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Review On: Mayasthenia Gravis and Telithromycin-Myasthenia Crisis

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Abstract: *Myasthenia Gravis (pronounced My-as-theen-ee-a Grav-us) comes from the Greek and Latin words meaning "grave muscular weakness." The most common form of MG is a chronic autoimmune neuromuscular disorder that is characterized by fluctuating weakness of the voluntary muscle groups.*
Myasthenia gravis (MG) was first described by Thomas Willis in 1672. Myasthenia Gravis occurs in all races, both genders, and at any age. MG is not thought to be directly inherited nor is it contagious. It does occasionally occur in more than one member of the same family.
It is an acquired autoimmune disease with antibodies against the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction or muscle-specific tyrosine kinase (MuSK). This leads to muscular weakness with easy 'fatiguability', which is worse on exercise and improves with rest.
MG shows clinical presentations like weakness of Muscle fatigues more readily after exercise,Droop of the upper eyelids, Small muscles of the hands, Seizures, Deltoid and triceps muscles,Bulbar muscles common,causing a nasal sound to speech that is slurred. Facial muscles.
MG can be managed by administering Corticosteroids, ACEinhibitors Azathioprine, Cyclosporine, Mycophenolate mofetil, Plasma exchange, Intravenous immunoglobulin, Thymectomy.
Telithromycin is a macrolide antibiotic which inhibits the nicotinic acetylcholine receptors (nAChR) at the neuromuscular junction (α3β2 and NMJ) which shows exacerbation of MG in all the patients leading to myasthenia gravis crisis.
KeyWords: *Drug Interactions, Management, Myasthenia Gravis Crisis, Pathophysiology, Telithromycin.*

I. Introduction

1.1 myasthenia gravis.

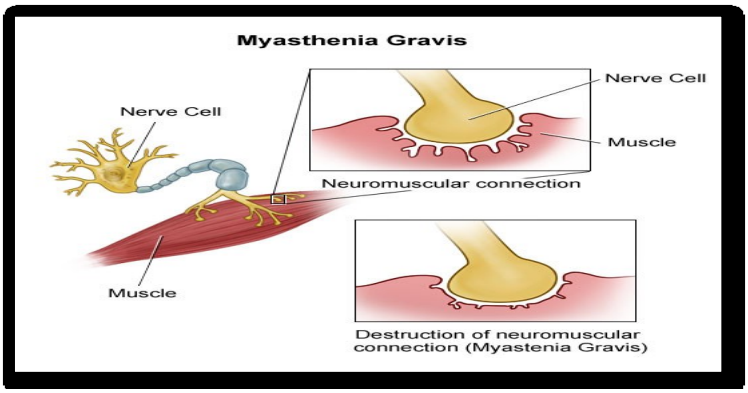

Figure: 1- Neuro Muscular Connection in Myasthenia Gravis

Myasthenia Gravis (pronounced My-as-theen-ee-a Grav-us) comes from the Greek and Latin words meaning "grave muscular weakness." Myasthenia gravis (MG) was first described by Thomas Willis in 1672. The most common form of MG is a chronic autoimmune neuromuscular disorder (shown in figure: 1) that is characterized by fluctuating weakness of the voluntary muscle groups. However, MG is probably under diagnosed and the prevalence may be higher. Myasthenia Gravis occurs in all races, both genders, and at any age. MG is not thought to be directly inherited nor is it contagious. It does occasionally occur in more than one member of the same family. The voluntary muscles of the entire body are controlled by nerve impulses that arise in the brain. These nerve impulses travel down the nerves to the place where the nerves meet the muscle fibers. Nerve fibers do not actually connect with muscle fibers. There is a space between the nerve ending and muscle fiber; this space is called the neuromuscular junction. When the nerve impulse originating in the brain arrives at the nerve ending, it releases a chemical called acetylcholine. Acetylcholine travels across the space to the muscle fiber side of the neuromuscular junction where it attaches to many receptor sites. The muscle contracts when enough of the receptor sites have been activated by the acetylcholine. In MG, there can be as much as an

80% reduction in the number of these receptor sites. The reduction in the number of receptor sites is caused by an antibody that destroys or blocks the receptor site. Antibodies are proteins that play an important role in the immune system. They are normally directed at foreign proteins called antigens that attack the body. Such foreign proteins include bacteria and viruses. Antibodies help the body to protect itself from these foreign proteins. For reasons not well understood, the immune system of the person with MG makes antibodies against the receptor sites of the neuromuscular junction. Abnormal antibodies can be measured in the blood of many people with MG. The antibodies destroy the receptor sites more rapidly than the body can replace them. Muscle weakness occurs when acetylcholine cannot activate enough receptor sites at the neuro muscular junction.It is an acquired autoimmune disease with antibodies against the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction or muscle-specific tyrosine kinase (MuSK) **[1]**. This leads to muscular weakness with easy fatiguability, which is worse on exercise and improves with rest.

Although the main cause behind its development remains speculative, the end result is a derangement of immune system regulation. MG is clearly an autoimmune disease in which the specific antibody has been characterized completely. In as many as 90% of generalized cases, IgG to AChR is present [2]**.** Even in patients who do not develop clinical myasthenia, anti-AChR antibodies can sometimes be demonstrated.

Patients who are negative for anti-AChR antibodies may be seropositive for antibodies against MuSK. Muscle biopsies in these patients show myopathic signs with prominent mitochondrial abnormalities, as opposed to the neurogenic features and atrophy frequently found in MG patients positive for anti-AChR. The mitochondrial impairment could explain the oculobulbar involvement in anti-MuSK–positive MG [3].Thymic abnormalities are common: Of patients with MG, 75% have thymic disease, 85% have thymic hyperplasia, and 10-15% has thymoma. Extrathymic tumors may include small cell lung cancer and Hodgkin disease [4] [5]. Hyperthyroidism is present in 3-8% of patients with MG and has a particular association with ocular MG.

Myasthenia gravis (MG) has a prevalence of 150 per million, with nearly one million MG patients worldwide. The yearly incidence is 10–15 per million per year [6]. Before any treatment was available the prognosis was severe, with an expected 50% 10-years' mortality. With modern treatment facilities such as immunotherapy, thymectomy, and intensive care facilities available, population-based studies show that MG and non-MG individuals have the same life expectancy [7], but still often with reduced physical abilities, reduced quality of life, and risk of complications.

There are three key aspects of MG which define the therapeutic opportunities.

MG is a well-defined autoimmune disease and thus responds to immunoactive treatment.

MG is caused by impaired acetylcholine receptor (AChR) stimulation in the postsynaptic skeletal muscle membrane and thus responds to an increase in AChR activity.

MG has muscle weakness as the only symptom, and consequently should respond to measures that increase muscle function and counteract muscle weakness.

MG treatment is firmly established as the domain of neurologists. Neurologists should be in charge even if the target organ is skeletal muscle, disease mechanisms are systemic, thymus is a target organ for diagnostic, therapeutic and scientific approach, hypoventilation is a life-threatening symptom, and diplopia often the most troublesome symptom. Ten percent of MG patients have another autoimmune disorder in addition, further supporting the need for complementary medical competence. Close cooperation with other fields of medicine provides knowledge regarding new immunoactive drugs, thus expanding the therapeutic opportunities for MG.

II. Classification Of M.G

The various subgroups of autoimmune MG respond differently to treatment. Thus, before deciding any treatment, all individual MG patients should be defined according to subgroups.

Classification aspects reflect the investigations of each patient that are necessary to undertake.

- Early-onset MG: age at onset <50 years. Thymic hyperplasia.
- Late-onset MG: age at onset >50 years. Thymic atrophy.
- Thymoma-associated MG.
- MG with anti-musk antibodies.
- Ocular MG: symptoms only from periocular muscles.
- MG with no detectable achr and musk antibodies.

The MG group with no detectable antibodies is heterogeneous. Some of these patients have low-affinity AChR antibodies that are not detectable by the routine assays and sometimes also thymic hyperplasia.Some may similarly have undetectable MuSK antibodies, and some most probably have autoantibodies against other antigen(s) in the postsynaptic membrane. There are not yet any commercial tests available for the low-affinity AChR antibodies. MG patients with a thymoma have nearly always detectable AChR antibodies in serum. Necessary investigations include tests for AChR and MuSK autoantibodies and

CT/MR of the anterior mediastinum. Titin and ryanodine receptor antibodies may be helpful for classification. For patients with no AChR and MuSK antibodies, it is necessary with thorough examinations to exclude other causes for their muscle weakness, including nonautoimmune myasthenic syndromes. Neurophysiological examinations with repetitive nerve stimulation and jitter measurements are important to establish the initial diagnosis, especially in patients without detectable antibodies.

MG should be classified according to severity. This is important when deciding specific treatment in the individual patient. It is also important in the followup to evaluate effects of various interventions. MG represents a challenge for such evaluation due to variation among muscle groups and variation during the day.

MG in early childhood poses special treatment challenges linked to growth and development in general and of the immune system. The same is true for treatment of MG women in childbearing age, mainly due to potential effects of the disease and the therapies on the developing child in utero [8]. Epidemiology differrs between ethnic populations and also regarding the frequency of the various MG subgroups.

2.1 clinical classification

The Myasthenia Gravis Foundation of America (MGFA clinical classification divides MG into 5 main classes and several subclasses. It is designed to identify subgroups of patients with MG who share distinct clinical features or severity of disease that may indicate different prognoses or responses to therapy. It should not be used to measure outcome and is as follows:

- **CLASS I MG:**

Any ocular muscle weakness.
May have weakness of eye closure.
All other muscle strengths are normal.

- **CLASS II MG**

Mild weakness affecting muscles other than ocular muscles.
May also have ocular muscle weakness of any severity.

- **CLASS IIA MG**

Predominantly affecting limb, axial muscles, or both.
May also have lesser involvement of oropharyngeal muscles.

- **CLASS IIB MG**

Predominantly affecting oropharyngeal, respiratory muscles, or both.
May also have lesser or equal involvement of limb, axial muscles, or both.

- **CLASS III MG**

Moderate weakness affecting muscles other than ocular muscles.
May also have ocular muscle weakness of any severity.

- **CLASS IIIA MG**

Predominantly affecting limb, axial muscles, or both.
May also have lesser involvement of oropharyngeal muscles.

- **CLASS IIIB MG**

Predominantly affecting oropharyngeal, respiratory muscles, or both.
May also have lesser or equal involvement of limb, axial muscles, or both.

- **CLASS IV MG**

Severe weakness affecting muscles other than ocular muscles.
May also have ocular muscle weakness of any severity.

- **CLASS IVA MG**

Predominantly affecting limb, axial muscles, or both.
May also have lesser involvement of oropharyngeal muscles.

- **CLASS IVB MG**

Predominantly affecting oropharyngeal, respiratory muscles or both.
May also have lesser or equal involvement of limb, axial muscles, or both.

❖ **CLASS V MG**

Intubation with or without mechanical ventilation, except when employed during routine postoperative management.

The use of feeding tube without intubation places the patient in class ivb [8].

III. Pathophysiology

3.1Structure and function of the NMJ:

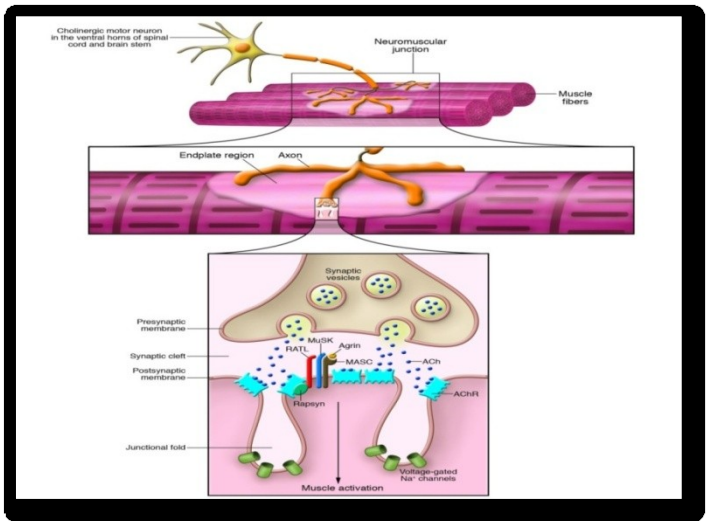

Figure: 2-functioning of NMJ

The terminal arborization of α–motor neuron axons from the ventral horns of the spinal cord and brainstem provides the nerve terminals that form the NMJ (shown in Figure2). These myelinated axons reach the muscles through peripheral nerves; then each axon divides into branches that innervate many individual muscle fibers. As it approaches its target fiber, each branch loses the myelin sheath and further subdivides into many presynaptic boutons, which contain ACh-loaded synaptic vesicles and face the surface of the muscle fiber at the NMJ (shown in Figure 2). The synaptic bouton and the muscle surface are separated by the synaptic cleft, a 20 nm–thick space that contains acetylcholinesterase (AChE) and other proteins and proteoglycans involved in stabilizing the NMJ structure.

The NMJ postsynaptic membrane has characteristic deep folds, and the AChR is densely packed at the fold top. When the nerve action potential reaches the synaptic bouton, ACh is released into the synaptic cleft, where it diffuses to reach and bind the AChR. ACh binding triggers the AChR ion channel opening, permitting influx of Na^+ into the muscle fiber. The resulting EPP activates voltage-gated Na^+ channels at the bottom of the folds, leading to further Na^+ influx and spreading of the action potential along the muscle fiber. Other proteins, including Rapsyn, MuSK, and agrin, which are involved in AChR clustering, are also present on the muscle membrane in close proximity to the AChR. MASC, myotube-associated specificity component; RATL, rapsyn-associated transmembrane linker.

Muscle AChR molecules are transmembrane proteins formed by 5 subunits: 2 identical α subunits, which contribute important structural elements to the ACh-binding sites, and 3 different but homologous subunits, termed β, γ (or ε; see below), and δ. Muscle expresses 2 developmentally regulated AChR isoforms. Embryonic muscle expresses AChRs formed by α, β, γ, and δ subunits. After innervation, expression of the γ subunit gene is substituted by that of the homologous ε subunit gene to yield the adult AChR isoform, a complex of α, β, δ, and ε subunits. Some adult muscles, notably the EOM, still express embryonic AChR.

When the nerve action potential reaches the synaptic bouton, the depolarization opens voltage-gated Ca^{2+} channels on the presynaptic membrane. This Ca^{2+} influx triggers fusion of synaptic vesicles with the presynaptic membrane and ACh release. Quantal content of a nerve impulse refers to the number of ACh vesicles (quanta) released by that impulse. The ACh diffuses into the synaptic cleft (where it can be hydrolyzed by AChE) and reaches and binds to AChR, thereby triggering the opening of its cation channels and influx of Na^+ into the muscle fiber. The resulting endplate potential (EPP) activates voltage-gated Na^+ channels, leading to further influx of Na^+ and spreading of the action potential along the muscle fiber.

The postsynaptic transmembrane protein, muscle-specific tyrosine kinase (MuSK) (shown in Figure 2), is the main autoantigen in some MG patients MuSK expression in both developing and mature muscle is similar to that of AChR. In mature muscle, MuSK is present prominently only at the NMJ, where it is part of the receptor for agrin. Agrin is a protein synthesized by motor neurons and secreted into the synaptic basal lamina.

The signaling mediated by agrin/MuSK interaction triggers and maintains rapsyn-dependent clustering of AChR and other postsynaptic proteins Rapsyn, a peripheral membrane protein exposed on the cytoplasmic surface of the postsynaptic membrane, is necessary for clustering of AChR, with which it coclusters. Rapsyn and AChR are present in equimolar concentrations at the NMJ, and they may be physically associated. Rapsyn causes clustering of NMJ proteins other than the AChR, including MuSK. Mice lacking agrin or MuSK fail to form NMJs and die at birth of profound muscle weakness, and their AChR and other synaptic proteins are uniformly expressed along the muscle fibers.

3.1.1 NMJ properties that influence susceptibility to muscle weakness in MG.

The EPP generated in normal NMJs is larger than the threshold needed to generate an action potential. This difference may vary in different muscles. Neuromuscular transmission safety factor is defined as the ratio between the actual EPP and the threshold potential required to generate the muscle action potential. Its reduction is the electrophysiological defect that causes MG symptoms.

The quantal content of an impulse, the conduction properties and density of postsynaptic AChR, and the activity of AChE in the synaptic cleft all contribute to the EPP **.**Also, the postsynaptic folds (shown in Figure 2) form a high-resistance pathway that focuses endplate current flow on voltage-gated Na^+channels in the depths of the folds, thereby enhancing the safety factor. A reduction in the number or activity of the AChR molecules at the NMJ decreases the EPP, which may still be adequate at rest; however, when the quantal release of ACh is reduced after repetitive activity, the EPP may fall below the threshold needed to trigger the action potential.

NMJ properties vary among muscles and may influence muscle susceptibility to MG**.** This is well illustrated by the NMJ of the EOMs, which are especially susceptible to developing myasthenic weakness. The NMJs of EOM differ from those of skeletal muscle in several ways. They have less prominent synaptic folds, and therefore fewer postsynaptic AChRs and Na^+ channels, and a reduced safety factor they are subject to very high neuronal firing frequency, making them prone to fatigue. Also, they express less intrinsic complement regulators, making them more susceptible to complement-mediated injury In skeletal muscles, fast-twitch fibers have NMJs with greater quantal contents, a greater degree of postsynaptic folding **[**and higher postsynaptic sensitivity to ACh than slow-twitch NMJs and they have increased Na^+ current in the NMJ region .These properties may make fast-twitch skeletal muscle fibers less susceptible to myasthenic failure than slow-twitch fibers.

3.2 Effector mechanisms of anti-achr Abs.

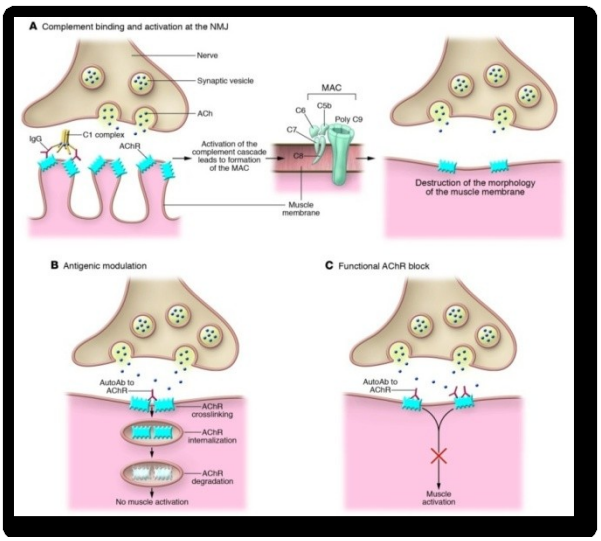

Figure: 3- Effector mechanisms of anti-AChR Abs.

Anti-AChR Abs affects neuromuscular transmission by at least 3 mechanisms (shown in figure 3):

3.2.1 Binding and activation of complement at the NMJ (Figure 3 [A]).

Ab binding to the AChR activates the complement cascade, resulting in the formation of membrane attack complex (MAC) and localized destruction of the postsynaptic NMJ membrane. This ultimately leads to a simplified, altered morphology of the postsynaptic membrane of the NMJ of MG patients, which lacks the normal deep folds and has a relatively flat surface.

Abs cross-links AChR molecules on the NMJ postsynaptic membrane, causing endocytosis of the cross-linked AChR molecules and their degradation (antigenic modulation). This ultimately leads to a reduced number of AChR molecules on the postsynaptic membrane.

Ab binding the ACh-binding sites of the AChR causes functional block of the AChR by interfering with binding of ACh released at the NMJ. This results in failure of neuromuscular transmission.

The NMJs of MG patients and EAMG animals contain activation fragments of complement component 3 (C3), the terminal and lytic complement component 9 (C9), and the membrane attack complex (MAC). Different lines of indirect evidence suggest that complement activation at the NMJ might be the primary cause of AChR loss and failure of neuromuscular transmission.Complement depletion protects animals from EAMG. Administration of Abs that block complement component 6 (anti-C6) or a complement inhibitor (soluble CR1) protects rodents from EAMG;

Mice with a reduced complement function because of a genetic deficit of complement components are resistant or less susceptible to EAMG induction than mice with normal complement IL-12–deficient mice,which synthesize Th1-driven, complement-fixing Abs develop minimal EAMG symptoms after achr immunization in spite of robust anti-achr Ab synthesis; moreover, their nmjs contain Abs but not complement, suggesting that anti-achr Abs that do not activate complement do not effectively compromise neuromuscular transmission.

Cells are protected from activation of autologous complement on their surfaces by the so-called intrinsic complement regulators. These include the decay-accelerating factor (DAF or CD55), the membrane cofactor protein (MCP or CD46), and the membrane inhibitor of reactive lysis (MIRL or CD59) Consistent with an important role of complement in EAMG, passive transfer of EAMG with anti-AChR Abs causes more severe muscle weakness in DAF-deficient mice than in wild-type mice .

3.2.2 Antigenic modulation (Figure 3 [B])

Antigenic modulation is the ability of an Ab to cross-link 2 antigen molecules, thereby triggering a cellular signal that causes accelerated endocytosis and degradation of the cross-linked molecules.IgG from MG patients causes antigenic modulation of muscle AChR in vivo and in vitro if accelerated degradation is not compensated by increased AChR synthesis it will lead to a reduction of the available AChR molecules at the NMJ and myasthenic symptoms. This property can be used as a diagnostic test for MG However, not all anti-AChR Abs cause antigenic modulation because, even though all IgG Abs have 2 antigen-binding sites, the epitope location on the AChR surface may restrict the ability of Abs to cross-link a second AChR molecule.

3.2.3 Functional achr (Figure 3 [c])

Functional AChR block due to Ab binding to the ACh-binding site is an uncommon pathogenic mechanism in MG, yet it may be clinically important. This is because the presence of Ab to the ACh-binding site of the AChR causes acute, severe muscle weakness in rodents without either inflammation or necrosis of the NMJ Many MG patients have low levels of anti-AChR Abs that recognize the ACh-binding site these might block the AChR in spite of their low concentration and contribute to acute myasthenic crises.

3.3 Role of $CD4^+$ T cells in MG.

Pathogenic anti-AChR Abs are high-affinity IgGs, whose synthesis requires that activated $CD4^+$ T cells interact with B cells, resulting in low-affinity anti-AChR Abs. This triggers somatic mutations of the Ig genes, leading to synthesis of high-affinity Abs. B cells secreting low-affinity anti-AChR Abs are common; for example, about 10% of monoclonal IgGs in multiple myeloma patients bind muscle AChRs Myelomas are rarely associated with MG, perhaps because of the low affinity of their anti-AChR Ab**.**

MG patients have AChR-specific $CD4^+$ T cells with T helper function in the blood and thymus and their symptoms improve after thymectomyor treatment with anti-CD4 Abs Moreover, in MG patients with AIDS, a reduction in $CD4^+$ T cells correlates with myasthenic symptom improvement Studies in experimental systems directly demonstrated that $CD4^+$ T cells are necessary for the development of MG symptoms. SCID mice engrafted with blood lymphocytes from MG patients produce anti–human AChR Abs and develop MG symptoms only if the grafted cells include $CD4^+$ T cells Also, mice genetically deficient in functional $CD4^+$ T cells do not develop EAMG Healthy subjects may have AChR-specific $CD4^+$ T cells, which do not cause a clinically significant autoimmune response, probably because of mechanisms of immunological tolerance, which fail in autoimmunity.

Blood $CD4^+$ T cells from both gMG and oMG patients respond to the AChR in vitro. Those from gMG patients respond to all the AChR subunits and their epitope repertoire expands as the disease progresses A few AChR sequences were recognized by most gMG patients .$CD4^+$ T cell lines specific for these “universal” AChR epitopes, when grafted into SCID mice, support anti-AChR Ab production by B cells, which result in MG symptoms The responses to AChR and AChR epitopes of $CD4^+$ T cells from oMG patients were weaker and less stable over time than in those of gMG patients Also, $CD4^+$ T cells from individual .MG patients rarely

recognize all AChR subunits, even when the disease has lasted for many years It is not clear whether $CD4^+$ T cells from oMG patients recognize the embryonic γ or the adult ε subunit or both.

The pathogenic role of anti-AChR $CD4^+$ T cells in MG and EAMG explains the important role of MHC class II molecules, which present the antigen epitopes to the specific $CD4^+$ T cells. In mice, susceptibility to EAMG correlates with the class II molecule alleles that they express Moreover, a mutation of the gene encoding the β subunit of the $I\text{-}A^b$ molecule converts the highly susceptible C57BL/6 strain of mice into the EAMG-resistant BM12 strain of mice MG patients, like patients with other autoimmune diseases, express some MHC (HLA) alleles with higher frequency than expected in the general population. HLA gene products found frequently in MG patients include the B8 and A1 class I molecule, the DR3/DW3 class II molecule, and certain DQ allele products. Some studies have used mice that express individual DR or DQ alleles transgenically, to determine whether some DR or DQ molecules influence the development of EAMG. Those studies confirmed that expression of the DQ8 and DR3 molecules correlated with EAMG susceptibility and expression of the DQ6 molecule correlated with resistance.

3.3.1Role of $CD4^+$ T cell subtypes and cytokines in MG and EAMG:

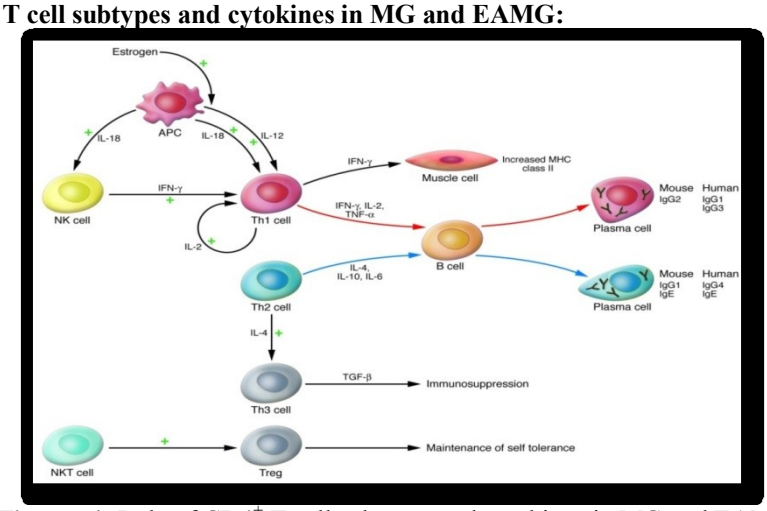

Figure: 4- Role of $CD4^+$ T cell subtypes and cytokines in MG and EAMG

Differentiated $CD4^+$ T cells are classified into subtypes based on the cytokines they secrete (figure-4).

Among them, Th1 and Th2 cells have different and at times opposing functions.Th1 cells secrete proinflammatory cytokines, such as IL-2, IFN-γ, and TNF-α, which are important in cell-mediated immune responses. Th2 cells secrete antiinflammatory cytokines, such as IL-4, IL-6, and IL-10, which are also important inducers of humoral immune responses. Moreover, IL-4 stimulates differentiation of Th3 cells, which secrete TGF-β and are involved in immunosuppressive mechanisms Both Th1 and Th2 cytokines may induce Ab synthesis. However, they support the synthesis of different Ig types. In mice (and likely in humans) Th1 cells induce IgG subclasses that bind and activate complement efficiently whereas Th2 cells induce Ig isotypes and IgG subclasses that fix complement poorly or not at all. In rats, both Th1 and Th2 cells induce complement-fixing Ig G subclasses.

Cytokine network and cells involved in the pathogenesis and immunoregulation of MG. Th1 cytokines stimulate production of IgG subclasses that bind and activate complement effectively, whereas Th2 cytokines stimulate the production of Ig classes and IgG subclasses that do not. The Th2 cytokine IL-4 is also a differentiation factor for Th3 cells, immunosuppressive cells that secrete TGF-β. The Th1 cytokine IFN-γ stimulates expression of MHC class II molecules on the muscle cell membrane, thus facilitating presentation of muscle AChR. The IL-18 secreted by APCs favors the differentiation of Th1 cells both directly and indirectly through the action of NK cells. CD1-d–restricted NKT cells can activate Tregs, thereby inhibiting autoimmune processes. See text for further details.

MG patients have abundant anti-AChR Th1 cells in the blood that recognize many AChR epitopes and induce synthesis of pathogenic anti-AChR Abs when grafted together with B cells and macrophages from the same patient into SCID mice MG patients also have anti-AChR Th2 and Th3 cells in the blood Mice congenitally lacking or overexpressing a cytokine have been used to study the role of cytokines in EAMG. Those studies suggested that Th1 cells and their cytokines are needed for EAMG development, probably because they induce expression of complement-binding pathogenic anti-AChR Abs).The resistance to EAMG induction conferred by genetic deficiency in TNF-α or TNF receptor proteins is overcome by treatment with IL-12, confirming that sensitization and differentiation of Th1 cells is important for EAMG development Other

studies demonstrated the important role of Th1 cells in EAMG by changing the concentration of Th1 cytokines in rodents with normal genes for cytokines and their receptors. For example, treatment of rats with anti–TNF-α Abs suppresses EAMG development and treatment of mice with a soluble recombinant form of the human TNF receptor, able to outcompete mouse TNF-α for binding to the mouse receptor, significantly improves symptoms of established EAMG Moreover, estrogen enhances EAMG development in mice by promoting augmented IL-12 production by AChR-specific Th1 cells, suggesting that estrogens mediate sex differences in autoimmunity because of a Th1-mediated mechanism (Figure 4). Proinflammatory Th1 cytokines induce expression of MHC class II molecules in muscle, thereby facilitating presentation of muscle AChR epitopes and further expansion of activated anti-AChR $CD4^+$ T cells. Increased IFN-γ production may explain the increased expression of IFN-γ–induced chemokines and monokines and their receptors in muscle, thymus, and lymph nodes in MG patients and rats with EAMG. A decrease in chemokine expression correlates with decreased severity of symptoms.Anti-AChR Th2 cells has complex and contrasting roles in EAMG. They can be protective), but the Th2 cytokines IL-5, IL-6, and IL-10 also foster EAMG development The resistance to EAMG of mice genetically deficient in IL-6 is associated with a reduced formation of germinal centers in the spleen and a reduced synthesis of anti-AChR IgG Abs while the anti-AChR IgM response is normal, suggesting a defect in T cell help and in the switching from IgM to IgG isotypes Other $CD4^+$ T cell subtypes may have a role in MG. $CD4^+$ T cells that express the CD25 marker and the transcription factor Foxp3 are known as Tregs and are important in maintaining self tolerance (Figure 3). Tregs in MG patients may be functionally impaired. In addition, the number of circulating Tregs has been shown to increase after thymectomy, and the increase correlated with symptom improvement.

3.3.2 Role of NK and NKT cells in MG and EAMG.

CD1-d–restricted NKT cells may be involved in maintaining self tolerance. In EAMG and MG, NKT cells and Tregs may cooperate in regulating the anti-AChR response. In AChR-immunized mice, activation of NKT cells by a synthetic glycolipid agonist inhibits EAMG development; these therapeutic effects are likely mediated by the increase in number and modulatory function of Tregs induced by the glycolipid .NK cells can also influence the development of EAMG and possibly MG. In mice, NK cells are necessary for EAMG development the "permissive" role of NK cells in EAMG is due to their secreting IFN-γ, thereby permitting and enhancing the sensitization of Th1 cells. IL-18 is an important growth and differentiation factor for both NK cells and Th1 cells, especially in cooperation with IL-12 Thus, IL-18 may be especially important in MG and EAMG pathogenesis. This is supported by the finding that IL-18–deficient mice are resistant to EAMG and pharmacologic block of IL-18 suppresses EAMG The finding that MG patients have increased serum levels of IL-18, which are higher in gMG than in oMG patients and tend to decrease with clinical improvement, supports a role for IL-18 in human MG[9].

IV. Diagnosis

4.1 Diagnostic procedures:

The diagnosis of MG is often delayed months or even years (in the mildest cases). The unusual distribution and fluctuating symptoms often suggests psychiatric disease. Patients with drooping eyelids, double vision and difficulty with speech or swallowing symptoms suggest intracranial pathology and often lead to an evaluation for stroke, brain tumor or multiple sclerosis. Patients with anti-MuSK-antibody positive MG may have focal or regional weakness and muscle atrophy that are more suggestive of motor neuron or muscle membrane (myopathy) disease. The Edrophonium Chloride (Tensilon®) Test Weakness caused by abnormal neuromuscular transmission characteristically improves after intravenous administration of edrophonium chloride. Some patients who don't respond to intravenous edrophonium chloride may respond to intramuscular neostigmine, because of the longer duration of action. Intramuscular neostigmine is particularly useful in infants and children whose response to intravenous edrophonium chloride may be too brief for adequate observation. In some patients, a therapeutic trial of daily oral pyridostigmine may produce improvement that can't be appreciated after a single dose of edrophonium chloride or neostigmine. Serum Antibodies in Myasthenia Gravis Several types of antibodies are found in the majority of patients with MG and include forms directed against the acetylcholine receptor (AChR) and muscle-specific receptor tyrosine kinase (MuSK). Ten percent of patients with acquired, presumably immune-mediated MG do not have detectable serum antibodies to AChR or MuSK. In these seronegative patients, the diagnosis is based on the clinical presentation, the response to cholinesterase inhibitors and electrodiagnostic findings. Anti-striational muscle antibodies (StrAbs), which react with contractile elements of skeletal muscle, are not pathogenic. They are found in more than 90% of MG patients with thymoma, and in one-third of patients with thymoma who do not have MG. One-third of MG patients without thymoma also have these antibodies; they are more frequent in older patients and in those with more severe disease. StrAbs are also elevated in other disorders including autoimmune liver disease and infrequently in Lambert-Eaton syndrome and in primary lung cancer. StrAbs are rarely, if ever, elevated in MG in the

absence of acetylcholine receptor antibodies and are therefore of limited use in confirming the diagnosis. The main clinical value of StrAbs is in predicting thymoma: 60% of patients with MG with onset before age 50 who have elevated StrAbs have thymoma. At least seventy four percent of patients with acquired generalized myasthenia and 54% with ocular myasthenia have serum antibodies that bind human acetylcholine receptor (AChR). The serum concentration of AChR antibody varies widely among patients with similar degrees of weakness and its level cannot predict the severity of disease in individual patients. Approximately 10% of patients, who do not have binding antibodies, have other antibodies that modulate the turnover of AChR in tissue culture. The concentration of binding antibodies may be low at symptom onset and become elevated later. AChR binding antibodies concentrations are sometimes increased in patients with systemic lupus erythematosus, inflammatory neuropathy, amyotrophic lateral sclerosis, rheumatoid arthritis taking D-penicillamine, thymoma without myasthenia gravis, and in normal relatives of patients with myasthenia gravis. False positive tests are reported when blood is drawn within 48 hours of a surgical procedure involving the use of general anesthesia and muscle relaxants. In general, an elevated concentration of AChR binding antibodies in a patient with compatible clinical features confirms the diagnosis of myasthenia gravis, but normal antibody concentrations do not exclude the diagnosis. Antibodies to muscle-specific receptor tyrosine kinase (MuSK), a surface membrane component essential in the development of the neuromuscular junction, have recently been identified and are found in up to 50% of MG patients who are seronegative for AChR antibodies. Emerging data suggests that the patterns of weakness and response to certain treatments may be different from those with AChR "positive" MG. Electromyography Repetitive Nerve Stimulation (RNS) The amplitude of the compound muscle action potential (CMAP) elicited by repetitive nerve stimulation is normal or only slightly reduced in patients without MG. The amplitude of the fourth or fifth response to a train of low frequency nerve stimuli falls at least 10% from the initial value in myasthenic patients. This decrementing response to RNS is seen more often in proximal muscles, such as the facial muscles, biceps, deltoid, and trapezius than in hand muscles. A significant decrement to RNS in either a hand or shoulder muscle is found in about 60% of patients with myasthenia gravis. Single Fiber EMG (SFEMG) SFEMG is the most sensitive clinical test of neuromuscular transmission and shows increased jitter in some muscles in almost all patients with myasthenia gravis. Jitter is greatest in weak muscles but may be abnormal even in muscles with normal strength. Patients with mild or purely ocular muscle weakness may have increased jitter only in facial muscles. Increased jitter is a nonspecific sign of abnormal neuromuscular transmission and can be seen in other motor unit diseases. Normal jitter in a weak muscle excludes abnormal neuromuscular transmission as the cause of weakness. Comparison of Diagnostic Techniques Intravenous edrophonium chloride is often diagnostic in patients with ptosis or ophthalmoparesis, but is less useful when other muscles are weak. Elevated serum concentrations of AChR binding and probably MuSK antibodies virtually assures the diagnosis of myasthenia gravis, but normal concentrations do not exclude the diagnosis. Repetitive nerve stimulation confirms impaired neuromuscular transmission but is not specific to myasthenia gravis and is frequently normal in patients with mild or purely ocular disease. The measurement of jitter by SFEMG is the most sensitive clinical test of neuromuscular transmission and is abnormal in almost all patients with myasthenia gravis. A normal test in a weak muscle excludes the diagnosis of myasthenia gravis, but an abnormal test can occur when other motor unit disorders cause defects in neuromuscular transmission.

4.2 Differential diagnosis:

4.2.1 Causes of generalised muscle weakness

- Multiple sclerosis (MS) - hyperreflexia and extensor plantar response can be seen, which help differentiate it from MG.
- Motor neurone disease (MND) - usually features of lower motor neurone (LMN) disease with wasting and fasciculation are present.
- Hyperthyroidism.
- Myalgic encephalomyelitis (ME) - 'chronic fatigue syndrome' - will have vague feelings of exhaustion made worse by any effort and no neurological signs to accompany it unless from sdisuse. The specific tests for MG will be negative.
- Other myopathies - may show fasciculation and elevated creatine kinase (CK).
- Toxins and drugs - eg, botulinum, organophosphate poisoning.
- Acute Guillain-Barré syndrome - the motor type will have LMN features.
- Lambert-Eaton myasthenic syndrome - initially causes slight benefit from exercise before deterioration; no autoantibody or electromyographic (EMG) findings, and ocular weakness does not occur [10]**.**

4.2.2 Causes of ocular symptoms:

- Horner's syndrome - is usually unilateral. The eyelid may droop but the pupil is smaller than the other and sweating is reduced or absent on that side of the face.

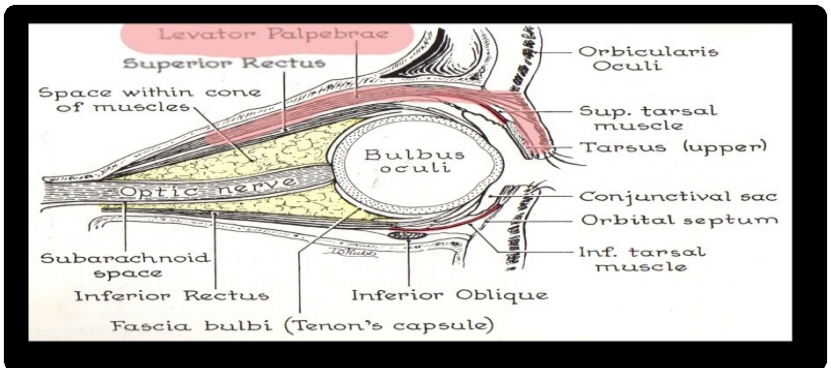

Figure: 5 Oculopharyngeal muscular dystrophy.

Figure: 6 - ptosis

4.3 Diagnostic test:

4.3.1 Antibody blood tests:

Blood tests can detect the presence of high levels of abnormal antibodies that prevent normal nerve-to-muscle transmission. Most people with MG have abnormally high levels of acetylcholine receptor antibodies. But some people with MG test negative for these antibodies. Recently, another type of antibody, called MuSK antibodies, has been found in some MG patients who test negative for acetylcholine receptor antibodies. For these patients, a blood test that detects MuSK antibodies can be a useful diagnostic tool. Just how MuSK antibodies alter or damage nerve-muscle transmission isn't clear. But patients who test positive for MuSK antibodies often have symptoms involving face muscles, swallowing, speech, and breathing. Abnormal antibodies may not be found if only eye muscles are affected by MG**.**

4.3.2 **Edrophonium test:**

When this drug is injected into someone with MG, his or her normally weak eye muscles will get stronger for a few minutes**.**

4.3.3 **Nerve conduction test/repetitive stimulation:**

With this test, a nerve linked with a specific muscle is stimulated to see if the muscle action is weakened.

4.3.4 **Single fiber electromyography (EMG);**

In this test, single muscle fibers are stimulated by electrical impulses. Muscle fibers of people with MG do not respond to repeated electrical stimulation as well as muscles that function normally. With this test, the EMG can detect problems with nerve-to-muscle transmission

4.3.5 **Computed tomography (CT) or magnetic resonance imaging (MRI):**

This test can show if you have an abnormal thymus gland or a thymus gland tumor.

V. Epidemiology

Acquired myasthenia gravis (MG) is a relatively uncommon disorder, with prevalence rates that have increased to about 20 per 100,000 in the US population. This autoimmune disease is characterized by muscle weakness that fluctuates, worsening with exertion, and improving with rest. In about two-thirds of the patients, the involvement of extrinsic ocular muscles (EOMs) presents as the initial symptom, usually progressing to involve other bulbar muscles and limb musculature, results in generalized myasthenia gravis (gMG). In about 10% of myasthenia gravis patients, symptoms are limited to EOMs, with the resultant condition called ocular

MG (oMG). Sex and age appear to influence the occurrence of myasthenia gravis. Below 40 years of age, female, male ratio is about 3: 1; however, between 40 and 50 years as well as during puberty, it is roughly equal. Over 50 years, it occurs more commonly in males.Childhood MG is uncommon in Europe and North America, comprising 10% to 15% of MG cases. In Asian countries though, up to 50% of patients have onset below 15 years of age, mainly with purely ocular manifestations.

5.1.1 United States Statistics

MG is uncommon. The estimated annual US incidence is 2 per 1,000,000. The prevalence of MG in the United States ranges from 0.5 to 14.2 cases per 100,000 people. This figure has risen over the past 2 decades, primarily because of the increased lifespan of patients with MG but also because of earlier diagnosis.About 15-20% of patients will experience a myasthenic crisis. Three fourths of these patients experience their first crisis within 2 years of diagnosis.

5.1.2 sex-related demographics

Classically, the overall female-to-male ratio has been considered to be 3:2, with a female predominance in younger adults (ie, patients aged 20-30 years) and a slight male predominance in older adults (ie, patients older than 50 years).Studies show, however, that with increased life expectancy, males are coming to be affected at the same rate as females. Ocular MG shows a male preponderance. The male-to-female ratio in children with MG and another autoimmune condition is 1:5.

5.1.3 race-related demographics

The onset of MG at a young age is slightly more common in Asians than in other races.

5.2 historical aspect

The first reported case of MG is likely to be that of the Native American Chief Opechancanough, who died in 1664. It was described by historical chroniclers from Virginia as "the excessive fatigue he encountered wrecked his constitution; his flesh became macerated; the sinews lost their tone and elasticity; and his eyelids were so heavy that he could not see unless they were lifted up by his attendants… he was unable to walk; but his spirit rising above the ruins of his body directed from the litter on which he was carried by his Indians".. In 1672, the English physician Willis first described a patient with "fatigable weakness" involving ocular and bulbar muscles described by his peers as "spurious palsy." In 1877, Wilks (Guy's Hospital, London) described the case of a young girl after pathological examination as "bulbar paralysis, fatal, no disease found" . In 1879, Wilhelm Erb (Heidelberg, Germany) described three cases of myasthenia gravis in the first paper dealing entirely with this disease, whilst bringing attention to features of bilateral ptosis, diplopia, dysphagia, facial paresis, and weakness of neck muscles. In 1893, Samuel Goldflam (Warsaw, Poland) described three cases with complete description of myasthenia and also analyzed the varying presentations, severity, and prognosis of his cases. Due to significant contributions of Wilhelm Erb and later of Samuel Goldflam, the disease was briefly known as "Erb's disease" and later for a brief time, it was called "Erb-Goldflam syndrome".

In 1895, Jolly, at the Berlin Society meeting, described two cases under the title of "myasthenia gravis pseudo-paralytica". The first two words of this syndrome gradually got accepted as the formal name of this disorder. He also demonstrated a phenomenon, that later came to be known as "Mary Walker effect" after she herself observed and described the same finding in 1938. This was reported as "if you stimulate one group of muscles to exhaustion, weakness is apparent in muscles that are not stimulated; an evidence of a circulating factor causing neuromuscular weakness".

In 1934, Mary Walker realized that MG symptoms were similar to those of curare poisoning, which was treated with physostigmine, a cholinesterase inhibitor. She demonstrated that physostigmine promptly improved myasthenic symptoms. In 1937, Blalock reported improvement in myasthenic patients after thymectomy. Following these discoveries, cholinesterase inhibitor therapy and thymectomy became standard and accepted forms of treatment for MG.

In 1959-1960, Nastuk et al. and Simpson independently proposed that MG has autoimmune etiology. In 1973, Patrick and Lindstrom were able to induce experimental autoimmune MG (EAMG) in a rabbit model using muscle-like acetylcholine receptor (AChR) immunization. In the 1970s prednisone and azathioprine were introduced as treatment modalities for MG followed by plasma exchange that was introduced for acute treatment of severe MG, all supporting the autoimmune etiology[11-13].

VI. Clinical Presentation

In MG, patients present with fluctuating and fatigable weakness of specific muscle groups rather than with generalized fatigue or pain. The weakness is variable from day to day and from hour to hour, but it is generally worse later in the day. Sustained exercise and increased body temperature may increase the degree of

weakness. Ocular weakness with asymmetric ptosis and binocular diplopia is the most common initial presentation, while early or isolated oropharyngeal or limb weakness is less common.

Ocular weakness presents as fluctuating, fatigable, and sometimes alternating ptosis and binocular diplopia that resolves with closing or covering one eye. Many patients report difficulties with driving, reading, or watching television. Bright lights may be quite bothersome. Retrospectively, many patients report periods of intermittent blurred vision before they were able to discern dual visual images. Examination may demonstrate asymmetrical weakness of multiple extraocular muscles that cannot be attributed to a single cranial neuropathy. Pupillary function is normal. Ptosis may be elicited or increased with sustained upgaze. In MG, ptosis is generally asymmetrical, and it may be associated with ipsilateral frontalis muscle contraction to help compensate for the weak levator palpebrae. Excessive lid elevation or Cogan's lid twitch sign may be observed when gaze is directed from down to upward.

Dysthyroid (Graves) ophthalmopathy may coexist with ocular MG. Although external ophthalmoplegia may occur in either disorder, dysthyroid ophthalmopathy produces proptosis, not ptosis, owing to enlarged extraocular muscles. The enlarged muscles may be demonstrated by orbital magnetic resonance imaging (MRI).
Jaw closure muscles are frequently affected in MG, but strength is usually normal in jaw opening muscles. Patients may complain of difficulty in chewing candy or tough meats, and some modify their diet to compensate for this difficulty. Some patients assume a thoughtful resting posture by placing the thumb beneath the chin in order to hold the jaw closed. The jaw closure muscles can be examined by exerting several seconds of sustained downward pressure on the chin while the patient attempts to hold the jaw closed.

Many patients exhibit a depressed or expressionless facial appearance. Actions such as whistling, using straws, or inflating balloons may be impaired. A "myasthenic snarl" may be observed when the patient attempts to smile. The snarl follows contraction of the middle portion of the upper lip while the upper mouth corners fail to contract. On examination, many patients exhibit weak forced eye closure that can easily be overcome by the examiner. Bell's phenomenon with upward and lateral rotation of the eyes on attempted closure is observed when the examiner defeats a patient's forced eye closure. Patients with mild lower facial weakness develop a transverse pucker when they attempt to hold air within inflated cheeks. With more overt lower facial weakness, air readily escapes through the lips when the cheeks are squeezed. In severe lower facial weakness, the lips cannot be voluntarily opposed.

Oropharyngeal muscle weakness produces dysarthria and dysphagia. With weakness of palatal muscles, nasal speech develops as air escapes through the nose. This may become increasingly apparent with prolonged speaking. Liquid may also escape through the nose during attempted swallowing with nasal regurgitation. Myasthenic weakness of laryngeal muscles is associated with a hoarse, breathy voice. Incomplete glottic closure during swallowing may produce aspiration. Examination may reveal reduced or absent palate elevation. Tongue weakness may be demonstrated when the patient attempts to protrude either cheek with the tongue against the resistance of the examiner's finger applied to the cheek. With marked tongue weakness, the patient may be unable to protrude the cheek in the absence of applied resistance by the examiner. With severe lingual weakness, the tongue may not protrude beyond the lips. When myasthenic tongue weakness is chronic, tongue atrophy and triple furrowing may develop with accentuated median and lateral lingual furrows.
Neck flexor and extensor muscles are often weak in MG. Though the neck flexors are usually weaker, a "dropped head syndrome" due to neck extensor muscle weakness may occur. Although painless weakness is the rule in MG, patients with neck extensor weakness may experience posterior neck myalgias.

Limb weakness in MG may be associated with complaints of difficulty performing overhead tasks with the arms, and there may be difficulty climbing stairs due to lower extremity weakness. Examination reveals asymmetrical weakness involving any muscle group in the limbs, though the deltoids, triceps brachii, wrist and finger extensors, and foot dorsiflexors are often involved.
Many patients present with problems of the ocular muscles and most experience them at some stage. The clinical presentation varies from mild weakness of limited muscle groups (class I or ocular MG) to severe weakness of multiple muscle groups (class V or severe generalised MG).

- Muscle fatigues more readily after exercise - a feature used in making the diagnosis.
- Droop of the upper eyelids is typical with weakness of external ocular muscles producing diplopia. Patients may tilt their head upwards to compensate.
- Weakness is more marked in proximal muscles and isolated weakness of limb muscles is the presenting feature in a minority of patients.
- Weakness of the following muscles may also be seen:
  - Small muscles of the hands (finger extensors).
  - Deltoid and triceps muscles.
  - Bulbar muscles - common, causing a nasal sound to speech that is slurred.
  - Facial muscles - very common, producing an abnormal horizontal smile with a furrowed brow that compensates for ptosis.

- Muscles involved in chewing - thus eating can become difficult and weak muscles may make the jaw drop so that the patient may sit with chin on hand to support it.
- Flexors and extensors of the head - are often weak.
- Symmetrical weakness of a number of other muscles may produce difficulty with walking, sitting or even holding the head up.
- Seizures may occur and there is a case report of undiagnosed MG mistakenly thought to be eclampsia [14].

VII. Pharmacological Management

Treatment must be individualized to each patient with MG. The overall goal is to reestablish or to approximate normal clinical neuromuscular function while minimizing adverse effects. Few treatments have been subjected to rigorous, prospective, placebo-controlled study in MG. Factors to be considered in selecting treatment include the distribution, duration, and severity of myasthenic weakness and functional impairment, the risk for treatment complications related to medical comorbidities, age, and gender, and the ability of the patient to obtain medication and comply with drug dosing schedules and toxicity monitoring. In general, the increased risks related to long-term immune modulation become more acceptable in more severe MG to offset increased morbidity and mortality related to uncontrolled disease.

The below shown flowchart gives us a brief idea of management of myasthenia gravis.

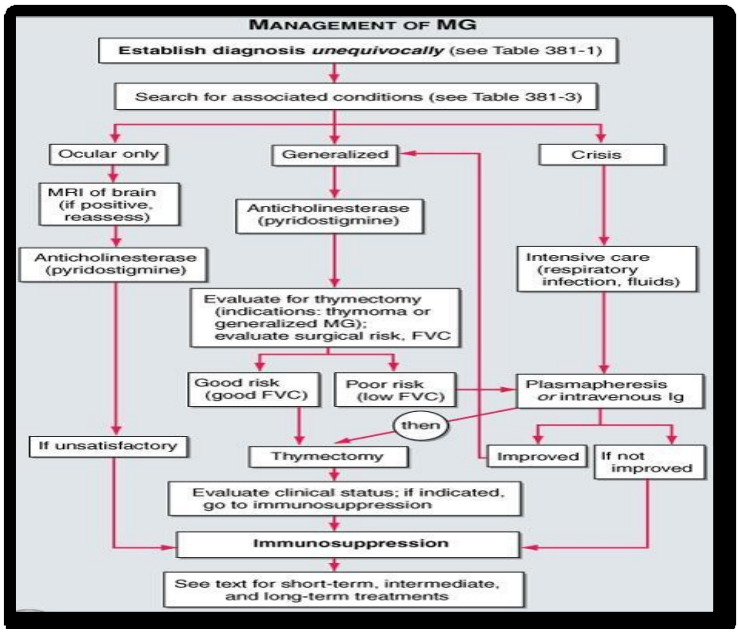

Figure: 7-FlowChart Showing Management of MG

7.1 Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors slow the hydrolysis of acetylcholine at the neuromuscular junction and provide temporary improvement in strength in many patients with MG. Although acetylcholinesterase inhibitors were among the earliest and remain one of the most widely prescribed treatments for MG, there are no controlled clinical trials of these agents in MG. Acetylcholinesterase inhibitors are a symptomatic therapy for MG and do not retard the underlying autoimmune attack on the neuromuscular junction. The roles for acetylcholinesterase inhibitors in MG include treatment of ocular and mild generalized disease, treatment in patients who cannot receive immune suppression, and adjunctive treatment for patients receiving immunotherapy with residual or refractory myasthenic weakness.

Effective dosing of acetylcholinesterase inhibitors reduces myasthenic weakness, minimizes muscarinic medication side effects, and must be individualized to each patient's distribution of weakness and diurnal symptom fluctuation. For example, patients with prominent dysphagia may benefit by taking pyridostigmine 30 minutes before meals and those with more symptoms in the afternoon and evening may shift their dosing to later in the day to better target symptoms. Pyridostigmine bromide is generally better tolerated than neostigmine bromide due to fewer gastrointestinal side effects. A long-acting form of pyridostigmine bromide is available, though it is absorbed irregularly and tends to be overdosed. Initial dosing of pyridostigmine bromide is usually 30 mg three times a day and may be advanced to 90 mg three to four times a day. Improvement in strength

begins about 20 to 30 minutes after ingestion. Peak improvement is usually observed at about 45 minutes after ingestion, and benefits may last four hours or more.

The most salient side effects of acetylcholinesterase inhibitors relate to increased muscarinic activity and include nausea, vomiting, abdominal cramping, diarrhea, diaphoresis, and increased lacrimation, salivation, and bronchial secretions. These dose dependent and self-limited side effects may be treated with glycopyrrolate, and the gastrointestinal side effects may be treated with diphenoxylate hydrochloride with atropine or loperamide hydrochloride.

Cholinergic crisis may develop with excessive dosing of acetylcholinesterase inhibitors in patients with more severe MG. In cholinergic crises, depolarization blockade at diseased neuromuscular junction's results in increased weakness, and increased muscarinic activity generates copious oropharyngeal and bronchial secretions that may obstruct the airway or be aspirated. Signs of cholinergic crisis include weakness indistinguishable from myasthenic weakness, muscle fasciculations, and symptoms of increased muscarinic activity including bradycardia.

7.2 Corticosteroids

Corticosteroids are the most widely used immune modulating agents for MG. Although the mechanism of action in MG is unknown, corticosteroids have numerous effects on the immune system including reduction of cytokine production .Corticosteroids are often used as the initial immunotherapy in patients with ocular and generalized MG, particularly in patients with unsatisfactory responses to acetylcholinesterase inhibitors. These agents may produce rapid improvement in MG, though they are often associated with the liability of significant dose-dependent side effects and occasionally elicit transient and potentially serious myasthenic exacerbations within the first two weeks of treatment. Prednisone treatment produced significant improvement in strength within two to three weeks in retrospective studies of MG and a Cochrane review cites significant short term benefit in MG with corticosteroids Marked improvement or remission was achieved in 80% MG patients in one large series with a 3.1 month mean time to marked improvement and a median time to maximum benefit between five and six months

The most reliable clinical responses to corticosteroids occur with a high-dose daily regimen that is gradually tapered based on clinical improvement in strength. The initial prednisone dose is typically 60–80 mg/day or 1.5–2.0 mg/kg/day. This initial dose is maintained for two to four weeks, and strength is reassessed. If strength is definitely improved, dosing is transitioned to an alternate day schedule of 100–120 mg/alternate day to minimize adrenal suppression. Occasional patients are unable to tolerate an alternating-day regimen due to mood instability, variation in MG, or difficult glycemic control in occasional diabetic patients.

Myasthenic relapses may be delayed for three weeks after reductions in corticosteroid dosing, and rapid tapering may precipitate myasthenic exacerbations or crises. Therefore, corticosteroid tapering must be slow, judicious, and proceeded by clinical reassessment of strength. Patients are reassessed at four to eight week intervals, and if they have maintained or improved strength and no recurrent symptoms, the prednisone dose is tapered by 10 mg/alternate day to 30 mg/alternate day, and then by 5 mg/alternate day to 20 mg/alternate day. Subsequent tapering by 2.5 mg/alternate day should be performed over longer intervals of at least 12 weeks, since many patients will begin to experience recurrent symptoms in this dosing range unless they are being treated with another immune modulating agent.

The adverse effects of corticosteroids are numerous, well known, and largely dose-dependent. These include: hypertension, fluid retention, weight gain, potassium loss, hyperlipidemia, diabetes mellitus, osteoporosis, gastric ulceration, cataracts, glaucoma, moon facies, obesity, acne, skin friability, juvenile growth suppression, and mood/personality changes. Individuals at particular risk for side effects include those who are diabetic or glucose intolerant, obese, hypertensive, osteoporotic or post-menopausal, and those with affective or thought disorders. An alternative immune modulator may be considered in such patients.

A high protein, low fat, low carbohydrate, low sodium diet is recommended to prevent untoward weight gain, hyperlipidemia, and fluid retention. Serum electrolytes, glucose, blood pressure, and weight are monitored periodically during treatment. To minimize osteopenia, calcium carbonate 1500 mg/day and vitamin D 600 IU/day are recommended. In post-menopausal women, a baseline bone density evaluation is performed and repeated every six months during treatment. Before initiating treatment with corticosteroids or any long-term immunotherapy, PPD testing should be considered as a screen for tuberculosis.

Corticosteroid-related MG exacerbations may produce transient but potentially serious increases in myasthenic weakness in up to 15% of patients beginning treatment with corticosteroids .The increased weakness develops within 7–10 days after treatment begins and may last for up to one week before strength improves Patients at greatest risk for morbidity related to this phenomenon are those with more severe bulbar or generalized weakness and/or compromised respiratory function. When beginning corticosteroid treatment in such patients, strength and respiratory function should be closely monitored. Plasma exchange (PEX) may be performed prior to starting corticosteroids to circumvent or minimize corticosteroid-related MG exacerbations.

In such cases, corticosteroids are initiated after a clear improvement in strength attributable to PEX is documented.

An alternative dosing strategy of starting corticosteroids at a low initial dose with gradual dose increases has been advocated to reduce the risk for corticosteroid-related MG exacerbations However, this strategy does not eliminate the risk for exacerbation [and onset of strength improvement is less predictable and may be significantly delayed.

7.3 azathioprine

Azathioprine is hepatically converted to 6-mercaptopurine, an active anti-metabolite that blocks nucleotide synthesis and T-lymphocyte proliferation. Azathioprine is an effective agent for long-term immune modulation in MG as a steroid sparing drug or as initial immunotherapy. Compared to corticosteroids, azathioprine has a favorable side effect profile for long-term use. However, the typically long delay of four to eight months from beginning treatment with azathioprine to improved strength in MG is a significant liability to its usefulness, particularly in MG patients with progressive disease or functionally limiting symptoms.

In a prospective, randomized, double-blind study comparing prednisolone with prednisolone plus azathioprine, the prednisolone plus azathioprine treatment group exhibited longer remissions, fewer treatment failures, fewer side effects, and reduced maintenance doses of prednisolone.The initial dose is 50 mg/day is increased by 50 mg/day every week to a target therapeutic dose of 2–3 mg/kg/day.

Side effects include dose dependent myelosuppression with macrocytic anemia, leukopenia, and thrombocytopenia, toxic hepatitis, and alopecia. Hypersensitivity pancreatitis represents a rare, but serious idiosyncratic reaction, and patients with sustained abdominal pain taking azathioprine should be screened with serum amylase and lipase assays. With long-term use, there is a small increased risk for lymphoma

Azathioprine is potentially teratogenic, and women of child bearing potential using azathioprine should practice effective contraception. An idiosyncratic allergic reaction with rash, fever, nausea, vomiting, and abdominal pain occurs in 10–15% patients within the first three weeks of treatmentThe reaction resolves within one day of stopping azathioprine, and will recur if the patient is rechallenged with the drug.

Monitoring for myelosuppression is recommended with weekly blood count and liver transaminase measurements weekly for the first month of treatment, then monthly for the first year, then every three months thereafter unless the dosage is increased. Erythrocyte macrocytosis is expected and acceptable within the therapeutic dosage range. If white blood cell count (WBC) falls below $3500/mm^3$, the dosage should be reduced, and if WBC falls below $3000/mm^3$, azathioprine should be discontinued.

7.4 cyclosporine

Cyclosporine exerts an immunomodulatory effect by blocking interleukin-2 production and T lymphocyte proliferation. Although effective, the use of cyclosporine in MG has been limited by its nephrotoxicity and numerous drug interactions. In light of this, cyclosporine is used in MG as a steroid-sparing agent or for refractory generalized disease. After therapeutic levels of cyclosporine are achieved and maintained, improvement in strength is usually observed within two months.

In a population of steroid-dependent patients with MG, a randomized, double blind, placebo-controlled study of cyclosporine demonstrated significantly improved strength in the cyclosporine treatment group.In a long-term retrospective study, 96% MG patients improved with cyclosporine treatment, and steroids could be tapered or discontinued in 95% patients The typical cyclosporine dose is 2.5 mg/kg every 12 hours to achieve a target serum trough level of 100–150 microgram/L.

Side effects of cyclosporine include hypertension, nephropathy, tremor, hirsutism, gingival hypertrophy, headaches, and nausea. Accordingly, relative contraindications to cyclosporine include poorly controlled hypertension, renal insufficiency or failure, malignancy, and inability to comply with blood monitoring or medication precautions.

Periodic monitoring is necessary to achieve therapeutic trough cyclosporine levels and to prevent nephrotoxicity. Assessments of blood pressure, serum creatinine and the trough serum cyclosporine level should be performed frequently until a stable, therapeutic dose of cyclosporine is achieved and after new medications are begun that have the potential to interact with cyclosporine.

Cyclosporine has problematic interactions with numerous drugs that may result in nephrotoxicity, significant increases in serum drug levels, and/or significant increases or decreases in serum cyclosporine levels .The most common cyclosporine interactions and potential complications include non-steroidal anti-inflammatory agents with impaired renal function, angiotensin converting enzyme inhibitors eliciting hyperkalemia, and HMG CoA reductase inhibitors precipitating cholesterol-lowering agent myopathy.

7.5 Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a relatively novel immune modulator that selectively inhibits T and B lymphocyte proliferation by blocking purine synthesis exclusively in lymphocytes. In human kidney transplant trials, MMF exhibited minimal toxicity. Given a paucity of side effects, MMF is used in MG both as a steroid-sparing agent and as initial immunotherapy in patients at risk for corticosteroid complications. Improved strength is observed within about two months after reaching a therapeutic dose of MMF.

Significantly improved strength in MG patients taking MMF has been demonstrated in a retrospective case series , in an open label pilot study in steroid dependent or refractory MG, and in a double-blind placebo control pilot trial in MG .

However, in a recently concluded multi-center, randomized, controlled trial of low dose prednisone versus low dose prednisone with MMF, there was no clinically significant benefit in MG patients treated with MMF combined with low dose prednisone beyond that observed in MG patients treated with low dose prednisone only during the initial three month trial period. Analysis of the open label phase of this study is currently pending.

The standard MMF dosage in MG is 1000–1500 mg twice a day. Higher doses are associated with myelosuppression, and periodic blood counts are performed during treatment as surveillance against leukopenia or anemia. There is a small increased risk for lymphoproliferative disorders in transplant patients, and a case of central nervous system (CNS) lymphoma has been documented in a patient with MG after three years of MMF treatment .Side effects are relatively mild. In one series, diarrhea, abdominal pain, and nausea were reported in 27% patients, though only 6% patients discontinued MMF due to these side effects.

7.6 Plasma exchange

PEX is used in MG to achieve rapid, temporary improvement in strength. During PEX, plasma containing AChR antibodies is separated from whole blood and replaced by albumin or fresh frozen plasma. The procedure requires catheterizing large caliber veins. Although many patients have large antecubital veins that may be accessed serially for PEX procedures, some patients require placement of large bore dual lumen central venous catheters. PEX is generally reserved for short-term treatment to achieve rapid strength improvement in myasthenic exacerbations or crises, to prepare patients for thymectomy or another surgical procedure, to prevent steroid-related MG exacerbations in susceptible patients beginning corticosteroid treatment, and for rare patients refractory to all other treatments. An National Institutes of Health (NIH) consensus statement supports use of PEX in these instances.Although there have been no controlled clinical trials of PEX in MG, several series demonstrate significantly improved strength in most patients with severe MG undergoing PEX . Typically, a PEX series consists of five to six exchanges of two to three liters on alternate days. Most PEX complications are related to issues of vascular access, particularly to complications of large bore central venous catheters. Excessive fluid volume shifts during the procedure may result in hypotension or fluid overload and congestive heart failure. Sepsis and hypotension are contraindications to PEX.

Improved strength is generally observed after the second or third exchange procedure in most MG patients. Unless another form of treatment is employed, the improved strength is temporary and lasts only a few weeks at best.

7.7 Intravenous immunoglobulin

IVIg has been utilized in a number of autoimmune neuromuscular disorders including acute and chronic inflammatory polyneuropathy. It is thought to act by down regulation of autoantibodies and/or induction of anti-idiotypic antibodies. In MG, IVIg may provide short-term improvement in strength for MG exacerbations and crises, for surgical preparation in patients who are poor PEX candidates because of vascular access issues, and in patients with septicemia.

A number of studies demonstrate efficacy for IVIg in MG. A small randomized, controlled trial of IVIg 1.2 and 2.0 gm/kg compared with PEX in MG patients with exacerbation or crisis showed comparable efficacy between the PEX and IVIg treatment groups. Another retrospective multicenter study demonstrated that PEX was better than IVIg in ability to successfully extubate patients in crisis at two weeks and in functional outcome at one month. However, the PEX groups in both studies sustained more cardiovascular and infectious complications. Although the magnitude of responses appears to be comparable between PEX and IVIg, treatment failures have been reported to IVIg with subsequent response to PEX .IVIg trials in MG are summarized in a Cochrane review The time to improved strength following IVIg infusions is somewhat variable, as demonstrated by a trial of IVIg given to prepare MG patients for thymectomy in which maximal response was delayed by up to 19 days .IVIg is generally administered as 10% solution, and the standard dosage is 2 gm/kg over two to five days. However, one randomized trial found no added benefit for doses of 2 gm/kg over 1 gm/kg for MG exacerbations. Pretreatment with acetaminophen and diphenhydramine may reduce the frequency and severity of idiosyncratic reactions.

Side effects include volume overload, particularly for patients with cardiomyopathy or valvular heart disease, solute-induced renal failure, especially in patients with preexisting renal insufficiency or diabetic nephropathy, and idiosyncratic reactions such as fever, chills, nausea, vomiting, vascular headaches, and aseptic meningitis. High infusion rates may be associated with thrombosis and stroke. Serum immunoglobulin quantitation to screen for IgA deficiency is recommended, since IVIg preparations contain traces of IgA.

7.8 thymectomy

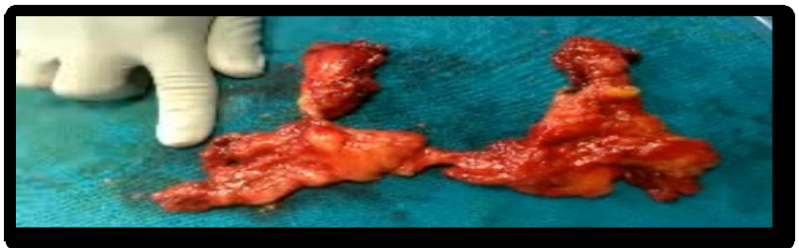

Figure: 8-thoracoscopic thymectomy

Thymectomy may be performed via several approaches. Though more Thymectomy has been widely performed in an effort to achieve medication-free remission in MG following Blalock's early observations of remissions following thymectomy in non-thymomatous MG. To date, there have been no prospective, randomized studies completed to assess the technique or effectiveness of thymectomy in non-thymomatous MG. Fortunately, a large, international multicenter trial is currently enrolling subjects to assess the benefit of thymectomy in non-thymomatous MG. An evidence-based review was recently performed to address the role of thymectomy in the management of MG, and outcomes of thymectomy in controlled, nonrandomized studies were systematically reviewed. Although patients undergoing thymectomy in non-thymomatous MG were more likely to achieve medication-free remission, become asymptomatic, or exhibit clinical improvement, the association between thymectomy and improved outcomes could attribute either to thymectomy or to differences in the study populations. Therefore, in non-thymomatous MG, thymectomy should be considered as an option to increase the probability of remission or improvement. The response to thymectomy is not immediate and may be delayed for several years.

Controversies related to thymectomy in non-thymomatous MG include the ideal timing of the procedure with respect to MG onset, course, and patient age, the optimal surgical technique, whether patients with exclusively ocular MG should undergo thymectomy, and whether patients with SN or MuSK MG benefit from thymectomy.

Because of increased surgical risk and reduced life span, thymectomy is rarely performed in patients at greater than age 60 years for non-thymomatous MG. There is evidence to suggest that the best clinical responses occur if thymectomy is performed early in the course of MG, though this may attribute to a non-linear remission rate, as remission is more likely to occur shortly after diagnosis rather than with more chronic disease. The role for thymectomy in non-thymomatous ocular MG is also uncertain. In MuSK MG, no thymomas have been reported to date, and findings in recent clinical series raise doubt about benefits of thymectomy in MuSK MG patients.

Invasive than other approaches, a combined transsternal-transcervical technique is considered to be optimal as it provides the widest exposure for complete removal of thymic tissue that may be widely distributed in mediastinum and neck. Surgical techniques for thymectomy have been reviewed by Jaretzki and colleagues. Preoperative PEX or IVIg is performed to improve strength in patients with moderate or severe generalized or bulbar MG or in patients with MG-related respiratory insufficiency. In contemporary series of thymectomy for MG, mortality is less than 1%. Complications include respiratory failure due to myasthenic crisis in 6%, infection in 11%, and recurrent laryngeal or phrenic nerve injury in 2% [14].

VIII. Prognosis

Most patients develop initial symptoms of extraocular muscle weakness with asymmetric ptosis and diplopia. The course is frequently variable, particularly within the first year of disease. Nearly 85% of patients with initial ocular symptoms progress to develop weakness of bulbar and limb muscles within the first three years. Initial presentations with oropharyngeal and limb weakness are less common. Maximum disease severity is reached within the first year in almost two-thirds of patients. Myasthenic crisis or respiratory failure due to myasthenic weakness occurs in about 20% of patients, usually within the first year of illness. Myasthenic symptoms and signs may worsen in the setting of systemic illness, particularly viral upper respiratory infections, thyroid disease, pregnancy, increased body temperature, and exposure to drugs that impair neuromuscular transmission. Early in the course of MG, symptoms may fluctuate and occasionally remit, although such

remissions are rarely permanent. Three major stages of generalized MG have been proposed. An active stage characterized by relapses and remissions lasting approximately seven years is followed by an inactive stage lasting about 10 years. The inactive stage is characterized by less disease volatility, though patients may experience exacerbations related to intercurrent illnesses, pregnancy, or exposure to medications that compromise neuromuscular transmission. In the ultimate stage of "burned-out" disease, untreated weakness may become fixed in association with muscle atrophy.

Prior to the widespread use of immunomodulators, prognosis for patients with MG was grim with about 30% mortality. Along with advances in mechanical ventilation and intensive care, immunotherapy has been one of the major factors contributing to improved outcome in MG, and contemporary disease-specific mortality is less than 5%. There are a number of drugs that can aggravate the condition and they should be used with caution if essential but are best avoided (table 1) [14].

Table: 1- Medication That May Exacerbate Weakness In Myasthenia Gravis

Drugs that can exacerbate Myasthenia Gravis	
Drug group	**Examples**
Antibiotics	Aminoglycosides - eg, gentamicin Ciprofloxacin Macrolides - eg, erythromycin, azithromycin Tetracycline Ampicillin Clindamycin
Beta-blockers	Propranolol Atenolol Timolol eyedrops
Anti-arrhythmic drugs	Verapamil Quinidine and procainamide (both withdrawn)
Neuromuscular blocking agents	Atracurium Vecuronium (May cause unexpectedly long paralysis)
Other drugs	Lithium D-penicillamine Opiates - eg, pethidine Phenytoin Statins Magnesium Chloroquine Prednisolone

IX. Symptoms

The symptoms of myasthenia gravis may include:

- Eye Muscle Weakness.
- Eyelid Drooping (Ptosis).
- Blurry or Double Vision (Diplopia).
- Unstable Gait.
- A Change in Facial Expression.
- Difficulty in Swallowing.
- Shortness of Breath.
- Impaired Speech.
- Weakness in the Arms, Hands, Fingers, Legs, and Neck.

X. Telithromycin

Telithromycin ($C43H65N_5O_{10}$) which is a ketolide antibiotic has a structural formula shown in (figure 9). Adverse effects have limited the clinical use of telithromycin. Preferential inhibition of the nicotinic acetylcholine receptors (nAChR) at the neuromuscular junction (α3β2 and NMJ), the ciliary ganglion of the eye (α3β4 and α7), and the vagus nerve innervating the liver (α7) could account for the exacerbation of myasthenia gravis, the visual disturbance, and the liver failure seen with telithromycin use.

Telithromycin, a semi-synthetic erythromycin derivative, belongs to a new chemical class of antibiotics called ketolides. Ketolides have been recently added to the macrolide-lincosamide-streptogramin class of antibiotics. Similar to the macrolide antibiotics. Not only in the exacaration of myasthenia gravis. Telithromycin also showed many drug interactions and interaction with enzymes (table 3).

10.2 Structural Formula:

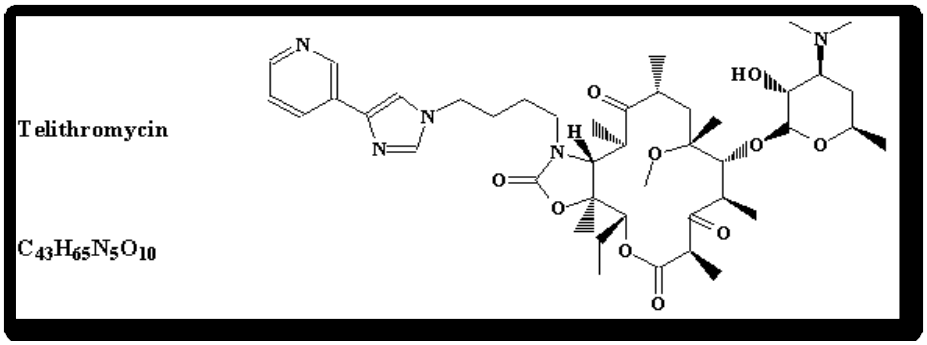

Figure :9 chemistry of telithromycin

10.1 Mechanism

Telithromycin prevents bacterial growth by interfering with bacterial protein synthesis.

↓

Telithromycin binds to the 50S subunit of the 70S bacterial ribosome.

↓

Blocks further peptide elongation.

↓

Binding occurs simultaneously at to two domains of 23S RNA of the 50S ribosomal subunit.

↓

Domain II and V, where older macrolides bind only to one.

10.3 Pharmacology Of Telithromycin

Table:2- Pharmacology Of Telithromycin

Indication	➢ For the treatment of Pneumococcal infection, acute sinusitis, ➢ Acute bacterial tonsillitis, acute bronchitis and bronchiolitis, lower respiratory tract Infection And lobar (pneumococcal) pneumonia
Uses	➢ Telithromycin is a ketolide antibiotic which has an antimicrobial spectrum similar or slightly broader than that of penicillin. ➢ It is often used as an alternative in patients who have an allergy to penicillins. ➢ For respiratory tract infections, it has better coverage of atypical organisms'including mycoplasma. ➢ Telithromycin prevents bacterial growth by binding to bacterial 50S ribosomal subunits ➢ And interfering with bacterial peptide translocation and elongation
Bioavailability	➢ Absolute bioavailability is approximately 57%. ➢ Maximal concentrations are reached 0.5 - 4 hours following oral administration. Food intake does not affected absorption.
Volume of distribution	2.9 L/kg
Protein binding	60 - 70% bound primarily to human serum albumin
Metabolism	➢ Hepatic - estimated 50% metabolized by CYP3A4 50% metabolized independent of cytochrome P450
Route of elimination	➢ The systemically available telithromycin is eliminated by multiple pathways as follows: ➢ 7% of the dose is excreted unchanged in feces by biliary and/or intestinal secretion;

	➢ 13% of the dose is excreted unchanged in urine by renal excretion; 37% of the dose is metabolized by the liver.
Half life	➢ Main elimination half-life is 2-3 hours; terminal elimination half-life is 10 hours
Toxicity	➢ LD50>2000 mg/kg. ➢ Adverse effects: diarrhea, nausea, vomiting, loose stools, abdominal pain, ➢ Flatulence and dyspepsia. ➢ It may also cause dizziness, headache and taste disturbances.

10.4 Drug Interactions With Telithromycin:

Table: 3-Telithromycin Drug Interactions

DRUG NAME	INTERACTIONS WITH TELITHROMYCIN
Abiraterone	➢ Strong CYP3A4 inhibitors may increase levels of abiraterone. ➢ Monitor concomitant therapy
Acenocoumarol	➢ Telithromycin may increase the anticoagulant effect of acenocoumarol.
Alfentanil	➢ Telithromycin may reduce clearance of Alfentanil. Consider alternate therapy ➢ or monitor for changes in the therapeutic/adverse effects of Alfentanil ➢ If Telithromycin is initiated, discontinued or dose changed.
Alfuzosin	➢ Telithromycin may reduce clearance of Alfuzosin. Consider alternate therapy
Alprazolam	➢ Telithromycin may increase the effect and toxicity of the benzodiazepine, alprazolam.
ambrisentan	➢ Telithromycin may reduce clearance of Ambrisentan. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Ambrisentan. ➢ If Telithromycin is initiated, discontinued or dose changed.
Aminoglutethimide	➢ Aminoglutethimide may decrease the plasma concentration of Telithromycin
Amiodarone	➢ Telithromycin may reduce clearance of Amiodarone. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Amiodarone if Telithromycin is initiated discontinued or dose changed.
Amlodipine	➢ Telithromycin may reduce clearance of Amlopidine. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Amlopidine if Telithromycin is initiated discontinued or dose changed.
Amprenavir	➢ Co-administration may result in altered plasma concentrations of ➢ Amprenavir and/or Telithromycin. ➢ Consider alternate therapy or monitor the therapeutic/adverse effects of both agents
Anisindione	➢ Telithromycin may increase the anticoagulant effect of anisindione.
Aprepitant	➢ Telithromycin may reduce clearance of Aprepitant. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Aprepitant if Telithromycin is initiated discontinued or dose changed.
Aripiprazole	➢ Telithromycin may reduce clearance of Aripiprazole. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Aripiprazole if Telithromycin is initiated discontinued or dose changed.
armodafinil	➢ Telithromycin may reduce clearance of Armodafinil. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Armodafinil if Telithromycin is initiated discontinued or dose changed.
Artemether	➢ Additive QTc-prolongation may occur. ➢ Concomitant therapy should be avoided.
Astemizole	➢ Increased risk of cardiotoxicity and arrhythmias
Atazanavir	➢ Co-administration may result in altered plasma concentrations of Atazanavir Telithromycin. ➢ Consider alternate therapy or monitor the therapeutic/adverse effects of both agents.
Atorvastatin	➢ The macrolide antibiotic, telithromycin, may increase the serum concentrationof atorvastatin by decreasing its metabolism. ➢ Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of atorvastatin. ➢ Telithromycin is initiated, discontinued or dose changed.
Benzphetamine	➢ Telithromycin may reduce clearance of Benzphetamine.
Bisoprolol	➢ Telithromycin may reduce clearance of Bisoprolol. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Bisoprolol if Telithromycin is initiated discontinued or dose changed.
Bortezomib	➢ Telithromycin may reduce clearance of Bortezomib. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Bortezomib if Telithromycin is initiated discontinued or dose changed.
Bosentan	➢ Co-administration may cause decreased Telithromycin and increased ➢ Bosentan plasma concentrations. Consider alternate therapy.
Bretylium	➢ Increased risk of cardiotoxicity and arrhythmias
Bromazepam	➢ Telithromycin, a strong CYP3A4 inhibitor, may increase the serum ➢ Concentration of bromazepam by decreasing its metabolism. Consider ➢ alternate therapy or monitor for changes in the therapeutic and adverse ➢ effects of bromazepam if telithromycin is initiated, discontinued or dose ➢ Changed. Dosage adjustments may be required.

Bromocriptine	➢ Telithromycin may reduce clearance of Bromocriptine. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Bromocriptine if Telithromycin is initiated discontinued or dose changed.
Budesonide	➢ Telithromycin may reduce clearance of Budesonide. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Budesonide if Telithromycin is initiated discontinued or dose changed.
Buprenorphine	➢ Telithromycin may reduce clearance of Buprenorphine. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Buprenorphine if Telithromycin is initiated discontinued or dose changed.
Buspirone	➢ Telithromycin may reduce clearance of Buspirone. Consider alternate therapy ➢ or monitor for changes in the therapeutic/adverse effects of Buspirone if ➢ Telithromycin is initiated, discontinued or dose changed.
Busulfan	➢ Telithromycin may reduce clearance of Busulfan. Consider alternate therapy ➢ or monitor for changes in the therapeutic/adverse effects of Busulfan ➢ If Telithromycin is initiated, discontinued or dose changed.
Cabazitaxel	➢ Concomitant therapy with a strong CYP3A4 inhibitor may increase ➢ Concentrations of cabazitaxel. Avoid concomitant therapy.
Calcitriol	➢ Telithromycin may reduce clearance of Calcitriol. Consider alternate therapy ➢ or monitor for changes in the therapeutic/adverse effects of Calcitriol if ➢ Telithromycin is initiated, discontinued or dose changed.
Carbamazepine	➢ Co-administration may cause decreased Telithromycin and increased ➢ Carbemazepine plasma concentrations. Consider alternate therapy.
Chlordiazepoxide	➢ Telithromycin may reduce clearance of Chlordiazepoxide. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Chlordiazepoxide if Telithromycin is initiated discontinued or dose changed.
Chloroquine	➢ Telithromycin may reduce clearance of Chloroquine. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Chloroquine if Telithromycin is initiated discontinued or dose changed.
Chlorphenamine	➢ Telithromycin may reduce clearance of Chlorpheniramine. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Chlorpheniramine if Telithromycin is initiated discontinued or dose changed.
Ciclesonide	➢ Telithromycin may reduce clearance of Ciclesonide. Consider alternate ➢ therapy or monitor for changes in the therapeutic/adverse effects of ➢ Ciclesonide if Telithromycin is initiated discontinued or dose changed.
Cilostazol	➢ Telithromycin may reduce clearance of Cilostazol. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Cilostazol if Telithromycin is initiated, discontinued or dose changed.
Cinacalcet	➢ Telithromycin may reduce clearance of Cinacalcet. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Cinacalcet if Telithromycin is initiated, discontinued or dose changed.
Cisapride	➢ Telithromycin may reduce clearance of Cisapride. Concomitant therapy is contraindicated.
Citalopram	➢ Telithromycin may reduce clearance of Citalopram. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Citalopram if Telithromycin is initiated, discontinued or dose changed.
Clarithromycin	➢ Co-administration may result in altered plasma concentrations of Clarithromycin and/or Telithromycin. Consider alternate therapy or monitor the therapeutic/adverse effects of both agents.
Clobazam	➢ Telithromycin may reduce clearance of Clobazam. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Clobazam if Telithromycin is initiated, discontinued or dose changed.
Clonazepam	➢ Telithromycin may reduce clearance of Clonazepam. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Clonazepam if Telithromycin is initiated, discontinued or dose changed.
Clorazepate	➢ Telithromycin may reduce clearance of Clorazepate. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Clorazepate if Telithromycin is initiated, discontinued or dose changed.
Cocaine	➢ Telithromycin may reduce clearance of Cocaine. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Cocaine if Telithromycin is initiated, discontinued or dose changed.
Colchicine	➢ Telithromycin may reduce clearance of Colchicine. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Colchicine if Telithromycin is initiated, discontinued or dose changed.
Conivaptan	➢ Co-administration may result in altered plasma concentrations of Conivaptan and/or Telithromycin. Consider alternate therapy or monitor the therapeutic/adverse effects of both agents.
Cyclosporine	➢ Telithromycin may reduce clearance of cyclosporine. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of cyclosporine if telithromycin is initiated, discontinued or dose changed.
Dantrolene	➢ Telithromycin may increase the serum concentration of dantrolene by decreasing its metabolism. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of dantrolene if telithromycin is initiated, discontinued or dose changed.

Dapsone	➢ Telithromycin may reduce clearance of Dapsone. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Dapsone if Telithromycin is initiated, discontinued or dose changed.
Darifenacin	➢ Telithromycin may reduce clearance of Darifenacin. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Darifenacin if Telithromycin is initiated, discontinued or dose changed.
Darunavir	➢ Co-administration may result in altered plasma concentrations of Darunavir and/or Telithromycin. ➢ Consider alternate therapy or monitor the therapeutic/adverse effects of both agents.
Dasatinib	➢ Telithromycin may reduce clearance of Dasatinib. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Dasatinib if Telithromycin is initiated, discontinued or dose changed.
Delavirdine	➢ Delavirdine may increase the plasma concentration of Telithromycin. Consider alternate therapy or monitor therapeutic/adverse effects.
Dexamethasone	➢ Co-administration may cause decreased Telithromycin and increased Dexamethasone plasma concentrations. Consider alternate therapy.
Diazepam	➢ Telithromycin may reduce clearance of Diazepam. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Diazepam if Telithromycin is initiated, discontinued or dose changed.
Dicoumarol	➢ Telithromycin may increase the anticoagulant effect of dicumarol.
Digitoxin	➢ Telithromycin may reduce clearance of Digitoxin. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Digitoxin if Telithromycin is initiated, discontinued or dose changed.
Digoxin	➢ Telithromycin may increase the plasma concentration of Digoxin. Monitor for changes in Digoxin efficacy/toxicity if Telithromycin is initiated, discontinued or dose changed.
Dihydroergotamine	➢ Telithromycin may reduce clearance of Dihydroergotamine. Concomitant therapy is contraindicated.
Diltiazem	➢ Telithromycin may reduce clearance of Diltiazem. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Diltiazem if Telithromycin is initiated, discontinued or dose changed.
Disopyramide	➢ Telithromycin may reduce clearance of Disopyramide. ➢ Concomitant therapy should be avoided.
Docetaxel	➢ Telithromycin may reduce clearance of Docetaxel. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Docetaxel if Telithromycin is initiated, discontinued or dose changed.
Dofetilide	➢ Increased risk of cardiotoxicity and arrhythmias
Doxepin	➢ Telithromycin may reduce clearance of Doxepin. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Doxepin if Telithromycin is initiated, discontinued or dose changed.
Doxorubicin	➢ Telithromycin may reduce clearance of Doxorubicin. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Doxorubicin if Telithromycin is initiated, discontinued or dose changed.
doxorubicin TransDrug	➢ Telithromycin may reduce clearance of Doxorubicin. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Doxorubicin if Telithromycin is initiated, discontinued or dose changed.
Dronedarone	➢ Telithromycin is a strong CYP3A4 inhibitor in which concomitant use with dronedarone will significantly increase its exposure. ➢ Avoid concomitant use.
Efavirenz	➢ Efavirenz may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Eletriptan	➢ Telithromycin may reduce clearance of Eletriptan. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Eletriptan if Telithromycin is initiated, discontinued or dose changed.
Eplerenone	➢ Telithromycin may reduce clearance of Eplerenone. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Eplerenone if Telithromycin is initiated, discontinued or dose changed.
Ergoloid mesylate	➢ Telithromycin may reduce clearance of Ergoloid mesylates. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Ergoloid mesylates if Telithromycin is initiated, discontinued or dose changed.
Ergonovine	➢ Telithromycin may reduce clearance of Ergonovine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Ergonivine if Telithromycin is initiated, discontinued or dose changed.
Ergotamine	➢ Telithromycin may reduce clearance of Ergotamine. Concomitant therapy is contraindicated.
Erlotinib	➢ Telithromycin may reduce clearance of Erlotinib. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Erlotinib if Telithromycin is initiated, discontinued or dose changed.
Erythromycin	➢ Telithromycin may reduce clearance of Erythromycin. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Erythromycin if Telithromycin is initiated, discontinued or dose changed.
Escitalopram	➢ Telithromycin may reduce clearance of Escitalopram. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Escitalopram if Telithromycin is initiated, discontinued or dose changed.

Eszopiclone	➢ Telithromycin may reduce clearance of Eszopiclone. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Eszopiclone if Telithromycin is initiated, discontinued or dose changed.
Ethosuximide Ethosuximide	➢ Telithromycin may reduce clearance of Ethosuximide. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Ethosuximide if Telithromycin is initiated, discontinued or dose changed.
Felbamate	➢ Telithromycin may reduce clearance of Felbamate. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Felbamate if Telithromycin is initiated, discontinued or dose changed.
Felodipine	➢ Telithromycin may reduce clearance of Felodipine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Felodipine if Telithromycin is initiated, discontinued or dose changed.
Fentanyl	➢ Telithromycin may reduce clearance of Fentanyl. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Fentanyl if Telithromycin is initiated, discontinued or dose changed.
Flunisolide	➢ Telithromycin may reduce clearance of Flunisolide. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Flunisolide if Telithromycin is initiated, discontinued or dose changed.
Flurazepam	➢ Telithromycin may reduce clearance of Flurazepam. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Flurazepam if Telithromycin is initiated, discontinued or dose changed.
Flutamide	➢ Telithromycin may reduce clearance of Flutamide. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Flutamide if Telithromycin is initiated, discontinued or dose changed.
Fluticasone Propionate	➢ Telithromycin may reduce clearance of Fluticasone. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Fluticasone if Telithromycin is initiated, discontinued or dose changed.
Fosamprenavir	➢ Fosamprevavir may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Fosphenytoin	➢ Fosphenytoin may decrease the plasma concentration of Telithromycin. Consider alternate therapy.
Gefitinib	➢ Telithromycin may reduce clearance of Gefitinib. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Gefitinib if Telithromycin is initiated, discontinued or dose changed.
Halofantrine	➢ Telithromycin may reduce clearance of Halofantrine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Halofantrine if Telithromycin is initiated, discontinued or dose changed.
Haloperidol	➢ Telithromycin may reduce clearance of Haloperidol. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Haloperidol if Telithromycin is initiated, discontinued or dose changed.
Ifosfamide	➢ Telithromycin may reduce clearance of Ifosfamide. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Ifosfamide if Telithromycin is initiated, discontinued or dose changed.
Imatinib	➢ Co-administration may result in altered plasma concentrations of Imatinib and/or Telithromycin. ➢ Consider alternate therapy or monitor the therapeutic/adverse effects of both agents.
Indinavir	➢ Indinavir may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Irinotecan	➢ Telithromycin may reduce clearance of Irinotecan. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Irinotecan if Telithromycin is initiated, discontinued or dose changed.
Isoniazid	➢ Isoniazid may increase the plasma concentration of Telithromycin. Consider alternate therapy or monitor therapeutic/adverse effects.
Isosorbide Dinitrate	➢ Telithromycin may reduce clearance of Isosorbide Dinitrate. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Isosorbide Dinitrate if Telithromycin is initiated, discontinued or dose changed.
Isosorbide Mononitrate	➢ Telithromycin may reduce clearance of Isosorbide Mononitrate. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Isosorbide Mononitrate if Telithromycin is initiated, discontinued or dose changed.
Isradipine	➢ Telithromycin may reduce clearance of Isradipine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Isradipine if Telithromycin is initiated, discontinued or dose changed.
Itraconazole	➢ Itraconazole may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Ivacaftor	➢ Strong CYP3A4 inhibitors may increase levels of ivacaftor. Monitor concomitant therapy closely.
Ixabepilone	➢ Telithromycin may reduce clearance of Ixabepilone. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Ixabepilone if Telithromycin is initiated, discontinued or dose changed.
Ketamine	➢ Telithromycin may reduce clearance of Ketamine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Ketamine if Telithromycin is initiated, discontinued or dose changed.
Ketoconazole	➢ Ketoconazole may increase the plasma concentration of Telithromycin.

	➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Lapatinib	➢ Telithromycin may reduce clearance of Lapatinib. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Lapatinib if Telithromycin is initiated, discontinued or dose changed.
Lidocaine	➢ Telithromycin may reduce clearance of Lidocaine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Lidocaine if Telithromycin is initiated, discontinued or dose changed.
Lopinavir	➢ Lopinavir may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Lovastatin	➢ Telithromycin may increase the adverse effects of lovastatin by decreasing its metabolism. ➢ Concomitant therapy should be avoided.
Lumefantrine	➢ Additive QTc-prolongation may occur. ➢ Concomitant therapy should be avoided.
Maraviroc	➢ Telithromycin may reduce clearance of Maraviroc. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Maraviroc if Telithromycin is initiated, discontinued or dose changed.
Mefloquine	➢ Telithromycin may reduce clearance of Mefloquine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Mefloquine if Telithromycin is initiated, discontinued or dose changed.
Methadone	➢ Telithromycin may reduce clearance of Methadone. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Methadone if Telithromycin is initiated, discontinued or dose changed.
Methylergometrine	➢ Telithromycin may reduce clearance of Methylergonovine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Methylergonovine if Telithromycin is initiated, discontinued or dose changed.
Methysergide	➢ Risk of ergotism and severe ischemia with this association
Metoprolol	➢ Telithromycin may possibly increase metoprolol effect
Miconazole	➢ Miconazole may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Midazolam	➢ Telithromycin may increase the effect and toxicity of the benzodiazepine, midazolam.
Mirtazapine	➢ Telithromycin may reduce clearance of Mirtazapine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Mirtazapine if Telithromycin is initiated, discontinued or dose changed.
Modafinil	➢ Telithromycin may reduce clearance of Modafinil. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Modafinil if Telithromycin is initiated, discontinued or dose changed.
Moricizine	➢ Telithromycin may reduce clearance of Moricizine. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Moricizine if Telithromycin is initiated, discontinued or dose changed.
Nafcillin	➢ Nafcillin may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Nateglinide	➢ Telithromycin may reduce clearance of Nateglenide. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Nateglenide if Telithromycin is initiated, discontinued or dose changed.
Nefazodone	➢ Co-administration may result in altered plasma concentrations of Nefazodone and/or Telithromycin. ➢ Consider alternate therapy or monitor the therapeutic/adverse effects of both agents.
Nelfinavir	➢ Nelfinavir may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Nevirapine	➢ Nevirapine may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Nicardipine	➢ Co-administration may result in altered plasma concentrations of Nicardipine and/or Telithromycin. Consider alternate therapy or monitor the therapeutic/adverse effects of both agents.
Nifedipine	➢ Telithromycin may reduce clearance of Nifedipine. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Nifedipine if Telithromycin is initiated, discontinued or dose changed.
Nilotinib	➢ Telithromycin may reduce clearance of Nilotinib. Concomitant therapy should be avoided.
Nimodipine	➢ Telithromycin may reduce clearance of Nimodipine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Nimodipine if Telithromycin is initiated, discontinued or dose changed.
Nisoldipine	➢ Telithromycin may reduce clearance of Nisoldipine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Nisoldipine if Telithromycin is initiated, discontinued or dose changed.
Nitrendipine	➢ Telithromycin may reduce clearance of Nitrendipine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Nitrendipine if Telithromycin is initiated, discontinued or dose changed.
Oxcarbazepine	➢ Oxcarbazepine may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Paclitaxel	➢ Telithromycin may reduce clearance of Paclitaxel. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of

	Paclitaxel if Telithromycin is initiated, discontinued or dose changed.
Pentobarbital	➢ Pentobarbital may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Pergolide	➢ Telithromycin may reduce clearance of Pergolide. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Pergolide if Telithromycin is initiated, discontinued or dose changed.
Phencyclidine	➢ Telithromycin may reduce clearance of Phencyclidine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Phencyclidine if Telithromycin is initiated, discontinued or dose changed.
Phenobarbital	➢ Phenobarbital may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Phenytoin	➢ Phenytoin may decrease the plasma concentration of Telithromycin by increasing its metabolism. ➢ Consider alternate therapy.
Pimozide	➢ Telithromycin may reduce clearance of Pimozide. ➢ Concomitant therapy is contraindicated.
Pipotiazine	➢ Telithromycin may reduce clearance of Pipotiazine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Pipotiazine if Telithromycin is initiated, discontinued or dose changed.
Ponatinib	➢ Strong CYP3A4 inhibitors may increase levels of ponatinib. ➢ Monitor concomitant therapy closely.
Posaconazole	➢ Posaconazole may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Praziquantel	➢ Telithromycin may reduce clearance of Praziquantel. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Praziquantel if Telithromycin is initiated, discontinued or dose changed.
Primidone	➢ Primidone may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Quetiapine	➢ Telithromycin may reduce clearance of Quetiapine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Quetiapine if Telithromycin is initiated, discontinued or dose changed.
Quinidine	➢ Co-administration may result in altered plasma concentrations of Quinidine and/or Telithromycin. ➢ Consider alternate therapy or monitor for changes in the the therapeutic/adverse effects of both agents during concomitant therapy.
Quinidine barbiturate	➢ Increased risk of cardiotoxicity and arrhythmias
Quinine	➢ Telithromycin may reduce clearance of Quinine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Quinine if Telithromycin is initiated, discontinued or dose changed.
Ranolazine	➢ Telithromycin may reduce clearance of Ranolazine. ➢ Concomitant therapy should be avoided.
Regorafenib	➢ Strong CYP3A4 inhibitors may increase levels of regorafenib.
Repaglinide	➢ Telithromycin may reduce clearance of Repaglinide. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Repaglinide if Telithromycin is initiated, discontinued or dose changed.
Rifabutin	➢ Rifabutin may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Rifampicin	➢ Rifampin may decrease the plasma concentration of Telithromycin. ➢ Concomitant therapy should be avoided.
Rifapentine	➢ Rifapentine may decrease the plasma concentration of Telithromycin. ➢ Consider alternate therapy.
Ritonavir	➢ Ritonavir may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Rivaroxaban	➢ Telithromycin may reduce clearance of Rivaroxaban. ➢ Concomitant therapy is contraindicated.
Salmeterol	➢ Telithromycin may reduce clearance of Salmeterol. ➢ Concomitant therapy is contraindicated.
Saquinavir	➢ Saquinavir may increase the plasma concentration of Telithromycin. ➢ Consider alternate therapy or monitor therapeutic/adverse effects.
Sibutramine	➢ Telithromycin may reduce clearance of Sibutramine. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Sibutramine if Telithromycin is initiated, discontinued or dose changed.
Sildenafil	➢ Telithromycin may reduce clearance of Sildenafil. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Sildenafil if Telithromycin is initiated, discontinued or dose changed.
Simvastatin	➢ Telithromycin may increase the adverse effects of simvastatin by decreasing its metabolism. ➢ Concomitant therapy should be avoided.
Sirolimus	➢ Telithromycin may reduce clearance of Sirolimus. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Sirolimus if Telithromycin is initiated, discontinued or dose changed
Solifenacin	➢ Telithromycin may reduce clearance of Solifenacin.

	➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Solifenacin if Telithromycin is initiated, discontinued or dose changed.
Sotalol	➢ Additive QTc-prolongation may occur increasing the risk of serious ventricular arrhythmias. ➢ Concomitant therapy should be used with caution
Spiramycin	➢ Telithromycin may reduce clearance of Spiramycin. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Spiramycin if Telithromycin is initiated, discontinued or dose changed.
Sufentanil	➢ Telithromycin may reduce clearance of Sufentanil. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Sufentanil if Telithromycin is initiated, discontinued or dose changed
Sunitinib	➢ Telithromycin may reduce clearance of Sunitinib. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Sunitinib if Telithromycin is initiated, discontinued or dose changed.
Tacrolimus	➢ Additive QTc-prolongation may occur increasing the risk of serious ventricular arrhythmias. ➢ Concomitant therapy should be used with caution. ➢ Telithromycin, a strong CYP3A4 inhibitor, may also increase the serum concentration of Tacrolimus by inhibiting its metabolism and clearance.
Tadalafil	➢ Telithromycin may reduce the metabolism of Tadalafil. ➢ Concomitant therapy should be avoided if possible due to high risk of Tadalafil toxicity.
Tamoxifen	➢ Telithromycin may reduce clearance of Tamoxifen. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Tamoxifen if Telithromycin is initiated, discontinued or dose changed
Tamsulosin	➢ Telithromycin, a CYP3A4 inhibitor, may decrease the metabolism and clearance of Tamsulosin, a CYP3A4 substrate. ➢ Consider alternate therapy or monitor for changes in therapeutic/adverse effects of Tamsulosin if Telithromycin is initiated, discontinued, or dose changed.
Temsirolimus	➢ Telithromycin may inhibit the metabolism and clearance of Temsirolimus. ➢ Concomitant therapy should be avoided.
Teniposide	➢ The strong CYP3A4 inhibitor, Telithromycin, may decrease the metabolism and clearance of Teniposide, a CYP3A4 substrate. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Teniposide if Telithromycin is initiated, discontinued or dose changed.
Terfenadine	➢ Increased risk of cardiotoxicity and arrhythmias
Tetrabenazine	➢ Telithromycin may increase the QTc-prolonging effect of Tetrabenazine. ➢ Concomitant therapy should be avoided.
Theophylline	➢ Telithromycin may reduce clearance of Theophylline. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of initiated, discontinued or dose changed. Theophylline.
Thioridazine	➢ Telithromycin may increase the QTc-prolonging effect of Thioridazine. ➢ Concomitant therapy should be avoided.
Thiothixene	➢ May cause additive QTc-prolonging effects. ➢ Increased risk of ventricular arrhythmias. ➢ Consider alternate therapy. ➢ Thorough risk: benefit assessment is required prior to co-administration.
Tiagabine	➢ The strong CYP3A4 inhibitor, Telithromycin, may decrease the metabolism and clearance of Tiagabine, a CYP3A4 substrate. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of Tiagabine if Telithromycin is initiated, discontinued or dose changed.
Tolterodine	➢ Telithromycin may decrease the metabolism and clearance of Tolterodine. Adjust Tolterodine dose and monitor for efficacy and toxicity.
Toremifene	➢ Additive QTc-prolongation may occur, increasing the risk of serious ventricular arrhythmias. ➢ Consider alternate therapy. A thorough risk:benefit assessment is required prior to co-administration.
Tramadol	➢ Telithromycin may decrease the metabolism and clearance of tramadol. ➢ Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of tramadol if telithromycin is initiated, discontinued or dose changed.
Trazodone	➢ The CYP3A4 inhibitor, Telithromycin, may increase Trazodone efficacy/toxicity by decreasing Trazodone metabolism and clearance. ➢ Consider alternate therapy or monitor for changes in Trazodone efficacy/toxicity if Telithromycin is initiated, discontinued or dose changed.
Triazolam	➢ Telithromycin may increase the effect and toxicity of the benzodiazepine, triazolam.
Trimipramine	➢ Additive QTc-prolongation may occur, increasing the risk of serious ventricular arrhythmias. ➢ Telithromycin, a strong CYP3A4 inhibitor, may also decrease the metabolism and clearance of Trimipramine, a CYP3A4 substrate. ➢ Concomitant therapy should be used with caution.
Valproic Acid	➢ The macrolide antibiotic, Erythromycin, may increase the serum concentratin of Valproic acid. ➢ Consider alternate therapy or monitor for changes in Valproic acid therapeutic and

	adverse effects if Telithromycin is initiated, discontinued or dose changed.
Vardenafil	➢ Telithromycin, a strong CYP3A4 inhibitor, may reduce the metabolism and clearance of Vardenafil. ➢ Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of Vardenafil.
Vemurafenib	➢ Strong CYP3A4 inhibitors may increase levels of vemurafenib. ➢ Monitor concomitant therapy closely.
Venlafaxine	➢ Telithromycin, a CYP3A4 inhibitor, may decrease the metabolism and clearance of Venlafaxine, a CYP3A4 substrate. ➢ Monitor for changes in therapeutic/adverse effects of Venlafaxine if Telithromycin is initiated, discontinued, or dose changed.
Verapamil	➢ Telithromycin, a CYP3A4 and p-glycoprotein inhibitor, may increase the Vinblastine serum concentration and distribution in certain cells. ➢ Consider alternate therapy to avoid Vinblastine toxicity. ➢ Monitor for changes in the therapeutic/adverse effects of Vinblastine if Telithromycin is initiated, discontinued or dose changed.
Vinblastine	➢ Telithromycin, a CYP3A4 and p-glycoprotein inhibitor may increase the Vinblastine serum concentration and distribution in certain cells. ➢ Consider alternate therapy to avoid Vinblastine toxicity. ➢ Monitor for changes in the therapeutic and adverse effects of Vinblastine if Telithromycin is initiated, discontinued or dose changed.
Vincristine	➢ Telithromycin, a CYP3A4 and p-glycoprotein inhibitor may increase the Vincristine serum concentration and distribution in certain cells. ➢ Consider alternate therapy to avoid Vincristine toxicity. ➢ Monitor for changes in the therapeutic and adverse effects of Vincristine if Telithromycin is initiated, discontinued or dose changed.
Vinorelbine	➢ Telithromycin, a CYP3A4 and p-glycoprotein inhibitor may increase the Vinorelbine serum concentration and distribution in certain cells. ➢ Consider alternate therapy to avoid Vinorelbine toxicity. ➢ Monitor for changes in the therapeutic and adverse effects of Vinorelbine if Telithromycin is initiated, discontinued or dose changed.
Voriconazole	➢ Voriconazole, a strong CYP3A4 inhibitor, may increase the serum concentration of telithromycin by decreasing its metabolism. Telithromycin may increase the serum concentration of voriconazole by decreasing its metabolism. ➢ Monitor for changes in the therapeutic and adverse effects of both agents if concomitant therapy is initiated, discontinued or dose changed. ➢ QTc interval prolongation may also occur.
Vorinostat	➢ Additive QTc prolongation may occur. ➢ Consider alternate therapy or monitor for QTc prolongation as this can lead to Torsade de Pointes (TdP).
Warfarin	➢ Telithromycin may increase the anticoagulant effect of Warfarin. INR should be monitored and Warfarin dose adjusted accordingly during concomitant therapy.
Ziprasidone	➢ Additive QTc-prolonging effects may increase the risk of severe arrhythmias. ➢ Concomitant therapy should be avoided
Zolpidem	➢ Telithromycin, a strong CYP3A4 inhibitor, may increase the serum concentration of zolpidem by decreasing its metabolism. ➢ \Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of zolpidem if telithromycin is initiated, discontinued or dose changed.
Zonisamide	➢ Telithromycin, a strong CYP3A4 inhibitor, may increase the serum concentration of zonisamide by decreasing its metabolism. ➢ Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of zonisamide if telithromycin is initiated, discontinued or dose changed.
Zopiclone	➢ Telithromycin, a strong CYP3A4 inhibitor, may increase the serum concentration of zopiclone by decreasing its metabolism. ➢ Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of zopiclone if telithromycin is initiated, discontinued or dose changed.
Zuclopenthixol	➢ Additive QTc prolongation may occur. ➢ Consider alternate therapy or use caution and monitor for QTc prolongation as this can lead to Torsade de Pointes (TdP).
Zuclopenthixol acetate	➢ Additive QTc prolongation may occur. ➢ Consider alternate therapy or use caution and monitor for QTc prolongation as this can lead to Torsade de Pointes (TdP
Zuclopenthixol decanoate	➢ Additive QTc prolongation may occur.

10.5 Drug Interaction With Enzymes

Table: 4- Interaction of Telithromycin with Enzymes

ENZYME NAME	KIND	ORGANISM	ACTION
CytochromeP450 3A7	Protein	Human	Substrate, inhibitor
Cytochrome P450 1A2	Protein	Human	Substrate
Cytochrome P450 3A4	Protein	Human	Substrate, inhibitor
Cytochrome P450 3A5	Protein	Human	Substrate, inhibitor
Cytochrome P450 2D6	Protein	Human	Inhibitor

XI. Myasthenia Gravis Crisis

11.1 definition:

A myasthenic crisis is a severe form of myasthenia gravis. A myasthenia gravis crisis is defined as myasthenia gravis weakness severe enough to require mechanical ventilation. It is a life-threatening condition that happens if the muscles you use for breathing become very weak. It can cause severe breathing problems and lead to lung failure.

11.2 introduction

Myasthenic crisis is a reversible cause of neuromuscular paralysis, which needs to be diagnosed and treated promptly. It is typically associated with autoimmune myasthenia gravis, which has an estimated population prevalence of 200–400 per million. The commonest form of myasthenia gravis is characterized by acquired antibodies against post-synaptic acetylcholine receptors (AChR) in the motor end plate of skeletal muscles. Injury from immune complex deposition and complement activation reduce the contact area of the post-synaptic surface, which, together with the loss of functional AChR molecules, reduce the safety of neuromuscular transmission leading to impulse blockade at the motor end plate .Here, we review the diagnosis and management of myasthenic crisis, a life-threatening medical emergency which may potentially challenge emergency physicians and neurologists.

11.3 mechanism

Myasthenic crisis is caused by severe weakness of respiratory muscles, upper airway muscles (bulbar myasthenia) or both. It is typically precipitated by poor control of generalized disease, medical treatment for bulbar myasthenia (steroids and anticholinesterases);concomitant use of certain antibiotics, muscle relaxants, benzodiazepines, β-blockers and iodinated radiocontrast agents systemic infections often involving the respiratory tract, aspiration and surgery. Other recognized triggers for crisis in refractory myasthenia are emotional stress, hot environment, sudden elevation of body temperature and hyperthyroidism, with autoimmune thyroid disease being a common association of myasthenia gravis.

11.4 differential diagnosis

Acute respiratory paralysis due to neuromuscular weakness may be a presenting feature of a number of disorders affecting motor neurons, peripheral nerve; neuromuscular junction and muscles Respiratory paralysis is a recognized feature of drug overdose and envenomation and may complicate central nervous system disorders due to brainstem (medullary) or high cervical spinal cord pathology. Weakness of eye muscles (ptosis and external ophthalmoplegia) is common in AChR-MG and patients may have any combination of weak eye movements, even simulating internuclear ophthalmoplegia. Myasthenia gravis is probably the most frequent cause of bulbar palsy presenting as dysphonia, dysarthria and dysphagia in conjunction with ptosis and ocular palsy. Atrophy of tongue is a typical feature of MuSK-MG, but presence of both wasting and fasciculations of tongue muscle clearly point away from myasthenic crisis and are more likely to be the result of motor neuron disease (progressive bulbar palsy), bulbospinal muscular atrophy (Kennedy's disease, Fazio-Londe and Brown-Vialetto syndromes), syringobulbia or skull base pathology. Bulbar palsy and respiratory muscle weakness is also a feature of acute inflammatory demyelinating polyneuropathy (Guillain Barre Syndrome), which may occasionally be associated with bilateral ptosis. Although tendon reflexes may be retained early in the course of evolving Guillain Barre Syndrome, presence of normal tendon reflexes in an established case with severe muscle weakness and respiratory failure would be most unusual. Marked autonomic symptoms, poorly reactive, dilated pupils with loss of accommodation and diminished tendon reflexes are suggestive of botulism. Paralytic poliomyelitis and acute diphtheritic paralysis, both extremely rare in the Western world, may also present with bulbar weakness and respiratory failure.

Weakness of facial muscles is a feature which is common to myasthenia gravis, Guillain Barre Syndrome and acute polymyositis. AChR-MG patients have weakness of both neck flexors and extensors, occasionally selectively affecting the extensor muscles (the hanging or dropped head sign). Patients with MuSK-MG and acute polymyositis have marked weakness of neck flexors. Weak neck flexors are also a feature of Guillain Barre Syndrome and often correlate with respiratory muscle weakness. Disproportionate weakness of anterior neck muscles is a feature shared by progressive muscular dystrophies (such as type 1 myotonic dystrophy), motor neuron disease, spinomuscular atrophy and syringomyelia. Limb weakness is usually most obvious in proximal muscles in myasthenia gravis and acute polymyositis, and both proximal and distal in Guillain Barre Syndrome. Primary disorders of muscle and neuromuscular junction do not generally weaken arm muscles disproportionately and respiratory muscle weakness in conjunction with paralysis of arms and shoulders would be more typical of anterior horn cell disease (motor neuron disease or poliomyelitis) and peripheral neuropathy. Guillain Barre Syndrome and spinal cord pathology are the two likely causes of respiratory failure associated with severe leg weakness. Adult-onset acid maltase deficiency may present with

respiratory muscle weakness and these patients often have contracture of calf muscles. Features of marked and symptomatic autonomic disturbance are typical of botulism, less commonly observed in Guillain Barre Syndrome and rarely reported in myasthenic crisis.

11.4.1 Common differential diagnosis of myasthenic crisis

Previously, it was customary to differentiate between cholinergic crisis and myasthenic crisis in patients with a known diagnosis of myasthenia gravis taking high doses of oral anticholinesterases as the mainstay of therapy. Cholinergic crisis in myasthenic patients is uncommon in today's practice as most symptomatic patients with generalized disease receive immunotherapy as preferred treatment and anticholinesterases are largely restricted to short-term symptom control. More commonly, cases of respiratory paralysis due to cholinergic crisis are associated with toxic exposure to organophosphate insecticides. In occasional patients with myasthenia gravis on higher doses of oral anticholinesterases (pyridostigmine or neostigmine), the clinical features are sufficiently distinct from myasthenic crisis (no ptosis, small pupils, muscle fasciculations, hypersalivation, bradycardia, diarrhoea, bowel and bladder incontinence).

Neuromuscular weakness in critically ill patients is commoner than anticipated, with reports estimating 33–82% of patients being affected after receiving ventilation for >4 days. Diaphragmatic weakness is common and there may be superimposed neuromuscular junction transmission defect (‘critical illness neuromuscular junction abnormality’). However, review of the patient's primary illness, drug chart (therapeutic use of neuromuscular blocking agents, corticosteroids), absence of eye signs and poor reflexes on examination and electrophysiology findings (myopathic EMG and/or nerve conduction abnormality) easily distinguish critical illness myoneuropathy from myasthenic crisis.

11.5 investigations

An experienced clinician should be able to suspect the diagnosis of myasthenic crisis at bedside after neurological examination and basic investigations Peripheral nerve electrophysiology (repetitive motor nerve stimulation and single fibre EMG) is the preferred investigation to confirm the diagnosis. Edrophonium (Tensilon) test is not to be recommended in any patient who is suspected to be in crisis because of false positive and negative results, and the risk of worsening muscle weakness in patients with anticholinesterase overdose. In addition, worsening of bulbar and respiratory symptoms in MuSK-MG after anticholinesterase administration is known and could confound the clinical diagnosis.

11.6 management

The management of myasthenic crisis does not differ between patients with AChR-MG, MuSK-MG and seronegative patients. Prompt recognition of impending respiratory paralysis is the key to successful management of myasthenic crisis. The evolution of respiratory muscle weakness in AChR-MG often follows a pattern where the intercostals and accessory muscles for respiration weaken first, followed by the diaphragm. In MuSK-MG, bulbar weakness always precedes respiratory failure. Respiratory muscle weakness may be precipitated by steroid therapy and presence of bulbar symptoms and older age were risk factors associated with steroid-induced exacerbation in myasthenia gravis.The most important threat to life in myasthenic crisis is respiratory failure and patients must be offered elective ventilation on clinical diagnosis without waiting for blood gas changes to show hypoxemia. Careful observation and bedside measurements (vital capacity, peak flow measurement, pulse rate and blood pressure) are more important than repeated monitoring of blood gases.
The standard 20/30/40 rule (vital capacity <20ml/kg; peak inspiratory pressure <−30 cm H_2O and peak expiratory pressure <40 cm H_20) is probably the most helpful guide to decide when intubation is necessary.Other clinical rules for predicting impending ventilator failure and need for airways protection are inability to raise the head due to neck muscle weakness and paradoxical breathing. As in any other condition with neuromuscular paralysis, an experienced clinician should anticipate the need for respiratory assistance in myasthenic crisis rather than deal with emergency intubation (‘when in doubt, intubate’). Non-invasive ventilation (NIV) has been used as an alternative to intubation and mechanical ventilation for patients in myasthenic crisis, but the experience of NIV in acute neuromuscular paralysis is still relatively limited. NIV has the potential, however, to reduce the incidence of prolonged intubation and tracheostomy in neuromuscular paralysis.

There have been few randomized controlled treatment trials in myasthenic crisis and both plasma exchange and human intravenous immunoglobulin (IVIg) are comparable in terms of efficacy on the basis of clinical evidence, only one of which was a prospective study. However, response to plasma exchange may be more predictable and we take the view that plasma exchange is probably more effective than IVIg in myasthenic crisis. In one retrospective multi-centre review of 54 episodes of myasthenic crisis, plasma exchange had a superior outcome for ventilatory status at 2 weeks ($P = 0.02$) and functional outcome at 1 month ($P = 0.04$). The recommended therapeutic dose of IVIg is 2 g/kg but a randomized double-blind clinical trial found no

significant superiority of 2 g/kg dose over 1 g/kg dose in patients with exacerbation of myasthenia gravis. A randomized trial of daily versus alternate day plasma exchange in severe myasthenia gravis found no superiority of one over the other in terms of outcome. The clearance of MuSK-antibody during serial sessions of plasmapheresis for MuSK-MG was comparable to the experience in AChR-MG. IgA-deficient myasthenic patients should not receive IVIg; plasmapheresis is not recommended in patients with cardiac failure, sepsis, hypotension and pregnancy; it is also not considered to be a suitable procedure in paediatric patients. The wider availability and ease of administration of IVIg makes it an automatic choice as the first-line therapy for myasthenic crisis since access to plasmapheresis, particularly during out-of-hours, is restricted to selected centres and major teaching hospitals only.

The use of continuous anticholinesterase (intravenous pyridostigmine) as a therapy for myasthenic crisis remains controversial, especially because of the risk of cardiac complications (arrhythmia and myocardial infarction). Coronary vasospasm form excessive anticholinergic treatment is known to be an iatrogenic cause of myocardial infarction in myasthenia gravis.Besides the risk of cardiac complication, large doses of anticholinesterases promote excessive salivary and gastric secretions, which may increase the risk of aspiration pneumonia. Immunoadsorption therapy was used to treat a case of post-operative myasthenic crisis successfully, but experience with this procedure is very limited.

The protocol that we have generally followed with success in our patients with myasthenic crisis. There is no significant advantage of an initial pulse of intravenous methylprednisolone over regular prednisolone, which is given by nasogastric tube at a pharmacological dose (1 mg/kg) and must be continued by mouth for several months after recovery from the crisis until alterative immunosuppressive or steroid-sparing agents (such as azathioprine or ciclosporin) become effective. Cause of death in treated myasthenic crisis is usually cardiac (arrhythmia) or infection (sepsis).

11.6.1 Thymus and myasthenic crisis

Nearly 65% of young patients AChR-MG, mostly women, will have thymic hyperplasia and about 15% of all patients may have thymic tumour (thymoma). Thymectomy is always recommended in patients with thymoma. Early thymectomy within the first 2 years of symptom onset is an option in adults with non-thymomatous AChR-MG and generalized disease.Thymectomy is usually carried out after symptom stabilization with plasmapheresis, which is considered to improve outcome from thymic surgery in myasthenic patients.In our experience, thymectomy is the only intervention in myasthenia gravis which offers the realistic prospect of complete remission (defined as no need for medication or only requiring low-dose single drug). The 5-year outcome of both transsternal and extended transcervical thymectomies appear to be comparable. Pre-operative history of myasthenic crisis and presence of bulbar symptoms are risk factors associated with post-operative myasthenic crisis after thymectomy and a higher daily dose of pyridostigmine (>270 mg) and body mass index (BMI >25.6) predicted worse outcome after videothoracoscopic thymectomy in one study.

In our practice, we saw the best benefit of thymectomy in younger AChR-MG patients (<60 years) with thymic hyperplasia. The role of thymectomy in non-thymomatous patients with myasthenia gravis is currently being evaluated in a randomized controlled clinical trial. There is some evidence that non-thymectomized patients may have a higher risk of myasthenic crisis ($P = 0.001$, odds ratio 2.8 with CI of 1.5–5.2). In addition, attacks may be more severe in non-thymectomized patients who may require longer duration of ventilatory support and hospital admission. In MuSK-MG, role of thymectomy is less clear as thymus is not considered to be a major player in the disease pathogenesis. The unpredictable effect of thymectomy on disease remission in some cases of non-thymomatous, generalized AChR-MG may reflect inadequate immunosuppressive therapy during post-thymectomy period and presence of residual thymic tissue, but there are few systematic studies to address these issues. Since true seronegative myasthenic patients are considered to have same disease as seropositive cases, the indication of thymectomy would be very similar as in AChR-MG (younger patients, generalized disease and thymic hyperplasia).

XII. Conclusion

Myasthenia gravis is a motor disorder marked by muscular fatigue that develops with repetitive muscle use and improves with rest.it is caused by an antibodies to the acetylcholinereceptor in the neuromuscular junctionand a decrease in receptor site for acetylcholine.because the smallest concentration of acetylcholine receptors in the body is in the cranial nerves, weakness and fatigue of eye muscles, muscles of mastication and pharyngeal muscles are the most prominently affected in most patients.patients with myasthenia gravis shows exacerbation when the drug telithromycin is administered which is a ketolide antibiotic, inhibits the nicotinic acetylcholine receptors (nAChR) at the neuromuscular junction ($\alpha3\beta2$ and NMJ), the ciliary ganglion of the eye ($\alpha3\beta4$ and $\alpha7$), and the vagus nerve innervating the liver ($\alpha7$) that may leads to myasthenia gravis crisis which is life threatening condition were breathing problem may takes place and should be on mechanical

ventilation.the primary treatment include administration of ACE inhibitors and steroids and in severe cases thymectomy is advised.

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