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MuSK and Myasthenia Gravis due to other Antibodies

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Summary

Around 20% of MG patients are ACHR antibody negative. In 2001, MuSK antibodies were identified as the cause of MG in 70% of these patients. MuSK antibodies are found in around 30–40% of ACHR negative MG patients and are associated with specific clinical phenotypes. One is a predominantly bulbar form with fewer ocular symptoms than in ACHR positive MG. Others show an isolated head drop or symptoms indistinguishable from ACHR positive MG. These patients usually respond well to immunosuppressive therapy but not as well to cholinesterase inhibitors. Other antibodies associated with MG including LRP4 are discussed.

Keywords

Myasthenia Gravis; MuSK; Cortactin; Agrin; LRP4; Rapsyn

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Introduction

Acetylcholine receptor (AChR) antibodies are found in approximately 80% of patients with myasthenia gravis (MG) leaving approximately 20% antibody negative (SNMG)¹. It was suspected that SNMG patients had an autoimmune etiology since they responded to autoimmune therapy including plasma exchange^{2,3}. In addition, passive transfer of disease to mice from the serum of seronegative patients^{2,4}, the development of transient neonatal myasthenia in infants of seronegative myasthenic women⁵⁻⁷, and the binding of IgG from seronegative MG patients to muscle⁸ suggest an autoimmune etiology. In 2001, Hoch and colleagues⁹ discovered that antibodies to muscle specific tyrosine kinase (MuSK) were responsible for producing Myasthenia Gravis in about 70% of these SNMG patients. More recently antibodies to LRP4 (Low Density Lipoprotein Receptor-Related Protein 4)¹⁰⁻¹² and agrin^{13,14} have been discovered in patients with MG. Other antibodies including titin^{15,16}, cortactin¹⁷ and rapsyn¹⁸ are associated with MG. Defects of these proteins are associated with congenital myasthenic syndromes¹⁹⁻³⁴. The functions of these newly identified target proteins differ from AChR since they are responsible for the proper formation and maintenance of the neuromuscular junction rather than serving as AChR. In this chapter, we will discuss the roles of these proteins and the known features of myasthenic patients who have antibodies to them.

When muscles are denervated there is a significant alteration at the neuromuscular junction including the expression of fetal AChR remote from the neuromuscular junction and increased muscle sensitivity to acetylcholine. With reinnervation, neuromuscular junctions are reformed, the fetal AChR are eliminated as normal sensitivity to acetylcholine returns. This indicates that muscles are innervated and receive signals from motor neuron terminals. In addition, denervated muscle attracts neighboring neurons to sprout and form new connections. Agrin, a heparin sulfate proteoglycan³⁵, released by the axon terminal plays an important role in the development and maintenance of neuromuscular junctions. Activation of MuSK, anchored in skeletal muscle is responsible for the clustering of AChR at the neuromuscular junction. While it is known that agrin is necessary for the activation of MuSK there is no direct interaction between agrin and MuSK. In the last decade, LRP4^{36,37} was discovered to be the agrin receptor which is responsible for activating MuSK. Agrin signaling including MuSK and LRP4 have additional roles in inhibiting neurite outgrowth³⁸, which may be responsible for the inhibition of sprouting. In addition, MuSK along with ColQ is responsible for anchoring acetylcholinesterase to the neuromuscular junction³⁹⁻⁴¹.

Figure 1 illustrates that interaction between the axon terminal and muscle. Agrin released by the axon terminal binds to LRP4 in muscles to activate MuSK. The formation of a agrin-LRP4 tetrameric complex (2 agrin molecules and 2 LRP4 molecules) is critical for MuSK activation⁴². DOK7 a muscle cytoplasmic protein is also involved in the activation of MuSK⁴³⁻⁴⁶. Activated MuSK interacts with Rapsyn, a scaffolding protein,⁴⁷⁻⁵² causing the clustering of AChR at the neuromuscular junction. Rapsyn binds all subunits of the AChR^{51,53} and is bound to actin⁵⁴. For further review of the molecular anatomy of the neuromuscular junction as well as the electrophysiological properties, the reader is referred to Chapter 2.

These elements of the neuromuscular junction are necessary for its proper development and maintenance. In addition to these actions, LRP4, agrin and MuSK act on the axonal terminal. Congenital defects of these proteins are linked to defects in neuromuscular transmission and will be discussed further in chapter 11 of this volume. While there are many proteins of the neuromuscular junction that might be susceptible to antibodies it is those that are exposed to the extracellular space namely agrin, LRP4, MuSK and ACHR, that are most likely to be vulnerable.

MuSK antibody-positive MG

MuSK was first described by Valenzuela et al. in 1995 and was localized to the post-junction region of the neuromuscular junction⁵⁵. MuSK was shown to be involved in agrin signaling causing aggregation of acetylcholine receptors at the neuromuscular junction^{56,57}. In 2001 Hoch et al⁹ described 17 cases of MuSK antibody-positive MG out of 24 SNMG patients. IgG from MuSK antibody-positive patients produce MG-like symptoms including muscle weakness and destruction of the neuromuscular junction when injected into mice⁵⁸. Mice who developed anti-MuSK antibodies after being injected with rat MuSK acquire symptoms consistent with myasthenia gravis including weakness, a decrement to repetitive stimulation and reduced amplitude miniature end plate potentials⁵⁹. MuSK antibodies produce wasting of muscles when injected in mice with predilection to the masseter and facial muscles⁶⁰ which might explain why these muscles are more involved clinically. Around 7 to 10% of all MG patients have antibodies to MuSK. Initially, Hoch et al reported MuSK antibodies in 70% of AChR antibody negative cases⁹. However, subsequently most believe that this figure is closer to 30–40%^{61,62}. Early studies indicate that MuSK antibody-positive MG patients have important clinical differences when compared to ACHR antibody-positive MG^{63,64}. These patients have more bulbar, neck and respiratory symptoms along with less ocular symptoms. The patients are less responsive to cholinesterase inhibitors, but responded to plasma exchange and other immunosuppressant medications.

Based on 16 years of experience, clinicians now recognize some characteristic features of MuSK antibody-positive MG. They are more likely to be female than male⁶⁵; blacks are more likely to have these antibodies compared to whites^{66–68}. There is considerable variation of the incidence of MuSK antibody-positive MG depending on geographic location^{66,69–71}. Anti-MuSK antibody positive patients have HLA-DRB1, DQB1, DQ5 and DR14 alleles^{72–74}. Patients have marked bulbar weakness⁶⁵ often having marked wasting and fasciculations of the tongue and must be distinguished from patients with bulbar ALS^{75,76}. They often have facial, neck and respiratory weakness. Their ocular symptoms are less prominent than other MG patients. They are less likely to respond to anticholinesterase medication perhaps because of deficient binding of acetylcholinesterase to the neuromuscular junction^{77,78}. "In addition to a case report (ref 79), our experience suggests that, while only 16% of MuSK MG respond to cholinesterase inhibitors, hypersensitivity or worsening of symptoms occurred in 20% of cases (ref 76). Others have also reported worsening symptoms in response to cholinesterase inhibitors in 5% of MuSK MG cases, while 57% improved (143)..

A patient of one of the authors (MHR) illustrates a typical case of MuSK antibody positive MG. He is a 50-year-old black man who was in his usual state until he developed a flu-like illness. He displayed dysarthria, swelling of tongue, facial weakness and bilateral ptosis, but without diplopia. He lost 50 pounds over a 3-month period. He noticed some weakness of his right shoulders, which became worse later in the day. Chest CT scan was normal. Pulmonary function tests showed mild restrictive airway disease. Pyridostigmine produced little improvement of his symptoms; however, prednisone improved his symptoms. On examination, the patient had moderate ptosis without fatigue, with 4/5 strength of his orbicularis oculi and 4+/5 strength of orbicularis oris (Figure 2a). He was unable to wrinkle his brow (figure 2b) and his voice was dysarthric and there was mild weakness of his uvula. His tongue exhibited moderate wasting, fasciculations and had mildly slowed rapid alternating movements (figure 2c). His neck and limbs were normal as was the remainder of his exam. He was Myasthenia Gravis Foundation of America (MGFA) Class⁸⁰ IIIb at his worst. He was negative for ACHR and anti-striatal muscle antibodies but anti-MuSK antibodies were markedly elevated at 5.91 (< 0.03). Repetitive stimulation of his left facial nerve was normal, but needle exam revealed slight increased insertional activity of his orbicularis oculi with markedly diminished motor unit size with short duration motor units. Other muscles studied were normal. Stimulated SFEMG of the right orbicularis oculi was very abnormal with an average MCD of 260 μ sec with 80% of the fibers having blocks.

While MuSK antibody-positive MG patients have less prominent ocular findings compared ACHR antibody-positive MG, cases of patients with pure ocular and predominantly ocular disease are described^{81–86}. Cases of isolated neck weakness and wasting are described associated with anti-MuSK antibodies^{63,87–89}. In addition, mutations of the MuSK protein have been associated with dropped head⁹⁰. Vocal cord paralysis is seen in some patients with MuSK antibody-positive MG^{91–93}. While most patients just have anti-MuSK antibodies, patients with antibodies to MuSK and ACHR^{94,95} and voltage gated calcium channels (VGCC)^{96,97} are described. Anti-MuSK antibody level is generally correlated with symptoms⁹⁸. MuSK antibodies have crossed the placenta in pregnant women, producing neonatal myasthenia^{99–103}. Gupitll and Sanders described three different clinical presentations of MuSK antibody-positive MG¹⁰⁴. Firstly, patients with predominantly bulbar and respiratory symptoms, secondly, patients indistinguishable from ACHR antibody-positive MG and thirdly, patients presenting with head drop as their most prominent symptom. The above described MuSK antibody-positive MG patient was an example of the first clinical presentation pattern. While thymic pathology including thymoma has been described in patients with MuSK antibody-positive MG^{105–107} this is far less common than in ACHR antibody-positive MG^{64,67,108–110}. It is unknown if thymectomy is of any value in these patients^{63,78}. In the Pasnoor et al case series, some patients with MuSK MG who had thymectomy did improve over time. Since several other therapies were also being administered, we cannot definitively say that thymectomy was the driver behind their improvement.⁷⁶ There have been reports of patients who initially presented as ACHR antibody-positive and after thymectomies, developed MuSK antibody-positive MG^{95,111–114}.

MuSK antibody-positive MG patients are more likely to have abnormal repetitive nerve studies in facial and proximal limb than in distal muscles^{64,115,116}. Repetitive studies are less likely to be abnormal than in MuSK antibody-negative patients^{65,117}. Single fiber EMG

is usually abnormal in the facial muscles but less likely to be abnormal in the limbs^{68,117,118}. EMG findings often show severe myopathic changes with reduced amplitude and duration without polyphasia in affected muscles^{115,119–121}. Fibrillation potentials are reported more frequently than in ACHR antibody-positive MG¹¹⁵. In our patient, increased insertional activity was seen and only a few very small units were seen in the orbicularis oculi. Muscle atrophy particularly in the face and tongue midline atrophy are very prevalent in these patients^{104,122–124} but some series found tongue atrophy to be uncommon^{78,107,115}. Muscle biopsies from MuSK antibody-positive MG patients have severe myopathic and mitochondrial abnormalities^{125,126}. MRI studies have shown that facial muscle bulk is less in abnormal patients^{122,127}. Following successful treatment, previously seen tongue atrophy improves in MuSK antibody-positive MG^{76,128}. The increased atrophy preferentially seen in the facial muscles compared to limb muscles might be related to reduced levels of MuSK found in facial and respiratory muscles^{129,130}. The type of immunoglobulins causing MuSK antibody-positive MG might play a role in the differences in the clinical course. Unlike ACHR antibody-positive MG where IgG1 and IgG3 antibodies cause complement activation, IgG4 antibodies are found in MuSK antibody-positive MG^{131–133}. It is believed that IgG4 antibodies may block MuSK signaling by interfering with the binding of LRP4 to MuSK thereby destabilizing the neuromuscular junction^{131,132,134,135}.

Treatment of MuSK antibody-positive MG differs somewhat from ACHR antibody-positive MG. MuSK antibody-positive MG patients tend to respond less to pyridostigmine and other cholinesterase inhibitors^{78,136,137}. There have been reports of worsening of symptoms with pyridostigmine in MuSK antibody-positive MG⁷⁹. These patients respond less often and have lower tolerance to cholinesterase inhibitors with more nicotinic and muscarinic side effects¹³⁷. One explanation for this is that COLQ which binds acetylcholinesterase to the neuromuscular junction is also bound to MuSK and antibodies to MuSK might affect this connection^{132,138}. These interactions might impair acetylcholinesterase activity at baseline in MuSK antibody-positive MG and further interference by cholinesterase inhibitors might produce worsening symptoms. In a mouse model of MuSK antibody-positive MG, 3,4 diaminopyridine has been shown to be efficacious¹³⁹. In addition, 3,4 diaminopyridine which enhances the release of acetylcholine from the axonal terminal has been shown to be of benefit in MuSK antibody-positive MG patients¹⁴⁰. This is due to 3,4 diaminopyridine increasing the amount of acetylcholine in the neuromuscular junction rather than increasing its duration of action as pyridostigmine would¹⁴¹. Generally, pyridostigmine should be tried at a low dose initially in MuSK antibody-positive MG patients but its actions need to be monitored since it is often not beneficial and could worsen symptoms. If not beneficial at 90 mg q4h, no further dose escalation should be considered. 3,4 diaminopyridine, if available, might be considered as an alternative treatment.

In most instances, patients respond to immunosuppressant therapy. Prednisone, azathioprine, mycophenolate, tacrolimus, methotrexate and cyclosporine have been tried with success in these patients^{64,78,115,125,142–144}. Initial therapy would include prednisone combined with a steroid sparing immunosuppressant. Prednisone should be started at a dose of 40–60 mg a day and reduced to the lowest effective dose. In most instances, these patients respond similarly to patients with ACHR antibody-positive MG. For acute exacerbations of MuSK antibody-positive MG, IVIG and plasma exchange have been used, but IVIG is less

efficacious than plasma exchange in most patients^{63,78,143,145}. On occasion patients will respond to IVIG who have not responded well to plasma exchange but this is less common^{125,146,147}. Patients with poorly responsive disease have responded well to rituximab 375 mg/m², weekly for 4 weeks. Often the response to rituximab is better than what is seen in ACHR antibody-positive MG and can lead to long lasting remissions lasting 6 months to longer than a year. There is a report of a patient responding to high dose cyclophosphamide at 50mg/kg for 4 days who had failed other therapies including rituximab¹⁴⁸. There have also been reports of patients going into spontaneous remission¹⁴⁹.

In summary, while many cases of MuSK antibody-positive MG present with distinct symptoms consisting of bulbar, facial and respiratory weakness and may have a more severe course of the disease, other patients present with head drop or with symptoms typical of ACHR antibody-positive MG. In most MuSK antibody-positive MG patients, with proper immunosuppressant therapy, symptoms can be well controlled⁷⁸.

LRP4 antibody-positive MG

After the discovery of MuSK antibody-positive MG, around 10 to 13% of patients with MG remain negative (i.e., for antibodies against ACHR and MuSK, thus double-negative MG or DNMG for short). Since the discovery of LRP4^{36,37} it was felt that it would be a good target for autoimmune attack since much of this molecule is extracellular. Three groups simultaneously reported the presence of LRP4 antibodies in MG^{10–12}. Shen et al showed that mice injected with LRP4 developed weakness, a decremental response to repetitive stimulation and produced LRP4 antibodies¹⁵⁰. These antibodies reduced cell surface LRP4 level, agrin activation of MuSK and the aggregation of ACHR at the neuromuscular junction. Furthermore, these antibodies were predominantly IgG1 followed by IgG2 and IgG3 which are known to activate complement. Using mice that are genetically designed to delete the LRP4 gene when exposed to doxycycline, LRP4 has been shown to be essential to the preservation of the neuromuscular junction¹⁵¹. These mice develop weakness and neuromuscular transmission failure. LRP4 also has been shown to have retrograde effects on the axonal terminal producing presynaptic differentiation^{152,153}. Since the discovery of LRP4 antibody-positive MG some data has been reported on these patients but there is only limited information about the characteristics of these patients.

The following case of one of the authors (MHR), illustrates a patient with LRP4 antibody-positive MG. The patient is a 49-year-old white female who developed shortness of breath, soft voice and generalized fatigue 2 years prior to her first visit. She complained of intermittent facial weakness and fatigue while chewing and periodic difficulty swallowing both liquids and solids. She had ptosis and diplopia. She fatigues, feeling that her weakness is worse in the afternoon. Her ACHR, MuSK and VGCC antibodies were negative. She had normal repetitive nerve and pulmonary function testing. She is unable to tolerate pyridostigmine because of gastrointestinal side effects. She had a gastric bypass in the past. She had bilateral ptosis with mild diplopia. She had mild weakness of her orbicularis oculi, orbicularis oris, masseter and sternocleidomastoid muscles. She had mild dysarthria. The remainder of her cranial nerves were normal. She had moderate neck weakness. She had mild proximal arm weakness. Needle exam of her right deltoid was normal. SFEMG of her

orbicularis oculi was abnormal with 50 % of her fibers having increased jitter and 8% showing block. Left biceps muscle biopsy showed mild type II atrophy. Her LRP4 antibody level is 0.471 (<0.267). Her agrin antibody level is also elevated at 0.446 (<0.264). She is on prednisone, methotrexate and azathioprine and is uncertain of improvement. She responds very well to plasma exchange noting improvement of strength following every treatment. She recently received a course of rituximab but it is too early to know if she received benefit. When weakest she was MGFA class⁸⁰ IIIb.

In most cases described in the literature LRP4 antibodies are more common in women than men¹⁵⁴. The prevalence in DNMG has been as low as 2–4 % in Asian populations^{10,155} to as high as 53% in the study of Pevzner et al¹¹. In the largest reported series, Zisimopoulou et al found a prevalence of 18.7 %¹⁵⁴. Regional variation in prevalence has been reported¹⁵⁴.

Most cases are described as mild to moderate and ocular muscles are usually involved^{154–156}. Despite this, some patients have more severe symptoms (class III–IV)^{10,11,154}. Patients having myasthenic crises have been described (class V)^{10,11,154,157}. Patients with antibodies for both LRP4 and ACHR or MuSK are more symptomatic and do less well than patients with only LRP4 antibodies^{154,156}. One of our patients with LRP4 antibodies had VGCC antibodies and has features of both MG and Lambert Eaton Myasthenic syndrome. Currently, these patients generally present similarly to ACHR antibody-positive MG patients but are usually milder. Most patients respond to pyridostigmine, steroids and immunosuppressant medications like other MG patients. Thymus pathology is usually not present but has been described including thymomas^{154,155,158}. While in most cases respiratory dysfunction is mild, respiratory failure has been described¹⁵⁷.

LRP4 is an important signaling receptor in many other systems and is important for development. LRP4 antibodies have not been seen in control patients with other diseases except in 10 % of ALS patients^{159,160} and 2 cases of NMO¹². Whether it is pathogenic in ALS is not currently known. Since LRP4 antibodies are present in approximately 13–18% of patients with DNMG and LRP4 antibodies have been shown to produce pathology in mice it could in the future be part of routine MG patient screening. Further research is needed to understand what features are seen in these patients and determine its prevalence.

Agrin and other antibodies in MG

Agrin is another potential target for antibodies that can produce MG. Four papers found agrin antibodies in MG patients^{13,14,156,161}. In these studies, most of the patients are positive for other antibodies as well^{13,14,156,161}. Four of the patients reported by Gasperi¹³, but none of the patients reported by Cossins¹⁶¹, Zhang¹⁴ or Cordts¹⁵⁶ had antibodies to MuSK. In all four studies, agrin positive MG patients had antibodies to ACHR as well: 13 reported by Cossins¹⁶¹, 1 reported by Gasperi¹³, 5 reported by Zhang¹⁴ and 3 reported by Cordts¹⁵⁶. In addition, one patient who was positive for agrin and MuSK antibodies also had antibodies to LRP4¹³. There is a total of 14 patients reported who have antibodies only to agrin but clinical data was available for only 1 patient^{14,156,161}. This patient was MGFA Class III and only partially responded to pyridostigmine and prednisone¹⁵⁶. Based on this limited data the incidence and clinical characteristics of agrin antibody-positive MG patients are unknown.

Further research is required before we know the role of agrin antibodies in MG. Perhaps the coexistence of these antibodies might have implications on the severity of the disease. Similar to LRP4 antibodies, agrin antibodies have been seen in ALS patients even though their role is unknown in this disease state¹⁵⁹.

Titin, is a large structural protein found in muscle that extends the entire length of the sarcomere and has an important role in muscle elasticity. While this protein is very large, antibodies are directed against a small segment at the A/I band junction representing less than 1% of this protein. These antibodies have been found in patients with MG often in association with other pathogenic antibodies¹⁶. Titin antibodies are age related often being found in older patients with MG. These antibodies have been associated with thymoma in thymectomized patients¹⁶ and may have predictive value in determining which patients have thymomas. More recently, two studies looked at titin antibodies in seronegative MG^{15,156}. Cordts et al¹⁵⁶ found that 23% of seronegative MG had titin antibodies, while Stergiou et al¹⁵ found 18 % were positive. In both studies, patients positive for only titin antibodies have milder disease and are responsive to therapy. Patients with ACHR and titin antibodies have more severe disease and are more likely to have thymomas. Further research is needed to determine if this antibody is causative or just a bystander antibody.

Agius et al, describe Rapsyn antibodies in MG patients¹⁸. This was found in around 13% of the limited number of patients tested. However, these antibodies were non-specific and are of uncertain significance. Congenital defects in rapsyn are associated with congenital MG^{21,22,25}. Antibodies to ColQ have been found in 6 patients with MG (4%) of which 4 patients had DNMG¹⁶¹. The significance of these antibodies is unknown.

Gallardo et al¹⁷, describes antibodies to cortactin in 19.7 % of 91 DNMG patients. These antibodies were found in only 4.8% of either ACHR antibody-positive or MuSK antibody-positive patients. None of these patients were positive for LRP4. These patients were predominantly women (68%) and most were less than 50 years old at disease onset. Twenty-two percent had ocular disease while the remainder had generalized disease with ocular predominance. One patient had a thymoma. Cortactin antibodies are also detected in 12.5% of patients with other autoimmune neurological diseases. In a study of 250 MG cases, most (201) had ACHR antibodies, 11 had MuSK antibodies while 28 had antibodies to cortactin¹⁶². Of those, only 9 were DNMG and most (19) had ACHR antibodies. The frequency of cortactin antibodies were significantly higher in the DNMG group (23.7%) compared to the ACHR positive group (9.5%). No patients in this study had antibodies to both cortactin and MuSK. The 9 DNMG cortactin antibody positive patients had either ocular MG or mild MG (MGFA grade IIA) and fewer bulbar symptoms. Of 17 patients with ocular DNMG, 23.5% had antibodies to cortactin. The role of these antibodies is still unknown and requires further study.

Conclusion

In summary, new antigenic targets have been discovered that might account for many of the ACHR antibody-negative MG patients. The best studied of these is Anti-MuSK antibody MG. In some instances, their distinctive phenotype might raise clinical suspicion for this

form of the disease. Treatment of these patients is similar to that of ACHR antibody-positive MG with the notable exception that they are less responsive to cholinesterase inhibitors such as pyridostigmine. In addition, difficult to treat MuSK antibody-positive MG patients generally have an excellent response to rituximab. Anti-Striatal muscle antibodies seen in a third of MG cases are non-specific to MG and are not a reliable predictor of thymic pathology. While there is less experience with LRP4 antibody-positive MG, there is evidence that antibodies to LRP4 can cause neuromuscular defects. At this point, there are no specific phenotypes for this form of MG but it usually causes a milder form of the disease even though there are notable exceptions. Treatment for these patients is like that of ACHR antibody-positive patients. The role of agrin, titin and cortactin antibodies are currently unknown and more research is needed. These antibodies are associated with the disease but we do not know if they cause the disease or are an epiphenomenon. With more information about the role of these antibodies, we might be able to diagnose patient with MG earlier and design better therapies.

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Key Points

1. Approximately 20% of MG patients are ACHR negative. In some of these patients, antibodies to proteins responsible for the maintenance of the neuromuscular junction have been found. Antibodies associated with MG are directed against MuSK, LRP4, Agrin, Cortactin, Rapsyn and Titin.
2. MuSK antibodies are found in around 30–40% of DNMG patients. Three clinical presentation are associated with these antibodies. Firstly, a predominantly bulbar presentation with facial and tongue atrophy, often with few ocular symptoms. Secondly, presenting with head drop as the predominant symptom. Thirdly, presenting like ACHR positive MG.
3. MuSK positive patients generally respond well to immunosuppressive therapy but may not respond to pyridostigmine as well as ACHR positive MG patients. They respond well to rituximab often with a prolonged remission.
4. LRP4 antibodies are present in around 18% of DNMG patients. There is evidence that these antibodies are pathogenic as they cause MG in mice. We do not have enough clinical experience to identify specific clinical characteristics of these patients but most patients have milder disease.
5. The role of antibodies to agrin, rapsyn, cortactin in myasthenia gravis are not well defined at present and further research is needed.

Figure 1.
Structure of the Neuromuscular junction.

Figure 2.
Patient with Anti-MuSK MG