



# Grave's disease associated with myasthenia gravis: a case report

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## Abstract

**Purpose:** The unfortunate association between myasthenia gravis and Graves' disease is not widely appreciated. It would be consistent with a genetic predisposition for autoimmune disease. The frequency of this association is variously appreciated in the literature.

**Case:** We report a case of a 20 years old patient with a two years history of Graves' disease, who presented with a myasthenic syndrome leading to an acute respiratory failure. This was found to be reversible with prostigmine, and the diagnosis of myasthenia gravis (MG) was confirmed by EMG and positive immunology. There was a positive response to medical treatment.

**Discussion:** The frequency of this association is variously appreciated in the literature. MG has been reported to be discovered simultaneously with, or prior to, the diagnosis of Graves' disease, but is most commonly subsequent to it. The similarity of symptoms makes diagnosis difficult. Furthermore, an excess of thyroid hormones worsens MG and the existence of MG imposes certain precautions in the management of hyperthyroidism.

**Conclusion:** Research is called for into the surveillance and management of specific manifestations of the co-occurrence of these conditions.

**Keywords:** Grave disease, myasthenia gravis, association, senegal

## Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular condition characterized by the presence of anti-acetylcholine receptor antibodies. It can be generalized, or localized to specific muscle groups, and can be an isolated finding, or in association with other auto-immune conditions such as Hashimoto's thyroiditis, Graves' disease [1], systemic lupus erythematosus (SLE), or rheumatoid arthritis. Although the association of Graves' disease and MG is known [2], it has been rarely described in the African medical literature [3,4].

The following description of a case in Senegal permits us to consider clinical, therapeutic and prognostic aspects of this association.

## Case presentation

We present a case of a 20 years old nulliparous patient, with a background of a psycho-affective shock in 2009 (parental divorce) and a family history of Graves' disease (her father). She had been diagnosed with Graves' disease in June 2010 and was being treated medically with carbimazole (30 mg/day) and

propranolol (20 mg/day).

She first noticed a fatigability of the lower limbs during walking and stair climbing in January 2012, which spread to involve the upper limbs. She then began to have visual difficulties (variable, bilateral ptosis and intermittent diplopia) and developed a difficulty in chewing solid food. After a fall, caused by collapse of her legs, she was admitted in a local clinic from April 13<sup>th</sup> to 21<sup>st</sup> 2012.

Investigations performed on admission showed an hyperthyroidism-with a suppressed TSH of <0.005 (Normal: 0.1 to 4 mUI/L) and a raised T4 of 183 ng/L (Normal: 7 to 23 ng/L)-prompting an increase in treatment doses (carbimazole 60 mg/day and Propranolol 40 mg/day). There were no abnormalities seen on cranial magnetic resonance imaging (MRI).

Given the lack of improvement of muscular symptoms, she presented to a different local clinic on the April 30<sup>th</sup>. On admission, she was found to have:

- 1) A nasal voice, bilateral ptosis predominant on the right side, associated with intermittent diplopia,
- 2) A vascular, non-compressive goiter and acquired, bilateral,

reducible exophthalmos,

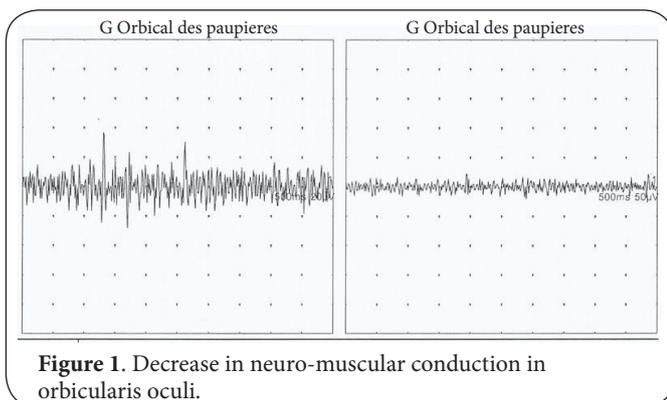
- 3) A myogenic syndrome associating: fatigability at effort, reduced idiomuscular reflexes, and an amyotrophy of the scapular muscles associated with an inability to raise the arms above the horizontal.

Sensitivity was intact, with normal reflexes. Skin and joints were normal, and there were no abnormalities on examination of the cardiovascular and respiratory systems.

Approximately two hours after admission, the patient presented acute respiratory failure, with pharyngeal pain and quickly progressive respiratory arrest. This was reversed after 5 minutes of cardiopulmonary resuscitation (CPR), Ambu mask ventilation, and a test dose of Prostigmine. A hypothesis of Graves' disease complicated by myasthenia gravis was formed.

Electrophysiology, performed on day three of admission after 3 doses of sub-cutaneous prostigmine, demonstrated a decrease in neuro-muscular conduction of 19 to 62% in orbicularis oculi (**Figure 1**) and abductor pollicis brevis, supporting a diagnosis of a generalized, severe myasthenia.

Computer Tomography (CT) scan of the thorax showed no abnormalities, apart from a small (15 mm) thymic remnant. Doppler- Ultrasound of the neck demonstrated hypertrophy of the thyroid gland with hypervascularisation (**Figure 2**).



**Figure 1.** Decrease in neuro-muscular conduction in orbicularis oculi.

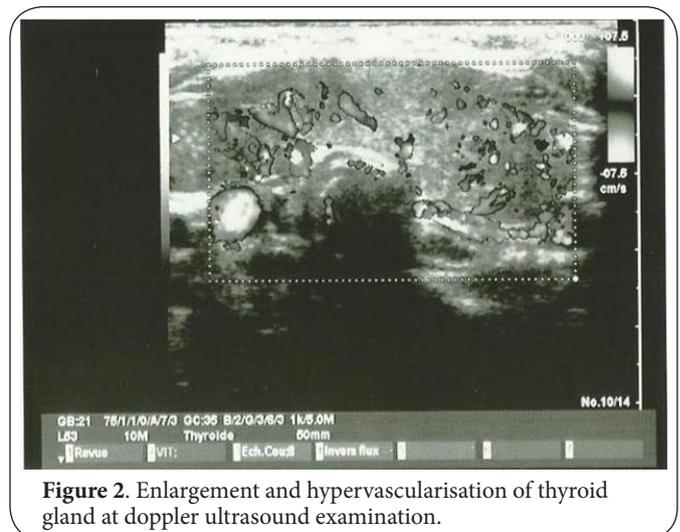
### Immunology findings

- 1) Anti-Nuclear-Antibodies (ANA): positive (1/160, homogeneous)
- 2) Anti-U1 RNP antibodies: positive (9 IU)
- 3) Anti-DNA antibodies and Anti-Sm antibodies: negative
- 4) Anti-Acetylcholine Receptors antibodies: positive (16.9 nmol/L, N<0.2 nmol/L)
- 5) Anti-TSH Receptors antibodies: positive (2.4 UI/L, N<1 UI/L)

Thyroid function tests demonstrated free T4 of 17 ng/L and TSH of 0.127 UI/L.

Full blood count, muscle enzymes, and 24 hours urinary protein collection were all normal.

Treatment was initiated as follows: pyridostigmine 240 mg/day, prednisolone 10 mg/day, with a reduction in the dose of carbimazole from 20 mg to 10 mg daily.



**Figure 2.** Enlargement and hypervascularisation of thyroid gland at doppler ultrasound examination.

The patient improved on treatment with a regression of myasthenic signs, including reduced fatigability and an improvement of difficulties in mastication.

### Discussion

Myasthenia gravis is an autoimmune disease of the neuro-muscular junction. Its clinical expression is variable, ranging from a localized ocular form, to a severe, generalized attack [5,6]. It can be associated with other autoimmune conditions, such as autoimmune thyroid disease, especially hyperthyroidism [1-6].

The prevalence of autoimmune thyroid disease is higher in MG patients compared to the general population [4]. The reasons for the co-occurrence of the two conditions have not yet been elucidated. The chemokine CXCL10 and its receptor CXCR3 seem to play an important role in the pathogenesis of systemic or organ specific autoimmune diseases. High levels of CXCL10 are found in case of organ specific autoimmune disease like Grave disease or systemic autoimmune diseases and seems to be marker of amplified host immune response that perpetuate the autoimmune process and could lead to the association of the two diseases [7].

However, the association is most often described in families where there is a previous history of one of the conditions, which suggests that it may be related also to a genetic predisposition for autoimmune disease [4,8]. In our case, there was a family history of Graves' disease in the patient's father. The estimated frequency of the association is variable: 2-3% of those with hyperthyroidism also have MG, and 2-17.5% of those with MG suffer thyrotoxicosis [3,4]. Epidemiologically, MG shares the female predominance of Graves' disease, with an age of incidence peaking between 20-40 years of age.

In our case, Graves' disease preceded MG by two years. According to the literature, the diagnosis of MG preceded that of hyperthyroidism in 30-35% of cases, the conditions were diagnosed simultaneously in 20-25% of cases, and hyperthyroidism preceded the MG diagnosis in the majority (40-50%) of cases.

The most common etiology of hyperthyroidism is Graves' disease [4], as in our case.

The patient presented a generalized myasthenia. Amongst previously reported cases however, hyperthyroidism is preferentially associated with spino-bulbar forms of MG [2,9]. The principal ocular signs of Graves' disease are exophthalmos and retraction of the superior eyelid. An associated MG should be considered if there is ptosis and/or nystagmus [6,9]. The disproportionate association between thyroid eye disease and MG seems to be related to cross-reactivity against an epitope or autoantigen that is common to the thyroid and the ocular muscles in the context of genetic predisposition [6]. Myasthenia gravis illustrates the importance of the thymus in autoimmune diseases by its frequent association with thymus anomalies, and the important role of the thymus in its pathogenesis [4,8,10]. Thymus anomalies which may be associated with MG are: follicular thymus hyperplasia in 65% of cases; thymoma (epithelial tumor) in 10-15% of cases [8,10]. Thymus hyperplasia has also been described in cases of Graves' disease without associated myasthenia. In these cases, the thymus mass was assessed, and a shrinkage or regression was universally observed following medical anti-thyroid treatment [8]. These findings justify investigation for a thymus anomaly, but in our case thoracic CT scan showed a non-significant (15 mm) thymus remnant.

With regards to immunology, ANA positivity led us to search for an associated SLE. Clinically however, there were no cutaneous or articular symptoms. Full blood count showed no cytopenia, 24 hour urinary protein collection and anti-DNA and anti-Sm antibody titers were also negative. ANA positivity was therefore thought to be related to the MG; it has been described in 50% of MG patients [3,11]. Equally, weak positivity of anti-U1 RNP antibodies has been reported in autoimmune diseases other than Mixed Connective Tissue Disease (Sharp syndrome). In our case, myositis was ruled out, given normal muscle enzymes.

Anti-TSH receptor antibodies were positive, as in a quarter of cases of MG [3]. Anti-acetylcholine receptor antibodies are positive in 85% of cases of generalized MG, and 66% of cases of ocular myasthenia, but only in 35 to 50% of cases where there is an associated hyperthyroidism [8,11]. In our case anti-Ach R antibodies were strongly positive.

The prognosis of combined MG - Graves' co morbidity is variable: in about 40% of cases the myasthenia improves whilst the hyperthyroidism worsens; in 20% of cases the hyperthyroidism is clinically controlled but the myasthenia is not.

Both thyrotoxicosis and synthetic thyroid hormones worsen neuromuscular blockade, probably due to a direct interaction at the neuromuscular junction [4,9].

This relationship between thyroid hormones and the neuromuscular junction could explain the fact that in our case the myasthenia syndrome appeared when there was a high excess of thyroid hormone (free T4 of 183 ng/l). It is important to reach euthyroid status rapidly, most often with radical treatment;

either with radioiodine or with a subtotal thyroidectomy where indicated.

The presence of MG imposes precautions in the management of Graves' disease, whether treatment is medical (beta-blockers and anxiolytics) or surgical, because of the risk of a life-threatening myasthenia crisis [3,9]. The CXCL10 chemokine could be a therapeutic target and studies are conducted to determine if the modulation of the interleukin related secretion of chemokine by antichemokine agent is effective [1].

High dose corticosteroids may achieve remission of both pathologies. In our case, we started with a low dose of steroids, because a transitory worsening of MG that is sometimes observed on initiation of corticosteroids would have carried significant risk.

## Conclusion

A co-occurrence of myasthenia gravis and Graves' disease is not a coincidence, and it is one that clinicians should always have in mind. MG should be thought of if a patient with Graves' disease presents with ptosis, nystagmus, and palsy of the superior-inferior oblique muscles or a myogenic syndrome which persists despite thyroid hormone control. Diagnosis will be more obvious if hyperthyroidism presents on a background of known MG. Co-existence is variable with time, and therefore requires careful follow-up.

## Competing interests

The authors declare that they have no competing interests

## Authors' contributions

Authors' contributions	AP	DGD	SN	AF	NDS	FSN
Research concept and design	✓	--	--	--	--	--
Collection and/or assembly of data	✓	✓	--	✓	✓	--
Data analysis and interpretation	✓	✓	✓	--	✓	✓
Writing the article	✓	✓	--	--	--	--
Critical revision of the article	--	--	✓	✓	--	✓
Final approval of article	✓	--	--	--	--	--
Statistical analysis	✓	✓	✓	✓	✓	✓

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