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Lambert-Eaton Myasthenic Syndrome Unmasked by Administration of Aggravating Medications

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Abstract We present a case of an elderly female patient presenting with symptoms strongly suggestive of Myasthenia Gravis (MG), but later serological workup was shown to be more consistent with Lambert Eaton Myasthenic Syndrome (LEMS). On presentation, the patient had both profound ptosis and generalized weakness of the upper and lower extremities that were suspected clinically to be due to MG. The case was further complicated by the administration of several medications, which were believed to have unmasked her disease. Diagnostic imaging to assess for thymoma and lung cancer was negative. Screening with the ice-pack test was positive; however, serology for MG was negative. This case illustrates the importance of keeping the differential of LEMS in view in every suspected MG case, even if there is a low suspicion of LEMS initially. In addition, it demonstrates the possibility that the "ice-pack test" can also be positive in LEMS, and MG-unmasking medications may also unmask LEMS, an association that has not been described in our literature review.

Keywords: *format, microsoft word template, style, insert, template*

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1. Introduction

Myasthenia Gravis (MG) and Lambert-Eaton Myasthenic Syndrome (LEMS) are both autoimmune disorders of the neuromuscular junction, often associated with malignancies [1]. Classically, MG can be differentiated from LEMS by various clinical, electrophysiologic, and serologic features.

The classic presentation of LEMS is a patient that presents with more profound bilateral lower extremity proximal muscle weakness. The patient would have difficulty standing from a sitting position, making it easily confused with common myopathies [1]. Shoulder girdle weakness is not generally as dramatic. Ptosis and diplopia are seen in a minority of patients but may be prominent features. Symptoms will classically improve with exercise and use. Approximately half of these patients have cancer, most often small cell lung cancer (SCLC) [1]. Electrophysiologic testing with repetitive nerve stimulation (RNS) at high rates results in an incremental response of the compound muscle action potential (CMAP) amplitude. The primary serologic marker for LEMS is antibodies against P/Q-type voltage-gated calcium channels (VGCC), present in over 95 percent of patients with LEMS [2]. The combination of clinical presentation, a positive serologic marker, and typical RNS findings is diagnostic of LEMS.

In contrast to LEMS, patients with MG classically present primarily with ocular symptoms of ptosis and/or diplopia [3]. Approximately 50 percent of patients who develop ocular symptoms will subsequently develop symptoms of generalized disease within two years of initial presentation. Generalized disease results in proximal muscle weakness, with arms being more commonly involved than legs. Distal muscle weakness involving the wrist, fingers, and foot dorsiflexors are also common [4]. Bulbar symptoms such as dysarthria, dysphagia, and fatigable chewing develop in approximately 15 percent of patients. Screening bedside tests, like the "ice pack" and edrophonium challenge tests, have been shown to have good sensitivity [5,6]. Specifically, a recent 2020 study of 155 participants showed that the ice pack test had a sensitivity of 86% and a specificity of 79% [7]. Of note, our review of the literature did not uncover any study using the ice pack test for evaluation of LEMS, and current diagnostic work-up for LEMS does not include using the ice pack test. The edrophonium challenge test has been discontinued as of 2018.

The diagnosis of MG is generally made through a combination of clinical, serological, and electrophysiological findings. Acetylcholine receptor antibodies (AChR-Ab) are present in 85 percent of patients with generalized MG. 98 to 100 percent of patients with both thymoma and generalized disease will be positive for AChR-Ab. Additionally, the absence of both thymoma and AChR-Ab serology has a negative predictive value of 99.7 percent

for MG [8]. Electrophysiology with RNS will result in a decremental response, a progressive decline in CMAP amplitude greater than 10 percent [9].

Moreover, several drugs have been shown to reveal MG symptoms in an otherwise asymptomatic, undiagnosed patient, known as "unmasking" MG. The list of these medications is extensive, including several antibiotic categories, cardiovascular drugs, anticonvulsants, antipsychotics, and glucocorticoids. Of significance to our case, azithromycin, levofloxacin, beta-blockers, statins, and magnesium are known MG-unmasking or aggravating medications [10].

2. Case Presentation

A 73-year-old female who initially presented to a neighboring emergency department (ED) for frequent falls and a urinary tract infection (UTI) associated with an altered level of consciousness (ALOC) was transferred to our care due to insurance considerations. Because of her altered mentation and lack of close contacts on record, the team was unable to obtain a complete symptomatic and medical history. The patient was new to our institution and had no records of previous admissions or home medications. Work-up performed prior to her transfer showed a normal complete blood count (CBC) and a normal comprehensive metabolic panel (CMP), except for a mild elevation of the creatinine (Cr). Creatine phosphokinase (CPK) was 119, within normal limits. Computed tomography (CT) of the brain was unremarkable as well. Upon arrival, lab results showed elevated blood urea nitrogen (BUN) of 32, serum creatinine of 0.9, glomerular filtration rate of 66, mildly elevated troponin I (0.22 ng/ml) from normal values of less than 0.04ng/ml, hypomagnesemia (1.4 mg/dL), urinalysis positive for leukocytes and white blood cells. Right-sided pulmonary infiltrates were seen on chest x-ray. She was started on ceftriaxone and azithromycin for empiric antibiotic treatment of suspected UTI and pneumonia. Because of the mildly elevated troponin, Cardiology was consulted and recommended starting a beta-blocker and statin. The patient's low magnesium was repleted with intravenous (IV) magnesium sulfate.

On the second day of admission, the patient developed significant bilateral ptosis not evident on the initial presentation. On the third day, the patient developed complete ptosis and was unable to elevate her eyelids without the aid of her hands. In addition, the patient developed profound bilateral lower and upper extremity weakness. Her lower and upper extremity strengths were 2/5, and she was unable to have active movement against gravity. Serological tests for CPK and aldolase to rule out common myopathies were negative. It was then suspected that the patient might have MG. A CT chest without contrast was ordered and confirmed the presence of a pulmonary infection. However, it did not find other significant abnormalities, including the presence of a thymoma. A bedside ice-pack test was performed, resulting in temporary improvement of the patient's ptosis. This positive result increased our suspicion that the patient was suffering from undiagnosed MG. Neurology was consulted and agreed with the preliminary diagnosis of MG. It was believed that the patient's symptoms were unmasked by multiple offending agents, including azithromycin, beta-blockers, statin, and magnesium sulfate. Accordingly, all suspected offending agents were discontinued, an MG panel was ordered, and the patient was started on empiric pyridostigmine. In the following days, the patient appeared to show some improvement in her ptosis and upper extremity weakness following treatment. However, improvement was fleeting throughout the day and did not sustain. Pyridostigmine was gradually titrated up to a maximum dose with minimal to no improvement in her symptoms. Despite this, it became clear that the patient had not responded to the trial of pyridostigmine.

The team decided to escalate therapy to include a trial of pulse-dose steroids for two days (methylprednisolone 1 gram intravenously daily), which also resulted in minimal improvement. Following steroid administration, the patient became more altered and developed hallucinations and delirium. After 1.5 weeks, the send-out panel for MG returned negative. A negative serology and negative imaging results with no evidence of a thymoma effectively ruled out the diagnosis of MG. Because of the lower prevalence of LEMS compared to MG and the lack of evidence of SCLC in imaging studies, the primary team did not initially pursue the evaluation of LEMS. However, with MG ruled out, LEMS was the only other plausible explanation for the patient's symptoms. Unfortunately, the hospital's limited capacity for neurological evaluation did not provide for electrophysiological testing. At this juncture, the team decided to perform a P/Q-type VGCC antibody send-out serology test for LEMS. A repeat CT of the chest with contrast was performed for better evaluation of pulmonary neoplasms and was again negative for malignancy. However, the serology came back positive for P/Q-type VGCC-Ab.

With MG ruled out, the patient's clinical presentation and a positive serology result highly suggested the diagnosis of LEMS, despite not being able to perform electrophysiologic testing. Unfortunately, the patient developed sepsis secondary to multifocal pneumonia prior to this final diagnosis. Her condition was further complicated by ventricular arrhythmias and hemodynamic instability, requiring cardiopulmonary resuscitation and intubation. She was intubated for approximately ten days before her family, whom social services were finally able to contact after several weeks of investigations, decided on terminal extubation due to the patient's poor prognosis. The patient subsequently passed a few hours post-extubation.

3. Discussion

Our case illustrates the importance of a thorough investigation in patients with ptosis and generalized weakness. When encountering a patient with ptosis and generalized weakness, MG and LEMS must be in the differential. Therefore, it is important to recognize the clinical manifestations of both MG and LEMS and their prevalence and associated malignancies. In addition, it is not enough to rule out LEMS by indirect association. For example, LEMS is generally thought to be a

paraneoplastic syndrome associated with lung cancer. However, in this case, the search for a lung neoplasm with imaging did not reveal an underlying malignancy. As previously noted, approximately half of LEMS cases are associated with a malignancy, which means that the other 50% of LEMS cases are not associated with any malignancy [1]. Therefore, given the appropriate clinical scenario, negative imaging should not deter serological and EMS investigations.

Furthermore, initial presentation with ptosis is generally attributed to MG, while generalized, progressive proximal weakness, as the initial presenting symptom, is attributed to LEMS [1,3]. In this case, the patient was admitted to the hospital following a fall, with rapid onset of severe ptosis after initiation of "MG-unmasking" drugs. Thus, it was unclear whether her frequent falls at home were caused by her proximal muscle weakness from LEMS, which progressively worsened during hospitalization. Complicating her clinical picture was the striking development of complete ptosis after admission. In her case, the clinical presentation alone would not have been sufficient to differentiate between MG and LEMS. In hindsight, the patient could have benefited from the immediate send-out of both MG and LEMS antibodies to discriminate between these two disorders.

Other tests performed in this case were informative but were not able to differentiate between MG and LEMS. The ice-pack test was initially performed early in her admission, showing temporary improvement of the patient's ptosis. This test was mainly described as a screening method for MG, shown to have good sensitivity and specificity [7], but it is unclear whether it would also be positive for patients with LEMS [6]. This case demonstrates the possibility that the "ice-pack test" can also be positive in LEMS. This is significant, as our literature review did not reveal studies comparing the effectiveness of the ice-pack test in screening for LEMS, nor has there been studies published showing that the ice-pack test can lead to the misdiagnosis of LEMS for MG.

One final point is that the patient's symptoms appear to have been unmasked using MG-aggravating medications. Her profound ptosis and generalized weakness were not observed prior to administering azithromycin, beta-blockers, magnesium sulfate, and statin. These medications were well-recognized as MG-aggravating agents [10], but this case shows that they may also have similar effects in patients with LEMS.

4. Conclusion

This case illustrates that it is important for practitioners to be vigilant when differentiating between MG and LEMS, two major neuromuscular junction disorders. It is important to recognize that whenever one of the conditions is in the differential, the other should also be ruled out. Clinical presentations and screening tests help narrow the diagnosis, but serological and EMS testing needs to be performed, especially if the initial presentation is not classical. It is also insufficient to rule out LEMS based on common associations, such as its association with lung cancer and progressive proximal muscle weakness on initial presentation. The classic presentations of these two diseases are taught to all practitioners during medical school and residency. However, to quote a favorite phrase of many physicians, "patients do not read textbooks," and practitioners must be diligent and thorough in their investigations of what seems to be classic textbook disorders.

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