

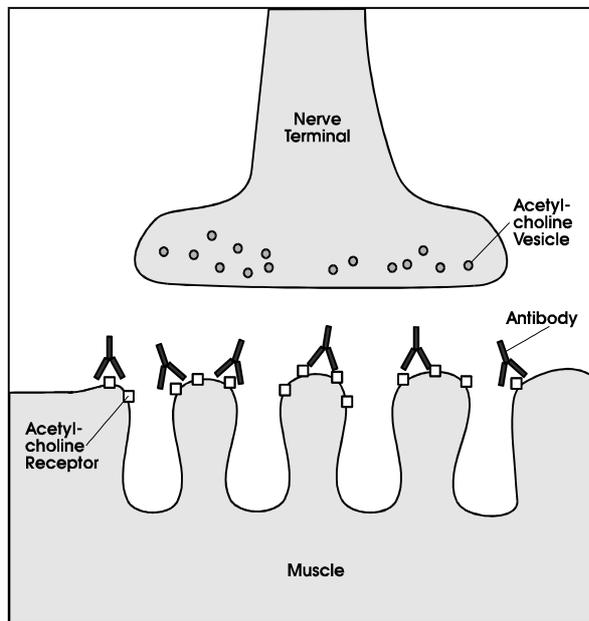
## Differential Diagnosis of Myasthenic Syndromes

### Acetylcholine Receptor Autoantibodies

#### *Diagnosis of Myasthenia gravis*

Myasthenia gravis is an acquired, humoral autoimmune disease. Specific **acetylcholine receptor autoantibodies (ACHRAB)** lead to a reduced impulse transmission to the postsynaptic membrane of the neuromuscular end-plate.

T-helper cells which have been activated in the thymus probably stimulate the production of the acetylcholine receptor autoantibodies. These react mainly with the  $\alpha$ -subunit of the receptors, reducing the functional activity at the postsynaptic membrane.



#### **Myasthenia gravis**

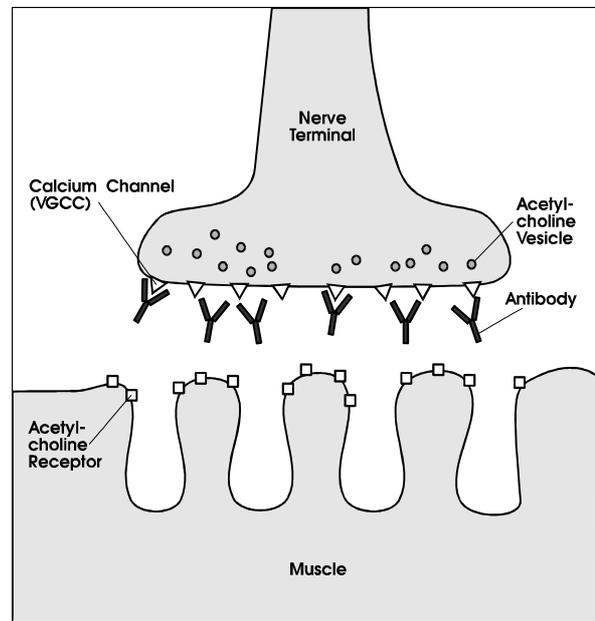
Autoantibodies against the postsynaptic acetylcholine receptor

### Calcium Channel Autoantibodies

#### *Diagnosis of Lambert-Eaton Syndrome*

The primary physiological disorder in the **Lambert-Eaton myasthenic syndrome (LEMS)** is a reduced release of the neurotransmitter acetylcholine from the nerve terminals into the synaptic gap.

This presynaptic disorder is caused by autoantibodies against a membrane protein of the nerve cell, the **voltage-gated calcium channel (VGCC)**. These channels are also described as active zone of the presynaptic membrane.



#### **Lambert-Eaton Syndrome**

Autoantibodies against the presynaptic voltage-gated calcium channels

## Clinical Features

The main features in myasthenia gravis are weakness and fatiguability of skeletal muscles. Ptosis and diplopia occur early in the majority of patients. Weakness remains localized to the extraocular and eyelid muscles in about 15 % of patients (ocular myasthenia). The facial and bulbar muscles can be affected (mild generalized disease). Generalized weakness develops in about 85 % of patients and can lead to a life-threatening impairment of respiration (severe generalized disease and crisis).

The disease occurs during all ages, from infancy up to old age. The prevalence is 5-12 cases per 100,000 population. Women are affected twice as often as men.

In the severe generalized disease even low strain causes respiratory insufficiency. Sitting up as well as walking or standing is no longer possible without help. The limb muscles are almost immobilized. Chewing and swallowing may be strongly impaired and patients may aspirate. Because of these life-threatening conditions it can be necessary to look after the patients in an intensive care unit.

Patients with an initially severe generalized myasthenia gravis have a poor prognosis. Sometimes a myasthenic crisis with respiratory insufficiency can occur within a short time.

Many factors like infections, stress or psychological impairment can cause a change for the worse.

The Lambert-Eaton syndrome occurs less often than myasthenia gravis. The main characteristics are a weakness of the proximal muscles, reduced tendon reflexes as well as autonomous disorders like visual disorders, dry mouth, reduced transpiration and tear fluid, constipation and sexual impotence.

In about 60 % of cases LEMS appears as paraneoplastic syndrome, associating specifically with small-cell lung carcinoma (SCLC). In the remaining cases no carcinoma can be found even after long periods of observation.

LEMS is usually diagnosed prior to any clinical manifestation of the tumour. Typically the neurological symptoms may precede the radiological appearance of the cancer by 2 years and sometimes by 5 years or more. The diagnosis of LEMS can give the earliest clue to an underlying tumour.

Therefore, patients with LEMS should have repeated pulmonary check-ups. X-ray examinations of the chest are recommended every 3 months and a bronchoscopy every 6 months.

The Lambert-Eaton syndrome usually occurs after the age of 30 and is twice as common in men as in women. The disease is rare with children and adolescents.

The typical symptoms in LEMS are very similar to the generalized symptoms of myasthenia gravis (MG). Therefore, LEMS may initially be misdiagnosed as MG.

The most important different characteristics of the two diseases are shown in the following table:

	<b>Myasthenia gravis</b>	<b>Lambert-Eaton syndrome</b>
muscle strength	decreasing during ongoing exercise	maximum contraction delayed
ocular muscles paresis	typical	rare
autonomic nervous system	normal	anti-cholinergic syndrome
tendon reflexes	normal	reduced with post-tetanic facilitation
single nerve stimulation	normale amplitude	reduced amplitude
repetitive stimulation	decrement at 3-Hz stimulation	additional increment at 20-Hz stimulation
acetylcholine receptor autoantibodies	positive	negative
calcium channel autoantibodies	negative	positive

## Diagnosis

The history and physical findings are usually the most important initial clues to the diagnosis of MG. Confirmatory laboratory testing like the Tensilon® test, the 3-Hz repeated stimulation and the single-fiber electromyography are essential. Especially the measurement of circulating antibodies against acetylcholine receptors is of great importance for the differential diagnosis. The most common method is the immunoprecipitation test (ACHRAB® Assay).

Pathological concentrations of antibodies are detectable in about 90 to 95% of patients with generalized myasthenia gravis and in about 45% of patients with ocular MG. The absolute antibody concentration does not correlate with the severity of the disease, but in more than 90% of the patients there is a good individual correlation between the change of antibody concentration and clinical features. Therefore, the measurement of the antibodies is of great help in the therapeutic management and follow-up of myasthenia gravis. Above all it has been shown, that an increase of the autoantibodies can often be found several weeks before the onset of clinical deterioration. Consequently, the measurement of the antibodies enables a preventive therapeutic management.

## Therapy

Anticholinesterase agents (Prostigmine, Pyridostigmine) are used as the first line of treatment for myasthenia gravis at all stages of severity and grades of the disease. They are the basis used for the focal disease, restricted to ocular muscles. Either surgical thymectomy or immunosuppressive treatment with corticosteroids and azathioprine is indicated for more severe generalized disorders. The single steps of treatment depend on the severity of the clinical symptoms.

After thymectomy, clinical remission occurs in approximately 30 % of the patients (mainly at females) and improvement is seen in another 45 %. Plasma exchange produces short-term clinical improvement. It is used primarily to stabilize the condition of patients in myasthenic crisis or in patients who do not respond to other methods.

For the diagnosis of the Lambert-Eaton syndrome methods like testing of the tendon reflexes and repetitive nerve stimulation can be used. In addition the radioimmunological measurement of antibodies against the voltage-gated calcium channels are of help. The use of P/Q-VGCCs, labelled with <sup>125</sup>I- $\omega$ -Conotoxin MVIIC results in a high sensitivity and specificity.

90% to 100% of patients with Lambert-Eaton syndrome and small-cell lung carcinoma are positive in the test. 80% to 90% of the patients with LEMS but without SCCL are found positive. There are only very few cases of normal healthy blood-donors and patients with other neurological disorders and autoimmune diseases like rheumatoid arthritis or SLE, who are found low positive in the test.

Like in myasthenia gravis, the absolute concentration of antibodies seems not to be correlated with the severity of the disease. But for the individual patient the increase or decrease of the concentration of antibodies may reflect the clinical course of the disease.

For a Lambert-Eaton syndrome associated with small-cell carcinoma of the lung, priority is given to the therapy of the tumour. The surgical removal of the tumour often causes a temporary improvement of the neurological symptoms. Immunosuppressive drugs are usually not indicated.

4-Aminopyridine (possibly in combination with pyridostigmine) seems to be ideally suited for the symptomatic treatment of the Lambert-Eaton syndrome. It enhances the release of acetylcholine from the presynaptic nerve terminals. If there is no sufficient improvement, particularly in patients without tumour, an immunosuppressive therapy with prednisolone and/or azathioprine is indicated. In some cases even remissions have been reported. Plasmapheresis is an effective treatment for patients with severe symptoms.

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