

## Myasthenia Gravis Associated with Diabetes about an Observation in Dakar, Senegal (West Africa) and Review of the Literature

Soumaila Boubacar<sup>1\*</sup>, Ngor Side Diagne<sup>1</sup>, Djibrilla Ben Adji<sup>2</sup>, Yannick F Fogang<sup>1</sup>, Youssoufa Maiga<sup>3</sup>, Douma Maiga<sup>4</sup>, Moustapha Ndiaye<sup>1</sup>, Amadou G Diop<sup>1</sup> and Mansour Ndiaye M<sup>1</sup>

<sup>1</sup>Department of Neurology, Fann National Teaching Hospital Po Box 5035 Dakar, Senegal

<sup>2</sup>Department of Medicine, National Hospital Po Box 238 Niamey, Niger

<sup>3</sup>Department of Neurology, Gabriel Touré University Hospital Po Box 267 Bamako, Mali

<sup>4</sup>Faculty of health sciences, University of Maradi Po Box 465 Maradi, Niger

\*Corresponding author: Soumaila Boubacar, Department of Neurology, Fann National Teaching Hospital Po Box 5035 Dakar, Senegal, Tel: 971556864636; E-mail: [abounadjma@yahoo.fr](mailto:abounadjma@yahoo.fr)

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### Abstract

Myasthenia gravis is a rare disease with very few confirmed cases described in the African setting. We report the case of a 41-year-old woman with a history of type 2 diabetes, high blood pressure (well monitored), and migraine with aura. She was received at the outpatient neurology consultation for a left ptosis, diplopia, chewing and walking difficulties. She reported abnormal and fluctuating muscle fatigability at effort, responsible for several falls. These symptoms were marked at evening, and were evolving since four years before her consultation in our center. She also reported a history of palpitations, exertional dyspnea, dysphonia, dysphagia and 20 kg weight loss. Neurological examination found a horizontal diplopia, a left ptosis and abnormal weakness at dynamic eyes and limb muscles testing. Otherwise the remaining neurological examination was unremarkable. Repetitive nerve stimulation found a significant compound muscle action potentials decrement. The immunological tests showed a very high level of antibodies to acetylcholine receptors (anti-AChR) at 1220.00 nmol/l (normal value <0.40 nmol/l). Thyroid tests and the remaining biological tests were normal. Thorax CT-scan was normal, with no thymoma. Considering these results, the diagnosis of anti-AchR myasthenia gravis was established. She was started on pyridostigmine 60 mg four times daily associated to her previous hypertension and diabetes therapy. Outcome after five months of treatment was marked by a complete recovery of muscle weakness and weight. Myasthenia gravis is a rare disease, frequently leading to a misdiagnosis. His association with diabetes is well established. It is worth to think about it when dealing with patients presenting fatigue with a history of diabetes.

**Keywords:** Myasthenia gravis; Autoimmunity; Anti-acetylcholine receptors; Senegal

### Introduction

Myasthenia gravis is an autoimmune disease of the neuromuscular junction characterized by fatigability and muscle weakness interesting oculomotor muscles, bulbar or skeletal muscles [1]. It is due to specific autoantibodies responsible for dysfunction of neuromuscular transmission inducing muscle fatigability [2]. Very few confirmed cases of myasthenia gravis associated with diabetes have been described in the African setting. We report a case of anti-acetylcholine receptor myasthenia gravis associated with diabetes mellitus.

### Case Report

A 41-year-old woman with a history of type 2 diabetes, well monitored hypertension and migraine with aura, was received at the outpatient neurology clinic of Fann teaching Hospital in Dakar, for a left ptosis, diplopia, chewing and walking difficulties. She reported abnormal and fluctuating muscle fatigability at effort responsible for several falls. These symptoms were marked at evening, and were evolving since four years before her consultation in our center. She also reported a history of palpitations, exertional dyspnea, dysphonia, dysphagia and 20 kg weight loss. Neurological examination found a

horizontal diplopia, a left ptosis and abnormal weakness at dynamic eyes and limbs muscles testing. Otherwise the remaining neurological examination was unremarkable.

Repetitive nerve stimulation showed significant decrements of compound muscle action potentials (CMAP) of deltoid, anconeus, abductors of trigeminal and orbicular of the left eye muscles. Immunological testing revealed a very high level of antibodies directed against receptors for acetylcholine (anti-AChR) at 1220.00 nmol/l (normal value <0.40 nmol/L), no other antibody dosage was carried out. Thyroid tests including free T3, thyroid hormones (Triiodothyronine) and free T4 (Tetraiodothyronine) were normal. The rest of the biological work-up including full blood count, serum creatinine and urea, serum electrolytes, the C-reactive protein (CRP), erythrocyte sedimentation rate, glycemia, creatinine phosphokinase (CPK), HIV serology was unremarkable. There was no thymoma on chest CT scan which was otherwise normal.

Considering these results, the diagnosis of anti-AchR myasthenia gravis was established. The patient was started on pyridostigmine 60 mg four times daily, associated to her ongoing hypertension and diabetes treatments. A list of drugs contra-indicated in myasthenia gravis was also given to the patient.

Outcome after five months of treatment was marked by a complete disappearance of the ptosis, regression of diplopia, motor and important weight recovery.

## Discussion

Autoimmune myasthenia gravis is a rare disease, with an estimated prevalence of 50-200 per million [3], and an incidence of 2-5 cases per year per million population [4]. Myasthenia gravis can be observed at all ages and within the two genders, but there is a clear predominance of female cases (60%-70%) before 50 years of age; Beyond the age of 50 years the incidence and prevalence gaps between males and females are reduced [5]. Difference in the clinical presentation, age of onset, autoantibody profile and the presence or absence of thymic pathology allow to identify several subclasses of myasthenia gravis. Antibodies involved in various forms of myasthenia gravis are directed against proteins of the motor end-plate at the neuromuscular junction [5]. In myasthenia gravis with anti-AChR antibodies, the AChR density is reduced, thereby reducing end-plate potential [5].

Genetic factors for autoimmune susceptibility to myasthenia gravis and diabetes mellitus have been identified. A gene linked to the early phase of the disease (sialadenitis and insulinitis perished), has been localized on chromosome 1, near the Bcl-2 locus. This location coincides with increased resistance of lymphocytes to apoptosis. This abnormality may facilitate the persistence of autoreactive clones. In myasthenia gravis, the role of the gene encoding for the alpha sub-unit of the muscle acetylcholine receptor may encode an alpha sub-unit, which may be presented to the immune system by HLA class II molecules, leading to an auto-immune process [6].

Our patient is known with diabetes mellitus for many years, with a good control of her disease, and in whom the diagnosis of anti-AChR myasthenia gravis was recently confirmed. Three forms of auto-antibodies are conventionally described in autoimmune myasthenia gravis: anti-AChR antibodies, anti-muscle-specific receptor tyrosine kinase (anti-MuSK MG), anti-LRP4 antibody (MG-LRP4). In seronegative myasthenia gravis, patients seem to have low titers of anti-AChR antibodies that are not detected by conventional tests available. This was demonstrated through genetically modified HEK cells expressing different subunits of muscular AChR, and rapsyn which is an intra-cytoplasmic protein stabilizing the AChR [6,7]. This study showed that up to 60% of seronegative myasthenia gravis patients had antibodies against AChR aggregate at the cell surface. These patients have a similar profile in terms of clinical presentation, response to treatment and thymic abnormalities compared to patients with anti-AChR antibodies [7].

At least three different mechanisms seem to be involved in the reduced number of AChR at the neuromuscular junction in patients with myasthenia gravis: AChR blocking by antibodies [8]; antigenic modulation corresponding to acceleration of the internalization of AChR with endocytosis and intracellular proteolytic degradation by lysosomal enzymes [9]; and destruction of postsynaptic membrane by complement attack complex [5].

The diagnostic confirmation is based on the following criteria [3]: Favorable effect with cholinesterase inhibitors, electrophysiological examination revealing abnormal neuromuscular transmission; presence in the serum of acetylcholine receptors antibodies (anti-AChR). If negative anti-MuSK antibodies research should be considered; Chest CT scan or MRI to look for a thymoma, a benign or

malignant tumor present in about 20% of patients with myasthenia gravis.

Diagnosis of autoimmune myasthenia gravis with anti-acetylcholine receptor antibody was established in our patient based on the presence of a clinical myasthenia syndrome, significant decrement at repetitive nerve stimulation, highlighting a post-synaptic neuromuscular blockade, presence of very high level of antibodies against acetylcholine receptor AChR and the absence of another cause that could explain her condition. Chest CT carried out in our patient did not objectify thymoma.

Autoimmune diseases associated with myasthenia gravis must be systematically sought: dysthyroidism (Basedow thyroiditis) affects 5%-10% of patients (T4, TSH, thyroid antibodies), lupus, rheumatoid arthritis, Biermer and other rare diseases [3]. Thyroid function test and inflammatory parameters were normal for our patient.

Concerning treatment of myasthenia gravis, the use of cholinesterase inhibitors and avoiding of contra-indicated drugs are always recommended [3]. This was the case for our patient, who had received a treatment with pyridostigmine, and the delivery of a list of contraindicated drugs in case of myasthenia.

When myasthenia gravis remains disabling despite the maximal use of cholinesterase inhibitors, these options should be considered [3]: short-term treatment of a severe relapse with plasmapheresis or intravenous immunoglobulin; disease-modifying treatment including thymectomy for patients under 45 years, corticosteroids, azathioprine or mycophenolate mofetil which are immunosuppressive, can be used as second-line treatments.

When myasthenia gravis becomes refractory to conventional treatments, more potent immunosuppressive drugs can be used (cyclosporine A, cyclophosphamide, rituximab). Physical activity, monitoring and dietary measures to prevent or treat long-term corticosteroid therapy side-effect should be started [3]. Our patient evolved well under cholinesterase inhibitor treatment and education. Neither corticosteroids nor any immunomodulatory treatment were administered to our patient because of a good clinical outcome. Correlations have been shown between the disease severity and loss of AChR measured in muscle biopsies [10], but not with the antibody level [5]. The case of our patient is in line with these findings. In fact, despite the very high level of antibodies, there was a good clinical response to treatment.

## Conclusion

Myasthenia Gravis is a rare autoimmune disease with clinical presentations which can be misleading, with potentially many cases of misdiagnosis or diagnostic delay. Its association with diabetes mellitus is reported by some neurogenetic researches. It is worth to think about it when dealing with patients presenting fatigue with a notion of diabetes.

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