INTRODUCTION

This 'How to do it' series presents a paradox. The aim is simple—an expert advises a relative novice on the best approach to a particular problem, in this case the confirmation of a suspected diagnosis of myasthenia gravis. However, in reality the approaches of the expert and the novice are quite different. The expert subconsciously uses their enormous experience of the condition to make a *gestalt* diagnosis, and might then use one or two carefully chosen tests to provide laboratory confirmation, being familiar with the false-positive and false-negative implications of each test. The less experienced misinterprets the clinical picture, arranges inappropriate investigations, and is then caught out by false-positive findings. It is partly because of such considerations that patients increasingly demand access to specialist rather than general clinics. This paradox aside, the aim of this review is to offer some advice from the experienced to the less experienced, particularly noting some of the pitfalls.

CLINICAL ASSESSMENT

This is not the place to review the clinical features of myasthenia (see 'Further Reading'). But one or two points are worth emphasizing. Although fatigue is a classical feature, it is not always present or readily demonstrable, and furthermore not everything that appears to fatigue is myasthenia. Striking fatigue, such as rapidly evolving ptosis during up gaze (Figure 1), eye drift on sustained lateral or vertical gaze, or profound dysarthria developing during history taking, are near-enough pathognomonic. On the other hand, some apparent increase in weakness when repeatedly testing shoulder

HOW TO DO IT

Diagnose myasthenia gravis

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Figure 1 Marked fatigue is virtually pathognomonic of myasthenia gravis. (a) Immediately after eyes opened, following resting with eyes closed. (b) 15 s later.

abduction or hip flexion may be evident in a wide range of disorders, including nonorganic conditions, and in isolation should be viewed with considerable caution.

INVESTIGATIONS

The various investigative techniques will be reviewed, commenting on sensitivity and specificity, followed by recommendations as to their practical application.

Anti-acetylcholine receptor antibody assay

For all practical purposes, this can be considered a gold standard because false positive results are exceedingly rare. Unfortunately, this remarkable specificity is not matched by sensitivity. With the most commonly used (and indeed the only generally available) assay, the test is positive in about 50% of patients with purely ocular myasthenia and in 85% with generalized myasthenia gravis. Assays for other specific antibodies in apparently seronegative patients may become available soon (e.g. antimuscle specific kinase antibodies).

Therefore, in a patient with clinical evidence of myasthenia gravis and a positive antiacetylcholine receptor antibody, no further investigations to establish the diagnosis are required. However, a scan of the thymus is essential (see below).

Neurophysiological studies

The most widely-used test is supramaximal stimulation at 3Hz of a peripheral nerve, with recording of the compound muscle action potential of an the appropriate muscle. An abnormal response is defined as a drop in amplitude of more than 10% between the first and fifth responses (Fig. 2). Lesser falls are seen in normal individuals and may be misinterpreted as sug-

gestive of myasthenia. The test is more likely to be positive in somebody with generalized myasthenia gravis than with purely ocular disease, and in those with readily-demonstrable weakness, but even then it has limited sensitivity (~70%).

The most sensitive neurophysiological test for myasthenia is single fibre electromyography, with the demonstration of increased jitter with or without blocking (Fig. 3). This is technically very demanding and the most reliable results come from those operators who perform the test day-in and day-out. Few centres can offer such expertise. Studies of orbicularis oculi are particularly useful in patients with suspected ocular myasthenia who are anti-acetylcholine receptor antibody negative. However, increased jitter may also be seen in mitochondrial chronic progressive external ophthalmoplegia, which is an important differential diagnosis from ocular myasthenia, but blocking is rarely seen, in contrast to myasthenia gravis.

The Tensilon test

Edrophonium (Tensilon; Cambridge Laboratories, Newcastle-upon-Tyne, UK) is a short-acting anticholinesterase, which may transiently improve the weakness associated with myasthenia gravis. The pharmacological principle is simple, and the drug is readily available, even in non-specialist units, because it is used by anaesthetists. In some patients the response is dramatic with Lazarus-like rising from the bed. These factors have combined to make the 'Tensilon test' very popular, but caution needs to be exercised because both false-positive and false-negative results are fairly common and, albeit rarely, adverse reactions can occur.

False-positives

Transient, objective, improvement in strength may be seen in other neuromuscular disorders including amyotrophic lateral sclerosis (motor neurone disease). Indeed, some authors have advocated the use of anticholinesterase drugs to improve swallowing in patients with motor neurone disease. I have seen patients with mitochondrial chronic progressive external ophthalmoplegia referred as having myasthenia on the basis of a positive Tensilon test, but haven't repeated the test myself to see if such patients really do truly respond (accepting that some response may indeed occur). It may be possible to reduce some false-positive responses by blinding the patient to the test, as outlined below.

Figure 2 Compound muscle action potential in response to repetitive nerve stimulation. Note the decrement between the first (black arrow) and fifth (grey arrow) responses. Courtesy of Dr R. Kennett.

Figure 3 Variable interpotential interval ('jitter') when recording from two muscle fibres within the same motor unit. Courtesy Dr R. Kennett.

False-negatives

Quite simply, some patients with myasthenia, whether ocular or generalized, may simply not respond to edrophonium (in the same way that some do not gain any useful benefit from pyridostigmine used therapeutically – although one does not necessarily predict the other). The overall false-negative rate is probably about 10%.

The test

It is not possible to perform the test in truly double-blind fashion. The injection of edrophonium almost invariably produces symptoms and signs evident to the subject and observer. Abdominal cramping and twitching of the eyelids and watering of the eyes are common. Rarely, bowel evacuation is induced. These symptoms are largely prevented by prior administration of atropine. Thus, the patient can be told that they will receive two injections, only one of which is the active agent, implying that the order will be random, whereas in fact the atropine is always given first. Whether this minor subterfuge is truly helpful is perhaps open to question!

An intravenous canula is positioned and atropine 0.6 mg is injected (like the edrophonium injection about to be discussed, this may also be given in two steps). The appropriate muscle strength testing is performed. After a couple of minutes, edrophonium 2 mg is injected. If there is no certain muscle response and there are no adverse effects, then after about 30 s the remaining bolus of 8 mg is injected and muscle testing repeated.

It is generally much easier to be certain of an objective improvement of ptosis or an increase in the range of eye movements than it is to be certain of an increase in limb strength, which is fortunate as it is ocular myasthenia that presents more diagnostic difficulties than generalized myasthenia.

A marked objective response is strongly supportive of myasthenia gravis (imagine pictures in Fig. 1 being reversed and the eyelid opening representing a response to Tensilon!). Lesser responses may represent a false-positive and be misleading. If there is uncertainty about the response it is best to assume it is negative. A patient was recently referred to me with a diagnosis of myasthenia gravis solely on a Tensilon test that was judged positive on the result of a democratic poll of 10 observers! The diagnosis was wrong.

Complications

These are uncommon but when they do happen can be serious, including cardiac arrhythmias, respiratory failure and seizures. Resuscitation facilities should always be available and the test should not be performed in the dark recesses of a busy out-patient clinic.

Despite the reservations expressed, the Tensilon test can be a useful diagnostic aid, particularly if the patient is anti-acetylcholine receptor antibody negative, has normal neurophysiological studies, and has predominant ocular signs. It is not necessary in all patients, and specifically not in those in whom the diagnosis of myasthenia has already been established by antibody tests or neurophysiological studies.

Ice test

This test seems to be more popular with ophthalmologists than neurologists. In one series a positive result was seen in 80% of patients with ptosis due to myasthenia, with no positive responses in patients with ptosis not due to myasthenia. Given these figures (if they are true) and its simplicity and safety, it should perhaps be more widely used, but there seems to be something of an aversion to such 'low-tech' methods.

An ice pack is placed over the ptotic eyelid for two minutes. Improvement of the ptosis (e.g. 2 mm or more of improvement) is indicative of myasthenia. More positive responses are seen in myasthenia when the ptosis is partial rather than complete.

Figure 4 MR scans showing periaqueductal lesion (presumed glioma) causing obstructive hydrocephalus in a patient who had been treated for one year, without success, for 'seronegative' ocular myasthenia (unilateral ptosis and diplopia). The diplopia resolved following shunting but the ptosis, which showed mild fatiguability, was unchanged. Courtesy of Dr P. Anslow.

Ancillary investigations

In seronegative patients, with normal neurophysiological results and an absent or weak response to Tensilon, other diagnoses must be considered. This situation is most often encountered in patients with purely ocular symptoms and signs, and in all such cases it is wise to perform brain MRI (Fig. 4). The literature abounds with cases of intracranial structural disease initially masquerading as 'seronegative myasthenia', usually involving the brainstem; III, IV or VI cranial nerves; or orbit.

In seronegative patients with limb symptoms and signs, other neuromuscular disorders must be considered and estimation of serum creatine kinase, electromyography, and muscle biopsy may be required. Congenital myasthenic syndromes, due to a variety of genetic defects affecting proteins involved in the neuromuscular junction, and the Lambert–Eaton myasthenic syndrome may also show neurophysiological changes that can be confused with myasthenia gravis. Although most congenital myasthenic syndromes present in childhood, the slow-channel syndrome may present in adulthood.

Other investigations, once the diagnosis of myasthenia has been confirmed, although not part of the diagnostic process, are important:

- *Thymus scanning* is necessary in all patients who are anti-acetylcholine receptor antibody-positive. About 10% have a thymoma. A chest X-ray is not sufficient. Local facilities will dictate whether CT or MRI is preferred.
- *Thyroid function* should be assessed. The frequencies of both hypo- and hyperthy-

roidism are increased in myasthenia and altered activity of the thyroid gland can exacerbate myasthenic weakness. It is therefore reasonable to repeat the study during periods of otherwise unexplained exacerbation of weakness.

The Tensilon test is useful, particularly when there are striking ocular, and to a lesser extent bulbar and limb, signs and the antibody and neurophysiological tests are either unavailable, or rapid diagnosis is required before the outcome of these tests is known

DIAGNOSTIC APPROACH

This is influenced not only by the experience of the clinician, as noted above, but also by the acuteness of the presentation and the local availability of investigative techniques. The very high specificity of the anti-acetylcholine receptor antibody assay makes it a relative gold-standard and it should be requested in all patients suspected of having myasthenia gravis.

In a neuromuscular centre with immediate access to specialized neurophysiology and a turn around time for anti-acetylcholine receptor antibody assay of less than 10 days, the Tensilon test is rarely required.

If the antibody assay result is available within a few weeks, and the presentation is with relatively long-standing symptoms, then it may be reasonable to await the result of the assay and if positive not to pursue further diagnostic investigations. If the assay is negative, appropriate neurophysiological studies should be performed, but if they are not available, or the waiting list is unacceptably long, then a Tensilon test may be appropriate. In such circumstances there must be a question as to whether the patient should be transferred earlier rather than later for specialist assessment.

If the presentation is more acute, neurophysiological studies are unavailable or are normal, and early therapeutic intervention is required (i.e. before the antibody assay result is available), then a Tensilon test is appropriate.

Don't forget the very simple ice test if partial ptosis is a feature.

CONCLUSIONS

In the majority of patients with myasthenia gravis, the diagnosis can be made with fair certainty on the basis of clinical evaluation alone – the more experienced the assessor the easier the diagnosis. The presence of anti-acetylcholine receptor antibodies confirms the diagnosis. In those patients who are antibody-negative, specialized neurophysiology is very valuable, but not widely available. The Tensilon test is useful, particularly when there are striking ocular, and to a lesser extent bulbar and limb, signs and the antibody and neurophysiological tests are either unavailable, or rapid diagnosis is required before the outcome of these tests is known. The limited sensitivity and specificity, and potential hazards, of the Tensilon test must be recognized. When partial ptosis is a feature, the simple ice test may be supportive of the diagnosis.

FURTHER READING

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