The M.G. Rally

Newsletter of the Carolinas Chapter, Myasthenia Gravis Foundation of America, Inc.
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Carolinas Chapter to meet in Greenville, NC

Date: Saturday, March 6
Time: 2:30 to 4 PM
Speaker: James F. Howard, Jr., M.D.
James F. Howard Distinguished Professor of Neuromuscular Disease
Chief, Neuromuscular Disorders Section
Department of Neurology
University of North Carolina-Chapel Hill

Myasthenia Gravis, the New Frontier

Location:
Sheppard Memorial Library
Meeting Room A
530 Evans Street
Greenville, North Carolina
252-329-4580

Directions to Sheppard Memorial Library

Coming into Greenville from the west on US 264 proceed to the intersection of 264 and Memorial Drive (US 13 / NC11) (There will be a McDonalds on the left) Right on Memorial for approximately 3/4 mile to intersection of Memorial and Dickerson Ave. This intersection is the first traffic signal beyond (less than 1/4 mile) crossing railroad tracks. Turn left onto Dickerson for about 1 mile (through 2 traffic lights - the second light is at rail crossing) proceed straight through to the third light at Reade Circle. Immediately beyond this light turn right into library parking lot.

Coming into Greenville from the north on NC 33 (Rocky Mount & Tarboro areas) NC 33 intersects with Memorial Drive (US 13 / NC11). There is traffic light and Memorial Drive is a 4 lane divided highway. Proceed through the light (across the highway) to the next light just beyond the rail tracks. This is the intersection of 33 and Green Street. Turn right onto Green Street and proceed to downtown Greenville. Green Street crosses the Tar River via a (new) two lane "one way" bridge. The Street continues as one way into town. Approximately 1/2 mile past the river it becomes Reade Circle intersects with Dickerson Avenue. The Library parking lot will be on the left.

Coming into Greenville from the East on 264 (Washington NC areas). Highway 264 intersects with Greenville Blvd at a light. Greenville is the first 4-lane highway after leaving US 17 in Washington (approx 18 miles from Washington). Turn left on Greenville Blvd, approximately 2 miles it will intersect with 10th Street. There is a car dealership (Hastings Ford) on the right and a Burger King across the intersection on the right. Right on 10th for approximately 1 1/2 miles to Evans Street. Right on Evans for two blocks to the intersection of Evans & Reade Circle. Turn left onto Reade; the parking lot will be on the right.

Directions continued on page 5

We are extremely pleased to have Dr. "Chip" Howard as our featured speaker at our upcoming meeting in Greenville, NC. Dr. Howard serves as the current Chairperson of MGFA's National Medical/Scientific Advisory Board. He is well known throughout the United States and abroad as an expert MG clinician and researcher.
The annual scientific session of the Myasthenia Gravis Foundation of America (MGFA) was held on October 18, 2003 in San Francisco, California at the Marriott Hotel. Drs. Henry Kaminski and P. Christadoss organized the session.

MGFA supports two types of research and educational grants. The Henry R. Viets Fellowship is targeted to healthcare professionals in training. The Viets award provides monies to expose healthcare professionals to clinical or basic science research in MG via a short-term research project. The Osserman/Sosin/McClure fellowships provide support for post-doctoral training in basic science or clinical research in MG. The Viets & Osserman/Sosin/McClure fellowships are designed to get promising healthcare professionals interested in MG so that these individuals will direct their future energies toward elucidating the cause, treatment and eventually the cure for MG. The meeting demonstrated the success of the Viets and Osserman awards. Two Osserman fellows, two Viets fellows and their mentors presented research supported by MGFA. In the descriptions below of the presentations, the Osserman and Viets presenters are identified in boldface print.

There were ten presentations from around the world. Many of the presentations related to immunology. A brief review of the role of the immune system in MG is provided to enhance understanding of these 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. The lymphocyte class of immune cells 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 epitopes at the neuromuscular junction. The antibodies binding to the AChR trigger 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.

Congenital Myasthenic Syndrome Due to Calcium Channel Mutations

JiJun Wan - Osserman/Sosin/McClure Fellow
R.W. Baloh, J. Jen, UCLA, Los Angeles, CA

Congenital disorders of neuromuscular transmission, also called congenital myasthenias, are diseases that can resemble MG or Lambert-Eaton Myasthenic Syndrome (LEMS). These disorders usually manifest in childhood or infancy and are genetic rather than immune disorders. They are usually caused by mutations involving important components of the neuromuscular junction. The calcium channel that is responsible for transmitter release at the neuromuscular junction is also present in the central nervous system. That calcium channel is targeted by antibodies in Lambert-Eaton myasthenic syndrome (LEMS). The antibodies do not enter the brain well so that people with LEMS do not have prominent problems with brain function. The study examined people who have mutations of the nerve terminal/brain calcium channel to determine if they had problems with neuromuscular transmission. The prominent clinical feature these people had was clumsiness, also called ataxia. However, when questioned and examined these people also had fluctuating weakness and EMG findings that resembled LEMS. The neuromuscular impairment was likely overlooked in the past due to the severity of the ataxia. This work is important because treatments that are effective in improving neuromuscular transmission in LEMS may help people with nerve terminal calcium channel mutations.

Induction of Myasthenia Gravis and Thyroiditis in HLA transgenic mice by immunization with human acetylcholine receptor and thyroglobulin pathogenic peptide

Evangelos Karras (Viets fellow in 2002)
P. Lymberi and P Christadoss, University of Texas, Galveston

Experimental autoimmune myasthenia gravis (EAMG) is an experimental model of clinical MG. There are two important classes of lymphocytes, T-cell and B-cells. T-cell are involved in cellular immunity, where immune cells attack a target. B-cells produce antibodies that attack markers, called epitopes, on cells and other targets of immune attack. T-cells interact with B-cells and are responsible for activating or suppressing antibody production by B-cells. In EAMG, T-cells play a critical role in directing production of antibodies against the acetylcholine receptor (AChR). Autoimmune thyroiditis is a disease with similarities to MG and EAMG. Therefore, characteristics of altered immune responses that are common to both conditions may be particularly important. This study suggested that in EAMG in mice and in the mouse model of autoimmune thyroiditis that variations on a component on the surface of T-cells, called DR-3 can influence disease severity. This study is important because
The Fc-gamma receptor is located on the surface of antigen presenting cells (APCs). The researchers studied mice with knockouts of complement pathway elements (genetically engineered mice that lacked specific parts of the complement system). These mice can be induced to make anti-AChR Abs, but do not show disease because there is no damage at the NMJ. These mice did not form the membrane attack complex (MAC) of complement. Different variants of the Fcgamma receptor can up- or down-regulate EAMG due to changing the amount of complement activation by reducing antibody production. Deficiency of Fcgamma receptor type III results in an attenuated immune response with reduced antibody production, which prevents the induction of EAMG. This study is important because surface markers on cells are potential targets of biopharmaceutical agents. Hence, this study could serve as the stimulus to develop drugs that target specific elements of the immune system that are important in MG.

Pre-clinical trial of myasthenia gravis with IL-1 receptor antagonist

P. Christadoss, H. Yang, X. Yu, B. Scott, E. Tuzun (2003 Osserman/Sosin/McClure Fellow), University of Texas, Galveston

Pro-inflammatory cytokines (IL-6, TNF, IL-1 and IL-18) enhance the intensity of auto-immune diseases such as MG. Other cytokines such as IL-4 attenuate the immune response and reduce the severity of experimentally induced auto-immune diseases such as EAMG (experimental auto-immune myasthenia gravis). Work in this laboratory and elsewhere showed that genetically engineered mice that lacked pro-inflammatory cytokines (KO's) are resistant to EAMG. In contrast KO's of IL-4 are more sensitive to EAMG. These finding suggest that targeting pro-inflammatory cytokines may alter human MG. The researchers tested two strategies: 1) administering receptors of the pro-inflammatory cytokines to block the cytokines and 2) using an agent that bound to the receptors for pro-inflammatory cytokines to block the action of those cytokines. Treatment with soluble TNF receptor suppresses EAMG and in an initial clinical trial it showed promise with 6/9 patients showing clinical improvement. Treating B6 mice with IL-1 receptor antagonist (IL-1Ra) during induction of EAMG made them resistant to development of EAMG. Stopping IL-1Ra resulted in appearance of clinical disease. IL-1Ra treatment produced a slight reduction in the production of other pro-inflammatory cytokines. Giving IL-1Ra in rats who had already developed EAMG produced two results. Most mice had improved clinical performance scores,
lower AChR antibody titers and increased amount of AChR at the NMJ. IL-1Ra blocks action of IL-1 and this in turn reduces the level of other inflammatory cytokines, reduction of antibody formation. Suppression of ongoing EAMG is a major finding. Perhaps IL-1Ra and soluble TNF treatments can be combined. Question raised by Dr. Lennon was about side effects. The response from Dr. Christados was that in the on-going TNF trial the treatment was well tolerated. Dr. Drachman questioned how agents directed against cytokines could be effective in clinical MG because clinical MG has much less active inflammation compared with EAMG. Dr. Lennon suggested that the cytokines play a role in maintaining antibody production, which could be how cytokine-directed agents could be clinically useful.

Anti-ryanodine receptor antibodies and FK506 in myasthenia gravis

M. Takamori, N. Kawaguchi, M. Motomura, K. Otsuka, Neurological Center, Kanazawa-Nishi Hospital, Ekinishihonmachi, Kanazawa Japan

The researchers studied sera from 10 patients with MG associated with thymoma and 10 MG patients without thymoma for antibodies against the ryanodine receptor (anti-RyR1-Abs). Patients with thymoma were more likely to have anti-RyR1-Abs. The antibodies were predominantly directed toward the C-terminus of the RyR. In vitro studies showed that the anti-RyR1-Abs reduced muscle force production. This part of the study suggests that more severe muscle weakness in patients with MG who have a thymoma may be due in part to anti-RyR1-Abs.

The authors also studied an experimental drug, FK506, which acts on T-cells. FK506 acts with the IL-2 receptor and enhances cell death of activated T-cells. In an initial clinical trial treatment with FK506 was well tolerated and led to reduction in clinical symptoms. The results of the trial with FK506 are encouraging, but need to be substantiated by a larger study.

The Prevalence of Depression in Myasthenia Gravis

Suzanne E. Biehn (Viets recipient), K.R. Robertson, K.M. Johnson, J.F. Howard, University of North Carolina, Chapel Hill

Literature has conflicting information on MG and depression in part because many of the symptoms used to assay for depression are features of MG, for example fatigue. The overlap of the symptoms of depression and MG may in part explain why people with MG are often initially misdiagnosed with a psychiatric diagnosis. The researchers studied people with MG and treated at the UNC MG clinics. They compared 35 patients with MG and 13 patients with other neuromuscular diseases. The MG and non-MG neuromuscular disease patients had higher prevalence of depression compared to the general population, but similar to people with non-muscular chronic diseases such as diabetes and rheumatoid arthritis. The findings suggest that the elevated incidence of depression was primarily due to consequences of the disease and not specific effects of anti-AChR antibodies. Dr. Drachman pointed out that this presentation also argues against a "myasthenic personality disorder". Dr. Ruff suggested that people might have more prominent depression when MG first presents and advances and that depression becomes less severe when the MG has stabilized. Drs. Drachman and Newsom-Davis also suggested that steroid treatment can lead to depression and may contribute to depression in patients with MG.

Characterization of the Quantitative Myasthenia Gravis Score

Richard S. Bedlack, D. Simel, H. Bosworth and D.B. Sanders, Duke University Medical Center, Durham, NC

The Quantitative Myasthenia Gravis Score is increasingly used in MG clinical trials. Prior studies evaluated how reliable the QMG score were when determined by different examiners and how valid it was (how well it actually reflected disease severity). The QMG was reliable and valid. This study evaluated how well the QMG score responded to changes in disease severity. Determining the responsiveness of the QMG scoring system is important to know if the QMG is to be used to ascertain improvements in clinical trials. They also studied how well the QMG remained valid over time. They evaluated 53 MG patients from the Duke MG clinic. QMG was very responsive to changes in clinical condition. The QMG closely followed two other measures of change in clinical condition. The QMG was well suited to clinical trials.

Update on Plans for a Multinational Thymectomy Trial in Nonthymomatous MG Patients on Prednisone

G.I. Wolfe, University of Texas Southwestern Medical Center, Dallas, H.J. Kaminski (Cleveland, OH, US), A. Jaretzki, (NYC, NY, US), A. Swan (UK) and J. Newsom-Davis (Oxford, UK)

This is an important, but difficult study to carry out. The study group has not yet received funding from the National Institutes of Health. They are responding to suggestions from NIH and will resubmit a revised grant application.

PLEASE READ THIS IMPORTANT DISCLAIMER: The articles in this newsletter are intended for information and education only. They are not a substitute for professional medical advice or a medical examination. If you have questions about your health care or the health care of another, always seek the advice of your physician or other qualified health professional before making any adjustments to your medical therapy.
News You Can Use...

Plan to Attend
2004 MGFA Annual Meeting

When: May 6-8, 2004
Where: Marriott Airport Hotel
       Bloomington, MN (next to the Mall of America)

Plan now to attend this informative and fun meeting where you will meet many others interested in myasthenia gravis, including patients, caregivers and professionals. Hear speakers who are leaders in the field talk about issues of concern to you.

Registration materials will be available soon.

If you are interested in receiving registration materials, please contact
Carolinias Chapter, MGFA
506 East Forest Hills Boulevard
Durham, NC 27707
or email carolinasmgfa@nc.rr.com

Mestinon® Savings Coupons Released by Valeant Pharmaceuticals

Valeant Pharmaceuticals offers a Mestinon® Savings Certificate. Patients can use one certificate per prescription, and Valeant will provide AS MANY certificates as needed. In addition to offering a $20.00 (maximum) patient rebate for each Mestinon® 60 mg tablet prescription, Valeant will also make a donation of $2.00 to the Myasthenia Gravis Foundation of America, Inc. for each certificate redeemed. The program will run through April 30, 2004. Patients can download the certificate via the internet at www.Mestinon.com. Patients can also write to the Carolinas Chapter office to request a certificate.

Directions to Sheppard Memorial Library continued,

Coming into Greenville from the East on NC 33. NC 33 becomes 10th Street. Follow 10th to Evans Street. Right on Evans for 2 blocks to the intersection of Evans & Reade Circle. Turn left onto Reade. Parking lot will be on the right.

Coming into Greenville from the South on NC 11 (Kinston area). NC 11 becomes Memorial Drive. Memorial intersects with Greenville Blvd & there will be a Cracker Barrel Restaurant on the left. Proceed through this intersection, staying on Memorial, for approximately 2 miles / 3 lights. The 3rd light is the intersection of Memorial & Dickerson. Turn right onto Dickerson for about 1 mile (through 2 traffic lights - the second light is at a rail crossing). Proceed straight through to the third light at Reade Circle. Immediately beyond this light, turn right into the library parking lot.

Many thanks to Tom Wilbourne for his diligence in composing these very complete directions!

Our love and concern is extended to the family of Shirley Johnson who recently passed away. Shirley was a Carolinas Chapter leader for a number of years.

"Double Vision, Scrambled Voice: Clinical Presentations of Myasthenia Gravis" has won two awards, the CINE Golden Eagle Award and The Communicator Award, for excellence in video production and for the directness of communicating its message. Congratulations to Sandra Jacobi, the creator of this excellent video. Copies of the video may be purchased from the National Office (800-541-5454).

How Can I Help?

Thank you for your support of MGFA. Your continued financial support is necessary to conduct vital research and to provide patient education and support. Please consider volunteering your time to support activities of the Carolinas Chapter. Donations to the Carolinas Chapter are tax deductible to the extent provided by law. MGFA is a 501C3 nonprofit agency under the IRS Code.
CHANGE OF CONTACT INFORMATION

Please be certain to inform us of any change in your address so we can keep our mailing list up to date. If you want to be removed from our mailing list, we would appreciate knowing that too. The chapter pays a substantial fee for returned mail. Please print all information clearly and return to:

Carolinias Chapter MGFA
506 East Forest Hills Boulevard, Durham, NC 27707

THANKS!

Last Name ___________________________ First Name ___________________________

Street ___________________________ City _____________ State _____ ZIP _______

Telephone (_____ ) ____________ Email ______________________________________

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