



MYASTHENIA GRAVIS

FOUNDATION OF AMERICA, INC.

2010 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 6, 2010 in Quebec, Canada at the Quebec Convention Center. The session was organized by Drs. Ted M. Burns and Linda Kusner. For the second time the scientific session was held in conjunction with the annual meeting of AANEM – a professional society of physicians who focus on neuromuscular medicine and electromyography (EMG). This session had an audience of more than 150 clinicians. Members of the National Board of the MGFA also attended.

There were seven platform presentations (where a person speaks to the audience) and six poster presentations from around the world. Many of the presentations were related to clinical treatment studies and evaluations of instruments used to follow how patients with MG are responding to treatment.

Inmaculada B. Aban, MD
University of Alabama Birmingham

Incidence of MG based on screening data of MGTX Study

This study is really not an evaluation of incidence, but a description of the patients seen in the MG Thymectomy (MGTX) trial. The MGTX is an international study funded by NIH. This study aims to study the benefits of TX, the patients who benefit most, and the relative benefit compared to prednisone treatment. The target enrollment is 150 patients and currently is at 100 patients. Top recruitment is from US, Argentina, British Columbia, Chile and South Africa. Screening data is a canvassing of all MG patients within a center. Out of 6,110 patients screened, only 194 were eligible and 100 enrolled. US screened 2,800 patients and enrolled 27. The major reason for ineligibility has been MGFA classification has to be I or IV. Not able to make a true incidence because they do not have a very accurate value of the population that the patients come from and do not know how many were not diagnosed. Women under 50 years old were more common among the enrollees and men older than 50 were more common among the study subjects. The median age of onset of MG for women was 36 years of age and 52 years of age for men. Other sources of bias are referral bias – not everyone with MG has been referred for evaluation.

Hans D. Katzberg, MD, MSc, FRCP
University of Toronto

Relationship between the Quantitative Myasthenia Gravis Scale (QMGS) and Clinical, Immunological and Electrophysiological Markers of Disease Status in Myasthenia Gravis

There are several scores that evaluate the severity of MG. The QMGS measures strength in the limbs, mouth and throat muscles, how long it takes for weakness to develop, and the severity of the weakness. This score is very useful when trying to determine if an intervention has improved muscle function. There is a good correlation between QMGS and the more general MGFA clinical classification scale, which evaluates the overall severity of disease. Therefore the muscle performance is a good measure of overall state of the disease. The AChR antibody titres (amount of antibodies present in the blood) do not correlate well with QMGS scores – i.e. AChR antibody titres

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are a marker for disease presence, not disease severity. There were strong correlations with overall EMG and particularly with the EMG measure of “jitter”. Jitter is a measure of the variability of the neuromuscular junction function among individual muscle fibers that are innervated by a single nerve fiber.

Robert Ruff, M.D., Ph.D

Cleveland VA Medical Center, Case Western Reserve University

How Myasthenia Gravis Alters the Safety Factor for Neuromuscular Transmission

This presentation addresses what goes wrong with the connection (synapse) between nerve and muscle in people with MG. The normal process is for the nerve to release a transmitter acetylcholine (ACh) that travels a very short distance (much less than 1/100th of the width of a hair) to interact with acetylcholine receptors (AChR) on the muscle, called the endplate. The rapid interaction between ACh and AChRs produces an electrical signal called the Endplate Potential (EPP) that does not travel very far, just a fraction of an inch. The EPP works basically as a fuse to stimulate another class of channels, sodium channels. The sodium channels are concentrated at the endplate, which makes it easier for the EPP to trigger the endplate sodium channels. The endplate sodium channels generate a large electrical signal called the action potential which rapidly travels along the surface of a muscle fiber. The action potential traveling along the muscle surface triggers the entire muscle fiber to contract. The traditional understanding of MG is that loss or impaired function of AChRs compromises the connection between nerve and muscle by making the EPP too small to trigger the sodium channels to fire. With MG the endplate is damaged and both AChRs and sodium channels are lost. This study showed that loss of sodium channels at the endplate also contributes to impaired neuromuscular transmission by making it harder to trigger an action potential. Hence in MG there are two problems: 1) the EPP is too small and 2) there are too few sodium channels so that it is harder to generate an action potential.

Jennifer Brealy, Joel Auger

University of British Columbia

Detection of Muscle Specific Tyrosine Kinase Antibodies in Myasthenia Gravis: Comparison of an ELISA and Radioimmunoprecipitation

This presentation addressed the sensitivity of different techniques to diagnose the presence of antibodies in MG. About 15% of people with MG do not have antibodies to AChR (antibody negative MG). The most frequently recognized antibody present in patients with antibody negative MG are antibodies to MuSK. MuSK is a protein present on the muscle endplate that modulates the function and number of AChRs. On the muscle side of the neuromuscular junction, the connection between MuSK and AChRs is that a protein called Agrin activates MuSK and MuSK connects to AChRs via Rapsyn. This group is working to develop a more sensitive and accurate test compared to what is currently used. A technique that is being worked on involves using the target protein such as MuSK to a surface and then measure with a light technique the amount of binding of antibodies from patients serum to the surface that is impregnated with the specific target protein. This technique could be applied to the detection of antibodies to a number of different proteins.

JT Guptill, MD – he is a recipient of a fellowship from the MGFA and American Academy of Neurology

Duke University

Outcomes in a large cohort of MuSK antibody positive patients

The group at Duke University probably studies one of the largest populations of patients with MuSK positive MG. This group is studying different strategies for treating MuSK positive MG and for this

study, they combined findings with clinicians at Catholic University in Rome. A common treatment approach is to start with Mestinon or similar drugs. If this is not adequate then prednisone up to 60 mg per day is used and the prednisone is tapered when the patient improves. If additional treatment is needed then an immunosuppressant treatment such as azathiaprine, cytoxan or cell cept is used. For patients who are refractory to the prior interventions a white cell monoclonal antibody treatment, Retuximab is used. IVIG or plasma exchange is used for disease flares. Patients tended to not improve with Mestinon or similar agents. Patients improved after using prednisone and an immunosuppressant. Most patients received 2 or more immunosuppressant medications (prednisone plus another agent). A small number received Retuximab and all improved with this Rx. After treatment about 65% of patients were in remission or had minimal manifestations.

Robin Conwit, MD

Update on NINDS clinical trials

NIH, National Institute for Neurological Diseases and Stroke

Dr. Conwit updated the group on the ongoing clinical trials relevant to MG. There is a Common Data Elements initiative that works to have all clinical trials, including those related to MG, have common data elements so that the findings from different studies can be compared. More information on this initiative is available at www.commondataelements.ninds.nih.gov. The NINDS is working to have programs that promising treatments are able to move through the process of animal studies to studies of toxicity in humans (phase I) to studies that establish a dosing schedule to studies of efficacy of a treatment (phase III). The aim is to enable treatment to speed the process of moving through the different phases of study needed for an agent to receive FDA approval. One of the major problems of clinical studies in the US is low enrollment rates, in part because people object to being “guinea pigs.” **Unless people with a specific disease such as MG are willing to participate in clinical trials, the process of finding improved treatments and a cure for MG will not move forward.** NIH will fund additional studies on MG once the MGTX trial is completed.

Henry Kaminski

Chair of the MSAB and Chair of Neurology at Saint Louis University

Announcement of MGFA RFA

The MGFA has coupled with the American Academy of Neurology to fund fellows who are neurologists early in their careers to study MG. Dr. Guptill was funded by this mechanism. There is a new initiative to support high impact research programs for MG. An important aspect of this program is that researchers need to leverage the MGFA funding with support from other agencies such as NIH or the Muscular Dystrophy Association. This program is aimed at using the funding available from the MGFA as seed money to develop programs that can be supported by larger agencies. This is a start up program. The aim of this funding is to encourage individuals to devote their energies to improving the lives of people with MG.

Posters

Ted Burns, MD

The MG-QOL-15 for following the health-related quality of life of patients with myasthenia gravis. University of Virginia

This presentation dealt with an instrument to measure the quality of life of patients with MG. The MG-QOL-15 is a tool that quantifies how patients with MG rate their quality of life. The quality of life considers how MG is impacting an individual's ability to function day to day and how satisfied patients are with their current life situation as it is impacted by MG. This is an important measure that is being increasingly used to determine how an intervention affects MG in terms of how much a patient feels that the MG impacts their lives. This tool was developed by Dr. Burns in conjunction with Dr. Donald

Sanders at Duke. Several other clinical researchers such as Gil Wolfe at University of Texas use the MG-QOL-15 to measure the quality of life in people with MG.

Mazen Dimachkie

Rituximab in Refractory Generalized Myasthenia Gravis

University of Kansas (also M. Pasnoor, A.I. McVey, L Herbelin and R.J. Barohn)

University of Texas – San Antonio (C.E. Jackson)

This poster presented information about a new treatment for MG, using monoclonal antibodies against a specific subset of white cells. The monoclonal antibody treatment is called Rituximab. Rituximab specifically targets a B-cell lymphocytes with a CD20 marker. This treatment is used to treat individuals with B-cell non-Hodgkin lymphoma and rheumatoid arthritis. There is not a lot of available information on using Rituximab for MG. This treatment is presently used for individuals with MG who are not responding well to other more traditional treatments. This study reported the results from five patients with MG. Rituximab was safe and all of the patients improved for a six month period after receiving two treatments of Rituximab. This work provides justification for a larger randomized study of Rituximab in MG.

Maria E. Farrugia

The OBFR is a useful tool to assess bulbar function in MG

Southern General Hospital, Glasgow Scotland (C. Carmichael)

University of Virginia (H.D. Harie and Ted Burns)

About 30% of people with MG have involvement of the face or throat (bulbar MG). Impaired ability to speak, swallow and breath causes major problems for people with MG. The oculobulbar facial respiratory (OBFR) score is a tool that assesses facial, throat and breathing function in people with MG. This scale was validated and found to be reproducible among different raters. This is a valuable tool for assessing changes in the swallowing, speaking, facial muscle control, and breathing function in patients with MG who are receiving an intervention or to track how people are changing over time.

James T Guptill – recipient of MGFA/American Academy of Neurology MG Fellowship

The Cost of Misdiagnosis of Myasthenia Gravis

Duke University (D. Sanders and J. Massey)

Greensboro NC (A. Krueger, A. Marana and A. Adams)

This study really examined the medical/pharmaceutical costs associated with having MG. Costs went up with age. For people over 65 years of age, the average overall cost for MG care was \$13,281 and the cost of medications alone was \$6,620 per year. Although most people with MG received Mestinon or a similar agent (>77%) and only about 11% received IVIG, more than 67% of overall pharmacy costs were due to IVIG. In this age, it is important to keep track of medical costs. This study also emphasizes the importance of having a correct diagnosis of MG.

Srikanth Muppidi

MG-ADL: Is it still a relevant outcome measure?

University of Texas (Gil Wolfe, M.R. Conaway)

University of Virginia (Ted Burns)

The MG activities of daily living scale (MG-ADL) is a simple instrument to measure how people with MG are able to carry out activities of daily living such as eating, dressing, bathing, and house work. This study showed that the MG-ADL is a useful tool for measuring how well individuals with MG are

able to complete daily life skills. It also provides an indication of how much assistance is needed. This is a useful tool to measure the benefits of interventions given to people with MG. This tool will be useful in MG clinical trials.

Zahra Pakzad

**Increasing incidence of Anti-AChR Seropositive Myasthenia Gravis in British Columbia, Canada
University of British Columbia (T. Aziz, J. Oger)**

This group has a unique situation of seeing many people with MG in British Columbia. This report found that during the period of 1984 to 2008, 1,243 individuals were identified with AChR antibodies (648 women, 587 men and 8 uncertain). An interesting finding was the average annual incidence of new AChR antibody seropositivity for the period of 13.2/million/year. The incidence increased dramatically for people over 65 years of age from 21.4/million (1984-1988 average) to 52.9/million (2004-2008 average). The reason for the increase was not clear, but it was not because the testing technique had improved. I spoke with Dr. Oger at the poster and he indicated that an appreciable fraction of the older individuals with elevated AChR antibody titers did not have clinical MG nor had minimal manifestations of MG at the time that the antibodies initially were found to be positive. It may be that the MG does not manifest until an individual has antibodies present for several years. This kind of study provides insight into potential changes in frequency of development of MG and a way to more precisely understand the link between the appearance of antibodies and the development of clinically apparent MG.