Austra & Lian Journal of Basic Sciences

australiansciencejournals.com/aljbs

E-ISSN: 2643-251X

VOL 06 ISSUE 05 2025

The Relationship Between Myasthenia Gravis and Thymoma and Advanced Treatment Methods

Qizhen Han
University of Liverpool

Abstract: *Thymoma-associated myasthenia gravis (TAMG) is a complex autoimmune disease whose pathogenesis involves the production of anti-acetylcholine receptor antibodies induced by the abnormal thymoma immune microenvironment, leading to neuromuscular junction dysfunction. This article reviews the immunological role, pathological features, and epidemiological characteristics of thymoma in TAMG. We analyze the clinical manifestations, classification, and diagnostic methods of TAMG, explore the challenges of differential diagnosis, and systematically review the therapeutic applications and efficacy of thymectomy, novel immunosuppressive therapies, and biologic agents (such as rituximab and eculizumab). Studies have shown that thymectomy significantly improves TAMG symptoms, and novel therapies targeting B cells and the complement system offer new options for refractory cases. Future research is needed to optimize combination therapy strategies and strengthen long-term efficacy and safety studies to enhance patient quality of life and improve prognosis.*

Keywords: *myasthenia gravis, thymoma, immunological mechanism, thymectomy, biological agents*

1 Mechanism of association between myasthenia gravis and thymoma

1.1 Immunological role of thymoma in myasthenia gravis

As an epithelial tumor, thymoma is closely related to the occurrence of myasthenia gravis (MG). Its immunological role is mainly reflected in the abnormal activation of T cells and B cells in the abnormal thymic microenvironment, leading to the production of autoantibodies against acetylcholine receptors (AChR). Studies have shown that AChR-like proteins are expressed in thymoma tissues. These proteins can act as self-antigens to induce abnormal differentiation of T cells, especially the clonal expansion of CD4+ T cells, thereby promoting the production of high-affinity IgG antibodies by B cells [1]. Further, under TAMG conditions, the tumor epithelial cells themselves may take an active role in the autoimmunity process by the release of cytokines like IL-6 and TNF-α, disruption of the negative selection process by the T cells, causing the survival of autoreactive T cells to AChR from the thymus [2]. The resultant immune dysregulation is localized but also

extends to the peripheral compartment by the action autologous lymphocytes, broadening the clinical presentations of MG. Experiment studies also justified that transplantation of thymoma possessed the ability to elicit MG-like autoimmunitary responses under experiment animals, focusing the key role played by the tumors during etiology. Immunohistochemical studies also uncovered that the percentage of mature single-positive T cells present among the thymoma TAMG sufferers was found substantially increased. The aforementioned cells had predominantly expressed elevated versions of the Vβ T cell receptors, suggesting toward clonality during AChR-specific immune responses [3]. Meanwhile, abnormal recruitment of tumor-associated macrophages and dendritic cells amplified antigen presentation function and intensified the inflammatory cascade of MG. Although the mechanism remains debatable, the above studies offer the theoretical foundation for the intervention focusing on the thymoma immune microenvironment, such as utilizing the JAK inhibitors regulating downstream signaling pathways.

1.2 Pathological characteristics of thymoma and its impact on myasthenia gravis

The pathological characteristics of thymoma are based on the WHO classification, including type A, type B, and mixed types. Among them, the B2 and B3 subtypes are most closely associated with MG. These subtypes show obvious lymphocytic infiltration and epithelial cell proliferation, accompanied by necrosis and active mitosis [4]. Radiologically, thymoma often presents as a mediastinal space-occupying mass with calcification or cystic changes, while histological examination reveals that the tumor capsule has poor integrity and easily invades adjacent structures. This invasive feature directly affects the prognosis of MG patients [5]. The presence of MG does not seem to significantly change the histological grade of the tumor, but it can promote early diagnosis because MG symptoms often precede tumor manifestations, leading patients to receive intervention before tumor progression. In terms of prognosis, the overall survival rate of thymoma patients with MG is slightly better than that of the non-MG group, which may be attributed to regular imaging follow-up and timely thymectomy induced by MG [6]. However, the risk of tumor recurrence is higher in TAMG, especially type B3, and immunosuppressive treatment with MG may exacerbate infectious complications. Long-term follow-up data show that the 5-year survival rate of MG-related thymoma is over 85%, but patients should be alert to the occurrence of myasthenic crisis, which is often associated with increased tumor burden, emphasizing the clinical guidance value of pathological classification.

1.3 Epidemiological characteristics of thymoma in patients with myasthenia gravis

The incidence of thymoma in patients with myasthenia gravis is approximately 10%-15%, mainly in young and middle-aged women, with a peak age of 40-60 years, which is much higher than the incidence in the general population[7]. Epidemiological surveys have shown that the AChR antibody positivity rate in TAMG patients is as high as 95%, and most tumors are in the early Masaoka stage (stage I-II), which is related to the slow growth characteristics of thymoma[8]. There are significant regional differences. The proportion of TAMG is higher in the Asian population, which may be affected by genetic factors such as HLA-DR3 alleles, and environmental exposures such as living in mining areas further increase the risk. Long-term cohort studies have confirmed that the recurrence rate of TAMG is approximately 6%-10%. Compared with non-tumor MG, patients have more

severe myasthenia symptoms and the incidence of other autoimmune diseases such as lupus erythematosus increases by 20% [9]. Although thymectomy can improve more than 80% of TAMG cases, the detection rate of subclinical MG in thymoma patients is as high as 10.8%, suggesting the importance of screening.

2 Clinical manifestations and diagnosis of myasthenia gravis

2.1 Symptoms and classification of myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease caused by neuromuscular junction transmission disorders. Its clinical symptoms are mainly skeletal muscle weakness and fatigability. Symptoms worsen with activity and are relieved after rest. Typical symptoms include ptosis and diplopia caused by extraocular muscle involvement. About 85% of patients have this as the first symptom. Some patients progress to systemic type, involving the limbs, swallowing and respiratory muscles [10]. According to the Osserman classification, MG can be divided into type I (ocular muscle type), type IIa (mild generalized type), type IIb (moderate to severe generalized type), type III (acute fulminant type) and type IV (late severe type). Thymoma-associated MG (TAMG) often presents as type IIb or more severe, with a higher risk of respiratory muscle weakness [11]. Patients with generalized MG may experience dysphagia, slurred speech, and even myasthenic crisis, which is seriously life-threatening. Fluctuation and diurnal changes in symptoms are characteristic of MG and need to be distinguished from other diseases of the nervous system. In addition, TAMG patients often have other autoimmune diseases, such as thyroid disease, suggesting a more complex immunopathological background.

The classification not only leads the therapeutic strategy but also is significantly correlated with the prognosis. The prognosis of ocular muscle MG is good, but TAMG is hard to control the symptoms by the immune induction from the thymoma and tends to develop into the generalized type. The newest study discovered that the anti-MuSK antibody-positive MG is less frequent for thymoma, but the clinical picture is virtually exclusively restricted to the facial and medullary muscle groupings, forming an independent classification subgroup [12]. The classification is determined by clinical evaluation and serological investigations. With the supplementation by the thymic imaging, the features of TAMG will be made clearer, the establishment will lay the foundation for the individual therapy.

2.2 Diagnostic methods for thymoma-related myasthenia gravis

The diagnosis of thymoma-associated myasthenia gravis is dependent on an overall evaluation of clinical presentation, serological studies, and neurophysiological testing. The definitive diagnostic marker is the presence of anti-acetylcholine receptor (AChR) antibodies in the serum. The positive rate among TAMG patients is up to over 90%, significantly higher than that among non-thymoma MG[13]. The diagnosis marker for TAMG is thymic imaging. Due to the excellent resolution and mediastinal mass sensitiveness, the first choice is CT thorax. It is able to identify the morphology, size, as well as the invasiveness of thymoma. In conjunction with MRI, the correlation between the growth with the adjoined structures is also able to be better defined[14]. In

neurophysiological examinations, repetitive nerve stimulation (RNS) shows a decremental response, which is a characteristic manifestation of MG, while single-fiber electromyography (SFEMG) has a higher diagnostic sensitivity for early or mild patients, with an abnormality rate of up to 95%[15]. In addition, ice pack tests and anticholinesterase drug tests (such as neostigmine tests) can quickly evaluate the improvement of ocular muscle symptoms and provide auxiliary evidence for clinical diagnosis. In TAMG, the histological classification of thymoma (WHO A-B3 type) is crucial for diagnosis and treatment decisions. Type B2/B3 is more closely associated with MG and needs to be confirmed in combination with biopsy results. During the diagnosis process, attention should be paid to excluding false negative cases, especially in patients with negative antibodies but high suspicion of TAMG. Combined imaging and electrophysiological examinations are particularly important. The establishment of standardized diagnostic procedures has improved the early detection rate of TAMG and laid the foundation for subsequent thymectomy and immunotherapy.

2.3 Key challenges in differential diagnosis

The differential diagnosis of thymoma-related myasthenia gravis faces multiple challenges because its symptoms overlap with a variety of neuromuscular diseases and thymus-related lesions. Ptosis and diplopia need to be distinguished from ophthalmoplegic diseases such as chronic progressive external ophthalmoplegia (CPEO) or brainstem lesions, the latter of which have no symptom fluctuations and often show brain abnormalities on imaging [16]. Systemic MG needs to be differentiated from Lambert-Eaton myasthenic syndrome (LEMS). LEMS patients often have small cell lung cancer. Antibody testing targets P/Q calcium channels, and electrophysiology shows an increasing response rather than a decreasing pattern of MG [17]. In addition, hyperthyroidism can mimic the myasthenic symptoms of MG, but thyroid function tests and eye signs (such as exophthalmos) can assist in differentiation. The particularity of TAMG is that thymoma may have no obvious symptoms. Some patients only seek medical attention for MG symptoms, which can easily lead to misdiagnosis as simple MG, and chest CT screening is required [18]. Another challenge is the diagnosis of antibody-negative TAMG. About 5%-10% of patients have negative AChR antibodies, which may involve anti-LRP4 or anti-MuSK antibodies, and the range of serological testing needs to be expanded. False-positive results may also interfere with diagnosis due to differences in laboratory technology or cross-reactions, and a comprehensive judgment needs to be made based on clinical and electrophysiological evidence. The complexity of differential diagnosis requires multidisciplinary collaboration and the integration of professional evaluations from neurology, endocrinology, and thoracic surgery to ensure the accuracy of diagnosis and timely treatment.

3 Research Progress in Advanced Treatments

3.1 Thymoma Resection and Its Efficacy

Thymoma resection is the cornerstone of treatment for thymoma-associated myasthenia gravis (TAMG), aiming to alleviate immune dysregulation and improve myasthenia symptoms by removing the tumor. Studies have shown that thymectomy has significant clinical benefits for TAMG patients. About 70%-80% of patients experience significant

symptom relief within 1-2 years after surgery, and some patients even achieve complete remission [19]. Surgical methods include traditional thoracotomy, thoracoscopically assisted thymectomy (VATS), and robot-assisted surgery. VATS has gradually become the first choice due to its minimal trauma and rapid recovery, especially for Masaoka stage I-II thymomas [20]. The improvement of postoperative neuromuscular symptoms is closely related to tumor stage and WHO histological type. Patients with type B2/B3 thymoma have a slightly lower postoperative remission rate than type A due to their higher immunogenicity, but the overall survival rate can reach more than 90% [21]. The thoroughness of surgery is crucial to the efficacy. Patients with incomplete resection have a high recurrence rate of about 10%-15%, and are prone to myasthenic crisis. Although thymectomy is effective, long-term follow-up is still required to monitor the recurrence of MG symptoms and tumor recurrence. Studies have shown that the complete remission rate of MG is approximately 40% 5 years after surgery, but some patients need to continue immunosuppressive therapy to control residual symptoms [19]. Postoperative complications such as infection and respiratory failure require special attention, especially in patients with systemic MG. The long-term efficacy of thymectomy is also affected by the patient's age, antibody titer, and preoperative immunotherapy. Young patients and those with high AChR antibody titers generally have a better prognosis [21]. Therefore, surgical decisions need to be made based on the patient's general condition and tumor characteristics to ensure the best treatment outcome.

3.2 New immunosuppressive therapies and targeted therapies

New immunosuppressive therapies and targeted therapies provide options for TAMG patients in addition to traditional hormones and nonspecific immunosuppressants. JAK inhibitors (such as tofacitinib) show potential efficacy in refractory MG by inhibiting the JAK-STAT signaling pathway and regulating the activation of T cells and B cells. Clinical trials have shown that about 60% of patients have improved symptoms within 6 months [22]. B cell-targeted therapies, such as anti-CD20 monoclonal antibodies (rituximab), reduce the production of AChR antibodies by depleting B cells, and are particularly effective in patients with MuSK antibodies, with a remission rate of over 70% [23]. In addition, complement inhibitors such as eculizumab effectively reduce neuromuscular junction damage by blocking the cleavage of C5 complement protein. Studies have shown that it can significantly improve the quality of life of patients with AChR antibody-positive refractory MG [24]. The advantage of these therapies is that they target specific immune pathways and reduce the nonspecific side effects of traditional immunosuppressants. However, JAK inhibitors may increase the risk of infection and thrombosis, and the high cost of complement inhibitors limits their widespread use. Long-term follow-up information is still lacking, and confirmation of the enduring therapeutic effect is still required. As the result of the immune activation from the thymoma, TAMG patients could present an entirely different response to targeted therapy, so combined treatment approach is required alongside thymectomy. The direction for the future is the development of the combination therapy tactics to ensure maximum effectiveness and minimal toxicities.

3.3 Application of Biologics in the Treatment of Myasthenia Gravis

The use of biologics in the treatment of myasthenia gravis represents an advancement in precision medicine, particularly in patients with refractory TAMG and TAMG. Rituximab, an anti-CD20 monoclonal antibody, significantly reduces autoantibody levels by selectively depleting B cells. Clinical trials have shown that its remission rates in patients with AChR and MuSK antibodies are 65% and 80%, respectively, and it is particularly effective in patients with thymoma [25]. Eculizumab is another key biological agent that blocks antibody-mediated neuromuscular junction destruction by inhibiting complement C5 activation. Phase III clinical trials have shown that after 12 weeks of treatment, symptom scores in approximately 60% of refractory MG patients have significantly decreased [26]. In addition, anti-IL-6 receptor antibodies (such as tocilizumab) have shown potential in regulating the inflammatory microenvironment. Preliminary studies have shown that they can improve the symptom stability of TAMG patients, especially in patients with high IL-6 levels [27]. Although biological agents have significant efficacy, their application faces challenges, including high treatment costs and potential immune-related adverse reactions, such as infection and allergic reactions. Due to the continued immune stimulation of thymoma, TAMG patients may need combined thymectomy and biological agent treatment to achieve optimal results. Further data on long-term efficacy and safety are needed, particularly regarding differences in efficacy across antibody subtypes and thymoma histological types. In the future, novel biologic agents such as FcRn inhibitors are expected to further optimize treatment strategies, reduce antibody levels, and improve patient compliance.

4. Conclusion

The studies on the relationship between Myasthenia Gravis (MG) and thymoma have revealed complex immunological mechanisms and clinical presentation, providing important information for diagnosis and treatment. Theproduction of autoantibody is triggered by an abnormal immune microenvironment induced by thymoma, significantly affect the course and the degree of MG. Theepidemiological characteristics show that TAMG patients are young and middle-aged adults with intensified afflictions. The clinical presentation is characterized by the precise classification and the diagnostic strategy (such as serological test and imaging), permitting the early diagnosis of TAMG, but thechallenge faced by the differential diagnosis require the cross cooperation between disciplines. Thymectomy remains the cornerstone treatment for TAMG, significantly improving the signs and the survival. Theremodeling of the new immunosuppressive drugs and the biologic drugs (such as rituximab and eculizumab) have provided new therapeutic strategies for refractory ones, representing the evolution toward precision medicine.

Continuous research must optimize the combined therapeutic strategies, decipher the changing interaction among the thymoma microenvironment and MG symptoms, and affirm the sustained effectiveness and security of novel treatments. Individual TAMG therapy must take the patient's antibody status, the type of the tumor, as well as their overall status, into full account to reduce recurrence and complication probability. Clinical practice must heighten the screening as well as follow-up among the high-risk groups with the help of improved diagnostic tools combined with targeted treatments to optimize the

quality of the patient's life as well as improve the prognosis. These advances not only deepen the understanding of the interaction among MG as well as thymoma but also lay the foundation for the establishment of improved therapeutic strategies.

References

[1] Sommer, N., Willcox, N., Harcourt, G. C., Newsom-Davis, J.: A pathogenetic role for the thymoma in myasthenia gravis. Autosensitization and high-frequency of anti-acetylcholine receptor antibody-secreting cells. J Neurol 245(4), 212-217(1998).

[2] Okumura, M., Fujii, Y., Shiono, H., Inoue, M., Minami, M., Utsumi, T., Kadota, Y., Sawa, Y.: Immunological function of thymoma and pathogenesis of myasthenia gravis. Gen Thorac Cardiovasc Surg 56(5), 225-232(2008).

[3] Marx, A., Strobel, P., Shrestha, B., Rose-Petruck, B., Schmid, K. W., Mautner, K., Hübner, M., Schalke, B., Keller, S. M., Gold, R., Wilisch, A., Müller-Hermelink, H. K.: Thymoma related myasthenia gravis in humans and potential animal models. Front Immunol 6, 32(2015).

[4] Zhang, Y., Li, H., Zhang, Z., Wang, Y., Li, Y., Li, J., Zhang, Z.: Pathological Features and Prognosis of Thymoma With or Without Myasthenia Gravis. Ann Thorac Cardiovasc Surg 28(3), 165-171(2022).

[5] Okumura, M., Ohta, M., Tateyama, H., Nakagawa, K., Maeda, H., Tashima, K., Nakagawa, T., Ohde, Y., Kondo, K., Monden, Y.: Thirty-five-year follow-up analysis of clinical and pathologic outcomes of thymoma surgery. Ann Thorac Surg 89(2), 245-250(2010).

[6] Gu, Z., Fu, J., Shen, Z., Wei, S., Wu, C., Liu, Y., Liu, Y., Fang, W., Yang, Y., Mao, T.: Does myasthenia gravis influence overall survival and causes of death in thymoma patients? J Thorac Dis 6(12), 1710-1715(2014).

[7] Okumura, M., Ohta, M., Fujii, Y., Nakagawa, K., Maeda, H., Kawano, N., Matsui, K., Kitamura, S.: Thymoma and myasthenia gravis: a clinical study of 1089 consecutive tumors of the thymus. Gen Thorac Cardiovasc Surg 52(11), 425-431(2004).

[8] Chen, Y., Wang, Y., Zhang, J., Li, J., Wang, Z., Li, Y., Zhang, X., Zhang, L.: Clinical characteristics and outcomes of thymoma-associated myasthenia gravis: a 20-year experience from a single tertiary center. Front Neurol 12, 649852(2021).

[9] Fattoruso, A., Marino, M., Evoli, A., Mele, D., Eufemi, S., Iorio, R., Sabatelli, M., Antonelli, G., Mastrangelo, A., Ceccarelli, G., Galli, F., Moresi, C., Scarpino, S., Mirabella, M., Lauriola, L., Ranieri, E., Vincent, A., Bartoccioni, E.: Subclinical myasthenia gravis in thymomas. Muscle Nerve 63(3), 367-371(2021).

[10] Gilhus, N. E., Verschuuren, J. J.: Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 14(10), 1023-1036(2015).

[11] Evoli, A., Batocchi, A. P., Minisci, C., Di Schino, C., Tonali, P.: Clinical characteristics and prognosis of myasthenia gravis with thymoma. Neurol Sci 22(1), 113-114(2001).

[12] Niks, E. H., Kuks, J. B., Verschuuren, J. J.: Epidemiology and clinical aspects of MuSK antibody-positive myasthenia gravis. Neuromuscul Disord 18(4), 289-295(2008).

[13] Vincent, A., Palace, J., Hilton-Jones, D.: Myasthenia gravis. Lancet 357(9274), 2122-2128(2001).

[14] Priola, A. M., Priola, S. M.: Imaging of thymus in myasthenia gravis: from thymic hyperplasia to thymic tumor. Clin Radiol 69(5), e230-e245(2014).

[15] Oh, S. J., Kim, D. E., Kuruoglu, R., Bradley, R. J., Dwyer, D.: Diagnostic sensitivity of the laboratory tests in myasthenia gravis. Muscle Nerve 15(6), 720-724(1992).

[16] Meriggioli, M. N., Sanders, D. B.: Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 8(5), 475-490(2009).

[17] Titulaer, M. J., Lang, B., Verschuuren, J. J.: Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol 10(12), 1098-1107(2011).

[18] Marx, A., Pfister, F., Schalke, B., Saruhan-Direskeneli, G., Melms, A., Strobel, P.: The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev 12(9), 875-884(2013).

[19] Masaoka, A., Yamakawa, Y., Niwa, H., Fukai, I., Kondo, S., Kobayashi, M., Fujii, Y., Monden, Y.: Extended thymectomy for myasthenia gravis patients: a 20-year review. Ann Thorac Surg 62(3), 853-859(1996).

[20] Rückert, J. C., Ismail, M., Swierzy, M., Sobel, H., Rogalla, P., Meisel, A., Wernecke, K. D., Rückert, R. I., Müller, J. M.: Thoracoscopic thymectomy with the da Vinci robotic system for myasthenia gravis. Ann N Y Acad Sci 1132, 329-335(2008).

[21] Nakajima, J., Murakawa, T., Fukami, T., Sano, A., Takamoto, S., Ohtsu, H.: Long-term outcome of thymectomy in patients with myasthenia gravis and thymoma. World J Surg 32(6), 1203-1207(2008).

[22] Dalakas, M. C.: Advances in the management of myasthenia gravis: new therapies and future perspectives. Lancet Neurol 20(11), 957-967(2021).

[23] Díaz-Manera, J., Martínez-Hernández, E., Querol, L., Klooster, R., Rojas-García, R., Suárez-Calvet, X., Muñoz-Blanco, J. L., Mazia, C., Straasheijm, K. R., Gallardo, E., Juarez, C., Verschuuren, J. J., Illa, I.: Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology 78(3), 189-193(2012).

[24] Howard, J. F., Utsugisawa, K., Benatar, M., Murai, H., Barohn, R. J., Illa, I., Jacob, S., Vissing, J., Burns, T. M., Kissel, J. T., Muppidi, S., Nowak, R. J., O'Brien, F., Wang, J. J., Mantegazza, R.: Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol 16(12), 976-986(2017).

[25] Tandan, R., Hehir, M. K., Waheed, W., Howard, D. B.: Rituximab treatment of myasthenia gravis: a systematic review. Muscle Nerve 56(2), 185-196(2017).

[26] Mantegazza, R., Wolfe, G. I., Muppidi, S., Wiendl, H., Fujita, K. P., O'Brien, F. L., Booth, H. D., Howard, J. F.: Post-intervention status in patients with refractory myasthenia gravis treated with eculizumab during REGAIN and its open-label extension. Neurology 92(6), e610-e618(2019).

[27] Jonsson, D. I., Pirskanen, R., Piehl, F.: The role of IL-6 in myasthenia gravis and potential for IL-6 targeted therapy. Front Neurol 11, 49(2020).