Myasthenia Gravis

Jan Damoiseaux (PhD)

Department of Internal Medicine, Division of Clinical and Experimental Immunology, Maastricht University Medical Centre, P.O.Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: jdam@limm.azm.nl

Adriano Fontana ( )

Zurich, Switzerland. E-mail: adriano.fontana@usz.ch

Hauke Schneider ( )

Dresden, Germany. E-mail: Hauke.Schneider@neuro.med.tu-dresden.de

Franz Blaes ( )

Giessen, Germany. E-mail: Franz.Blaes@neuro.med.uni-giessen.de

Marc de Baets (MD, PhD)*

Institute for Neuroscience, Euron, Maastricht University Medical Centre, P.O.Box 616, 6200 MD, Maastricht, The Netherlands. E-mail: m.debaets@immuno.unimaas.nl

Tel : +31-43-3881021

Fax : +31-43-3884021

**Corresponding author*

Introduction

Myasthenia gravis (MG) is an autoimmune disease associated with antibodies directed to the postsynaptic nicotinic acetylcholine receptor (AChR) at the neuromuscular junction [1,2]. These antibodies reduce the number of AChR, which leads to muscle weakness. Antibodies were found to block receptor function or cause local damage to the muscle resulting in interference with the neuromuscular transmission. The resultant muscle weakness usually starts with eye muscles (Figure 1), and results in ptosis and double vision. MG may also involve other limb, bulbar and respiratory muscles (Table 1).

The annual incidence of MG is 3-4/million and the prevalence is about 60/million. The prevalence seems to increase in the last decades probably by the increased sensitivity and frequency of testing in combination with a decrease in mortality rates. In general women are affected twice as much as men. At presentation between the ages of 20 – 40 the female/male ratio is even 3/1. In patients over the age of 40 years at the time of presentation men and women are equally affected.

Diagnostic measurements for experts

MG is a disease of progressive muscle weakness during exercise. This can be made obvious by testing muscle stamina, for instance by sustained up-gaze for about 1 minute, making the eyelids droop. Next, the diagnosis can be confirmed by detecting anti-AChR antibodies and, if negative, anti-muscle specific kinase (MuSK) antibodies. Details on the relevant autoantibody tests are described below. Although both autoantibodies are highly specific for MG, about 15% of the patients with generalized MG are seronegative. In these patients the diagnosis MG can be confirmed either by measuring an increase in muscle strength after treatment with an ACh-esterase inhibitor (e.g. edrophonium or pyridostigmine), or by repetitive nerve stimulation. The most sensitive (95 – 99%) and specific (~100%) electrodiagnostic test for MG is single-fibre electromyography (EMG), measuring action potentials from a small number of muscle fibres innervated by a single motor unit [3]. Despite the excellent association with MG, single-fibre EMG is not often performed because it is dependent on operator skills. The American Association of Neuromuscular & Electrodiagnostic Medicine has developed guidelines for electrodiagnostic testing for evaluation of MG [2, and references therein].

Finally, once MG is diagnosed, the possible presence of a thymoma should be evaluated by scanning of the chest. MG patients at risk for thymoma can be selected by the presence of autoantibodies to skeletal muscle (see below).

Requirements for family practitioners

MG is a neuromuscular transmission disorder. Typically, signs and symptoms fluctuate: aggravating upon exertion and improving after rest. However, clinical manifestations may also spontaneously vary in time.

The disease usually starts with ptosis and diplopia and stays confined to the ocular muscles in about 15% of the patients. In the majority of the patients the disease generalizes and affects ocular, bulbar, limb and in the end stage respiratory muscles. The patients typically consult their general practitioner with fatigue and at that time the ocular symptoms may be minimal because of the rest during the preceding night. The diplopia usually is intermittent and thus has to be asked to the patient.

When the diagnosis is suspected the patient should be referred to a neurologist for further examination and laboratory testing. The presence of anti-AChR antibodies confirms the diagnosis. If the serum antibody tests for AChR or MUSK is negative further electrophysiological tests are necessary including repetitive nerve stimulation and if negative, stimulated single fibre electromyography [3].

Follow up

Clinical observations

During symptomatic or immunosuppressive treatment signs and symptoms gradually improve, varying from weeks to months.

Expectations

MG is a chronic disease with variable prognosis. However, with the present immunosuppressive therapy most patients can achieve a partial or complete remission. Spontaneous remissions also occur.

Blood tests

During treatment clinical improvement can be assessed by the quantitative (Q)MG score and no laboratory testing is necessary. In patients that fail to improve during immunosuppressive treatment anti-AChR antibody titre can be measured. If the titre fails to drop after 6-12 months a change in the immunosuppressive regimen is desirable.

Management

The treatment must be individualized according to the severity of disease, the patient's wishes and the presence of associated diseases. Altogether, two distinct treatment approaches can be considered [4]:

1. *Cholinesterase inhibitors*

Cholinesterase inhibitors (e.g. edrophonium or pyridostigmine), which increase the amount of acetylcholine in the synaptic cleft, are the initial treatment in all patients with MG. The dose used is about 3 to 5 tablets of 60 mg a day. The effect is variable and lasts for about 4 hours. The cholinergic side effects (salivation, abdominal cramps and diarrhoea) can be treated with anti-muscarinic drugs.

2. *Immunosuppressive treatment*

If treatment with cholinesterase inhibitors alone is insufficient to control the signs and symptoms of the disease, immunosuppressive treatment is started. The cornerstone of this treatment is the combination of prednisone and azathioprine. Azathioprine has a steroids sparing effect. If this combined treatment is not effective other immunosuppressive drugs are available, including cyclosporine and mycophenylate. In severe forms of MG plasmapheresis is performed in combination with immunosuppression. Finally, in patients under the age of 50 a thymectomy may be performed if anti-AChR antibodies are present. In thymoma cases a thymectomy is always performed irrespective of the age of the patient.

Diagnostic tests

Autoantibodies to the AChR are detected by radio-immuno assays (RIA) as originally described by Lindstrom et al. [5]. In contrast to the classical RIA it is not the autoantigen itself that is radiolabelled, but the snake toxin α-Bungarotoxin (*Bungarus multicincus*). Since α-Bungarotoxin shares high affinity and high specificity for AChR there is no need for extensive purification of the autoantigen from muscle extracts. If autoantibodies are present in the serum, these antibodies will form small immune complexes with the α-Bungarotoxin/AChR complex. These immune complexes are next enlarged by the addition of anti-human IgG enabling precipitation of the immune complexes by centrifugation (Fig. 2). The amount of radiolabel in the precipitate is directly related to the amount of autoantibodies in the serum. Values below 0.25

nmol/L are considered negative. Anti-AChR antibodies are detected in ~85% of patients with generalized MG and ~50% of patients with ocular MG. Importantly, anti-AChR antibodies are highly specific for MG.

More recently another antibody associated with MG has been discovered. These antibodies are directed to the muscle specific kinase (MuSK), a protein also found at the neuromuscular junction. These antibodies can be detected by a classical RIA, since the autoantigen has been cloned and sequenced and the extracellular domain is readily available as purified recombinant protein. Anti-MuSK antibodies are only detected in patients with generalized MG that are negative for anti-AChR antibodies.

About 15% of MG patients have a thymoma. These patients are always positive for anti-AChR antibodies, but 80 – 100% additionally have antibodies to skeletal muscle antigens. However, also ~30% of non-thymoma MG patients have anti-skeletal antibodies. These antibodies are detected by indirect immunofluorescence. In this test serum is incubated on skeletal muscle slides (monkey) and antibody binding is visualized by a second incubation with fluorochrome-labelled anti-human IgG (Fig. 2). Bands of cross striations can be observed under a fluorescence microscope. The autoantigen recognized is thought to be titin, a protein in the I-band of the myocyte.

Testing methods

The benefits of the diagnostic laboratory tests, i.e. anti-AChR and -MuSK antibodies, are the excellent performance characteristics, in particular with respect to specificity (~100%).

Limitations of the assays concern the need of radiolabels in combination with the low prevalence of disease. This indicates that the number of tests run in a laboratory is relatively low, while the half-life of the reagents is short. Furthermore, special laboratory equipment, facilities, and training of technicians are required. These issues significantly raise the cost per test, unless the tests are restricted to a few reference laboratories. There is a continuous search for alternatives that solve these shortcomings.

References

1. Vincent, A., Palace, J., Hilton-Jones, D. 2001. Myasthenia gravis. *The Lancet 357:* 2122-2128.

2. Conti-Fine, B., Milani, M., Kaminski, H.J. 2006. Myasthenia gravis: past, present, and future. *J Clin Invest 116:* 2843-2854.
3. Katirji, B. 2003. Electrodiagnosis of Neuromuscular junction disorders in *Myasthenia gravis and related disorders*. H.J. Kaminski, ed. Humana Press, Totowa (NJ), pp 149-175.
4. Kaminski, H.J. 2003. Treatment of myasthenia gravis in *Myasthenia gravis and related disorders*. H.J. Kaminski, ed. Humana Press, Totowa (NJ), pp 197-221.
4. Lindstrom, J.M., Seybold, M.E., Lennon, V.A., Whittingham, S., Duane, D.D. 1976. Antibody to acetylcholine receptor in myasthenia gravis. Prevalence, clinical correlates and diagnostic value. *Neurology 26:* 1054-1059.

Legends to the figures.

Figure 1. Patient with ocular myasthenia gravis. Ptosis due to weakness of the eye muscles is often the presenting clinical manifestation of myasthenia gravis. Typically, the ptosis may be asymmetric.

Figure 2. Test principles for autoantibody detection in myasthenia gravis. Anti-acetylcholine receptor (AChR) antibodies are classically detected by radio-immuno assay (upper panel). Radiolabelled α-Bungarotoxin (yellow triangles) specifically binds AChR (blue symbol) in muscle extract. Anti-AChR antibodies in the serum will bind the radiolabelled complex. The formed immune complexes are precipitated by addition of anti-human immunoglobulin and subsequent centrifugation. The amount of radiolabel in the precipitate corresponds to the amount of anti-AChR antibodies in the serum. Anti-skeletal muscle antibodies are detected by indirect immunofluorescence (lower panel). Slides of monkey skeletal muscle are incubated with patient serum and visualized by FITC-labelled anti-human immunoglobulin. Fluorescent microscopy reveals a classical cross-striated staining pattern.

Table 1: Signs and symptoms of disease

Affected Muscle	Clinical Manifestation
Ocular	
Diplopia	External eye muscle paresis
Ptosis	Drooping of one or both eye lids
Ptosis and diplopia	
Bulbar	
Articulation	Nasality of speech
Face	Weakness, sensation of stiffness of the mouth, inability to whistle, myasthenic snarl
Chewing	Difficult chewing
Swallowing	Regurgitation of fluids through the nose, choking
Neck muscles	Inability to keep the head in balance
Combined	
Oculobulbar	
Limbs	Sudden loss of power during sustained exertion
Arms	
Hands and fingers	
Legs	Sudden falls
Combined	
Generalized	
Respiration	Respiratory difficulties

Table 2: Diagnostic Criteria

Clinical Criteria
• Muscle weakness during exercise • Positive pyridostigmine test
Laboratory Criteria
• Presence of autoantibodies to AChR[a] • Presence of anti-MuSK antibodies (only in absence of anti-AChR antibodies) • Abnormal EMG (progressive decrease in electrical discharge)

[a]Abbreviations: AChR, acetylcholine receptor; EMG, electromyography; MuSK, muscle specific kinase.

Figure 1: Patient with ocular myasthenia gravis.

Figure 2: Test principles for autoantibody detection in myasthenia gravis.