e-ISSN: 2807-7970
doi: 10.20473/aksona.v5i1.56359

AKSONA

Volume 5 Number 1, January 2025

Lambert-Eaton Myasthenic Syndrome: A Review of Rare Neuromuscular Disease Related to Paraneoplastic and Autoimmune

Ichlasul Mahdi Fardhani[1], Cindy Graciella[1], Muhammad Isra Rafidin Rayyan[1]
[1] Faculty of Medicine, Universitas Jember, Jember, Indonesia

Article info

Article History:
Received Mar 27, 2024
Revised Oct 20, 2024
Accepted Dec 5, 2024
Published Jan 29, 2025

Keywords:
Autoimmune
Lambert-Eaton myastenic syndrome
Neuromuscular disease
Paraneoplastic

ABSTRACT

A rare condition known as Lambert-Eaton myasthenic syndrome (LEMS) affects the neuromuscular junctions, which are the connections between muscles and nerves. Tumor-associated or autoimmune causes trigger this condition. This mechanism depends on the presence of antibodies that directly attach to voltage-gated calcium channels located on the presynaptic nerve terminals. LEMS disease is divided into non-paraneoplastic or non-tumor LEMS (NT-LEMS) and paraneoplastic LEMS (P-LEMS). NT-LEMS is believed to be caused by an autoimmune process. On the other hand, P-LEMS has an underlying tumor, and LEMS symptoms are paraneoplastic manifestations of the tumor. Clinical signs of LEMS include proximal muscle weakness, autonomic dysfunction, and decreased deep tendon reflexes. The predominant sign of LEMS is weakness of the lower extremities. The defining characteristic of LEMS is a weakness that spreads from caudal to cranial, causing oculobulbar manifestations, and from proximal to distal, potentially involving the feet and hands. The diagnosis of LEMS depends on clinical, electromyographic, and serological findings of anti-VGCC antibodies. Therefore, comprehensive oncologic screening and monitoring should promptly follow a diagnosis of LEMS. The standard approach to treating LEMS symptoms is administering drugs that improve neurotransmission, such as potassium channel blockers and amifampridine. In refractory cases, immunosuppressants or immunomodulator agents, such as a combination of prednisone and azathioprine, are used. If a tumor is detected, oncological therapy should be a priority.

Corresponding Author
Ichlasul Mahdi Fardhani
Faculty of Medicine, Universitas Jember, Jember, Indonesia
email: dionichsl@gmail.com

INTRODUCTION

The rare disorder, Lambert-Eaton Myasthenic Syndrome (LEMS), affects the neuromuscular junction (NMJ), which connects the muscles and nerves. A cohort study in the Netherlands and the United States estimated the prevalence at approximately 3.3–3.4 cases per million individuals. Symptoms typically appear between the ages of 55 and 60.[1] Up to 50% of cases are classified as P-LEMS, a paraneoplastic form associated with malignant tumors originating from small cell lung cancer (SCLC). Other cases are autoimmune (NT-LEMS) and commonly coexist with other disorders.[2]

In order to find LEMS, antibodies bind directly to voltage-gated calcium channels (VGCC) in the presynaptic nerve terminal. VGCC facilitates calcium entrance to nerve terminals. This increased number of incoming signals triggers presynaptic signaling pathways. Acetylcholine (ACh) is released when VGCC antibodies prevent calcium from entering the cell. Presynaptic compensatory mechanisms initiate this process. Less ACh release in the synaptic gap manifests as Mmuscle weakness in the proximal extremities and problems with the autonomic nervous system.[3]

The clinical triad usually includes proximal muscular weakness, autonomic abnormalities, and areflexia. Though subacute episodes occur infrequently, the onset is usually subtle and gradual. Initial symptoms included leg weakness (60%), general weakness (18%), muscle discomfort or stiffness (5%), dry mouth (5%), arm weakness (4%), diplopia (4%), and dysarthria (2%). Muscle weakness was found in 96% of the 227 patients with LEMS, especially in the legs. Oculobulbar symptoms were reported in 51% of patients, while 49% reported autonomic symptoms. Respiratory symptoms were seen in 16% of the patients, while 15 reported sensory symptoms.[4]

Until now, there has been no specific treatment for LEMS patients. Patients with LEMS are treated based on their symptomatic symptoms, and if LEMS manifests as a paraneoplastic syndrome, they receive oncological treatment.[5] Establishing a diagnosis of LEMS is crucial for providing appropriate therapy and detecting the risk of malignancy in LEMS. Given that LEMS is a rare neurological disease with fluctuating symptoms, delays and errors in diagnosis often occur.[6,7,8] Neuromuscular diseases, including myasthenia gravis, often misdiagnose LEMS. LEMS can appear idiopathically, although it is most often the result of a paraneoplastic syndrome with SCLC.[9] This review aimed to help medical doctors recognize pathophysiology, clinical features, and diagnostic procedures, as well as provide an overview of treatment options based on current treatment findings.

REVIEW

Eligibility criteria

LEMS has a global prevalence of 5 per 1,000,000 people, which is 46 times lower than myasthenia gravis. In the last ten years, there have been two published epidemiological studies on this condition.[10,11] According to a survey by Ebenroth et al. on United States Army War Veterans (USA VA), the point prevalence of LEMS was estimated at 2.6–3.3 per 1,000,000 population.[10] Meanwhile, an epidemiological study in Japan by Yoshikawa et al. found that the prevalence of LEMS was 2.7 (95% CI 1.9–3.5) in a population of 1,000,000. SCLC is commonly associated with LEMS; around 50% of LEMS patients are also diagnosed with SCLC-type lung cancer.[11]

Etiology

Lambert-Eaton Myasthenic Syndrome is divided into two categories: paraneoplastic and non-paraneoplastic. An autoimmune mechanism is believed to cause the non-paraneoplastic category, also known as NT-LEMS (non-tumor LEMS). In contrast, paraneoplastic LEMS (P-LEMS) is associated with malignant disease.[12] A tumor is the main cause of LEMS in about 60% of cases, and the paraneoplastic type of LEMS is mostly linked to SCLC. Several types of cancer, such as mixed-type lung carcinoma, non-SCLC, thymoma, prostate cancer, and lymphoproliferative disease, can happen at the same time as this illness.[8,12] The development of LEMS is helped by the fact that cancer patients make too many antibodies against voltage-gated calcium channels (VGCC). Approximately 85% to 90% of LEMS patients tested positive for anti-VGCC. In LEMS patients with SCLC, this number was closer to 100%. All patients with LEMS linked to SCLC had a prolonged smoking history, but only half of LEMS-related patients did. [13,14]

Several gene loci, though to be associated with disease emergence, link to non-paraneoplastic LEMS disease. On antibody examination, around 65% of autoimmune-related LEMS patients had the HLA-B8 gene locus. LEMS patients have other gene loci, including HLA-DR3, HLA-DQ2, and HLA-A1. Apart from these antibodies, non-paraneoplastic LEMS patients also suffer from immune-related diseases, like thyroid disease and type 1 diabetes mellitus.[15,16]

Pathophysiology

The neuromuscular junction is the leading site of disruption in LEMS disease, where calcium ions play an essential role. Physiologically, a neuromuscular junction is a connection, or synapse, that lets action

potentials from motor neurons reach motor end plates and cause muscles to contract.[17] When there is a depolarization in the presynaptic nerve membrane, an action potential starts. This makes presynaptic transmission possible.[18] The depolarization process opens up the VGCC, which makes it easier for calcium ions to reach the motor nerve terminals. This causes a lot of the neurotransmitter acetylcholine (Ach) to be released into the neuromuscular junction. Then, the ACh molecule binds to its receptor on the postsynaptic membrane of the motor end plate. This process causes the opening of sodium and potassium channels at the postsynapse. Finally, cations can enter through these channels and cause depolarization of the motor end plate. This depolarization, in turn, causes the emergence of an action potential and results in muscle contraction.[17,18]

LEMS disease has two main pathways, which are divided based on their etiologies: paraneoplastic and autoimmune.[19] In paraneoplastic etiology, the occurrence of LEMS is closely related to the presence of malignant disease. The function of the VGCC is impaired by antibodies generated by the body in response to tumor cells that express antigens against this pathway. Anti-Sry-like high-mobility group box 1 (SOX1) antibodies or anti-glial nuclear antibodies (AGNA) are immunogenic antigens that are mostly produced by malignant cells. As a result, these antigens can act like each other, which lets IgG antibodies cross-link the surface of VGCC channels.[8] More specifically, this antibody explicitly targets the P/Q subtype of VGCC. Approximately 85% of LEMS patients show positive test results for type P/Q VGCC antibodies. These antibodies may also target N- and L-type VGCC channels, M1 muscarinic acetylcholine receptors, and synaptotagmin, which has been seen sometimes in LEMS disease.[8,14,20] Autonomic symptoms in LEMS disease are caused by antibodies that target VGCC channels other than the P/Q type.[5] It is estimated that approximately 60% of LEMS patients also suffer from malignancy, the majority being SCLC. LEMS is also sometimes found in other types of cancer, like mixed-type lung carcinoma, non-SCLC, thymoma, prostate cancer, and lymphoproliferative disorders.[8]

The autoimmune pathway is believed to be the second mechanism underlying the development of LEMS. It is believed that Individuals without cancer exhibit a genetic tendency toward HLA and LEMS genotypes. HLA (human leukocyte antigen), a cell surface protein, regulates the human immune system. However, the mechanism behind the degradation of these proteins and subsequent antibody generation remains unknown.[21] Approximately 65% of NT-LEMS patients are estimated to have HLA-B8 positivity, while 50% test positive for HLA-A1. The same frequency is observed for HLA-DQ2 and HLA-DR3.[13,22]

Clinical manifestations

Proximal muscle weakness, autonomic dysfunction, and decreased deep tendon reflexes are the three main signs of LEMS disease.[8] The most common symptom of LEMS disease is weakness in the lower extremities. LEMS disease is characterized by weakness that spreads from caudal to cranial, causing oculobulbar manifestations, and from proximal to distal, affecting the feet and hands. Usually, the weakness is symmetrical. In contrast, myasthenia gravis (MG), a neuromuscular junction disorder, is common, with weakness starting in the craniobulbar area and progressing caudally. The weakness in LEMS patients comes gradually, but in some cases, it can appear more quickly.[4,17] Symptoms of weakness in the extremities develop more clearly and quickly in P-LEMS patients than in NT-LEMS. P-LEMS patients experience weakness in their proximal legs and arms three months following symptoms. In contrast, most NT-LEMS patients only experience weakness in their proximal legs.[15]

Other symptoms of LEMS include muscle pain or stiffness, dry mouth, postural hypotension, erectile dysfunction, constipation, palpitations, diplopia, dysphagia, and dysarthria.[4] Young and Leavit did a study that looked back at medical records from LEMS patients. They found that ptosis (23%) and diplopia (23.5%) are the most common signs of oculobulbar weakness in LEMS patients who also have cranial nerve disorders. Oculobulbar symptoms usually do not appear at first but occur when the patient has experienced severe limb muscle weakness.[4,23]

In autonomic disorders, the most common complaint is dry mouth. Other disorders that can arise are difficulty urinating, erectile dysfunction, constipation, and dry eyes. Autonomic disorders appear in approximately 80–96% of patients.[13]

Decreased tendon reflexes, or areflexia, are signs often found during physical examination in LEMS patients. When LEMS patients go through post-exercise facilitation, muscle strength and tendon reflexes return to normal because of muscle contractions. This can lead to a wrong interpretation when looking at tendon reflexes. Approximately 40% of LEMS patients may experience these symptoms, so tendon reflex examination should be done after rest.[17,24] Sensory disturbances, limbic encephalitis, and cerebellar ataxia are among the less common symptoms. The appearance of these findings indicates a link with paraneoplastic incidents.[4,24]

Differential diagnosis

Despite its rarity, LEMS is an important differential diagnosis to consider when diagnosing

neuromuscular junction disease in neurological clinical practice. LEMS' clinical manifestations frequently overlap with those of other myasthenic syndromes. A cohor study found that 58% of 241 patients with LEMS from the Netherlands or England initially received a misdiagnosed. Myasthenia gravis was the most common diagnosis (21%), followed by unspecified myopathy (11%), polyradiculopathy or polyneuropathy (3%), and psychosomatic depression (4%). In some existing literature, LEMS and MG can appear simultaneously, making diagnosis more difficult.[4,6] Symptoms of LEMS are similar to those of neuropathies such as amyotrophic lateral sclerosis (ALS) and Guillain-Barre syndrome (GBS). In LEMS, symptoms that can help confirm the diagnosis include the disease getting worse, muscles getting weaker from proximal to distal and caudocranial areas, symmetrical weakness symptoms, and fluctuating levels of symptom severity. Patients may also experience prominent autonomic problems and cerebellar ataxia. Prominent pain and sensory symptoms are rare.[6,9]

Table 1. Comparison of characteristics of LEMS with MG and GBS[13,17,25]

	LEMS	MG	GBS
Defect location	Presynaptic	Postsynaptic	Peripheral nerves
Motor symptoms	Weakness spreads from caudal to cranial and from proximal to distal. Weakness can improve with repetition	Weakness occurs due to fatigue and exercise. Weakness mainly occurs in the extraocular muscles. Weakness improves if the patient rests	Ascending muscle weakness and usually symmetrical
Autonomic symptoms	Dry mouth	No symptoms	Fluctuating blood pressure and pulse (labile)
Sensory symptoms	Not found	Not found	Found in 50% of patients as a sensation of paresthesia
Deep tendon reflexes	Normal	Normal	Hyporeflexia to areflexia
Antibody	AntiVGCC at the presynaptic	AntiAch at postsynaptic	Anti-GM1, Anti-GD1a, Anti-GQ1B
RNS			
- CMAP at rest	Low	Normal	Normal or slightly decreased
- CMAP after brief exercise	Increase response	No change	Significant increase response
- LRS	Decrease response	Decrease response	No decrease response or stable
- HRS	Increase response	Decrease response or normal	Increase response
EMG(fasciculations/fibrillations)	Not found	Not found	Found
Tumor	SCLC (50%)	Thymoma (16%)	No tumor

Diagnosis

Look at the patient's symptoms and use the LEMS disease triad to figure out if they have LEMS. This triad includes weak proximal muscles, problems with autonomic function, and decreased tendon reflexes. People who are clinically thought to have LEMS can get more tests to confirm the diagnosis, such as repetitive nerve stimulation (RNS), electromyography (EMG), and an autoantibody serological examination (anti-VGCC antibodies). These tests help establish the diagnosis.[6,22]

1. Repetitive Nerve Stimulation (RNS)

Lambert and Eaton found symptoms that are typical of LEMS during the RNS exam. These symptoms have since become pathognomonic signs that help find the patient with LEMS. There are three classic findings typical of LEMS on RNS examinations, including: (1) On motor nerve conduction studies, there is a significant reduction in the amplitude of the compound muscle action potential (CMAP) (< 50%). It is common for this to happen, and it does in 96% of cases of LEMS and all presynaptic neuromuscular junction disorders; (2)

When the RNS is stimulated with a low frequency (2-5 Hz), the CMAP response shows down, and the CMAP amplitude also gradually decreases. A decrease of more than 10% can be suspected as LEMS. Approximately 94-98% of those diagnosed with LEMS exhibit this finding; (3) In conditions after voluntary muscle contraction for 10-30 seconds, there is an increase in the CMAP response of up to 100%. This condition is also known as post-exercise facilitation. A very high increase in response also occurs during RNS stimulation with a frequency of 20-50 Hz.[9,25,26]

The CMAP response to low-frequency RNS stimulation goes down because of the neurotransmitter ACh levels drop in the synaptic cleft. Sanders et al. found that with repeated stimulation in LEMS, the pattern of CMAP decreasing with low-frequency RNS stimulation was more obvious. However, it was less evident in myasthenia gravis how repetitive low-frequency stimulation led to a decrease in CMAP.[26] Increase calcium ions cause a CMAP response that is up to 100% higher after short periods of voluntary exercise compared to rest. As a result, the release of the neurotransmitter ACh into the synaptic cleft also increases. The difference in training duration of 10 seconds compared to 30 seconds affects the sensitivity and specificity of the RNS examination. The sensitivity and specificity of the 10-second training are 97% and 99%, respectively, while the 30-second training has a lower level.[9,27]

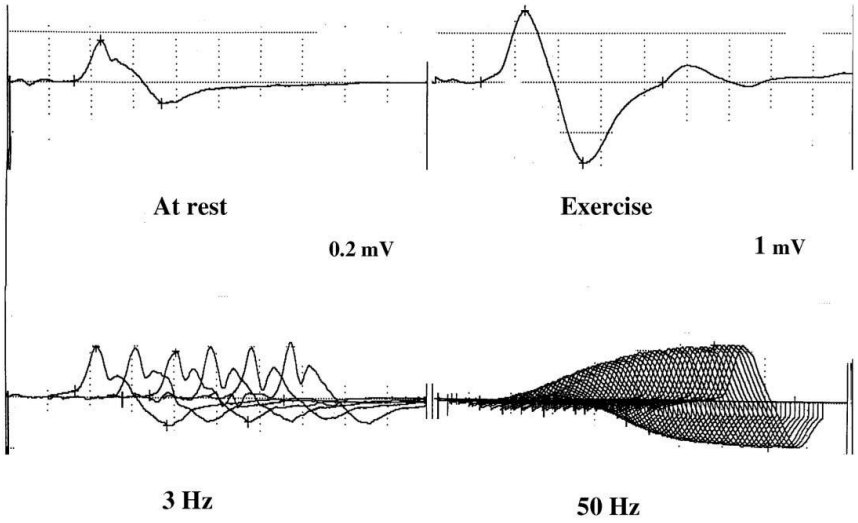

Figure 1. Classic triad pattern of RNS in LEMS. With a low CMAP of 0.28 mV at rest and a 217% decrease in low-rate stimulation (LRS) at 3 Hz. There is significant facilitation, with post-exercise facilitation (PEF) at +1030% and high-rate stimulation (HRS) at +1043%.[25]

2. Electromyography (EMG)

On the RNS exam, there may also be abnormal findings in other neuromuscular diseases. To help rule out diseases that cause other proximal muscle weaknesses, like myopathy and radiculopathy, a conventional needle electromyography (EMG) test can be used. On the RNS exam, there may also be abnormal findings in other neuromuscular diseases. To help rule out diseases that cause other proximal muscle weaknesses, like myopathy and radiculopathy, a conventional needle electromyography (EMG) test can be used. The single-fiber EMG examination reveals increased jitter and resistance to transmission. An increase in jitter indicates an obstacle in transmitting action potentials from the neuromuscular junction to the end of the motor plate so that muscle contraction is hampered. Barriers to transmission are thought to be related to the severity of LEMS disease.[4,27]

3. Serological Examination

P/Q type anti-VGCC antibodies are one component that is strongly suspected of being implicated in the pathophysiology of LEMS. The presence of antibodies that induce damage to VGCC supports the diagnosis of LEMS. P/Q type anti-VGCC antibodies are highly sensitive; 90% of patients with paraneoplastic and autoimmune LEMS have these antibodies, and the number raises to 100% for paraneoplastic types of LEMS. The low specificity (36%) of this antibody test is one of its weaknesses. Antibodies against VGCC have been detected sporadically in healthy individuals and some patients with autoimmune and other paraneoplastic disorders.[4,20]

VGCC type N antibodies are also the second most prevalent antibodies found in LEMS patients (33–49%), especially those associated with primary lung malignancies. If N-type antibodies are identified, the likelihood of an additional underlying malignancy increases. These antibodies can also be found together with P/Q-type anti-VGCC antibodies, a phenomenon known as cross-reactivity.[20] Another antibody

detected in LEMS patients is the SOX1 antibody. It is reported that around 64% of LEMS patients with SCLC are positive for this antibody. Anti-SOX1 antibodies are immunogenic tumor antigens in SCLC. Positive findings for these antibodies suggest that patients with SCLC will develop LEMS in the future. The anti-SOX1 antibody has 95% specificity for LEMS associated with SCLC. However, the sensitivity is only 65% because this antibody is also seen in most patients with other paraneoplastic neurological disorders, as well as SCLC patients without LEMS.[28]

Management

In cases with LEMS associated with malignancy, such as SCLC, the underlying malignancy must be treated first. There is currently no treatment that can cure LEMS. Therefore, the main focus of managing LEMS patients is to reduce or eliminate symptoms. However, the most effective and theoretically sound interventions aim to increase presynaptic ACh release.[4,8]

1. Amifampridine or 3,4-diaminopyridine (3,4-DAP)

Amifampridine is being used as the first-line treatment for LEMS symptoms. The U.S. Food and Drug Administration (FDA) approved amifampridine phosphate (Firdapse) tablets in late 2018 as the first medicine to treat LEMS in adults over the age of 17. Amifampridine phosphate is a salt form of 3,4-DAP. It works by blocking voltage-gated potassium channels in motor nerve terminals. This causes prolonged depolarization, which lets damaged VGCCs stay open, an influx of calcium ions. Increased intracellular calcium further increases exocytosis of acetylcholine-containing vesicles and enhances impulse transmission at central, autonomic, and neuromuscular synapses.[29,30,31]

Shieh *et al*. did a phase 3 clinical trial in 2019 to evaluate the safety and efficacy of amifampridine phosphate in the treatment of LEMS symptoms. [31] This study used a randomized, double-blind, withdrawal, and controlled trial design, which was done in 3 different locations in the United States. Prior to the study, all participants had received amifampridine at a dose (three or four doses per day, 30–80 mg) with a stable frequency for one week before randomization. Next, 26 participants who met the criteria were randomly assigned to receive amifampridine phosphate (at the optimal dose) or placebo in a 1:1 ratio. The amifampridine phosphate group did better than the controls on day four in terms of the subject global impression (SGI) and quantitative myasthenia gravis (QMG) scores. In this study, the mifampridine phosphate group also did much better on other efficacy measures, such as clinical global impression-improvement (CGI-I), triple timed up and go (3TUG), and QMG extremity domain scores. During the four days of study, only three patients (23.08%) in the amifampridine phosphate group reported side effects; one patient each experienced back pain, extremity pain, and mild headache.[32]

For adults, the starting dose of amifampridine should be 15–30 mg taken orally three to four times daily. Generally, the dose can be increased by 5 mg daily every 3–4 days until optimal response is achieved. Based on the FDA's approval, the maximum dose can be 20 mg taken once or 80 mg taken daily.[23]

2. Acetylcholinesterase inhibitors

AChE inhibitors usually do not significantly improve LEMS, although they may improve dry mouth. As an acetylcholinesterase inhibitor, pyridostigmine can be used to help treat LEMS patients, though it doesn't work as well as it does for myasthenia gravis patients. However, its limited benefits, rapid action, favorable safety profile, wide accessibility, and cost-effectiveness make it a viable option for certain individuals. The recommended pyridostigmine dose for LEMS patients is 30–60 mg three to four times per day. Side effects of pyridostigmine are mild, such as nausea, abdominal cramps, and diarrhea.[4,22,30]

3. Guanidine

Guanidine is approved as a first-line treatment for LEMS, although use is limited due to its high toxicity. Guanidine enhances acetylcholine secretion in response to nerve stimulation. Furthermore, this medicine can slow down the depolarization and repolarization of the plasma membrane of muscle cells. Assume that amifampridine is unavailable or cannot be tolerated. In this case, administration of guanidine, either alone or in combination with pyridostigmine at moderate doses (1000 mg/day), may be recommended due to its toxicity profile. Common side effects include nephrotoxicity and gastrointestinal problems include anorexia, diarrhea, gastric irritation, and bone marrow failure.[2,22]

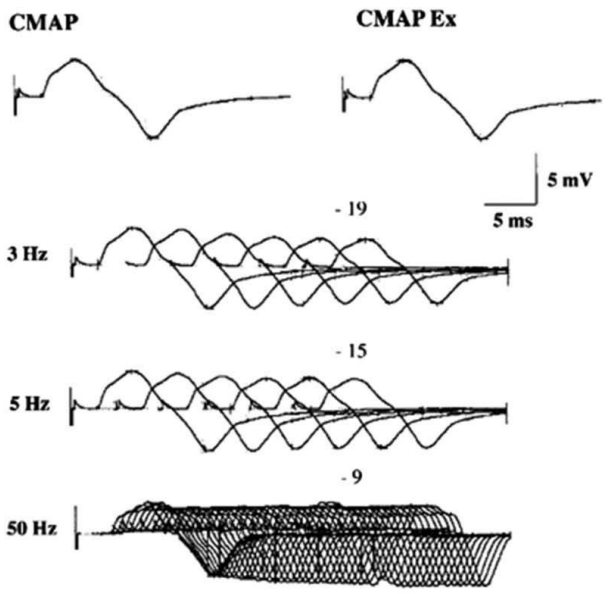

Figure 2. The most common abnormal pattern of RNS in MG. Shows an abnormal RNS pattern with a normal CMAP of 0.4 mV at rest and no increase after exercise. LRS decreases by 215-219% at 3 and 5 Hz while remaining stable at HRS (50Hz)

4. Immunomodulator

Immunomodulators may be able to target the immune system in patients with refractory weakness to acetylcholine-elevating agents. This is because the immune system has played an important role in showing resistance to treatment.[33]

5. Intravenous immunoglobulin (IVIG)

IVIG is a first-line treatment option for those who do not respond to other therapies. Although its exact mechanism of action remains unclear, it is widely assumed to include the neutralization of autoantibodies and the regulation of autoreactive B cells. IVIG in a general regimen (total dose of 2 g/kg for 2–5 days) has been used successfully to treat a variety of immune-mediated neurological diseases. A 4- to 12-week maintenance regimen with repeated infusions is also valuable for patients who respond well to IVIG therapy. This treatment can cause issues and mild side effects such as laboratory abnormalities, rash, headache, and, in rare cases, deep vein thrombosis.[2,8,16,23]

6. Steroids and Immunosuppressive Agents

Long-term oral immunosuppression with prednisolone and azathioprine is usually recommended for patients whose LEMS symptoms do not respond well to symptomatic therapy. The recommended dose of prednisone is 1–1.5 mg/kg daily. After recovery, the dose may be reduced according to the patient's clinical condition. At the same time, the dosage of azathioprine can be started at 50 mg twice a day and increased to a total dose of 2–3 mg/kg/day.[2,8,29]

7. Rituximab

Rituximab is an anti-CD20 monoclonal antibody used to manage lymphoproliferative and autoimmune conditions. Rituximab works by inducing cytotoxicity in B cells. As a result, this process effectively blocks the immunological response mediated by this specific pathway. This medication is recommended when other immunosuppressive agents do not provide an adequate clinical response. The standard dose for LEMS patients is 375 mg/m^2 body surface once a week for four weeks, followed by monthly dosing for the next two months. However, data to support its broader application still needs to be provided.[2,8,34]

8. Plasma Exchange

Traditionally, therapeutic plasma exchange (TPE) has been used to remove autoantibodies, abnormal proteins, immune complexes, or toxins from patient plasma that are thought to be harmful.[35] This medicine has minimal efficacy for LEMS patients, but when combined with other immunosuppressive drugs, it may benefit certain patients. In patients with myasthenia gravis (MG), five plasma exchanges within 7–14 days are advised. However, there is no current recommendation for LEMS. Because the pathophysiology of both disorders is similar, it is recommended that the same procedure be used in LEMS as well.[2,8,16,29]

Risk of Malignancy

As a result of the strong association between LEMS and malignancy, screening for malignant conditions should be done as soon as LEMS is diagnosed. LEMS malignancy screening consists of two steps. The first step is a study that uses chest computed tomography (CT) or magnetic resonance imaging (MRI) as the initial imaging screening to identify the malignant part of the LEMS. If the results of the first step are negative, we proceed to the second step, which includes positron emission tomography (PET) as an additional screening test. If a negative result is detected during the first screening, the test must be continued and repeated every 3–6 months for at least two years. High-risk patients, those with a positive anti-SOX1 antibody test or a Dutch-English LEMS Tumor Association Prediction (DELTA-P) score more than two, must be monitored quarterly.[16]

DELTA-P is a simple clinical assessment based on age, weight loss, smoking history, bulbar symptoms, erectile dysfunction, and Karnofsky activity. The interpretation of this score is 0.2–6% for

DELTA-P 0-1 and 83.9–100% for DELTA-P 3-6. This scoring system may assist clinicians in identifying and monitoring LEMS patients at high risk for malignancy, particularly SCLC.[8,35]

Prognosis

Patients with LEMS often have a lower quality of life due to autonomic nerve weakening and pharmacological side effects. However, an LEMS prognosis combined supportive and immunosuppressive therapy can enhance quality of life. After a year of treatment, LEMS patients' quality of life improved by 85%. The prognosis of paraneoplastic LEMS is determined on the underlying cancer. Meanwhile, the prognosis for non-paraneoplastic LEMS is similar to that of the general population.[8]

Complications

LEMS complications can be grouped into two: those related to pathophysiology and those relaed to therapy. Complications of LEMS include weakness, such as falls, broken bones, and aspiration pneumonia. Furthermore, autonomic nerve involvement causes symptoms such as dry mouth, constipation, dysphagia, and erectile dysfunction, which ultimately leads to weight loss and emaciation. LEMS therapeutic complications are associated with drug side effects. Immunosuppressive medications can result in cytopenias and infections. 3,4-DAP is associated with symptoms of tingling and numbness.[8]

CONCLUSION

Lambert Eaton's myasthenic syndrome, a rare autoimmune or paraneoplastic etiology, is caused by a decrease in in the neurotransmitter AcH in the presynaptic cleft. Despite its rarity, LEMS is the major differential diagnosis of neuromuscular disease. Clinical symptoms of LEMS include proximal muscle weakness, autonomic dysfunction, and decreased deep tendon reflexes. Lower limb weakness is a significant symptom of LEMS, as is caudal weakness radiating to the skull. LEMS is diagnosed using clinical, electromyographic, and serological manifestations of anti-VGCC antibodies. The standard approach to treating LEMS symptoms is to deliver neurotransmission-enhancing medications such as potassium channel blockers and amifampridine. In immune cases, immunosuppressants or immunomodulators can be used. When tumors are detected in LEMS patients, oncology therapy is the first priority.

Acknowledgement

Appreciation is given to all authors who helped complete this article from writing to publication.

Conflict of Interest

The authors reported no conflicts of interest in writing this article.

Funding

This review did not receive a specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author Contributions

IMF prepared the abstract, introduction, and correction of the article. CG and MIRR helped collect data for the article review.

REFERENCES

1. Lehnerer S, Herdick M, Stegherr R, Gerischer L, Stascheit F, Stein M, et al. Burden of disease in Lambert-Eaton myasthenic syndrome: Taking the patient's perspective. *J Neurol*. 2024; 271(5):2824-39. doi: 10.1007/s00415-024-12206-6
2. Ivanovski T, Miralles F. Lambert-Eaton Myasthenic syndrome: Early diagnosis is key. *Degener Neurol Neuromuscul Dis*. 2019: 27-37. doi: 10.2147/dnnd.s192588
3. Meriney SD, Tarr TB, Ojala KS, Wu M, Li Y, Lacomis, et al. Lambert–Eaton myasthenic syndrome: Mouse passive-transfer model illuminates disease pathology and facilitates testing therapeutic leads. *Ann N Y Acad Sci*. 2018; 1412(1):73-81. doi: 10.1111/nyas.13512
4. Kesner VG, Oh SJ, Dimachkie MM, Barohn RJ. Lambert-Eaton myasthenic syndrome. *Neurol Clin*. 2018; 36(2):379-94. doi: 10.1016/j.ncl.2018.01.008
5. Tarr TB, Wipf P, Meriney SD. Synaptic pathophysiology and treatment of Lambert-Eaton myasthenic syndrome. *Mol Neurobiol*. 2015; 52(1):456-63. doi: 10.1007/s12035-014-8887-2
6. Schoser B, Eymard B, Datt J, Mantegazza R. Lambert–Eaton myasthenic syndrome (LEMS): A rare autoimmune presynaptic disorder often associated with cancer. *J Neurol*. 2017; 264(9):1854-63. doi: 10.1007/s00415-017-8541-9
7. Mansukhani SA, Bothun ED, Diehl NN, Mohney BG. Incidence and ocular features of pediatric myasthenias. *Am J Ophthalmol*. 2019; 200:242-49. doi: 10.1016/j.ajo.2019.01.004
8. Jayarangaiah A, Lui F, Kariyanna PT. Lambert-Eaton myasthenic syndrome. In: StatPearls. StatPearls Publishing; 2023. [Book]
9. Murai H. The Japanese clinical guidelines 2022 for myasthenia gravis and Lambert-Eaton myasthenic syndrome: An overview. *Brain Nerve = Shinkei Kenkyu no Shinpo*. 2024; 76(1):7-12. doi: 10.11477/mf.1416202551
10. Abenroth DC, Smith AG, Greenlee JE, Austin SD, Clardy SL. Lambert–Eaton myasthenic syndrome: Epidemiology and therapeutic response in the national veterans affairs population. *Muscle Nerve*. 2017; 56(3):421-26. doi: 10.1002/mus.25520
11. Yoshikawa H, Adachi Y, Nakamura Y, Kuriyama N, Murai H, Nomura Y, et al. Nationwide survey of Lambert-Eaton myasthenic syndrome in Japan. *BMJ Neurol Open*. 2022; 4:e000291. doi: 10.1136/bmjno-2022-000291
12. Graus F, Vogrig A, Muñiz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflammation*. 2021; 8(4):e1014. doi: 10.1212/NXI.0000000000001014

13. Nicolle MW. Myasthenia gravis and Lambert-Eaton myasthenic syndrome. *Contin Lifelong Learn Neurol*. 2016; 22(6):1978-2005. doi: 10.1212/CON.0000000000000415
14. Bekircan-Kurt CE, Çiftçi ED, Kurne AT, Anlar B. Voltage gated calcium channel antibody-related neurological diseases. *World J Clin Cases WJCC*. 2015; 3(3):293. doi: 10.12998/wjcc.v3.i3.293
15. González CS, Vivero CM, Castro JL. Paraneoplastic syndromes review: The great forgotten ones. *Crit Rev Oncol Hematol*. 2022; 174:103676. doi: 10.1016/j.critrevonc.2022.103676
16. de Souza FF, Trevisani JP, dos Reis FI. Clinical, pathophysiological and electrodiagnostic aspects of Lambert-Eaton myasthenic syndrome. In: Topics in Autonomic Nervous System. *IntechOpen*; 2023. doi: 10.5772/intechopen.111700
17. Rodríguez Cruz PM, Cossins J, Beeson D, Vincent A. The neuromuscular junction in health and disease: Molecular mechanisms governing synaptic formation and homeostasis. *Front Mol Neurosci*. 2020; 13:610964. doi: 10.3389/fnmol.2020.610964
18. Muñiz-Castrillo S, Vogrig A, Honnorat J. Associations between HLA and autoimmune neurological diseases with autoantibodies. *Autoimmun Highlights*. 2020; 11(1):2. doi: 10.1186/s13317-019-0124-6
19. Zalewski NL, Lennon VA, Lachance DH, Klein CJ, Pittock SJ, Mckeon A. P/Q-and N-type calcium-channel antibodies: Oncological, neurological, and serological accompaniments. *Muscle Nerve*. 2016; 54(2):220-7. doi: 10.1002/mus.25027
20. Hemati M, Esmaeli NS, Asadi S. The role of mutations on HLA genes in Lambert-Eaton myasthenic syndrome. *Ann Case Rep*. 2021; 6:710. doi: 10.29011/2574-7754.100710
21. Young JD, Leavitt JA. Lambert–Eaton myasthenic syndrome: Ocular signs and symptoms. *J Neuro-ophthalmology*. 2016; 36(1):20-2. doi: 10.1097/WNO.0000000000000258
22. Bispo BA, Aguiar PHSP de, Caso AC, Pedreira M de S, Cursius MU, Aguiar PHP de, et al. Management and pathophysiology of meningiomas during pregnancy. Literature review and case report. *JBNC - J Bras Neurocir*. 2022; 32(4):379-88. doi:10.22290/jbnc.v32i4.1989
23. Li H, Zhang A, Hao Y, Guan H, Lv Z. Coexistence of Lambert–Eaton myasthenic syndrome and autoimmune encephalitis with anti-CRMP5/CV2 and anti-GABAB receptor antibodies in small cell lung cancer: A case report. *Medicine (Baltimore)*. 2018; 97(19):e0696. doi: 10.1097/MD.0000000000010696
24. Merino-Ramírez MÁ, Bolton CF. Review of the diagnostic challenges of Lambert–Eaton syndrome revealed through three case reports. *Can J Neurol Sci*. 2016; 43(5):635-647. doi: 10.1017/cjn.2016.268
25. Oh SJ. Distinguishing features of the repetitive nerve stimulation test between Lambert–Eaton myasthenic syndrome and myasthenia gravis, 50-year reappraisal. *J Clin Neuromuscul Dis*. 2017; 19(2):66-75. doi: 10.1097/CND.0000000000000190
26. Sanders DB, Cao L, Massey JM, Juel VC, Hobson-Webb L, Guptill JT. Is the decremental pattern in Lambert–Eaton syndrome different from that in myasthenia gravis? *Clin Neurophysiol*. 2014; 125(6):1274-7. doi: 10.1016/j.clinph.2013.11.007
27. Sun X, Tan J, Sun H, Liu Y, Guan W, Jia J, Wang Z. Anti-SOX1 antibodies in paraneoplastic neurological syndrome. *J Clin Neurol*. 2020; 16(4):530-46. doi: 10.3988/jcn.2020.16.4.530
28. Bodkin C, Pascuzzi RM. Update in the management of myasthenia gravis and Lambert-Eaton myasthenic syndrome. *Neurol Clin*. 2021; 39(1):133-46. doi: 10.1016/j.ncl.2020.09.007
29. Pascuzzi RM, Bodkin CL. Myasthenia gravis and Lambert-Eaton myasthenic syndrome: New developments in diagnosis and treatment. *Neuropsychiatr Dis Treat*. 2022: 3001-22. doi: 10.2147/ndt.s296714
30. Yoon CH, Owusu-Guha J, Smith A, Buschur P. Amifampridine for the management of Lambert-Eaton myasthenic syndrome: A new take on an old drug. *Ann Pharmacother*. 2020; 54(1):56-63. doi: 10.1177/1060028019864574
31. Shieh P, Sharma K, Kohrman B, Oh SJ. Amifampridine phosphate (Firdapse) is effective in a confirmatory phase 3 clinical trial in LEMS. *J Clin Neuromuscul Dis*. 2019; 20(3):111-9. doi: 10.1097/cnd.0000000000000239
32. Bakker WR, Remijn-Nelissen L, Schimmel K, Tannemaat M, Verschuuren J, van Gelder T. Pharmacological treatment of Lambert-Eaton myasthenic syndrome. *RRNMF Neuromuscul J*. 2023; 4(3). doi: 10.17161/rrnmf.v4i3.19550
33. Wiendl H, Abicht A, Chan A, Marina DA, Hagenacker T, Hekmat K, et al. Guideline for the management of myasthenic syndromes. *Ther Adv Neurol Disord*. 2023; 16:17562864231213240. doi: 10.1177/17562864231213240
34. Rohrer L, Yunce M, Montine TJ, Shan H. Plasma exchange in Alzheimer's disease. *Transfus Med Rev*. 2023;37(1):10-15.
35. Maddison P, Lipka AF, Gozzard P, Sadalage G, Ambrose PA, Lang B, et al. Lung cancer prediction in Lambert-Eaton myasthenic syndrome in a prospective cohort. *Sci Rep*. 2020; 10(1):10546. doi: 10.1038/s41598-020-67571-9