FcRn and Myasthenia Gravis: Pathophysiology

Dr. Richard Nowak:

I will be talking today about FcRn and myasthenia gravis, with a focus on pathophysiology. My name is Dr. Richard Nowak, associate professor of neurology at the Yale School of Medicine. These are my relevant disclosures.

Our learning objective today will be to describe the role of FcRn in myasthenia gravis.

What is myasthenia gravis? Specifically, what is autoimmune myasthenia gravis? This is a rare condition that is characterized by fluctuating muscle weakness, specifically weakness that involves the ocular muscles, bulbar muscles, and limb muscles. Many individuals are characterized by having acetylcholine receptor autoantibodies that target their neuromuscular junction. In fact, many patients present as their initial symptoms having ocular symptoms. Things like diplopia or orthosis. In fact, up to 90% of individuals, their initial symptom does involve an ocular finding or symptom.

Treatment is very highly individualized and often includes medications that are off-label. Things like azathioprine or mycophenolate are not uncommon. Non-steroidal immunosuppressive therapies that have been used for myasthenia gravis in the past and also currently. However, there are five drugs that are FDA approved, eculizumab, efgartigimod, ravulizumab, rozanolixizumab and zilucoplan.

Symptoms and diagnosis. As I noted on the prior slide, the condition is characterized by having fluctuating symptoms fluctuating weakness on exam. It's not unusual for patients to report things like difficulty with chewing, specifically fatigue in chewing, difficulty with swallowing. Symptoms such as choking with certain consistency of food. Shortness of breath, and more proximal than distal muscle weakness. In fact, the characteristic is really proximal weakness that's fatigable. As we consider the diagnosis and the approach to making a diagnosis for our patients with myasthenia gravis, certainly the physical examination and their clinical presentation is very important.

We think about this as an autoimmune condition, it's very typical for us to move forward with serologic evaluation as well as electrodiagnostic studies. In fact, 70 to 80% of individuals do have autoantibodies directed against the acetylcholine receptor, and that is something that helps us and sometimes definitively establishes a diagnosis. However, we also have electrodiagnostic studies such as the repetitive nerve stimulation test, which is approximately 60 to up to 70% sensitive at picking up an abnormality in those that have this condition. We have also the single-fiber EMG that can be used in select patients where their diagnostics have been unrevealing, so they don't have the presence of autoantibodies or the repetitive nerve stimulation testing is normal. Single-fiber EMG can be 95+% sensitive, but it is less specific for a neuromuscular junction disorder such as myasthenia gravis. The interpretation of that test is something that needs to be considered in the context of the clinical presentation for a patient and their presence or absence of autoantibodies, for instance.

I also wanted to note that a smaller group of autoimmune myasthenia gravis patients have other antibodies besides the AChR autoantibodies. MuSK antibodies can be seen in somewhere between five to maybe up to 10% of individuals with generalized myasthenia gravis. Lrp4 antibodies can also be present in some of our autoimmune EMG patients, but the presence of that antibody is observed in maybe somewhere between two and 4% of all patients with myasthenia gravis. Again, the most common autoantibody here is the acetylcholine receptor binding autoantibodies. Looking at myasthenia gravis in general and focusing on, well, what is really the burden of disease? The way I think about myasthenia gravis is that it has a range of severities from mild to severe, and then we have those that have moderate disease. This is a study that was done by Cutter et al. that looked at a sample of registry patients and who self-reported disease burden based on the MG-ADL scale and also the MG-QoL scale.

The MG-ADL is a patient-reported clinical outcome measure that ranges from zero to 24 at max. The higher score represents a greater disease burden.

The mean MG-ADL score in this registry population was 6.2. And 6.2 represents moderate or greater disease burden based on patient self-reported clinical outcome measures. It's important to note that our patients do deal with a great disease burden if you take a registry sample. Similarly, the MG-QoL is a patient-reported quality of life outcome measure. It specifically addresses symptoms that affect our MG patients. Again, this ranges from zero to 60, and if you look at the self-reported scores here most patients in fact do have moderate or greater disease severity based on these scales. Again, the focus of this slide is to really communicate with the community that there are a number of patients that have continued ongoing active disease that is potentially not adequately managed at this time. Looking more so at the general pathophysiology. I noted before that this is an autoimmune condition. It's a T-cell dependent B-cell mediated autoimmune disorder via IgG autoantibodies. This slide represents where the acetylcholine receptor autoantibodies target the postsynaptic neuromuscular junction. There's three main ways that this disease can actually affect the neuromuscular junction.

We have number one, blocking antibodies that prevent the acetylcholine from actually getting to the acetylcholine receptor and hence causing muscle weakness. We have modulating antibodies that increase the internalization of the acetylcholine receptors, and so less receptors the less likely the neurotransmitter is able to engage with a postsynaptic junction and cause muscle contraction, hence resulting in muscle weakness. Then we have binding autoantibodies that can also activate complement, a very critical component of the immunopathophysiology here where there's binding of the complement, and then there is actually the formation of what's termed membrane attack complex that essentially pokes holes and destroys the surface of the motor end plate, again causing a reduction in the available receptors, again translating into muscle weakness. MuSK antibodies are IgG4, and they are not known to have any role in the complement system. They're more so akin to blocking antibodies. LRP4, the characterization of those is not clearly understood at this point in time. That's something that is an area of active research.

Switching gears a little bit in terms of FcRn and MG. This is an important slide to understand, well, what is it that we're doing? What is it that we're potentially targeting by the FcRn and understanding the IgGs? I noted this a little bit earlier that MuSK autoantibodies are IgG4. Whereas AChR autoantibodies, it's important to note that these are IgG1 and IgG3 subtype. But taking a step back, looking at the endogenous IgG binding to FcRn and reducing IgG from entering lysosomes, the way that the FcRn works is that it protects IgGs in that they bind to that particular receptor and they essentially get spit back out without being degraded. It increases the ability or allows for the IgGs to be recycled over time. This, as we talk about the targeting strategies for FcRn, what is it that they're doing? But if we were able to block the FcRn, what we would then do is reduce the recycling of endogenous IgG or specifically autoantibodies like the acetylcholine receptor antibodies, which are IgG. We essentially reduce the levels of not only IgG in total, but also pathogenic autoantibodies by targeting the FcRn receptor.

This is another way to look at this, but the end is the same. I think the concept here is to really understand that by targeting or antagonizing the FcRn, we're reducing the recycling, and hence that translates into lowering IgG and hence lowering pathogenic autoantibodies. Looking at the history of treatment, so these are reports that are summarized here, looking at the overall mortality of myasthenia gravis over the last century, essentially. Mortality was as high as 90% as reported around 1920. Mortality has declined over time as critical care has improved and just in general medical care has improved. The biggest, I think, step in terms of reducing mortality at least as I see it occurred somewhere between the mid-1960s into the 1970s. Why is that timeframe important? That is around the time where myasthenia gravis was recognized or characterized as being an autoimmune condition. Prior to that time, it was not clear why myasthenia gravis... What the underlying driver to myasthenia

gravis was. Prior to that time, treatments such as neostigmine or pyridostigmine were offered, but it was not clear that targeting the immune system would have any benefit.

Really getting into the 1970s immunosuppressive therapies started to be initiated. Things like corticosteroids and then later things like cyclosporine and cyclophosphamide, azathioprine. Then fast forwarding to present time over the last five to eight or so years, we have targeted treatment strategies that have emerged. The first targeted treatment strategy was eculizumab, which targeted C5 complements. Here we have the most recently FDA approved treatments. The way that I see these as falling into two main buckets, we have the neonatal FC receptor antagonist, and then we have the complement inhibitors. Under the FcRn antagonists, we have efgartigimod, which is intravenous. We have efgartigimod, which is the hyaluronidase, which is the subcutaneous formulation. Then we have rozanolixizumab. These are all FDA approved FcRn antagonists at this time. Then looking at the other bucket, the C5 complement inhibitors, we have eculizumab and ravulizumab, which are both intravenously administered medications. Then we have zilucoplan, which is the most recently C5 complement inhibitor therapy that we have approved

Our clinical pearls are as follows. We have FcRn prevents IgG degradation. Blocking or reducing FcRn activity increases IgG degradation. It's important to understand the role of FcRn, the role of FcRn antagonism and how FcRn antagonists help with lowering IgG and pathogenic autoantibodies. That's really the key in terms of understanding FcRn, FcRn antagonism, and its role in the treatment of antibody-positive myasthenia gravis.

Thank you again for your attention and participation in today's CME. Hopefully this is of value to your practice. Thank you again.