The Cause and Therapy of Myasthenia Gravis

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Abstract: Myasthenia Gravis is essential for people to have a clearer understanding of the cause as well as the potential treatments since this disease can happen to every person at any age and at any time. Deep research and data collection have shown the main causes of physiological problems and gene regulation and the three most effective types of treatments- thymectomy, blood-derived, and medications. Some clinical research data results indicate the effectiveness of using the medication, rituximab, by using placebo studies. It turns out that rituximab helps people lower the rate of doing blood-derived treatments. The three treatments, especially the medication and blood-derived treatments should be used together to remain the muscle contraction of the Myasthenia Gravis patient. With all the information collected, it is crucial for people to raise attention to myasthenia gravis and look forward to the innovation of new treatments.

1 INTRODUCTION

The most common form of Myasthenia Gravis (MG) is a chronic autoimmune neuromuscular disorder characterized by fluctuating weakness of the voluntary muscle groups. In recent days, six categories are Ocular MG, early-onset MG, late-onset MG, MG with thymoma, MG with anti-muscle-specific tyrosine kinase antibodies and MG with no defined antibodies (Gilhus 2009, Gilhus, Nacu, Andersen, & Owe 2015).

There is no known cure for MG, but there are many effective treatments that can make managing life with MG easier, the symptoms can be relieved after resting or controlled by medications. There is a need for attention for this disease because it can happen to anyone of any race and gender, especially for young women, whose ages are between 20 and 30, and men, whose ages are 50 and older. In the US, it is estimated that 20 in 100,000 have MG; approximately 36,000 to 60,000 cases. However, as myasthenia gravis often remains underdiagnosed, the prevalence is most likely higher.

The general cause of MG is the dysfunction of nerve-muscle junction transmission. MG is considered an autoimmune disease, which is a neuromuscular transmission disorder related by acetylcholine receptor (AChR), the muscle Specific Kinase (MuSK) and the low-density lipoprotein receptor-related protein (LRP4). The researchers found that the HLA locus, the locus for cytotoxic T-lymphocyte-associated protein 4 (CTLA4), PTPN22, IL-1β, IL-10, TNF-α and IFN-γ are related to MGound (Berrih-Aknin, & Le Panse 2013).

There are currently a lot of treatments, and most of the medications and therapies are based on the cause of the disease. Three main treatments are considered more effective. Firstly, thymectomy is the only surgical treatment that completely removes the thymus gland, causing the MG. Secondary, blood-derived treatments include plasmapheresis, the replacement of good antibodies with abnormal antibodies in the blood. Last but not least, various medications such as anticholinesterase immunosuppressive medicines are trying to make the antibodies not bind to the acetylcholine receptors or make the acetylcholine stay in the junction longer, so they have more chance to bind to the receptors. Also, there is an emphasis on some traditional Chinese medications that can help relieve the symptoms and minimize the side effects of immunosuppressive medications (table 2) (Giraud, Vandiedonck, &

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Garchon 2008). This article introduces what MG is and main causes and the recent treatment of the MG.

2 BACKGROUND INFORMATION: WHAT IS MG, PATIENT DISTRIBUTION

Myasthenia gravis (MG) is a disease caused by an autoimmune disorder related by antibodies of the neuromuscular junction, resulting in Visual problems, skeletal muscle weakness and fatigability of body function; however, the cause of myasthenia gravis and the cure are unknown (Meriggioli, & Sanders 2009). In clinical diagnosis, MG may be classified by different factors, such as the different parts of the muscles, the age of MG onset (Guptill, Soni, & Meriggioli 2016), and the nature of thymic pathology.

According to the data, table 1 shows that geographical variations affect the different incidences of MG (Dresser, Wlodarski, Rezania, & Soliven 2021). Different epidemiological studies estimate the incidence rate of MG with a range between 1.7 and 21.3 per million people each year (Bettini, Chaves, Cristiano, Pagotto, Perez, Giunta, & Rugiero 2017). In Poland, the incidence rate is only 2.36 per million in 2019, which is lower than in other countries (Sobieszczuk, Napiórkowski, Szczudlik, & Kostera-Pruszczyk 2021). In Norway, the data shows the average incidence rate of 1.6 per million each year with a stable incidence rate over the last 25 years, and the prevalence rate is 3.6–13.8 per million people (Popperud, Boldingh, Brunborg, Faiz, Heldal, Maniaol, Müller, Rasmussen, Oymar, & Kerty 2016). In Sweden, the incidence of MG is 2.9 per million people and the prevalence is 36.1 per million people in 2016, but the incidence rate is increasing each year (Westerberg, & Punga 2020). In addition, in North American and Asian areas, the annual incidence rate is not too high compared to other countries. In China, MG's estimated annual incidence rate is between 1.55 to 3.66 per million people each year, and the estimated prevalence of MG is 2.19–11.07 per million people based on insurance records (Fang, Li, Mo, Wang, Qiu, Ou, Lin, Huang, Feng, He, Wang, Xu, Wang, Ran, & Liu 2020). In Canada, the incidence rate is 2.1–2.6 per million, and the prevalence rate ranges from 25.4 to 27.3 per million in 2013 (Breiner, Widdifield, Katzberg, Barnett, Bril, & Tu 2015). In South Africa, an annual incidence rate is 8.5 per million (Mombaur, Lesosky, Liebenberg, Vreede, & Heckmann 2015). However, the incidence of MG is 38.8 cases per million in the Argentina area (Dresser, Wlodarski, Rezania, & Soliven 2021). But the data in table 1 may have some issues to cause the different results in geographical regions.

Table 1: The recent increasing rate of MG in different regions.

Region	Country	Rate (per million each year)
Europe	Poland	2.36
	Norway	1.6
	Sweden	2.9
Asia	China	1.55-3.66
North American	Canada	2.1–2.6
South Africa	Argentina	38.8

3 CAUSES OF DISEASE

3.1 Antibodies

Myasthenia gravis (MG) is an autoimmune disorder caused by antibodies against acetylcholine receptors (AChR) or other structural proteins of the neuromuscular junction. This diminishes cholinergic transmission, thus leading to exercise-induced fatigue and sometimes manifest muscle weakness, including the bulbar and ocular musculature (Müllges, & Stoll 2019).

These autoantibodies bind to the nicotinic acetylcholine receptor (AchR) itself, or muscle-specific tyrosine kinase (MuSK), lipoprotein receptor-related protein 4 (LRP4) and agrin involved

in clustering of AchRs within the postsynaptic membrane and structural maintenance of the neuromuscular synapse. This results in the disturbance of neuromuscular transmission and thus the clinical manifestation of the disease (Melzer, Ruck, Fuhr, Gold, Hohlfeld, Marx, Melms, Tackenberg, Schalke, Schneider-Gold, Zimprich, Meuth, & Wiendl 2016).

In the US there are about 18,000 people with MG. Myasthenia gravis crisis (MGC) is defined as any MG exacerbation necessitating mechanical ventilation. Most patients presenting with MGC have an identifiable risk factor. The diagnosis of MGC should be suspected in all patients with respiratory failure, particularly those with unclear etiology. Acute management of MGC requires supportive general and ventilatory therapy and institution of measures to improve the neuromuscular blockade (Bershad, Feen, & Suarez 2008).

3.2 The Thymus Gland

The thymus gland is a small gland located in the upper chest beneath the sternum. It helps control the immune system, and when it malfunctions, it may cause MG. Many people with MG have a large or overactive thymus gland. Some even develop tumors on their thymus gland. These tumors are called thymomas. These tumors can be harmless, but also can turn into cancer or cause lasting health issues.

Research has shown that in most cases, MG patients have increased numbers of cells in the thymus, and about 10-15 percent of affected individuals have thymomas (tumors) in the thymus. Researchers suggest that the thymus of an MG patient may trigger or maintain the production of the antibodies that block the transmission of nerve signals. Thus, the malfunction of the thymus gland may cause MG, and the treatment was directed at the thymus gland.

3.3 Human Leukocyte Antigen (HLA)

The HLA gene contains several genetic loci (HLA-A, B, C and D) (COMPSTON, VINCENT, NEWSOM-DAVIS, & BATCHELOR 1980). It has a relationship with a large number of diseases, such as hemochromatosis. According to the bulk clinical experiments, the major histocompatibility complex has been identified to be associated with autoimmune MG with thymus hyperplasia, and the major histocompatibility complex plays an important role in MG as the first and the most important factor (Giraud, Vandiedonck, & Garchon 2008). In addition, MG and thymus hyperplasia are associated with HLA, and HLA-DR3 and HLA-DR7 show opposite influences on MG patients (Giraud, Beaurain, Yamamoto, Eymard, Tranchant, Gajdos, & Garchon 2001).

In previous studies, the relationship between the disease and different ethnic groups was identified (Giraud, Vandiedonck, & Garchon 2008). Myasthenia gravis (MG) in European Caucasoids has found that they are associated with HLA-B8 and HLA-DR3. The significant increase in HLA-A1, HLA-B8 and HLA-DR5 in American blacks with generalised adult-onset myasthenia gravis or ocular myasthenia gravis (OMG) (Christiansen, Pollack, Garlepp, & Dawkins 1984). MG in China shows differences with the patients in Caucasians. Patients, who are in the first 20 years of life, restricted ocular myasthenia in them has a relationship with absence or low titres of acetylcholine receptor antibody and HLA-DR9; however, restricted ocular myasthenia in the patients, whose age is older than 20 years old, has high titres of acetylcholine receptor antibody (Hawkins, Yu, Wong, Woo, Ip, & Dawkins 1989). In another study, OMG in Chinese is associated with HLA-BW46 (Hawkins, Ip, Lam, Ma, Wy, Yeung, & Dawkins 1986). In conclusion, compared to European Caucasoids, MG in Chinese is at an earlier age at onset, more ocular forms, and less clinically severe illness. HLA-DR9 and HLA-Bw46 (Chen, Chiu, & Hseih 1993) have strongly impacted them. In other Asian countries, Japanese in the childhood with MG are associated with HLA-DR9 and HLA-DRw13 (or DQw1 and DQw3), which act synergistically in the disease; however, no significant association was shown in Japanese with adult-onset MG, and the risk of MG decreases with the age of onset. Moreover, no patients had HLA-B8 and HLA-DR3 which are related to European Caucasoids. So MG in Japanese individuals differs from European Caucasoids with MG (Matsuki, Juji, Tokunaga, Takamizawa, Maeda, Soda, Nomura, & Segawa 1990). Thus, according to the previous studies, patients in China are similar to those in Japan because both of them are associated with HLA-DR9.

3.4 Other Genes

Cytotoxic T-lymphocyte-associated protein 4(CTLA4), Protein tyrosine phosphatase, non-receptor type 22(PTPN22), meanwhile, Fc fragment of IgG, low-affinity IIIb(FCGR3B) are not specific to MG, which also encode proteins related to lymphoid cell activation and other autoimmune diseases (Giraud, Vandiedonck, & Garchon 2008). CTLA4 plays an important role in downregulating to control

the cellular and the humoral responses by controlling responses of activated T cells (Huang, Liu, Norén, Xia, Trifunovic, Pirskanen, & Lefvert 1998). It is estimated to protect patients from MG in thymoma patients against several autoimmune diseases; however, it also increases the risk to lead to paraneoplastic MG in thymoma patients (Chuang, Ströbel, Gold, Nix, Schalke, Kiefer, Opitz, Klinker, Müller-Hermelink, & Marx 2005). PTPN22 reduces T-cell activation and generation of interleukin-2, and it has been associated with various autoimmune diseases. Hungarian and German MG patients are highly overrepresented of the common autoimmune polymorphism PTPN22 1858C/T (Greve, Hoffmann, Illes, Rozsa, Berger, Weissert, & Melms 2009). Moreover, PTPN22 is associated with early-onset MG and thymoma-associated MG (Chuang, Ströbel, Belharazem, Rieckmann, Toyka, Nix, Schalke, Gold, Kiefer, Klinker, Opitz, Inoue, Kuo, Müller-Hermelink, & Marx 2009). The Fcgamma receptors include FcgammaRIIa, FcgammaRIIIa, and FcgammaRIIIb, and they have different abilities for IgG binding and phagocytosis. Thymoma MG patients have a high expression on the FcgammaRIIA-H/H genotype, so FcgammaRIIa-R/R131 genotype is a biomarker for susceptibility to MG (Raknes, Skeie, Gilhus, Aadland, & Vedeler 1998). In summary, different associations with MG are highly diverse and in order to better define their relationship, future studies need to focus on different controls, such as the region, age and gender of patients, thymus pathology, subtypes of MG.

4 TREATMENT

4.1 Thymectomy

Thymectomy is considered the first treatment that people have found, as well as the only surgical treatment that is found to be effective. However, there are still a lot of controversies and risks about it. Thymus anomalies can occur in the majority of MG patients with MG and AChr antibodies. It is observed that 60% -70% have abnormalities of the gland, including hyperplasia and 10%–15% tend to develop thymoma. These findings lead to the development of thymectomy, but this procedure heavily depends on the age of the patient, the severity of the disease, the presence of AChr antibodies or MuSK antibodies, and so on (Romi 2011). Until today, those researchers have settled down the age limit of thymectomy surgery for patients under 65 years old. It is because the elderly cannot respond well due to “high thymic involution incidence,” and the side effects may overturn the benefits. Other than the age limit, thymectomy is best processed with mild and moderate MG. The remission of the mild MG patient is much higher through studies from 1985 to 2014 and especially effective when it is performed 6 to 12 months after the first symptoms occurred (Mao, Hu, Lu, & Hackett, 2015). In addition, MG patients with the absence of AChR are recommended if they do not respond well to IS therapy that thymectomy can minimize the effects of IS therapy (Mao, Hu, Lu, & Hackett 2015). After the surgical procedure, it was found that patients in the surgical group had approximately twice the rate of remission and improvement as those in the control group. Within a few months after surgery, about 60% to 80% of patients were in remission (U.S. Department of Health and Human Services.). However, there are also risks for patients who have thymic tumors. Patients with thymoma should have surgery to remove the tumor, but it will not guarantee an improvement in MG, and further treatments need to be based on patients. If thymectomy is performed aggressively, these patients did not respond well to the thymectomy and were generally more seriously ill (Mao, Hu, Lu, & Hackett 2015).

There is always a desire for the best procedure of thymectomy. Some common procedures are transsternal thymectomy, transcervical thymectomy, and it turns out that minimally invasive techniques, which use some tiny incision in the chest, have become increasingly popular due to their low procedural morbidity and mortality, short hospital stay, optimal cosmesis, minor surgical access trauma, better preservation of pulmonary function (Marulli, & Rea 2015). Especially for young patients, clinicians want to ensure that the young patients can have a regular and comfortable life after the surgery, especially for children with generalized AChR antibody-positive MG, “possibility of a congenital myasthenic syndrome or other neuromuscular condition should be entertained” and these should be exclaimed before the thymectomy (Sanders 2016).

4.2 Blood-derived Treatments

As time goes, blood-derived treatments, plasmapheresis, becomes accessible as people get more knowledge that the antibodies in the blood are blocking the receptors in the neuro junction. Plasmapheresis (PLEX) is simply replacing the plasma in MG patients with healthy plasma. And later, intravenous immunoglobulin (IVIg), the injection of healthy antibodies to temporarily change

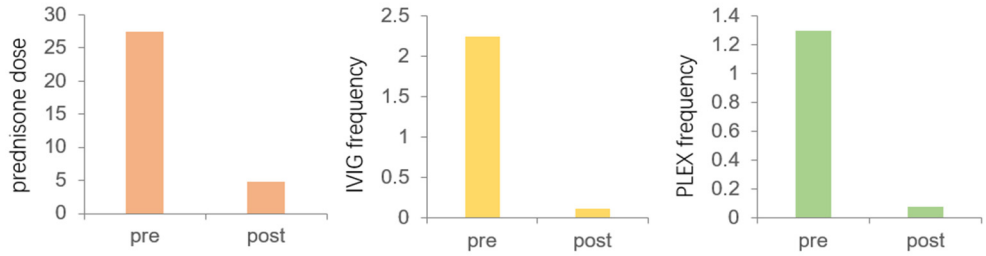
the immune system's working (U.S. Department of Health and Human Services.). Unlike thymectomy that has a chance to remission the disease, PLEX and IVIg can only keep the symptoms away within six days to six weeks depending on the half-life of AChr Ab, as a result, patients have to do the procedure repeatedly. It is recommended to serve MG patients with life-threatening problems. Other than that, people often use them as an add-on to medication to enhance the best effect of restoring muscle contraction. However, there are also some unavoidable side effects. As the clinical studies show, 10%~15% of patients produce toxic symptoms due to plasma exchange therapy to enter more citron acid, which causes low blood calcium. Some symptoms include numbness around the mouth and lip, nausea, vomiting, cardiac arrhythmia, which can be alleviated by using supplemental calcium. The other side effects are Hypovolemic or hypotension that can occur during plasma separation because more blood volume is required for cardiopulmonary bypass. In mild cases, tachycardia, sweating, nausea, tinnitus, and other symptoms may occur. In severe cases, seizures of syncope or heart or cerebral infarction may occur. It is required that the blood sampling speed should not be too fast, and the colloidal substances should be properly supplemented to correct the adverse reactions (Sedef Iskit 2018). In short, both PLEX and IVIg also do need a lot of caution with the consultation of patients' conditions.

4.3 Medications, the Rising of Rituximab

With more interest as well as a deeper understanding of the cause and process of MG, clinicians start to figure out drugs that can make the acetylcholine stay long during the junction so it has a better chance to bind to the receptor or try to remove the bad antibodies. Anticholinesterase medications, which slow down the breakdown of acetylcholine, and immunosuppressive drugs that suppress the production of antibodies are some conventional medications that can treat MG. For children MG patients. It is shown that steroid medications can have some severe side effects, such as the probability of infection, growth failure. Considering all the factors, it illustrates that immunosuppressive drugs, corticosteroids, should be used as a long-term treatment to minimize side effects. The more novel medications have shown for better effectiveness, including monoclonal antibodies, attack the process when the bad antibodies bind to the acetylcholine receptors (U.S. Department of Health and Human Services.) and B cell depletion, such as, rituximab (RTX), which was developed in the 2000s for cancer and other autoimmune disorders and is a murine-human chimeric anti-CD20 glycoprotein monoclonal antibody (Menon, Barnett, & Bril 2020). The clinicians gave a placebo test to the MG patients, it turned out that the MMT score has been stable for patients who took rituximab and the frequency of doing the blood-derived treatments had been lowered (Anderson, Phan, Johnston, & Siddiqi 2016) as shown in Figure 1. Traditional Chinese medicine treatment of myasthenia gravis is getting more and more attention. MG is considered in the category of "impotence". According to the theory of traditional Chinese medicine, the addition of traditional Chinese medicine in the treatment can reduce the side effects caused by immunosuppressants, play an escort role in the treatment of myasthenia gravis, and rebuild the effect of the autoimmune function. Other than that, Chinese therapy, acupuncture, also can be add-on treatments to delay and reduce the symptoms of MG.

Table 2: Summary of Three Treatments.

Therapy	Purpose	Outcome
Thymectomy	Removal of thymoma or hyperplastic	60 to 80% are in remission.
Intravenous immunoglobulin (IVIg)	Inject the healthy antibodies to alter the operations of the immune system.	Only last within six days to sie weeks
Plasmapheresis (PLEX)	Plasma exchange to get the health antibodies.	Only last within six days to sie weeks
Immunosuppressive	Reduce the production of abnormal antibodies	Corticosteroid, cyclophosphamide
Monoclonal antibody	Targets the process by which acetylcholine antibodies injure the neuromuscular junction	Rituximab



The left, intermediate and right graphs represent prednisone dose, IVIG frequency, PLEX frequency, respectively.

Figure 1: Rituximab Effectiveness (compare premedication with post medication) (Anderson, Phan, Johnston, & Siddiqi 2016).

5 CONCLUSIONS

To sum up, Antibodies to the acetylcholine receptor, the muscle-specific tyrosine kinase, and the lipoprotein receptor protein 4, characterize disease subtypes with distinct clinical traits and immune-pathogenic mechanisms. Also, experiments found that MG and thymus hyperplasia are associated with HLA, and HLA-DR3 and HLA-DR7 show the opposite influence on MG patients. Besides, CTLA4, PTPN22, and FCGR3B are not specific to MG, which also encode proteins related to lymphoid cell activation and other autoimmune diseases. In order to solve this disease, there are many kinds of treatment, like Thymectomy, Intravenous, immunoglobulin, plasmapheresis, immunosuppressive and Monoclonal antibodies, which both are effective treatments that can make managing life with MG easier. However, some issues need to be addressed to find better treatment in future research. For example, it is unclear how HLA or other genes control MG. In the future, a huge amount of clinical research is needed to find out the other causes or treatments of MG. In this article, understanding the disease mechanism, the cause and the treatment method of MG will provide a brief summary to future researchers and conduct further research.

REFERENCES

Anderson, D., Phan, C., Johnston, W. S., & Siddiqi, Z. A. (2016). Rituximab in refractory myasthenia gravis: a prospective, open-label study with long-term follow-up. Annals of Clinical and Translational Neurology, 3(7), 552–555.

Berrih-Aknin, S., & Le Panse, R. (2013). Myasthenia gravis: A comprehensive review of immune dysregulation and etiological mechanisms. Journal of Autoimmunity, 52, 90–100.

Bershad, E. M., Feen, E. S., & Suarez, J. I. (2008). Myasthenia gravis crisis. Southern medical journal, 101(1), 63–69.

Bettini, M., Chaves, M., Cristiano, E., Pagotto, V., Perez, L., Giunta, D., & Rugiero, M. (2017). Incidence of Autoimmune Myasthenia Gravis in a Health Maintenance Organization in Buenos Aires, Argentina. Neuroepidemiology, 48(3-4), 119–123.

Breiner, A., Widdifield, J., Katzberg, H. D., Barnett, C., Bril, V., & Tu, K. (2015). Epidemiology of myasthenia gravis in Ontario, Canada. Neuromuscular Disorders: NMD, 26(1), 41–46.

Chen, W. H., Chiu, H. C., & Hseih, R. P. (1993). Association of HLA-Bw46DR9 combination with juvenile myasthenia gravis in Chinese. Journal of neurology, neurosurgery, and psychiatry, 56(4), 382–385.

Christiansen, F. T., Pollack, M. S., Garlepp, M. J., & Dawkins, R. L. (1984). Myasthenia gravis and HLA antigens in American blacks and other races. Journal of Neuroimmunology, 7(C), 121–129.

Chuang, W. Y., Ströbel, P., Belharazem, D., Rieckmann, P., Toyka, K. V., Nix, W., Schalke, B., Gold, R., Kiefer, R., Klinker, E., Opitz, A., Inoue, M., Kuo, T. T., Müller-Hermelink, H. K., & Marx, A. (2009). The PTPN22 gain-of-function+1858T (+) genotypes correlate with low IL-2 expression in thymomas and predispose to myasthenia gravis. Genes and immunity, 10(8), 667–672.

Chuang, W. Y., Ströbel, P., Gold, R., Nix, W., Schalke, B., Kiefer, R., Opitz, A., Klinker, E., Müller-Hermelink, H. K., & Marx, A. (2005). A CTLA4 high genotype is associated with myasthenia gravis in thymoma patients. Annals of neurology, 58(4), 644–648.

COMPSTON, D. A. S., VINCENT, A., NEWSOM-DAVIS, J., & BATCHELOR, J. R. (1980). CLINICAL, PATHOLOGICAL, HLA ANTIGEN AND IMMUNOLOGICAL EVIDENCE FOR DISEASE HETEROGENEITY IN MYASTHENIA GRAVIS. Brain (London, England: 1878), 103(3),

579–601.
Dresser, L., Wlodarski, R., Rezania, K., & Soliven, B. (2021). Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. Journal of clinical medicine, 10(11), 2235.
Fang, W., Li, Y., Mo, R., Wang, J., Qiu, L., Ou, C., Lin, Z., Huang, Z., Feng, H., He, X., Wang, W., Xu, P., Wang, L., Ran, H., & Liu, W. (2020). Hospital and healthcare insurance system record–based epidemiological study of myasthenia gravis in southern and northern China. Neurological Sciences, 41(5), 1211–1223.
Gilhus, N. E. (2009). Autoimmune myasthenia gravis. Expert Review of Neurotherapeutics, 9(3), 351–358.
Gilhus, N. E., Nacu, A., Andersen, J. B., & Owe, J. F. (2015). Myasthenia gravis and risks for comorbidity. European Journal of Neurology, 22(1), 17–23.
Giraud, M., Beaurain, G., Yamamoto, A. M., Eymard, B., Tranchant, C., Gajdos, P., & Garchon, H. J. (2001). Linkage of HLA to myasthenia gravis and genetic heterogeneity depending on anti-titin antibodies. Neurology, 57(9), 1555–1560.
Giraud, M., Vandiedonck, C., & Garchon, H.-J. (2008). Genetic Factors in Autoimmune Myasthenia Gravis. Annals of the New York Academy of Sciences, 1132(1), 180–192.
Giraud, M., Vandiedonck, C., & Garchon, H.-J. (2008). Genetic Factors in Autoimmune Myasthenia Gravis. Annals of the New York Academy of Sciences, 1132(1), 180–192.
Greve, B., Hoffmann, P., Illes, Z., Rozsa, C., Berger, K., Weissert, R., & Melms, A. (2009). The autoimmunity-related polymorphism PTPN22 1858C/T is associated with anti-titin antibody-positive myasthenia gravis. Human immunology, 70(7), 540–542.
Guptill, J. T., Soni, M., & Meriggioli, M. N. (2016). Current Treatment, Emerging Translational Therapies, and New Therapeutic Targets for Autoimmune Myasthenia Gravis. Neurotherapeutics, 13(1), 118–131.
Hawkins, B. R., Ip, M. S., Lam, K. S., Ma, J. T., Wy, C. L., Yeung, R. T., & Dawkins, R. L. (1986). HLA antigens and acetylcholine receptor antibody in the subclassification of myasthenia gravis in Hong Kong Chinese. Journal of neurology, neurosurgery, and psychiatry, 49(3), 316–319.
Hawkins, B. R., Yu, Y. L., Wong, V., Woo, E., Ip, M. S., & Dawkins, R. L. (1989). Possible evidence for a variant of myasthenia gravis based on HLA and acetylcholine receptor antibody in Chinese patients. The Quarterly journal of medicine, 70(263), 235–241.
Huang, D., Liu, L., Norén, K., Xia, S. Q., Trifunovic, J., Pirskanen, R., & Lefvert, A. K. (1998). Genetic association of Ctla-4 to myasthenia gravis with thymoma. Journal of neuroimmunology, 88(1-2), 192–198.
Mao, Z., Hu, X., Lu, Z., & Hackett, M. L. (2015). Prognostic factors of remission in myasthenia gravis after thymectomy. European Journal of Cardio-Thoracic Surgery, 48(1), 18–24.
Marulli, G., & Rea, F. (2015). Myasthenia gravis and thymectomy: many doubts and few certainties. European Journal of Cardio-Thoracic Surgery, 48(1), 46–47.
Matsuki, K., Juji, T., Tokunaga, K., Takamizawa, M., Maeda, H., Soda, M., Nomura, Y., & Segawa, M. (1990). HLA antigens in Japanese patients with myasthenia gravis. The Journal of clinical investigation, 86(2), 392–399.
Melzer, N., Ruck, T., Fuhr, P., Gold, R., Hohlfeld, R., Marx, A., Melms, A., Tackenberg, B., Schalke, B., Schneider-Gold, C., Zimprich, F., Meuth, S. G., & Wiendl, H. (2016). Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. Journal of neurology, 263(8), 1473–1494.
Menon, D., Barnett, C., & Bril, V. (2020). Novel Treatments in Myasthenia Gravis. Frontiers in Neurology, 11, 538–538.
Meriggioli, M. N., & Sanders, D. B. (2009). Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurology, 8(5), 475–490.
Mombaur, B., Lesosky, M. R., Liebenberg, L., Vreede, H., & Heckmann, J. M. (2015). Incidence of acetylcholine receptor-antibody-positive myasthenia gravis in South Africa. Muscle & Nerve, 51(4), 533–537.
Müllges, W., & Stoll, G. (2019). Myasthenia gravis [Myasthenia gravis]. Der Nervenarzt, 90(10), 1055–1066.
Popperud, T., Boldingh, M., Brunborg, C., Faiz, K., Heldal, A., Maniaol, A., Müller, K., Rasmussen, M., Oymar, K., & Kerty, E. (2016). Juvenile myasthenia gravis in Norway: A nationwide epidemiological study. European Journal of Paediatric Neurology, 21(2), 312–317.
Raknes, G., Skeie, G. O., Gilhus, N. E., Aadland, S., & Vedeler, C. (1998). FcgammaRIIA and FcgammaRIIIB polymorphisms in myasthenia gravis. Journal of neuroimmunology, 81(1-2), 173–176.
Romi, F. (2011). Thymoma in Myasthenia Gravis: From Diagnosis to Treatment. Autoimmune Diseases, 2011(1), 474512–474515.
Sanders, D. B., Wolfe, G. I., Benatar, M., Evoli, A., Gilhus, N. E., Illa, I., Kuntz, N., Massey, J. M., Melms, A., Murai, H., Nicolle, M., Palace, J., Richman, D. P., Verschuuren, J., & Narayanaswami, P. (2016). International consensus guidance for management of myasthenia gravis: Executive summary. Neurology, 87(4), 419–425.
Sedef Iskit, P. D. (2018, April 18). Plasmapheresis. Myasthenia Gravis News. https://myastheniagravisnews.com/role-plasmapheresis-myasthenia-gravis/.
Sobieszczuk, E., Napiórkowski, L., Szczudlik, P., & Kostera-Pruszczyk, A. (2021). Myasthenia Gravis in Poland: National Healthcare Database Epidemiological Study. Neuroepidemiology, 55(1), 62–69.
U.S. Department of Health and Human Services. (n.d.). Myasthenia gravis fact sheet. National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/Disorders/Patient-

Caregiver-Education/Fact-Sheets/Myasthenia-Gavis-Fact-Sheet#4.
Westerberg, E., & Punga, A. R. (2020). Epidemiology of Myasthenia Gravis in Sweden 2006–2016. Brain and Behavior, 10(11), e01819–n/a.