The Lambert-Eaton myasthenic syndrome

Wirtz, P.W.

Chapter 1

The Lambert-Eaton myasthenic syndrome: introduction and aims

History

In 1953, Anderson, Churchill-Davidson and Richardson described a 47-year old man with progressive muscle weakness of the legs, later of the arms and neck, with transient diplopia and swallowing difficulties.[1] Clinical examination revealed dysarthria, proximal muscle weakness and diminished tendon reflexes. The patient was very sensitive to succinylcholine, decamethonium and d-tubocurarine, but improved on edrophonium and neostigmine. A small cell lung carcinoma was surgically removed, leading to a dramatic symptomatic improvement. The authors concluded to "a possible relation between carcinoma of the lung and myasthenia". This was the first description of the clinical features of the Lambert-Eaton myasthenic syndrome (LEMS).

In the following years several reports of patients with signs and symptoms suggesting a neuromuscular defect accompanying a lung carcinoma were reported. Although the clinical features resembled those of myasthenia gravis (MG), several aspects of the disorder were unusual for MG.[2,3] Heathfield and Williams described a 54-year old man with a history of dull aching pain in the ventral parts of the thighs, followed by difficulty walking up and down stairs.[3] The weakness varied from day to day and was more severe in the evenings. "At times it seemed to him that he had to wait for the muscles to contract." Furthermore, he complained of dryness of the mouth. At examination, proximal muscle weakness of the legs with absent reflexes was found. Injection of neostigmine had a "dramatic" effect on the muscle weakness. The patient was discharged with oral neostigmine. After a month, "his condition was less satisfactory than might be expected in a case of myasthenia gravis." After more than a year, a bronchial carcinoma was detected. The authors discussed that the diagnosis in this patient was obscure, but that he was thought to be suffering from atypical MG or myopathy. Henson et al. presented nineteen patients in whom various neurological disorders had arisen in conjunction with carcinoma.[2] Five of them were considered to have a myasthenic syndrome, as they suffered from muscular fatiguability. All five patients had leg weakness and lowered or absent tendon reflexes, and most of them had arm weakness, dysarthria, dysphagia, diplopia and ptosis as well, whereas two patients had a dry mouth. In one of the patients they noticed that the reflexes were "only obtainable on reinforcement." In three patients a small cell lung carcinoma (SCLC) was found. The authors stated that they were not dealing with classical MG, because there was early muscle atrophy (in two patients) with loss of tendon reflexes, or signs of central lesions ("little cerebellar ataxia" of one arm in one patient), or sensory symptoms (impaired vibration sense below the knees in one patient).

Furthermore, there were "conflicting results" of neostigmine injection, which was only clearly positive in two patients.

It took two more years for Lambert, Eaton and Rooke to notice that the small group of patients with clinical features of myasthenia and lung carcinoma had electromyographical evidence of a defect in neuromuscular transmission that was different from that of classical MG.[4-5] In 1956, they described these electromyographical findings in six patients with a malignant chest tumour and proximal muscle weakness, easy fatiguability and decreased tendon reflexes.[4] These findings were a low amplitude of compound muscle action potential (CMAP) (2-30% of normal after ulnar stimulation), a further decline during repetitive nerve stimulation (RNS) at a rate of 1 to 10 Hz, but a marked facilitation, to up to 10 times the initial amplitude, during stimulation at higher rates and during voluntary contraction. As the authors stated, these findings resembled that of MG, "however the depression of the initial response and the phenomenon of facilitation were more marked than is usually observed in the latter disorder." Until today, EMG diagnosis of LEMS is made on the basis of these findings.

Lambert and Rooke already noted that not all patients with this myasthenic syndrome developed a carcinoma[5] and Gutmann et al. described the concurrence of the syndrome with other autoimmune disorders.[6] Elmqvist and Lambert showed a decreased release of acetylcholine from motor nerve terminals in a microphysiological study on intercostal muscle of a patient.[7] In the years that followed, it became clear that LEMS is an autoimmune disease, which is caused by antibodies directed against voltage gated calcium channels (VGCC).[8-11]

Epidemiology

At the start of our studies, the prevalence and incidence of LEMS were unknown. In a study of the epidemiology of MG in Denmark, patients with LEMS were found as well, the annual incidence of LEMS being 0.17×10^{-6} and about 25 times lower than that of MG.[12] However, the Danish study was not designed to include patients with LEMS and could therefore result in underestimation. In the Mayo Clinic EMG laboratory, the frequency of new LEMS diagnoses was about 1 for every ten cases of acquired MG.[13] Accordingly, LEMS is probably much rarer than MG, but so far the epidemiology of both disorders has not been systematically compared within a well-defined region.

In two prospective studies of the prevalence of LEMS in 71 and 150 SCLC patients respectively, a prevalence of 3% was found.[14,15] This would predict, assuming a frequency of SCLC of 60% in patients with LEMS, an annual incidence of LEMS of

approximately 8 per million in the United States, but LEMS is diagnosed much less frequently.[16] In the Dutch literature no epidemiological data on LEMS were available. In the Netherlands, an annual incidence of LEMS, given a SCLC incidence of 82 per million per year, of four per million can be expected. However, the frequency of LEMS in SCLC patients has not been studied in a well-defined region over a prolonged period, which could result in a higher detection rate than in cross-sectional studies.

Clinical characteristics

The main symptom in LEMS is proximal muscle weakness.[17] In all patients the legs are affected, in most patients the arms are involved as well. In most patients leg weakness is the presenting symptom.[17] Weakness is frequently accompanied by muscle aching or stiffness.[17] During the course of the disease weakness of oculobulbar muscles can occur, but this is mostly mild and transient. Most patients with LEMS have signs of autonomic dysfunction, most frequently a dry mouth.[17] Other frequent manifestations are impotence and constipation. Previous studies describing the symptoms of LEMS have been retrospective and based on reviews of the case records; consequently, figures could be underestimates.[5,17]

Neurological examination generally reveals low or even absent tendon reflexes. Immediately after contraction of the muscle being tested the reflexes may increase. This post-exercise facilitation is characteristic of LEMS. Frequently, muscle strength as such increases after initial voluntary contraction. This effect is only short lasting, however, and does not seem to provide a functional gain to the patient. Part of the patients has cerebellar ataxia, which may rarely be the presenting symptom. Sensory disorders have not been reported in LEMS.

In patients with underlying SCLC, the tumour is found after the onset of LEMS in most patients, generally within two years.[17] Specific symptoms of LEMS do not seem to distinguish between patients with and without underlying SCLC,[17] but it is unknown whether LEMS associated with SCLC has a more progressive course, as there has been no specific study of the rate of occurrence of symptoms.

In patients with idiopathic LEMS, other immunological diseases have been described, like thyroid disorders, vitiligo and pernicious anaemia,[6,17] and a positive family history of other autoimmune disorders is frequently encountered.[17] However, this suggestion has not been investigated by a systematic family study in patients with LEMS. Furthermore, it is not known whether this relation, if real, would also apply to LEMS with SCLC.

Diagnosis

The diagnosis is reached on the basis of clinical findings and typical results of repetitive nerve stimulation (RNS). These are a low initial CMAP amplitude, that decreases at low-frequency RNS ("decrement"), and increases following high-frequency RNS or maximum voluntary contraction ("increment"). In fact, an incremental response is a return of an initially lowered CMAP amplitude to its normal size. Most frequently, CMAP amplitudes are derived from hypothenar muscles during stimulation of the ulnar nerve. In recent years, an anti-P/Q-type VGCC antibody assay has become available to confirm the diagnosis of LEMS.

Differential diagnosis

The differential syndrome of LEMS includes other myasthenic syndromes. MG is the most common alternative diagnosis.[17] Like LEMS, MG is an acquired autoimmune disorder with a defective neuromuscular transmission, characterised by variable weakness. However, several clinical differences between MG and LEMS are known. Decreased tendon reflexes and autonomic dysfunction are features of LEMS, and not of MG.[17] The distribution of muscle weakness may be similar in both diseases, which makes it difficult to decide for the diagnosis MG or LEMS on clinical grounds. Some authors have stressed a more frequent involvement of cranial muscles in MG and a more predominant limb muscle weakness in LEMS,[5,16,17] but there are no studies to substantiate these differences in distribution. MG can however be distinguished from LEMS by different findings after RNS and by autoantibody testing.

In patients with a malignancy the signs and symptoms of LEMS could be interpreted as cachexia, a neuropathy or a consequence of therapy.[16]

Pathophysiology

Neuromuscular symptoms in LEMS are caused by antibodies against presynaptic P/Q-type VGCC, which play an important role in acetylcholine release. Injection of LEMS serum IgG into mice produces the same clinical and electrophysiological signs.[8] Autonomic dysfunction is probably caused by both P/Q-type and N-type VGCC antibodies,[18] whereas ACh release from parasympathetic nerve terminals is probably reduced specifically by Q-type VGCC antibodies.[19]

SCLC is a neuroendocrine tumour, which expresses neuronal VGCC.[20] Presumably this expression of VGCC elicits the production of VGCC antibodies which crossreact with presynaptic VGCC. Other malignancies than SCLC were also found in patients with LEMS, but in these cases a causal relationship is unclear. Several other paraneoplastic neurological syndromes have been described to occur in association

with SCLC, like cerebellar degeneration,[21-23] encephalomyelitis/sensory neuronopathy,[24] neuromyotonia,[25] stiffman syndrome,[26] opsoclonus-myoclonus-ataxia,[27] and retinopathy.[28] Several reports suggest that the presence of these syndromes could inhibit growth and spreading of SCLC,[29,30] increase response to chemotherapy, and favour survival in patients with SCLC.[31] In a case control study, LEMS was associated with prolonged survival in patients with SCLC.[32] This suggests that in LEMS the immune response to the tumour epitopes inhibits its growth, increasing the survival time. A small subgroup of SCLC-patients had P/Q-type VGCC antibodies without clinical features of LEMS.[33,34] It is not known whether these patients had a survival advantage similar to that reported for patients with low titre Hu antibodies without a neurological syndrome[31] or for patients with LEMS.[32] Moreover, in a substantial number of patients with paraneoplastic cerebellar degeneration (PCD) and SCLC P/Q-type VGCC antibodies, but no other antineuronal antibodies are detected.[34] About half of these patients had no clinical evidence of LEMS, but it is unknown whether these patients had a survival advantage as well.

There is no relation between the P/Q-type channel antibody titre and CMAP amplitude and muscle weakness.[35] Presumably antibodies against both extracellular and intracellular parts of the VGCC circulate. Because in vivo only extracellular epitopes can be bound by antibodies, probably only the antibodies directed against extracellular epitopes are responsible for the symptoms of LEMS. A LEMS patient with a high antibody titre, in whom many antibodies are directed against intracellular epitopes could have less severe symptoms than a patient with a low titre of antibodies directed solely against extracellular epitopes. In sera with the highest titres of anti-VGCC antibodies the highest titres of antibodies against the intracellularly located β-subunit of the VGCC are found.[36] Indeed, antibodies against this β-subunit did not cause synaptic dysfunction in rats.[36]

Immunopathogenesis

The HLA genotype is considered to be the most important genetic factor of susceptibility to many autoimmune diseases. An increased frequency of HLA-B8 was found in both tumour and non-tumour cases, but the association in non-tumour LEMS (NT-LEMS) was much stronger.[37] Recently, an association of NT-LEMS was found with HLA-DR3 and -DQ2 in a study of HLA class II alleles in 23 patients.[38] Although HLA-B8, -DR3 and –DQ2 are known to be in strong linkage disequilibrium, it is unclear whether these associations of class II alleles with NT-LEMS are secondary to the class I association, and whether the HLA-associations are related to other clinical parameters of NT-LEMS.

After antigen presentation, in the subsequent immune cascade the cytokines tumour necrosis factor-α (TNF-α) and interleukin-10 (Il-10) could play an important role. TNF-α, the gene of which maps within the MHC, enhances the immune reaction, and Il-10 stimulates proliferation of activated B-cells and their production of antibodies.[39] In MG, several studies suggest a stimulatory role of these cytokines in the disease, but in LEMS the role of these cytokines is unknown.[40-42]

Treatment

Treatment of LEMS is based on drugs which act at the neuromuscular synapse by increasing either the release or the concentration of acetylcholine, drugs which suppress the immune response or treatment of the underlying malignancy. Aminopyridines increase the release of acetylcholine by blocking voltage-gated K^+ channels, which prolongs the action potential. Several studies describe a beneficial effect of 3,4-diaminopyridine (3,4-DAP) in patients with LEMS, but only two studies were done in a prospective, double-blind and placebo-controlled manner.[43,44] Both studies describe an additional therapeutic effect of pyridostigmine, an acetylcholinesterase inhibitor, although this effect has not been quantified. No studies have been done in which the therapeutic effect of an acetylcholinesterase inhibitor, alone or in combination, in LEMS has been investigated.

When response to above mentioned therapy is insufficient, immunosuppressive therapy is used. Plasmapheresis and intravenous immunoglobulins have been reported to have a swift, but rather short lasting effect.[45,46] The improvement in muscle strength after administration of immunoglobulins is maximal after two to four weeks and than subsides.[45] To obtain a long lasting clinical response immunosuppressive drugs like prednisone[47] or azathioprine[48] were used.

In patients with LEMS, an extensive search for SCLC must be performed. In case of SCLC, effective treatment of the tumour can improve LEMS,[49] probably because the

initiating factors of the immune response in LEMS, the VGCC on SCLC cells, wane. Moreover, chemotherapy in SCLC treatment has an immunosuppressive effect of its own.

Aims of the thesis

The introduction (chapter 1) gives an overview of the current knowledge of LEMS and raises several questions about the epidemiology, clinical aspects, pathophysiology and therapy of LEMS.

We studied the epidemiology of LEMS both in our region in the province of South Holland, where we could make a comparison with the epidemiology of MG (chapter 2), and in the Netherlands (chapter 3).

Chapters 4-7 concern the clinical features of LEMS. Chapter 4 compares the distribution of muscle weakness between LEMS and MG. To compare the clinical features of LEMS patients associated with carcinoma with patients having LEMS but no cancer, case reports on LEMS patients were analysed systematically in chapter 5. In chapter 6, the frequency and course of symptoms of LEMS between Dutch patients with and without SCLC were compared. In chapter 7, we studied the frequency and nature of additional autoimmune disorders in LEMS patients and their family members, in both SCLC related and non-tumour related cases.

Chapters 8-11 address immunopathological mechanisms underlying LEMS. In chapter 8, the strength of HLA-associations with non-paraneoplastic LEMS and the relation of HLA-haplotypes with age at onset of LEMS and other clinical features were studied. In chapter 9, we compared immunogenetic factors in SCLC-LEMS and non-paraneoplastic LEMS and study their role in the pathogenesis of LEMS and survival from SCLC. We analysed the production of Il-10 and TNF-α after whole-blood stimulation in first-degree family members of patients with LEMS without SCLC, as a measure of innate production in the patients in chapter 10. In chapter 11, we studied the frequency of P/Q-type VGCC antibodies and the frequency of LEMS and their relation with SCLC staging and survival in a large group of consecutive patients with SCLC and in a group of SCLC patients with paraneoplastic cerebellar degeneration.

Chapter 12 evaluates the efficacy of two drugs acting on the neuromuscular synapse, 3,4-DAP and pyridostigmine.

In chapter 13, the results and conclusions of this thesis are summarized.

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