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Mechanisms of Neuromuscular Damage in Patients With Myasthenia Gravis

Announcer:
Welcome to ReachMD. This Medical Industry Feature titled, Mechanisms of Neuromuscular Damage in Patients with Myasthenia Gravis, is sponsored by Alexion Pharmaceuticals.

Dr. Gelfand:
Hello, my name is Dr. Erwin Gelfand. I'm a professor of pediatrics and immunology at National Jewish Health and the University of Colorado Medical School.

For more than three decades I've been interested in neuromuscular diseases, particularly those mediated by autoantibodies.

Myasthenia gravis is a prototypical autoantibody mediated disease, and one in which the complement activation is a mechanism involved in the disease.

So today we're going to review the pathophysiology of myasthenia gravis, the production of autoantibodies, and importantly the activation of the complement system by these anti-acetylcholine receptor antibodies.

We're going to begin with an overview of the pathophysiology of autoantibody-mediated myasthenia gravis. And central to the development of any autoantibody is a loss of immune tolerance and this begins in the thymus.

In the thymus, we negatively select autoreactive T cells. These autoreactive T cells can lead to the formation of autoantibodies, in this case targeting the acetylcholine receptor resulting in disruption of the neuromuscular junction and development of myasthenia gravis.

Autoreactive T cells, which develop as a consequence of failure of immune tolerance development leads to the differentiation of B cells into plasma cells that produce these autoantibodies, many of which are specific to the acetylcholine receptor.

The most common autoantibodies in myasthenia gravis are anti-acetylcholine receptors of the IgG class. Roughly 85% of individuals with myasthenia gravis have autoantibodies to the acetylcholine receptor. The vast majority of these autoantibodies target this receptor. A small percentage target the muscle-specific kinase. Others, an even lower percentage, target the low-density lipoprotein receptor-related protein 4 (LRP4). A small number may still target as yet unknown receptor proteins.

Important in the pathophysiology of the disease are the subclasses of IgG anti-autoantibodies that develop and are key determinants in the pathophysiology of the disease. Both IgG1 and IgG3 autoantibodies are important complement activating autoantibodies. And complement activation is a key pathway in the development of the disease.

So, if we think of the anti-acetylcholine receptor antibodies, primarily of the IgG1 or IgG3 class, they're able to activate the complement system of interest is the anti-muscle-specific kinase autoantibodies they're primarily of IgG4 class and therefore don't readily fix complement.

If we think of the mechanisms then, how do these autoantibodies lead to impaired neuromuscular transmission? There are three major pathways that we think about.

The first is functional blockade of the acetylcholine receptors where the autoantibody directly prevents the binding of acetylcholine to the acetylcholine receptor.

A second mechanism is antigenic modulation and it's common with autoantibodies or antibodies linking or being bound to a receptor,

crosslinking these receptors, and this leads to receptor internalization and degradation.

So in the case of acetylcholine, antibodies binding to the receptor, the receptors are internalized, degraded resulting in a smaller number of accessible acetylcholine receptors.

The third and important mechanism that we will focus on today is complement-mediated postsynaptic membrane destruction, which is caused by complement activation leading to the formation of the membrane attack complex (MAC) on the postsynaptic membrane.

Now you may be familiar with complement activation and MAC formation, for example in hemolytic anemia, where there's an autoantibody binding to a protein on the red cell activating complement leading to lysis of the red cell.

A similar mechanism occurs with complement activation of the neuromuscular junction.

Activation of MAC at the postsynaptic membrane leads to destruction and diminished number or function of acetylcholine receptors. This leads to reduction of the motor end plate potential leading to muscular weakness.

So we have complement activation, formation of MAC on the postsynaptic membrane leading to destruction. And we know that this leads to impaired end plate potential and the failure to generate sufficient muscle cell action potential leading to impaired muscular contraction.

So if we look at the complement system it's a series of many proteins that circulate in the serum. On one hand complement activation plays a major role in host defense as part of the innate immune system targeting for example and helping the phagocytosis of encapsulated bacteria such as pneumococcus or H influenza.

On the other hand, autoantibody mediated activation of the complement system, plays an important role in causing damage at the neuromuscular junction in anti-acetylcholine receptor antibody positive myasthenia gravis and its this activation of the cascade beginning with C1q RNS C3 and activation of the terminal components from C5 to C9 that forms the membrane attack complex on a cell surface

If we look at evidence for complement activation in myasthenia gravis, we can actually demonstrate deposition of C9 at the postsynaptic membrane leading to disruption at the neuromuscular junction.

So the complement system is a key element in the innate immune system, but in myasthenia gravis it plays an important role in the pathophysiology of the disease.

So we can summarize by saying that loss of immune tolerance is central to the development of myasthenia gravis, resulting in the production of autoantibodies that bind components of the neuromuscular junction.

The pathogenic autoantibodies are heterogeneous and are responsible for a number of pathogenic pathways. One, a functional blockade of the acetylcholine receptor preventing access of acetylcholine to the receptor. The second is antigenic modulation where we lead to internalization and degradation of the receptor resulting in fewer receptors at the membrane.

And the third and important mechanism, is complement activation from C1 to C9 formation of the membrane attack complex on the postsynaptic membrane leading to destruction at the neuromuscular junction resulting in impaired end plate potential and impaired muscular contraction.

Patients with myasthenia may have a spectrum of autoantibodies that bind to different sites on the acetylcholine receptor and this underlies the diversity likely of the symptoms across the entire patient population with myasthenia gravis.

In your patients with myasthenia gravis, the role of autoantibodies targeting the acetylcholine receptors are likely to play a major role in the pathogenesis of their disease. The mechanisms leading to myasthenia may be diverse and overlapping in your patients, but central to the disease are the autoantibodies targeting the acetylcholine receptor.

These autoantibodies, with the capacity to fix complement, leading to activation of the complement cascade and formation of the membrane attack complex at the neuromuscular junction may be a very important mechanism in the pathophysiology of your patient's disease.

Announcer:

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