Case Report

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Myasthenia gravis with clinical facilitation: a case series

Murat Mert Atmaca, Hacer Durmuş Tekçe, Elif Kocasoy Orhan, Mehmet Barış Baslo, Feza Deymeer

Department of Neurology, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Turkey

Abstract

Patients having features of both myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) have been reported and have been collected under the term MG-LEMS overlap syndrome (MLOS). These patients have clinical characteristics of MG and LEMS, but electrophysiological features of presynaptic pathology. Three patients who were initially diagnosed as LEMS because of presentation with predominant extremity weakness which showed clinical facilitation (transient increase in muscle strength on repeated muscle strength examination) were reported in this case series. All three patients were finally diagnosed as anti-acetylcholine receptor positive MG. None of them had voltage gated calcium channel antibodies. Electrophysiological features were compatible with LEMS in one patient who was considered to have MLOS. The other two patients had electrophysiological features of MG. Patients showing features of both disorders were reported previously, but to our knowledge no patient with MG showing clinical facilitation was reported. It would be interesting to check MG patients with predominant extremity weakness for clinical and electrophysiological features of LEMS.

Keywords: Myasthenia Gravis, Lambert-Eaton myasthenic syndrome, MG-LEMS overlap syndrome, presynaptic electrophysiology, facilitation

INTRODUCTION

Myasthenia gravis (MG), most frequently caused by antibodies (Abs) against postsynaptic nicotinic acetylcholine receptors (AChR), and Lambert-Eaton myasthenic syndrome (LEMS), caused by Abs against presynaptic voltage gated calcium channels (VGCC), are two autoimmune disorders that disturb neuromuscular transmisson (1).

Oculobulbar symptoms are characteristic features of MG while weakness of proximal lower extremity muscles with transient improvement after brief exertion suggests LEMS (2). Autonomic features, especially dryness of the mouth is common in patients with LEMS (2). MG and LEMS can be differentiated from each other by nerve conduction studies (NCS) and repetitive nerve stimulation (RNS) tests (3, 4). In LEMS, the presence of low amplitude compound muscle action potentials (CMAPs) at rest is typical; low frequency RNS shows decrement while high frequency RNS or brief maximal voluntary contraction results in marked increment (4). Patients having features of both MG and LEMS have been reported and have been collected under the term MG-LEMS overlap syndrome (MLOS) (5, 6). These patients have clinical characteristics of MG and LEMS, but electrophysiological features of presynaptic pathology. We report one such patient fitting the diagnosis of MLOS and two others clinically considered as LEMS (proximal extremity weakness showing facilitation) but without the electrophysiological features of LEMS. All patients had positive anti-AChR Abs and were diagnosed as MG. Informed consents were obtained from the patients.

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Corresponding Author: Murat Mert Atmaca **E-mail:** drmuratmertatmaca@hotmail.com **Submitted:** 15 April 2018 **Accepted:** 22 September 2018

CASE PRESENTATION

PATIENT 1

A 66 year-old woman presented with fluctuating weakness in the extremities, worse in the hands, followed by neck weakness, droopy eyelids, double vision, swallowing and breathing difficulties, developing within 20 days. Past medical history was significant for cancer of the cervix 26 years ago, for which she received radiotherapy with resultant severe left lower extremity weakness secondary to lumbosacral plexopathy. On neurological examination, she had bilateral asymmetrical ptosis, mild eye movement limitation in all directions, and moderately weak eye closure and masseter muscles. Muscle strength was Medical Research Council (MRC) 3 in upper extremities, right lower extremity and neck flexors. Strength in the left lower extremity was 2 due to MRC scale. On repeated muscle strength examination, MRC grade became 4 in triceps and right iliopsoas. Deep tendon reflexes were absent in lower extremities and normoactive in upper extremities. She did not have autonomic symptoms.

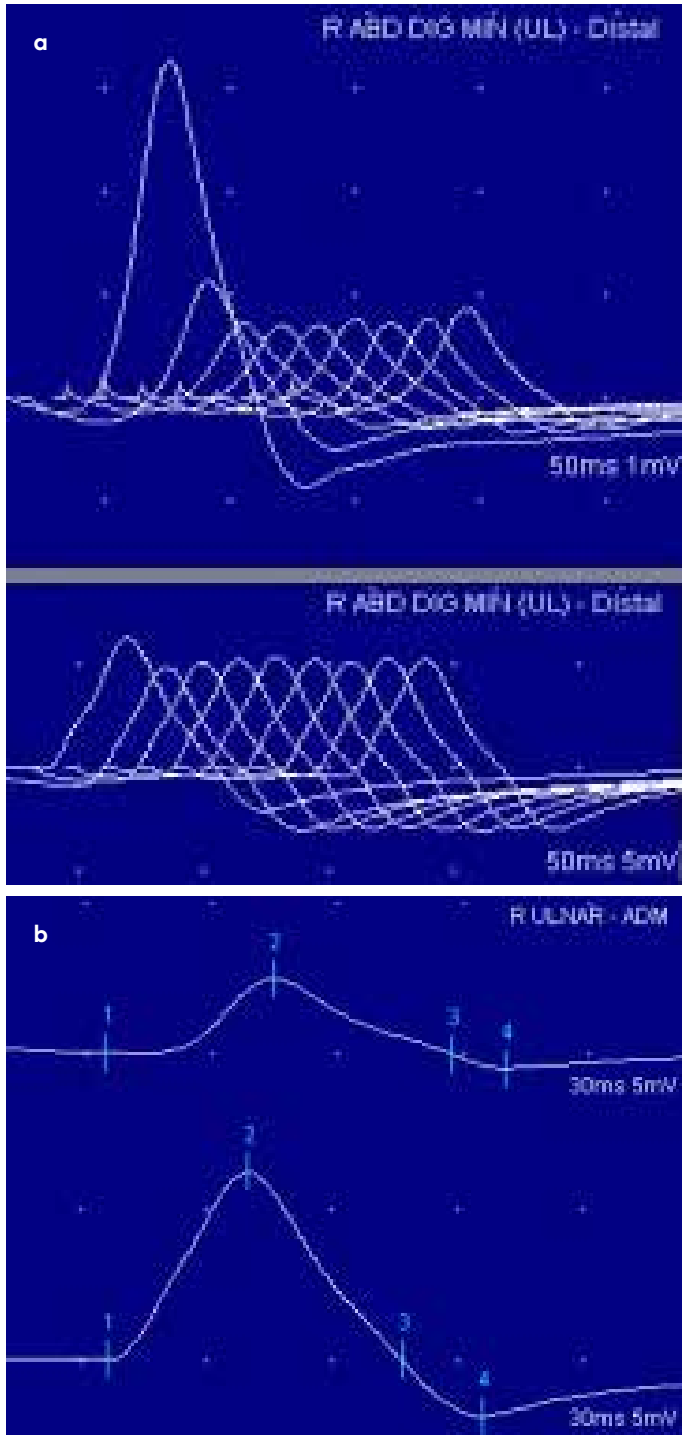
Due to predominant extremity weakness and marked facilitation in muscle strength, a preliminary diagnosis of LEMS was made. EMG revealed low amplitude ulnar and median CMAP's. Ulnar CMAP, recording on abductor digiti minimi (ADM), showed 248% facilitation after 10 seconds of maximal voluntary contraction. RNS at 3 Hz, recording on ADM, showed decrement of 75%, with marked facilitation after maximal voluntary contraction (Figure 1 a, b).

Initial response to pyridostigmine was found to be dramatic, however, it later diminished and upon pronounced response to 3,4-diaminopyridine (3,4-DAP), it was added to pyridostigmine. The patient gradually improved on prednisolone and initially administered bilevel positive airway pressure. Clinical facilitation, EMG findings consistent with presynaptic neuromuscular conduction pathology and good response to 3,4-DAP all pointed to LEMS and an intensive search for malignancy was negative. However, anti-AChR Abs were positive (3.2 nmol/L) and P/Q type anti-VGCC Abs were negative. Neurological examination a year and a half later was normal except for the known disability in the left lower extremity. She was receiving low dose prednisolone, azathioprine and occasional pyridostigmine. No cancer was found in follow-up.

PATIENT 2

A 15 year-old girl had fluctuating weakness with difficulty in climbing stairs for 2 years, followed by arm weakness, ptosis, double vision, and swallowing/talking difficulties within six months. On neurological examination, she had mild bilateral ptosis, mild eye closure weakness and snarl upon smiling. Muscle strength was MRC 2 in upper and proximal lower extremities and neck flexors; it was MRC 4 in distal lower extremities. On repeated muscle strength examination, MRC grade became 4 in deltoids, biceps, triceps and finger extensors (A video of the patient's repeated muscle strength examination was added as supporting material). Deep tendon reflexes were normoactive. Her neurological examination was otherwise unremarkable.

Figure 1. a, b. RNS at 3 Hz, recording on right ADM, showed myasthenic decrement of 75% in patient 1 (top). There was marked facilitation after maximal voluntary contraction with increase of initial CMAP amplitude and reduction of decrement to 9% (bottom) (a) Patient 1 had low amplitude ulnar CMAP's recorded on ADM (2.5 mV) at rest which showed 248% facilitation (6.2 mV) after 10 seconds of maximal voluntary contraction (b)

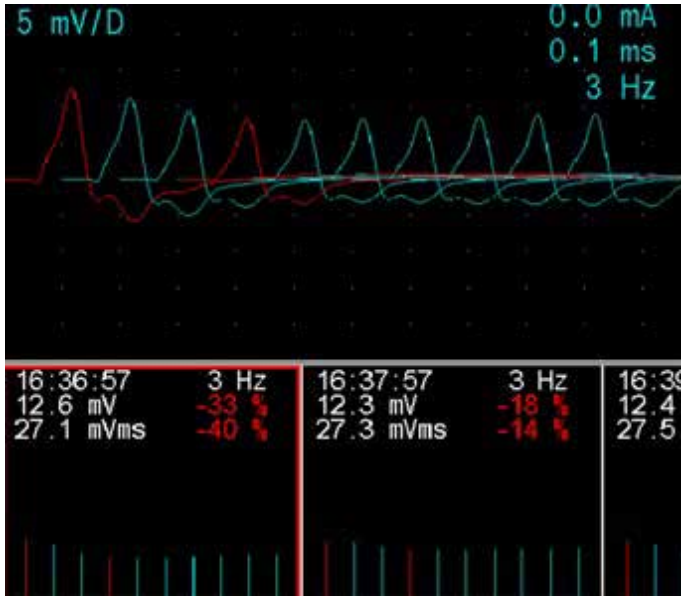


Due to predominant extremity weakness and marked facilitation in muscle strength, a preliminary diagnosis of LEMS was made. She had normal amplitude CMAPs. RNS at 3 Hz, recording on ADM, abductor pollicis brevis and abductor hallucis, showed myasthenic decrement with facilitation after maximal voluntary contraction (Figure 2). Anti-AChR Abs were positive (26.7nmol/L) and P/Q type anti-VGCC Abs were negative. The patient, now diagnosed as MG, had dramatic response to pyridostigmine. A videothoracoscopic thymectomy revealed thymus hyperplasia. During 4 years of follow-up, she complained only of intermittent mild fatigue and double vision, responding well to pyridostigmine 60-120 mg/day. Her last neurological exam revealed mild bilateral ptosis only.

PATIENT 3

A 61 year-old man had fluctuating right arm and finger (4. and 5. fingers), then left arm and bilateral lower extremity weakness followed by double vision, evolving within 10 days. On neurological examination, cranial nerves including eye closure were normal. Muscle strength was MRC 2 in the right 4. and 5. finger extensors, MRC 4 in the other upper extremity muscles and in proximal lower extremity muscles. Lower extremity distal muscles were normal. On repeated muscle strength examination, the MRC grade became 5 in biceps and triceps. Deep tendon reflexes were normoactive. His neurological examination was otherwise unremarkable.

Figure 2. RNS at 3 Hz, recording on right ADM, showed myasthenic decrement of 33% in patient 2. There was facilitation after one minute of maximal voluntary contraction with decrement reducing to 18% (not shown in the figure)



The patient with preliminary diagnosis of LEMS had normal amplitude CMAP's. RNS at 3 Hz, recording on ADM, showed decrement of 12%. Single fiber EMG showed increased jitter as well as block in the examined fiber pairs of extensor digitorum brevis. Anti-AChR Abs were positive (26 nmol/L) and P/Q type anti-VGCC Abs were negative. The patient, diagnosed with MG, benefited very much from pyridostigmine. Thorax CT was normal. Oculobulbar symptoms were later added. He improved on prednisolone and mycophenolate mofetil which was later changed to azathioprine because of a severe fungal pulmonary infection. His last neurological exam, after 6 years of follow-up, revealed mild left ptosis and mild proximal weakness. He was receiving low dose prednisolone and azathioprine and was working productively as a doctor.

DISCUSSION

All of the patients presented with predominant extremity weakness showing transient improvement after repeated contractions (facilitation), a finding characteristics of LEMS. Only patient 1 showed electrophysiological features characteristic of LEMS. They were all later diagnosed as anti-AChR antibody positive MG and none of them had P/Q type anti-VGCC Abs. Neither thymoma nor any malignancy was detected in the patients. Patients 2 and 3 responded very well to pyridostigmine which is not expected in LEMS. Patient 1 responded well to pyridostigmine initially, but then the response deteriorated and she responded very well to 3,4-DAP. Clinical, electrophysiological, serological features, condition of the thymus and response to symptomatic treatment of the patients are summarized in Table 1.

Table 1. Clinical, electrophysiological, serological features, condition of the thymus and response to symptomatic treatment of the patients

Patient no	Onset age and gender	Predominant extremity weakness	Clinical facilitation	Electrophysiological features of LEMS (presynaptic)	Antibodies	Thymus Thorax CT (pathology)	Response to pyridostigmine	Response to 3,4 DAP
1	66, F	Yes	+	Yes	AChR Abs (+) VGCC Abs (-)	Normal	Fairly good	Very good
2	13, F	Yes	+	No	AChR Abs (+) VGCC Abs (-)	Normal (thymic hyperplasia)	Very good	Not given
3	61, M	Yes	+	No	AChR Abs (+) VGCC Abs (-)	Normal	Very good	Not given

F: Female; M: Male; AChR Abs: Acetylcholine receptor antibodies; VGCC Abs: Voltage gated calcium channel antibodies; CT: Computed tomography; 3,4-DAP: 3,4-diaminopyridine

A small group of patients with predominant extremity weakness, electrophysiological features of LEMS, but other features resembling MG were designated as MLOS. Similarities to MG included onset age, response to anticholinesterases, rate of associated thymoma and lack of associated malignancy (6). Two comprehensive reviews have searched the literature and identified close to forty patients with MLOS (5, 6). A few of them had both anti-VGCC and anti-AChR Abs, one had anti-MuSK Abs instead (7-12). However, Abs were not tested/reported in many patients (anti-VGCC Abs not reported in about three fourths and anti-AChR Abs in about one third) (5). In those tested, anti-AChR Abs were found to be positive in the majority and anti-VGCC Abs were usually found to be negative (5). It should be emphasized that these patients did not have important features usually associated with LEMS: They neither had an associated malignancy such as small cell lung cancer nor anti-VGCC Abs, detected by radioimmunoassay in 85-90% of patients with LEMS (13). Thus, one can probably say that patients with MLOS are generally non-thymomatous AChR-MG patients who have striking extremity weakness and electrophysiological features of LEMS.

Patient 1 in our study appears to fit well into the category of MLOS. Interestingly, she showed another characteristic of LEMS, that is clinical facilitation, which was not reported in any of the MLOS patients. Patients 2 and 3 did not fulfill any of the criteria for MLOS: They did not have presynaptic electrophysiological findings or VGCC antibodies. Their only resemblance to LEMS was predominant extremity weakness which showed clinical facilitation.

Presentation with limb weakness without oculobulbar involvement occurs in about 10-20% of patients with MG (14, 15). Weakness spreads to cranial muscles in the course of the disease in most of them. Weakness remains confined to extremity muscles in about 2% of the patients, a subgroup defined as chronic limb-girdle MG (14, 16). Our patients can certainly not be defined as limb girdle myasthenia since all of them became generalized in time. However, both presenting and later predominant symptoms were extremity weakness in all of them.

High frequency RNS or maximal voluntary contraction in MG increases the release of acetylcholine and as a result decrement decreases or disappears (post-tetanic facilitation). This short-lasting effect is not noticeable clinically in MG. The effect of facilitation is much more prominent in LEMS where the initial potential is small because of disturbance in the release of acetylcholine (17). Electrophysiological increment is reflected by the clinical finding of facilitation in LEMS (3). Clinical facilitation in our MG patients (patients 2 and 3), despite the lack of electrophysiological features of LEMS, is remarkable and suggests that electrophysiological post-tetanic facilitation can be clinically noticeable in some MG patients with predominant extremity weakness.

CONCLUSION

Our patients are of interest because of the presence of clinical facilitation of muscle strength in all of them. To our knowledge, no patient with MG was reported to have clinical facilitation. Thus, clinical, electrophysiological and immunological features of LEMS and MG can be found in various combinations in the same patient. It would be interesting to check all MG patients with predominant or profound extremity weakness for the presence of clinical facilitation, presynaptic electrophysiological findings and anti-VGCC Abs.

Informed Consent: Verbal informed consent was obtained from patient 2 and her parents, patient 1 and patient 3 who participated in this study.

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