The Lambert-Eaton Myasthenic Syndrome — an Overview

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ABSTRACT

The Lambert Eaton myasthenic syndrome (LEMS) has a prevalence of around 5/100 0000 and is around 10–20 times rarer than myasthenia gravis (MG). Although LEMS does have a number of similarities to MG, there are important differences. The syndrome is characterized by a mostly proximally localised exercise induced muscle weakness that can lead to respiratory failure often accompanied by autonomous dysfunction. Disease symptoms are caused by autoantibodies directed against P/Q type voltage gated calcium channels (VGCC) that are expressed in the presynaptic motoric nerve terminals. The diagnosis of LEMS is based on the detection of the pathogenic anti-VGCC antibodies as well as the observation of an increment of at least 60 % in the electrophysiological examination of an affected muscle. An increment is defined by an increase of the at rest reduced compound muscle action potential (CMAP) either after voluntary maximal innervation or after high frequent (≥ 20 Hz) stimulation. In almost one third LEMS is of paraneoplastic origin. Therefore an intensive tumor screening is necessary after diagnosis. There are some differences in the clinical presentation between paraneoplastic (pLEMS) and the exclusively autoimmune (aiLEMS) form of LEMS. With respect to this the DELTA-P-Score and the detection of SOX1-antibody are important. The most frequent tumor associated with LEMS is small cell lung carcinoma (SCLC). Therapy is based on the initial distinction between paraneoplastic and autoimmune ethiology. pLEMS necessitates therapy of underlying neoplasia. Usually, aiLEMS- as well as pLEMS patients respond well to 3,4 diaminopyridine (3,4 DAP) often augmented by pyridostigmine. Similar to treatment of myasthenia gravis long-term immunosuppressive treatment is usually required to control symptoms effectively. Myasthenic crisis in LEMS can be controlled by intensive care and immunoglobulins, plasmaphereses or immunoadsorption. Based on case reports more specific immunomodulatory treatment approaches such as the B-cell depleting therapeutic antibody rituximab should be considered in therapy refractory courses of LEMS. Long-term prognosis of autoimmune LEMS with respect to clinical stabilization with (pharmacological) remission is good, although in around 75 % of patients significant reductions in quality of life remain. Prognosis of tumor-associated LEMS is largely determined by the tumor and its effective therapy. Curative treatment of the tumour as well as complete remission of pLEMS are possible.

Historical Background

The Lambert-Eaton-Rooke syndrome was named after the three physicians who in 1956 first described a myasthenic condition very similar to myasthenia gravis (MG), but distinguished from it by some characteristic features [1]. Key differences to MG include absent or diminished deep tendon reflexes, additional autonomic dysfunction, usually lack of clinical improvement after acetylcholinesterase inhibitor (AChEI) administration, and association with lung cancer instead of thymoma which is associated with MG (▶Table 1). While the syndrome is still occasionally referred to as Lambert-Eaton-Rooke syndrome according to the 3 first describers, today it is commonly known as Lambert-Eaton myasthenic syndrome (LEMS) or Lambert-Eaton syndrome (LES). By transferring serum to mice, typical myasthenic symptoms could be induced, making

▶ **Table 1** Key differentiators between LEMS and myasthenia gravis.

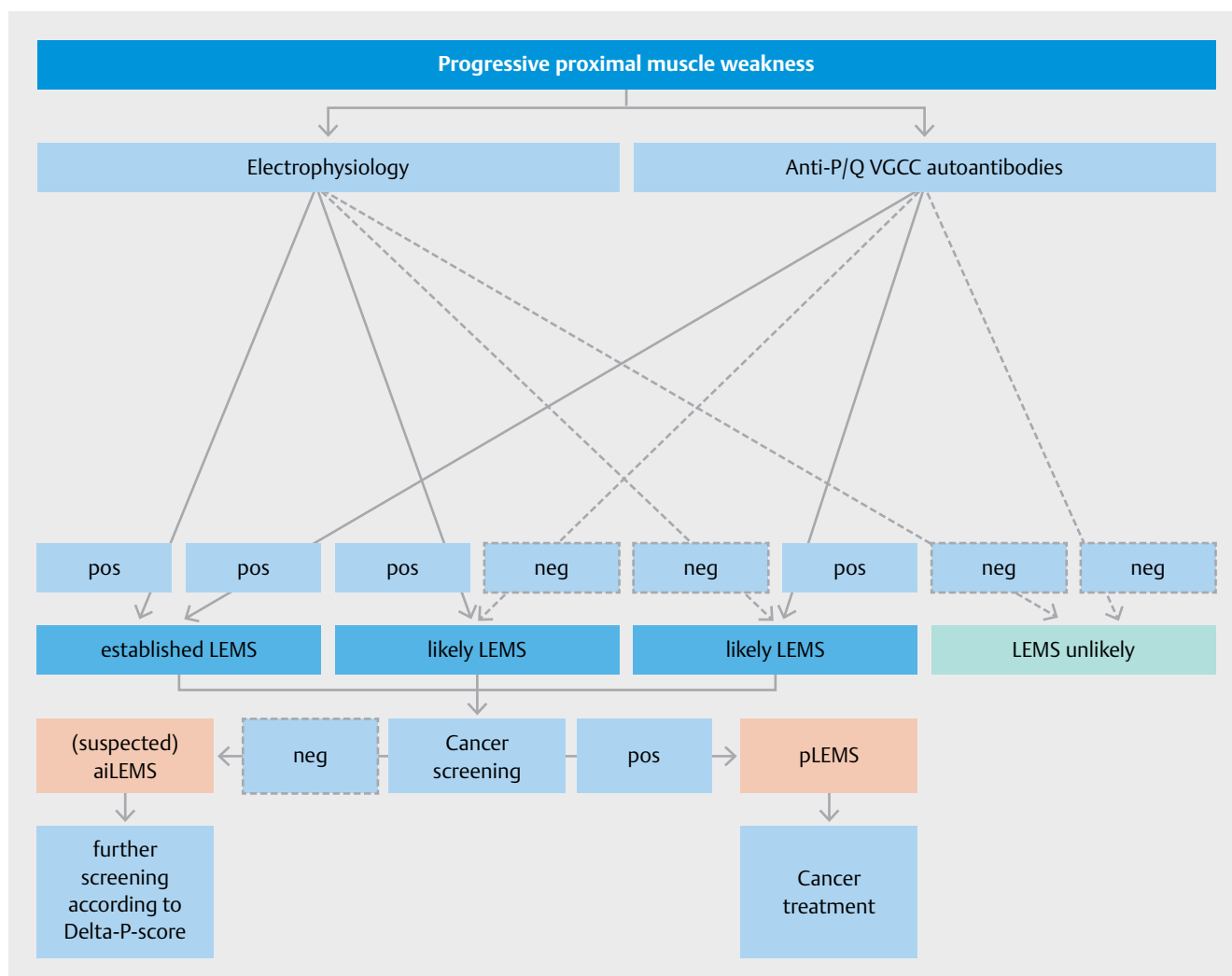|	Myasthenia gravis	LEMS
Prevalence	– 50-200/1000000	– 5/1000000
Age, sex	– 20–40, F > M – 60–70, M > F	< 50 F = M (aiLEMS) > 50 M > F (pLEMS)
Antibodies	– Anti-AChR – Anti-MuSK – Anti-LRP4	– Anti-VGCC – Anti-Sox1 (pLEMS)
Commonly associated tumor	– Thymoma (rarely thymic carcinoma)	– SCLC
Cancer screening	– Chest CT with contrast	– Chest CT with contrast potentially PET CT (up to 2 years after LEMS diagnosis), – Delta P score for risk assessment
Clinical presentation	– MGFA I: only ocular – MGFA II –IV (a/b): II-IV = generalized (mild, moderate, severe); (a/b) = -/ + bulbar – MGFA V (myasthenic crisis) – normal reflexes	– similar to MG – rarely only ocular – aiLEMS rarely bulbar – Severity aiLEMS < pLEMS – Reflexes diminished or absent
Electrophysiology	– Decrement (2–3 Hz) – Single-fiber EMG: jitter or blocks	– Decrement (2–3 Hz) – Increment after serial stimulation (20–60 Hz),or maximum voluntary contraction – SF EMG: jitter or blocks
Autonomic symptoms	– none	– Constipation, hypohidrosis, erectile dysfunction
Prognosis	– good – about 10 % refractory to treatment	– aiLEMS good – pLEMS dependent on tumor
Treatment	– Thymectomy – ACh-esterase inhibitors – Immunosuppressants	– pLEMS: treatment of tumor – 3,4 DAP, potentially ACh-esterase inhibitors – Immunosuppressants

autoantibodies a likely mediator in the pathophysiology of the disease, as it is the case in MG [2]. Direct detection of specific autoantibodies was achieved in 1989 [3], enabling confirmation of the diagnosis by means of laboratory testing. Evidence that these antibodies block neurotransmitter release at the P/Q-type voltage-gated calcium channels (VGCC) has only recently become available [4].

Clinical Presentation

The prevalence of LEMS is approximately 5 per 1000 000, the incidence approximately 0.5 per 1 million. LEMS has 2 age peaks: the first between 30 and 40 years of age where women are more frequently affected than men und the disease is less often associated with neoplasia. The second age peak is between 60 and 70 years of age. Here, men are more frequently affected than women and most cases are of neoplastic etiology. Clinically, the muscle weakness first manifests in the proximal lower extremities. Altogether about 80 % of patients develop weakness of the proximal lower extremities; myopathic facies, ocular and bulbar symptoms may also occur. Characteristically, deep tendon reflexes are diminished or absent and autonomic dysfunction, manifesting as xerostomia, erectile dysfunction, constipation or hypohidrosis, is common [5–6].

If LEMS is suspected based on clinical findings, the diagnosis is confirmed by electrophysiological studies and the detection of anti-P/Q VGCC autoantibodies (▶ **Fig. 1**). Electrophysiological studies should always be performed on the clinically affected muscle

group. Low-frequency serial stimulation (3 Hz) can show an amplitude and/or area decrement of the compound muscle action potential (CMAP), a phenomenon commonly observed in MG too. Typically, however, CMAP in LEMS initially has a markedly reduced amplitude and shows a significant amplitude and/or area increase (= increment) after repeated high-frequency serial stimulation (20–60 Hz) or after maximum voluntary contraction performed over a period of 30–60 s. The two latter findings are indicative of the presynaptic location of the neuromuscular transmission dysfunction. However, serial stimulation is painful to the patient and regarded as unnecessary if the other phenomena described above (decrement with low baseline amplitude/area before and increment [≥ 60 %, typically > 100 %] after maximum voluntary contraction) are present (see also 2015 DGN guideline). The technically more demanding single-fiber electromyography (SFEMG) can also be used to demonstrate the impairment of neuromuscular transmission at the affected muscle, but it cannot distinguish between LEMS and MG. While its sensitivity is high (85–100 %) in the differential-diagnostic exclusion of other neuromuscular conditions, its specificity is comparably low (70 %) [7]. Despite the important role of electrophysiology in establishing the diagnosis of LEMS, the detection of the characteristic antibody against voltage-gated calcium channels (Cav2.1 VGCC P/Q type) in the presynaptic endings of peripheral motor and autonomic neurons is increasingly used to confirm the diagnosis in patients with clinically suspected LEMS. Testing for this antibody has a sensitivity of about 85–90 %

Progressive proximal muscle weakness

Electrophysiology — Anti-P/Q VGCC autoantibodies

pos · pos · pos · neg · neg · pos · neg · neg

established LEMS · likely LEMS · likely LEMS · LEMS unlikely

(suspected) aiLEMS ← neg ← Cancer screening → pos → pLEMS

further screening according to Delta-P-score

Cancer treatment

▶ **Fig. 1** Diagnosis of LEMS

and a specificity of almost 100 % [8, 9], also with regard to excluding other neuromuscular diseases [10]. The proportion of "seronegative" LEMS patients is about 10 % [8, 9].

Differential Diagnoses

The primary objective of the differential diagnostic workup is to distinguish between LEMS and MG. Clinical, electrophysiological and laboratory criteria are useful in this respect (▶ **Table 1**). In patients with seronegative MG, the possibility of LEMS should always be considered, especially in patients with absent tendon reflexes. Clinical presentation determines which other differential diagnoses are to be considered (▶ **Table 2**). For example, the differential diagnosis in predominantly generalized LEMS includes, among others, intoxications (e. g. botulism), myopathies, myositis, axonal and motor polyneuropathies, and inflammatory demyelinating polyradiculopathies (GBS, CIDP). In patients presenting with mostly bulbar symptoms, motor neuron diseases and brain stem disorders should also be considered. With regard to electrophysiology, it should be borne in mind that axonal motor neuropathies and dis-

orders of the second motor neuron are also associated with diminished deep tendon reflexes and a decrease of MSAP. However, with disease progression, signs of denervation are to be expected in electromyography, in contrast to LEMS. The differential diagnosis of the rare ocular form of LEMS includes mitochondrial diseases (CPEO), oculopharyngeal muscular dystrophy and myositis (Table 2). If exercise does not influence symptoms or affected muscles are painful, myositis, mitochondrial disease or muscular dystrophy are the more likely diagnoses. Electrophysiological studies and autoantibody testing frequently help to distinguish between LEMS and these differential diagnoses, while imaging studies (spinal, cerebral and muscular MRI) usually contribute little to establishing the proper diagnosis. In atypical cases, additional histological and genetic studies can be useful to exclude LEMS in patients with suspected myositis, CPEO or muscular dystrophy.

Autoimmune vs. Paraneoplastic LEMS

Even though LEMS frequently is triggered by neoplasia, in about two-thirds of patients no underlying cancer can be detected

[11, 12]. In most cases of paraneoplastic LEMS (pLEMS; international nomenclature: SCLC-LEMS), an underlying small-cell lung cancer (SCLC) is detected. However, other types of cancer have also been reported to cause LEMS, including carcinomas, such as adenocarcinoma of the esophagus, epidermoid carcinoma of the true vocal cord, breast cancer, renal cell carcinoma, colon cancer and Merkel cell carcinoma, as well as malignant thymoma and multiple myeloma [12]. LEMS without associated tumor is referred to as autoimmune LEMS (aiLEMS; international nomenclature: NT-LEMS). However, this terminology can be misleading, because autoimmune pathogenesis may also occur in the presence of a neoplasia. In patients with LEMS solely of autoimmune origin, no trigger can be identified, while in patients with pLEMS, a tumor triggering the autoimmune reaction can be detected. Several studies have shown that SCLC cells express the VGCC proteins as an autoantigen against which the abnormal antibodies are directed [13–17]. Besides pathophysiology, the two patient groups differ in several clinical characteristics (▶ Fig. 2 data from [11, 18]). Autoimmune LEMS patients are likely to be younger, female and, most importantly, present with less severe bulbar and distal extremity symptoms compared to pLEMS patients.

To differentiate between aiLEMS and pLEMS is not only important with regard to pathophysiology, but more so from a clinical perspective. For several reasons it is crucial to detect an underlying neoplasm that may be present in the patient. On the one hand, it is important to diagnose the cancer as early as possible and to provide curative treatment, whenever possible. On the other hand, the tumor mass—and with it the triggering antigen—is reduced by treating the underlying cancer. Consequently, the tumor-induced autoimmune reaction should be decreased, as further stimulation of autoreactivity is prevented. During cancer therapy, an initial aggravation of myasthenic signs and symptoms is common, especially in patients receiving chemo(radio)therapy. Presumably, this phenomenon is caused by tumor lysis-induced immune stimulation. Chemotherapy has an unspecific immunosuppressive effect which may help to reduce the immune reaction and improve symptoms in the further course of the disease. However, when evaluating the clinical course, it should be taken into account that many chemotherapeutic agents can cause axonal polyneuropathy.

Given the strong association between SCLC and LEMS, a chest CT scan should be performed in all patients diagnosed with LEMS.

If this does not detect a tumor, a PET-CT scan should be performed. As with other paraneoplastic disorders, LEMS can precede the detection of the underlying cancer. It can be assumed that the majority of SCLC can be identified within a period of 2 years after clinical manifestation of LEMS if adequate screening methods are used [19] [20]. Additional antibody testing, which has recently become available, is a useful diagnostic tool to differentiate aiLEMS from pLEMS. In almost two-thirds of patients with pLEMS, antibodies to Sox-1 are detected in serum, while none of the patients with aiLEMS tested positive for this antibody [21].

Consequently, a LEMS patient with anti-Sox1 antibodies is likely to have pLEMS and thus great effort should be made to detect the underlying tumor. To be able to classify patients according to tumor risk, the so-called DELTA-P score was developed. Using this score, a patient-specific likelihood of the presence of an underlying cancer can be calculated based on clinical criteria [18]. The score includes bulbar symptoms (**d**ysarthria), **e**rectile dysfunction in male patients, **l**oss of weight, **t**obacco use, **a**ge and low Karnofsky **p**erformance index (Table 3). A score of 0 or 1 virtually excludes paraneoplasia, while at a score of 3 the likelihood that the patient has SCLC is already > 80 %. Thus, at a score of ≥ 3 the patient should undergo a second screening already 3 months after the first screening, while with a lower score an interval of 6 months between screenings should be sufficient. In general, however, at least a chest CT scan should be performed at 6-month intervals for further 2 years after initial diagnosis and primary screening.

Treatment

The treatment of LEMS combines symptomatic and disease-modifying therapies [22]. In patients with pLEMS, treatment of the underlying tumor is the cornerstone of therapy. However, symptomatic and, if necessary, rapid immunomodulating treatments (see below) are frequently required early in the treatment course to mobilize the patient and to prevent complications. Furthermore, the goal should be to aggressively treat an underlying tumor, even in patients with low Karnofsky index, given the good results often achieved with this approach in patients with paraneoplastic syndromes in general and LEMS in particular. Symptomatic treatment comprises 3,4-diaminopyridine (3,4-DAP; amifampridine base as a New German Formulary (NRF) 22.3 formulation or amifampridine

> age 50
active smoker
weight loss > 5 %
bulbar symptoms ↑
generalized muscle weakness ↑
erectile dysfunction, dry mouth, sweating ↑

< age 50

HLA-B8, HLA-DR3 ↑

paraneoplastic

autoimmune

▶ **Fig. 2** Differences between paraneoplastic and autoimmune LEMS.

phosphate as Firdapse®, a commercially available product) [12]. The active ingredient 3,4 DAP has already been used to treat LEMS for decades [23]. Evidence from smaller studies and clinical experience support the efficacy of 3,4 DAP [24]. A recently completed phase III study with amifampridine phosphate (Firdapse®) has confirmed these results. With regard to the primary endpoint, 3,4 DAP significantly improved muscle strength among LEMS patients [25]. The mechanism of action of 3,4-DAP is based on an increase in transmitter release and consequently an augmented release of acetylcholine at the neuromuscular junction. The total daily dose of 3,4-DAP should typically be divided into 3 to 6 individual doses and not exceed 60 mg. In some patients, doses of 80 mg to 100 mg are required; however, adverse drug reactions (ADRs) occur more frequently with these higher doses. The most important ADRs are seizures, cardiac arrhythmia, asthma attacks, and commonly paresthesia. Especially due to the risk of seizure, it is recommended to gradually increase the dose, in particular in patients requiring a higher total daily dose. In addition, dose adjustment is required in patients with hepatic or renal impairment. Some patients respond positive to (supplemental) pyridostigmine (Mestinon®, Kalymin®) at the doses typically used in MG.

As in patients with MG, long-term treatment is usually based on corticosteroids in combination with immunosuppressants, such as azathioprine, mycophenolate mofetil, cyclosporine A or methotrexate [12]. While receiving chemotherapy for cancer, pLEMS patients often do not require additional immunosuppression initially. Whether immunosuppression weakens the anti-cancer defense system is subject of controversy. Immunosuppressive therapy should be initiated in patients with uncontrolled pLEMS. In refractory cases, the use of rituximab, a B cell-depleting anti-CD20 antibody, should be considered. So far, 3 LEMS patients have been described in the literature who significantly benefited from this treatment [26, 27]. Acute LEMS crisis with deterioration to the point of respiratory failure with need for mechanical ventilation is treated with immunoglobulins or plasmapheresis/immunoadsorption and supportive critical care management as required. Despite the lack of reliable data, it is likely that patients with LEMS have a lower risk of myasthenic crisis compared to patients with MG.

Prognosis

The overall prognosis of patients with pLEMS is typically determined by the underlying cancer. Yet, even pLEMS patients tend to have a good prognosis because curative cancer treatment is frequently achieved, as long as it is started early in the course of the disease. This highlights the importance of consistent cancer screening to enable early initiation of treatment for the underlying malignancy. In addition, it has recently been shown that the presence of LEMS with SCLC conferred a better prognosis—independent of an early diagnosis. However, it remains unclear whether this advantage results from a general immune activation or a specific effect of anti-VGCC antibodies [28]. Overall, patients with aiLEMS have a good prognosis with regard to life expectancy. As mentioned above, patients with aiLEMS are usually less affected than patients with pLEMS and immunotherapy contributes to considerable stabilization in most cases. However, the majority of patients reports permanent and significant reduction in quality of life [12, 29].

Conflict of Interest

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