Review Article

MYASTHENIA GRAVIS, THYMOMA, AND THYMOMECTOMY: THE CLINICAL INTERPLAY

Oyewole Samuel[1], Otohinoyi David A.[1], Akinfisoye Toluwalase[1], Oshobu Ibukun[1], Babatunde Ajibola[1], Abe Temidayo[1], Olunu Esther[2], Fakoya Adegbenro O.J.[3]

[1]Medical Student, [2]Instructor, [3]Associate Professor, All Saints University School of Medicine, Dominica.

ABSTRACT

Myasthenia gravis is an autoimmune disorder that places patients in debilitating condition. It currently affects 14 to 20 per 100,000 population. Its pathogenesis involves the destruction of acetylcholine receptor by antibodies produced by lymphocytes in the thymus gland. Symptoms could vary from impair extraocular muscles to generalized weakness. The antibodies have also been reported to affect other muscle structure within the body such as cardiomyocytes, leading to arrhythmia episodes which could be fatal. This review is a student project and involves the assessment of myasthenia gravis and the interplay between thymoma and thymomectomy.

KEYWORDS: Myasthenia gravis; Thymoma; Thymomectomy; Autoimmune; Acetylcholine receptors.

INTRODUCTION

Myasthenia graves (MG) is an autoimmune disorder which presents as a result of antibodies which act against the acetylcholine receptors at the neuromuscular junction mostly immunoglobulin G (IgG) from T-cells in the thymus [1]. Myasthenia graves are usually characterized by fluctuating skeletal muscle weakness that often affects specific muscle groups [2]. It is uncommon in the western world but more common in Asia, presenting mostly as extraocular muscle myasthenia graves (EOMG) with a growing prevalence rate and a stable mortality rate, elderly people with the disorder usually exhibit bulbar palsy signs [1, 3]. The illness is usually associated with the acetylcholine receptor (AChR), which is a pentameric transmembrane protein with an alpha subunit of the alpha2, beta, delta, and epsilon complex forms the adult receptor but the others such as the beta, delta and epsilon can also induce myasthenia graves [4, 5].

MHC-II antigen and invariant chain processing HLA -DRB, as well as polymorphism of cathepsin V (Cat V), is usually associated with the early onset of myasthenia gravis [6]. For EOMG patients, the RNA expression of the epsilon subunit is about 50% of myasthenia graves because the automatic sensitivity in myasthenia graves may occur in the thymus [4].

The antibodies are usually intrathymic therefore people who undergo thymomectomy exhibit improved clinical symptoms. Patients with myasthenia graves exhibit symptoms like thymus hyperplasia and thymoma (which is a paraneoplastic disease associated with myasthenia graves). The etiology of MG is hypothesized as the possibility of an intrathymic protein becomes cleaved by granzyme B (GrB) which is a protease present in cytolytic T-cells. Nk-cells also produces a neoantigen which is then recognized as foreign antigens. This mechanism of action is also common in most autoimmune diseases [7]. Patients without known antibodies are zero negative for myasthenia graves while those with antibodies like the anti -AChR are positive myasthenia graves patients, they usually present with thymic hyperplasia which 60% are seropositive. Inflammatory cytokines like IL-2, IFN-gamma, IL-1, and IL-6 have been linked with myasthenia graves [7].

Classification of myasthenia gravis and its interplay between thymoma and thymomectomy:

MG is classified into various subgroups according to; the age of onset; presence or absence of abnormal thymus findings; muscle autoantibodies

DOI: 10.5455/ijcbr.2018.42.17

eISSN: 2395-0471
pISSN: 2521-0394

Corresponding author: Dr. Adegbenro Omotuyi John Fakoya, All Saints University School of Medicine, Dominica.
Email: gbenrofakoya@gmail.com

involved; and the skeletal muscles affected, such as ocular MG meaning only extraocular muscles are affected or generalized MG which implies muscle weakness in different body parts[8].

The cutoff age used to differentiate between early, and late-onset usually varies across studies but is generally between ages 40-60. This review will consider the age groups of early onset (<50 years) and late onset (>50 years) [9].

Early onset MG is more commonly associated with females, patients usually have thymic hyperplasia and thyroid dysfunction. Late-onset MG is more commonly associated with males, patients usually have normal thymic histology and are associated with the severe form of the disease and may occur concurrently with thymoma [1, 10]. Aside from these differences, *titin* can also be used to differentiate between early onset and late onset [11]. They are an indicator of thymoma in early-onset MG while those without thymoma are usually late onset MG [11].

Some other muscles proteins like muscle-specific tyrosine kinase (MUSK) are usually attacked by antibodies in some cases of MG which present with severe symptoms that are mainly respiratory related to ocular muscles spared [10]. It usually has an earlier onset and is more common in females with a normal thymus histology [10]. There also some cases of MG in which no antibodies are discovered in the patient, and this is referred to as Seronegative MG [10].

Congenital myasthenia which occurs when antibodies to AChR are transferred from mother to a child usually do not last long and does not recur later in life [12, 13]. Thymectomy and immunosuppressive treatment usually do not affect this condition because it is not an immunologic disease [13].

Thymoma-associated MG can occur in either male or female usually within 40-60 years with peak age onset at 50 [10]. It is usually associated with high level of AChR receptors, and antibodies to titin and ryanodine receptors (striated muscle proteins) [10, 14]. Thymoma results from the excessive growth of epithelial and regional thymic cells which can differentiate immature T-cells into mature T-cells and have them transported into the periphery which is known to cause MG [14]. The T -cells produce epitopes causing cross-reactions with the striated muscle proteins and their receptors (AChR, titin, and ryanodine receptors) [15].

MG Patients with thymoma have generalized weakness of the bulbar, neck, and respiratory muscles. It is a more severe disease which indicates its worse prognosis compared to non-thymoma associated MG and involves a higher level of immunosuppressive treatment [8]. Patients with thymoma are usually recommended for thymomectomy, which is the surgical resection of the thymic tissue, but studies reveal it usually does not affect the prevalence of MG in patients [8]. It was also noted that patients diagnosed at the age of 55 or older with thymoma-associated MG had a poorer prognosis when the period between the time of diagnosis and thymectomy was less than a year [13].

Myasthenia gravis and extrathymic manifestations

MG has also been reportedly associated with extrathymic manifestations. The consumption of immunosuppressant by patients also increase the chances for malignant tumors in other location of the body to manifest. Although, the risk and characteristics of the tumors have not been well understood [16]. Myasthenia Gravis is an autoimmune disorder affecting AChR on skeletal muscles amongst other places. Cardiac muscles are also included as it has a parasympathetic innervation and thus presents as arrhythmias and heart failure. Another study investigating reports from 2003-2013 showed that 97% of patients with MG had antibodies against cardiac muscles. Other complications reported in the study included anticholinesterase induced AV block with abnormal ECG readings, cardiomyopathy, and giant cell myocarditis (GCM) [17]. GCM was also recorded in a 72-year-old patient medicating on azathioprine with no relationship amongst the area of inflammation and IgG deposition. Cases of GCM after thymoma resection was also reported with the presence of CD3 lymphocytes, CD68 histiocytes and giant cells on histopathology. Autopsy proven myocarditis occurred in a case of stage IVa thymoma with positive AChR antibody titers but without clinical MG following chemotherapy. Two cases of invasive thymoma developing GCM and myositis were also reported [18].

Asymptomatic GCM in patients with MG with strongly positive striational antibodies were fatal.

The etiology behind GCM remains unclear, and its

relationship with MG is not exclusive. GCM has been reported in other autoimmune disorders including Crohn's disease, rheumatoid arthritis, and systemic lupus erythematosus [17]. Risk factors for GCM include increased age and thymoma. In some cases, pericarditis has been linked to GCM.

Treatment modalities: The treatment for myasthenia gravis could either be medical or surgical (thymectomy).

As is well-known acetylcholine is the major neurotransmitter implicated in MG, so it is not farfetched that the first line of treatment for the disease is anticholinesterase drugs [10]. Anticholinesterase works by preventing the breakdown of acetylcholine by cholinesterase thus increasing the amount of acetylcholine in the synaptic cleft [18]. It causes a temporary relief from symptoms which reappears when the effect of the drug wears off [10]. Another form of treatment is immunomodulatory (immunosuppressive) drugs which modify the functioning of the immune system either by suppressing the number of activated lymphocytes. Examples of such drugs are azathioprine, mycophenolate, mofetil, cyclosporine, and tacrolimus [10]. Steroids such as prednisolone are also used for MG, they are fast acting but could have side effects such as temporary weakness [10, 14]. Cyclophosphamide and rituximab are used for refractory cases of MG [10]. Steroids and immunomodulatory drugs are usually used for long-term treatment [14].

Myasthenia gravis and thymectomy : An indication of Thymectomy is one of the most debated topics in the treatment of MG for many years, and no concrete consensus is reached for this indication so far. Several factors like patient's age, sex, the presence of Thymoma and severity of MG, the presence of AChR antibodies or MuSK antibody, and seronegative myasthenia formation are usually considered with great caution before any resection [19]. Studies have shown that most patients with MG and AChR autoantibodies have thymus anomalies, with thymus hyperplasia seen in 60% - 70% of cases and thymoma in 10% - 15% of cases. It is suggested that the removal of the thymus can reduce symptoms and occasionally cure patients possibly by rebalancing the immune system and benefitting patients with or without thymoma [18]. This is because the thymus is the primary organ that produces the antibodies that affect the AChR [18]. Cultured human thymic lymphocytes have been observed to produce AChR antibodies in vitro. Therefore, it is safe to say that the removal of the MG thymus will reduce the effect and autoreactivity of immune cell response that causes severe damage, impairment, and blockage of transmission to the AChR that ultimately lead to MG [18]. Thymectomy is considered a mainstay therapy for MG; leading to clinical improvement in 70 – 80% and clinical remission is seen in about 33 -38 % of cases [8].

CONCLUSION

Myasthenia gravis is an autoimmune disease with various etiologies. As a result, several factors are considered in approaching treatment with most patients opting out for medication rather than surgery. However, the beneficial role of thymomectomy is unprecedented and should be encouraged in either early or late onset surgery. Another advantage could also be that thymomectomy will prevent prolong usage of immunosuppressants which could lead to further complications such as paraneoplastic presentations.

Acknowledgement: The authors wish to acknowledge the support of the administration of All Saints University School of Medicine, Dominica.

Conflict of Interest: The authors declare that there is no conflict of interest

REFERENCES

1) Murai H, Yamashita N, Watanabe M, Nomura Y, Motomura M, Yoshikawa H et al. Characteristics of myasthenia gravis according to onset-age: Japanese nationwide survey. Journal of the Neurological Sciences. 2011;305(1-2):97-102.

2) Huang K, Luo Y, Yang H, Yang X, Li J. Myasthenia gravis accompanied by Graves' disease, thyrotoxic hypokalemic periodic paralysis and thymic hyperplasia. Neurology India. 2016;64 (4):783.

3) Karni A, Asmail A, Drory V, Kolb H, Kesler A. Characterization of patients with ocular myasthenia gravis — A case series. eNeurologicalSci. 2016;4:30-33.

4) Marx A, Porubsky S, Belharazem D, Saruhan-Direskeneli G, Schalke B, Ströbel P et al. Thymoma related myasthenia gravis in humans and potential animal models. Experimental

Neurology. 2015;270:55-65.

5) Bruno R. Different patterns of nicotinic acetylcholine receptor subunit transcription in human thymus. Journal of Neuroimmunology. 2004;149(1-2):147-159.

6) Chu D, Johnson R, Pun S. Cathepsin B-sensitive polymers for compartment-specific degradation and nucleic acid release. Journal of Controlled Release. 2012;157(3):445-454.

7) Casciola-Rosen L, Miagkov A, Nagaraju K, Askin F, Jacobson L, Rosen A et al. Granzyme B: Evidence for a role in the origin of myasthenia gravis. Journal of Neuroimmunology. 2008;201-202:33-40.

8) Evoli A, Batocchi A, Minisci C, Di Schino C, Tonali P. Therapeutic options in ocular myasthenia gravis. Neuromuscular Disorders. 2001;11(2):208-216.

9) Cho E, Min J, Lee S, Yoon C, Seok J, Cho H et al. Late-onset non-thymomatous myasthenia gravis: Comparison with early-onset and very late-onset myasthenia gravis. Neurology Asia. 2017;22(2):123-131.

10) Meyer A, Levy Y. Chapter 33: Geoepidemiology of myasthenia gravis. Autoimmunity Reviews. 2010;9(5):A383-A386.

11) Aarli J. Titin, Thymoma, and Myasthenia Gravis. Archives of Neurology. 2001;58(6):869.

12) López-Cano M, Ponseti-Bosch J, Espin-Basany E, Sánchez-García J, Armengol-Carrasco M. Clinical and pathologic predictors of outcome in Thymoma-Associated myasthenia gravis. The Annals of Thoracic Surgery. 2003;76(5):1643-1649.

13) Willcox N. Thymus and Thymoma in Myasthenia Gravis Patients. The Thymus Gland. :33-39.

14) Conti-Fine B, Milani M, Kaminski H. Myasthenia gravis: past, present, and future. Journal of Clinical Investigation. 2006;116(11):2843-2854.

15) Maggi L, Andreetta F, Antozzi C, Baggi F, Bernasconi P, Cavalcante P et al. Thymoma-associated myasthenia gravis: Outcome, clinical and pathological correlations in 197 patients on a 20-year experience. Journal of Neuroimmunology. 2008;201-202:237-244.

16) Romi F. Thymoma in Myasthenia Gravis: From Diagnosis to Treatment. Autoimmune Diseases. 2011;2011:1-5.

17) Lin J, Lu J, Zhao C, Qiao K, Zhu W, Yue D et al. Giant cell polymyositis associated with myasthenia gravis and thymoma. Journal of Clinical Neuroscience. 2014;21(12):2252-2254.

18) Wolfe G, Kaminski H, Aban I, Minisman G, Kuo H, Marx A et al. Randomized Trial of Thymectomy in Myasthenia Gravis. New England Journal of Medicine. 2016;375(6):511-522.

19) Aydin Y, Ulas A, Mutlu V, Colak A, Eroglu A. Thymectomy in Myasthenia Gravis. The Eurasian Journal of Medicine. 2017;49(1):48-52.

How to Cite this article: Oyewole Samuel, Otohinoyi David A, Akinfisoye Toluwalase, Oshobu Ibukun, Babatunde Ajibola, Abe Temidayo, et al. Myasthenia gravis, thymoma, and thymomectomy: the clinical interplay. *Int. j. clin. biomed. res. 2018;4(2):* 80-83.