A review on autoimmune diseases Myasthenia Gravis: Causes, pathogenesis, symptoms and treatment

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Abstract. Native and foreign microorganisms, such as viruses, bacteria, and parasites, are actively protected by the immune system. This defense can however be improperly misdirected against tissues and cells in some people, giving rise to autoimmunity and eventually autoimmune diseases. Autoimmune disorders are a wide variety of illnesses which can affect any part of the body, either localized (such as thyroiditis) or systemic to specific organs or tissues and affect several organs or tissues (such as systemic lupus erythematosus). As an example of autoimmune diseases that affect the voluntary muscles, myasthenia gravis (MG) is an autoimmune neuromuscular junction disease (NMJ) triggered by antibodies that target postsynaptic membrane components, impede neuromuscular transmission and contribute to skeletal muscle weakness and fatigue. Here is a review of the past and clinical aspects of MG to explain the mechanisms of AChR, MuSK and Lrp4 antibodies, the history and clinical aspects of MG are explored with an emphasis on the structure and role of myasthenic autoantigens at the NMJ and how they are influenced by the pathogenic mechanisms of the autoantibodies.

1. Introduction
Autoimmune disease is a disorder affected the immune system and attached self-molecules. In most cases, the initiation of attacks against the body's self-molecules in autoimmune disorders is unclear, although a number of studies indicate that some factors such as biology, pathogens and/or the environment are closely related[1]. Since the immune system responds by generating certain forms of lymphocytes, such as white blood cells and antibodies, it has the potential to kill or neutralize various germs, poisons and other foreign agents[2]. On the other hand, autoimmunity describes a diseased state in which an organism does not recognize its own cells and tissues and thus causes the immune system to cause a reaction against its own components[3]. Due to the disruption of the normal control mechanism, autoimmune disorders arise, thus causing the system to malfunction and attack healthy cells and tissues[4]. A common autoimmune example
Type I Diabetes 5 is a common example of an autoimmune disorder[5]. Rheumatoid arthritis, systemic lupus erythematosus (lupus), and vasculitis 6 are some other common autoimmune disorders[6]. Immunity is a very broad scientific discipline, can be inherent (native) or acquired (adaptive), involving principle mechanisms that are required to protect against infectious agent, but they can also affect the host organism called autoimmunity. Immunity is of various kinds that immunity[7].

2. Myasthenia gravis (MG)

In 1672, for the first time, Thomas Willis described the disease as' spurious palsy.' The name 'Myasthenia Gravis pseudoparalytica' was proposed by the German neurologist Friedrich Jolly in 1895[8]. In response to repeated stimulation of the innervating nerve, Jolly also showed a decrease in myasthenia gravis (MG) muscle contraction. The chemical inherent in neurotransmissions has been identified during the 1920s and acetylcholine (ACh) was recognized as a neuromuscular transmitter.
medication. In 1934, when there were clinical parallels between MG and curare poisoning, Mary Walker[9] successfully treated MG patients with one of the acetylcholinesterase inhibitors (AChEI), phystostigmine, and also the curare antidote. An autoimmune mechanism was proposed during the following decades to resolve thymus defects and the reported high incidence of other ADs in patients with MG. The Scottish neurologist John A, demonstrated a theory of autoantibodies directed toward an endplate protein at the NMJ Simpson in 1960[10].

In the 1970s, however, Jim Patrick and Jon Lindstrom[11] finally consolidated the autoimmune hypothesis when acetylcholine receptor (AChR) immunized rabbits and showed an elevation of AChR-directed antibodies. The autoantibodies targeted neuromuscular junction (NMJ) molecules, such as nicotinic acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and low-density protein-related lipoprotein receptor 4 (Lrp4) that alter in tissue architecture and decrease the density or functionality of AChR and decrease neuromuscular transmission by various mechanisms. Therefore, a serious weakness of the fatigued skeletal muscle[12]. MG tends to be affected by sex and age; below 40 years, the female: male ratio is around 3: 1; however, the ratio is approximately equal when the age is between 40 and 50 years or during puberty. MG is more likely to occur in males in 50 years. In Europe and North America, childhood MG is uncommon (10 % - 15 % only). In Asian countries, however, up to 50 % of patients, primarily with purelyocular symptoms, have an onset below 15 years of age.[13][14]

2.1. Causes of M.G

Myasthenia gravis begins to develop later in life when normal receptors on the muscle attack antibodies in the body. This blocks a chemical stimulation for muscle contraction. When a woman with myasthenia gravis passes the antibodies on to the fetus, a temporary form of myasthenia gravis may develop in the fetus, but generally, it resolves within 2 to 3 months[10]. The main causes of this disease are antibodies and thymus. Normally, the immune system produces proteins called "antibodies " that help preventing or frightening the infection. Specific autoimmune disorder characterized by weakness of voluntary muscle caused by autoantibodies to the postsynaptic membrane at neuromuscular junction against the nicotinic acetylcholine receptor (AChR)[15]. The second cause of the MG is thymus. In anti-AChR antibody-positive MG, the thymus is an important pathogenic role, with thymic hyperplasia present in 65% of the cases and thymoma present in 10% of the cases[16]. In addition, MG presents a paraneoplastic phenomenon in 30% of patients with thymoma[17]. Thymus is a main site of autosensitisation. In the presence of the inflammatory environment within the thymus, AChR expression by myoid cells in the thymus is thought to induce and maintain the anti-AChR auto-immune response in MG[18]. There are minimal thymic changes in anti-MuSK antibody-positive patients, suggesting that no pathogenic role of the thymus in this subtype. To date, no thymus disorder has been identified in anti-LRP4 antibody-positive patients with MG[19].

2.2. Symptoms of myasthenia gravis

The primary symptom is muscle weakness, which results in ptosis (droopy eyelids), diplopia (blurry vision or double vision), troubles in food chewing, trouble in swallowing, dysarthria (trouble talking) or sound like he has a cold nose, loss of face expression, heavy head, trouble breathing and weakness.[20][21][22]

2.3. Pathogenesis of MG

Natural neuromuscular transmission and the anatomy of NMJ is imperative to understand the pathophysiology of MG. While basic junction function mechanisms have been well developed for decades to transmit signals from nerve to muscle, there has been an explosion of knowledge regarding
the molecular under-pinning of transmission over the last 10 years. The intricacies of the autoimmune response that underlie the degradation of the muscle's postsynaptic surface have increased. [23]

2.3.1. MG associated with AChR Abs
Neuromuscular junctions are the areas of communication between nerve endings and skeletal muscle fibres. The neurotransmitter acetylcholine (ACH) that transmits impulses to muscle fibres is released from the nerve endings, eventually triggering their contraction. However, antibodies are inappropriately directed against the receptors on the surface of certain muscle cells that associate with ACH receptors in individuals with MG. These antibodies are known as anti-acetylcholine receptor antibodies (anti-AChR) [24]. The abnormal autoimmune response lowered the number of ACHRs, thereby reducing the Transmission of nerve at certain neuromuscular junctions, and weakening the muscle contraction. A wide clinical range of isolated ocular signs of extreme life-threatening is characterized by MG with Abs to AChR (AChR-MG). In the early-onset population, there is a female predominance and a high prevalence of thymus alterations such as thymic follicular hyperplasia (TFH) and thymoma. AChR-Abs are IgG1/IgG3 and induce MG through two mechanisms: post-synaptic membrane complement-mediated focal lysis and increased AChR internalization through cross-linked with IgG molecules (antigenic modulation). Both mechanisms cause the postsynaptic membrane to lose AChR. In several patients, the thymus gland is involved, and experimental and genetic methods exist to explain the failure of AChR immune tolerance [25].

Figure 1. Neuromuscular transmission assessment. A) Healthy transmission of the neuromuscular ACH. By exocytosis, the nerve terminal will release the contents of each vesicle (quanta) of ACH. In the postsynaptic membrane, spontaneous release of single quanta of ACH activates the intrinsic cation channels of ACHR to create a small, transient depolarization called miniature endplate potential (mEPP). The potential for nerve action opens voltage-gated calcium channels (VGCCs) and activates exocytosis of several ACH quanta, releasing the much larger EPP, simultaneously. The amplitude of the EPP is more than enough in healthy individuals to exceed the threshold needed to activate the postsynaptic voltage-gated sodium channels (VGNaCs) and generate a potential for muscle action. B) The neuromuscular junction NMJ of the MG. AChR (primarily immunoglobulin IgG1) antibodies activate the complement, resulting in complex-mediated damage to the post-junctional membrane architecture by membrane attack.

By divalent antibodies, the postsynaptic AChR numbers are decreased which induces the internalization of AChR. Reduction in AChR leads to smaller mEPP and EPP amplitudes. Hence, the Epp cannot reach the threshold, especially when the nerve is repetitively activated. [14]
2.3.2. MuSK IgG4 blocks MuSK signaling

In the absence of AChR antibodies, antibodies to muscle-specific kinase (MuSK) or associated proteins (such as agrin and low-density lipoprotein-related protein-4 receptors) are present[26]. MuSK antibodies are primarily IgG4 and induce NMJ disassembly by disrupting the physiological role of MuSK in synapse maintenance and adaptation[27].

MuSK is known as an anti-MuSK antibody and also decreases the ACHR. Antibodies to the lipoprotein receptor protein-4 were recently identified for patients without antibodies to MuSK or AChR. Sometimes, the antibody in the blood cannot be identified in five to eight % of patients, but patients are also screened for myasthene gravis[28].

Tyrosine kinase is activated when the nerve terminal proteoglycan (agrin) binds to MuSK via low-density lipoprotein receptor-related protein 4 (LRP4). The MuSK antibodies of (LRP4) of MG patient bind mainly Ig-like regions in the MuSK ectodomain, thus blocking the assembly and activation of the agrin-LRP4-MuSK complex. This explain that agrin-induced AChR clustering in the C2C12 cell model has been inhibited by incubation in MuSK MG sera and IgG preparations [29]. When mice injected with MuSK MG IgG, reduction in post-synaptic tyrosine phosphorylation was correlated with rapid loss of acres from the post-synaptic AChR cluster and failure of neuromuscular transmission. Thus, both cell culture and mouse studies suggests that MuSK autoantibodies, primarily IgG4, block the usual activation of MuSK, progressive loss of AChRs from the motor endplate and then synaptic failure[30].

Figure 2. An overview of the signaling cascade of MuSK. A) Activation of MuSK and MuSK-interacting proteins in healthy individuals. B) Agrin is released by the motor neuron, binds Lrp4 and together they stimulate MuSK dimerization and activation of its intracellular kinase domain.
Activation of MuSK further requires Dok7 (postsynaptic protein associated with the AChR clustering pathway) to remain active and stimulate downstream signaling towards AChR clustering. Binding of functional bivalent MuSK antibodies can bypass the need for agrin-Lrp4 in this pathway and directly stimulate MuSK dimerization and phosphorylation. C) MuSK is thereby fully activated, and clustering of AChR is partially induced. Monovalent binding by bispecific MuSK antibodies or antigen-binding fragment (Fab-fragments) inhibits the binding of Lrp4 to MuSK, MuSK dimerization and AChR clustering. The loss of AChR clustering impairs neuromuscular transmission, which results in myasthenic muscle weakness observed in experimental animal models of this disease and MuSK MG patients [31].

2.3.3. MG associated with binding of Abs to Lrp4

MG associated with binding of Abs to Lrp4. The frequency of auto-ABS binding to Lrp4 in patients with neither AChR nor MuSK Abs (double seronegative) varies in different studies from 2 to 50%. This remarkable variability might be explained by differences in assay sensibility and patients’ genetic backgrounds. A recent study included 635 double seronegative MG patients from 10 countries, the overall frequency of Lrp4 Abs was 18.7%, with differences among populations. A sensitive cell-based assay using HEK 293 cells transfected with the cDNA encoding Lrp4 tagged with the green fluorescent protein was used. In some cases, Lrp4 Abs associated with AChR or MuSK Abs, more commonly with the latter [REFERENCE]. Furthermore, in a recent report, Lrp4 Abs were detected in 23% of patients with myotrophic lateral sclerosis. This finding requires confirmation, as it might cast doubt on the Ab specificity for MG Lrp4 Abs have been found to be associated, in some cases, with AChR or MuSK Abs, more commonly with the latter. Furthermore, Lrp4 Abs were detected in 23% of patients with myotrophic lateral sclerosis. The characteristics of Lrp4-MG are not yet defined, and most clinical details were retrospectively ascertained in limited patient samples. The disease appears prevalent in women, with a male-to-female ratio of 1:2, and mean age of onset in the mid-thirties. In severe cases, more than 20% of patients had purely ocular myasthenia, and most cases with generalized disease had mild to moderate symptoms. Interestingly, double positive cases (AChR/Lrp4 Abs or MuSK/Lrp4 Abs) appeared to be more severely affected. Although some patients with Lrp4-MG experienced bulbar or respiratory weakness at the disease onset, a respiratory crisis at presentation was much more frequent in patients harboring both Lrp4 and MuSK Abs [32]. A thymoma has never been detected, so far, in patients with isolated Lrp4 Abs, whereas a thymic hyperplasia was described in a minority of these patients, suggesting that pathogenic mechanisms might differ from those in AChR-MG. From the information available to date, both clinical presentation and response to therapy of Lrp4-MG seem to be more similar to those in AChRMG than in MuSK-MG [33].
**Figure 3.** Schematic representation of muscle-specific kinase (MuSK) and low-density lipoprotein-related protein 4 (Lrp4) complex at the neuromuscular junction and antibody binding sites. MuSK interacts with Lrp4 on the postsynaptic membrane. The extracellular portion of MuSK consists of three immunoglobulin (Ig)-like domains connected to a rich cysteine domain. The extracellular domain of Lrp4 consists of eight LDLa repeats (red boxes), two epidermal growth factor-like domains, and four domain of β-propeller (red hexagons) connected to other domains of epidermal growth factor-like. Binding agrin to Lrp4 activates the interaction between Lrp4 and MuSK and the phosphorylation of MuSK. Once phosphorylate in the juxtamembrane zone, MuSK attracts Dok-7. AChE binds Perlecan and MuSK via its collagen Q (ColQ) tail. MuSK-specific antibodies (blue) bind to the first Ig protein domain, blocking contact between MuSK and Lrp4, and MuSK and ColQ. [34]

### 2.4. How is M.G treated?

For treating MG, there are several specific therapies available. Significant differences in treatment, however, are noted, because high quality randomized controlled trials of MG therapies are rare and the availability of evidence is difficult. Therefore, several clinical recommendations have been established through consensus by experts and societies to advise clinicians on the multipronged approach to MG management[35]. The treatment limitations depend on the components of the expert panel and need to be revised every few years with new information[36].

Different specific treatment options are available for managing M.G, such as using inhibitors of ACHE (pyridostigmine and neostigmine), corticosteroids (prednisolone), plasma exchange (PLEX), intravenous immunoglobulin (IVIG) and immunosuppressive agents (azathioprine, rituximab, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus) [33].

Treatment of MG consists of either IVIG or PLEX rapid immunotherapy. At the same time, it is important to diagnose other disease that may enhance MG. As the effects of IVIG or PLEX are restricted to several weeks long-term immunosuppression, up to 100 mg/dL or the intravenous equivalent of methylprednisolone, should be increased simultaneously. While ACHE inhibitors are available intravenously, patients should stop taking these medicines because they can increase respiratory secretions and complicate the management of the airways.[37]

#### 2.4.1. Acetylcholinesterase Inhibitors

ACHE inhibitors slow down ACH degradation at a first-line treatment of mild MG. In order to minimize its side effects, oral administration of Pyridostigmine, intramuscularly of Neostigmine, along with anticholinergic drugs is used (excessive secretions, bradycardia). Immunosuppressant medications are prescribed when treatment with these drugs fails[38].

#### 2.4.2. Corticosteroids

Prednisone is one of the most widely used medications for three-fourths of patients with ocular or generalized MG, helping to substantial improvement. The effective dosage is based on how serious the
symptoms are. Approximately 50% of patients may experience worsening weakness during the initial 1 to 2 weeks. Therefore, along with PLEX or IVIG, the high-dose regimen is started in the hospital. Other immune suppressants with delayed onset of action should be added early in therapy to either replace or lower the dose of corticosteroids and to reduce the long-term adverse effects of corticosteroids. [39] [40]

2.4.3. Plasma Exchange (PLEX)
Another treatment choice includes apheresis with removing of the circulating immunoglobulins, vitamins, immune complexes, cytokines, and other inflammatory mediators[41]. Immunoglobulin from pooled blood donors is collected and comprises purified immunoglobulin G (IgG). The specific mechanism by which it works is unknown, but likely to include blocking off Fc receptors on macrophages, decrease activation of complements, and decrease production of antibodies and cytokines. Common side effects of IVIG are chills, fever, headache, and abnormal side effect are serious stroke, leukopenia, renal dysfunction, and aseptic. [42] [43]

2.4.4. Immuno-suppressants: (azathioprine, rituximab, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus). Azathioprine effect starts after 6 to 12 months and reaches a plateau after 1 to 2 years. With azathioprine alone or with concurrent prednisone, more than 90 percent of patients improve. Rituximab is a monoclonal antibody against the CD20 marker of the B cell membrane. It has been found to effect in generating MG[44], particularly, for MuSK antibody-positive diseases. Common side effects include depletion and susceptibility to infection in peripheral B cells (within 2 weeks), flushing and chills (with the first dose) [45]. Cyclosporine has a faster onset of action (1–2 months) relative to other nonsteroidal immunosuppressant medications. This medicine has significant side effects of renal, hepatic, and hematological, toxicity, and significant drug interactions.

Therefore, it is recently under limitation. [46] Mycophenolate Mofetil has not confirmed yet for the efficacy to treat MG patients. However, with a few side effects, this medication is well tolerated. Common side effects include nausea, diarrhea, leukopenia, and infections that requires regular monitoring of blood counts during therapy course. Significant fetal malformations during pregnancy are recorded with mycophenolate use [47]. Methotrexate is a dihydrofolate selective inhibitor and is stated to have a steroid-sparing effect, closer to that of azathioprine[48]. Tacrolimus is an immunosuppressant macrolide which inhibits interleukin-2 production. The adverse effects are mild and, most often include elevated levels of hemoglobin A1C and neutrophil count and renal and liver function test alterations. Tacrolimus with sufficient duration of treatment may have a steroid-sparing effect without serious side effects in the management of MG[49]

3. Conclusion

Autoimmunity is the process through which an organism does not recognize its own constituent parts (down to sub-molecular levels), resulting in an immune response to its own cells and tissues. Any disease is considered an autoimmune disease when results from such an aberrant immune response. It can affect any system in the body and produce physical, psychological and social impairment. In order to treat lowest postsynaptic AChRs and failure of neuromuscular transmission, various subsets of MG patients produce autoantibodies with distinct target specificities, isotypes, and pathogenic mechanisms. Therefore it is important to examine the immunological abnormalities unique to each of these MG groups, as well as any common factors or pathways that could give parsimonious therapeutic targets. Whenever there is a challenge to the function of the NMJ, Agrin/MuSK signalling offers a more general adaptive/protective response. The changes in presynaptic are less stable than the changes in postsynaptic. Nevertheless in MuSK MG models, the adaptive increase in the release of presynaptic acetylcholine that regularly occurs in AChR MG models and in AChR MG patients failed. Such results indicate that MuSK signalling can help mediate the presynaptic adaptive response. Oral corticosteroids, other immunosuppressive drugs, and short term immunomodulation with PE/PP and IVIg are used in traditional immunotherapy for MG. While there is still a shortage of antigen-specific
therapy, recent clinical and basic research has greatly enhanced MG treatment. Several monoclonal antibodies may be successful in preventing the development of post-synaptic membrane complement complexes and in reducing blood pathogenic autoantibodies. Recent development of the biologics is promising new treatment options for MG. Thymectomy is another option in selected MG patients. Clinical trials in the pipeline are anticipated to generate further evidence leading to the development of additional treatment options for MG.

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4. References

[1] D. Sahu and A. Das, “An update review on autoimmune disease,” Int. J. Psychosoc. Rehabil., vol. 23, no. 6, pp. 94–100, 2019, doi: 10.37200/IJPR/V23I6/PR190741.

[2] L. B. Nicholson, “The immune system,” Essays Biochem., vol. 60, no. 3, pp. 275–301, 2016, doi: 10.1042/EBC20160017.

[3] D. U. Languedoc, R. D. E. C. N, Z. Lili, R. U. E. D. E. La, and C. Romaine, “CREDIT AGRICOLE Votre Conseiller Vos contacts Zhang Lili RELEVE DE COMPTES N ° 006 Date Date,” vol. 125, pp. 826–828, 2015, doi: 10.1016/j.jaci.2009.12.980.

[4] M. D. Rosenblum, K. A. Remedios, and A. K. Abbas, “Mechanisms of human autoimmunity,” J. Clin. Invest., vol. 125, no. 6, pp. 2228–2233, 2015, doi: 10.1172/JCI78088.

[5] D. O. F. Diabetes, “Diagnosis and classification of diabetes mellitus,” Diabetes Care, vol. 36, no. SUPPL.1, pp. 67–74, 2013, doi: 10.2337/dc13-S067.

[6] A. Krzewska and I. Ben-Skowronek, “Effect of Associated Autoimmune Diseases on Type 1 Diabetes Mellitus Incidence and Metabolic Control in Children and Adolescents,” Biomed Res. Int., vol. 2016, 2016, doi: 10.1155/2016/6219730.

[7] J. Jose, R. M. Naidu, P. Sunil, and S. S. Varghese, “Pathogenesis of Autoimmune Diseases: A Short Review,” Ompj, no. September 2016, pp. 434–436, 2014, doi: 10.5005/10037-1005.

[8] C. G. Croitoru, D. M. Turliuc, F. Danciu, A. I. Cucu, S. Turliuc, and C. F. Costea, “Myasthenia Gravis – a beginning with no end,” Rom. Neurosurg., vol. 30, no. 1, pp. 77–82, 2016, doi: 10.1515/romneu-2016-0012.

[9] V. M. de Carvalho, E. de A. G. Nogueira, G. R. Rosa, and Y. D. Fragoso, “Mary Broadfoot Walker: 83 years since a historical discovery,” Arq. Neuropsiquiatr., vol. 75, no. 11, pp. 825–826, 2017, doi: 10.1590/0004-282x20170138.

[10] E. Westerberg, Environmental factors of importance in myasthenia gravis: emphasis on physical activity. 2018.

[11] T. Batchelor, “Surgery for the treatment of myasthenia gravis The role of thymectomy.”

[12] Koneczny and Herbst, “Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture,” Cells, vol. 8, no. 7, p. 671, 2019, doi: 10.3390/cells8070671.
[13] G. K. Schwalfenberg and S. J. Genuis, “The Importance of Magnesium in Clinical Healthcare,” *Scientifica (Cairo)*, vol. 2017, 2017, doi: 10.1155/2017/4179326.

[14] N. J. Silvestri and G. I. Wolfe, “Myasthenia gravis,” *Semin. Neurol.*, vol. 32, no. 3, pp. 215–226, 2012, doi: 10.1055/s-0032-1329200.

[15] M. M. Dimachkie, “MYASTHENIA GRAVIS: SUBGROUP CLASSIFICATION & THERAPEUTIC STRATEGIES Executive Vice Chair & Vice Chair for Research Director of Neuromuscular Division University of Kansas Medical Center,” 2019.

[16] S. Sathasivam, “Diagnosis and management of myasthenia gravis,” *Prog. Neurol. Psychiatry*, vol. 18, no. 1, pp. 6–14, 2014, doi: 10.1002/pnp.315.

[17] F. Romi, “Thymoma in myasthenia gravis: From diagnosis to treatment,” *Autoimmune Dis.*, vol. 1, no. 1, 2011, doi: 10.4061/2011/474512.

[18] N. York and M. Downtown, “13th International Conference on Myasthenia Gravis and Related Disorders POSTER SESSION,” pp. 1–61, 2017.

[19] 2013 Dien et al., “基因的改变NIH Public Access,” *Bone*, vol. 23, no. 1, pp. 1–7, 2008, doi: 10.1038/jid.2014.371.

[20] J. Stackhouse, “Myasthenia gravis,” *L’ Infirm. Can.*, vol. 16, no. 3, pp. 28–33, 1974.

[21] A. Jayam Trouth, A. Dabi, N. Solieman, M. Kurukumbi, and J. Kalyanam, “Myasthenia gravis: A review,” *Autoimmune Dis.*, vol. 1, no. 1, 2012, doi: 10.1155/2012/874680.

[22] B. R. Thanvi and T. C. N. Lo, “Update on myasthenia gravis,” *Postgrad. Med. J.*, vol. 80, no. 950, pp. 690–700, 2004, doi: 10.1136/pgmj.2004.018903.

[23] B. W. Hughes, M. L. M. De Casillas, and H. J. Kaminski, “Pathophysiology of myasthenia gravis,” *Semin. Neurol.*, vol. 24, no. 1, pp. 21–30, 2004, doi: 10.1055/s-2004-829585.

[24] “Autoimmune Resource and Research Centre Information Sheet.”

[25] L. Djingri Labodi, C. Kadari, Y. Muriel A, N. Christian, and K. B Jean, “Myasthenia gravis at Ouagadougou (Burkina Faso): about 14 cases,” *Brain and Nerves*, vol. 1, no. 2, pp. 1–7, 2017, doi: 10.15761/jbn.1000112.

[26] K. Takata et al., “Characterization of pathogenic monoclonal autoantibodies derived from muscle-specific kinase myasthenia gravis patients,” *JCI Insight*, vol. 4, no. 12, 2019, doi: 10.1172/jci.insight.127167.

[27] R. Klooster et al., “Muscle-specific kinase myasthenia gravis IgG4 autoantibodies cause severe neuromuscular junction dysfunction in mice,” *Brain*, vol. 135, no. 4, pp. 1081–1101, 2012, doi: 10.1093/brain/aws025.

[28] W. D. Phillips and A. Vincent, “Pathogenesis of myasthenia gravis: Update on disease types, models, and mechanisms [version 1; referees: 2 approved],” *F1000Research*, vol. 5, no. 0, pp. 1–10, 2016, doi: 10.12688/F1000RESEARCH.8206.1.

[29] Y. Zong and R. Jin, “Structural mechanisms of the agrin-LRP4-MuSK signaling pathway in neuromuscular junction differentiation,” *Cell. Mol. Life Sci.*, vol. 70, no. 17, pp. 3077–3088, 2013, doi: 10.1007/s00018-012-1209-9.
[30] N. Ghazanfari et al., “Forced expression of muscle specific kinase slows postsynaptic acetylcholine receptor loss in a mouse model of musk myasthenia gravis,” *Physiol. Rep.*, vol. 3, no. 12, 2015, doi: 10.14814/phy2.12658.

[31] D. L. E. Vergoossen, R. Augustinus, and M. G. Huijbers, “MuSK antibodies, lessons learned from poly- and monoclonality,” *J. Autoimmun.*, no. March, p. 102488, 2020, doi: 10.1016/j.jaut.2020.102488.

[32] Y. Wang et al., “Coronavirus nsp10/nsp16 Methyltransferase Can Be Targeted by nsp10-Derived Peptide In Vitro and In Vivo To Reduce Replication and Pathogenesis,” *J. Virol.*, vol. 89, no. 16, pp. 8416–8427, 2015, doi: 10.1128/jvi.00948-15.

[33] R. J. B. Constantine Farmakidis, Mamatha Pasnoor, Mazen M. Dimachkie, “Treatment of Myasthenia Gravis Constantine,” *Physiol. Behav.*, vol. 176, no. 3, pp. 139–148, 2017, doi: 10.1016/j.physbeh.2017.03.040.

[34] A. Evoli and R. Iorio, “Neuroimmunology Characteristics of myasthenia gravis with antibodies to protein 4,” vol. 6, pp. 40–48, 2015.

[35] D. A. Godoy, L. J. V. de Mello, L. Masotti, and M. Di Napoli, “Pacientes miastênicos em crise: Uma melhora de conduta na unidade de terapia intensiva,” *Arq. Neuropsiquiatr.*, vol. 71, no. 9 A, pp. 627–639, 2013, doi: 10.1590/0004-282X20130108.

[36] D. B. Sanders et al., “International consensus guidance for management of myasthenia gravis: Executive summary,” *Neurology*, vol. 87, no. 4, pp. 419–425, 2016, doi: 10.1212/WNL.0000000000002790.

[37] E. E. Perez et al., “Update on the use of immunoglobulin in human disease: A review of evidence,” *J. Allergy Clin. Immunol.*, vol. 139, no. 3, pp. S1–S46, 2017, doi: 10.1016/j.jaci.2016.09.023.

[38] D. B. Sanders et al., “Developing treatment guidelines for myasthenia gravis,” *Ann. N. Y. Acad. Sci.*, vol. 1412, no. 1, pp. 95–101, 2018, doi: 10.1111/nyas.13537.

[39] L. A. Jones and N. P. Robertson, “An update on treatments in myasthenia gravis,” *J. Neurol.*, vol. 264, no. 1, pp. 205–207, 2017, doi: 10.1007/s00415-016-8359-x.

[40] A. Kamali, M. Reza, and H. Tehrani, “Transcranial direct current stimulation to remediate myasthenia gravis symptoms.”

[41] D. Disorders, S. De Neurologie, and H. F. Mitterrand, “Plasma Exchange for Severe Attacks in the Spectrum of Central Demyelinating Disorders,” *Front. Clin. Drug Res. - CNS Neurol. Disord.*, no. September, pp. 55–109, 2013, doi: 10.2174/9781608057757113020006.

[42] L. Ferretti et al., “Quantifying dynamics of SARS-CoV-2 transmission suggests that epidemic control and avoidance is feasible through instantaneous digital contact tracing,” *medRxiv*, no. December 2019, p. 2020.03.08.20032946, 2020, doi: 10.1101/2020.03.08.20032946.

[43] S. Q. Nagelkerke and T. W. Kuijpers, “Immunomodulation by IVIg and the role of Fc-gamma receptors: Classic mechanisms of action after all?,” *Front. Immunol.*, vol. 6, no. JAN, 2015, doi: 10.3389/fimmu.2014.00674.

[44] K. Kridin, “Emerging treatment options for the management of pemphigus vulgaris,” *Ther. Clin. Risk Manag.*, vol. 14, pp. 757–778, 2018, doi: 10.2147/TCRM.S142471.
[45] S. Aschermann, A. Lux, A. Baerenwaldt, M. Biburger, and F. Nimmerjahn, “The other side of immunoglobulin G: Suppressor of inflammation,” Clin. Exp. Immunol., vol. 160, no. 2, pp. 161–167, 2010, doi: 10.1111/j.1365-2249.2009.04081.x.

[46] “Cyclosporine,” no. Md, 2020.

[47] E. W. Montroll et al., “Science;,” vol. 172, no. June, p. 10036, 1971.

[48] H. Park and J. Q. del Rosso, “The emergence of mycophenolate mofetil in dermatology: From its roots in the world of organ transplantation to its versatile role in the dermatology treatment room,” J. Clin. Aesthet. Dermatol., vol. 4, no. 1, pp. 18–27, 2011.

[49] R. N. Schwendimann, E. Burton, and A. Minagar, “Management of myasthenia gravis,” Am. J. Ther., vol. 12, no. 3, pp. 262–268, 2005, doi: 10.1055/s-0039-1689739.