Transcript: Myasthenia Gravis and the Complement System: Pathophysiology

Welcome to this program, Myasthenia Gravis and the Complement System, Pathophysiology. I'm Professor James Howard, Chip Howard to many of you, Professor of Neurology, Medicine, and Allied Health at the University of North Carolina in Chapel Hill. These are my requisite disclosures. This educational program is funded through an unrestricted grant from UCB, an acknowledgement to Check Rare CE for their production.

Let's begin.

What is Myasthenia Gravis or MG for short? It's an autoantibody mediated B cell disorder dependent upon T cells and complement. Characteristically, there's fluctuating weakness in a variety of muscle groups. Typically, the eyelid, the muscles of ocular motility, but may also include those of speech and swallow as well as limbs.

Ocular weakness is the most common presentation in generalized MG, with limb and bulbar function occurring in about one third of patients as the presenting symptom as well. Its treatment is highly individualized and often includes off-label medications. Currently, there are five approved drugs by the USFDA. Eculizumab, the first in 2017, efgartigimod, ravulizumab, rozanolixizumab, and zilucoplan, most recently. The symptoms in the diagnosis of Myasthenia Gravis can be varied and difficult to make. Characteristically, there's fatigable muscle weakness, exertional muscle weakness that is made worse by activity, improved with rest, only to recur with a resumption of the activity.

As such, individuals may develop variable double vision, droopy eyelids, intermittent slurring of speech and intermittent weakness of their limbs. Hence, a long odyssey from a symptom onset to diagnosis. The diagnostic strategy is first and foremost, in exquisite neuromuscular clinical examination and history. This is supported by electrophysiology and serology. There are many protocols in terms of the algorithm which one uses to achieve that diagnosis. Often if it's not severe, individuals have serology performed, looking for antibodies, particularly to the acetylcholine receptor, which we find in about 85% of patients. If it's more urgent, in addition to serology, electrodiagnostic testing is performed.

Classically, repetitive nerve stimulation studies and more recently, in very selected centers, single-fiber EMG. In many institutions, these studies are performed simultaneously. With a confirmation of diagnosis, treatment is initiated, however, should serology be absent, then there are a couple of other antibodies that can be looked for. One is to muscle-specific kinase, MuSK, and the other is to Lrp4. These occur in much less frequency, about 8% for MuSK and probably 1% or less for Lrp4. Characteristically, if one can demonstrate a normal single fiber EMG in a clinically weak muscle, that is proof pudding, so to speak, that the weakness cannot be due to disorder of neuromuscular transmission.

Myasthenia Gravis is associated with burdens. There is burden of disease and there's burden of treatment and we'll speak about these as we go. When we talk about disease burden, talking about the impact on the psychosocial productive aspects of one's life, the Myasthenia Gravis activities of daily living score, an MG-specific outcome measure that has been well validated is shown here. And on the left, one sees that scores range from zero, normal, to fairly high, in the twenties, which is abnormal. In more than 50% of individuals in this single data cut of a Myasthenic registry demonstrated that the average score was 6.2. Highly significant disease impact on one's quality of life. To the right, we see an MG-specific quality of life index and one sees that there are broad responses and lower numbers reflect better quality of life. So despite the therapeutics that any of these individuals had received, substantial numbers of these individuals still have persistent impact on both their activities of daily living as well as their quality of life.

This graph reflects where we've been and where we are recently going. Back in the early 1900's, there was a near 100% mortality with Myasthenia Gravis. This was primarily due to respiratory failure, the advent of antibiotics, the advent of assisted ventilation, dramatically altered the slope in the course of Myasthenia with improvement. Clearly with antibiotics there is more than a 50% reduction in mortality and then over the last 50 years we have seen this slope start to level out become more asymptotic, as we've added a variety of new therapeutics to our treatment toolbox. The early sixties and the early seventies, it was thought that Myasthenia was an autoimmune disorder and drugs like ACTH and corticosteroids were used with clear improvement in the patient outcome. With a recognition that there was indeed an antibody directed to the acetylcholine receptor, and this occurred in the mid to late 1970's.

Then there was a switch in our philosophy to utilize things like azathioprine and cyclophosphamide and the cyclophilins, along with the advent and the use of plasma exchange in the mid-1970's. And as you can see over the course of time, we've added different immune suppressants all nonspecific in their mechanism to aid us in the treatment of this disease. And it was not until 2017 when the first targeted therapy and first FDA-approved therapy for Myasthenia Gravis came about, and that was eculizumab, a monoclonal antibody directed to C5, complement protein 5 in the complement cascade. And subsequent to that, additional complement inhibitors and another class of drugs called neonatal FC receptors or developed in clinical use at this time. Let's speak about the complement system, and if we go back to our medical school days, and much of it wasn't even known when I was in medical school in my training, it is one of the pathogenic mechanisms in ACHR positive myasthenia gravis.

There are three pathways that have entry into the complement cascade, if you will. One is the alternative pathway, the second is the lectin pathway, and the one we're most interested in is in the classical pathway, where antigen-antibody complexes initiate a complement response through the activation of C1. As the algorithm evolves or the cascade evolves through C3, ultimately to C5, which is where our latest targets are, C5 is cleaved into C5a and C5b through the enzyme C5 convertase. C5b then combines to C6, C7, C8, multiple copies of C9, to form a ring-like structure that attaches to the surface of a membrane. It literally drills holes through the membrane, leaks its contents, leading to the destruction of that tissue. And this was initially recognized in paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and in myasthenia gravis was recognized in the mid-1970's by Andrew Engel at the Mayo Clinic.

Antibodies to the acetylcholine receptor are of the subclasses, immunoglobulin subclasses of IgG1 and IgG3. And that becomes important because these two subclasses activate complement through C1qrs. And so the binding of antibody to the surface of the membrane of the acetylcholine receptor activates C1q and initiates the complement cascade. As I said, and as shown in this graph, the ultimate formation is the lytic structure, the membrane attack complex, now referred to the terminal complement complex, that drills holes and destroys the membrane tissue. However, there are other mechanisms involved in Myasthenia Gravis from a pathogenic perspective. Clearly antibody binds to the target, not directly to the binding site in most instances, but to some other epitope on the membrane surface, sterically hindering the ability of neurotransmitter to get to the binding site on the receptor. And there are two binding sites per receptor complex and both must be occupied by neurotransmitter for that ionic channel to open and allow flux of sodium to depolarize that membrane, leading to the activation of an actual potential that is then propagated down the cell surface.

In addition, binding of antibodies complex with each other, cross-link if you will, and accelerate a normal turnover process of receptor protein. Receptors are internalized, degraded and new receptors are popped to the surface every seven to 10 days. That's muscle dependent, that's species dependent. And the presence of antibody accelerates that process. So in these first two mechanisms, the net result is a loss of available receptors for depolarization, a reduction in receptor density, if you will, which then

leads to synaptic failure on the part of synaptic transmission. And then as already mentioned, the third mechanism is the activation of complement and the subsequent destruction of the tissue.

This slide here shows a little bit more of a closeup of what's occurring on. In the right, left-hand panel is a normal neuromuscular junction. One sees the classic post-junctional folds and on the crest of these folds are where the receptors lie. The leg-like structures, they're drawn in black, are the terminus of the nerve that releases acetylcholine. Then one sees to the right of that, the activation of complement destroying that end plate zone and it's only in that left part that we're demonstrating this to you, which results in additional loss of synaptic transmission. More clearly shown here is what's going on. And on the left panel A, I'm showing you the location of acetylcholine receptors directly below the nerve terminal on the surface of these post-junctional folds. Binding of antibody in panel B inhibits the ability of transmitter to get to these receptors as already mentioned, but more importantly, the activation of complement demonstrated by the large blue circles, which then results in this architectural destruction, if you will, by this membrane attack complex, terminal complement complex destruction of that post-junctional membrane.

There has been data over the last 10 years that suggests there is weak correlations in serum complement levels and what's called the QMG, Quantified Myasthenia Gravis score. This is a manual muscle testing outcome measure that includes limb strength, eye movements, eyelid movements, speech, swallow, and respiratory function. And while the correlation is not phenomenal, there was a suggestion back then that there was indeed complement attack that was playing a role and related to the severity of Myasthenia. More animal studies have been done than in humans and our therapeutics have leapfrogged the basic science we need to fully understand what's going on at the neuromuscular junction in complement inhibition, but we have some good ideas. In the left panel, you see an experimental model of Myasthenia Gravis, in which anti-complement protein 5 therapy was initiated and the score range is worse is greater, and is based on a clinical outcome measure.

And we see that those individuals, the wild type, as seen here in the open bars and those treated with complement inhibitors in the black bars, that there is clearly a better response in the clinical outcome over time when treated with complement inhibition. To the right, we're looking at immunocytochemistry on muscle in terms of experimental model EAMG in the top row, the wild type, in the bottom row, and then EAMG treated with a different complement inhibitor EV576. The first vertical column, looking at bungarotoxin, BTX, which binds irreplaceably to the acetylcholine receptor. To the right of that in green is looking at complement protein C9 and then a merged photograph of the two. And one sees that bungarotoxin, which localizes receptors, merges with that of C9. Essentially overlays the same territory against supporting the presence of complement at the neuromuscular junction playing its critical role. Other studies were done as well in experimental models with animals back in the mid-seventies, our laboratory as well, passive transfer models demonstrating that complement was needed to induce the experimental model of myasthenia gravis.