

The Autoimmune Myasthenia Gravis- Study of a Series of 18 Cases

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Abstract: Myasthenia gravis is a rare disorder of autoimmune origin, caused by dysfunction of neuromuscular transmission. Clinically it manifested by a muscular weakness accentuated to the effort. We report the results of a retrospective study of 18 cases of myasthenia gravis in the department of neurology of the military hospital Moulay Ismail of Meknes during a period of 10 years. The sex ratio for our patients was 3.5. 67% of them were between 20 and 40 years old. The average deadline to diagnosis was two years. A personal history of Graves' disease was present in 11% of our patients and type 1 diabete in siblings in 11% of cases. The inaugural symptoms were progressive in 50 % of the cases, affecting mainly the eye (94 %), the pharyngo-laryngeal region (67 %) the jaw (44 %), the roots of the members (33 %), the infringement of the respiratory muscles (22 % of the cases) and the fall of the head (6 %). The generalized form of the disease predominated at the time of diagnosis (67%), and the search for anti-acetylcholine receptor (anti-RAch) antibodies was positive in 89% of the cases. Thoracic imaging revealed thymoma in 33% of cases and thymic hyperplasia in 17% of cases. All patients received an acetyl cholinesterase inhibitor. 33% of the patients in our series required a background treatment, consisting of corticosteroids alone (22%) or corticosteroids and immunosuppressive agents (11%). Thymectomy was performed in 56% of our patients.

Keywords: Autoimmune myasthenia gravis, Corticosteroids, Thymectomy, Immunosuppressive agents.

INTRODUCTION

The Myasthenia gravis is an autoimmune disease due to specific autoantibodies that induce a dysfunction of neuromuscular transmission, the consequence of which is an excessive fatigability of the muscle striated in the effort. It was described for the first time in 1672 by Thomas Willis, and then repeatedly evoked in the medical literature until 1973 when its autoimmune character was demonstrated by Patrick and Lindstorm in an experimental try in the rabbit [1]. Relatively rare, its prevalence is estimated between 14 and 20 cases per 100 000 inhabitants and can occur at any age but all the same keep a clear female predominance. It is characterized by a very heterogeneous and variable clinical symptomatology according to the various affected muscular territories and a whimsical evolution marked by episodes of pushes interrupted with remission phases with possibility of an attack of the respiratory muscles which makes it all its gravity.

We collected observations of myasthenia in the service of neurology of the military hospital Moulay Ismail of Meknes. We analyzed the epidemiological, clinical, paraclinical, therapeutic and evolutionary data

in our series and compare our results to those of the literature.18

PATIENTS AND METHODS

This is a retrospective study carried out in the department of neurology of the Military Hospital Moulay Ismail of Meknes between March 1, 2005 and March 1, 2015 concerning 18 patients whose diagnosis of myasthenia gravis was retained in front of a compatible clinical syndrome (muscular fluctuating oculomotor, bulbar or limb muscle, worsening stress) associated with at least two of the following criteria:

- Clinical answer to an acetylcholinesterase inhibitor injection.
- Compatible Electromyogramme (décrément of more than 10 % with stimulation between 2-5 Hz).
- High Rate of antibody anti receivers of the acetylcholine.

All the patients had, during the diagnosis, a thoracic imaging: thoracic scanning (TDM) or a lung radiography (RX). An immunological assessment (TG antibody, anti-TPO antibody, anti-FI antibody, anti-DNA antibody, AAN) and a metabolic assessment including dosage of thyroid hormone (TSH, T3, T4) and dosage of vitamin B12). The severity of the

disease was evaluated according to the Myasthenia Gravis Foundation of America (MGFA) classification [13]. All the clinical data and complementary examinations were collected from the medical file.

RESULTS

In this series, the average age of patients at the time of diagnosis was 36.4 years. Patients aged between 20 and 40 accounted for 67% of all patients, followed by the 40-50 year age group (22% of cases), while the group of patients with myasthenia gravis before the age of 20 accounted for only 11% of cases.

The sex-ratio woman / man was 3.5. The mean age in the appearance of the first revealing sign was of 33 years and the median of the diagnosis delay (the interval between the first revealing sign and the date of the first one EMG) is of approximately 2 years. In the analysis of the personal histories, Graves' disease was found in 11 % of our patients, and histories of type 1 diabetes in sibling in 11 % of the cases.

Inaugural symptoms were progressive in 50% of cases with ocular involvement in 94% of cases with unilateral or bilateral ptosis, with or without diplopia, bulbar in 67% of patients, limb root involvement in 33% patients. Respiratory muscle involvement (22%) and head loss (6%) were much rarer.

In the clinical classification of the Myasthenia Gravis Foundation of America (MGFA), our patients were distributed as follows:

- Stage I: 4 patients (22%).
- Stage II A: 7 patients (38%)
- Stage II B: 5 patients (28%)
- Stage III A: 1 patient (6%)
- Stage IV A: 1 patient (6%)

89% of our patients had antibodies to acetylcholine receptors. No patient had a positive anti-Musk in anti-RACH seronegative patients. The thoracic imaging revealed a thymoma in 33% of cases and thymic hyperplasia in 17% of cases. Immunological assessment and metabolic assessment allowed the diagnosis of autoimmune thyroiditis in two patients (11% of cases) and Biermer anemia in three patients (17% of cases). At the time of diagnosis, 33% of patients had ocular myasthenia gravis on admission, of which 50% developed myasthenia gravis after 2 years of follow-up. 67% of patients had myasthenia gravis at admission. All the patients were treated with an acetylcholinesterase inhibitor. Only 33 % of the patients required at the same time a treatment of bottom constituted by corticoid only in 22 % of cases and the association corticosteroid therapy and Aziathoprine in 11 % of cases. The mean age at onset of treatment was 36.5 years, with extremes ranging from 4 years to 68 years. Thymectomy was performed in 65% of patients. 80% of these patients had radiological abnormalities

(thymoma, thymic hyperplasia) and 20% had no abnormalities in thoracic imaging. Thymectomy was followed by complementary radiotherapy in 20% of patients (malignant thymoma)

DISCUSSIONS

The Autoimmune myasthenia gravis is a relatively rare disease. Its prevalence has increased over time with recent estimates being situated between 14 to 20 by 100,000 [2]. This increase in prevalence is due to improvements in the means of diagnosis and treatment and to the increase in longevity of the population generally. Its incidence varies from 1.7 to 10.4 / million / year depending on the populations studied, being able to reach 21 / million in Barcelona for example [3]. The autoimmune Myasthenia gravis is traditionally considered as a disease of young subjects with a higher incidence in young women than in young men [4, 5], but recent studies showed that myasthenia autoimmune can appear at any age and That its incidence is influenced by sex and age with the presence of 2 frequency peaks: women are affected almost three times more often than men in early adulthood (age <40 years), while the incidence is approximately equal during puberty and after the age of 40 years. After age 50, the incidence is higher in men [6].

In our series, we listed 18 cases of myasthenia gravis between 2005 and 2015. This figure is not representative of all the cases of myasthenia gravis in the region because this series is very selective (military and their families) and concerns only One hospital in the region. However, we also observed a feminine ascendancy. The global sex ratio is 3.5 with a peak frequency in early adulthood with a very clear female predominance (8 women per 1 man), an equality of incidence among the under-20 and a slight male predominance Beyond 50 year, not significant enough to be considered a peak. These results are almost similar to those of most studies.

The Myasthenia gravis is not a hereditary disease, but there is, however, a predisposing genetic field, which has been demonstrated in an HLA study and has highlighted the high frequency of some alleles that appear to favor The appearance of myasthenia gravis [7]. In our series the association with Graves' disease and the typical diabetes 1 was found in 11 % our patients, This is the way frequently in the literature, associations are described with other autoimmune diseases such as rheumatoid arthritis, Biermer anemia, systemic lupus erythematosus, sarcoidosis, Gougerot-Sjögren's syndrome, polymyositis, hemorrhagic rectocolitis, pemphigus, thrombocytopenic purpura or autoimmune hemolytic anemia[8].

However, the autoimmune disease most commonly associated with the myasthenia gravis stays autoimmune thyroiditis, particularly Graves' disease,

whose frequency according to the series varies from 2-17.5% [7]. Thus, the thyroid balance sheet must be systematic in front of any suspicion of myasthenia, and the cervico-thoracic scanner should not only seek the presence of a thymoma but also try hard to eliminate a thyroid goiter.

In the literature a thymoma is found in 10 to 15 % of the patients, however in our study, the number of thymomas diagnosed seems more important, seen that 33 % of the patients of our series presented a thymoma with an average age of 42 years. While 17 % of the remaining patients had thymic hyperplasia.

The clinical forms of the myasthenia gravis are classified according to the age of onset, clinical signs, the presence or not the antibodies anti-RACH and the presence of thymic abnormalities. Classically, irrespective of age, the initial symptomatology begins in 60% of cases with ocular involvement, 20% with bulbar or facial involvement, and 20% with axial or peripheral muscle deficiency [9] what suits to the results of our study.

Myasthenia gravis with positive antibodies are the most frequent shape of autoimmune myasthenias gravis. Anti-RACH Antibodies are usually found in 80 to 90 % of the generalized myasthenias and in 50 to 60 % of the ocular myasthenias [10, 11]. Anti-Musk antibody was detected in 40% of patients with seronegative myasthenia [10, 12]. Recently, forms with LRP4 antibodies have been identified. This subtype was described independently in 2011 by two groups from Japan and Germany, mainly at women of early adulthood with a clinical phenotype that closely resembles that of myasthenia anti-RACH positive while being less severe than myasthenia anti-Musk (+) [13,11]. However, even after the identification of anti-LRP 4, some myasthenic patients remain still triply-seronegative (on the order of 2 to 5% of patients) [12].

The treatment of autoimmune myasthenia gravis aims to directly improve neuro-muscular transmission and also to reduce the production or presence of the nicotinic acetylcholine receptor (achR). The therapeutic arsenal available in myastheniagravis includes symptomatic treatments and immunoregulatory treatments acting in short or in long-term [13]. Acetylcholinesterase inhibitors are the first line treatment with a rapid onset of effect, for all types of myasthenia gravis (ocular, generalized myasthenia gravis seronegative or positive patients). Plasmapheresis and intravenous immunoglobulin (IVIg) share the same indication and constitute the treatment of choice for severe flare-ups and myasthenic crisis. Their main advantage is the rapid onset of the effect. Three to five plasma exchanges or IVIg infusions (1.2 to 2 g/b.w administered over 2-5 days) are usually recommended. In case of suspected thymoma, thymectomy should be

always performed. The option of thymectomy is discussed in young patients less than 50 years old with unstable myasthenia gravis, even if thymoma lesions are not suspected.

Corticosteroids and / or immunosuppressive agents are used in severe forms of disease (a persisted disabling muscular deficit or swallowing disorders and / or fatal respiratory failure) despite a well-conducted treatment by acetylcholinesterase inhibitors. A few randomized studies have shown the efficacy of the therapeutic agents.

Corticosteroids are considered a major treatment of myasthenia gravis but the doses and periods of time are still being debated. The combination of corticosteroids and immunosuppressive agents are recommended early to spare corticosteroids. Whatever the evolution, the treatment of myasthenia gravis is an evolutionary treatment that it should be modulated regularly.

CONCLUSIONS

Our retrospective study, coupled with the analysis of the latest data from the literature, allowed us to reaffirm fundamental characteristics of myasthenia gravis:

- It's an affection that can be seen at any age, with 2 frequency peaks, the first occurring between the second and fourth decades, with a strong female predominance. And the second peak, observing from the age of 50 with a clear masculine tendency.
- It's pathology with a highly variable and heterogeneous clinical presentation according to the clinical form and the serological form. Hence the importance of distinguishing the immunological form to allow better therapeutic management.
- The pillars of the treatment of myasthenia gravis used today were introduced more than 40 years ago with a therapeutic arsenal constituted mainly by pyridostigmine, corticotherapy, azathioprine and thymectomy. However, with the advent of promising new drugs such as Rituximab and the questioning of the beneficial effect of thymectomy on myasthenia , it would be possible that the treatment of the myasthenia undergoes some change by the end of this decade

Competing interests

- The authors declare no competing interest.

Authors' contributions

- All the authors have read and agreed to the final manuscript

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