= Lambert ? Eaton myasthenic syndrome =

Lambert ? Eaton myasthenic syndrome (LEMS , also Lambert ? Eaton syndrome , or Eaton ? Lambert syndrome) is a rare autoimmune disorder that is characterized by muscle weakness of the limbs . It is the result of an autoimmune reaction in which antibodies are formed against presynaptic voltage @-@ gated calcium channels , and likely other nerve terminal proteins , in the neuromuscular junction (the connection between nerves and the muscle that they supply) . The prevalence is 3 @.@ 4 cases per million . Around 60 % of those with LEMS have an underlying malignancy , most commonly small cell lung cancer ; it is therefore regarded as a paraneoplastic syndrome (a condition that arises as a result of cancer elsewhere in the body) .

LEMS usually occurs in people over 40 years of age , but it may occur any age . The diagnosis is usually confirmed with electromyography and blood tests ; these also distinguish it from myasthenia gravis (MG) , a related autoimmune neuromuscular disease .

If the disease is associated with cancer , direct treatment of the cancer often relieves the symptoms of LEMS . Other treatments often used are steroids , azathioprine , which suppress the immune system , intravenous immunoglobulin , which outcompetes autoreactive antibody from Fc receptors and pyridostigmine and 3 @,@ 4 @-@ diaminopyridine , which enhance the neuromuscular transmission . Occasionally , plasma exchange is required to remove the antibodies .

= = Signs and symptoms = =

The weakness from LEMS typically involves the muscles of the proximal arms and legs (the muscles closer to the trunk) . In contrast to myasthenia gravis , the weakness affects the legs more than the arms . This leads to difficulties climbing stairs and rising from a sitting position . Weakness is often relieved temporarily after exertion or physical exercise . High temperatures can worsen the symptoms . Weakness of the bulbar muscles (muscles of the mouth and throat) is occasionally encountered . Weakness of the eye muscles is uncommon . Some may have double vision , drooping of the eyelids and difficulty swallowing , but generally only together with leg weakness ; this too distinguishes LEMS from myasthenia gravis , in which eye signs are much more common . In the advanced stages of the disease , weakness of the respiratory muscles may occur . Some may also experience problems with coordination (ataxia) .

Three quarters of people with LEMS also have disruption of the autonomic nervous system . This may be experienced as a dry mouth , constipation , blurred vision , impaired sweating , and orthostatic hypotension (falls in blood pressure on standing , potentially leading to blackouts) . Some report a metallic taste in the mouth .

On neurological examination , the weakness demonstrated with normal testing of power is often less severe than would be expected on the basis of the symptoms . Strength improves further with repeated testing , e.g. improvement of power on repeated hand grip (a phenomenon known as " Lambert 's sign ") . At rest , reflexes are typically reduced ; with muscle use , reflex strength increases . This is a characteristic feature of LEMS . The pupillary light reflex may be sluggish .

In LEMS associated with lung cancer , most have no suggestive symptoms of cancer at the time , such as cough , coughing blood and unintentional weight loss . It has been suggested that LEMS associated with lung cancer is more severe .

= = Causes = =

LEMS is often associated with lung cancer (50 ? 70 %) , specifically small @-@ cell carcinoma , making LEMS a paraneoplastic syndrome . Of the people with small cell lung cancer , 1 ? 3 % have LEMS . In most of these cases , LEMS is the first symptom of the lung cancer , and it is otherwise asymptomatic .

LEMS may also be associated with autoimmune diseases , such as hypothyroidism (an underactive thyroid gland) or diabetes mellitus type 1 . Myasthenia gravis , too , may happen in the presence of tumors (thymoma , a tumor of the thymus in the chest) ; people with MG without a

tumor and people with LEMS without a tumor have similar genetic variations that seem to predispose them to these diseases . HLA @-@ DR3 @-@ B8 (an HLA subtype) , in particular , seems to predispose to LEMS .

= = Mechanism = =

In normal neuromuscular function , a nerve impulse is carried down the axon (the long projection of a nerve cell) from the spinal cord . At the nerve ending in the neuromuscular junction , where the impulse is transferred to the muscle cell , the nerve impulse leads to the opening of voltage @-@ gated calcium channels (VGCC) , the influx of calcium ions into the nerve terminal , and the calcium @-@ dependent triggering of synaptic vesicle fusion with plasma membrane . These synaptic vesicles contain acetylcholine , which is released into the synaptic cleft and stimulates the acetylcholine receptors on the muscle . The muscle then contracts .

In LEMS , antibodies against VGCC , particularly the P / Q @-@ type VGCC , decrease the amount of calcium that can enter the nerve ending , hence less acetylcholine can be released from the neuromuscular junction . Apart from skeletal muscle , the autonomic nervous system also requires acetylcholine neurotransmission ; this explains the occurrence of autonomic symptoms in LEMS . P / Q voltage @-@ gated calcium channels are also found in the cerebellum , explaining why some experience problems with coordination . The antibodies bind particularly to the part of the receptor known as the " domain III S5 ? S6 linker peptide " . Antibodies may also bind other VGCCs . Some have antibodies that bind synaptotagmin , the protein sensor for calcium @-@ regulated vesicle fusion . Many people with LEMS , both with and without VGCC antibodies , have detectable antibodies against the M1 subtype of the acetylcholine receptor ; it is thought that their presence participates in a lack of compensation for the weak calcium influx .

Apart from the decreased calcium influx , there is also a disruption of active zone vesicle release sites , which is also thought to be antibody @-@ dependent since people with LEMS have antibodies to components of these active zones (including voltage @-@ dependent calcium channels) . Together , these abnormalities lead to the decrease in muscle contractility . Repeated stimuli over a period of about 10 seconds eventually lead to sufficient delivery of calcium , and an increase in muscle contraction to normal levels , which can be demonstrated using an electrodiagnostic medicine study called needle electromyography by increasing amplitude of repeated compound muscle action potentials .

It has been shown that the antibodies found in LEMS associated with lung cancer also bind to calcium channels in the cancer cells , and it is presumed that the antibodies originally develop as a reaction to these cells . It has been suggested that the immune reaction to the cancer cells suppresses their growth and improves the prognosis from the cancer .

= = Diagnosis = =

The diagnosis is usually made on electromyography (EMG) , which is one of the standard tests in the investigation of otherwise unexplained muscle weakness . This involves the insertion of small needles into the nerves supplying several muscles , administering small electrical impulses through these needles , and measuring the electrical response of the muscle in question . Two EMG investigations can be characteristic in LEMS : compound motor action potentials (CMAP) and single @-@ fiber examination .

CMAP shows small amplitudes but normal latency and conduction velocities . If repeated impulses are administered (two per second or 2 Hz) , it is normal for CMAP amplitudes to become smaller as the acetylcholine in the motor end plate is depleted . In LEMS , this decrease is larger than observed normally . Eventually , stored acetylcholine is made available , and the amplitudes increase again . In LEMS this remains insufficient to reach a level sufficient for transmission of an impulse from nerve to muscle ; all can be attributed to insufficient calcium in the nerve terminal . A similar pattern is witnessed in myasthenia gravis . In LEMS , in response to exercising the muscle , the CMAP amplitude increases greatly (over 200 % , often much more) . This also occurs on the

administration of a rapid burst of electrical stimuli (20 impulses per second for ten seconds) . This is attributed to the influx of calcium in response to these stimuli . On single @-@ fiber examination , features may include increased jitter (seen in other diseases of neuromuscular transmission) and blocking .

Blood tests may be performed to exclude other causes of muscle disease (elevated creatine kinase may indicate a myositis , and abnormal thyroid function tests may indicate thyrotoxic myopathy) . Antibodies against voltage @-@ gated calcium channels can be identified in 85 % of people with EMG confirmed LEMS . Once LEMS is diagnosed , investigations such as a CT scan of the chest are usually performed to identify any possible underlying lung tumors . 50 ? 60 % of these are discovered immediately after the diagnosis of LEMS . The remainder is diagnosed later , but usually within two years and typically within four years . As a result , scans are typically repeated every six months for the first two years after diagnosis . While CT of the lungs is usually adequate , a positron emission tomography (PET) scan of the body may also be performed to search for an occult tumour , particularly of the lung .

= = Treatment = =

If LEMS is caused by an underlying cancer , treatment of the malignancy usually leads to resolution of the symptoms . Treatment usually consists of chemotherapy , with radiation therapy in those with limited disease .

Three treatment modalities aimed at improving LEMS symptoms directly , namely pyridostigmine , 3 @,@ 4 @-@ diaminopyridine (amifampridine) and guanidine , work to improve neuromuscular transmission . Pyridostigmine decreases the degradation of acetylcholine after release into the synaptic cleft , and thereby improves muscle contraction . In LEMS , the potassium channel blocker 3 @,@ 4 @-@ diaminopyridine base or the water @-@ soluble formulation , 3 @,@ 4 @-@ diaminopyridine phosphate , (marketed under the name Firdapse) are also used . Both 3 @,@ 4 @-@ diaminopyridine formulations delay the repolarization of nerve terminals after a discharge , thereby allowing more calcium to accumulate in the nerve terminal . In the United States , 3 @,@ 4 @-@ diaminopyridine phosphate (Firdapse) a more stable formulation of 3 @,@ 4 @-@ diaminopyridine that does not require refrigeration and 3 @.@ 4 @-@ diaminopyridine free base are undergoing clinical trials to treat LEMS . Pending completion of these trials and submission to the FDA , both formulations are available to people with LEMS in the U.S. : the free base is available under a compassionate distribution program by Jacobus Pharmaceutical Company , and the phosphate salt is available to people with LEMS under an expanded access program by Catalyst Pharmaceuticals . Compounding pharmacies may also be a source of 3 @,@ 4 @-@ diaminopyridine salts in the U.S. In Europe , 3 @,@ 4 @-@ diaminopyridine phosphate is sold by BioMarin under the name Firdapse , and the free base is compounded , usually by hospital pharmacies . An older agent , guanidine , causes many side @-@ effects and is not recommended . 4 @-@ Aminopyridine (dalfampridine) , an agent related to 3 @,@ 4 @-@ aminopyridine , causes more side @-@ effects than 3 @,@ 4 @-@ DAP and is also not recommended .

Immune suppression tends to be less effective than in other autoimmune diseases . Prednisolone (a glucocorticoid or steroid) suppresses the immune response , and the steroid @-@ sparing agent azathioprine may replace it once therapeutic effect has been achieved . Intravenous immunoglobulin (IVIG) may be used with a degree of effectiveness . Plasma exchange (or plasmapheresis) , the removal of plasma proteins such as antibodies and replacement with normal plasma , may provide improvement in acute severe weakness . Again , plasma exchange is less effective than in other related conditions such as myasthenia gravis , and additional immunosuppressive medication is often needed . According to a systematic review by the Cochrane Collaboration , the best evidence in the treatment of LEMS exists for 3 @,@ 4 @-@ aminopyridine and IVIG .

= = History = =

Anderson and colleagues from St Thomas ' Hospital , London , were the first to mention a case with

possible clinical findings of LEMS in 1953 , but Lambert , Eaton and Rooke at the Mayo Clinic were the first physicians to substantially describe the clinical and electrophysiological findings of the disease in 1956 . In 1972 , the clustering of LEMS with other autoimmune diseases led to the hypothesis that it was caused by autoimmunity . Studies in the 1980s confirmed the autoimmune nature , and research in the 1990s demonstrated the link with antibodies against P / Q @-@ type voltage @-@ gated calcium channels .