible increased risk of generalization of disease and the need of emergency treatments. A careful clinical follow-up of patients with suspected OMG by systematically assessing changes in ocular weakness patterns between visits can aid in confirming the diagnosis. In addition, the ice pack test can be a diagnostic aid in cases of both evident ptosis and ophthalmoparesis. In the foreseeable future, cell-based assays (CBA) for antibodies to clustered acetylcholine receptor might aid in the diagnostic confirmation of OMG. There is a need of studies that investigate the yield of new and not-routinely used diagnostic tests in suspected OMG with negative antibody and inconclusive EMG and SF-EMG, such as the repetitive ocular vestibular evoked myogenic potentials (RoVEMP) test and CBA. Lastly, the effect of early immunosuppressive treatment should be further investigated in OMG.

Key Words: myasthenia gravis, ocular myasthenia gravis, diagnosis, differential diagnosis, diagnostic tests

Introduction

Myasthenia gravis (MG) is a heterogenous autoimmune disease characterized by fatigable muscle weakness with clinical patterns ranging from purely ocular to different combinations of limb/bulbar and axial weakness. In the second half of the 19th century, the disorder was known as Erb's or Erb–Goldflam disease.[1,2] Jolly observed that MG could be distinguished from 'true' paralyses and coined the term 'myasthenia gravis pseudoparalytica' (myo, muscle; asthenia, weakness; gravis, severe).[3] The broad phenomenological rather than etiological/pathophysiological name for this disease is in concordance with various clinical presentations of MG and the absence of a single laboratory of neurophysiological test that can confirm or exclude the diagnosis.

In 1976, Lindstom showed the presence of antibodies directed towards the acetylcholine receptor (AChR) in 85% of MG patient cohort.[4] This both confirmed the pathophysiological hypothesis of MG being an autoimmune disorder and boosted MG research towards identifying additional antibody targets in the remaining 15% 'seronegative' MG patients. Even though new antibody targets have been identified and neurophysiological tests were developed to support the diagnosis, there remain cases in which the diagnostic tools are not satisfactory. The aim of this review is to discuss diagnostic challenges and to offer a clinical approach for hard-to-diagnose MG patients.

Routine diagnostic procedure

When there is a clinical suspicion of MG due to a typical history of fluctuating fatigable muscle weakness without neurological deficits in other domains, the first line of testing is antibodies, starting with AChR and MuSK antibodies. Testing for striated antibodies (such as for ryanodine receptor and titin) have less of a diagnostic value and are mostly used for prognostic purposes.[5] When antibody tests are negative, electrophysiological tests can be employed to confirm the diagnosis of MG. Firstly, electromyography (EMG) repetitive stimulation is performed and, in the case of no significant decrement, single-fibre EMG (SF-EMG) can be used to find jitter blocking. SF-EMG is not widely available as it requires a certain level of expertise. If all above mentioned tests result negative, the acetylcholinesterase (AChE) inhibitor test can be used. For this test, there must be a clear form of weakness that can be objectively improved during the test, such as a severe ptosis. Lastly, the ice pack test can be used to confirm the diagnosis of MG in patients with evident ptosis (or severe objectifiable ophthalmoparesis).[6-8] Arguably when applicable, this test should be done at the start of the diagnostic procedure. This bedside test, however, does not widely have a specific place

in the diagnostic sequence and is not routinely used in all MG expertise centers.

New and experimental diagnostic tests

In "double-seronegative" MG, when AChR and MuSK antibodies have not been found (~ 5% of all MG patients), antibodies against low-density lipoprotein receptor-related protein 4 (LRP4) and agrin can be tested.[9-11] In addition, cell-based assays (CBA) can be used to increase the sensitivity of antibody detection: Rodríguez et al. showed that 38.1% of radioimmunoassay-negative cases showed positive results on CBA for antibodies to clustered acetylcholine receptor.[12] Regarding new electrophysiological tests, repetitive ocular vestibular-evoked myogenic potentials (RoVEMP) test is used in an experimental setting and is not yet part of the standard diagnostic procedure. In the studies performed until now, RoVEMP test had a sensitivity of 71-89% and a specificity of 64-86%.[13,14] RoVEMP differentiated between MG patients and patients with other neuromuscular disorders, and a significant correlation was found between the magnitude of decrement and the time since the last intake of pyridostigmine.[14] With regards to imaging, quantitative MRI of extra-ocular muscles has been investigated and shown to reveal EOM atrophy and fatty replacement, but until now has not shown to be a potential addition in the diagnostic process.[15,16]

Hard-to-diagnose MG patients

Patients that are particularly hard to diagnose are isolated ocular MG (OMG) patients. Around 50% of these patients have no positive antibody test and around 71% have no significant decrement with repetitive stimulation EMG; see figure 1.[17] SF-EMG has a relatively high sensitivity in OMG of 86%, as high as 94% in a single-center study, but has the problem of not being widely available as discussed earlier and has a relatively low specificity (73-79%) even in specialized centers.[17,18] Particularly in other neuromuscular disorders, SF-EMG results can be abnormal. The AChE inhibitor test is not widely used, because of the risk of serious side-effects and the necessity of an evident and objectifiable form of ocular muscle weakness at the time of testing, such as severe ptosis. Alternatively, a beneficial response to treatment with acetylcholinesterase inhibitors can be used to support the diagnosis of MG. Another problem with suspected OMG is that with it comes a more expansive differential diagnosis as compared to generalized MG.

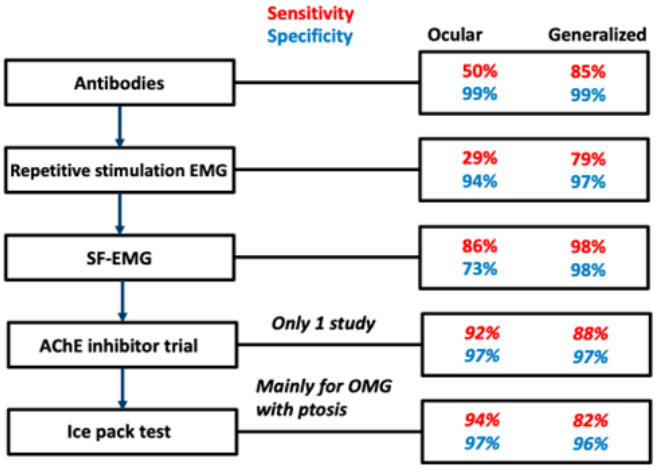

Figure 1. A summary of the sensitivity (red) and specificity (blue) of routine diagnostic tests in ocular and generalized myasthenia gravis derived from Benatar's systematic review.[17] The bottom two tests have a note and italicized numbers because of the lesser generalizability of the study findings.
Abbreviations: EMG = electromyography; SF-EMG=single-fiber-EMG; AChE = acetylcholinesterase.

Comparable disorders and risks of late diagnosis

Virtually all disorders that can cause a pupil-sparing ptosis or diplopia have been reported to be confused with OMG.[19] The most commonly mentioned disorders are Graves ophthalmopathy (GO), cranial nerve palsies, ocular tendinomuscular deficits (such as levator dehiscence), myopathy, demyelinating disease and stroke.[19,20] Especially GO is often reported to be confused with OMG.[20-25] It is controversial whether early treatment with corticosteroids might prevent the progression of ocular MG to a generalized form of MG as the only randomized controlled trial on this topic (Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME) study) had a too small sample size and short follow-up to give a conclusive answer.[26] However, this trial provided support in favor of starting with a therapy of low-dose prednisone in OMG and several experts hold that early corticosteroid treatment in OMG might result in a better prognosis.[27,28] Therefore, early confirmation of the diagnosis of ocular MG is of great importance. Cases of OMG mimicking as GO have necessitated emergency treatments possibly because of diagnostic delay and the late start of adequate immunosuppressive therapy.[21,24]

Diagnostic tools in seronegative OMG

In the case of suspected OMG with negative antibody tests, negative repetitive stimulation EMG test and negative SF-EMG, the first test to consider – if not already performed – is the ice pack test. Several recent reports have again

confirmed the high yield of the test.[7,18] Marinos et al. showed that the ice test is superior to comparable tests (the rest test and the heat test).[8] If this bedside test does not confirm the diagnosis, the next step would be CBA. Studies have shown a relatively high sensitivity of CBA for antibodies to clustered acetylcholine receptor in OMG, probably because of relatively low circulating antibody levels in OMG compared to generalized MG.[12] In the future, RoVEMP might play a role in these hard-to-diagnose patients.[29] In one study, the RoVEMP test was positive in 6 of 7 seronegative OMG patients with a negative repetitive stimulation EMG test.[14] It has to be noted that there is no specific data on the yield of the above tests in the specific group of suspected OMG patients.

Clinical recommendations in diagnostic uncertainty

Besides the role of the above mentioned tests, a careful clinical follow-up of patients with suspected OMG is of great aid to make the diagnosis.[30-33] Detailed testing of extra-ocular muscle (EOM) weakness by assessing diplopia in all eight gaze directions for at least 30 seconds and carefully reporting of the extent and side of ptosis, might reveal changes in the specific ocular muscles that are involved. Such changes are typical of MG, and can help in excluding other causes of ocular muscle weakness.[20] In one study, at the second visit the side most affected by ptosis changed in 10% of MG patients. Over the whole follow-up, 50% of seronegative MG patients had a change in form of ptosis. In that cohort, patients with diplopia had double vision with both a vertical and horizontal component in 95%. In these patients, 83% manifested double vision in other gaze directions at the second visit. Of patients with ptosis, 42% manifested after 30 seconds of looking upwards. In the case of EOM weakness, diplopia manifested after 30 seconds only in 13% of gaze directions tested. So, in cases of suspected OMG it might pay off to invest time to test the upward gaze direction for 60 seconds (for ptosis and diplopia) and the other seven gaze directions for at least 30 seconds (for diplopia solely; even though sometimes ptosis might become more evident when a patient looks in a lateral direction).[30] Furthermore, specific clinical tests can be of aid to reveal ocular weakness. The Cogan's lid twitch is an overshoot of the eyelid on an upward gaze after a period of rest. Also, a "quiver" movement can be observed with saccadic examination in the case of severe ophthalmoplegia.[31]

Conclusions and future directions

Confirmation of suspected MG has improved over the years by the development of antibody tests and neurophysiological techniques. However, in the subgroup of MG patients with weakness restricted to ocular muscles, there still remains an unmet diagnostic need as these tests are less sensitive in this group. Moreover, the absence of generalized weakness makes it harder to clinically distinguish MG from other disorders that cause ptosis or diplopia. Early confirmation of the diagnosis of ocular MG is of great importance as a timely start of adequate immunosuppressive therapy might prevent generalization of disease and the need of emergency treatments due to a myasthenic crisis. A careful clinical follow-up of patients with suspected OMG, by systematically testing ptosis for 60 seconds and diplopia in eight gaze directions for 30 seconds each, might reveal changes in ocular weakness pattern between visits typical for OMG. In addition, specific clinical signs such as the Cogan's lid twitch and the ease-to-perform ice pack test (both for ptosis and evident ophthalmoparesis) can aid in making the diagnosis. Regarding diagnostic tools, CBA is most likely to aid in diagnostic confirmation of OMG in the foreseeable future. Other tests that are being used in an experimental setting, such as the RoVEMP test, might get a future role in the diagnostic process of hard-to-diagnose patients. There is a need of studies that investigate the yield of new diagnostic tests in suspected OMG with negative antibody tests and inconclusive routine electrophysiological tests. Lastly, the effect of early immunosuppressive treatment should be further investigated in randomized controlled trials including OMG patients.

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