Arq Neuropsiquiatr 1998;56(3-A):457-464

LAMBERT-EATON MYASTHENIC SYNDROME

REPORT OF TWO CASES

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ABSTRACT - Two cases of Lambert-Eaton myasthenic syndrome, in female patients whose neoplasm investigation was negative, are reported. Repetitive stimulation of ulnar nerve showed an incremental response (+187% and +198%). Needle EMG was normal in one of them, however, the other patient showed fibrillation potentials, positive sharp waves, potentials of low amplitude and short duration. The authors discuss the clinical, electrophysiological, and pathological features of the disease, as well as some aspects of the treatment and follow-up of these patients.

KEY WORDS: Lambert-Eaton myasthenic syndrome, neurophysiological study, muscular biopsy, treatment.

Síndrome miastênica de Lambert-Eaton: relato de dois casos

RESUMO - São descritos dois casos de síndrome miastênica de Lambert-Eaton em pacientes do sexo feminino, nas quais a investigação de neoplasias foi negativa. Os testes de estimulação repetitiva mostraram incrementos de 187 e 198%. A eletromiografia de agulha em um dos casos foi normal e no outro mostrou potenciais de fibrilação, ondas agudas positivas de curta duração e baixa amplitude de potenciais. São discutidos aspectos clínicos, neurofisiológicos, biópsia muscular, tratamento e acompanhamento desta condição rara.

PALAVRAS-CHAVE: síndrome miastênica de Lambert-Eaton, estudo neurofisiológico, biópsia muscular, tratamento.

Lambert-Eaton myasthenic syndrome is a rare condition, resulting from an acetylcholine release deficiency in the neuromuscular junction. Over 50% of the cases are related with oat cell lung carcinoma[1-3]. Lambert-Eaton syndrome has also been associated with squamous cell lung carcinoma, mixed tumors of the parotid glands, systemic mastocytosis, sarcomas, kidney carcinoma and other malignant neoplastic diseases[3-5]. As Lambert-Eaton syndrome presents mostly as a paraneoplastic condition, an extensive investigation of malignant tumors should be performed. However, approximately 40% of the patients do not show any evidence of cancer, and in these cases, the disease is considered to be of primary autoimmune origin[1,2].

We report two cases of Lambert-Eaton myasthenic syndrome in female patients whose investigation for neoplastic diseases was negative, and due to the rarity of this type of disease, we found it worth putting on record.

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CASE REPORT

Case 1. FMA, female, 49 years old, married; 10 months prior to admission, started with progressive muscular weakness (mostly in the lower limb), with bouts of improvement and aggravation. This progressive muscular weakness resulted in walking impairment. She also presented intense muscular pain, loss of 10 Kg in 10 months, xerostomia, and reduction of the libido. Physical examination did not reveal abnormalities. The neurological examination presented normal cognitive functions; cranial nerve examination showed a long-term right converging strabismus and diplopia. Muscle tonus and bulk were normal and muscular strength was grade IV globally. Deep reflexes were grade +/IV globally at rest and grade ++/IV after physical effort. Superficial sensitivity was normal. Hemogram, sedimentation rate, sodium, potassium, calcium, magnesium, urea, creatinine, glucose, bilirubin, aminotransferases, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, antinuclear factors, TSH, T3 and T4 were all normal. The electrophysiologic study revealed a marked reduction of the amplitudes of the compound muscular action potentials (CMAP) on right ulnar and fibular nerves (Table 1). Sensory and nervous conduction velocities had normal values. Due to the clinical state and the reduced CMAP, a repetitive stimulation study was performed on the ulnar nerve with stimuli at 3 Hz. This test produced decrement of 24.5% on the CMAP. Stimulation at 20 Hz produced potenciation of 187% (Table 1). Needle EMG was normal. Thorax roentgenography and CT scan were normal. Abdominal echography showed increased echogenicity of the liver compatible with fatty liver and pyelonephritis sequel on the left. Pelvic echography did not show abnormalities. Mammography was normal and Papanicolaou smear was negative for malignancy. Esophagogastroduodenoscopy demonstrated erosive esophagitis grade I. The muscle biopsy revealed, through fresh and histochemical stains, atrophy of type II fibers, and suggested an early stage of denervation. Autoantibodies tests were performed to detect the presence of calcium channel binding antibodies type-N and type P/Q, acetylcholine receptor binding antibodies and striational antibodies. Theses tests were negative (Table 2). The patient received pyridostigmine and had partial relief of the symptoms. Reassessment will be performed in 6 months.

Case 2. MFFA, 36 years old, female, married; 15 months prior to admission, the patient's symptoms began with intense pain in the lower limbs, which progressively became worse; after 4 months the patient showed symptoms of muscular pain in the upper limbs and weakness. At that point, she also had difficulty in walking, holding objects, speaking and eating. She also presented xerostomia and reduction of the libido. Clinical examination did not reveal abnormalities. The neurological examination presented normal cognitive functions and cranial nerve showed no abnormalities. Muscle tonus was mildly diminished and bulk was normal. Muscle strength in the upper limbs was grade IV globally. In the lower limbs, strength was grade IV on iliopsoas and

Table 1. Nerve conduction study.

Nerve	Case 1	Case 2	Normal values
Right ulnar (motor)			
Distal latency (ms)	2.92	2.80	< 3.4
Proximal latency (ms)	6.20	6.00	< 7.5
Distal amplitude (uV)	1630	4100	> 3700
Proximal amplitude (uV)	1600	3800	> 3500
Velocity (m/s)	52.8	53.1	> 52
Right fibular (motor)			
Distal latency (ms)	3.72	4.00	< 5.5
Proximal latency (ms)	9.16	9.20	< 12.9
Distal amplitude (uV)	1970	2800	> 2800
Proximal amplitude (uV)	1820	2500	> 3100
Velocity (m/s)	49.6	51.9	> 40

Table 2. Serum autoantibodies study of 2 patients with Lambert-Eaton syndrome.

Antibody	Case 1	Case 2	Unit	Expected values
Calcium channel binding antibody N-type	08	00	pmol/L	<20
Calcium channel binding antibody P/Q	00	00	pmol/L	<20
Acetylcholine receptor binding antibodies	0.00	0.00	nmol/L	< or = 0.02
Striational antibodies	Negative <1:60	Negative <1:60	titer	<1:60

quadriceps and grade V distally. Deep reflexes were grade +/IV globally, cutaneous-plantar reflex was indifferent and sensory was normal. The patient presented flaccid paraparetic gait. Hemogram, sedimentation rate, sodium, potassium, calcium, magnesium, urea, creatinine, glucose, bilirubin, aminotransferases, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, antinuclear factors, TSH, T3 and T4 were normal. The electrophysiologic study revealed normal motor potentials on the ulnar nerve and reduction of amplitude of the compound muscular action potentials (CMAP) on fibular nerve (Table 1). Sensory and nervous conduction velocities were normal on both nerves. Because of the clinical state and the reduced CMAP, a repetitive stimulation study was performed on the ulnar nerve with stimuli at 3 Hz. This test produced decrement of 15.3% on the CMAP. Stimulation at 40 Hz produced potenciation of 198% (Table 1). Needle EMG showed +/4 of fibrillation and positive waves on brachial biceps, ++/4 of fibrillation and positive waves on anterior tibial muscle and potential of short duration and low amplitude on both muscles. Thorax roentgenogram and mediastinum CT scan abdominal echography and pelvic echography were normal. Mammography was normal and Papanicolaou smear was negative for malignity. Rectosigmoidoscopy revealed anal fissures and plicomas, esophagogastroduodenoscopy demonstrated antral enanthematous gastritis, and gastric biopsy did not show neoplastic disease. Muscle biopsy was abnormal suggesting denervation and atrophy of type II fibers. Autoantibodies tests were performed to detect the presence of calcium channel binding antibodies type-N and type P/Q, acetylcholine receptor binding antibodies and striational antibodies. These tests were negative (Table 2). The patient was treated with pyridostigmine and presented relief of the symptoms. Reassessment will be performed in 6 months.

DISCUSSION

Lambert, Eaton and Rooke described Lambert-Eaton myasthenic syndrome for the first time in 1956. They presented patients with muscular weakness caused by a defect in the neuromuscular transmission different from myasthenia gravis associated with bronchogenic carcinoma[6]. The disease involves autoantibodies against the voltage operated calcium channels in the pre synaptic membrane[4,7,8]. These antibodies impair the acetylcholine release on the neuromuscular and on the autonomic neuroeffective junctions and cause the onset of the symptoms[9,10].

Most patients present fluctuating symptoms of muscular weakness in the lower limbs and many report muscular pains, aches and stiffness related to physical effort [2]. Autonomic dysfunctions, mostly xerostomia, occur in approximately 80% of the patients; other symptoms include impotence in men and loss of the libido in women [2,11]. Both patients in this report presented xerostomia and reduction of the libido. Involvement of the cranial nerves is less frequent and less intense than in myasthenia gravis [2]. Respiratory muscle involvement is very rare[12-14]. Hyporeflexia is also a common sign and muscular weakness presents the facilitation phenomena, which is functional improvement after physical effort [15]. Post exercise facilitation was well observed in Case 1, which presented hyporeflexia at rest and presented normorreflexia after 30 seconds of voluntary physical effort.

Approximately 60% of the cases of Lambert Eaton myasthenic syndrome are related to some sort of malignant neoplastic disease, most frequently with the oat cell lung cancer[1-3]. O'Neill et al. found this hystological type in 21 out of 25 cases of Lambert Eaton myasthenic syndrome associated with cancer in their series [2]. Although there is no malignancy sign in about 40% of the patients, an

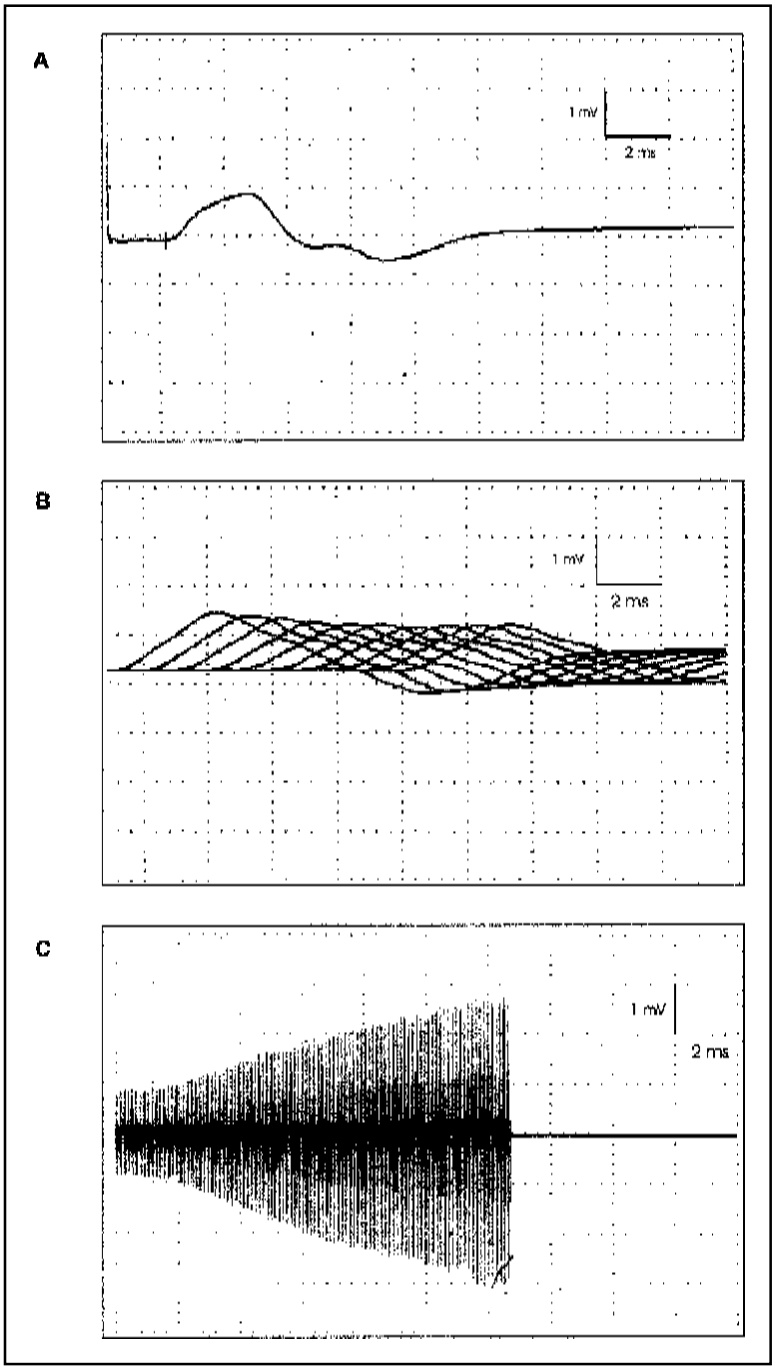

Fig 1. Case 1. (A) CMAP on ulnar motor nerve collected from the 5th digit abductor muscle showing amplitude of 1.6 mV. (B) 3 Hz repetitive stimulation on ulnar nerve (wrist) collected from the 5th digit abductor muscle showing 24.5% decrement. (C) 20 Hz repetitive stimulation on ulnar nerve with 100 stimuli produced a 187% potenciation.

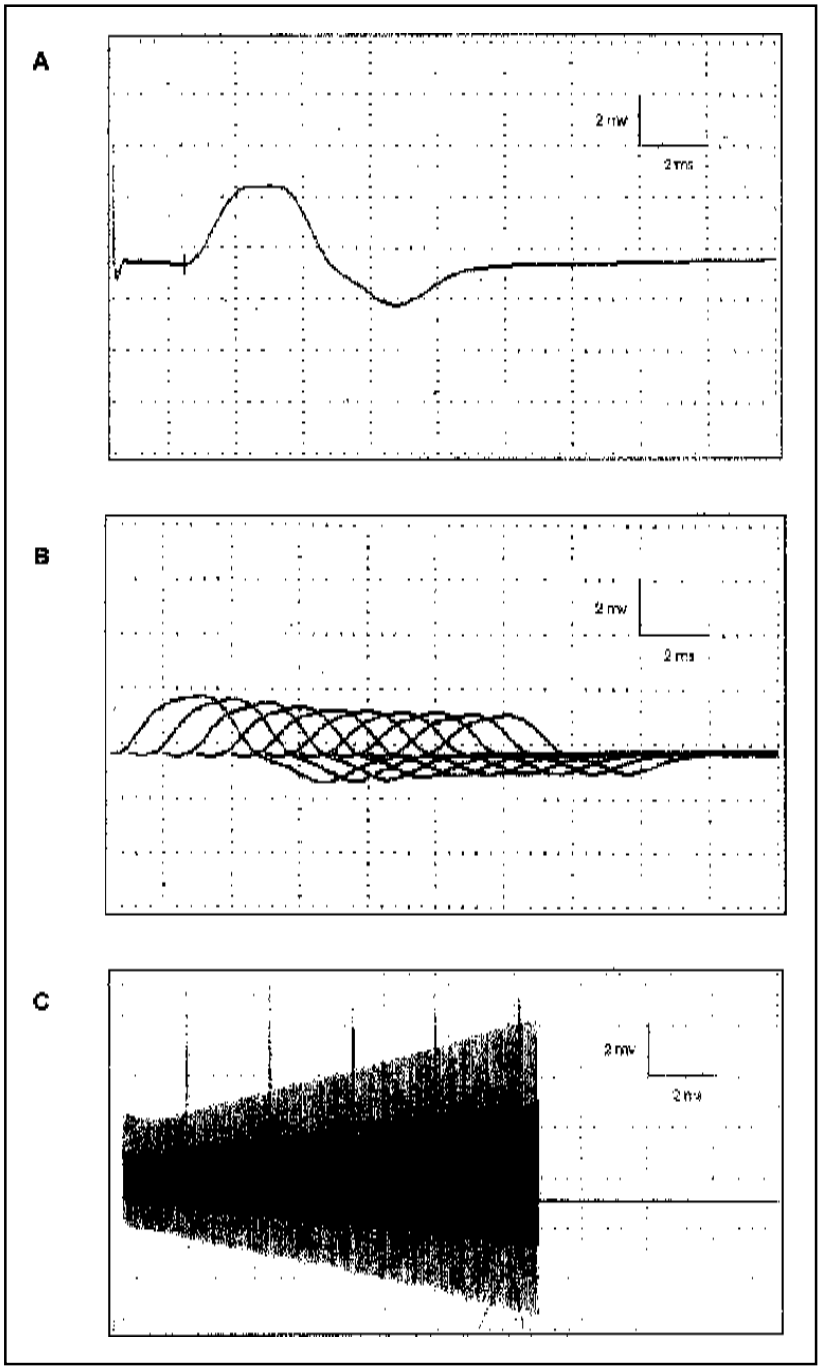

Fig 2. Case 2. (A) CMAP on ulnar motor nerve collected from the 5th digit abductor muscle showing amplitude 4.1 mV. (B) 3 Hz repetitive stimulation on ulnar nerve (wrist) collected from the 5th digit abductor muscle showing 15.3% decrement. (C) 40 Hz repetitive stimulation on ulnar nerve with 100 stimuli produced a 198% potenciation.

initial negative investigation does not exclude tumoral presence. In many occasions cancer is not detected at the time of the Lambert Eaton myasthenic syndrome diagnosis and, though most tumors become evident in 2 years, there have been reports of latency periods of up to 3.8 years [2]. This fact demonstrates the need for a patient follow-up in order to guarantee an early detection of tumors. This follow-up would require chest roentgenograms and/or CT scans generally every 6 months for, at least, 4 years after the onset of the symptoms. The primary autoimmune and the paraneoplastic forms of the Lambert Eaton myasthenic syndrome are identical in their clinical and neurophysiological features and cannot be differed by these parameters [2]. Every 2 months, our patients are reexamined. A new set of exams is performed every 6 months in order to investigate any underlying neoplastic disease.

Patients with Lambert Eaton myasthenic syndrome present an increased frequency of autoimmune diseases such as thyroiditis, systemic lupus erythematosus and also positive antibodies for myasthenia gravis[7,9,16-18]. This can be explained by a genetic predisposition to developing autoimmune diseases, which these patients (with primary or paraneoplastic disease) present. O'Neill et al. report that 34% of 50 patients with Lambert Eaton syndrome presented a personal or family history of autoimmune diseases [2]. In our two cases, both personal and family histories were negative for autoimmune diseases, thyroid function tests were normal, blood sedimentation rate was normal and antinuclear factor was non-reacting.

The repetitive stimulation test is instrumental for the diagnosis and for characterizing Lambert Eaton syndrome [1,6,19]. The electrophysiologic study on Lambert-Eaton syndrome shows great reduction of the muscular action potentials amplitude in response to a maximum nervous stimulus. Low frequency repetitive stimulation reveals a decrease of muscular response. High frequency repetitive stimulation (20–50 Hz) shows an increase of over 150%. This feature is characteristic of neuromuscular junction pre-synaptic dysfunction[1,6,19-21]. As high frequency repetitive stimulation is uncomfortable for the patient, it is possible to compare the action potential at rest and after 10 to 15 seconds of voluntary muscle contraction. This allows an equivalent analysis because both maneuvers induce Ca^{++} accumulation on the nervous terminal and, therefore, acetylcholine release on the synaptic gap [21]. In both cases, the repetitive stimulation test led to the diagnosis of Lambert-Eaton syndrome. Other diseases that can affect the motor pre-synaptic acetylcholine release, such as botulism, hypermagnesemia and hypercalcemia, may also present a similar response to repetitive stimulation but are easily discarded by their abrupt onset, clinical features, and laboratory findings [20]. Other neurophysiologic exams may also be altered but they are less specific. Needle electromyography may show motor unit potentials of low amplitude and short duration, increase on the poliphasic potential proportion and amplitude and format fluctuation of potentials during minimal voluntary activity. Increase of voluntary activity causes increase of the potential amplitude and reduction of fluctuation [3,22,23]. Motor nervous conduction studies reveal low amplitude action potentials and nervous conduction velocity is usually normal[1,19].

Abnormal muscular biopsy has been reported in patients with Lambert-Eaton syndrome and type 2 fiber atrophy has been the most common finding [2,15,24]. The type 2 fiber atrophy, found on the histochemical study of the brachial biceps muscular biopsy of both patients, is an non-specified finding. This finding, along with rare atrophic and angular fibers (mostly in esterase), suggest an initial phase of denervation. These features may also be present in myasthenia gravis, the initial phase of lower motor neuron diseases, immunodeficiency syndromes, peripheric neuropathies and use of corticoids [25,26].

Dosage of anti-voltage operated calcium channels antibodies may also be useful in diagnosing Lambert-Eaton syndrome, although this method is not available in most places. The first studies showed a great variability on sensitivity and specificity of these tests [8,27,28]. Recently, the detection of specific anti-voltage-operated calcium channels antibodies has become more accurate for diagnosing Lambert-Eaton syndrome [29,30]. The fact that no specific antibodies were found in any of the patients

does not discard the Lambert Eaton syndrome. Positive results, in these tests, are related to the presence of an underlying malignant disease. None of the patients presented any kind of neoplastic disease.

Lambert-Eaton syndrome's treatment consists in treating the underlying malignant tumor, when present [31,32], plus a symptomatic treatment of the acetylcholine deficiency as well as an immunosuppressive treatment. Some patients show symptom improvement simply by using cholinesterase inhibitors such as pyridostigmine. Others require drugs such as guanidine and 3,4-diaminopyridine that increase the pre-synaptic calcium influx and the acetylcholine release[5,33]. Patients unresponsive to these treatments may respond to corticoids, azathioprine, plasmapheresis and, most recently, endovenous gammaglobulin therapy[34-37].

No reports of Lambert-Eaton syndrome have been found in Brazil for the last 15 years, in contrast to other places that have presented a large number of cases with relative frequency [2,9]. Despite serving as a reference for diagnosis and treatment of neuromuscular disorders, these are the only two cases of Lambert-Eaton syndrome cataloged in our services over the last 20 years, besides one case of a superimposing syndrome [38]. This fact may be due to the lack of diagnosis or to rare occurrence of this disease in our country compared with other locations. Studies report that 3% of patients with oat cell lung carcinoma develop Lambert-Eaton syndrome [39], even though we do not have such associated cases registered in our service. This fact reinforces the theory that there is a lack of diagnosis.

Acknowledgement - We would like to thank Dr. Vanda A. Lennon for kindly performing the antibody tests.

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