Review

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Marcelo De Moura Campos *, Eduardo Pagliarini , Amanda Locks , Marcus Gonçalves

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Review

Lambert Eaton Myasthenic Syndrome: A Bridge Diagnostic for Occult Tumor

Marcelo Henrique De Moura Campos, Eduardo Eberle Pagliarini, Amanda Locks and Marcus Vinicius Magno Gonçalves

Department of Medicine, University of the Region of Joinville (UNIVILLE), Rua Ministro Calógeras, Bucarein, Joinville, Santa Catarina – 89202-207, Brazil; eduardopagliarini@hotmail.com (E.E.P.); amandalocks@gmail.com (A.L.); marcusribeirao@yahoo.com.br (M.V.M.G.)

* Correspondence: marcelo.campos88@hotmail.com; Tel: +55 (47) 99233-8077, Fax: +55 (47) 34379081

Abstract: Lambert-Eaton myasthenic syndrome is a primary autoimmune or paraneoplastic neuromuscular disorder, which causes muscle weakness, areflexia and autonomic disorders through the production of antibodies to voltage-gated calcium channels. Diagnosis may be challenging, yet at the same time extremely important, allowing the detection of a possible underlying malignancy, in cases of paraneoplastic presentation. Some antibodies have good sensitivity and specificity for malignancy and are also discussed. Although most of times being correlated to small cell lung cancer, other types of tumors may be also found in the paraneoplastic syndrome. Misdiagnosis with Myasthenia Gravis may occur and differences between these two disorders are discussed. Therapy choice may vary from each patient depending on drug response and the situation in which the patient is encounter. Overall, the present paper brings a review of Lambert-Eaton, involving the diagnosis, as well as, the pathophysiology, differential diagnosis, tumor investigation and treatment. Also, a brief overview through guidance on therapy during the Corona Virus Disease 2019 pandemic is analyzed.

Keywords: Lambert-Eaton; Paraneoplastic Syndrome; tumor; SCLC; antibodies; COVID-19

Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune neuromuscular disease. It is responsible for producing autoantibodies that affect voltage-gated calcium channels (VGCC), thereby reducing the release of acetylcholine, which consequently causes muscle weakness [1]. It is divided in two forms: the paraneoplastic LEMS (P-LEMS) - often associated with small cell lung cancer -, and the autoimmune LEMS (A-LEMS) [2,3], the former being the most prevalent type with accounting constituting 60% of cases [3]. The clinical aspects of the disease include (1) muscle fatigue, especially in the proximal regions of the extremities, (2) decreased tendon reflexes and (3) autonomic dysfunction [2–4].

Knowledge of this disease is of fundamental importance for the early identification of malignancies as well as for a differential diagnosis of autoimmune diseases, which would ensure a better prognosis for the patient.

Methods

This is a non-systematic review in which a search in the literature was carried out using Pubmed with the terms "Lambert-Eaton" AND "Paraneoplastic syndrome" AND "Tumor". No time restriction was applied to the search. The last search occurred in August 2022. Also, only articles written in English were considered.

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Clinical Features

The most common manifestations of LEMS involve muscle weakness, areflexia and autonomic dysfuntion [2–4]. Those symptoms are usually present in both P-LEMS and A-LEMS, however, in P-LEMS patients, they may appear earlier during the course of the disorder [3].

Muscle weakness of the legs is the first symptom to develop in most cases. Weakness of the arms can appear as well [2,3,5]. These features usually extends from proximal to distal direction [4]. Furthermore, those symptoms spread from the caudal region to the cranial region and, therefore, it is important to notice that ocular and bulbar features are only seen in late stages of LEMS [6]. Tendon reflexes may be absent as well [4]; however, a post exercise facilitation might camouflage that sign [7], in which muscle strength and tendon reflexes can return after muscle contraction. Thereby, it is recommended to test the reflexes after some time of rest. Autonomic disorders are also seen in LEMS patients, dry mouth being the most common one. Erectile dysfunction and constipation may be present as well. Dry eyes, impaired sweating and dizziness are less common [2,5]. Some studies also report cerebellar ataxia [3,5,8] as well as encephalitis [9,10] in cases of P-LEMS.

Pathophisiology

In LEMS patients, antibodies target the presynaptic VGCC [1]. Therefore, the influx of Ca^{2+} in cells is reduced, which in turn, results in a decreased release of acetylcholine on neuromuscular and autonomic junctions [11]. Antibodies to the P/Q-type VGCC are found in most of the patients [12], and are strongly related to motor and autonomic features seen in LEMS patients [13]. Also, antibodies to the N-type VGCC may be present as well in some patients; however, its impact on clinical features is still not totally clear [14].

In A-LEMS patients, the etiology of the antibodies is not properly understood. There might be a correlation between the expression of the HLA-DR3-B8 haplotype and the autoimmune disorder [15]. On the other hand, for P-LEMS patients, a cross reaction between malignancies cells and the immune system can result in the production of VGCC antibodies [16]. For example, in the most prevalent malignancy found in P-LEMS, the small cell lung cancer (SCLC) [2], tumor cells express VGCC and, consequently, an immune response from the body initiates an autoimmune reaction [16].

This parallel between malignancies and antibodies, resulting in paraneoplastic syndromes, may play a bigger role during the course of the disorder. For example, cerebellar ataxia seen in P-LEMS [3,5,8] may be caused by the antibodies to the P/Q-type VGCC, which are expressed by the Purkinje cells in the cerebellum. A breakdown of the blood brain barrier might be caused by the production of antibodies against glucose-regulated protein 78 (GRP78) that resulted from the body's response against the tumor. Therefore, it allows pathogenic antibodies to the P/Q-type VGCC to enter into the CNS and act on the Purkinje cells, resulting in cerebellar ataxia [17].

More rarely, autoimmune encephalitis may manifest in P-LEMS patients with SCLC, as a result of the production of anti GABAb antibodies [9,10]. Hence, cognitive changes, seizures, and personality changes may be present, although these are not the usual symptoms of LEMS [9,10]. In cases of uncommon LEMS syndrome presentation, a search for other antibodies, besides VGCC antibodies, is recommended [9]. This can be important to contraindicate conventional first-line therapy to LEMS when atypical symptoms are present. 3,4-diaminopyridine is the first choice in LEMS, however it carries a risk of seizure [9]. The identification of a second antibody could result in better outcomes, especially in autoimmune central nervous system neurologic disorders [9]. Still, the screening for second antibodies in classic LEMS may not be necessary [9]

Diagnosis

Clinical features should be considered to make the diagnosis. Moreover, a search for VGCC antibodies may be performed. In most LEMS patients - about 90% of cases - P/Q VGCC antibodies are present [12,14]. N-type antibodies may be found as well in about 30% of patients and, when present, are usually in coexistence with P/Q VGCC antibodies [12,14]. Patients may be considered as seropositive with values greater than 0.02 nmol/L, for P/Q VGCC antibodies, and 0.03 nmol/L, for N-

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type antibodies [18]. Nevertheless, the non-detection of VGCC antibodies should not rule out the diagnosis of LEMS. Nakao Y.W. and colleagues [19] conducted a study in which seronegative LEMS patients were identified in about 15% of cases. In these patients, although VGCC antibodies are not detected, the clinical features of LEMS are still present [19].

Electrodiagnostic findings show in the repetitive nerve stimulation (RNS): (1) a reduced compound muscle action potential (CMAP) at rest, (2) a decrease greater than 10% in the CMAP during low frequency and (3) an increase of the response of 100% or greater after post exercise facilitation [20]. Nevertheless, Oh S.J. and colleagues [21] proposed that a 60% increment in the post exercise facilitation test is a preferred alternative to the 100% increment, increasing the sensitivity for the diagnosis of LEMS from 85% to 97% while specificity remains at 99%. Also, although a more sensitive test than RNS, Single-fiber electromyography cannot differentiate LEMS from Myasthenia Gravis (MG) [4]. Those findings are necessary for the diagnosis of LEMS along with clinical analysis.

Tumor Presence

A tumor may be present in 60% of LEMS patients [3]. With that in mind, an anamneses should be carried out, in search of a possible malignancy, investigating the history of the patient, like smoking and loss of weight. Moreover, in P-LEMS patients usually the age of onset is around 60 and most of them are men [22], while in A-LEMS the age of onset is 35 and most of the patients are women [3,22].

Atypical clinical features may also imply a case of P-LEMS. As explained before, cerebellar ataxia might be caused from the production of antibodies against GRP78 that resulted from the body's response to the tumor [17]. Although the underlying mechanism of this clinical manifestation is not totally understood, its prevalence in A-LEMS is very low [23], which strengthens the correlation of this feature to a malignancy. Furthermore, cognitive changes, seizures and personality changes may also suggest a case of P-LEMS, due to the production of anti-GABAb antibodies, which have high sensitivity and specificity for SCLC [9,10,24].

It is also important to remember other types of malignancies, besides SCLC, that may develop P-LEMS. There are some studies [2,3,25–27] that report other types of tumor, found in P-LEMS patients, which may be checked in Table 1. Furthermore, there are also some case reports in literature associating P-LEMS with thymoma and lymphoproliferative disorders [28,29].

Table 1. Tumor types identified in LEMS patients.

	O' Neill J.H. et al. 1988 [2]	Wirtz P.W. et al. 2002 [3]	Lennon V.A. et al. 1995 [25]	Lambert E.H. et al. 1988 [26]	Tim R.W. et al. 2000 [27]
SCLC	**21**	**95**	**25**	**12**	**29**
Breast Carcinoma	**1**	**2**	**-**	**-**	**3**
Lymphoma	**-**	**7**	**1**	**1**	**-**
Leukemia	**-**	**6**	**-**	**-**	**-**
Prostate Carcinoma	**-**	**3**	**-**	**-**	**-**
Laryngeal Carcinoma	**-**	**3**	**-**	**-**	**-**
Lung Adenocarcinoma	**1**	**-**	**1**	**-**	**-**
Parotid Tumor	**-**	**-**	**1**	**1**	**-**
Others	**-**	**5***	**4****	**1*****	**1#**
Total LEMS patients	**50**	**227**	**65**	**26**	**73**

Abbreviations: SCLC, small cell lung cancer; LEMS, Lambert-Eaton myasthenic syndrome. * Includes: 1 gall bladder carcinoma, 1 rectal adenocarcinoma, 1 carcinoma of maxillar glandule, 1 malignant thymoma, 1 ameloblastoma; ** Includes: 1 renal carcinoma, 1 carcinoma of colon, 1 carcinoma of uterus, 1 carcinoma of skin; *** Includes: 1 colon adenocarcinoma; #Includes: 1 squamous cell lung carcinoma.

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Failure to detect any tumor at the first time of diagnosis of LEMS should not exclude the possibility of being a paraneoplastic case. A study [30] recommends a first screen of the lungs by CT-thorax, and if a negative result persists, a full body FDG-PET scan is recommended. If this first screen remains negative, a second CT-thorax or a FDG-PET scan should be made after 6 months from LEMS diagnosis. If negative again, a follow up is recommended, every 6 months for 2 years. An exception can be made for non-risk patients, who are individuals under 45 years of age without a history of smoking and carrying the HLA 8.1 haplotype. In this case, a negative result in the second CT-thorax made after 6 months from the first screening is sufficient to consider it as an autoimmune case of LEMS [30].

Moreover, a Dutch-English LEMS Tumor Association Prediction (DELTA-P) score, ranging from 0 (low risk) to 6 (high risk), was created to calculate the probability of the presence of SCLC in LEMS patients [22]. The score is attributed according to some characteristics of the patient, such as clinical findings and lifestyle habits, being a simple and useful tool to identify patients at high risk for developing SCLC.

Nevertheless, depending on the stage and location of the tumor, the search for SCLC may be more difficulty in some cases. Wada and colleagues [31] reported a case in which computer tomography failed to detect the lung tumor; however, through biopsy, the presence of SCLC was confirmed. In addition, in a study by Maddison and colleagues [24], 19% of LEMS patients with SCLC had a low mid-range DELTA-P score. Thus, considering that cancer survival is increased in early detection [32], it is important to consider other cancer predictors to improve the accuracy of SCLC diagnosis in patients with LEMS. Some antibodies have high sensitivity and specificity for SCLC and can serve as good biomarkers. Maddison et al [24] reported that 55% of SCLC-LEMS patients (n = 34) were positive for N-type VCGC antibodies, while in A-LEMS patients (n = 30) only 8% were positive as well. SOX-2 antibodies were present in 69% of patients with SCLC-LEMS and only 4% of patients with A-LEMS. Also, GABAb antibodies were positive in 21% of patients with SCLC-LEMS, whereas only 3% of patients with A-LEMS had positive result. Overall, the presence of either VCGC type N, SOX-2 or GABAb antibodies had a sensitivity of 84% and a specificity of 87% in patients with SCLC-LEMS. Furthermore, the sensitivity and specificity of these antibodies remained high even in patients with a low DELTA-P score [24].

Differential Diagnosis

MG is one of the main disorders in the differential diagnosis with LEMS. Thereby, it is important to note a difference in the progression between those two disorders. While in MG the progression of muscle weakness tends to occur craniocaudally, in LEMS it occurs at a caudocranial direction. Therefore, at the initial stage of MG, ocular symptoms, like ptosis and diplopia, are very common, whereas in LEMS patients the initial symptom is leg weakness [33]. An interesting feature in LEMS is the mild weakness, though able to cause difficulty in walking, noticed upon physical examination [33]. Furthermore, ptosis in the late stage of LEMS appears as a milder form compared to MG. Diplopia is common in both disorders; however, external ophthalmoplegia was only noticeable in MG patients [6]. Also, areflexia as well as autonomic features are usually not seen in MG patients [4,33].

In addition, differences in electrodiagnostic studies between LEMS and MG can be seen in the post-exercise facilitation test, in which an increase of 100% or more in CMAP suggest LEMS [33]. As explained earlier, an increase of 60% may already suggest LEMS, increasing the sensitivity of the diagnosis to 97%, while the specificity remains at 99% [21]. On the other hand, a decrement on RNS cannot confirm a LEMS diagnosis since it can be seen in MG patients as well [33].

Myopathy may be also considered – however, non-elevated muscle enzymes and the presence of autonomic symptoms suggest LEMS. An investigation for Guillain-Barré syndrome or amyotrophic lateral sclerosis may be also carried out, yet LEMS patients do not present sensory symptoms and some other typical features from those disorders [4].

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Myasthenia Gravis Lambert-Eaton Overlap Syndrome

Since 1972, there have been reports in the literature of possible coexistence of MG and LEMS in the same patients However, only in 2016, myasthenia-gravis Lambert-Eaton overlap syndrome (MLOS) was introduced as a new diagnostic for people who had both MG and LEMS clinical features [34,35].

A 2021 case report [36] described the first case of nivolumab-triggered MLOS used in a diagnosed metastatic melanoma patient. Retrospective laboratory analysis of pre-immunotherapy patient serum indicated positivity for acetylcholine receptors (AChR) and VGCC antibodies. So, the diagnosis of MLOS exacerbated by nivolumab was made, leading to discontinuation of treatment [36].

Although cases of MLOS are rare, none of them has been linked to immune checkpoint inhibitors yet [36]. Nevertheless the immunological toxicity must always be remembered as an immune-related adverse event trigger that may present as a paraneoplastic neurologic syndrome [36,37]. Therefore, neuro-muscular junctions diseases induced by checkpoint inhibitors require long-term follow-ups and they can be tricky to diagnose [36]. On the report of Oh [36] only 8 of 39 confirmed patients with MLOS had positivity of either AChR antibodies or muscle specific tyrosine kinase (MuSK) antibodies with VGCC antibodies, revealing that the absence of VGCC antibodies cannot rule out the MLOS diagnosis [36].

In conclusion, according to Oh [36] it is possible that some viral or bacterial epitope and a small sequence region in AChR and VGCCs may perform an important role as anti-coantigens of AChR and VGCCs, triggering 2 different autoimmune responses, in the post and presynaptic neuromuscular junction simultaneously, producing MG and LEMS in the same patient [36].

Treatment

Currently, there are some therapeutic options for LEMS that differ from the treatment of MG. The most effective are those that increase the release of acetylcholine in the synaptic cleft. However, this treatment is for patients who do not have a tumor. In case of malignancy, cancer treatment should be a priority [38].

The first drug of choice for the treatment of LEMS symptoms is 3,4-diaminopyridine (3,4-DAP). It acts on voltage channels dependent on potassium, prolonging the action potential of the nerve cell and keeping the VGCC channels open for a longer time [38]. In addition, a study suggest that aminopyridines can also potentiate neuromuscular transmission by targeting the β VGCC subunit [39]. Despite the benefits in LEMS patients, it is important to remember that this therapy may increase the risk of seizures [9].

Amifampridine is a more recent therapy. This drug is the salt form of the 3,4-DAP base, which gives the drug a greater stability. Similarly to 3,4-DAP, amifampridine acts as a potassium channel blocker. This therapy shows positive results, with a satisfactory safety. However, in patients with a history of seizures, amifampridine is also contraindicated [40].

The use of intravenous immunoglobulin is a reliable therapeutic option to treat refractory cases or patients with a continuous and rapid presentation of LEMS symptoms [38,41]. A double-blind crossover study [42] showed significant improvement of muscle strength and vital capacity with the use of immunoglobulins. Although there was no significant reduction of VGCC antibodies in the first week of treatment, a 23% reduction in antibodies was achieved in the second week and a 34% reduction was obtained in the third to the fourth week. Its mechanism of action is still not well understood, but it is believed to act on the autoantibodies that are preventing the correct functioning of the VGCC channels [42].

In cases of aggressive presentation of LEMS features, a plasma exchange might become an option for A-LEMS and P-LEMS as well [41]. Furthermore, for patients already in treatment, however, with uncontrolled symptoms, prednisolone and azathioprine are recommended [43].

The use of monoclonals, may be considered, as well, when other immunosuppressive agents, such as plasma exchange or intravenous immunoglobulin, fail [44]. Rituximab, which is the drug of choice in LEMS treatment, acts by blocking the CD20 receptor leading to B cell cytotoxicity.

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Consequently, a reduction in the immune response mediated by this pathway occurs [45]. Paul Maddison and colleagues [44] report significant improvement in LEMS patients treated with rituximab. In addition, LEMS patients presenting cerebellar ataxia have greater response with this therapy [46].

The use of immune checkpoint inhibitors (ICI) are also therapeutic options for LEMS. It is known that the immune recognition of cancer cells involves the binding of a tumor antigen-presenting cell to a T-cell, however, such immune response depends on inhibiting molecules. These molecules, commonly called checkpoints, act by avoiding excessive immune activation or autoimmunity and are also used by tumor cells to avoid detection [47].

ICIs aim to block the binding of checkpoint proteins to the receptor that disinforms T lymphocytes and allows cancer cells to remain proliferating [48]. There are three classes of ICI that act on different targets: anti-CTLA4 (ipilimumab), anti-PD1 (nivolumab, pembrolizumab) and anti-PDL1 (atezolizumab, avelumab, durvalumab) [49].

In the case report of Tadashi Sakaguchi and colleagues [50], it was seen that the use of monoclonal antibodies, such as Atezolizumab when associated with chemotherapy treatment for long-stage small cell lung cancer (ES-SCLC) in conjunction with LEMS, presents tumor regression and improvement of muscle weakness and myopathic gait [50]. The action of anti-PDL1 causes inhibition of B-cell-mediated autoimmune diseases and maintenance of self-tolerance [49].

However, although it is a well-tolerated treatment, in case of pre-existing active autoimmune diseases, this treatment may increase the chances of immune-related adverse events (irAE) [47]. In another case report by Yuki Nakatani and friends [51], it was demonstrated that the use of Nivolumab for pulmonary squamous cell carcinoma was positive for the manifestation of irAE in a period of higher use 20 weeks ago. The patient presented neurological symptoms: ptosis, weakness in the lower limbs and photophobia, as well as difficulty walking (myopathic gait), resulting in a diagnosis of LEMS [51]. Given the duality in the outcome of treatment, more research is needed to develop consensus and evidence-based guidelines for the use of IIC [48].

Meanwhile, during the world Corona Virus Disease 2019 (COVID-19) pandemic, doubts involving treatment management may surge. Recommendations state that current treatment for LEMS patients should not be stopped. Furthermore, there are no suggestions that 3,4-DAP therapy increases infections risks. In case of patients taking immunosuppressive therapies, cautions are needed to be taken along with social distancing to avoid agglomerations. At the same time, changes or withdrawal from current immunosuppressive therapy are not advised, as this may result in a rebound effect of the disorder. Also, there are no evidence of increased infection risks with the use of intravenous immunoglobulin nor plasma exchange therapies [52].

For patients who have not started monoclonal therapy yet, the recommendation is to wait until the contamination levels in the region decrease, as this therapy may increase the risk of viral infection. On the other hand, for other patients, it is a greater risk to not start therapy than to contract the COVID-19 infection. Because of that, a thorough pros and cons discussion must be carried out between the healthcare provider and the patient [52].

In case of patients who are currently infected with a benign infection of COVID-19, treatment should be continued normally. Nonetheless, in cases of severe infection, an interruption of immune depleting agents might be necessary. However, continuation of standard immunosuppressive therapies, as azathioprine, is recommended, since the elimination of these drugs from the organism and buildup of its effects posterior to discontinuation takes a significant time [52].

Conclusions

Diagnosis of Lambert-Eaton may be challenging. Identification of the clinical tried, formed by muscle weakness, areflexia and autonomic dysfunction [2–4], in conjunction with the presence of VGCC antibodies [12,14] and electrodiagnostic findings [20] may strongly suggest LEMS. Symptoms may be similar to those found in MG patients. In behalf of that, an attention to details, also regarding the spread of weakness, should guide the physician to make the correct diagnosis.

Furthermore, it is important to remember that the presence of a malignancy should be always considered after LEMS diagnosis. As explained before, serologic findings can also support the diagnosis of P-LEMS, as some types of antibodies, such as VGCC type N, SOX-2 or GABAb, have high sensitivity and specificity for SCLC. With that in mind, the chance of a tumor finding is increased in patients with the presence of these antibodies [24].

Also, treatment may vary between each patient. Close monitoring is required for refractory cases and uncontrolled symptoms, in which a change on therapy may be necessary. An interesting fact to remember is that, in cases of P-LEMS, antibodies against GABAb may be produced [9,10,24]. Hence, an interaction of these antibodies with 3,4-DAP and Amifampridine could cause an exacerbation of side effects, such as seizures [9]. Moreover, the cancer treatment should be a priority [38], and after tumor remission, a first line therapy treatment may be continued [43].

Lastly, during the world COVID-19 pandemic, LEMS treatment should not be stopped. There are only a few specific cases where interruption or delay in treatment is indicated. However, close monitoring for updates is advised, as recommendations are susceptible to change [52].

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