Diagnosis of Myasthenia Gravis

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ABSTRACT

Myasthenia gravis is an autoimmune disorder of the neuromuscular junction. The diagnosis of myasthenia gravis (MG) is based on clinical features, combined with neurophysiological and immunological parameters. Autoantibodies against the nicotinic acetylcholine receptor are the main finding in about 80 % of the patients. More recently, autoantibodies against muscle-specific kinase (MuSK) and lipoprotein receptor-associated protein 4 (LRP4) have been identified in a subset of MG patients. Additionally, anti-titin autoantibodies can point to an underlying thymoma in younger MG patients. Neurophysiological examination includes a repetitive stimulation to detect a possible decrement as the electrical correlate of pathological muscle fatigability. Single-fiber electromyography can identify neuromuscular transmission disturbances in otherwise unclear cases.

Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction mediated by autoantibodies. Clinically, pathological muscle fatigue occurs mainly in the eye muscles, but can other muscle groups can likewise be affected. MG can be limited to the eye muscles (ocular MG) or may extend to additional muscle groups (generalized MG).

In addition to clinical diagnostics with provocation of muscle fatigue and pharmacological testing, neurophysiological and laboratory tests are the most important investigations used to confirm the suspected diagnosis of myasthenia gravis. The identification of new antigens has not only changed antibody diagnostics; rather, MuSK antibody-positive MG has been clinically distinguished as a separate subform of the disease.

Autoantibodies and myasthenia gravis

A neuromuscular junction consists of 3 components: (1) the terminal nerve ending where acetylcholine is formed, deposited in vesicles and then released, (2) the synaptic gap (3) the postsynaptic (muscle) membrane containing the acetylcholine receptor and its helping proteins as well as cholinesterase. In myasthenia gravis, autoantibodies can occur that affect various structures of the neuromuscular junction. Some of these autoantibodies determine a separate clinical subtype, while others indicate comorbidities such as thymomas.

Acetylcholine receptor antibodies (anti-AChR-ab)

The acetylcholine receptor antibody was the first pathogenic antibody identified in MG patients, and can be detected in about 80–85 % of MG patients; it does not generally occur in healthy persons, and only rarely appears in patients with other autoimmune diseases (overview in [1]). Its pathogenetic effects were identified early. AChR antibodies belong to the complementary-binding IgG1 and IgG3 subclasses and thus mediate complement-dependent damage to the postsynaptic muscle membrane [2, 3]. In addition, the antibody links ACh receptors to each other, leading to internalization of the receptors and depletion of AChR at the postsynaptic membrane (overview in [4]). These antibodies can also somewhat block AChR directly.

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Antibodies against muscle-specific kinase (anti-MuSK-ab)

In 2000 it was first determined that approx. 50 % of patients with seronegative MG (no evidence of AChR-ab despite clinical myasthenia gravis) have autoantibodies against a muscular surface protein that is not identical to the AChR [5]. This antigen was identified as MuSK, a transmembrane protein directly associated with AChR [6]. The binding of antibodies to MuSK leads to a reduced clustering of AChR and thus to a reduced number of AChR at the neuromuscular junction. Interestingly, anti-MuSK antibodies belong to the IgG4 subclass and thus cannot activate a complement [7]. Clinically anti-MuSK-ab-positive MG patients frequently have an involvement of facial, bulbar and axial muscles as well as muscular atrophy [8]. Patients with anti-MuSK antibodies suffer respiratory crises more frequently than patients with anti-AChR antibodies. Thymus histology is as a rule normal; thymomas are almost never observed among anti-MuSK patients [9]. The frequency of anti-MuSK among myasthenia patients appears to be 3–4 % of all cases and 25–30 % of AChR-ab-negative cases of MG.

Antibodies against lipoprotein receptor-associated protein 4 (anti-LRP4)

In 2011 and 2012 two independent working groups first described antibodies against the protein LRP4 in cases of seronegative MG [10, 11]. According to these studies approx. 15–20 % of seronegative MG patients, 7.5 % of AChR-ab-positive MG patients as well as 15 % of MuSK antibody-positive MG patients have anti-LRP4 antibodies. In Germany anti-LRP4-antibody-positive patients appear to be a rarity, and it is estimated that they make up make up less than 1 % of all MG cases. In mice, passive transfer of the antibody leads to myasthenic symptoms. Whether only LRP4-ab-positive patients are less severely affected by myasthenia is a matter of controversy due to the low number of case histories. However, patients with anti-LRP4 and an additional antibody were more severely affected [10–12].

Titin antibodies

In patients less than 50 years of age, titin antibodies are indicative of the presence of a thymoma [13]. There is no clear selectivity here; thus a negative finding of titin antibodies does not exclude the possibility of a thymoma in patents under 50. Therefore, thymoma diagnosis by means of thoracic CT or MRI is a necessary part of a standard initial investigation of myasthenia gravis. In patients older than 50 years of age, such antibodies are more common even without presence of thymoma; the frequency of titin antibodies in late-onset MG increases with age [14].

Antibodies against agrin and other proteins

Agrin antibodies have been demonstrated in some myasthenia gravis patients who generally also had antibodies against AChR, MuSK or LRP4. The significance of these antibodies is currently unclear. In addition, antibodies against the intracellular protein cortactin have been detected; their relevance is likewise unexplained [1, 15].

Detection methods for myasthenia-associated antibodies

The radioimmunoassay (RIA) is the standard method of detecting acetylcholine receptor antibodies. With pertinent clinical symptoms, a positive test result confirms the diagnosis; however, approx. 50 % of all purely ocular myasthenia gravis and 15–20 % of generalized MG cases are negative for AChR antibodies. A so-called cell-based assay, in which cells are transfected with the acetylcholine receptor, is clearly more sensitive with the same specificity, but the test is currently not yet commercially available (as of 09/2017). Introduction of this test could make antibodies to the acetylcholine receptor detectable in up to 50 % of previously seronegative MG patients. Standard tests for anti-MuSK are radioimmunoassay or ELISA; in this case cell-based tests can achieve higher sensitivities. Currently such tests have been established only in the context of scientific inquiries. Titin antibodies can be detected using a commercially-available ELISA.

Neurophysiology

Repetitive stimulation represents the gold standard for the neurophysiological examination to confirm myasthenia gravis. In principle, this method reproduces pathological muscle fatigue through reiterated stimuli resulting in repeated muscle contractions (overview in [16]). A further neurophysiological examination method is single-fiber electromyography (SFEMG). This method utilizes differences in temporal blockages of different muscle fibers of a motor unit and is usually only used when clinical symptoms, repetitive stimulation and findings of autoantibodies do not provide a definite diagnosis. Neither repetitive stimulation nor SFEMG are specific for autoimmune myasthenia gravis. A pathological result only confirms a disturbance in neuromuscular transmission.
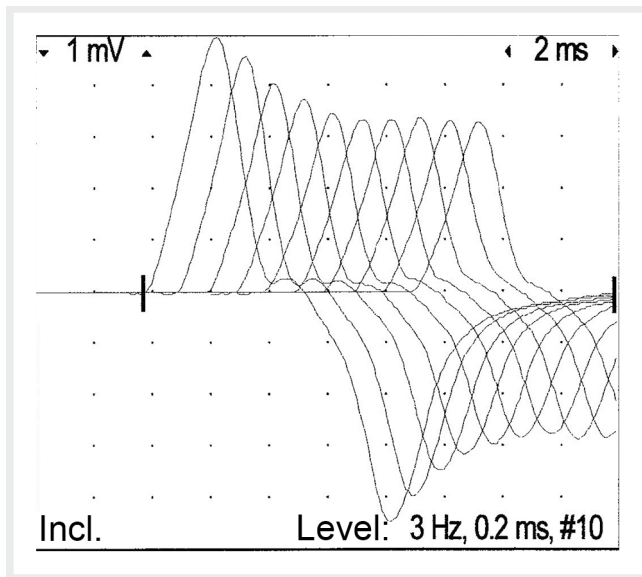
Repetitive stimulation

Repetitive stimulation relies on nerve stimulation and derivation of the potential along the relevant muscle analogously to motor neurography. However, during this procedure, after determination of the supramaximal threshold, stimulation is applied not once, but repeated several times, as a rule 5 to 10 times at a frequency of 3 Hz. The percent of decrement is measured between the 1st potential and the lowest of the first 5 potentials. A decrement of greater than 8 % is considered pathological. Suitable nerve-muscle pairs for this examination are (1) facial nerve / nasalis muscle, (2) spinal accessory nerve / trapezius muscle (upper edge) and (3) axillary nerve / deltoid muscle [17]. When this examination is performed, care should be taken to sufficiently stabilize the relevant extremity in order to avoid movement artifacts; non-supramaximal stimulation intensity is an additional source of error.

In about 50–70 % of myasthenia gravis patients repetitive stimulation is positive. If repetitive stimulation does not exhibit a decrement, repetitive stimulation can be used after applying stress, during which a one-minute load is applied over a period of 4–5 min, and then 10 s afterward, repetitive stimulation is performed. It should be noted that a decrement may also occur in other neuropathies or myopathies, and in the case of ambiguous clinical symptoms, detailed neurography and myography have to be carried out ▶ Fig. 1.

Increment test

The increment test is mainly performed for a Lambert-Eaton myasthenic syndrome (LEMS). During normal 3 Hz repetitive stimulation, LEMS also exhibits a decrement; an increment is detectable

► **Fig. 1** Repetitive stimulation (3 Hz) of the right axillary nerve and derivation via the right deltoid muscle of a patient with generalized myasthenia gravis. Decrement 31 % (amplitude reduction of 9.4 mV to 6.4 mV).

► **Fig. 2** Supramaximal stimulation of the ulnar nerve and derivation via the right abductor digiti minimi muscle before and after 20 s of finger spreading in a patient with Lambert-Eaton myasthenic syndrome (LEMS). Note the low final amplitude and the distinct increment (360 %).

only at high stimulation frequencies of 30–50 Hz [16]. Since this test is very painful, nowadays a test with two individual supramaximal stimuli is preferred before and after a 10–20 s muscle contraction. An increment greater than 100 % is demonstration of presynaptic neuromuscular transmission dysfunction; incremental values between 60–100 % are already highly suspicious, however. It should be noted that in LEMS a significantly reduced amplitude of the starting MSAP can normally be observed [16] ► **Fig. 2**.

Single-fiber electromyography

When a motor axon becomes depolarized, the stimulus is distended distally and excites the individual muscle fibers almost simultaneously within the motor units. The variation in the excitement interval from one muscle fiber to another is called jitter and is an expression of the variability of neuromuscular transmission. If there is a functional limitation of the neuromuscular junction, the jitter will be prolonged. A single-fiber EMG needle has a smaller receiving radius than a concentric needle electrode. Using this special needle it is possible to derive potential pairs of 2 fibers of the same motor unit and thus determine the jitter. The muscles most frequently used are the extensor digitorum muscle on the forearm or the frontalis muscle, since they can be constantly innervated over a longer period and since these muscles are less subject to age-related change (overview in [18]). In purely ocular forms, the SFEMG can also be performed by the orbicularis oculi muscle, but which places higher demands on the examiner and the patient. A normal SFEMG in a paretic muscle practically rules out myasthenia gravis [16]. Currently SFEMG is rarely employed due to the time factor and experience required of the examiner.
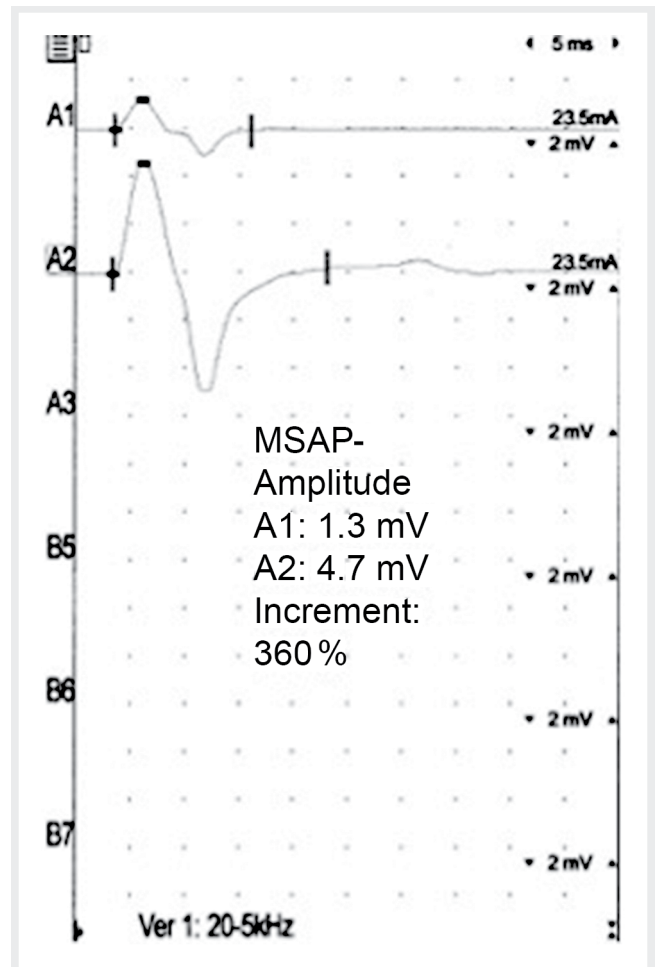
Pharmacological tests

The Tensilon test, once regularly performed, is still occasionally used today. This test uses the briefly active cholinesterase inhibitor edrophonium (Tensilon, Camsilon) injected intravenously. The patient should be connected to an ECG monitor; initially 2 mg of Tensilon are administered as a test dose, if bradycardia does not occur, the remaining 8 mg are subsequently injected. During the test, atropine should always be available as an antidote. Muscle force generally improves after 30–45 s and continues for about 4–5 min. The test can be combined with repetitive stimulation; after administration of Tensilon the decrement should decrease. The clinical interpretation of the test should take into account that Tensilon yields a false negative in approx. 25 % of myasthenia cases, and can produce false positive results in some muscular diseases or spinal muscular atrophy.

Another option is the provisional administration of pyridostigmine bromide in a dosage of 3–4 × 10 mg to 4 × 60 mg over several days.

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SUMMARY

The diagnosis of myasthenia gravis is based on clinical progression, diagnosis of autoantibodies and, as needed, electrophysiological examinations.

In the case of a negative finding of acetylcholine receptor antibodies, anti-MuSK, anti-LRP4 and anti-titin antibodies should be determined.

An electrophysiological examination is dispensable if the clinical symptoms are unambiguous and there is a positive autoantibody test.

Conflict of Interest

The author declares no conflict of interest.

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