DIAGNOSTIKA GMBH

Calcium Channel Autoantibodies in the Diagnosis of the Lambert-Eaton Syndrome

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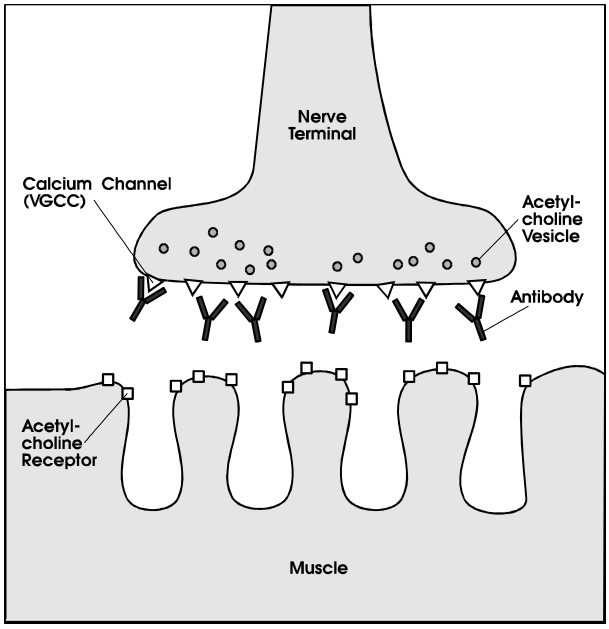
Pathophysiology

The primary physiological disorder in the **L**ambert-**E**aton **m**yasthenic **s**yndrome (LEMS) is a reduced release of the neurotransmitter acetylcholine from the nerve terminals into the synaptic gap.

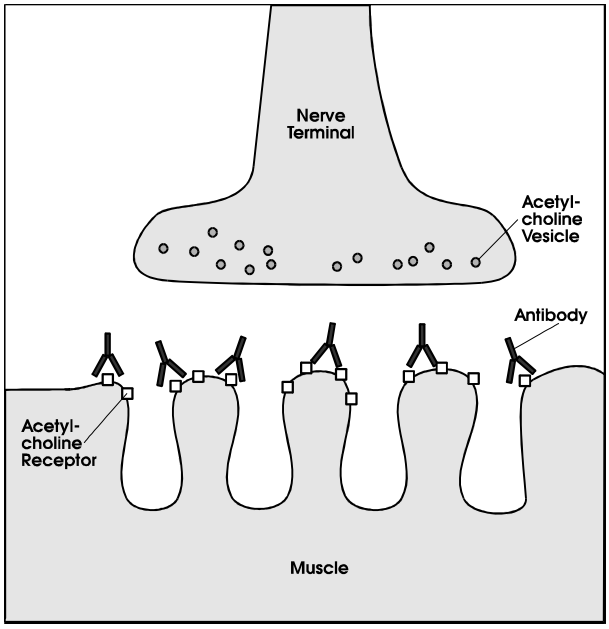
This presynaptic disorder is caused by autoantibodies against a membrane protein of the nerve cell, the **v**oltage-**g**ated **c**alcium **c**hannel (VGCC). These channels are also designated as active zone of the presynaptic membrane.

A transient depolarization of the presynaptic membrane causes the opening of the voltage-gated calcium channels, which allows the local influx of calcium ions into the nerve terminal. This rise in calcium ion concentration results in the release of acetylcholine from the vesicles. Autoantibodies as found in LEMS lead to a cross-linking of the channels with subsequent internalisation and degradation. As a consequence the number of channels is reduced and, therefore, the release of acetylcholine. The result is an interruption of the impulse transmission to the neuromuscular end-plate of the muscle cell which eventually causes the typical myastenic syndromes.

In myasthenia gravis the autoimmune process happens on the postsynaptic level at the acetylcholine receptor of the muscle cell. In LEMS the autoimmune process takes place on the presynaptic level at the nerve terminal. The following figures show schematically the difference between these two diseases at the neuromuscular junction.



Lambert-Eaton Syndrome
Autoantibodies against the presynaptic voltage-gated calcium channels



Myasthenia gravis
Autoantibodies against the postsynaptic acetylcholine receptor

Clinical Features

In examining patients with Lambert-Eaton syndrome, an initial short increase of the muscle strength followed by weakness and fatiguability ist typical. Affected are the proximal muscles, especially the lower limbs and gait. In some patients a mild degree of ptosis and bulbar weakness may be present, but diplopia or substantial involvement of respiratory muscles is rare. Depressed tendon reflexes are common, and may increase after maximum voluntary contraction (post-tetanic potentiation). Dysfunction of the autonomic nervous system is also common, which may be manifest as dry mouth, sexual impotence or constipation.

The typical syptomes in LEMS are very similar to the generalized symptomes of myasthenia gravis. Therefore, LEMS may initially be misdiagnosed as myasthenia gravis. The most important characteristics of both diseases are shown in the following table:

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

LEMS as paraneoplastic syndrome often is associated with small-cell carcinoma of the lung (SCLC), but can also occur as a primary disorder without any maligne disease.
Most patients are between 50 and 70 years old. The disorder is twice as common in men as in women. One third of the patients have either a personal or family history of other organspecific autoimmune diseases like autoimmune thyroid disease, pernicious anemia, coeliac disease or type I diabetes.

Lambert Eaton syndrome and small-cell carcinoma of the lung

About 60 % of LEMS patients have an associated small-cell lung carcinoma (SCLC).

This association between LEMS and SCLC seems to be quite specific. Other tumours have been reported with LEMS, but the association is far weaker and not necessarily significant. The reason for the association of SCLC with LEMS is, that SCLC is a tumour of neuroectodermal origin and, therefore, shares certain antigenetic determinants with the central nervous system. Functioning calcium channels can be expressed in the small-cell lung cancer. Because of the immune response of the patient against the tumour, antibodies against these calcium channels are developed. These antibodies cross react with the neuronal calcium channels. In this way the presynaptic calcium channels decline in number and the outbreak of the Lambert-Eaton syndrome follows. This immunological reaction actually takes place at a very early stage of the development of the tumour, when the carcinoma can not be detected yet.

As a consequence 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.

A search for malignancy, particularly for SCCL, should, therefore, be made in patients with newly diagnosed Lambert-Eaton syndrome, and should be repeated at intervals during the first years after the onset of symptoms. X-ray examinations and a CT or MR imaging scan of the chest may be supplemented by sputum analysis and bronchoscopy.

Measurement of autoantibodies against the calcium channel

For the diagnosis of the Lambert-Eaton syndrome the above mentioned 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 principle of the measurement is similar to that of the ACHRAB® assay for the determination of antibodies against the acetylcholine receptor.
^{125}Iodine labelled calcium channel proteins are used for the test. This membrane protein has a high affinity to conotoxin. Conotoxin is the toxin of sea snails and binds almost irreversibly to the VGCCs.

There are several subtypes of calcium channel proteins due to their electro-physiological characteristics. These different subtypes bind different conotoxins. The P/Q-VGCCs apparently control the release of neurotransmitter at the neuromuscular junction and probably are the target antigen of the autoantibodies. This subtype binds the ω-Conotoxin MVIIC derived from the cone snail *Conus magus*.

The use of P/Q-VGCCs labelled with ω-Conotoxin MVIIC results in a high sensitivity and specifity.
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, which are found low positive in the test.

For the assay ω-Conotoxin MVIIC is labelled with ^{125}Iodine and then mixed with purified VGCCs. In this way only calcium channels of the P/Q subtype are specifically and indirectly labelled. The labelled protein is incubated with the patient serum. During this incubation specific antibodies bind to the protein. Thereafter, the immune complexes are precipitated with anti-human IgG. The radioactivity in the pellet is proportional to the amount of antibodies in the patient serum. The concentration of the samples in pmol/l is calculated using the known specific activity of the conotoxin and considering the nonspecific binding of the individual patient sample.

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.

Therapy

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 symptomes. Immunosuppressive drugs are usually not indicated.

3,4-diaminopyridine 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 immunsupressive therapy with prednisolone and/or azathioprine usually is of help. In some cases even remissions have been reported. Plasmapheresis is an effective treatment for patients with severe symptoms.

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