J Neurol (2017) 264:1854–1863
DOI 10.1007/s00415-017-8541-9

REVIEW

Lambert–Eaton myasthenic syndrome (LEMS): a rare autoimmune presynaptic disorder often associated with cancer

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Received: 1 May 2017 / Revised: 6 June 2017 / Accepted: 7 June 2017 / Published online: 12 June 2017

Abstract Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune neuromuscular junction disorder that is related to the loss of functional P/Q-type voltage-gated calcium channels (VGCCs) on presynaptic nerve terminals. Up to 60% of cases occur as a paraneoplastic disorder (SCLC-LEMS), most commonly in association with small cell lung cancer. The remaining cases have an idiopathic non-tumor etiology but are associated with underlying autoimmune disease (NT-LEMS). Patients with LEMS invariably experience progressive proximal muscle weakness, often accompanied by general fatigue and autonomic symptoms. Some LEMS clinical symptoms overlap with those of other myasthenic syndromes, most commonly myasthenia gravis, which can contribute to misdiagnosis or delayed diagnosis. Prognosis is related to the presence of cancer or autoimmune disease and the severity/distribution of muscle weakness. Cause of death in patients with SCLC-LEMS is typically tumor progression, whereas NT-LEMS does not reduce life expectancy. LEMS diagnosis is supported by a threefold approach: clinical features, electromyography, and anti-VGCC antibody serology. LEMS is a clinically important early indicator of possible cancer; therefore, a LEMS diagnosis should immediately prompt rigorous oncological screening and surveillance. Symptomatic treatment of LEMS typically involves medications that improve neurotransmission (e.g., the potassium channel blocker amifampridine [3,4-diaminopyridine]), with addition of immunosuppressants/modulators (e.g., prednisone plus azathioprine) in individuals with persistent symptoms. Where a tumor is identified, oncological treatment should take priority. It should be remembered, however, that LEMS has a significant impact on a patient's quality of life and ability to perform daily activities, and therefore warrants timely diagnosis and appropriate treatment in and of itself.

Keywords Autoimmunity · Lambert–Eaton myasthenic syndrome · Neuromuscular junction · Quality of life · Small cell lung carcinoma · Voltage-gated calcium channels

Introduction

Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder of the neuromuscular junction that was first characterized in 1956 by Drs. Edward Lambert, Lee Eaton, and Douglas Rooke of the Mayo Clinic [1, 2]. This myasthenic disorder was given its eponym 15 years later when Dr. Lambert and Dr. Dan Elmqvist presented a detailed microelectrophysiological analysis of the pathological neuromuscular transmission that distinguished the disease from similar conditions such as myasthenia gravis (MG) [3].

Lambert–Eaton myasthenic syndrome (LEMS) may occur as a paraneoplastic disorder (SCLC-LEMS), most commonly in association with small cell lung cancer

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(SCLC), or as an autoimmune disease in the absence of cancer [non-tumor (NT)-LEMS] [4]. Symptoms include gradual onset of fatigue, skeletal muscle weakness, weight loss, and autonomic symptoms such as dry mouth, male impotence, and constipation [2, 5, 6]. Both CA- and NT-LEMS demonstrate circulating immunoglobulin G antibodies against presynaptic P/Q-type voltage-gated calcium channels (VGCCs); these antibodies modulate expression of functional VGCC and thereby inhibit neurotransmission [2].

Because LEMS is a rare disease with fluctuating symptoms, it can be misdiagnosed as MG or as an oncological sequela, or diagnosis can be significantly delayed [2, 5–8]. It is essential that neurologists are aware of LEMS so that affected patients can be correctly diagnosed in a timely fashion. This will allow proper treatment of the neurological disease and any underlying tumor. This review discusses the clinical picture and pathophysiology of LEMS, together with a recommended diagnostic approach.

Epidemiology

Lambert–Eaton myasthenic syndrome (LEMS) is a rare disease, with a world-wide prevalence of around 3–4 per million population [9]. A decade-long study performed from 1990 to 1999 in South Holland found that the annual incidence of LEMS was 0.48 cases per million, with a prevalence of 2.32 per million [10]; a follow-up study across all of the Netherlands indicated an annual incidence of 0.4 cases per million and a prevalence of 2.5 per million in 2003 [11]. Extrapolating the data from the Netherlands to the overall European population suggests that LEMS currently affects around 1850 individuals in this region, with potentially 300 new cases diagnosed each year. A recent study in the US Veterans Affairs population (2013) found a confirmed crude LEMS annual incidence of 0.6 cases per million (or 0.7 cases per million when confirmed and probable cases were combined) [12]. The crude confirmed and confirmed/probable prevalence of LEMS was 2.8 and 3.8 per million, respectively.

CA-LEMS accounts for between 47 and 62% of cases of the syndrome [4, 11, 13, 14]. SCLC is the most frequently occurring underlying tumor, although rare cases of other lung and non-lung cancers have been reported in patients with LEMS [13, 15–30]. Diagnosis of LEMS typically precedes detection of the tumor [31]. In an unselected population of 63 patients with SCLC, two individuals (3%) had a confirmed diagnosis of LEMS [32]. The median age of onset of CA-LEMS is around 60 years, with 59–70% of cases occurring in males [4, 31]. On the other hand, NT-LEMS has a closer age and sex distribution to that seen with MG. Median age of onset is 50 years [4], with the condition also affecting children [33]. In general, NT-LEMS has an equal representation of males and females, although a female predominance has been reported in individuals diagnosed at less than 45 years old, with a male predominance in those diagnosed after the age of 60 years [34]. NT-LEMS is often associated with an underlying autoimmune disease, including autoimmune thyroid disease, diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus [35–37]. In a 2003 study in the Netherlands, the annual incidence of LEMS associated with SCLC was around 0.2 cases per million, with a prevalence of 0.5 per million [11]. The incidence of NT-LEMS was similar in this population (0.2 per million) but the prevalence was higher (2.0 per million) [11], reflective of the better survival associated with NT-LEMS than with CA-LEMS.

Clinical picture and prognosis

Patients with LEMS almost invariably experience proximal weakness in the legs as a first symptom. This typically spreads to proximal weakness in the arms, distal weakness in the arms and legs, and finally weakness involving hands, feet, and cranial muscles [2, 31]. Other commonly reported symptoms include general fatigue, dry mouth, slurred or slow speech, male impotence, droopy eyelids, double vision, difficulty swallowing or chewing, neck weakness, dry eyes, and constipation [4, 5, 31]. Although usually a hallmark of MG, ptosis can also be reported by patients with LEMS, albeit generally in a mild form and later in the disease course, [6, 38]. Cerebellar ataxia is a relatively uncommon symptom, but it appears almost exclusively in patients with CA-LEMS [31]. Symptoms appear to develop more quickly in patients with CA-LEMS than those with NT-LEMS: in a cohort of 97 patients with LEMS, those with CA-LEMS reported a mean of seven different symptoms in the first 6 months of diagnosis, compared with a mean of two symptoms in patients with NT-LEMS [31]. The insidious nature of LEMS symptoms mean that patients may wait for months or years before presenting to their doctor, with a likely further delay from presentation until diagnosis [5]. Recently, a Firdapse registry based on voluntary submission of data by investigators from 29 EU centers has been established. Data are entered into a centralized database via a validated web-portal application. Interestingly, results from specific clinical assessments using the quantitative myasthenia gravis (QMG) score showed that the raw QMG score was 7.2 ± 6.8 and the % standardized QMG total score 20.4 ± 18.8, thus indicating that the severity of muscle weakness and fatigability was mild to moderate [39].

Little formal documentation has been undertaken to define the burden of illness associated with LEMS. In one of the only studies published in this area, researchers in Germany performed a series of interviews in 12 patients with LEMS (three of whom had a diagnosis of SCLC) and found that leg weakness and general fatigue were considered the most troublesome symptoms [5]. Tellingly, all respondents had mobility issues, 50% reported severe pain or discomfort, and 75% reported frequent restrictions in their activities of daily living. In a study of 47 consecutive patients with NT-LEMS, 25% required a wheelchair at all times or while mobilizing outside [7]. Health-related quality of life, measured by the generic EuroQol five-dimensions five-level (EQ-5D-5L) instrument, was similar in patients with LEMS to that in patients hospitalized with a severe exacerbation of asthma or those with severe multiple sclerosis [5].

The prognosis of patients with LEMS is related to the presence of cancer or autoimmune disease and the severity/distribution of muscle weakness. Given that SCLC is typically an aggressive cancer, the cause of death in patients with CA-LEMS is likely progression of the underlying tumor. Interestingly, however, patients with SCLC have longer overall survival when they have LEMS than when they do not (median of 17.3 months vs 10 months, respectively) [40]. It has been debated whether this is a lead-time bias in identifying SCLC tumors in patients presenting with LEMS or whether it is related to a biological mechanism such as elevated anti-VGCC antibodies [41, 42]. Prognosis in NT-LEMS is variable but is notably different from that in CA-LEMS as the condition does not appear to reduce life expectancy [7]. In a series of 47 patients with NT-LEMS treated at a UK center between 1987 and 1998, around half achieved sustained clinical remission [7]. The majority of patients were symptomatically treated with amifampridine (Firdapse; BioMarin Europe Ltd, London, UK; 79% at final follow-up or death). In most cases, significant and ongoing immunosuppressant treatment was required for patients to remain clinically stable. The only independent predictor of clinical remission or independent ambulation was initial clinical score, comprising strength measurements in proximal limb muscles. Interestingly, neither electrophysiological findings nor anti-VGCC antibody levels correlated with outcome. In a US-based analysis of the Veterans Affairs population, the majority of patients with LEMS treated pharmacologically had some degree of improvement (37/46; 80%) [12]. Of the more frequently used medications, amifampridine was associated with the highest rate of clinical improvement or resolution (14/18; 78%).

Mechanisms of disease

Etiology and risk factors

Voltage-gated calcium channels (VGCCs) are heteromeric multi-subunit complexes and can be classified according to their characteristic voltage activation threshold (high- or low-voltage activated), their sequence similarities at the pore-forming alpha-1 subunit (Ca.v1, Ca.v2, or Ca.v3) or their pharmacological properties (P/Q, N, L, T, or R). The P/Q-type VGCC is primarily involved in neurotransmitter release from motor nerve terminals, while the effects of the other subtypes include neurotransmitter release from autonomic nerve terminals (N-type) and specialized terminals such as the retina or auditory hair cells (L-type) [43].

Lambert–Eaton myasthenic syndrome (LEMS) is an autoimmune disease caused by the interaction of autoantibodies with P/Q-type VGCCs on presynaptic nerve terminals [44]. Antibodies against the P/Q-type VGCC have been demonstrated in serum for approximately 90% of non-immunosuppressed patients with LEMS [45]. Recent studies have indicated that autoantibodies from patients with LEMS bind to multiple subunits of the P/Q-type VGCC complex [46]. This autoimmune etiology is additionally supported by the observations that immunomodulation improves muscle weakness in many patients with LEMS [2] and that transfer of immunoglobulins from patients with LEMS to mice results in changes at the neuromuscular junction that are consistent with clinical observations [47].

The etiological basis for the development of CA-LEMS is the presence of high concentrations of functional P/Q-type VGCC on SCLC cells, which presumably induce autoimmune production of pathogenic anti-VGCC antibodies [2, 48, 49]. These autoantibodies then cross-react with components of VGCC on presynaptic nerve endings [2, 50, 51], affecting neuromuscular function. Autoantibody production appears to begin at an early stage in tumor development, typically before detection of the tumor itself. As cigarette smoking is a strong risk factor for SCLC, it is also a risk factor for CA-LEMS.

The specific trigger for NT-LEMS is unknown; however, the syndrome is strongly associated with underlying autoimmune disease [4, 35] with a notable maternal link [35]. Furthermore, there is a correlation between NT-LEMS and haplotypes associated with autoimmunity (e.g., HLA-B8, -A1, -A2, and -DR3), particularly in patients with young-onset disease [2, 34, 52].

Pathophysiology

Under physiological conditions, transmembrane P/G-type VGCCs are expressed on the presynaptic membrane in regular arrays [53]. Depolarization of the presynaptic membrane causes the VGCCs to open, allowing an influx of calcium ions into the nerve terminal. This influx induces fusion of acetylcholine (ACh)-containing synaptic vesicles with the presynaptic membrane, resulting in quantal release of ACh from areas known as "active zones" into the synaptic cleft. ACh binds to ACh receptors on the adjacent postsynaptic endplate of the muscle fiber; this opens ligand-gated sodium and potassium ion channels, inducing depolarization of the endplate. Once the depolarization threshold is met, an action potential occurs and the muscle contracts [4].

In the situation of LEMS, presynaptic ACh stores and postsynaptic response to ACh quanta at the neuromuscular junction are normal, but there is a reduction in release of ACh from the presynaptic nerve terminal that translates into a reduced postsynaptic endplate action potential [4, 54]. The reduction in ACh quanta is attributed to loss of functional P/Q-type VGCCs at the presynaptic terminal, presumably due to autoantibody binding. Immunoelectron microscopy has shown that P/Q-type VGCCs in the presynaptic membrane decrease in number and are expressed in a clustered pattern in LEMS [47, 53]. This not only reduces calcium ion influx at depolarization, but may also decrease the number of presynaptic active zones. P/Q-type and N-type VGCCs act as scaffolding proteins in active zones and are involved in tethering ACh vesicles and bringing them into proximity to the presynaptic membrane [55, 56]. The autoimmune response seen in LEMS not only affects muscle function, but also has an impact on the autonomic nervous system (presumably through interaction of autoantibodies with N-type VGCCs [57]) and, in some patients, on the central nervous system [31] (through interaction of autoantibodies with P/G-type VGCCs located in the cerebellum [3]).

Around 10% of patients with LEMS (predominantly those with NT-LEMS) are seronegative for anti-P/Q-type VGCC antibodies [45]. Clinical features are similar in seronegative and seropositive patients, although the electrophysiological profile may be less pronounced in seronegative patients [58, 59]. It may be that seronegative patients do actually have anti-P/Q-type VGCC antibodies, but at concentrations below the level of detection with current assays; alternatively, they may have antibodies to a different VGCC epitope or a different molecule that generates a similar phenotype [58, 60, 61]. Interestingly, antibodies to SOX1 (a transcription factor expressed in the developing nervous system) have been reported with higher frequency in patients with CA-LEMS (64–65%) than those with SCLC without LEMS (22–32%), and in very few patients with NT-LEMS (0–5%) [62, 63]; however, no conclusive pathogenicity of anti-SOX1 antibodies has yet been established.

A diagnostic approach

Diagnosis of LEMS is supported by a threefold approach: history and physical examination, electromyography (showing a presynaptic deficit of neuromuscular transition), and autoantibody (anti-VGCC antibody) serology (Box 1; Fig. 1). Patients with suspicion of LEMS should be examined and treated by a neurologist and, if appropriate, an oncologist. If an underlying tumor is identified, then the treatment priority should be the cancer.

History and physical examination

Lambert–Eaton myasthenic syndrome (LEMS) should be considered in a patient presenting with progressive proximal muscle weakness (particularly in the legs, but may also include arms), together with reduced or absent tendon reflexes (areflexia) [2, 8]. A waddling gait may be noted. One of the hallmarks of LEMS is that tendon reflexes normalize and muscle strength improves immediately after brief maximal contraction; however, not all

Box 1 Diagnostic assessment of LEMS

Features
Risk factors
Small cell lung cancer
Cigarette smoking
Autoimmune disease
Family history of autoimmune disease
Clinical features
Progressive proximal muscle weakness (should be present)
Areflexia
Autonomic symptoms
Ocular/bulbar symptoms
General fatigue
Postoperative muscle weakness after neuromuscular blockers
Electromyography
Repetitive nerve stimulation studies (should all be present)
Low CAMP at rest (0.1–6 mV)
Decrease of >10% in CAMP at low frequency (2–5 Hz)
Increase of >60% in CAMP after maximum voluntary contraction or at high frequency (20–50 Hz)
Autoantibody serology
Anti-P/Q-type VGCC antibodies

CAMP compound muscle action potential, *LEMS* Lambert–Eaton myasthenic syndrome, *VGCC* voltage-gated calcium channel

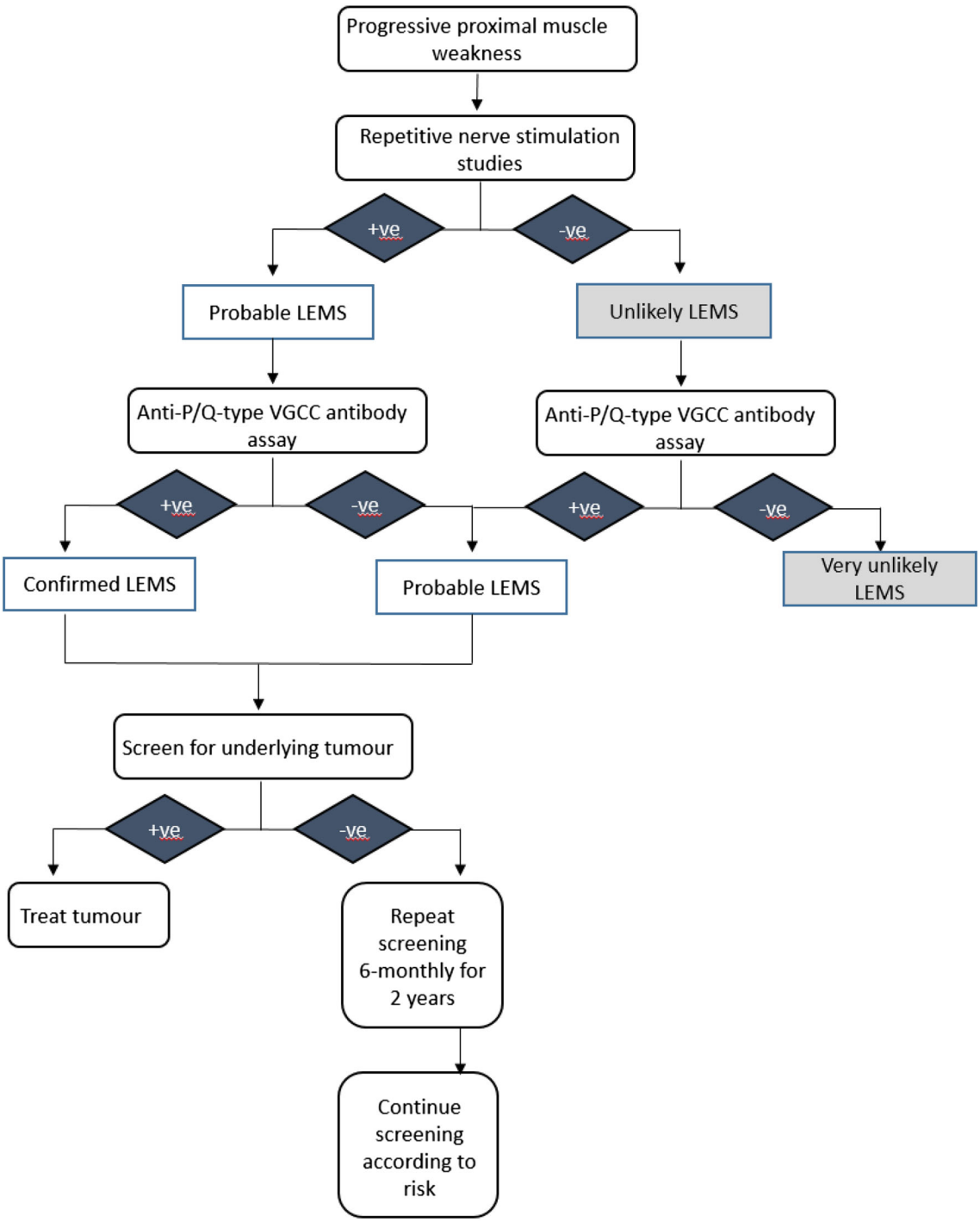

Fig. 1 LEMS diagnosis and oncological screening algorithm. *LEMS* Lambert–Eaton myasthenic syndrome, *VGCC* voltage-gated calcium channel

patients demonstrate this post-exercise facilitation [64]. Because this phenomenon can mask lowered tendon reflexes, these should be tested after a rest period [2, 8]. Additional indicative signs of LEMS include general fatigue, autonomic dysfunction (e.g., dry mouth, impotence, or constipation), or weakness of facial or ocular muscles (e.g., ptosis or double vision) [2, 5, 38]. These symptoms may fluctuate throughout the day. LEMS should also be considered in the case of any unexplained postoperative muscle weakness after neuromuscular-blocking drugs [65]. History should include an assessment of LEMS risk factors such as underlying SCLC or autoimmune disease, a family history of autoimmune disease, or cigarette smoking.

Electromyography

Repetitive nerve stimulation (RNS) tests should be performed on at least two distal muscles, with positive tests showing (1) low amplitude of the compound muscle action potential (CMAP) at rest (0.1–6 mV), and (2) further decrease of the CMAP amplitude (at least 10%) during low-rate (2–5 Hz) RNS [2, 8]. These are the most sensitive diagnostic tests. However, as the decrease in CMAP amplitude during low-rate RNS does not discriminate in total between LEMS and MG, at least two muscles should be tested with either the painful high-frequency (20–50 Hz) RNS or much better and preferably RNS immediately after a brief maximal voluntary contraction (15–20 s) [8]. An increase in the CMAP amplitude (increment) of at least 100% is considered specific for LEMS, although it has been suggested that the threshold can be decreased to 60% to improve sensitivity (97%) while retaining specificity (99%) [66]. RNS after maximal contraction is less painful than high-frequency RNS and involves applying a single supramaximal stimulus to generate a baseline CMAP [8]. After the brief period of maximal voluntary contraction, the post-exercise CMAP is produced by applying a second stimulus. Consideration should be given to withdrawing symptomatic medication 12 h before electrophysiological testing and to maintaining the temperature of the examined muscles at above 35 °C to further increase sensitivity [67].

Single-fiber electromyography is slightly more sensitive than RNS for diagnosis of LEMS [66] and jitter appears to correlate with clinical and electrophysiological disease severity [68]. However, single-fiber electromyography is less specific than RNS and has limited availability [67]. For these reasons, RNS is the preferred initial test for LEMS [67].

Autoantibody serology

Detection of anti-P/Q-type VGCC antibodies is a highly specific diagnostic confirmation of LEMS; however, the absence of detectable VGCC antibodies does not exclude LEMS [2, 8]. It should be noted that there is no correlation between antibody titres and disease severity [7] and that antibody levels may be affected by the use of immunosuppressants [69]. The presence of antibodies to domain IV of the alpha-1A P/Q-VGCC subunit is highly suggestive of NT-LEMS (occurring in 38% of patients with NT-LEMS and 5% of patients with SCLC-LEMS) [70]. Conversely, the presence of SOX1 antibodies is indicative of SCLC-LEMS [62, 63, 71, 72]. While antibodies against synaptotagmin and M1 muscarinic ACh receptors have been detected in some patients with LEMS, these specific antibodies have no diagnostic value [8].

Misdiagnosis and differential diagnosis

Many clinical symptoms of LEMS overlap with those of other myasthenic syndromes, most commonly MG. In a cohort of 241 Dutch or British individuals diagnosed with LEMS between 1990 and 2009 [14], 58% were initially misdiagnosed [2]. The most common diagnosis was MG (21%), with other diagnoses including myopathy not otherwise specified (11%), polyneuropathy (3%), and depression or psychosomatic causes (4%). Although rare, co-occurrence of LEMS and MG have been previously reported in the literature and might render the diagnosis of LEMS more complicated [73, 74].

SCLC-LEMS is typically diagnosed more quickly after the onset of symptoms than NT-LEMS [11]. Reasons for this are not clear, but it may be that SCLC-LEMS has a more progressive course, which could shorten both patient presentation time and doctor delay in diagnosis [11].

Clinical features that strongly support a diagnosis of LEMS include progression of symptoms over weeks to months, spreading from proximal to distal muscles and in a caudocranial direction. Symptoms are likely to be symmetrical, with fluctuating severity over the course of the day. Patients may exhibit prominent autonomic symptoms, normal (or slightly elevated) creatine kinase, and cerebellar ataxia. Sensory symptoms or prominent pain are unlikely [2, 8].

While LEMS typically starts with leg weakness, which progresses in a caudocranial direction, MG typically begins with oculobulbar weakness, and muscle weakness spreads craniocaudally [75]. Autonomic dysfunction and diminished tendon reflexes are rarely seen with MG [75]. High-frequency RNS or post-exercise RNS below 60% may differentiate LEMS from MG [2].

Polymyositis or immunogenic necrotizing myopathy may also be suspected in patients with proximal symmetrical weakness, although these patients tend to have an absence of autonomic symptoms and instead experience pain, muscle atrophy, and raised creatine kinase, which are uncommonly seen in LEMS [2]. Difficulties getting out of a chair may be suggestive of early-stage Parkinson's disease, and subacute symptoms with abnormal electrophysiology may indicate neuropathy, Guillain–Barré syndrome, myotonic dystrophy type 2, or amyotrophic lateral sclerosis (ALS) [2]. However, these patients will likely have sensory symptoms or pronounced pain or myotonia not seen with LEMS. ALS patients will show fasciculations and progressive muscle atrophy.

Oncological screening

Clinical symptoms of LEMS nearly always precede detection of SCLC, so it is essential that screening for any underlying tumor begins as soon as a diagnosis of LEMS is

made (Fig. 1). With effective screening, 96% of cases of SCLC were diagnosed within a year of LEMS diagnosis [76]. Conventional radiography or bronchoscopy is unlikely to detect early-stage SCLC, so computed tomography (CT) of the thorax is warranted. If negative, this should be followed by ^{18}F-fluorodeoxyglucose-positron emission tomography (PET) or integrated PET/CT [77]. If the first screening is negative, oncological surveillance should be continued at 6-month intervals for at least 2 years after LEMS onset [77]. A simple SCLC prediction score, known as the DELTA-P score, has also been developed to guide assessment of the need for further screening early in the course of disease [14]. This tool scores a series of characteristics (age at onset, smoking status, bulbar involvement, weight loss, erectile dysfunction, and Karnofsky performance status) on a scale from 0 to 6, with a higher score indicative of greater SCLC risk. While this tool can prioritize high-risk patients for oncological cancer screening and reassure those with lower risk, neurologists should be vigilant about signs of possible SCLC in patients with a LEMS diagnosis.

Autoimmune disease screening

In the absence of malignancy, it is likely that the LEMS patient will have an underlying autoimmune disease. Assessment should be made if the patient is symptomatic (e.g., thyroid-stimulating hormone measurement for assessing comorbid thyroid dysfunction, or typical investigations if rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis, autoimmune inflammatory myopathies, or pernicious anemia is suspected); however, routine screening for autoimmune disease is not necessary.

Treatment

Symptomatic treatment of LEMS involves drugs that increase the release of neurotransmitters from the presynaptic terminal or that prolong the activity of ACh in the synapse.

The compound 4-aminopyridine (4-AP) has been used for the symptomatic treatment for LEMS [78]. Nevertheless, a few reports showed that this mono-aminopyridine has the ability to easily cross the blood–brain barrier causing central nervous system side effects such as seizures. Although limited, these results suggest that 4-AP might not be acceptable for the management of LEMS [6].

Unlike 4-AP, the potassium channel blocker 3,4-diaminopyridine or amifampridine is a viable and effective option for the symptomatic treatment of LEMS [2]. This agent may also directly stimulate the VGCC β-subunit, potentiating neurotransmission [79]. In four randomized placebo-controlled trials in patients with LEMS, amifampridine showed a significant benefit in terms of muscle strength and CMAP amplitude, and was generally well tolerated [80, 81]. Amifampridine (in any of the possible formulations) was used as a symptomatic drug by the vast majority of the patients included in the EU registry, and steroids or immunosuppressants were used in about one-third of the patients [39]. Patients experiencing persistent symptoms may also require immunosuppressants or immunomodulators (e.g., prednisone plus azathioprine or intravenous immunoglobulin) [2]. Where a tumor is identified, oncological treatment should take priority.

Intravenous immunoglobulin (IVIg) is considered an effective alternative for the management of diseases with immune pathogenesis such as LEMS [82]. In fact, in a placebo-controlled crossover study IVIg was associated with a significant improvement in the amplitude of resting CMAP and a decline in serum VGVV antibodies [83]. Additionally, other case reports have demonstrated the benefit of IVIg for the short and long-term management of LEMS, especially as adjuvant therapy in patients with resistant muscle weakness [82].

Plasma exchange therapy is another alternative for the management of LEMS and other neurological disorders of autoimmune etiology [84]. Several case series reported improvements in clinical and electrophysiological outcome measures. Nevertheless, a case study showing only a transient decrease in the levels of serum VGVV after plasma exchange therapy suggests a limited effect of this therapy in patients with LEMS [84].

Conclusions

While rare, LEMS is a clinically important early indicator of the possible presence of SCLC or another underlying tumor. A LEMS diagnosis initiates a mandatory oncology screening and surveillance process, which may allow identification of early-stage cancer and initiation of cancer treatment, with a positive impact on patient outcomes. Furthermore, it should be remembered that the presence of LEMS has a significant impact on a patient's quality of life and ability to perform daily activities and therefore warrants timely diagnosis and appropriate treatment in and of itself.

Acknowledgements Funding for the manuscript was provided by BioMarin Europe Ltd and editorial support was provided by Virgo Health.

Author contributions BS designed and initiated this review, selected the incorporated papers, supervised the writing with input from all coauthors and approved the final version of this manuscript. BE, JD

and RM contributed to the concept of this review, provided feedback at all stages of development and approved the final version of this manuscript.

Compliance with ethical standards

Conflicts of interest BS has received speaker honoraria from BioMarin, Sanofi Genzyme, CSL Behring, and Amicus Therapeutics. He is a member of the neuromuscular advisory board of Audentes Therapeutics and has received an unrestricted research grant from Sanofi Genzyme. BE has received honoraria from BioMarin Europe Ltd, Novartis and the LFB Group. JD is a EUMEA Medical Affairs Senior Director for BioMarin Europe Ltd. RM has received honoraria for participation in clinical trials, advisory boards, congresses and travel from Alexion Pharmaceuticals, Biomarin Europe Ltd. and Catalyst.

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