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Neuromuscular Disorders ■■ (2015) ■■–■■

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Case report

Myasthenia gravis with presynaptic neurophysiological signs: Two case reports and literature review

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Received 2 March 2015; received in revised form 15 April 2015; accepted 29 April 2015

Abstract

The distinction between myasthenia gravis and Lambert–Eaton myasthenic syndrome is based on clinical, neurophysiological and immunological features. We hereby report two cases with a clinical diagnosis of myasthenia gravis and neurophysiological features consistent with a pre-synaptic neuromuscular transmission defect. Both patients had increased anti-acetylcholine receptor antibody titres and showed a good response to cholinesterase inhibitors, along with a >100% facilitation of the compound muscle action potential on electrophysiological studies.

We provide a review of English literature studies on co-existing features of myasthenia gravis and Lambert–Eaton myasthenic syndrome, and discuss diagnostic controversies.

Keywords: Myasthenia gravis; Lambert–Eaton myasthenic syndrome; Presynaptic neurophysiological pattern; Cholinesterase inhibitors; 3,4-Diaminopyridine

1. Introduction

Myasthenia gravis (MG) and the Lambert–Eaton myasthenic syndrome (LEMS) are autoimmune disorders of the neuromuscular junction, characterized by muscle weakness and fatigability. MG is by far the most common, with a mean prevalence of 77.7/million [1]. It is caused by antibodies (Abs) to several proteins of the post-synaptic membrane, such as the acetylcholine receptor (AChR) (detected in 85% of cases), the muscle-specific kinase (MuSK) (in 5–8%) and the lipoprotein receptor-related protein 4 (in a low proportion of patients). MG typically shows broad variability in clinical pattern and severity, with frequent involvement of bulbar muscles [2]. LEMS is a much more rare disease, with a prevalence of 3.4/million [3]. It is a presynaptic disorder, associated in 85–90% of patients with Abs to the voltage-gated calcium channel (VGCC) of P/Q-type; limb proximal weakness, loss of tendon reflexes and autonomic dysfunction are the main clinical characteristics of the disease [3].

Several studies have reported the co-existence of MG and LEMS features (so-called "overlap syndrome") [4–6], although there is controversy on such entity definition [7,8].

We hereinafter report two patients with MG associated with a neurophysiological presynaptic pattern, together with a review of related studies in the English literature.

2. Case report

2.1. Case no. 1

A 46-year-old woman presented with fatigable limb weakness. Two months later, she developed dysphonia and dysphagia, the latter resulting in a marked weight loss (15 kg). Neurological examination detected fatigable weakness on limb proximal muscles, prevalent on legs. Deep tendon reflexes were normo-elicitable and no autonomic dysfunction was observed. Routine haematological and chemical exams revealed subclinical hypothyroidism. Definite clinical improvement of limb and bulbar weakness on neostigmine test and a positive AChR-Ab assay (1.20 nM/l; normal range <0.45) were consistent with a diagnosis of MG.

Stimulation of the right ulnar nerve, registering from the abductor digiti minimi muscle, showed normal compound motor action potential (CMAP) amplitude at rest (10 mV); low frequency (3 Hz) repetitive nerve stimulation (RNS) resulted in a 27% decrease of CMAP amplitude at the fourth stimulus, with a characteristic U-shaped pattern; high frequency (30 Hz) RNS produced no facilitation. Conversely, nerve conduction studies of the right axillary nerve, registering from the deltoid muscle revealed a marked reduction of CMAP at rest (1 mV), 30%

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http://dx.doi.org/10.1016/j.nmd.2015.04.012
0960-8966/

Please cite this article in press as: Paolo Emilio Alboini, Valentina Damato, Raffaele Iorio, Marco Luigetti, Amelia Evoli, Myasthenia gravis with presynaptic neurophysiological signs: Two case reports and literature review, Neuromuscular Disorders (2015), doi: 10.1016/j.nmd.2015.04.012

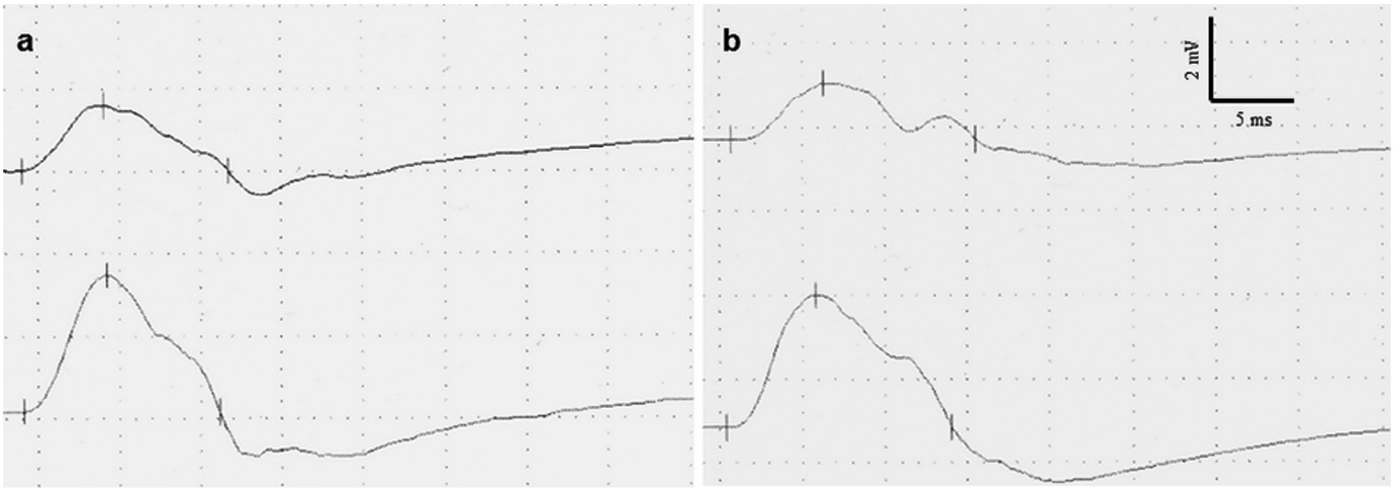

Fig. 1. Nerve conduction studies of peroneal nerve, registering from tibialis anterior, in Case 2. Upper traces: CMAP at rest (1.4 mV for right nerve in a, and 1.3 mV for left nerve in b). Lower traces: CMAP after brief exercise (3.3 mV for right nerve in a, and 3.1 mV for left nerve in b). A significant increment of CMAP amplitude is shown (around 135% for both nerves).

CMAP reduction on low frequency RNS at the ninth stimulus and a 400% CMAP increase (from 1 to 4 mV) after 15'' exercise. Neurophysiological examination of the contralateral nerve showed similar results. Anti-VGCC Ab assay was negative. Pyridostigmine (60 mg four times/day) was beneficial with incomplete control of symptoms; a six-month course of 3,4-diaminopyridine (3,4-DAP) up 40 mg/day brought no further benefit. The patient underwent thymectomy (histological examination revealed an atrophic thymus with sparse lymphoid infiltrates). Steroid treatment induced marked improvement, and prednisone was gradually tapered off. Currently, her status is of "minimal manifestations" on small pyridostigmine doses. Surveillance for a possible associated tumour was negative during the nine-year follow-up.

2.2. Case no. 2

A 56-year-old man was referred with a clinical diagnosis of MG, complaining of mild bilateral ptosis and generalized weakness. On neurological examination, weakness was definitely prevalent on leg proximal muscles, tendon reflexes were hypoactive in upper limbs and absent in lower limbs, no autonomic dysfunction was observed. Routine haematological and chemical exams were normal.

Low frequency RNS of the right ulnar nerve, registering from abductor digiti minimi muscle, revealed a 16% decrease of CMAP amplitude at the fourth stimulus, with a classical U-shaped pattern; CMAP amplitude at rest was normal (8.3 mV). Low frequency RNS of the axillary nerve, registering from the deltoid muscle, revealed a 34% decrease of CMAP amplitude at the fourth stimulus, with a classical U-shaped pattern; CMAP at rest was normal (6.9 mV). Conversely, stimulation of the right peroneal nerve, registering from the tibialis anterior muscle, showed a reduced CMAP at rest (1.4 mV), a 14% decrease of CMAP amplitude on low frequency RNS at the fifth stimulus and a 135% CMAP increase after a brief exercise (from 1.4 to 3.3 mV). Neurophysiological examination of the contralateral nerve showed similar results (Fig. 1). AChR Abs were positive (1.40 nM/l), while VGCC Abs were undetectable. Oral pyridostigmine (60 mg five times/day) improved clinical symptoms; a three-month course of 3,4-DAP (10 mg three times/day) resulted in no significant additional benefit. The patient underwent prednisone treatment with a very good response, and is currently in a minimal manifestation status on 25 mg prednisone every other day. Tumour screening, performed with total-body positron emission tomography/computed tomography (PET/CT) scan and neoplastic markers, has been negative after a 2-year follow-up.

3. Literature review

To date, 36 patients (18 men and 18 women) with coexisting features of MG and LEMS have been reported. Patients' data are shown in Table 1.

In 22 cases (61%) clinical and electrophysiological findings of MG and LEMS occurred at the same time; an interval ranging 1.5–40 years in the onset of the two conditions was observed in six cases (17%). Oculo-bulbar symptoms and limb weakness had the same frequency rate (in 35/36 patients, 97%). Twenty-three patients (64%) showed reduction of deep tendon reflexes and dysautonomia was reported in ten patients (28%). Neurophysiological studies were consistent with a pre-synaptic neuromuscular transmission defect in 33 cases (92%), with a postsynaptic defect in two and were within normal limits in a single patient (who had both AChR and VGCC Abs). AChR Abs were present in 20/24 tested patients (83%); VGCC Abs were tested in 12 patients and were detected in 8 (66%); six patients were positive for both AChR and VGCC Abs and one patient for MuSK and VGCC Abs. The effect of cholinesterase inhibitors (ChE-Is) was reported in 27 patients, of these 20 (88%) showed a definite improvement as evaluated either clinically or in neurophysiological studies; no patient responded to 3,4-DAP alone, but the association of ChE-Is and 3,4-DAP was beneficial in four cases. Ten associated tumours, of which five

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