The Lambert-Eaton myasthenic syndrome

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Chapter 13

Summary and conclusions

Within the large group of autoimmune diseases (AID), the neuromuscular synapse is the main target of the autoimmune response in few of them. The best known and most common of these myasthenic syndromes is myasthenia gravis (MG) with antibodies directed against the postsynaptic acetylcholine receptor (AChR). Recently, part of the formerly seronegative patients with MG has been shown to have antibodies against the muscle-specific tyrosine kinase (MuSK), which is located postsynaptically as well.[1] The Lambert-Eaton myasthenic syndrome (LEMS) is the only autoimmune myasthenic disorder known to have antibodies against the presynaptic part of the synapse, i.e. voltage gated calcium channels (VGCC). In analogy with MG, which is sometimes accompanied by thymoma, in about half of the patients with LEMS a small cell lung carcinoma (SCLC), a neuro-endocrine tumour expressing VGCC, is found, usually after the onset of LEMS.

At the start of our studies, the epidemiology of MG was well known, but the incidence and prevalence of LEMS had not yet been studied. In our region in South Holland with a population of 1.7 million inhabitants we found an annual incidence of LEMS 14 times lower than the incidence of MG, underscoring the relative rarity of LEMS (**Chapter 2**). LEMS was even 46 times less prevalent than MG, reflecting the poor survival of LEMS patients with SCLC. Only 0.44% of the patients with SCLC developed LEMS (Figure 1). These SCLC patients had a significantly lower age at diagnosis of SCLC as compared to SCLC patients without LEMS. Similarly, thymoma patients with MG had a younger age at diagnosis of thymoma than thymoma patients without MG. Early detection of the tumour as a result of the presence of the myasthenic syndrome could partly explain this age difference. However, the size of the difference in the SCLC patients also suggests that patients having a tumour at younger age are more prone to develop the associated myasthenic syndrome.

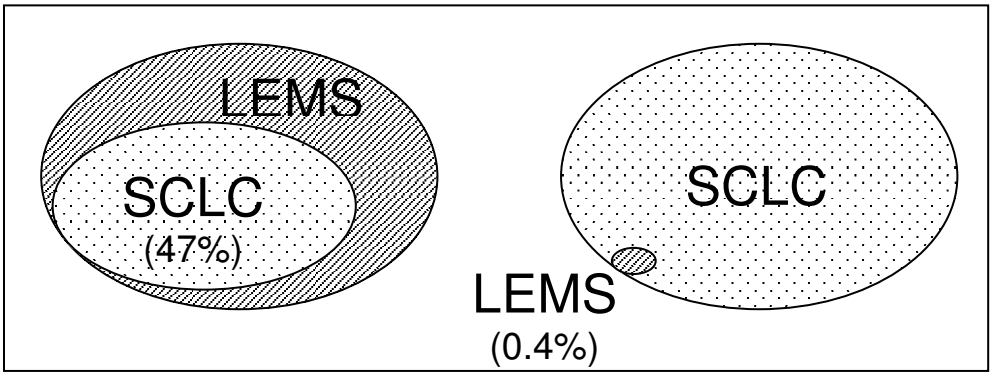

Figure 1. Frequency of SCLC in LEMS and LEMS in SCLC.

We extended the study region to the whole Netherlands with a population of over 16 million (**Chapter 3**). Incidence of SCLC associated LEMS equalled that of LEMS without SCLC, whereas the prevalence was lower, as a result of poor survival of patients with SCLC. In newly diagnosed LEMS patients SCLC was found in 47% (Figure 1). In these patients the duration of disease until LEMS diagnosis was significantly shorter. As the presence of SCLC could not explain this difference, we speculated that LEMS with underlying SCLC has a more progressive course, which might shorten both patient's and doctor's delay. Most patients received an alternative diagnosis before the correct diagnosis was made, particularly myasthenia gravis, probably because the distribution of muscle weakness may be similar in LEMS and MG.

To clarify the difference in clinical presentation we compared the localization of initial muscle weakness and distribution of weakness at the time of maximum severity between LEMS and MG (**Chapter 4**). Most MG patients (59%) had initial weakness in the extraocular muscles, whereas in LEMS no patients had ocular weakness as a first symptom. On the other hand, initial weakness was localized in the limbs in almost all LEMS patients, against in only 12% of the MG patients. At the point of maximum severity, weakness in MG had remained purely ocular in 25%, whereas in the remaining patients it had become generalized. By contrast none of the LEMS patients had weakness restricted to extraocular or bulbar muscles. Thus muscle weakness in MG tends to develop in craniocaudal direction, and in LEMS in the opposite direction, implying that in a myasthenic patient presenting with solely extraocular weakness LEMS is virtually excluded. Extraocular muscles are different from skeletal muscles, having higher firing frequencies, a lower safety factor and a different complement mediated immune response, which might explain their frequent involvement in MG.[2] The higher miniature endplate potential frequency in extraocular muscles suggesting greater calcium influx in the nerve terminal may be relatively protective in LEMS, explaining the lesser degree of involvement of these muscles in LEMS.

Specific symptoms of LEMS do not seem to distinguish between patients with and without underlying malignancy. When we analysed publications describing individual patients with LEMS systematically, in patients with a tumour, mostly SCLC, there was a male predominance (70%), whereas in patients without cancer no sex difference was found (**Chapter 5**). In patients with a tumour the age at onset of LEMS was higher and the interval between onset and diagnosis of LEMS was shorter, like in our own epidemiological study (Chapter 3). Patients without a tumour had additional AID more frequently, suggesting non-specific, common immunogenetic factors. The few

symptoms that were more frequently found in patients with a tumour (weight loss and need for prolonged artificial ventilation after anaesthesia) were probably more related to the tumour than to LEMS. LEMS related symptoms did not differ significantly between the two groups.

When we compared the frequency of symptoms in our LEMS patients with and without SCLC we did not find any significant differences either (**Chapter 6**). However, symptoms in patients with SCLC did appear within a shorter timeframe (Figure 2), indicating a more progressive course of LEMS and giving an explanation for the shorter delay in LEMS diagnosis we found in both our epidemiological (Chapter 3) and literature studies (Chapter 5). Apparently, SCLC initiates an immune reaction which is more aggressive than the response in LEMS without a tumour. Hence an aggressive onset of LEMS raises a strong suspicion of an underlying SCLC.

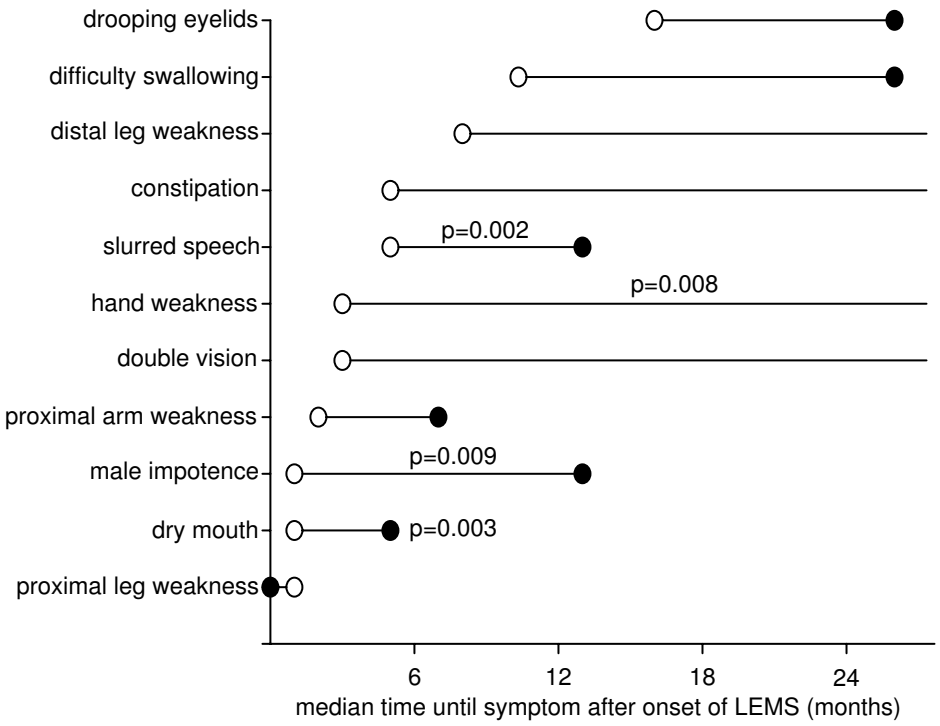

Figure 2. Median time until symptoms from onset of LEMS in patients with SCLC (open circle) and without SCLC (closed circle).

In view of the clustering of AID, we studied the frequency and nature of additional AID in patients with LEMS and in their family members (**Chapter 7**). Patients without SCLC had an additional AID more frequently than those with SCLC, like in our literature study (Chapter 5). Moreover, AID were significantly more frequent in families of patients without a tumour than in control families, a difference not found in SCLC-LEMS. In families of non-paraneoplastic LEMS patients, a remarkable preponderance of maternal inheritance of propensity to AID was seen, as was reported previously in MG. Our findings suggested that non-paraneoplastic LEMS shares with other AID immunogenetic factors like the HLA genotype, determining susceptibility to AID.

Non-paraneoplastic LEMS was strongly associated with alleles of both HLA-class I (i.e. HLA-B8) as well as -class II (i.e. HLA-DR3 and –DQ2) (**Chapter 8**). HLA-B8 positive patients had significantly younger age at onset of LEMS and tended to be female, analogous to MG without thymoma. This suggests that factors in the HLA-region contributing to the pathogenesis of both diseases are involved in the regulation of the general rather than antigen specific immune reactivity.

Other immunogenetic factors playing a role in the susceptibility to AID are interleukin-10 (Il-10) and tumour necrosis factor-α (TNF-α). Both Il-10 and TNF-α production after whole-blood stimulation were increased in the family members of patients with non-paraneoplastic LEMS, suggesting that high innate production of these cytokines is a susceptibility factor for non-paraneoplastic LEMS (**Chapter 9**). As we could not demonstrate a relation with HLA-B8DR3 carriership of the patients, they seem to be related to the risk of LEMS as independent variables.

SCLC expresses VGCC on its cell membranes. Therefore, it is thought to initiate the autoimmune reaction in LEMS. Patients with SCLC survive longer if they have LEMS, possibly because they produce an anti-tumour response that restricts the tumour growth. The highly significant associations in non-paraneoplastic LEMS with HLA-B8, -DQ2, -DR3 and six flanking microsatellite alleles were not found in SCLC-LEMS (**Chapter 10**). This indicates that two distinct immunopathogenetic routes can lead to one single phenotype of an autoimmune myasthenic syndrome (Figure 3).

SCLC apparently provides a powerful autoimmunogenic stimulus that overrules HLA restrictions in breaking tolerance to VGCC. In MG, the strong association between HLA-B8 and thymic hyperplasia does not exist in MG with thymoma. This analogy suggests that thymoma and SCLC play similar roles in the pathogenesis of these myasthenic disorders. However, in thymoma related MG a causal relationship is less suggestive. Where the thymic myoid cells in MG with thymic hyperplasia express

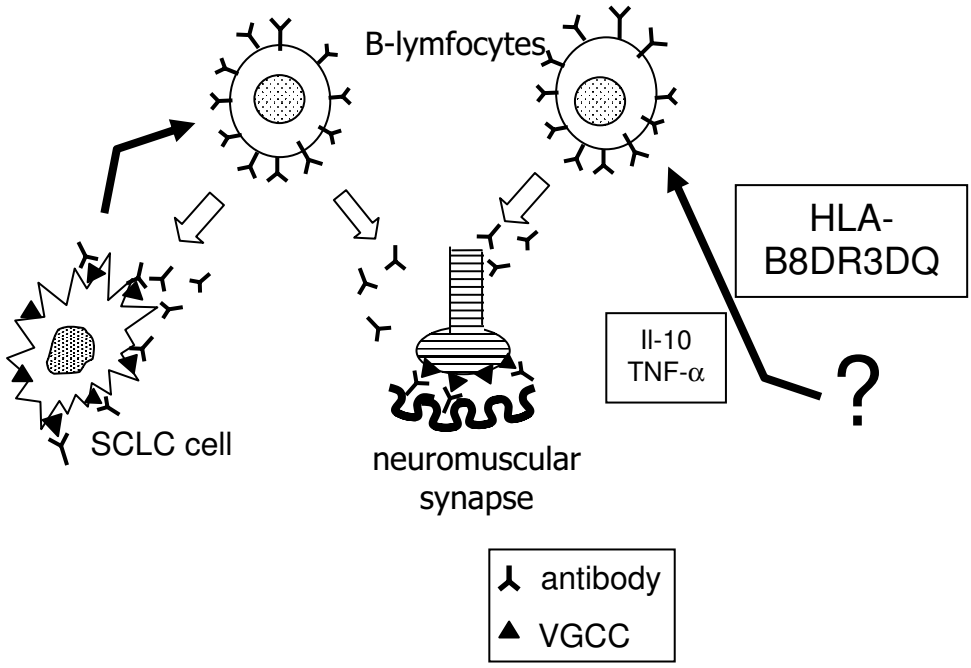

Figure 3. Two distinct immunopathogenetic routes can lead to one single phenotype of LEMS

AChR as the possible triggering autoantigen, the myoid cells in thymomas lack AChR.[3]

In LEMS patients, smoking was a strong predictor of SCLC, but HLA-B8 correlated with a decreased risk of SCLC, even among the smokers (**Chapter 10**). Moreover, in SCLC-LEMS patients, HLA-B8 correlated with prolonged survival after LEMS onset. This implicates that negativity for HLA-B8 – combined with smoking – points more strongly to an underlying SCLC, and predicts a poorer prognosis in LEMS patients with SCLC.

We studied the frequency of P/Q-type VGCC antibodies and of LEMS, and their relation with SCLC staging and survival in a cohort of consecutive patients with SCLC, and in a group of patients with SCLC and paraneoplastic cerebellar degeneration (PCD) **(Chapter 11**). In the consecutive SCLC patients, 7% had P/Q-type VGCC antibodies, but less than half of them had clinical signs of LEMS. In the SCLC-PCD patients, 44% harboured the antibodies and, again, less than half had LEMS. The presence of P/Q-type VGCC antibodies in SCLC patients without LEMS suggests that not all P/Q-type VGCC antibodies are pathogenic at the site of the

neuromuscular synapse. In both groups, P/Q-type VGCC antibody positive patients with LEMS had a remarkably long survival, whereas presence of P/Q-type VGCC antibodies without LEMS did not result in better prognosis. Possibly, these non-pathogenic antibodies are directed against intracellular epitopes of the VGCC, which are detected by the immunoprecipitation assay along with those directed against extracellular epitopes. Consequently, the anti-tumour immune response may be limited as well.

In the treatment of LEMS, both the neuromuscular acting drugs 3,4-diaminopyridine (3,4-DAP) and pyridostigmine are generally used. In a placebo-controlled, double-blind, randomized, cross-over study we found a significant increase in muscle strength and CMAP amplitude in LEMS patients during treatment with 3,4-DAP and with both drugs combined, but not with pyridostigmine alone (**Chapter 12**). As 3,4-DAP increases the release of acetylcholine in the neuromuscular cleft by prolonging the nerve terminal depolarisation, the reason for its beneficial effects in LEMS, in which the acetylcholine release is hampered by VGCC blockade, seems clear. For pyridostigmine to have an effect by decreasing the breakdown of acetylcholine ample availability of acetylcholine in the cleft is a prerequisite, which could explain its valuable effect in MG, but not in LEMS. Adding pyridostigmine to 3,4-DAP therefore might have a synergistic effect, which is suggested by the clinical experience of many neurologists and patients with LEMS. However, we could not show such an effect. Possibly, 3,4-DAP is such a potent acetylcholine releaser in patients with LEMS, that an additional pyridostigmine effect became negligible in our experimental setting.

In conclusion, LEMS is an important autoimmune disease, as it can serve as a model to unravel immunological mechanisms relevant to autoimmunity in general. Elucidating the two immunological pathways which can lead to LEMS can enlarge our knowledge about autoimmunity as well as cancer immunosurveillance. Future research focussing on these two pathways could therefore help to find more adequate therapies not only of LEMS, but of other autoimmune disorders and malignancies as well.

References

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