Christyn Edmundson:

Welcome. Thank you so much for joining us today. Today we're going to be discussing how to recognize and treat certain subtypes of myasthenia gravis, specifically MuSK, LRP4 and triple seronegative myasthenia gravis. My name's Christyn Edmundson. I'm a neurologist practicing in Seattle, Washington at the Swedish Neuroscience Institute. I'm joined today by Dr. Neelam Goyal, who's a clinical professor at Stanford University practicing in neuromuscular medicine. Here are our disclosures. So, today we'll be discussing why non-acetylcholine receptor antibody subtypes of myasthenia gravis are under-recognized.

Most MG education in most clinical trial data is actually built around acetylcholine receptor antibody-positive disease, which does represent the majority of generalized cases. In patients who have MuSK LRP4 and seronegative generalized myasthenia, they may have distinct clinical courses and diagnostic pitfalls that vary between subtypes. Treatment responses don't always map neatly onto acetylcholine receptor-based algorithm, so understanding how to recognize and treat these patients is particularly important.

Delayed or incorrect diagnosis is common, partly because atypical antibody profiles may be misread as mild disease, misattributed to other conditions, or left unexplored once the initial serology for acetylcholine receptor antibodies is negative. The activity today is going to use three real world cases to build a practical and subtype specific approach to diagnosing and treating patients with these rarer subtypes of generalized myasthenia gravis. So, let's take a look at myasthenia gravis sero status, a quick overview here. So, the most common subtype of myasthenia gravis are patients who have acetylcholine receptor antibody-positive disease.

This counts for about 85% of patients with generalized myasthenia gravis. The key mechanistic feature of this antibody is a functional acetylcholine receptor blockade paired with cross-linking internalization of receptors and/or complement activation. It's important to note that this antibody type does fix complement, which is different in some of the other subtypes. Next, there's MuSK antibody-positive generalized myasthenia gravis, which is much rarer representing about 5% to 7% of patients. The way that this antibody we think works is that it disrupts the MuSK LRP4 interaction, which then impairs acetylcholine receptor clustering via the DOC7 pathway.

So, acetylcholine receptors are not clustered and organized as one would want them at the neuromuscular junction. Really importantly here to know is that MuSK antibodies do not fix complement. They're IgG4 antibodies which are non-complement fixing, and this carries implications in terms of management. Third is the LRP4 antibody, which is very rare representing maybe 1% to 2% of generalized patients, perhaps 10% of acetylcholine receptor antibody or MuSK negative generalized patients. This works probably fairly similarly to MuSK disrupting that acetylcholine receptor clustering via the DOCS7 pathway. Complement fixation is variable.

And then finally, triple seronegative patients represent about 10% of generalized myasthenia gravis, probably or definitely significantly more in ocular pure ocular disease. We don't know what drives triple seronegative myasthenia gravis. It's presumed to be an antibody-mediated disease, but often no antibody is detectable or by definition, no antibody is detectable. Interestingly, in acetylcholine receptor cell-based assays, acetylcholine receptor can be identified in roughly 20% of patients who are considered triple CRM negative. And again, because we don't know in every case what the underlying antibody is, our knowledge of complement fixation is variable.

So, I'm going to turn this over to Neelam to discuss our first case, which is about MuSK antibody-positive myasthenia gravis.

Neelam Goyal:

Thank you, Christyn, for that overview. So, let's dive into our first case. So, this is going to be MuSK antibody-positive myasthenia gravis, a more severe treatment distinct phenotype that often demands earlier consideration of targeted therapy. So, let's go ahead with the case. So, here we have a 36-year-old female with several months of fluctuating diplopia, ptosis, proximal arm and leg weakness, and occasional dysphagia. She sees a neuromuscular physician who orders nerve conduction with repetitive nerve stimulation, which is abnormal and shows a decrement. Her serological testing shows negative ACHR antibodies, but her MuSK antibodies are positive.

She's initially started on pyridostigmine, which has a minimal effect, and then prednisone is started at 20 initially and then gradually increased to 60 milligrams daily. So, here, we highlight some of the features of MuSK antibody-positive gMG. Although we can see it in different phenotypes, the classic phenotype of MuSK antibody MG is a young woman with bulbar predominant disease that typically is refractory or difficult to control. Because of the pathophysiology, these patients don't have as robust of a response to acetyl-cholinesterase inhibitors, which can also contribute to your suspicion that this is MuSK-MG. So, let's go ahead with a question.

So, given this patient's fluctuating bulbar symptoms and the fact that you know that she's MuSK antibody-positive, which statement best reflects current practice for targeted therapy selection? Is it A, that IVIG is generally more effective than plasma exchange and MuSK antibody-positive MG? Is it that complement inhibitors are an appropriate first targeted therapy given IgG-mediated pathology? Is it C, rituximab should be considered as an early therapeutic option given consensus guidance and clinical experience in MuSK antibody-positive MG? Or would you send this patient for D for thymectomy because it often provides clear benefit regardless of MuSK serostatus?

So, we'll give you guys a couple of seconds to think about these options. Well, the correct answer is C. So, as Christyn discussed previously, MuSK IgG disease is IgG4-mediated, so it does not fix complement. So, complement inhibitors do not play a role in the treatment of MuSK-MG. Also, we know that these patients seem to respond less to acetylcholinesterase inhibitors and less to IVIG and respond better to prednisone as well as plasma exchange. After a few landmark papers in 2017, we know that CD20 depletion with rituximab plays a particular role in these patients. And so, for MuSK antibody-positive MG, there is international consensus guidance to really support the use of this agent early in its disease course.

In general, thymectomy does not play a role in MuSK-positive MG patients. So, here we review some of the features of MuSK antibody-positive MG. So, like I had mentioned previously, prior to 2017, MuSK-MG patients really represented the majority of our refractory and very challenging cases because of their poor response to our traditional therapies. So, the classic phenotype is again, a young woman with bulbar predominant disease. Bulbar MuSK-MG can also mimic motor neuron disease because these patients can actually get atrophy and fasciculations of the tongue muscle that does respond to therapy.

Because of this bulbar involvement and refractory phenotype, they can have respiratory involvement and crisis and have this severe presentation. Regarding diagnostic testing, we typically send our blood test to the Mayo Clinic, which will test for ACHR antibodies and if negative will automatically reflex to MuSK. So, it's important to make sure that if ACHR is negative, you check for MuSK. Very rarely you can have double positivity. So, in an ACHR patient that's refractory, sometimes I'll check for MuSK to see if they would benefit from CD20 depletion. And RNS and single-fiber EMG will be abnormal and support an abnormality of neuromuscular junction dysfunction.

Regarding to treatment, here we have a review of some of the agents. So, regarding traditional therapy as discussed before, plasma exchange, prednisone and non-steroids are all effective. However, really

early B-cell inhibition with CD20 depletion should be considered. We also know some of our newer generation therapies, including FcRn inhibitors and CD19 depletion are also effective in this phenotype. Going back to our patient. So, on follow-up two months later, the patient, as you recall, she's been on prednisone therapy after she didn't respond to acetylcholinesterase inhibitors.

So, she comes back two months later and she's clearly has shortness of breath, and she's unable to tolerate oral intake for several days due to dysphasia. On review of her history, you learn that she was recently diagnosed with UTI and was treated with ciprofloxacin, which is a known risk factor for neuromuscular junction decompensation. Unfortunately, due to this decompensation, she's admitted for impending crisis, requires intubation, and is treated with plasma exchange over 10 days. After extubation, her generalized and ocular symptoms improve after treatment with plasma exchange, and she also has benefit from high-dose prednisone.

After confirming hepatitis B serostatus, she's treated with rituximab one gram IV times two over two weeks and repeat dosing over the next four to six months. Here, she's noted to have a marked improvement and we're able to successfully wean her prednisone. This case really highlights that medications that impact the neuromuscular junction, antibiotics being known as one of those can really impact our patients with myasthenia gravis, and patients should be counseled about adding medications that can impact. And as you can see in this case, it can really have a big impact and lead to crisis for our patient. So, on review, safety and efficacy of targeted therapies in MuSK antibody-positive MG.

Really the case here highlights the use of early use of anti-CD20 rituximab for the use in these patients. We can use medications like prednisone, FcRn inhibitors, and plasma exchange for rapid efficacy, which can happen within days to weeks while we wait for the anti-CD20 drug to take effect. It's important to screen for hepatitis B because if they have evidence of latent infection, they will need antivirals during the treatment. As was discussed previously, complement inhibitors are not expected to work in MuSK antibody-positive disease because IgG4 antibodies do not activate the complement system. We now have multiple FcRn inhibitors which are approved for MuSK antibody-positive MG.

Nipocalimab is approved for pediatric population 12 and older, and FcRn inhibitors work to reduce the total level of circulating IgG antibodies. They can do this quite quickly within days to weeks after the first infusion, and we could see that clinical benefit. Also, new to the market is CD19 depletion with inebilizumab. Here through the MINT trial, we saw benefit in MuSK antibody-positive patients, and this is another agent that can be used. And of course, for our patients that do not respond to these agents or continue to not meet their treatment goals, clinical trial enrollment is also an option.

Christyn, anything else you'd like to add? Thank you for sharing this interesting case for us to present today.

Christyn Edmundson:

Yeah, absolutely. Thank you so much for that review. I think you've really hit the high points. Really just emphasizing that early B-cell depletion as a really important way of managing these patients with MuSK antibody-positive myasthenia gravis. It'll be really interesting to see over time what happens in these patients who in the real world are treated with CD19 inhibition as well since that's sort of a newer anti-B-cell agent that is just available in the last year or so.

Neelam Goyal:

Yeah, I think it's a great option. I have had a patient for another disease state develop serum sickness after rituximab treatment, and so we weren't able to use that, so it's always great to have multiple options for our patients. Yeah, great. So, moving on to quality of life and patient expectations, thinking

about comparing MuSK versus ACHR antibody-positive MG. So, as we discussed before, MuSK antibody-positive MG can have a severe initial course because it's high predilection to involving the respiratory muscles, the bulbar muscles. These patients can really get into trouble if not diagnosed and treated early.

Because of their very refractory state, these patients can have a prolonged steroid dependence. Prior to 2017, again, these patients represented really challenging cases for us in our clinic. However, after the availability of rituximab, most of my patients are doing very well. They're able to be on monotherapy and able to really get off many of these medications.

And something important to think about for our MuSK-MG, but really all of our MG patients is that many things impact neuromuscular transmission, including just ambient heat, so hot summers, but also medications like antibiotics, some blood pressure medications, and all of these things can really impact our patients, especially if they are not doing well on that cusp that can really push them over into crisis. So, really all of these things are important for us to be aware of. So, ending now with some clinical pearls for MuSK antibody-positive gMG.

So, please think about this disease state early in your patients with prominently lead bulbar, respiratory symptoms, a young female, and a lukewarm response to pyridostigmine. All of these clinical features should make you think about MuSK-MG. Choose PLEX over IVIG for rescue therapy when possible. Skip complement inhibitors, MuSK antibodies or IgG4, and do not fix complement. Think about treatment with rituximab early in the disease course to really get them better fast, but also to reduce exposures to long-term steroids. Think about our new approved agent, both FcRn antagonists, as well as CD19 depleters for patients with MuSK-positive MG.

And of course, for all of our patients, important to counsel on precipitants, including infection and antibiotics, and think about modifiable triggers for crisis. I'll now pass it on to Christyn to talk about LRP4-positive MG.

Christyn Edmundson:

Great. Thank you so much for that awesome review of MuSK-positive myasthenia gravis. So, this next case is going to highlight LRP4 antibody-positive myasthenia gravis, and specifically how important it is to reassess any given diagnosis rather than just sort of barreling down the path of adding additional treatment. So, looking at this case, this is a 65-year-old woman with several decades of intermittent neck and limb weakness that usually starts with a heavy feeling in the head and neck subsequently spreading to the extremities.

In 2022 and 2024, she has two more severe episodes that also include trouble chewing, swallowing, slurred speech, and milder double vision with prolonged eye use. She's admitted for both of these episodes, and during that second admission, she's checked for myasthenia gravis serologies. Anti-MuSK and anti-acetylcholine receptor antibodies were negative, but LRP4 antibodies were a weak positive. And on this basis, she's diagnosed with LRP4-positive generalized myasthenia gravis. She's put on pyridostigmine, 180 milligrams long-acting, and has a robust response to this. Subsequently, she's tried on IVIG without significant benefit.

So, a tip here is that LRP4-positive antibodies are often treated as being diagnostically definitive. But we can see in this patient that while she has responded to pyridostigmine, she's had a rapport response to IVIG, which is a standard first-line therapy in autoimmune myasthenia gravis, which should prompt a reassessment of her diagnosis rather than escalating immunotherapy purely for escalation's sake. So, quick question here for everyone to consider. In this LRP4 antibody-positive patient, she's had a poor response to IVIG, although she has had a response to pyridostigmine.

She also has a sibling with a similar unexplained syndrome. What would the most appropriate next step be? A, increase the pyridostigmine dose and reassess in three months. B, start a complement inhibitor. C, pursue genetic testing for a congenital myasthenic syndrome, or D, repeat the LRP4 antibody test to confirm the original result. So, in this case, the correct answer is C. This patient actually, it turns out, has a family history of similar symptoms and a poor response to a standard immunotherapy, which is a red flag for a genetic neuromuscular junction disorder.

Having this positive LRP4 antibody, particularly a weak positive, does not rule out congenital myasthenic syndrome or other genetic disorders. So, genetic testing would materially change management in this patient. So, there's a debate we'll have periodically. LRP4 antibody-positive myasthenia gravis. Is it a myth or is it real? I think many of us have seen patients come in with LRP4 antibodies with a diagnosis of generalized myasthenia gravis who are ultimately diagnosed with a different disorder. In terms of thinking about true LRP4 antibody-positive myasthenia gravis, the clinical phenotype often resembles acetylcholine receptor antibody-positive MG more than MuSK.

LRP4 antibodies vary in sensitivity and specificity across labs. Slow repetitive nerve stimulation and single fiber EMG support a neuromuscular junction diagnosis when the serology is ambiguous, but they don't exclude a genetic disorder of the neuromuscular junction. In a genetic disorder of the neuromuscular junction, you would expect abnormal repetitive nerve stimulation and single fiber EMG. So, a positive LRP4 result is not always the whole story. This has been reported in confounding disorders from genetic conditions to neuromuscular junction disorders to motor neuron disorders, and a poor response to treatment should be a red flag that the LRP4 antibody really isn't telling you the whole story.

In terms of treatments, when autoimmune LRP4 antibody myasthenia gravis is confirmed, patients are treated much like acetylcholine receptor antibody patients. Pyridostigmine steroids and steroid sparing agents are reasonable for steps. Additionally, efgartigimod is approved for all serotypes of generalized myasthenia gravis, so it remains a treatment option if someone has confirmed autoimmune LRP4 antibody-positive generalized myasthenia gravis. So, in this patient, she gets an EMG nerve conduction studies that show an abnormal decrement on slow rep stim.

Because of her clinical presentation, a periodic paralysis was being considered because of this sort of episodic weakness and she'd had, I think, a low potassium during one of her hospitalizations. However, because her sibling was also being treated for seronegative myasthenia gravis, we pursued genetic testing, which showed homozygous pathogenic wraps in mutations confirming a congenital myasthenic syndrome, not autoimmune LRP4 antibody-positive myasthenia gravis. The patient was trialed on amifampridine, but she didn't tolerate it because of orthostatic dizziness and syncope and also didn't feel that it provided her any clinical benefit.

Ultimately, she tends to do best on a long-acting pyridostigmine as a targeted mechanism specific management rather than immunosuppression. So, we're really targeting the function of the neuromuscular junction rather than the immune system since this is a genetic, not an immune or autoimmune disorder. So, tips for a patient like this are once a genetic neuromuscular junction disorder is confirmed, the therapeutic conversation shifts away from immunosuppression and more towards therapies that could modify the function of the neuromuscular junction.

In terms of quality of life and patient expectations, for someone with confirmed autoimmune LRP4 antibody-positive MG, treatment goals are going to be similar to acetylcholine receptor antibody-positive disease, and many patients do fairly well with the standard first or second-line therapies. If the diagnosis instead is a congenital myasthenic syndrome, the expectations need to be reset. This is the lifelong non-immune condition and escalation of immunotherapy would carry risk without any expected

benefit. So, things like a family history of a similar disorder, refractory symptoms to immunotherapies, maybe overlooked pieces of diagnostic information in this subtype of disease. A few pearls.

You want to treat confirmed LRP4 antibody myasthenia gravis, much like it's acetylcholine receptor antibody-positive counterpart using standard first and second-line therapy. Efgartigimod is FDA approved without serostatus restrictions, so it's an available option for LRP4 antibody-positive patients. Don't stop at a positive antibody. If there's a poor response to these standard therapies, you want to reassess the diagnosis, an LRP4-positive disease, not automatically escalate therapy. In this disorder and in many others, always ask about a family history.

Sometimes you have a positive blood test, an antibody test that's spurious, and digging a little bit deeper can show you a pattern of a similar disease in the family that suggests an underlying genetic disorder. And then the take-home isn't to do genetic testing in everyone, but certainly in patients who have atypical courses, refractory symptoms or a family history could merit genetic testing. If congenital myasthenic syndrome is confirmed, you want to shift away from immunotherapy and instead use treatments like pyridostigmine, amifampridine, and some other agents that have been reported to be effective on a case-by-case basis.

Any thoughts or comments on this, Neelam? I know this LRP4-positive disease is a little bit controversial in our field.

Neelam Goyal:

Yeah, thank you for sharing this case. I think this is really important. In my practice now, I don't test for LRP4. Because it's neither sensitive or specific, I don't find it to be helpful. Most of my cases of LRP4 are coming from the community or from colleagues in different subspecialties that have tested for it. And I have to say I don't have a confirmed LRP4 patient. So, I really liked this case because this patient actually had features of autoimmune myasthenia gravis. I think if you didn't really dive deeper, you would've missed this diagnosis and she could have gone for years with treatment.

And so, for patients, it's important to think about hereditary disease when they have features of neuromuscular junction disorder, but they're not responding to treatment. But also think about non-neuromuscular junction disorder diseases when patients have, let's say, just fatigue and your colleague from another specialty ordered the antibody and came back positive. So, you really want to look and look at the clinical phenotype and say, "Does this look like MG?" Because as mentioned, we've seen positive antibodies in patients that do not have myasthenia.

So, I think unlike MuSK and ACHR, which are very specific for the disease, I think in all my time, I've only seen one patient that had a positive antibody that I didn't think had MG. Of course, we see patients with ACHR antibodies that have thymoma that don't have clinical features, but really very important to pause when you have an LRP4 antibody-positive case to make sure the examination, the treatment response, the electrophysiology all fits. So, I completely agree with you that it's important to really take a deeper look when you have this antibody positivity.

Christyn Edmundson:

Absolutely. Thank you so much. I agree. In my practice, I don't think I have any true myasthenia gravis patients with LRP4 positive antibodies and have stopped testing it myself because I sort of go by clinical features to consider if someone has an autoimmune myasthenia gravis and whether they have LRP4 antibodies or truly seronegative, the treatment options are very similar. Great. Well, I'll hand it back to you for a third case talking about this triple seronegative myasthenia gravis.

Neelam Goyal:

Great. Thank you. So, let's dive into our last case, which is triple seronegative MG. So, here we have a 61-year-old female with a history of hypothyroidism, celiac disease, and a prior now resolved antiphospholipid antibody profile who's coming to see you for fluctuating diplopia, eyelid lag, which is worse at the end of the day. She also reports some shortness of breath when speaking, difficulty swallowing certain textures, along with a globus sensation with esophageal dysfunction on swallow study. She was seen by neuro-ophthalmology who felt that her diplopia was due to a refractory error and did not favor a neuromuscular junction disorder.

She underwent thorough antibody testing, including cell-based assay for all three antibodies, ACHR, MuSK, and LRP4, and these antibodies were negative. She had an EMG nerve conduction study with repetitive nerve stimulation, which was also negative. Despite these findings, she was given a trial of pyridostigmine, which responded and she noted improvement in her double vision, in her swallowing and her fatigue, which prompted further neuromuscular workup. So, here we have kind of a confusing picture. She seems to have some classic features of generalized myasthenia gravis. She's got diplopia, she's got some ptosis, she's got all the bulbar stuff. However, there seems to be some reasons to question this.

Neuro-ophthalmology didn't think her ocular symptoms are due to a neuromuscular junction disorder, and she had negative antibodies as well as repetitive nerve stimulation. However, because she has some features that are suggestive of myasthenia gravis and she did have a response to pyridostigmine, I think at this point really it could go either way, but it is important for us to move towards further diagnostic testing like single fiber EMG to understand what's happening within her case. So, let's ask this question.

So, we have this patient, she has a suggestive clinical history, symptomatic improvement with pyridostigmine, but normal antibodies, a normal standard repetitive nerve conduction study, What would be the most appropriate next step in excluding a neuromuscular junction disorder? Would you just stop there and say, "Nope, this is not MG. Let's look for something else." Would you do a single fiber EMG? Do you want to start treatment with high dose steroids or should we just repeat testing in six months? Okay, so here I would say we should go on to single fiber EMG. So, like I said earlier, I think this is definitely a confusing case, but not something that's rare in our clinic.

Often these patients can be confusing, and this is why certain types of MG like seronegative MG can have a long diagnostic journey before they're diagnosed. So, here, I think there's enough in the story to go to single fiber EMG for diagnosis. However, if your center doesn't have single fiber EMG or there's long wait times, I have in this type of patient also done a trial of steroids. Here, it's very important to have clear objective markers because you're really using this both for treatment, but also as a diagnostic test. We are lucky that our center does offer single fiber EMG.

So, if she's otherwise stable and we can wait for that single fiber EMG, I would wait, do that test, have a confirmed diagnosis because she's very symptomatic, and then move to treatment. I do want to highlight here that this is a patient that has generalized symptoms and has a normal repetitive nerve stimulation. So, remember, repetitive nerve stimulation is not as sensitive as single fiber EMG. So, if you have a case that you're suspicious, don't stop there. Especially if the symptoms are not where you're doing the repetitive stimulation, RNS can be negative. Christyn, would you agree with what I've said?

Have you also sometimes done treatment trials with prednisone if single fiber EMG was hard to get or had long wait times like we have in our clinic?

Christyn Edmundson:

Yeah, absolutely. So, start by saying I completely agree that repetitive nerve stimulation is not the most sensitive test for myasthenia gravis. So, if you suspect myasthenia gravis, especially if someone's antibodies have been negative and you get the rep stim and it's abnormal, great, that's extremely helpful. But when it's normal, it really does not rule out a neuromuscular junction disorder like autoimmune MG. I really like to get the single fiber EMG and it can take a long time.

So, there are certainly times where if there's a long diagnostic delay or if a patient lives a four-hour drive away and isn't going to be able to schedule the test for several months, that I will use empiric steroids as sort of a diagnostic maneuver and really agree that in that case it's important to have objective measures that you're following. Patient reported outcomes like the MG-ADL are helpful, but really getting a physical examination right before you start the steroids and then a month or maybe two later to really try to document that objective response. Lots of people feel a bit better on steroids, especially early on.

I will also say that this is a case that in some ways on its face doesn't look too different from the prior patient who ultimately had congenital myasthenic syndrome. So, until we get a little further along, that's also going to be sort of in the back of my mind wondering is this truly autoimmune triple seronegative myasthenia gravis, or could this also be a hereditary disorder?

Neelam Goyal:

Yeah, thank you. And I think one of the misconceptions is when we think about things that are hereditary, they're going to come on in childhood. And our experience tells us that hereditary things can come on in adulthood or they've been there for longer, but the patient only observed a subacute change. So, just important, if things are not adding up, definitely thinking about an alternative diagnosis, like something hereditary is important. So, let's dive a little bit deeper into seronegative gMG. And I think just like this case highlights, these patients can really have a diagnostic delay and misdiagnosis.

And it's really important for us, especially now that we have more therapies available for these patients, to really be able to diagnose them early. And so, diagnostic delay is common. Symptoms could be attributed to other disease states. There could be colleagues that stop at antibody testing or repetitive nerve stimulation and don't go to the next step for single-fiber EMG. So, it's important to think about that. And especially in patients that are elderly having other comorbidities. I've seen patients with MG get misdiagnosed as stroke because they went to the emergency room. So, really keeping this in mind, especially when the ocular symptoms are not as evident is important.

And misdiagnosis and mimics really structural eye disease, esophageal dysmotility, connective tissue disorders. And again, things like stroke can really mimic and these patients can have a delay in diagnosis. If the antibodies are negative, you can send for cell-based assays. So, Christyn and I have discussed this before. In the literature, there are different numbers for how high the yield is for in triple negative patients when you do cell-based assay. But I also have not had any positive cell-based assay come back. I have to admit that after five, six negative assays, I stopped checking, but my colleague continues to check and I think he has had a couple of comeback positive.

And of course, that can be super helpful in terms of confidence in our diagnosis, but also access to our newer generation therapies. So, definitely something to try. It is commercially available. And then of course, single-fiber EMG is very sensitive. So, in patients that you are suspecting this, it's important to do this. But remember, it is not specific, so it will be abnormal in other neuromuscular disorders as well as in genetic neuromuscular junction disorders as well. So, going back to our patient, her single fiber EMG did confirm an abnormal neuromuscular junction transmission defect, and thus she was diagnosed with seronegative autoimmune generalized myasthenia gravis.

She was put on prednisone with improvement. However, did not tolerate mycophenolate and azathioprine. She was then given IVIG, which produced a marked benefit. However, over time she had wearing off between infusions. We now have available efgartigimod, which is an FcRn inhibitor, which a few months ago in May of this year was approved for seronegative or all ACHR-negative myasthenia gravis generalized MG. And so, she was started on this medication and she had a benefit from five to two of her MG-ADL with symptoms recurring about two to three weeks after each cycle. Due to the way that it's written, we were able to shorten the cycle to two weeks on, two weeks off, which led to a nice steady benefit.

So, tip here, even without a detectable antibody, this patient responded meaningfully to an FcRn inhibitor. Efgartigimod is FDA approved for myasthenia gravis regardless of antibody status. So, it's a reminder that antibody-negative status does not equal no autoimmune pathology, and that dosing interval and not just drug selection is often the lever that restores control. Thinking about quality of life and patient expectations, patients often carry the emotional burden of a delayed or dismissed diagnosis. Validating the diagnostic journey is itself part of care. Wearing off between infusion-based therapies is a common under-discussed source of functional decline.

Ask about the days before the next dose, not just the days after. And importantly, efgartigimod is FDA approved regardless of antibody status, including seronegative MG. This is a relatively recent label expansion and antibody-negative testing should not by itself limit access to targeted therapy. And so, ending with clinical pearls for triple seronegative gMG. If you have high clinical suspicion, do not stop at a negative panel. Consider cell-based assays, which can identify antibodies in some case areas of up to 20% of those that are seronegative. A normal standard EMG nerve conduction study, even with repetitive nerve stimulation, does not rule out myasthenia gravis.

Please proceed to single fiber EMG if your clinical suspicion remains high. These patients can be treated like ACHR antibody-positive MG for first and second-line therapy while remaining alert for comorbid mimics. Watch for wearing off for any therapy that we're giving in a cyclical fashion because changing the interval can help restore that consistent benefit. And seronegative status does not exclude patients from FcRn inhibitor therapy. Efgartigimod is FDA approved regardless of antibody status, including seronegative gMG. And I'll pass it back to Christyn for the closing.

Christyn Edmundson:

Great. Thanks so much. So, a few reflections and particular areas with the potential to change practice. So, to review these non-acetylcholine receptor antibody-positive gMG subtypes, in patients who have MuSK antibody-positive gMG, you want to move to rituximab early, favor PLEX over IVIG for rescue, and completely skip complement inhibitors. I've seen MuSK patients treated with complement inhibitors. Usually they get worse, especially if other therapy is being stopped. So, be sure that you're not reaching for complement inhibitors in those MuSK antibody-positive patients. FcRn inhibitors are also a good therapy option, and several have FDA label approval for MuSK-positive disease.

For LRP4 antibody-positive gMG, really consider if that's the correct diagnosis. A poor response to standard therapy for autoimmune myasthenia gravis should definitely prompt a reconsideration of the diagnosis of LRP-positive autoimmune myasthenia gravis. Don't just reflexively escalate immunotherapy. In patients who truly have autoimmune LRP4 antibody-positive gMG, FcRn inhibitor therapy is a potential option. And then in those triple seronegative MG patients, consider cell-based assay if your clinical suspicion is high, and certainly consider single-fiber EMG before abandoning a neuromuscular junction hypothesis.

In these patients as well, don't withhold FcRn inhibitor based on serostatus alone, as there's now an FDA-approved labeled indication for efgartigimod in all myasthenia gravis serotypes. To revisit this,

which we looked at at the very beginning, reviewing these subtypes, making sure that diagnostic priorities for the acetylcholine receptor antibody-positive patients include the standard serologies, which are positive if they have antibody-positive disease. You always want to do a CT chest for thymoma. PLEX or IVIG can be used for rescue, and essentially all the targeted therapies are an option, complement inhibitors, FcRn inhibitors, and anti-CD20 agents, and/or CD19 agents in some cases.

For MuSK antibody-positive patients, consider repetitive nerve stimulation and single-fiber EMG while the MuSK antibody is pending. Although if you already have an antibody test, you don't need to do those electrodiagnostic tests. For rescue therapy, PLEX is preferred over IVIG, and then consider rituximab early. You can also consider FcRn inhibitors, CD19 inhibitors, but avoid complement inhibitors. For LRP4-positive disease, if you have that positive antibody, really be sure that you're taking a close eye to that diagnosis. And if there's a family history or if the disease is refractory to initial therapies, certainly reassess, which could include genetic testing.

For patients who truly do have LRP4-positive myasthenia gravis, PLEX or IVIG can be used for rescue, and you would use a similar treatment algorithm to acetylcholine receptor antibody-positive disease. Efgartigimod is approved. I will note that anti-B-cell agents and complement inhibitors don't carry a labeled indication for LRP4 antibodies. In those triple seronegative patients, think about cell-based assays and single-fiber EMG to confirm the diagnosis. PLEX or IVIG can be used as a rescue therapy. And now in addition to the traditional agents like corticosteroids and steroid-sparing immunotherapies, efgartigimod has an FDA approval for this disease regardless of sero status.

Thank you so much for attending this presentation. Thank you so much, Neelam, for being here as well, and we hope you enjoy.

Neelam Goyal:

Thank you.