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## Advancing gMG Clinical Decisions: Diagnosing Early, Treating Smarter, and Caring Holistically – A Case-Based Treatment Approach

### Announcer:

Welcome to CE on ReachMD. This activity, titled “Advancing gMG Clinical Decisions: Diagnosing Early, Treating Smarter, and Caring Holistically – A Case-Based Treatment Approach” is provided by Prova Education.

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### Dr. Goyal:

If you think every case of droopy eyelids is just stress or too many late nights, think again. Today's patient reminds us by looking beyond the obvious can change the entire treatment journey. Hello, I'm Dr. Neelam Goyal. I'm clinical professor of Neurology and Neurological Sciences in the Division of Neuromuscular Medicine at Stanford University.

### Dr. Edmundson:

And I'm Dr. Christyn Edmundson. I'm a neuromuscular specialist at the Swedish Neuroscience Institute in Seattle, Washington. This is CE on ReachMD. In today's session, we'll follow one patient's journey from those first easy-to-miss symptoms through the critical decisions about advanced therapies like FcRn antagonists, all the way to addressing the psychosocial challenges that too often go untreated. So let's get started. Our patient today is Maria, a 38-year-old teacher who presents with fluctuating eyelid droop double vision by late afternoon and overwhelming fatigue interfering with her teaching symptoms worsen later in the day. She has no clear bulbar or limb weakness and her PCP initially suspected this to be secondary from stress or thyroid disease.

### Dr. Goyal:

Yeah, so thank you for presenting this case. And you know, in some ways we're talking about how do we think about myasthenia, but in many ways, Maria is presenting with pretty typical symptoms of myasthenia gravis. So myasthenia gravis is an autoimmune disease. It can really come on at any age, but we see this bimodal peak with onset; women predominantly in the thirties and then predominantly male in the fifties. And really the presenting symptom is often eyelid, drooping or ptosis and double vision. And this is due to weakness of the eyelid muscles and the extraocular muscles. So really here, because Maria is presenting with very classic symptoms, physician should be thinking about myasthenia gravis. And really I think this is one of the take home messages that if you're seeing ocular symptoms – droopy eyelids, double vision – you should really be thinking about myasthenia gravis.

Now with these very classic symptoms, it's a little bit difficult to think about what else this could be, but of course, Maria is in her thirties, so this is also and, and a female. So this is also the age group where we may see the onset of CNS autoimmune diseases like multiple sclerosis. So because her presentation is very classic, I may go to antibody testing for myasthenia gravis and if negative, and of course if there are other upper motor neuron signs like hyperreflexia on examination, then move to imaging of her brain

to look for any lesions that might suggest an alternative diagnosis. Other things we might be thinking about is, hereditary muscle diseases like mitochondrial myopathies. They may also present with ocular symptoms, but really this new onset of symptoms and this fluctuating, eyelid droop really makes you think about myasthenia. For those mitochondrial myopathies, you may check a CK level, you might do an EMG nerve conduction study to look for myopathic findings on the EMG portion and may move on to genetic testing. What are your thoughts?

**Dr. Edmundson:**

So I agree with everything that you've said. So, you know, like the idea of considering CNS disease of some other neuromuscular diseases like my mitochondrial myopathy or even congenital myasthenic syndrome, this would be a very late presentation for that. But essentially when you see someone presenting in this way, the key next step is to perform the diagnostic testing to confirm a diagnosis of myasthenia, keeping in mind that it could be other things but not delaying diagnosis and really moving forward with the more definitive testing. What that can look like in terms of bedside maneuvers when a patient's there, in the room you can oftentimes demonstrate fatigability on examination, whether that's looking for sort of emerging eye symptoms with repeated use.

So having a patient look up for a prolonged period of time and looking for emergent diplopia with prolonged up gaze. Looking for ptosis with prolonged up gaze as well looking for curtaining, which is where you lift one lid and the other one droops down. And then looking for fatiguability on their limb tests. So, you know, testing deltoid strength or testing quad quadriceps or hip flexor strength, but then having the patient, you know, flap their arms or do some squats and then test them again to see if there's weakness that emerges clinically with sort of repeated use of muscles. And a patient like this really the first thing you're gonna do after seeing them in clinic is to send antibody testing. the antibodies associated with generalized myasthenia gravis include acetyl receptor antibodies, MuSK antibodies, and LRP4 antibodies.

Different clinicians will take different strategies. The most common antibody to find in a patient with generalized MG symptoms is the acetylcholine receptor antibody, usually the binding antibody. So oftentimes I will send an acetylcholine receptor binding antibody and if that's negative, send sort of blocking and modulating acetylcholine receptor antibodies, MuSK and sometimes LRP4 four. In general, if a patient has classic symptoms of myasthenia gravis and a positive antibody test, you have the diagnosis, you don't have to go on to do electrodiagnostic testing. In cases where you feel a patient likely has autoimmune myasthenia gravis, but they're not, coming back with a positive antibody, that's you when you would reach for something like repetitive nerve stimulation or even single fiber EMG. These tests are more time consuming and the case of single fiber EMG, can be really difficult to get done by a provider who's very competent at them. So really that sort of more detailed electrodiagnostic testing should be reserved for cases where a patient is antibody negative or the presentation is a typical in some other way that makes sort of confirming the electrical characteristics of the neuromuscular junction clinically useful.

**Dr. Goyal:**

Yeah, so I, I would agree. And you know, I think the only thing that I would add is right now it sounds like she has, Maria has primarily ocular symptoms. So in restricted ocular mg about 50% of the patients will not have antibody positivity. And so there you may be more likely to, go to electrodiagnostic testing. Also, you know, I'm not sure if you've experienced this as well, but I have seen patients, if you see them early in their disease course actually have negative antibodies and then you check within that first year again, especially because they have pretty classic symptoms and then they will seroconvert and be positive.

**Dr. Edmundson:**

In this patient's case, she's found to have positive acetylcholine receptor antibodies and she's graded as having MGFA class III disease, meaning she has moderate generalized, symptoms or findings. On examination, she started on pyridostigmine, which is a cholinesterase inhibitor as well as low dose prednisone. However, she returns in a few months and is unhappy with her treatment plan, reluctant to escalate steroids due to side effects. In the interim, she's actually developed proximal limb weakness that's making it difficult for her to brush her hair and go upstairs. She's also having slurred speech and occasionally choking with food. So in terms of this patient's case, this is an instance in which traditional therapies, this sort of first line of acetylcholinesterase inhibitor or pyridostigmine and low dose prednisone are not adequately treating, this patient.

In the past, this is someone who we would've had, you know, the option of using, oral steroids, bearing agents like mycophenolate or azathioprine, which can work well in some patients but have a long time, to their clinical onset, typically several months before we see any benefit. This is also a patient in the past who we might've considered for treatment with something like IVIG plasmapheresis less likely, or just really pushed her to increase her prednisone dose in spite of the side effects that she's experiencing. What's changed in the

past several years is that, there's been an introduction of novel targeted therapies that include the FcRn antagonists. drugs that fall on that class are efgartigimod, rosanolixizumab and nipocalimab, as well as another class of drugs, the complement inhibitors, which has several approved agents, for the treatment of generalized myasthenia gravis.

Looking specifically at the FcRn antagonists and these three agents that are on the market, efgartigimod has been shown to have a rapid and durable symptom improvement in a phase three clinical trial called the ADAPT trial. Rosanolixizumab, is a subcutaneous agent that's been shown to be effective in both acetylcholine receptor and MuSK antibody positive GMG, through the MycarinG and its extension studies and nivolumab, is an IV agent that was shown to have favorable results in the VIVACITY MG3 phase three trial, which improved MG-ADL scores and was overall well tolerated.

**Dr. Goyal:**

Yeah, thank you for reviewing that. So, you know, for Maria, we really need a medication that's going to work quickly and our options do include pushing her steroids, but it sounds like she's concerned about side effects and so I think an FcRn agent would definitely be an option for her. So as you discussed, we have three options that are available, efgartigimod, rosanolixizumab, and nipocalimab. Because she is an adult patient with AChR positive, generalized myasthenia gravis, all three will be indicated for her. Now, efgartigimod and rosanolixizumab, are given in a cyclic fashion. So efgartigimod is four weeks on, four weeks off, it's weight based and it can be given IV subcutaneously or even in prefilled syringes. So for patients that I start on efgartigimod, I will typically give them three cycles, but touch base between the cycles to see if they are having, response to treatment because we would wanna change therapy if, they were not working. During that time, you would keep patients on their other medications for her, since she's now progressed. You may want to add a long-term steroid sparing agent, as it sounds like she may need ongoing therapy, for her disease. Now, for rosanolixizumab, this is going to be similar. It's weight-based in three different weight groups. This is given subcutaneously but administered by a healthcare professional. So it has to be given either in the hospital or at an infusion service. And this is six weeks of infusions with four weeks off. So again, this is cyclical because the treatment cycles are longer. I would typically prescribe for three cycles, but again, touch base with the patient. in terms of nipocalimab, as was mentioned earlier, this is our newest FcRn on the market. And this is different in that it's not given cyclically.

So here we have a loading dose of 30 mg per kg and then followed by every two weeks, 15 mg per kg. And so here again, I would probably start the patient wait about three months and then see them back. Now for all three agents, the response is going to be fast within a week or two of starting infusions. And these medications, there is no specific guidelines for monitoring. Some colleagues do check IgG levels, but I really am monitoring more for side effects such as headache or infections. If patients do have infections, you do wanna pause treatment and reinstate. When we think about some of our subclasses, this is not Maria, but if a patient is MuSK MG, then here the indication would be nipo or rosy. If this was a pediatric patient, then we would go for nipo. And then thinking about patients that are childbearing age, FcRn antagonists have not been studied in pregnancy, but of course some of our non-steroidals such as the, mycophenolate mofetil, we would want to be very careful in the childbearing population.

**Dr. Edmundson:**

Absolutely, I agree with all of that. There's so many considerations when you're thinking about the individual patient. One thing that I get asked a lot is, you know, how long should I try these agents for before I've decided if they work or not? And for me, oftentimes it's kind of around that three month mark. I like to give patients, at least two, sometimes three cycles of efgartigimod, which is you, four weeks on, four weeks off, four weeks on, four weeks off or longer between cycles. And I find that usually if patients are gonna respond, they respond within the first one or two cycles there. If it's equivocal, I'll oftentimes give them a third cycle. And similar for the rosanolixizumab, with nipo calimab, because it's not cyclical, you know, it's something that I would probably consider treating a patient with, you know, three, maybe four months.

And then even though in many patients that onset is pretty rapid, a lot of people will see benefit within a week or two. Some people it can take a little bit longer to see the response, so I'll give them that time of a couple of cycles or a couple of months on the therapy, to see, to see how it affects them. Giving a couple of cycles can also give you a sense of, you know, how a patient is tolerating the time between cycles if they're wearing off before their next cycle and maybe need to be dosed a little bit more often or where they're actually switching over to a more continuous regimen, either sort of an off-label regimen with efgartigimod, rosanolixizumab, or nipocalimab, which is labeled as every two week dosing. another issue that can come up, is patients experiencing, you stress and anxiety related to flares and reduced work productivity and decreased quality of life. and that's something that comes up for this patient as well. Could you talk about how you might address that in this case?

**Dr. Goyal:**

Yeah, I think that's a great question. I mean, this is a young woman who's 38. She may otherwise be healthy. She may be taking care of young children at home. I mean, this is going to have a major impact. She has moderate MG so she has pretty scary symptoms, you know, that make her concerned about caring for herself, but also, serving as a caregiver for others. So really I think it's things that we've highlighted before, really getting to know the patient and making sure since we are in a stage where we have multiple options to really talk about them and see which one is going to best fit her lifestyle.

**Dr. Edmundson:**

So this has been a great discussion and I think my two key takeaways from this, are one that it's really important to recognize and, diagnose myasthenia gravis early, sort of understanding those, initial symptoms and sort of definitively diagnosing, at an early stage. And then second is, really treating patients depending on how they respond to their therapy. So if someone is not responding to their first line therapy, adjusting or escalating their treatment, to help improve their symptoms and improve their quality of life, as quickly as we can.

**Dr. Goyal:**

Yeah. Thank you. I agree. So thank you Dr. Edmundson for sharing your expertise. And thank you all for joining us. We hope you found today's conversation valuable and that you take away some practical insights to apply to your work.

**Announcer:**

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