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Non-paraneoplastic Lambert-Eaton myasthenic syndrome

A brief review of 10 cases

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ABSTRACT

Lambert-Eaton myasthenic syndrome (LEMS) is an immune-mediated disorder of the presynaptic neuromuscular transmission, which more frequently occurs as the remote effect of a neoplasm, in the paraneoplastic form (P-LEMS), or in a non-paraneoplastic form (NP-LEMS); but few studies describe the clinical features of NP-LEMS. We analyzed the clinical manifestations, laboratory findings, electrophysiological studies, and treatment responses in ten Brazilian patients suffering from NP-LEMS. The mean age was 41.5 years. More often neurological findings were hyporeflexia or areflexia with a post-exercise improvement. Treatment response occurred with pyridostigmine, guanidine, prednisone, azathioprine, and cyclosporine; but not response was observed after intravenous immunoglobulin and plasma exchange. Age at onset, clinical manifestations, and electrophysiological abnormalities can help more in the diagnosis than serum antibodies; the symptomatic treatment with pyridostigmine was effective; and the immunosuppressive treatment with prednisone, azathioprine, or cyclosporine was more beneficial than plasma exchange or intravenous immunoglobulin treatment.

Key words: Lambert-Eaton myasthenic syndrome, myasthenic syndrome, P/Q-type voltage-gated calcium channel antibody, repetitive nerve stimulation, electrophysiological study, treatment.

Síndrome miastênica de Lambert-Eaton não paraneoplásica: uma breve revisão de dez casos

RESUMO

A síndrome miastênica de Lambert-Eaton (LEMS) é uma desordem imunomediada da transmissão neuromuscular pré-sinaptica, que mais frequentemente ocorre como efeito à distância de uma neoplasia, na forma paraneoplásica (P-LEMS), ou na forma não paraneoplásica (NP-LEMS); porém poucos estudos têm descrito as características da NP-LEMS. Nós analisamos as manifestações clínicas, laboratoriais, eletrofisiológicas, e resposta ao tratamento em dez pacientes brasileiros com NP-LEMS. A idade média foi de 41,5 anos. A manifestação neurológica mais freqüente foi hiporeflexia ou arreflexia com melhora após o exercício. A resposta ao tratamento ocorreu com piridostigmina, guanidina, prednisona, azatioprina, e ciclosporina; mas não com imunoglobulina intravenosa e plasmaférese. A idade de início, manifestações clínicas e eletrofisiológicas ajudaram mais no diagnóstico do que os anticorpos séricos; o tratamento sintomático com piridostigmina foi efetivo; e o tratamento imunossupressor com prednisona, azatioprina, ou ciclosporina beneficiou mais do que a plasmaférese ou a imunoglobulina intravenosa.

Palavras-chave: síndrome miastênica de Lambert-Eaton, síndrome miastênica, anticorpo anti-canal de cálcio voltagem dependente, estimulação nervosa repetitiva, estudo eletrofisiológico, tratamento.

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Lambert-Eaton myasthenic syndrome (LEMS) is an immune-mediated disorder of the neuromuscular transmission in which serum autoantibodies against the P/Q-type voltage-gated calcium channels (VGCCs) at the presynaptic nerve terminal lead to a decrease in the presynaptic release of acetycholine[1-3]. These antibodies impair the acetylcholine release on the neuromuscular and on the autonomic neuroeffective junctions and cause the onset of the symptoms[3].

LEMS can frequently occur as remote effect of a neoplasm, in the paraneoplastic form (P-LEMS), usually in association with small cell lung cancer (SCLC), or in the non-paraneoplastic form (NP-LEMS)[1,2,4-8]. A review of 50 cases of LEMS demonstrated about a 60% risk of SCLC, which was diagnosed in most of these cases within 2 years of onset of the myasthenic syndrome[9]. Then, the diagnosis of NP-LEMS requires a long-term follow up because the neurological symptoms can precede a diagnosis of a neoplasm[1,5,8,9].

P-LEMS and NP-LEMS have different characteristics, but few studies describe the clinical features of NP-LEMS after a long-term follow up[4,8]. The objective of this study was to analyze the clinical manifestations, laboratory findings, electrophysiological studies and treatment responses in a series of Brazilian patients suffering from NP-LEMS.

METHOD

We retrospectively analyzed the LEMS patients seen in our hospital from 1976 to 2008, and we studied ten patients with a diagnosis of NP-LEMS. Our hospital is a reference neuromuscular center with a special interest and an expertise in disorders of the neuromuscular junction. The LEMS diagnosis was based on typical clinical features, characteristic electrophysiological changes, and an absence of cancer in a follow up at of least four years after the LEMS diagnosis[2,10,11]. Relevant data, including the age, gender, clinical evaluation, course of the disease, serum anti-P/Q-type VGCC antibody, serum anti-acetylcholine receptor (AChR) antibody, electrophysiological study, and treatment response were recorded.

The LEMS electrophysiological measurement criteria comprised a reduced compound muscle action potential (CMAP) amplitude with a CMAP amplitude increment of more than 100% after a brief maximal voluntary contraction or high frequency (20 Hz) repetitive nerve stimulation (RNS) according to standard procedures[1,10,11].

The treatment response was classified as total, partial, or absent according to the objective improvement in the neurological findings and autonomic symptoms during the drug therapy.

All studies were done following patient consent.

RESULTS

The sample consisted of ten patients (six female and four male), age 26 to 60 years (mean 41.5 years), showing predominance of young adult patients in this series (eight patients with age less than 45 years). The time of the follow-up varied between 4 and 13 years, with a mean time of 8 years (Table 1).

NP-LEMS was associated with another autoimmune disease (thyroiditis with hypothyroidism) in two cases (Table 1).

The neurological findings that were found more frequently in our group before treatment were hyporeflexia or areflexia (10/10) with a post-exercise improvement (6/6). The other neurological findings before treatment are described in Table 1. The more frequent autonomic dysfunction symptoms before treatment were dry mouth (6/10), constipation (2/10), a reduction in the libido (2/10), and blurred vision (2/10) (Table 1).

Serological analysis of the anti-P/Q-type VGCC antibody was performed in six patients and demonstrated

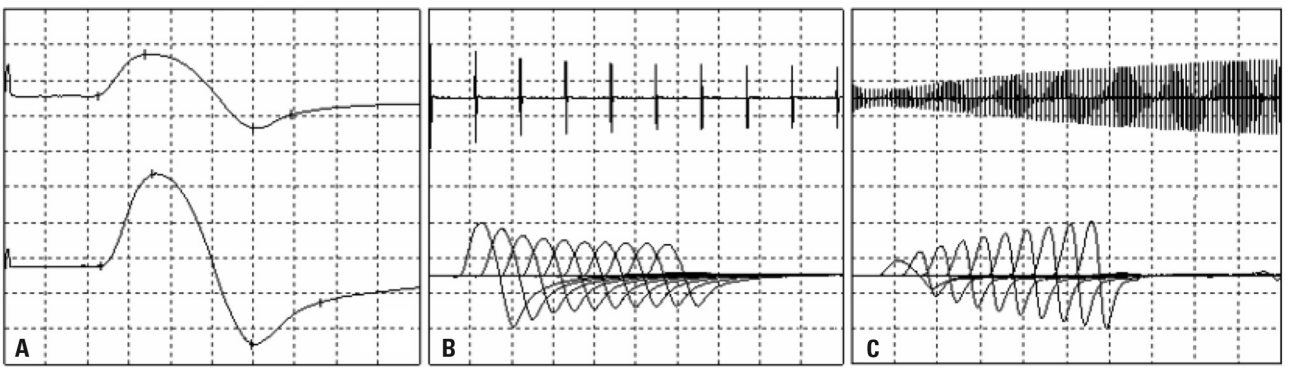

Figure. The electrophysiological study of the compound muscle action potential (CMAP) amplitude in the abductor pollicis brevis muscle following a median nerve stimulation in case 3: [A] before (superior CMAP) and after (inferior CMAP) a brief maximum voluntary contraction (2mV/3ms); [B] decrement of 34.1% in the repetitive stimulation at 3 Hz (2mV/5ms); and [C] increment of 276% after 100 repetitive stimulations at 20 Hz (5mV/5ms).

Table 1. Clinical manifestations, laboratory findings, eletrophysiological studies and treatment responses of our NP-LEMS patients.

Case	1	2	3	4	5	6	7	8	9	10
Gender	M	M	M	F	F	F	F	F	M	F
Age at onset (years)	60	38	39	26	42	48	34	45	39	45
Follow up time (years)	7	4	12	4	8	4	13	9	8	10
Associated autoimmune disorder										
Hypothyroidism	–	–	–	–	+	–	–	+	–	–
Neurologic findings										
Diplopia	+	+	+	–	–	+	–	–	+	–
Ophthalmoplegia	+	+	–	–	–	–	–	–	+	–
Ptosis	+	+	+	+	+	–	–	+	+	–
Dysphagia	+	+	+	+	+	–	+	–	–	+
Facial weakness	–	+	–	+	+	–	–	–	+	–
Proximal upper limb weakness	+	–	+	+	+	+	+	–	–	+
Distal upper limb weakness	–	–	–	–	–	+	–	–	+	–
Proximal lower limb weakness	+	+	+	+	+	+	+	–	–	+
Distal lower limb weakness	–	–	–	–	–	+	–	+	+	–
Hyporeflexia or areflexia	+	+	+	+	+	+	+	+	+	+
Increased reflex post-exercise	ND	ND	+	ND	+	+	+	+	+	ND
Muscular pain	–	–	–	–	+	+	+	–	–	–
Cerebellar ataxia	–	+	–	–	–	–	–	+	+	–
Respiratory failure	–	+	–	–	–	–	–	–	–	–
Autonomic dysfunction										
Dry mouth	–	+	–	–	–	+	+	+	+	+
Constipation	–	–	+	–	+	–	–	–	–	–
Libido reduction	–	–	–	–	–	+	+	–	–	–
Blurred vision	–	–	–	–	+	–	–	–	–	+
Serum antibodies										
Anti-P/Q-type VGCC antibody	ND	ND	ND	ND	–	–	–	+	+	+
Anti-AChR antibody	ND	ND	ND	ND	–	–	–	ND	–	–
Electrophysiological test										
Low CMAP amplitude	+	+	+	+	+	+	+	+	+	+
Incremental CMAP post–exercise	+	+	+	+	+	+	+	+	+	+
CMAP decrement at low-rate RNS	+	+	+	+	–	+	+	+	+	+
CMAP increment at high-rate RNS	ND	+	+	+	+	+	+	+	+	+
Treatment response										
Symptomatic therapy										
Pyridostigmin	+	+	+	+	+	±	+	+	+	+
Guanidine	ND	ND	ND	ND	ND	ND	ND	ND	ND	+
Immunosuppressive therapy										
Prednisone	+	+	+	±	±	ND	±	±	±	+
Azathioprine	ND	ND	+	ND	*	ND	±	±	±	±
Cyclosporin	ND	ND	ND	ND	+	ND	+	+	+	ND
Intravenous immunoglobulin	ND	ND	ND	ND	ND	ND	–	–	–	–
Plasma exchange	ND	ND	ND	ND	ND	ND	–	ND	–	ND

NP-LEMS: non-paraneoplastic Lambert-Eaton myasthenic syndrome; VGCC: voltage-gated calcium channel; AChR: acetylcholine receptor; CMAP: compound muscle action potential; RNS: repetitive nerve stimulation; F: female; M: male; +: present or total; ±: partial; –: absent; *intolerance; ND: not done.

Table 2. Characteristics of our NP-LEMS patients compared to previous published cohorts.

Characteristics	This study	Pellkofer et al.[14] (2009)	Titulaer et al.[7] (2008)	Maddison et al.[4] (2001)	Tim et al.[18] (2000)	O'Neill et al.[9] (1988)
Number of patients	10	25	45	47	42	25
Gender (male:female)	4:6	6:19	20:25	24:23	18:24	18:7
Mean age at onset in years (range)	41.5 (26-60)	44 (11-71)	54 (15-69)	47 (11-74)	51 (8-78)	54 (17-79)
Mean follow-up from diagnosis in years	8	–	–	10.5	–	–
Associated autoimmune disorder	20%	28%	–	–	33%	28%
Clinical features						
Weakness						
Proximal arms	70%	88%	73%	94%	100%	–
Distal arms	20%	–	42%	–	–	–
Proximal legs	80%	100%	100%	96%	100%	100%
Distal legs	30%	–	27%	–	–	–
Hyporeflexia or areflexia	100%	–	–	–	100%	92%
Ocular symptoms						
Ptosis	70%	40%	49%	–	–	44%
Diplopia	50%	52%	36%	–	–	56%
Bulbar symptoms						
Dysphagia	70%	56%	42%	22%	–	28%
Autonomic dysfunction						
Dry mouth	60%	84%	71%	–	–	84%
Constipation	20%	24%	29%	–	–	28%
Cerebellar ataxia	30%	4%	2%	–	–	–
Serum antibody						
Anti-P/Q-type VGCC antibody	50%*	100%	87%	86%	65%	–

NP-LEMS: non-paraneoplastic Lambert-Eaton myasthenic syndrome; VGCC: voltage-gated calcium channel; –: not available; * serum analysis were done only in six cases.

the antibody presence in three patients. The anti-AChR antibodies were tested in five patients and were negative (Table 1).

The most common abnormalities found in the electrophysiological studies were a low CMAP amplitude (10/10), an incremental CMAP amplitude post-exercise (10/10), a CMAP amplitude decrease with a low-rate RNS (9/10), and a CMAP amplitude increase with a high-rate RNS (9/9) (Table 1 and Figure).

A treatment response was total in patients who used pyridostigmine (9/10), guanidine (1/1), prednisone (4/9), azathioprine (1/5), and cyclosporine (4/4). Partial treatment response was observed with pyridostigmine (1/10), prednisone (5/9) and azathioprine (4/5). No treatment response was reported after intravenous immunoglobulin (4/4) and plasma exchange (2/2) (Table 1).

DISCUSSION

NP-LEMS has been rarely described in Brazil, including our previous reports (cases 1, 6, 7, 8, and 9), in contrast to other places[3,12,13]. NP-LEMS usually occurs in 30 to 50% of LEMS patients[6,8]. No gender difference was found in the NP-LEMS patients, as in our series (Table 2), while the P-LEMS patients show a male predominance[6,8]. The mean age at onset of LEMS in the NP-LEMS patients is lower than in the P-LEMS patients[7-9]. In NP-LEMS, onset can be from childhood to old age[2,9,14].

In NP-LEMS, a mean interval between the onset of symptoms and a diagnosis of LEMS is longer than in P-LEMS cases[7-9,14]. The probability of an underlying SCLC, at presentation of the myasthenic syndrome, range from 50 to 60%, which falls sharply after 2 years and becomes less than a few per cent after 4 years from onset[7-9].

LEMS almost invariably starts with a proximal weakness (Table 2), especially of the legs[7,14]. Hyporeflexia is also a common sign (Table 2), which shows a functional improvement after a physical effort by the facilitation phenomenon that occurs by Ca^{+2} accumulations on the nervous terminal and, therefore, acetylcholine release on the synaptic gap[3]. Ocular symptoms are regularly seen in pa-

tients with LEMS, but the severity is rather mild, especially compared to the severity in myasthenia gravis[7]. Cerebellar ataxia is found more in P-LEMS than in NP-LEMS, but our patients had a high incidence of this symptom (Table 2), which sometimes dominated the clinical picture so that the presence of LEMS was overlooked[7,12]. Anti-VGCC antibodies also underlie the autonomic symptoms in LEMS patients, especially dry mouth (Table 2), which occurs in between 71% and 84% of cases[4,7,9,14].

Despite all the symptoms that appear during the course of disease, no neurologic findings distinguished between the P-LEMS and the NP-LEMS patients, but weakness of the distal muscles in the legs (Table 2), weight loss, and respiratory failure appeared significantly less frequently in NP-LEMS[6-8]. In addition, NP-LEMS showed a slower progressive course of disease than the P-LEMS patients[7].

Associated autoimmune disorders can occur usually after an interval of six months in between 28% and 33% of NP-LEMS patients (Table 2), but only occur in 6% of P-LEMS patients[8,14]. The high frequency of associated autoimmune disorders, together with the high proportion of women and the relative younger age at onset, suggests a similar etiology as other non-paraneoplastic autoimmune diseases in NP-LEMS patients[8].

The antibodies to the P/Q-type VGCC can be detected in over 90% of the LEMS patients[2,4,7]. The antibodies are specific for LEMS, but the site of the antigenic stimulus in NP-LEMS is unknown[2]. Our patients had a low frequency of the anti-P/Q-type VGCC antibody (Table 2); therefore, the LEMS patients without the anti-P/Q-type VGCC antibody more frequently have NP-LEMS than P-LEMS[6].

The classic electrophysiological abnormalities (a low CMAP amplitude, a CMAP decrease at low rate of stimulation, and a CMAP increase above 100% after a brief maximal voluntary contraction or high-frequency RNS) are present in almost all of the NP-LEMS patients, similar to P-LEMS, although this is not seen in all muscles, and it may be necessary to examine several muscles to demonstrate this feature[1-3,10,13].

The NP-LEMS treatment consists of symptomatic treatment of the acetylcholine deficiency as well as an immunosuppressive treatment[3,15-17]. Some patients show symptom improvement by use of cholinesterase inhibitors such as pyridostigmine, but this drug is less effective in LEMS than in myasthenia gravis[3,15,17,18]. Other patients require drugs such as guanidine and 3,4-diaminopyridine, which increase the pre-synaptic calcium influx and the acetylcholine release improving LEMS symptoms[15-17]. Moreover, an additional therapeutic effect can be obtained if guanidine or 3,4-diaminopyridine are combined with pyridostigmine[15-18]. The unresponsive patients to symptomatic treatment may respond to immunosuppressive treatment with prednisone alone or combined with azathioprine, and, most recently, cyclosporine[15-17]. Although the evidence of benefit for the immunosuppressive treatment of LEMS is limited to a series of case reports, it is reasonable to adopt treatment procedures by analogy with myasthenia gravis[15-17]. In LEMS patients with respiratory failure or bulbar dysfunction, plasma exchange and intravenous immunoglobulin are useful in bridging the gap until other immunosuppressive therapy takes effect[15]. In NP-LEMS, where weakness is severe, plasma exchange or intravenous immunoglobulin treatment confers a short-term benefit, but this treatment did not alter the disease course in our patients, while corticosteroids and immunosuppressive drugs improved their symptoms[15-17].

Although about half of the NP-LEMS patients achieved sustained clinical remission, most of them required substantial and continuing doses of immunosuppressive medication[4]. A review of 47 cases of NP-LEMS demonstrated that the only predictor of long-term outcome (clinical remission or independent ambulation) was initial clinical score (comprising muscle strength measurements by Medical Research Council scale) in limb muscles[4]. The electrophysiological study in NP-LEMS can start to improve after one year of treatment in some patients, but no direct relation was seen between the NP-LEMS treatment, the anti-P/Q-type VGCC antibody titer and the CMAP amplitude[4,17]. Immunological and electrophysiological measurements were useful, however, for monitoring disease progression and response to treatment in individual patients[4].

In this study, the age at onset, clinical manifestations, and electrophysiological abnormalities helped more in the LEMS diagnosis than the serum antibodies; the symptomatic treatment with pyridostigmine was effective; and an immunosuppressive treatment with prednisone, azathioprine, or cyclosporine were more beneficial than plasma exchange or intravenous immunoglobulin treatment.

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