Case report: a case review of Lambert–Eaton myasthenic syndrome and low back pain

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Abstract The following is a case report which reviews the essential aspects of Lambert–Eaton myasthenic syndrome (LEMS) in a patient with long standing back pain and gait dysfunction. The patient was referred to our electrodiagnostics laboratory for a 9-month history of low back pain and difficulty walking following a charity breast cancer walk. A workup including magnetic resonance imaging of the brain, entire spine, and EMG/NCS at another institution were reportedly normal. A detailed history revealed symptoms of proximal weakness and autonomic dysfunction. Physical findings were consistent with proximal weakness, a bilateral gluteus medius gait, and diffusely absent reflexes obtainable in the biceps after 3 s of contraction. Electrical testing revealed an initial low compound muscle action potential amplitude in the deep peroneal nerve recording from the extensor digitorum brevis. Repetitive stimulation at 2 Hz revealed a decremental response of 42% from the 1st response to the 4th response. Following 3 s of exercise, the amplitude increased by 300%. After 30 s of exercise followed by 1 min of rest, there was a return of the decremental response. The history, physical examination, and electrical findings were illustrative of a presynaptic neuromuscular junction disorder, specifically LEMS.

Keywords Lambert–Eaton myasthenic syndrome · Neuromuscular junction · Proximal weakness · Low back pain · Repetitive stimulation

This patient is a 25-year-old woman who presented to our electrodiagnostic laboratory with a 9-month history of low back pain and difficulty in walking. These symptoms became progressively worse since their onset on October 12, 2003 after participating in a breast cancer walk. There was associated pain in the anterior right thigh. The pain in the anterior right thigh was moderate in severity and dull in quality; the low back pain was severe and sharp. The pain increased with activity. Approximately 1 week after the symptoms began, she noticed that her legs would “give out”, initially involving the right side more than left side, but progressed to affect both sides over 3 months prior to our encounter, resulting in multiple falls. She had difficulty ascending and descending stairs, as well as getting in and out of chairs. Her symptoms were initially associated with numbness over the dorsum of the big toe that had resolved by the time of her appointment. She received chiropractic spinal manipulations over the last few months without relief.

She had repeatedly visited the emergency room complaining of low back pain and was told she had a “back strain.” Workup prior to our visit included MRI of the brain, thighs and cervical, thoracic, and lumbar spines, all of which were unremarkable. An EMG/NCS performed in another university based neuromuscular laboratory 3 months prior was reportedly normal and was unavailable for review at the time of her appointment. One week prior to this visit, she went to the emergency room because of severe low back pain. She was prescribed tizanidine and naproxen for “back spasms;” these did not provide relief.

There is no past medical history and review of systems was significant for dry mouth, dry eyes, orthostatic

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hypotension, urinary frequency with small volumes, increasing difficulty with ambulation, difficulty rising from a chair, constipation, depression, and generalized fatigue. These all began 1 month after the onset of pain. Social history was positive for 1 pack-year of smoking. Family history was significant for breast cancer in the patient's mother. Medications at the time of her visit included tizanidine and naproxen. She was independent in self-care and was formerly employed as a certified nursing assistant, but had been out of work for the preceding 6 months. She was awaiting approval for disability.

On physical exam, blood pressure 110/70 mmHg, heart rate 80 beats per minute. There was no cervical lymphadenopathy. Cardiac, respiratory, and abdominal examinations were unremarkable. There was no effusion, increased temperature or erythema of any joint or adjacent skin in all extremities. The range of motion of the neck, shoulders, and all major joints of the upper and lower extremities was normal bilaterally. Muscular atrophy was absent. Coordination, pinprick, light touch, position, and vibratory sensation in the upper and lower extremities were normal. Motor examination revealed 4/5 strength in the upper and lower limbs except for 2/5 bilateral hip extensor and abductor strength. Reflexes were absent in the knees and ankles. The biceps reflexes were obtainable after 3 s of contraction. The toes were downgoing. Hoffman's sign was negative. Nystagmus was absent. Finger-to-nose and heel-to-shin testing were normal. She had a bilateral gluteus medius gait (Trendelenberg gait) with an extension lurch and a wide base of support (Fig. 1). The results of electrodiagnostic findings were consistent with presynaptic neuromuscular junction disorder, specifically Lambert–Eaton myasthenic syndrome (Table 1). The results of repetitive stimulation were as follows: in the right peroneal nerve, there was a low amplitude CMAP response of 0.54 mV, with 42% decrement (from 700 to 400 μ V) of CMAP amplitude upon repetitive stimulation. Immediately following 3 s of exercise, there was a 300% increase in the CMAP amplitude (Figs. 2, 3). In the right ulnar nerve, there was an initial CMAP response of 2.3 mV, with 17% decrement (from 2.35 to 1.96 mV) of CMAP amplitude upon repetitive stimulation. Immediately following 3 s of exercise, there was a 100% increase of the CMAP amplitude.

The patient was referred to a neurologist following the electrodiagnostic examination. She was admitted to the hospital and received a course of intravenous immunoglobulin, which resulted in marked improvement of her fatigue and gait dysfunction. Tests sent for antibodies to P/Q Calcium channels were positive while those to acetylcholine receptors were negative, further confirming the diagnosis of Lambert–Eaton Myasthenic Syndrome. A malignancy workup including chest radiograph, mammogram,

Fig. 1 Bilateral gluteus medius gait (Trendelenberg gait)

and CT of the abdomen and pelvis was negative. Several markers for autoimmune disorders were sent, including ANA, rheumatoid factor, and Sjogren's antibodies. Her titer for Sjogren's antibodies was significantly elevated and a rheumatologic consultant confirmed a diagnosis of Sjogren's syndrome. After 3 years follow up, the patient was feeling better. Her proximal strength improved, although she continued to have a Trendelenberg gait and diminished reflexes, which improved with exercise. She was being treated with prednisone and physical therapy. She was not hospitalized for the last 2 years and no other diagnosis was found. There was no evidence for malignancy or vasculitis.

Discussion

Many causes of low back pain (LBP) exist. The most common causes are age related degenerative disc disease and facet processes, spondylosis, spondylolithesis, spinal stenosis, radiculopathy, fractures, and muscle or ligament-related injuries. Mechanical conditions of the spine account for up to 98% of LBP cases, with the remaining ones due to systemic, visceral, or inflammatory disorders [1]. Non-mechanical syndromes include, myelopathy, lumbosacral plexopathy, neuropathy, myopathy, neoplasms, infections, inflammatory spondyloarthropathy, metabolic bone diseases, vascular, gastrointestinal, cardiorespiratory, and genitourinary disorders [2].

Table 1 Electrodiagnostic studies

Motor conduction	Latency (ms)	Amplitude (mV)	Distance (mm)	Velocity (m/s)	Comment	Normal values (mV)
Peroneal nerve R						
Ankle	4.5	0.545	80	–	Low amplitude	2.5 ^a
Below fib head	10.1	0.533	295	53	Low amplitude	–
Ulnar nerve R						
Wrist	3.2	2.307	80	–	Low amplitude	4.3 ^a
Below elbow	6.7	2.229	210	60	Low amplitude	–

^a Temperature: 30°C in bilateral feet

Fig. 2 Initial CMAP of right deep peroneal nerve (*top*) and after 3 s of exercise (*bottom*)

Fig. 3 Repetitive stimulation of the right deep peroneal nerve recording from the extensor digitorum brevis. There is a 42% decrement from the first response to the fifth response

The history and physical examination revealed proximal greater than distal weakness. The most common neuromuscular disorders causing this pattern of weakness include myopathies, acute/chronic inflammatory demyelinating polyradiculoplexopathy, disorders of the neuromuscular junction, and Spinal Muscular Atrophy Type III (Kugelberg–Weilander Syndrome). The differential diagnosis for neuromuscular junction disorders includes pre-synaptic disorders such as Lambert–Eaton Myasthenic Syndrome (LEMS) and botulism, and post-synaptic disorders, the classic example being Myasthenia Gravis.

This patient was not taking any medication known to induce myopathy. The absence of antecedent illness, joint complaints or skin lesions made acquired and autoimmune

myopathies less likely. She denied a prodrome or an ascending pattern of weakness making acute or chronic inflammatory demyelinating polyradiculoplexopathy less likely. Her age and negative family history of anterior horn cell disease made Spinal Muscular Atrophy unlikely. The presence of proximal weakness with autonomic nervous system complaints was suspicious for a neuromuscular junction disorder, particularly LEMS.

There were several clues in this case that point towards LEMS as the diagnosis. The history of frequent falls, trouble getting out of a chair (“theatre sign”), and a waddling gait suggest proximal weakness. This is often the pattern of weakness observed in neuromuscular junction disorders. Symptoms of autonomic dysfunction were present such as urinary frequency with small volumes, dry mouth and eyes, and orthostatic hypotension. There were no symptoms consistent with a small or large fiber polyneuropathy and the symptoms were proximal rather than distal. The physical examination revealed a bilateral Trendelenburg gait pattern and diffusely weak muscles with greater weakness in the proximal muscle groups. The absent reflexes that became obtainable following isometric contraction further point to the diagnosis of LEMS.

Our patient’s chief complaint of back pain can be explained by the sequelae of LEMS. The proximal weakness and weakness of the supporting structures of the low back contributed to an overwork syndrome. Her Trendelenburg gait pattern with an extension lurch further put a strain on her lower back musculature.

LEMS is characterized by responses to repetitive nerve stimulation. CMAP amplitudes are small, often less than 10% of normal, and a decrementing pattern is observed with low-frequency repetitive stimulation (2 Hz) [3]. In order to confirm this suspicion, it was necessary to evaluate for post-exercise facilitation (exercise for 3–10 s or repetitive stimulation at 50 Hz), defined by a greater than 100% increase in CMAP amplitude [4, 5]. Up to a 10% increase in amplitude can be seen in normal individuals and in patients with Myasthenia Gravis (“repair of the decrement”). In this case, the compound muscle action potential amplitude increased 300% recording from the extensor

digitorum brevis muscle with stimulation of the peroneal nerve after 3 s of exercise. Further evidence supporting the diagnosis of LEMS was a return of a decremental response upon 2 Hz repetitive stimulation, known as post-exercise exhaustion (30 s of exercise followed by one minute of rest).

LEMS is the second most common neuromuscular junction disorder after Myasthenia gravis (MG) [6]. LEMS is a rare condition which results from an autoimmune attack against voltage-gated calcium channels at the pre-synaptic motor nerve terminal. This causes an abnormality of acetylcholine release at the neuromuscular junction. MG is brought about by an acquired autoimmune reaction producing anti-AChR antibodies which results in reduced number of acetylcholine receptors (AChR) at the post-synaptic muscle membrane. On history and physical examination, patients with LEMS and MG have weakness and easy fatigability. MG patients typically have considerable bulbar weakness and those with LEMS usually do not. The most common presenting feature in LEMS is proximal weakness. In addition, patients with LEMS may report an increase in strength with repeated exercise rather than a decrease as in MG. With continued exercise, however, weakness will eventually develop [3, 7].

The pathophysiologic mechanism in LEMS primarily involves antibodies directed against P/Q voltage-gated calcium channels on the motor nerve terminals, but may also affect N-type calcium channels. These N-type channels are located on autonomic and peripheral nerves as well as cerebellar, cortical, and spinal neurons. Calcium facilitates the binding of acetylcholine to the presynaptic terminal of the neuromuscular junction. Since these channels are pre-synaptic, the antibodies block calcium from entering the nerve terminal during the generation of an action potential.

Autonomic symptoms such as dry mouth, dry eyes, constipation, urinary changes, and blurred vision are common [8]. Patients may complain of muscle aching or stiffness during or following physical activities. They may also report numbness and paresthesias of the distal limbs, but these symptoms should not contribute to any sensory nerve action potential abnormalities upon electrical testing.

It is important to rule out LEMS if suspected due to its high association with malignancy. It is reported that up to 67% of the cases of LEMS are secondary to a neoplasm [9]. The most common cancer associated with LEMS is small cell carcinoma of the lung (90% of the cases associated with cancer). It is also reported in breast, ovarian, lymphoproliferative, and pancreatic cancer. The symptoms of LEMS often precede the diagnosis of cancer by up to 10 months [9]. Approximately, 84% of those diagnosed with LEMS are older than 40 years of age [3].

The remaining 33% of patients have autoimmune LEMS or in conjunction with a rheumatologic disease, including

systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, inflammatory bowel disease, and Sjogren's syndrome [10]. It may also occur with myasthenia gravis [3]. Interestingly, antibodies to P/Q voltage-gated calcium channels are present in both the paraneoplastic and non-paraneoplastic varieties of LEMS [9, 11]. Those who have non-paraneoplastic LEMS tend to be younger, female, and have a higher likelihood of a coexisting rheumatologic condition [10], as with the patient in this case report.

The treatment of LEMS is largely targeted at controlling or eradicating the underlying cause, should one be identified. This includes treatment of a malignancy and aggressive treatment of an underlying autoimmune disorder. Immune modulating agents have proven to be of benefit because of the autoimmune nature of the disease. Treatments include intravenous immunoglobulin, steroids, and immunomodulating medications. The use of anticholinesterase medications may be helpful, but are often less effective than in the treatment of Myasthenia Gravis.

In summary, our patient has a disease of the neuromuscular junction, most likely Lambert–Eaton myasthenic syndrome. At the present time, it appears to be related to a new diagnosis of Sjogren's syndrome. Repetitive stimulation at 2–3 Hz looking for a decremental response and post-exercise facilitation is easy to perform in patients presenting with the above clinical scenario.

Conflict of interest None.

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