Focus on Myasthenia Gravis and Neuromyelitis Optica Spectrum Disorder
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THE COMPLEMENT SYSTEM: Focus on Myasthenia Gravis and Neuromyelitis Optica Spectrum Disorder

Abstract:
As a first defense against pathogens, the complement system is an integral part of immunity; however, its dysregulation may result in inflammation and tissue damage characteristic of various neurological disorders. The actions of complement differ depending on the disease. Here we discuss two neurologic diseases with complement-mediated pathophysiology. Myasthenia gravis (MG) is a rare autoimmune disorder characterized by disability from weakness of the voluntary muscles and a potential for life-threatening neuromuscular respiratory failure. Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disorder of the central nervous system that has an unpredictable, relapsing course, which can lead to severe and cumulative disability, vision loss, and death resulting from neurogenic respiratory failure.

THE COMPLEMENT SYSTEM
The complement system is an integral part of innate immunity, forming a bridge between the adaptive and innate immune systems and serving as a first line of defense against pathogens. In addition to pathogens, this system is responsible for clearing debris from apoptosis and immune complexes. The complement cascade is tightly balanced to protect the host from any over- or under-activation of the system. Failure to regulate over amplification of the complement cascade, results in inflammation and tissue damage in many acute and chronic conditions.

The complement system pathways operate similarly to coagulation pathways, with a catalytic cascade of enzymatic events involving more than 30 soluble and cell surface-associated proteins and regulators (see Figure 1 on page 4). The complement cascade begins with recognition of the target, whether pathogen or debris, which triggers one of the three activation pathways: classical, lectin, or alternative. Regardless of which one is activated, all three pathways catalyze the formation of opsonins, anaphylatoxins, and chemoattractants, converging in the final cell-killing pathway with the formation of the membrane attack complex (MAC). The MAC creates pores
Complement plays a role in several neurological disorders, including Guillain-Barré syndrome, MG, NMOSD, multiple sclerosis, ischemic stroke, and Alzheimer’s disease. The actions of complement differ depending on the disease. This article focuses on the roles of complement in MG and NMOSD.

Myasthenia Gravis
MG can affect the ocular, bulbar, facial, limb, and most critically, respiratory muscles with varying degrees of severity. The estimated worldwide incidence rate of MG is 5.3 per million person-years and the prevalence rate is 77.7 per million persons. Between 15% and 20% of patients experience an acute exacerbation of MG, termed a “myasthenic crisis,” that leads to life-threatening respiratory failure and may be the initial
presentation of MG in about 20% of patients.

In about 85% of patients, MG is caused by the production of autoantibodies against the nicotinic acetylcholine receptor (AChR) of the neuromuscular junction (NMJ) of skeletal muscles, which drives complement activation and the formation of cytotoxic MAC at the NMJ. This MAC-driven cytotoxicity destroys the normal morphology at the NMJ, leading to loss of neuromuscular transmission.

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—Dr. Henry Kaminski

AChR and ultimately impairing neuromuscular transmission. However, it is important to appreciate that there is not a single antibody behind MG,” says Henry J. Kaminski, MD, Meta A. Neuman Professor and Chairman of the Department of Neurology at George Washington University School of Medicine and Health Sciences in Washington, DC, “but a large population of polyclonal antibodies, some pathogenic.”

Professor B. Paul Morgan, Director of the Systems Immunity University Research Institute (SIURI) at Cardiff University School of Medicine in Wales explains that antibody binding may result in NMJ loss through three main mechanisms: complement-mediated injury, cross-linking and internalization of adjacent AChRs, and blocking of the acetylcholine binding site. This NMJ damage, in turn, leads to the muscle fatigue that marks the disease, which is characterized by general weakness and disability.

Dr. Kaminski agrees that research with animal models of MG suggest that, rarely, some AChR antibodies may block neuromuscular transmission or can cross-link receptors and remove them from the cellular surface at a high rate without actually destroying the cellular membrane. Nonetheless, he says, “In [patients with MG who have AChR-specific antibodies], I think the overwhelming evidence is that complement-mediated damage to the neuromuscular junction is the primary mechanism of disease.”

The importance of complement-mediated NMJ damage does become clear in experimental animal MG (EAMG) studies, says Professor Linda L. Kusner, PhD, Associate Professor of Pharmacology and Physiology at George Washington University School of Medicine and Health Sciences. Dr. Kusner has conducted extensive research into the role of complement and its regulation in EAMG. She says, “When you limit complement regulators in EAMG-induced animals, you see a profound effect.”

**Neuromyelitis Optica Spectrum Disorder**

NMOSD is an inflammatory disorder of the central nervous system (CNS) marked by attacks of optic neuritis and transverse myelitis. NMOSD has an unpredictable, relapsing course that can lead to loss of vision and neurologic disability that is severe and cumulative, as well as death resulting from neurogenic respiratory failure.

The disease process in NMOSD is driven by aquaporin-4 (AQP4) specific IgG1 autoantibody binding to AQP4, which is expressed abundantly on astrocytes. This binding is thought to activate the complement cascade, triggering inflammation and the formation of MAC, leading to the damage and death of astrocytes. These events are followed by granulocyte infiltration, oligodendrocyte death, and, ultimately, neuronal cell death in the CNS and optic nerve.

In addition to MAC formation, says Alan S. Verkman, MD, PhD, Professor of Medicine and Physiology at the University of California, San Francisco, complement also contributes to the neurological damage of NMOSD through the release of anaphylatoxins C3a and C5a. There is also evidence for complement-independent pathogenesis mechanisms.

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— Dr Alan Verkman

“The accepted thinking is that the antibody forms in the periphery, enters the central nervous system, binds to AQP4 on astrocytes, then initiates a series of pathogenic events that ultimately cause oligodendrocyte damage and demyelination,” says Dr. Verkman. One event is classical complement pathway activation with terminal pathway generation of C5a and MAC, which together drive inflammatory processes that contribute to the pathology seen in NMOSD.

Another activation process, Dr. Verkman says, is antibody-dependent cell-mediated cytotoxicity with direct Fc interaction, cell binding, and damage to astrocytes. In addition, he says, AQP4-sensitized T cells may be involved in promoting blood-brain barrier permeability and, potentially, astrocyte damage.
There is also evidence that cerebrospinal fluid (CSF) levels of C5a are strongly linked with the severity of the acute attack, which correlates with enhanced lesions and the increment of Expanded Disability Status Scale (EDSS) score during relapse. Levels of CSF-soluble C5b-9 also correlate with disease severity, as defined by the EDSS score.

In addition, attack severity and measures of complement-mediated injury appear to be linked to AQP4 antibody-expressing cells, although there does not appear to be any association with NMOSD-IgG titer. The general thinking is that complement is of central importance for NMOSD damage, both in terms of the MAC complex causing astrocyte damage as well as in promoting the entry of neutrophils and eosinophils, says Dr. Verkman. “However, there is also evidence that the antibody itself as well as antibody-sensitized T-cells may be involved in the disease. So, realistically, it’s not possible with confidence to quantify the relative importance of complement versus noncomplement mechanisms.”

BRINGING PERSONALIZED MEDICINE TO PATIENTS IDENTIFIED BY SEROSTATUS

The role of complement in MG and NMOSD appears to differ based on the subset of disease. In MG, complement may not be involved in patients who are seronegative for AChR antibodies but seropositive for antibodies against muscle-specific kinase (MuSK) and lipoprotein-related protein 4 (LRP4). In fact, as Dr. Kaminski notes, “For seronegative subtypes of myasthenia…, which may make up as many as 5% of patients, we do not know the contribution of complement to the disease.” However, complement is involved in the disease pathogenesis of patients who are seropositive for AChR antibodies.

Likewise, in NMOSD, a study of a subgroup of AQP4-seropositive patients demonstrated increased serum C3, C4, CH50, and IgG levels ($P < .01$). A separate study found that CSF-C5a concentrations were increased significantly in those patients with multiple enhanced lesions on MRI compared with those with a single lesion or no enhanced lesions ($P < .001$).

“Being able to stratify within these diseases to select those patients who have the best evidence for ongoing complement activation . . . is the way to proceed,” says Dr. Morgan.

REFERENCES


