

Systemic Lupus Erythematosus with muscle weakness due to Myasthenia Gravis

Sâmia Araújo de Sousa Studart¹, Cleonísio Leite Rodrigues²,
Carol Barroso Soares³, Maria Roseli Monteiro Callado⁴, Walber Pinto Vieira⁵

ABSTRACT

Systemic lupus erythematosus (SLE) and myasthenia gravis (MG) are autoimmune diseases, whose association in the same patient is rarely reported. Both pathologies share the following characteristics: affect mainly young women; alternate exacerbation and remission periods; and have positive antinuclear antibody (ANA) test. This case report assesses possible diagnostic hypotheses for the clinical findings of eyelid ptosis and proximal muscle weakness in a female patient recently diagnosed with SLE, who evolved with associated MG.

Keywords: systemic lupus erythematosus, myasthenia gravis, muscle diseases, autoimmunity.

[*Rev Bras Reumatol* 2011;51(3):289-94] ©Elsevier Editora Ltda

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystemic, autoimmune disease of unknown etiology and varied clinical presentation, which alternates remission and exacerbation periods. It mainly affects young women at a ratio of 9:10 women to each man, with a prevalence ranging from 14 to 50/100,000 inhabitants, according to the demographic characteristics of each region.¹

Myasthenia gravis (MG) is a neuromuscular disorder characterized by fatigability and proximal weakness of skeletal muscles. It is triggered by immune-humoral destruction of acetylcholine receptors at neuromuscular junctions. Its prevalence is 1:7,500 individuals, affects mainly women, and has a peak incidence between the second and third decade of life. Electroneuromyography (ENMG) evidences the presence of a significant, greater than 10%, decrease in the amplitude of motor evoked potentials on low frequency (3 Hz) repetitive nerve stimulation. The acetylcholine receptor antibody is detected in plasma in approximately 80% of patients.² Among patients with MG, 5% to 30% have another autoimmune pathology, the most common being Hashimoto's thyroiditis, followed by Graves Basedow disease, rheumatoid arthritis, and

SLE.^{3,4} Other less frequent diseases are polymyositis, Sjogren's syndrome, and scleroderma.⁵

Lupus and MG share the following characteristics: autoimmune-related pathogenesis; affect mainly young women; alternating exacerbation and remission periods; and positive antinuclear antibody (ANA) test.^{6,7} The prevalence of SLE in patients with MG ranges from 2.2% to 8.3%; however, the prevalence of MG in patients with SLE remains unknown.^{5,8} This statistics may be higher, because the use of immunosuppressants in the treatment of MG may mask SLE development.^{3,9}

This study aimed at reporting one case of MG in a patient previously diagnosed with SLE according to the American College of Rheumatology criteria.

CASE REPORT

The patient is an 18-year-old female admitted to hospital complaining of intermittent fatigability and muscle weakness, mainly in lower limbs, for two months, associated with episodes of diplopia, mandibular pain, perioral paresthesia, and slow speech. The patient had been diagnosed with SLE six months before, the initial findings being photosensitivity, malar rash, oral ulcers, arthritis, lymphopenia, and positive

Received on 04/17/2010. Approved on 01/24/2011. Authors declare no conflicts of interest. Rheumatology Service of the Hospital Geral de Fortaleza (HGF), Ceará, Brazil.

1. Resident physician at the Rheumatology Service of the HGF

2. Preceptor of the residency in Neurology of the HGF; Neurologist specialized in electroneuromyography by the Medical School of the USP

3. Undergraduate medical student of the Universidade Federal do Ceará; student of the Internal Medicine Course of the Rheumatology Service of the HGF

4. PhD in Sciences by the Medical School of the USP; Preceptor of residency of the HGF

5. Collaborating Professor of the Medical School of the Universidade Estadual do Ceará; Chief of the Rheumatology Service of the HGF

Correspondence to: Sâmia Araújo de Sousa Studart. Rua Thomaz Pompeu, 570, Apartamento 902, Meireles. CEP: 60160-080. Fortaleza, CE, Brazil. Phone: +55 (085) 9670-1115/ +55 (085) 8803-9291/ +55 (085) 3087-6823. E-mail: samiasousa@yahoo.com.br.

ANA test. Two months after the diagnosis, she developed severe psychosis associated with generalized tonic clonic seizures. The patient's general health status was good, and she was oriented to time, place and person. Her neurological exam showed alteration of the third cranial nerve, with bilateral incomplete eyelid ptosis, fluctuating proximal weakness of the pelvic girdle, gait alteration with walking difficulty, hesitation and widened base. The patient was on prednisone (40 mg/day), chloroquine (250 mg/day), valproic acid (500 mg/day), calcium carbonate (1 g/day), and monthly pulse therapy with cyclophosphamide (750 mg), in the third cycle. Laboratory tests showed erythrocyte sedimentation rate, 27 mm; lymphocytes, 866/mm³; C3, 84.6 mg/dL [reference value (RV): 90-180 mg/dL]; lactic dehydrogenase (LDH), 515U/L (RV: 230-460U/L); polyclonal hypergammaglobulinemia; nuclear and fine speckled cytoplasmic ANA pattern 1:1280, positive anti-SSA (Ro), negative anti-DNA. Serum testes for hepatitis, HIV, CMV, HTLV, toxoplasmosis, and syphilis were negative. Renal, liver, and thyroid functions, electrolytes, and muscle enzymes were within normal range. Therapy consisted of suspending chloroquine and gradually reducing prednisone to 15 mg/day, aiming at reducing the myopathic effects of these drugs. After two weeks, the patient remained with no clinical improvement. The ENMG evidenced chronic myopathy of moderate intensity affecting the proximal portion of the four limbs. The low frequency repetitive nerve stimulation evidenced the presence of abnormal and early fatigability in limb proximal muscles, suggesting impairment of the neuromuscular junction at the post-synaptic level, characterizing a generalized myasthenic finding (Figure 1). Chest computed tomography showed no abnormalities in anterior mediastinum, and the search for acetylcholine receptor antibodies was negative. Intravenous edrophonium test (Tensilon test) was considered unnecessary after the ENMG findings, and the therapeutic test with pyridostigmine (60 mg/day initially) provided significant improvement of the eyelid ptosis after 48 hours. From the third day onward, the patient could climb stairs, sit and stand up with no aid. She was discharged from hospital and referred to outpatient follow-up.

DISCUSSION

In SLE, myopathies may be part of the disease's clinical condition or associated with other autoimmune pathologies, mainly thyroid disorders, polymyositis, dermatomyositis, and, rarely, MG. Ionic alterations and myotoxicity due to drugs used in SLE treatment have also been reported as a cause of muscle strength reduction. In the present case report, diagnostic

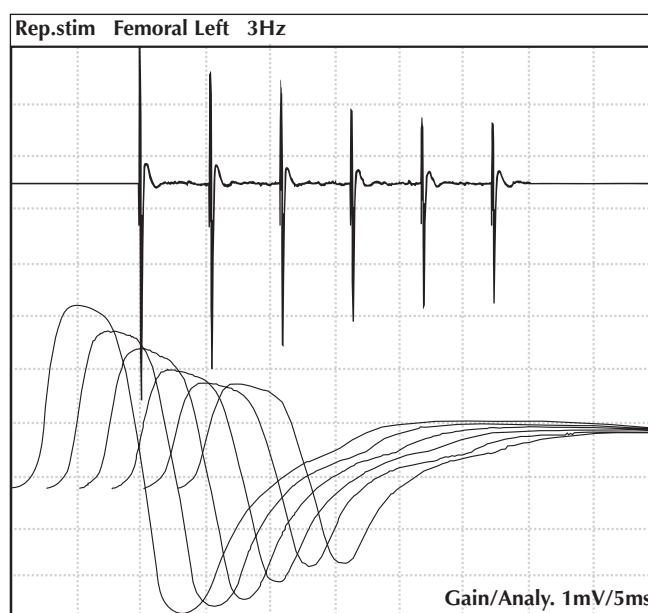


Figure 1
Electroneuromyography – Low-frequency (3 Hz) repetitive nervous stimulation performed in the left femoral nerve with uptake in the rectus femoris muscle. Presence of a significant decremental response, greater than 10%, after the first stimulus.

investigation was initially directed to the clinical hypotheses that are most frequently associated with SLE, which are lupus myositis and drug-induced myotoxicity.

Lupus myositis manifests in 5% to 10% of patients as a decrease in proximal muscle strength, an elevation in muscle enzymes, and ENMG findings similar to those of inflammatory myopathies.⁵ Our patient had no enzyme changes and the ENMG was suggestive of MG.

The use of chloroquine suggested possible drug-induced myotoxicity. Antimalarials act as neuromyotoxins, affecting both the nervous system and striated muscle.^{10,11} Drug-induced myotoxicity is characterized by symmetric and proximal muscle impairment, and typical signs of membrane instability and proximal myopathic potentials on ENMG. Casado *et al.* have assessed the development of myopathy in 119 lupus patients on antimalarials for three years, and have reported an accumulated prevalence of 12.6%.¹⁰ Ocular symptoms have been reported in only three patients, and, in one patient, the symptoms persisted ten years after drug withdrawal.^{12,13,14} The CPK and aldolase levels have been reported as within the normal range, but the LDH levels, a more sensitive enzyme for this impairment, are elevated.¹⁰ The diagnostic muscle biopsy evidences vacuolar myopathy on optical microscopy and characteristic curvilinear

bodies on electron microscopy.^{5,10,11} The treatment consists of drug withdrawal, which is followed by symptom regression in a few days. Our patient showed no clinical improvement two weeks after drug withdrawal.

Steroid-induced myopathy occurs in 2% to 21% of long-term users, being common with fluorinated corticosteroids (triamcinolone, dexamethasone, and betamethasone).^{5,15} Its pathogenesis is unknown, and muscle biopsy evidences only a nonspecific selective atrophy of type IIb fibers.² Steroid-induced myopathy manifests clinically as a progressive proximal muscle weakness in lower limbs, which eventually affects the four limbs, but spares the facial and sphincter muscles. Muscle enzymes are within the normal range. The ENMG evidences an increase in

Ic fiber and short polyphasic action potentials, a reduction in the fiber II motor unit action potentials, absence of fibrillation, and positive waves in muscle recovery.¹⁵ Treatment consists of drug dose reduction or its withdrawal, followed by symptom regression within weeks or months.

The presence of ocular manifestations, use of corticosteroid for only six months, persistence of myasthenic findings after chloroquine withdrawal, and ENMG findings suggestive of MG, despite the negative acetylcholine receptor antibody, supported the use of anticholinesterase agents in the case reported. The clinical response was excellent. The association of SLE and MG, although rare, should be investigated in lupus patients complaining of decreased muscle strength and fatigability.

REFERENCES
REFERÊNCIAS

1. Borba EF, Latorre LC, Brenol JCT, Kayser C, Silva NA, Zimmermann AF *et al.* Consenso de lúpus eritematoso sistêmico. *Rev Bras Reumatol* 2008; 48(4):196-207.
2. Drachman DB. Miastenia gravis e outras doenças da junção neuromuscular. *In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jamesson JL (eds.). Harrison Tratado de Medicina Interna, 15ª ed. Rio de Janeiro: Mc Graw Hill, 2002.*
3. Aracena RC. Coexistencia de miastenia gravis y lupus eritematoso sistêmico es más frecuente que lo que pensábamos? *Rev Med Chile* 2006; 134:1203-5.
4. Christensen PB, Jensen TS, Tsiropoulos I, Sorensen T, Kjaer M, Hojer-Pedersen E *et al.* Associated autoimmune diseases in myasthenia gravis. A population based-study. *Acta Neurol Scand* 1995; 9:192-5.
5. Vinagre F, Santos MJ, Silva JC. Lúpus eritematoso sistêmico e fraqueza muscular. *Acta Reum Port* 2006; 31:167-72.
6. Bhinder S, Majithia V, Harisdangkul V. Miasthenia gravis and systemic lupus erythematosus: truly associated or coincidental-two case reports and review of the literature. *Clin Rheumatol* 2006; 25:555-6.
7. Hrycek A. Systemic lupus erythematosus and myasthenia gravis. *Pol Arch Med Wewn* 2009; 119(9):582-4.
8. Carvalho MF, Abrahao TCM, Assaj M. Lúpus eritematoso sistêmico associado à miastenia gravis. *Arq neuropsiquiatria* 1998; 56(7):137-40.
9. Sthoeger Z, Neiman A, Elbirt D, Zinger H, Magen E, Burstein R *et al.* High prevalence of systemic lupus erythematosus in 78 myasthenia gravis patients: a clinical and serologic study. *Am J Med Sci* 2006; 331(1):4-9.
10. Casado E, Gratacós J, Tolosa C, Martínez JM, Ojanguren I, Ariza A *et al.* Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients. *Ann RheumDis* 2006; 65(3):385-90.
11. Gutiérrez SP, Martín JJB, Lara IC, Lebrón CV, Chocan JLC, Arias GM *et al.* Miopatia por cloroquina. *Rev Esp Patol* 2004; 37(3):321-4.
12. Pichon P, Soichot P, Loche D, Chapelon M. Myasthenic syndrome induced by chloroquine poisoning: an unusual clinical form confirmed by ocular involvement. *Bull Soc Ophtalmol Fr* 1984; 84(2):219-22, 225.
13. Sghirlanzoni A, Mantegazza R, Mora M, Pareyson D, Comelio F. Chloroquine myopathy and myasthenia-like syndrome. *Muscle Nerve* 1988; 1(2):114-9.
14. De Bleecker J, De Reuck J, Quatacker J, Meire F. Persisting chloroquine-induced myasthenia? *Acta Clin Belg* 1991; 46(6):401-6.
15. 15. Carvalho FN, Dias RJS, Carneiro AP. Miopatia por corticosteroide. *Acta Fisiátr* 2004; 11(1):39-42.