



# MYASTHENIA GRAVIS FOUNDATION OF AMERICA, INC.

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## **2009 Scientific Session of the Myasthenia Gravis Foundation**

Robert L. Ruff, MD, PhD

The annual scientific session of the Myasthenia Gravis Foundation of America (MGFA) was held on October 7, 2009 in San Diego, CA at the Hyatt Hotel. The session was organized by Drs. Matthew N. Meriggioli and Ted M. Burns. For the first time the scientific session was held in conjunction with annual meeting of AANEM – a profession society of physicians who focus on neuromuscular medicine and electromyography (EMG). This session had an audience of more than 150 clinicians. Members of National Board of the MGFA also attended.

There were seven presentations from around the world. Many of the presentations related to clinical treatment studies and evaluations of instruments used to follow how patients with MG are responding to treatment. Brief reviews of the role of the immune system in MG and how neuromuscular transmission is altered in MG are provided to enhance understanding of the presentations.

### **The Role of the Immune System in MG**

MG is an auto-immune disease involving the site of communication between nerve and muscle, the neuromuscular junction. In MG, the body's immune system malfunctions and attacks specific proteins at the neuromuscular junction. The most common target of the autoimmune attack is the acetylcholine receptor (AChR). Lymphocytes (one type of "white blood cells" in your blood) are a class of immune cells that are divided into two large groups: Thymus-derived lymphocytes (T-cells) and B-cell lymphocytes. T-cells are involved in cell-mediated immune responses in which cells attack immune targets. B-cells are responsible for producing antibodies that target specific parts of proteins called epitopes. Cells that process and present potential immune targets (also called antigens) to the immune system are called antigen presenting cells (APCs). T-cells can modulate the activity of B-cells. MG is T-cell dependent antibody mediated disease in which T-cells modulate the activity of B-cells that produce antibodies that are directed primarily against the AChR and secondarily against other sites (epitopes) at the neuromuscular junction. The antibodies binding to the AChR trigger a complement-mediated cellular immune attack against the neuromuscular junction. Complement is an immune-mediated chemical cascade that destroys proteins and injures or destroys cells. Cytokines are proteins produced by the body that modulate the immune system. Interleukins (IL) are a class of cytokines that are secreted by lymphocytes. IL regulate the activities of different classes of immune system cells. Interferons (IFN) are a different class of immune regulatory proteins. DAF is a recently recognized factor that can alter the immune response seen in different tissues. Tolerance refers to a process in which an immune response to a specific agent is suppressed. One mechanism of tolerance is for T-cells to become insensitive to a disease-inciting antigen.

## **Background for presentation on Seronegative MG**

Antibodies are proteins produced by the immune system that bind to and target substances for destruction by the immune system. Antibodies are designed to target foreign substances such as bacteria. In patients with MG, antibody production is disturbed and antibodies are produced against self (i.e., antibodies target normal body proteins). The most common and the major pathogenic autoantibodies in MG are directed against the AChR on skeletal muscle. Patients with antibodies against the AChR are considered to have seropositive MG. A fraction of patients with MG, about 20% of patients with MG, do not have anti-AChR antibodies. The MG in these patients is referred to as seronegative. Many people with seronegative MG have autoantibodies against other components at the neuromuscular junction. The autoantibodies cause additional problems for patients with MG. Serum from patients with seronegative MG can be injected into animals and cause a MG-like condition. Immunoglobulins from seronegative patients bind to muscle cells, but not to AChR. The most common target for antibodies in patients with seronegative MG appears to be a muscle protein called MuSK (muscle-specific receptor tyrosine kinase). MuSK is a muscle-specific protein that regulates how AChRs are incorporated into the neuromuscular junction. About 30-50% of seronegative MG patients have antibodies directed against MuSK. The seronegative patients who have antibodies against MuSK are sometimes referred to in studies as MuSK+ or MuSK-MG. For comparison, patients with antibodies against the AChR are sometimes referred to as having AChR-MG.

## **Neuromuscular Transmission**

The place where a nerve fiber connects to a muscle fiber is called the neuromuscular junction (NMJ). At the NMJ the nerve terminal releases a chemical, acetylcholine (ACh), which interacts with a specific receptor protein on the muscle side of the NMJ. This receptor is called the acetylcholine receptor (AChR). The interaction of ACh with the AChR causes the AChR to open a pore that allows an ionic current to flow across the endplate membrane. The flow of current through the AChRs produces a local change in the transmembrane potential. The local change in membrane potential referred to as the endplate potential (EPP) triggers sodium channels in the region of the endplate to open. The opening of the sodium channels (NaC) triggers a electrical pulse, called an action potential (AP) that propagates from the NMJ along the surface of the membrane to both tendon ends of the muscle fiber. The rapid propagation of the action potential over the muscle surface triggers the release of calcium from storage sites within the muscle fiber. The transient increase in calcium concentration within the muscle fiber is what triggers the muscle fiber to contract. Diagrammatically the sequence can be depicted as:

Nerve releases ACh -> activation of AChR -> EPP -> activation of NaC -> AP -> contraction

MG is a disease of the NMJ. In MG antibodies attack the AChRs resulting in reduced action of the AChRs which manifests with a reduced EPP. Weakness occurs when the EPP becomes too small to trigger an AP. MG treatment is directed towards stopping the antibody attack on AChRs or enhancing the size of the EPP. Many folks with MG take mestinon (pyridostigmine). This medication works by enhancing the concentration of ACh at the NMJ. A great deal of work has been done that demonstrates loss of AChRs and loss of endplate membrane as a result of the immune attack on the NMJ.

## Presentations

### **How Myasthenia Gravis Alters the Safety Factor for Neuromuscular Transmission**

Authors: Robert L. Ruff, M.D., Ph.D. (Dept. Veterans Affairs Medical Center, Case Western Reserve Univ. Cleveland, OH) Vanda A. Lennon, M.D., Ph.D. (Depts. Immunology, Neurology & Lab Med/Pathology, Mayo Clinic, Rochester, MN)

#### **Support: Dept Veterans Affairs Research Service**

This presentation focused on the impact of NaCs at the NMJ on neuromuscular transmission and the alteration of neuromuscular transmission in MG. The safety factor can be described as the ratio of the EPP to the amount of depolarization needed to trigger an AP.

Safety factor =  $EPP/E_{AP}$ , where  $E_{AP}$  is amount of depolarization at the NMJ that is needed to trigger an AP.

The safety factor reflects the concentration of AChR – the more AChRs the larger the EPP. The safety factor also reflects the concentration of NaCs in the region of the NMJ. There is an enhanced concentration of NaCs on the muscle side of the NMJ – the concentration is more than 20-fold higher at the NMJ compared to the rest of the muscle fiber. According to this presentation, the normal safety factor is about 3. About 40% of the safety factor can be attributed to the high concentration of NaCs at the NMJ.

This presentation described findings from 5 patients with moderate to severe MG. For these people with MG the safety factor was reduced from about 3 to 1.1. Measurements from muscle fibers from these patients showed that their EPPs were smaller and their values for  $E_{AP}$  were larger. The larger  $E_{AP}$  reflected about a 40% reduction in the concentration of NaCs near the NMJ. In these folks with MG, the concentrations of NaCs away from the endplate were normal. An explanation of the local loss of NaCs at the NMJ is that due to the autoimmune attack at the NMJ, there is damage to membrane that contains NaCs as well as membrane that contains AChRs. The AChRs and NaCs are located close to each other at the NMJ, thus it is reasonable to imagine that the damage to NMJ membrane leads to loss of NaCs as well as AChRs. The immune attack is directed at the AChRs and the NaCs are lost in a sense as “innocent bystanders.” At the present time, this observation does not suggest alteration in the treatment of MG because there are no therapies that enhance NaC numbers or function. The questions raised from the audience included comments from Drs. Sanders and Vincent that because the observations were made on muscle fibers from people with moderate to severe MG, that the observations may not apply to folks with mild MG because people with mild MG may not have sufficient damage to NMJ membrane to cause loss of NaCs. Dr. Linda Kusner also pointed out that the structure of some muscle fibers present in muscles that move the eyes function differently than other muscle fibers. A subset of eye muscle fibers do not have many NaCs so that loss of NaCs may not be important for some eye muscle fibers.

### **Withdrawal of Complement Inhibition May Lead to Recurrence of EAMG-induced Weakness**

Authors: Linda L. Kusner, Ph.D, Jessica A Montresor-Lopez, Michael J. Richards, Jindrich Soltys, Henry J. Kaminski – Saint Louis University, St. Louis MO

This study focused on how one could modulate the severity of MG that induced rats by injecting them with AChRs from an electric fish (Torpedo). After the rats are sensitized to the

AChRs from the fish, the animals generate antibodies to their own AChRs. The rats develop weakness. The weakness occurs in association with an immune attack directed to the NMJ. The rats have loss of AChRs at the NMJ that occurs in parallel to an activation of the immune system and deposition of complement on the NMJ membrane. This excellent laboratory at St. Louis Univ. has been working with a company that is developing an inhibitor of a component of complement, called C5. This factor is derived from the saliva of tics. For the tic, the complement inhibitor allows the tic to remain attached to the skin without an inflammatory response. The prevention of an inflammatory reaction allows the tic to remain attached to the skin without the host developing inflammation (which would cause pain or itching) so the host is not aware that the tic is there. The data presented showed that inhibiting complement resulted in a reduction in the severity of EAMG. The rats recovered strength in association with inhibition of complement. The inhibition of complement resulted in a reduction of deposition of complement at the NMJ, reduction of damage to the NMJ and improved function of the muscle fibers. The improvements occurred even though the concentration of antibody (antibody titre) did not change. This study pointed out that the severity of MG may not directly parallel the concentration of antibodies. In addition, it is possible to alter the severity of disease by disrupting the immune reaction to triggered by antibodies without eliminating the antibodies. The company is working on developing a form of complement inhibition that can be used in people. As the company succeeds in maturing the experimental inhibition of complement to a clinically useful product, the MG research group in St. Louis is prepared to work with other MG clinical research groups to develop clinical trials that would enable patients to benefit from the strategy of inhibiting complement. While this work is not yet ready for clinical trials, thanks to the continued work of the St. Louis group, this work continues to move forward.

### **Clinical and Serological Characteristics of Late-onset Myasthenia Gravis in the UK**

Authors: Angela Vincent, M Isabel Leite, Peregrine Green, John Newsom-Davis (died in 2007), David Hilton-Jones - Department of Clinical Neurology, Oxford England  
Supported by The Sir Halley Stewart Trust, the MG Association and the Muscular Dystrophy Campaign of Great Britain.

This was an epidemiological report of decades of research and clinical treatment in the United Kingdom. There were several interesting points made by the presentation. They reported that the most common form of MG (seropositive MG - that type of MG that is associated with antibodies to the AChR) tends to appear in people in their twenties to thirties and there is a larger group of people who develop MG when they are older than 50. There were more women than men in the group of people with earlier onset MG. In contrast, the men dominated the group of older onset-MG. There also appears to be an increase in the incidence of late-onset in the past 20 years. The presenters pointed out that it was not clear if the increased incidence of late-onset MG reflected a true increase in this type of MG, improved recognition of MG due to advances in diagnostic techniques such as antibody testing and improved electromyographic (EMG) techniques, or that there are more folks with late-onset MG because people in general are living longer. Another observation was that the incidence of MG declines among people who are older than 80. The decline in the rate of development of MG among people who are older than 80 years may represent a real decline in the appearance of MG as people age beyond 80 years of age. Alternatively, the decrease may reflect that MG is not as often recognized in older people because other health issues take precedence. In contrast, seronegative MG is more common in women and tends to appear when women are younger than 50. This presentation triggered a

spirited discussion. Drs. Sanders, Howard and others felt that they also observe a large cohort of patients who develop MG when they are older and that this group had more men than women. They also felt that the onset of MG may be under recognized in people over 80.

### **Do the New Cell-based Assays Help in the Diagnosis of Bulbar Myasthenia?**

Marina Elena Farrugia Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland (UK). Angela Vincent - Department of Clinical Neurology, Oxford England

Bulbar MG refers to a form of MG in which the manifestations are primarily caused by weakness of throat and facial muscles. The manifestations include facial weakness, difficulty chewing, swallowing and speaking. People with bulbar MG may have sufficient difficulty swallowing that they aspirate and can die due to pneumonia from aspiration. This form of MG may be difficult to recognize if many of the usual features of MG such as fatiguable eye lid weakness are not present. What also complicates recognition is that the usual assays for antibodies to AChR may not be abnormal. Diagnosis with EMG may also not detect the changes that indicate MG because the involved muscles in the throat are difficult to study with EMG. The authors presented 3 cases of bulbar MG. Features common to the 3 patients presented included: prominent atrophy of facial muscles, weakness and atrophy of the tongue and relative sparing of eye movements. The test that demonstrated the presence of antibodies directed toward the NMJ was a cell-based assay. The cell based assay used cell grown in tissue culture that express AChRs or that express MuSK. The test involves demonstrating an interaction between the serum from a patient with the cells expressing AChR or expressing MuSK. This test is more complicated to perform than the typical tests used to antibody assays and it is currently not commercially available. Dr. Vincent is beginning to work with a company to try to make this assay commercially available. Her aim is to make the test available to more people.

### **Distribution of Test Item Scores for the MG-QOL-15 for Patients with Ocular MG, Generalized MG and Patients in Remission.**

Authors: Carrie K. Grouse, Ted M. Burns, Donald Sanders\*, Mark R. Conaway and the MG Composite and MG-QOL-15 Study Group

University of Virginia, Charlottesville, VA and \*Duke University Medical Center, Durham, NC Note that Carrie Grouse is in training and her the funding for her travel to present at this meeting was supported by the John Newsom-Davis Travel Fund of the MGFA that was funded by contributions from the MSAB.

In order to follow how patients are doing from visit to visit and how folks respond to treatment it is very valuable to have instruments that can be used to provide quantitative indices of how people are doing. The MG-QOL-15 was one of several instruments that Dr. Burns has developed in conjunction with Dr. Sanders. The MG-QOL-15 is an easy to administer and easy to complete one page form that takes a few minutes to complete. The MG-QOL-15 measures how people with MG perceive the quality of their lives. This particular presentation provided data on the validity of this instrument. The data indicated that the MG-QOL-15 had concurrent validity which means that the information it provides agrees with other widely used measures of Quality of Life and that the findings from MG-QOL-15 agrees with information that is obtained from the MG-Manual Muscle Test instrument (designed to measure muscle strength), the MG-ADL scale (which measures how well people with MG are able to carry out activities of daily life such as dressing, eating, shopping) and the MG-Composite Score which is a 10 question instrument that evaluates the severity of MG (Dr. Burns presented the MG Composite Scale at

last years MG Scientific Session). This presentation provided data on the construct validity of the MG-QOL-15. Construct validity indicates that the instrument measures what you intend it to measure. Ms. Grouse presented data on the responses of groups of patients with MG who had ocular MG, generalized active MG and people with MG who were in clinical remission. In the discussion, Dr. Gil Wolfe stated that the MG-QOL-15 was a very valuable tools for clinicians because it provided an easy and inexpensive way to follow how patients are doing and that when it was used it could reduce the number of followup visits that patients had to travel to and miss work to attend.

### **The Test-Retest Reliability of the MG Composite and MG QOL-15**

**Authors: Ted M. Burns, MD, (University of Virginia) and Mark Conaway (University of Virginia)**

This was a study that included MG treatment sites in 9 countries, with several sites in the US. The MG Composite is designed to provide a measure of the severity of MG for a patient. At last years Scientific Session, Dr. Burns presented data on validity of the MG Composite , the prior talk addressed the validity of the MG QOL-15. Another important measure of the usefulness of an instrument is how reliable that instrument is. The consistency of the scores among different evaluators for the MG Composite was excellent. The test-retest reliability was 98%. The abilities of the MG Composite and the MG QOL-15 to detect changes in a patients condition (sensitivity) were very good at better that 85% for both tests. The liklihood that changes in the MG Composite and MG-QOL-15 scores were due to changes in a patient's MG as opposed to other changes (specificity) was also very good being greater than 85% for both tests. This presentation was important not only for the data that was presented, but also because so many MG treatment Centers around the world participated in this study and are using the MG Composite and MG QOL-15 instruments. Dr. Burns and others who developed these instruments are members of the MSAB of the MGFA. Therefore, this presentation was an example of how the MGFA is working to advance the diagnosis and treatment of MG.

### **Analysis of Health Care Costs in a Large Cohort of Patients with Myasthenia Gravis.**

**Authors: Donald Sanders\*, Lakevia M. Hall\*\*, Ronald E. Peeples\*\*, Jason G Cooper\*\*, Donald H Taylor\*\*, and Andrew C. Krueger\*\***

\* Duke University Medical Center, Durham NC

\*\* Accordant – a CVS Caremark Company

This was a poster showing collected by Accordant on the cost of care of MG for people with MG. The average cost of MG care was about \$24,000 per year, with \$14,000 being the charges for office and hospital visits, laboratory and other medical costs. The annual cost for medications was about \$10,000. The costs were higher for people with MG who were under 44 years of age. Dr. Sanders thought that the higher health care costs for younger people reflected the greater liklihood of surgical interventoins such as thymectomy. This type of information is important for advocacy organization such as MGFA to have. The information in this presentaton can also be used to follow the costs associated with specific interventions and medications.