The key manifestation of myasthenia gravis (MG) is fluctuating muscle weakness which typically increases during effort. Myasthenia gravis is a chronic autoimmune disease, sub-classified according to the Osserman und Genkins classification (2), and, more recently, that of the MGFA (Myasthenia Gravis Foundation of America) - Task-Force (3) (table 1). According to these criteria, ocular MG is characterized by fluctuating unilateral or bilateral ptosis, and, frequently, double vision, both deteriorating during the day. Generalized MG with additional involvement of arm, leg and trunk muscles as well as respiratory, facial and bulbar muscles is divided into different sub-categories dependent on disease severity. Muscle atrophy is rarely present and only in the late stages of severe, and insufficiently treated MG (1, 3). Generalized forms without typical ocular symptoms pose a particular diagnostic challenge.

The prevalence of MG is between 25 and 100 per million population (1). MG presents most commonly between the ages of 20 to 40 and 60 to 70 (female to male ratio 3:2) (1).

Clinical examination

The examination of the extra ocular musculature includes:

- the eyelid fatigue test while looking upwards for one minute, with recovery after brief maximal eyelid closure (4)
- the diplopia stress test (looking sideways for at least one minute)
- the red glass test (red glass in front of the right and light source in front of the left eye, to distinguish double images)
- the eliciting of the so-called Cogan sign, transient jerks of the eyelid immediately after looking quickly downwards and then upwards (4) and
- weakness of the periocular musculature (eyelash sign).

In the modified Besinger and Toyka myasthenia score (5), the weakness and fatigue of the preferentially affected proximal muscle groups, the vital capacity (via spirometry) and...
the spontaneous ocular and faciopharyngeal symptoms and their degree of worsening with
effort are presented in a summary score (table 2).

**Differential diagnosis of myasthenia gravis**
Among the differential diagnoses are mitochondrial myopathy, botulism from food poisoning,
myositis, congenital myasthenic syndrome and Lambert Eaton myasthenic syndrome
(LEMS). Lambert Eaton myasthenic syndrome is a neuromuscular disorder of presynaptic
neurotransmission mediated by auto-antibodies against voltage-gated calcium channels,
characterized by muscular weakness and autonomic disorders such as dry mouth, hyposalivation
and impotence (3). Its prevalence is around or below 1 to 2 per 100 000.

**TABLE 1**

<table>
<thead>
<tr>
<th>Class</th>
<th>Clinical form(s)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I*/MGFA I</td>
<td>Ocular form</td>
<td>Ptosis, diplopia</td>
</tr>
<tr>
<td>II a*/MGFA II</td>
<td>Mild generalized form</td>
<td>Mild generalized weakness</td>
</tr>
<tr>
<td>II b*/MGFA IIb</td>
<td>Faciopharyngeal form</td>
<td>Ila + bulbar weakness</td>
</tr>
<tr>
<td>III*</td>
<td>Severe acute generalized form</td>
<td>Acute severe general weakness + bulbar symptoms + respiratory insufficiency</td>
</tr>
<tr>
<td>MGFA III</td>
<td>Medium severity generalized form</td>
<td>Medium severity generalized weakness with involvement of the extremities/trunk muscles &gt; faciopharyngeal musculature</td>
</tr>
<tr>
<td>MGFA IIIa</td>
<td>Severe acute generalized form</td>
<td>Acute severe general weakness + bulbar symptoms + respiratory insufficiency</td>
</tr>
<tr>
<td>MGFA IIb</td>
<td>Severe chronic generalized form</td>
<td>Severe, often progressive generalized weakness</td>
</tr>
<tr>
<td>IV*</td>
<td>MGFA IV</td>
<td>Severe chronic generalized form</td>
</tr>
<tr>
<td>MGFA IVa</td>
<td>Severe generalized form</td>
<td>Severe, often progressive generalized weakness</td>
</tr>
<tr>
<td>MGFA IVb</td>
<td>Severe generalized form</td>
<td>Severe, often progressive generalized weakness</td>
</tr>
<tr>
<td>V*</td>
<td>MGFA V</td>
<td>Severe chronic form with muscle atrophy</td>
</tr>
</tbody>
</table>

MGFA, Myasthenia Gravis Foundation Association; the entries marked* refer to the Osserman and Genkins classification

**TABLE 2**

<table>
<thead>
<tr>
<th>Myasthenia score modified according to Besinger und Toyka (5)<strong>1</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm outstretched time*2</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>&gt; 180 Sec.</td>
</tr>
<tr>
<td>Leg outstretched time*3</td>
</tr>
<tr>
<td>Head outstretched time*4</td>
</tr>
<tr>
<td>Vital capacity*5 FEV1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Chewing/swallowing</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Facial expression</td>
</tr>
<tr>
<td>Diplopia</td>
</tr>
<tr>
<td>Ptosis</td>
</tr>
</tbody>
</table>

**1** This original score has been adapted and extended for clinical trials by the MGFA
**2** Dominant arm, outstretched horizontal during sitting; in semi prone, severely ill patients, lift arm by about 30–45° (the outstretched times are only approximate measures)
**3** Supine, dominant leg, outstretched 45°
**4** Supine, head lifted 45°
**5** Vital capacity measured while seated; m, men, w, women; FEV1 = forced expiratory volume at one second
Pathogenesis of myasthenia gravis

MG is a prototypical antibody-mediated, T-helper cell dependent autoimmune disease (6, 7, 8, 9, 10). The majority of MG patients have antibodies directed against the alpha subunit of the nicotinergic acetylcholine receptor (Ach-R) of skeletal muscle (6), which lead to loss of receptors and destruction of the postsynaptic membrane (6). Blocking antibodies bind at or in the immediate vicinity of the acetylcholine binding sites and are usually not detected on standard laboratory testing (see below) (9).

Autoantibodies directed against the acetylcholine receptor (Ach-R) are produced in the thymus and in the lymphatic system by ACh-R-specific auto-reactive T and B lymphocytes which are generated during thymus maturation (10). In the healthy individual, these autoimmune T-cells are eliminated or adequately controlled by regulatory T-cells. The primary triggering event is as poorly understood as in other autoimmune diseases. Ach-R antibodies are detected in 80% to 90% of patients with generalized MG and in about 50% of patients with ocular MG. In up to 40% of patients formerly classified as suffering from sero-negative MG, specific antibodies against muscle-specific tyrosine kinase (MuSK) can be identified (11). In MuSK positive MG bulbo-pharyngeal and respiratory muscles are preferentially affected (11). This form of MG accounts for around two to five percent of acetyl-choline receptor (Ach-R) antibody negative cases who have generalized myasthenia. In around five percent of patients with generalized MG no specific antibodies can be found, meaning that additional target antigens can be assumed to exist. In around 70% of acetyl-choline receptor (Ach-R) antibody positive patients under 40, the thymus shows the histological picture of thymitis with lymphofollicular hyperplasia. In MuSK-antibody-associated myasthenia, the thymus is for the most part morphologically normal (12).

Patients over 40 mostly have age-related thymic atrophy (1). Thymomas (figure) or thymic carcinomas (13) are found in five to fifteen percent of patients (paraneoplastic MG). Mature, potentially auto-reactive T-cells are produced in the non-neoplastic area of these tumors; the maturation and export of regulatory T-cells is reduced (14).

Additional investigations

Electrophysiology

The exhaustion of neuromuscular transmission due to a reduced number of functional postsynaptic acetylcholine receptors can be demonstrated electrophysiologically by means of supramaximal electrical repetitive 3Hz stimulation (serial nerve stimulation) of, for example, the accessory nerve, or the facial nerve, with measurement of the myoelectric response in the corresponding muscles. A positive decrement (reduction in the amplitude/area by more than 15%/10%) is found in up to 80% of patients with generalized MG and in less than 50% of patients with the ocular form (15).

Pharmacological testing

In the Tensilon test, 2 ml of edrophonium chloride are given initially in the adult patient intravenously (10 mg edrophonium chloride dissolved in 9 ml physiological saline solution). After a minute, if there is no response and there are no side effects, a further 8 ml are given,
with atropine sulphate held ready for administration as an antagonist, should muscarinic side effects (asthma attack, bradycardia) occur. The Tensilon test can be combined with the serial nerve stimulation test, used before and afterwards, in diagnostically difficult cases (15).

In high risk patients and in outpatients, a test with oral pyridostigmine should first be carried out, with subsequent testing after 60 minutes, and a clearly positive response may be sufficient to make the diagnosis.

Laboratory investigations
The analysis of patient serum for pathologically raised titers of acetylcholine receptor antibodies using an immune precipitation test (acetylcholine receptor extracts from human amputated muscle) is the most specific tool in the diagnosis of MG (6). Seronegative patients should be tested for antibodies against MuSK.

Imaging investigations
Imaging of the thorax with CT or MRI to investigate the thymus is mandatory in all new cases of MG and should be repeated at intervals of one to two years, even where the initial investigation was normal, to exclude incipient thymoma. Scintigraphy using indium-111-DTPA-D-phe-octreotide can be helpful in imaging the extent of growth of a thymoma by means of the somatostatin receptors expressed on the surface, even where there is considerable scarring following surgery (16).

Treatment
MG is one of the best treatable autoimmune diseases. The cornerstones of treatment are thymectomy, acetylcholinesterase inhibitors, immunosuppressive drugs and plasmapheresis (1, 3). The aim of treatment is remission with the best possible quality of life. In autoimmune MG, the use of glucocorticoids, cyclosporin A, combination therapy with azathioprine and glucocorticoids, as well as plasmapheresis and immunoglobulins, is supported by studies designed to provide class 1 evidence (17, 18, 19, 20). However, some of these studies fail to reach this level, due for example to problems with recruitment (box 1). Only class 2

<table>
<thead>
<tr>
<th>BOX 1</th>
<th>Stepwise approach to the pharmacological treatment of myasthenia gravis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acetylcholinesterase inhibitors (basic maintenance treatment)</td>
<td>Pyridostigmine 60 mg 4 hourly, optional 90–180 mg retard (time span) at bedtime *1</td>
</tr>
<tr>
<td>2. Glucocorticosteroids</td>
<td>60-100 mg methylprednisolone (or prednisone/prednisolone) p/o (gradual increase or start with maintenance dose, with gradual reduction on remission). Caution: transient worsening is possible</td>
</tr>
<tr>
<td>3. Immunosuppressive long term therapy</td>
<td>Azathioprine 2–4 × 50 mg/day (2–3 mg/kg) *2</td>
</tr>
<tr>
<td></td>
<td>Cyclosporin A 2 × 100–200 mg/day *3</td>
</tr>
<tr>
<td>Medication for non- or poor responders</td>
<td>Mycophenolat mofetil 1,000–2,000 mg/day *4</td>
</tr>
<tr>
<td></td>
<td>Methotrexate 7.5 mg/week *4</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 500 mg/m2 IV every 4–12 weeks or 1–2 mg/kg/day p/o *4, *5</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus 2 × 2–5 mg/day; reserved for intractable cases *6</td>
</tr>
<tr>
<td></td>
<td>Rituximab (Mabthera) *6</td>
</tr>
</tbody>
</table>

*1 Retard preparation only useful with definite over night or morning symptoms
*2 Administration in 3 daily doses following meals is better tolerated than 1–2 doses; prior test dose of 1 × 50 mg
*3 Only with regular monitoring of fasting plasma levels, class 1-evidence based, but not yet licensed for MG
*4 Unlicensed but successful in a number of case reports
*5 Only in severe refractory disease; higher doses required for “immune ablation” with rescue medication – off-label
*6 Very limited experience – off label
evidence exists for second line immunosuppressive treatments such as tacrolimus, methotrexate and cyclophosphamide, as well as for MTX and cyclosporin A, and for these there is no formal licence for this indication in many countries. The effect of thymectomy on the progression on MG has only been investigated by evidence class 2 studies (21).

A metaanalysis of available class 2 evidence studies on thymectomy in myasthenia gravis (21) suggests that complete thymectomy in patients under 45 can improve prognosis. The upper age limit for thymectomy is at around age 60. In purely ocular disease, thymectomy is not indicated. Where there is suspicion of a thymoma, radical surgery is essential to clarify the histological picture. Invasive or metastasizing cortical thymomas and well differentiated thymus carcinomas can additionally be treated with radiotherapy and chemotherapy, which is thought to improve prognosis. Pyridostigmine, given in a dose of 60 mg three to seven times daily has proved helpful as oral, symptomatic treatment. Its effect can be demonstrated electrophysiologically (6).

Pyridostigmine inhibits the hydrolytic cleavage of acetylcholine (15) and thereby improves neuromuscular transmission. Symptomatic treatment with pyridostigmine is, however, seldom sufficient in itself. Initial immunosuppressive treatment begins with glucocorticoids in rising doses (30 to 100 mg p/o) or with an intermediate dose of 60 mg/day. Due to a reinforcement of the acetylcholine receptor ion channel dysfunction, a transient worsening of symptoms may occur between two and twelve days after treatment has been given. Because of their toxicity, steroids as immunosuppressive monotherapy are only used in low doses (10–30 mg/day) in ocular myasthenia, and are otherwise tailored down once a significant improvement has been achieved. The effect of glucocorticosteroids is supported by class 1 evidence, although the class 1 criteria are only partially fulfilled in the individual studies (17). In order to limit the use of steroids, immunosuppressive drug maintenance therapy should be given in generalized MG from the acute phase, with azathioprine (AZA) in a dosage of 50 mg b.i.d. or t.i.d. (total daily dose 2.5 to 3 mg/kg) is the treatment of first choice (1) (box 1). From a practical point of view, a single test dose of 50 mg is advisable before commencing maintenance therapy, to exclude occasional severe idiosyncratic reactions (fewer than 0.5% of patients).

The biologically active form (6-mercaptopurine) inhibits T and B lymphocyte proliferation, thereby reducing antibody production. The therapeutic efficacy of AZA in combination with corticosteroids is supported by a single study of class 1 level evidence (19). During treatment with AZA the total leucocyte count should not drop down to less than at least 3,500/µL and the absolute lymphocyte count should be maintained between 500 and 900/µL. In thiopurine methyl transferase deficiency or in simultaneous treatment with allopurinol for gout, AZA is not, or is incompletely, broken down, so that a normal dose can lead to dangerous leucopenia. In these cases 25% to 50% of the normal dose should be used.

**BOX 2**

Management of myasthenic crisis

1. **Acetylcholine esterase inhibitors**
   - Physostigmine 8–24 mg/day IV (initially always with atropine sulphate)

2. **Glucocorticosteroids**
   - Up to 500 mg methylprednisolone IV or 100 mg p/o (with gradual reduction on remission)

3. **Plasma separation techniques**
   - Plasmapheresis (non-selective) or additional immune adsorption (semi-selective), Exchange of 1–2 plasma volumes 2–3 × weekly for 2 weeks

4. **Immunoglobulins IV (only for specific indications)**
   - 0.4 g/kg on 5 consecutive days

5. **Immunosuppressive long term therapy (see above)**
   - Begin as soon as possible or continue at a higher dose/combination
The measurement of thiopurine methyl transferase activity is advisable in early and marked AZA-associated leucopenia. Where enzyme activity is lacking, AZA is contraindicated. Treatment with AZA should be continued for at least two to three years, and be reduced by 25 mg every three months where there is remission and the acetylcholine receptor antibody titers are stable. If AZA is discontinued too abruptly or too soon, relapses can occur (22). Where there is intolerance or inadequate effect, another immunosuppressive drug should be used (box 1). Treatment must be under continual medical review, as must any chemotherapy.

Cyclosporin A (CYC A) works by inhibiting calcineurin synthetase, thereby inhibiting the synthesis of cytokines and the activation of T lymphocytes (1). CYCA is given at a dose of 2 × 50 mg to 2 × 150 mg orally (2 to 5 mg/kg). Its efficacy is supported by evidence class 1 studies (18). A fasting plasma level of 70 to 100 µg/ml after 12 hours should be aimed for, in myasthenia gravis. Significant side effects include arterial hypertension, nephropathy and neurotoxicity (encephalopathy).

Around 5% of patients are unable to tolerate AZA or CYC A, or respond inadequately. In these cases, mycophenolate mofetil may be used for long term immunosuppression.

Mycophenolate mofetil (2 × 500 to 1.000 mg/day) is first converted in the body to mycophenolic acid, which selectively, non-competitively and reversibly inhibits inosine monophosphate dehydrogenase and hence inhibits de novo synthesis of guanosine nucleotide synthesis (23).

Methotrexate is used on rare occasions (7.5 to 15 mg/week [1]). It inhibits lymphocyte proliferation via inhibiting folate synthesis. Significant side effects include pulmonary fibrosis and bone marrow suppression. Cyclophosphamide is a fallback treatment for the most intractable cases (1). It is cytotoxic and immunosuppressive, and is given either intravenously (500 mg/m² of body surface area (SA), at intervals of 4 to 12 weeks, or, less commonly, orally (1 to 2 mg/kg BW/day). A maximal cumulative lifetime dose of 45 g should not be exceeded due to cumulative toxicity.

A high dose therapy at 50 mg/kg BW and subsequent rescue therapy with granulocyte stimulating factor (G-CSF) (so-called immune ablation) should remain an option for the most intractable cases (24).

"Off label" use

With the exception of AZA, none of the above long term immunosuppressive treatments is licensed for use in MG in Germany and in some other European countries. Hence, these may only be used "off label" where AZA is not tolerated. The cost of such treatment is only reimbursable under health insurance arrangements by prior permission.

Approaches under investigation

Among newer treatment approaches is rituximab, an antibody against a surface antigen expressed by B-cell precursors (CD 20), which may be used off label at a dose of 375 mg/m² SA in refractory cases of MG.

Tacrolimus, like CYC A, blocks calcineurin activity and hence inhibits T lymphocyte proliferation. Although observational studies have shown benefit from tacrolimus in MG (23), its use is not currently established in Germany.

Treatment of myasthenic crisis

Severe generalized illness, infections and operations can precipitate myasthenic crisis with acute generalized weakness, swallowing difficulties and respiratory failure (1, 25). Myasthenic crises are rare nowadays, and occur primarily in the first two years of disease onset. Where the forced vital capacity falls below 1.2 l (15 ml/kg body weight) or where oxygen is required, artificial ventilation is indicated (1, 25).

The intensive care management of myasthenic crisis includes first a switch from pyridostigmine to physostigmine as an i.v. drip or in the perfusor, in combination with subcutaneous atropine, high dose intravenous glucocorticoids and plasmapheresis (1, 3, box 2). In general, one to two times the plasma volume is exchanged three times weekly over a two week period. Only where this is contraindicated (sepsis, poor venous access, age over 70) would we recommend intravenous immunoglobulin G as a first line treatment. This is only marginally less effective than plasmapheresis, given in a dose of 0.4 g/kg in
five consecutive days (class 1 evidence level 4) (box 2) (20). The efficacy of intravenous immunoglobulins rests in part on the neutralization of circulating antibodies, the inhibition of B-cell activation and complement binding, the blockade of Fc receptors, and the modulation of T-cell function (1).

With these measures, myasthenic crisis can usually be brought under rapid control. Adequate ongoing immunosuppression should be commenced or increased, at an early stage.

Total mortality in myasthenic crisis, of which elderly patients and those with comorbidity are at greatest risk, has fallen to under 5%, thanks to efficient short and long term treatments and improvements in intensive care (1, 25). These improvements also permit successful management of even complicated cases.

**Management during anaesthesia, surgery and pregnancy**

Muscle relaxants during anaesthesia should either be withheld, or given only in the form of a tenth of the usual dose, in the form of a medium acting non-depolarizing agent such as atracurium. A prolonged postoperative ventilation requirement is to be expected. For local anaesthesia, an amide type agent should preferably be used, such as lidocaine (1).

It is generally not needed to discontinue long term immune suppressants preoperatively. Pregnant women with MG should deliver in a center experienced in the management of this condition, and with neonatal intensive care facilities available. This is important because, regardless of the severity of maternal disease, 10% of neonates will suffer transient myasthenia (1). The maternal disease can also worsen. Medications which can worsen myasthenia gravis include: D penicillamine, antibiotics, antidepressants, beta-blockers, calcium antagonists and magnesium (table 3).

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Prof. Dr. med. Klaus Toyka has received consultancy fees from pharmaceutical companies involved in the area of immune therapy and has been paid as a reviewer in the licensing of Imurek (azathioprine) in myasthenia. In addition, he has advised companies on therapeutic studies of immunoglobulins in myasthenia, pro bane; he has authored and co-authored treatment guidelines for pharmaceutical companies and professional bodies, for which costs of printing were in part covered by educational grants from pharmaceutical companies.

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