The Scientific Session of the Medical/Scientific Advisory Board (M/SAB) was held at the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting in Honolulu, Hawaii on October 28, 2015. The Meeting Hall was packed with more than 200 attendees. There were 11 platform presentations (formal talks) and 5 posters (note that in my summary below I discuss one of the posters from China with the initial keynote talk from China).

The location was particularly convenient to attendees from Asia. Keynote talks were given by MG clinicians from China (Dr. W-B Liu and colleagues) and Japan (Dr. Utsugisawa). The session co-chairs, Drs. Jeffrey Guptill and Michael Hehir are rising stars in the MG research community and the MGFA M/SAB. Dr. Guptill received a coveted MGFA/American Academy of Neurology Fellowship for MG research. The abstracts of the talks will be published in the professional journal Muscle & Nerve. What is presented below are the talks including the titles, authors, the locations of the work and brief comments about why I felt the talks were important.

Background information for people who are new to MG – The most common forms of MG are autoimmune disorders in which a person’s body produces antibodies against specific proteins in the region where nerves that control muscles contact the muscle fibers. The contact regions are called neuromuscular junctions (NMJs). The most prevalent class of antibodies is directed against the acetylcholine receptor (AChR). A smaller number of people have MG that is caused by antibodies that are directed against a protein called muscle specific kinase (MUSK). MG can also result from genetic alteration (mutations) of specific components of the NMJ. Genetic forms of MG often manifest early in life and are referred to as congenital MG or congenital disorders of neuromuscular transmission.

1st Keynote Presentation

This meeting provided a forum for the leaders in MG care in China to present to an audience from the US. This talk was broken into three parts.

- A cohort study on the quality of life of Myasthenia Gravis patients using short form-36 health survey - L Qiu (Guangzhou, China), W Fang (Brookville, NY), C-Y Ou, J Deng, Y-F Luo, P Chen, H Feng, Y Li, R Mo, W-B Liu (Guangzhou, China)

- Epidemiology and Clinical Characteristics of Myasthenia Gravis patients in China
  W-B Liu (Guangzhou, China), W Fang (Brookville, NY), Y Li, R Mo, X Huang (Guangzhou, China)

- Clinical features of Juvenile Myasthenia Gravis in southern China -- X Huang, H Huang (Guangzhou, China), W Fang (Brookville, NY), L Qiu, J Deng, Y-F Luo, Y Li, H Feng, Z Chen, W-B Liu (Guangzhou, China)

- Summary –The speakers from China were from the Dept. of Neurology at Sun Yat-Sen University in Guanzhou, China. This University Hospital was established by an American missionary, Dr. Parker. Data for the presentations were obtained from 17 hospitals in Guangzhou (southern western China), 4 hospitals in Harbin (northern western China) and two healthcare insurance systems in Guangzhou. I was surprised that in spite of China being a major producer of laptop and desktop computers, electronic medical records are not widely used in China. Medical information is stored in paper records.

The first two parts of the presentation dealt with the Chinese application of MGFA quality of life measures and the prevalence of MG. The third was a study of clinical characteristics of juvenile MG (JMG) in China. It was pleasing that the clinical standards for assessing MG developed by the M/SAB of the MGFA are used in China as standards. The patterns of treatment closely follow US care with good results. Crisis survival rate was reported to be 99%.

Prevalence was based upon data obtained from Northwest and Southwest China. The prevalence of MG for hospitalized patients varied from about 40.5/100,000 in southern China compared with 12.8 in northern China. The large difference between the prevalence in northern and southern China may partially reflect a true difference in the MG prevalence between the north and south of western China. Alternatively, other factors likely contribute including differences in MG recognition, differences in access to health care and cultural differences affecting people who seek medical care. Among all hospitalized patients the prevalence was 10.93/100,000. The overall prevalence figures are similar to those reported in other parts of the world. The MGFA reports a prevalence in the US as 12 to 20/100,000 (see also Phillips LH (M/SAB member), Ann NY Acad Sci 998:407-12, 2003). Studies in Europe indicate prevalence values of 8-15/100,000 (Cooper et al. J Autoimmune 33:197-207, 2009). The Chinese physicians did not see a large gender difference in MG prevalence.

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Prevalence per 100,000 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>12 to 20</td>
</tr>
<tr>
<td>Europe</td>
<td>8 to 15</td>
</tr>
<tr>
<td>Southwestern China</td>
<td>40.5</td>
</tr>
<tr>
<td>Northwestern China</td>
<td>12.8</td>
</tr>
</tbody>
</table>

It was pleasing that the clinical standards for assessing MG developed by the M/SAB of the MGFA are used in China as standards.
The third presentation addressed juvenile MG (JMG) in China. Chinese patients had a fraction of patients presenting with Juvenile onset MG about 50% compared to about 15% in US. Patients come for assessment every 2 weeks. In part due to the child policy, parents are very attentive to children and bring them for care when they are sick. About half of patients had MG onset at 0-6 years of age. 48.8% were AChR antibody negative and all of the AChR Ab negative cases were also MUSK negative. 2% of cases of JMG were familial MG. More than 90% of JMG had ocular onset. The number of Chinese patients with JMG seen per year increased to 12,000 in 2014, with about 100-200 new patients per year. A relatively high percent >40 percent of new patients treated by this group had JMG. These presentations were important because they opened communication about MG between China and the rest of the world. The MGFA is already connected to sister organizations in Europe, South America, Japan and Australia and now we have opened communications with China.

<table>
<thead>
<tr>
<th>Juvenile MG in China</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients with Juvenile MG</td>
<td>50% (Note in the U.S. it's 15%)</td>
</tr>
<tr>
<td>Number of patients seen per year</td>
<td>12,000</td>
</tr>
<tr>
<td>Age of MG Onset</td>
<td>Approximately 50% are 0-6 years of age</td>
</tr>
<tr>
<td>Presentation</td>
<td>90% had Occular onset</td>
</tr>
<tr>
<td>AChR antibody negative</td>
<td>48%</td>
</tr>
<tr>
<td>AChR negative cases also MUSK negative</td>
<td>100%</td>
</tr>
</tbody>
</table>

2nd Keynote Presentation

An Example of treatment based on new Japanese clinical guidelines for MG: what should we target? -- Kimiaki Utsugisawa, Hanamaki General Hospital, Hanamaki, Japan (colleagues in Nagasaki, Sendai, and Tokyo, Japan)

**Background** – Dr. Utsugisawa is a distinguished MG physician in Japan. He adopted the MG QOL (quality of life) instrument developed by members of the M/SAB of the MGFA especially Drs. Ted Burns and Don Sanders for use in Japan (Masuda and Utsugisawa et al. Muscle Nerve 46: 166–173, 2012). He also led studies of the utility of calcineurin inhibitors in the treatment of MG(Utsugisawa, Clinical and Experimental Neuroimmunology 6 (2):195–200, 2015). Calcineurin inhibitors are a class of agents including imuran, cyclosporine, and a drug developed in Japan, tacrilimus. The study of the calcineurin inhibitor tacrilimus found, for elderly patients and patients with severe MG, that tacrilimus needed to be combined with prednisone for best clinical outcomes.

The current presentation suggested a new treatment strategy based on using prednisone and calcineurin inhibitors, particularly tacrilimus to treat patients who had generalized autoimmune MG. The suggestion was to use calcineurin inhibitors combined with prednisone, but to aim for a lower peak dose of prednisone than previously aimed for, to achieve initial clinical stabilization and then to taper the dose of prednisone to a dose of 10 mg per day or less as tolerated by the patient. Dr. Utsugisawa suggested the flares of MG should be treated with plasma exchange or IVIG in preference to increasing the prednisone dosing. The treatment strategy described by Dr. Utsugisawa will be evaluated in Japan and the results will likely be reported in a future meeting. This presentation is important because it examines another approach to treating MG that could be explored in the US. In the US tacrilimus is not heavily used, but other calcineurin inhibitors are used, particularly imuran and to a lesser extent cyclosporine. An interesting aspect of the Japanese approach is to use lower doses of prednisone in order to avoid several unwanted side effects of prednisone such as osteoporosis, skin fragility and muscle wasting. If lower dose prednisone is effective in Japan, this strategy may be considered in the US.

Background for the 3rd and 4th platform presentations addressing myasthenic syndrome aka Lambert-Eaton Myasthenic Syndrome (LEMS) – LEMS is a disorder of the neuromuscular junction caused by insufficient release of acetylcholine (ACh) from the nerve terminal. The result is that the muscle AChRs are incompletely stimulated producing weakness. Treatment is directed toward enhancing the release of ACh.

**Results From The Dapper Study: Inpatient Double-Blind Placebo-Controlled Withdrawal Study of 3, 4-Diaminopyridine Base (3,4-Dap) in Subjects with Lambert-Eaton Myasthenic Syndrome (LEMS).**

DB Sanders, VC Juel (Durham, NC), Y Harati (Houston, Texas), AG Smith (Salt Lake City, UT), A Peltier (Nashville, TN), T Marburger (Portland, Oregon), J-S Lou (Fargo, ND), RM Pascuzzi (Indianapolis, IN), DP Richman (Davis, CA), T Xie (Somerset, NJ), LR Jacobus, KL Aleš, DP Jacobus (Princeton, NJ), and The DAPPER Study Team

The 3rd talk focused on the efficacy of a drug 3,4 DAP used to treat LEMS and some forms of genetic or congenital MG. At the present time, Jacobus pharmaceutical company (JPC) has been providing 3,4 DAP on a compassionate use basis free to physicians to treat patients with LEMS. In order to be able to continue to supply 3,4 DAP, JPC wants to be able to obtain compensation to enable it to produce enough medication to meet the anticipated need. Therefore, JPC sponsored this study as a step to obtain licensure to produce the agent for clinical use treating LEMS. The primary inclusion criterion was that patients with LEMS had to have a large response to 3,4 DAP. In the study subjects were hospitalized to determine that symptoms worsened after withdrawal of DAP. Subjects were randomized to taper to placebo or continue DAP. Clinical measures assessed strength changes. Patients in the taper to placebo group had deterioration in motor function and recovered when DAP was restored. More people in the placebo group needed rescue than the subjects who maintained their DAP. The study will be used to obtain licensure for JPC to provide 3,4 DAP for patients with LEMS.
Effect of 3,4-diaminopyridine and its acetylated metabolite at the murine neuromuscular junction
RA Maselli, F Ng, DC Lee (Davis, CA)

The 4th talk looked at the effect on 3,4 DAP on NMJ and also looked at primary metabolite (3-Ac) of the agent. The drug enhances the release of ACh by increasing the entry of Ca2+ into the nerve terminal. The experimenter simulated the low ACh release of LEMS by increasing the concentration of Mg2+ in the bathing solution. Mg2+ competes with Ca2+ . 3,4 DAP produced a marked increase in the electrical response of the muscle membrane, 3-Ac had no effect. 3,4 DAP did not appear to increase the resting level of Ca2+ inside the nerve terminal suggesting that 3,4 DAP should not induce Ca2+ associated nerve terminal degeneration.

Rituximab In Resistant Myasthenia Gravis
D Anderson, Z Siddiqi (Edmonton, Canada)

The 5th presentation evaluated the utility of a monoclonal antibody Rituximab for treating the 15-20% of MG patients who did not respond to traditional treatment protocols. Rituximab targets CD20 B-cells. Half of patients 6/12 were MUSK MG. Peak response to Rituximab was about 4-6 months after a single dose. The benefits of Rituximab were to reduce the average daily prednisone dose by 15 mg/day and the need for PLEX or IVIG dropped about 4-fold. Some patients needed repeat infusions of Rituximab. During Q&A session, the folks from China indicated that in their patients Rituximab was not effective. Perhaps reflecting that Rituximab is better for MUSK positive MG, which was more common in the subjects in this study than in the patients described by the Chinese MG care providers.

Effect of Therapeutic Plasma Exchange on Immunoglobulins
JT Guptill, VC Juel, JM Massey, AC Anderson, JS Yi (Durham, NC), M Chopra, JF Howard Jr (Chapel Hill, NC)

Talk #6 focused on the action of plasma exchange (PLEX). The specific issue was how much does PLEX stimulate immunoglobulin (Ig) production and elevate Ig levels. They studied 10 patients, who were mostly older. The median age was 73 yrs. Most patients were grade III or higher (moderately severe). PLEX produced 70% drop in all classes of Ig. PLEX cut AChR binding levels by about 60-70%. Ig drop was most at 1.5 wks and recovered about halfway by 3 weeks. The researchers did not see an overshoot in Ig levels and specifically not in AChR antibody levels.

NT-1654 Attenuates the Clinical, Neurophysiologic and Pathologic Severity of Experimental Autoimmune Myasthenia Gravis (EAMG) in Lewis Rats
Z Li (Phoenix, AZ), S Hettwer, A Maeder (Schlieren, Switzerland), K Wood, F-D Shi, Q Liu, S Ladha (Phoenix, AZ)

Talk #7 dealt with a new compound, NT-1654, for treating MG that was being evaluated in an experimental animal model of MG (EAMG). The hoped for effect of NT-1654 is improvement of the repair process to enhance recovery after immune attack of the NMJ. NT-1654 can be used in conjunction with treatments that reduce immune attack of the NMJ. NT-1654 is a recombinant fragment of murine agrin that retains activity to promote clustering of AChRs. This compound is resistant to the normal breakdown of agrin. Rats with EAMG were treated with two different doses of NT-1654. Two NT-1654 treated groups had performance that was about halfway between untreated EAMG and control rats without EAMG. NT-1654 improved the presence of AChR clusters at the NMJ. Muscle fiber size was also improved to close to normal. NT-1654 treatment also improved the presence of MUSK, an important component of the NMJ.

To me the Scientific Sessions of the M/SAB and the International Conferences on Myasthenia Gravis, both of which are sponsored by the MGFA, are the most important international meetings that are devoted to MG. – Robert Ruff, MD, PhD, Chairman, Medical/Scientific Advisory Board

and the need for PLEX or IVIG dropped about 4-fold. Some patients needed repeat infusions of Rituximab. During Q&A session, the folks from China indicated that in their patients Rituximab was not effective. Perhaps reflecting that Rituximab is better for MUSK positive MG, which was more common in the subjects in this study than in the patients described by the Chinese MG care providers.

Myasthenia Gravis Following Nivolumab and Pembrolizumab/Ipilimumab Therapy
AC Guidon, W David (Boston, MA)

The 9th talk described rare cases of MG that developed following immunotherapy for cancer. The proposed mechanism is that the immunotherapy alters the immune system of patients with cancer to enhance the ability of a person to fight a cancer by having the immune system attack the cancer. An unfortunate side effect of the aggressive therapy is that the altered immune system can begin to attack non-cancer cells leading to autoimmune diseases such as MG. Patients with cancer treatment induced MG can respond to pyridostigmine and also to prednisone.

A Pilot Trial to Assess the Feasibility and Efficacy of Subcutaneous Immunoglobulin in Patients with Myasthenia Gravis Exacerbation – Preliminary Results
ZA Siddiqi, A Mallon, D Blackmore (Edmonton, Alberta Canada)

The 10th presentation dealt with an issue of healthcare delivery in remote rural areas. The western provinces of Canada from Alberta west to the middle of British Columbia are sparsely populated. A similar situation exists in the US from the Dakotas west to western Washington. These areas of the US and Canada are thinly occupied with few physicians, fewer specialists and widely spread medical centers. A serious problem is how to provide medical treatment to people who live hundreds of miles from medical centers. This presentation discussed a pilot study to provide immunoglobulin treatment to remotely located patients. The solution was to try providing immunoglobulin (Ig) by subcutaneous injection (subQ). A major advantage of subQ IG is that it removes venous access
issues. The challenges are that the volume that needs to be administered is about 1liter (more than a quart). So the subQ Ig needs to be given over several days and using multiple sites. The patients were instructed to give themselves or to have others give them daily injections of subQ Ig. The subQ Ig treatment was effective and represents an innovative approach to treating people with MG who live in remote areas.

Open Label study of subcutaneous immunoglobulin (SCIg) in Myasthenia Gravis: Study Design and Progress Update

MM Dimachkie (Kansas City, KS), T Levine (Phoenix, AZ), J Trivedi (Dallas, Texas), V Bril (Toronto, ON), NJ Silvestri (Buffalo, NY), D Saperstein (Phoenix, AZ), S Nations (Dallas, TX), H Katzberg (Toronto, ON), GI Wolfe (Buffalo, NY), M Glenn, M Pasnoor, J Statland, AL McVey, G Rico, L Herbelin, P Miller, A Harrington, A Abuzinadah, RJ Barohn (Kansas City, KS)

The 11th talk is related to the 10th talk. This presentation described a study of subQ Ig treatment for patients in the US and Canada. The multisite study has been approved and just started with 2 patients enrolled.

Posters

Six posters dealt with clinical and research aspects of MG. [A “poster” presents the research project and results in a large poster like display. The researcher represents his work in person but does so in conversation with viewers, who drop by in a hall likely to be filled with posters and presenters.] Why would someone elect to present as a poster rather than to deliver a talk? The exchange between the presenter and interested colleagues is limited for platform presentation by the limited time the speaker has. Posters provide a means for researchers to discuss in detail the nature of their work with interested colleagues. Posters provide an excellent means for presenters to throw new ideas to the audience and get detailed feedback. Posters are also a good venue for presenters to discuss how to proceed with a line of study. People who are developing a new line of study will present posters in order to get detailed feedback from colleagues. I thought that the posters were excellent. I discuss the posters in their order in the scientific session handout. I already discussed one poster from China that addressed using quality of life measures developed in the US for patients in China.

MuSK induced experimental autoimmune Myasthenia Gravis is anti-MuSK IgG1 independent

M Küçükerden, R Huda (Galveston, TX), E Tuzun (Istanbul, Turkey), RT Strait, FD Finkelman (Cincinnati, OH), N Trakas, S Tzartos (Athens, Greece), P Christadoss (Galveston, TX)

This poster dealt with an animal model of muscle specific tyrosine kinase (MuSK or MUSK)-antibody positive MG. In this form of MG, antibodies are directed against MuSK, an NMJ protein that is involved in organizing AChRs in the NMJ. Such models are critical for researchers to evaluate the utility of possible treatment strategies for MuSK MG. This poster examined the character of the antibodies

Hope, Well-being, Coping, and Quality of Life in Adults with Myasthenia Gravis

WJ Koopman, N LeBlanc (London, Canada), S Fowler (New Brunswick, NJ), D Hulley, MW Nicolle (London, Canada)

Wilma Koopman is an MG nurse who has devoted her professional life to addressing the needs of people with MG. Wilma is a former member of the MGFA Board of Directors. She is an active member of the MGFA Nurses Advisory Board. This poster addressed the importance of a person’s mood on their perceived quality of life and on their ability to cope with life challenges. This poster demonstrated that hope and an optimistic outlook can alter the lives of people with MG for the better.

Super resolution microscopy analysis of NMJ active zones in adult and aged mice

H Nishimune (Kansas City, MO), S Mori (Tokyo, Japan), Y Badawi (Kansas City, MO), K Shigemoto (Tokyo, Japan)

This poster presented fascinating images of how the NMJ changes with age. The study focused on the region of the nerve terminal where ACh is released from nerve endings to stimulate the AChRs on the muscle membrane. Ion channels that conduct calcium ions (Ca2+) play a critical role in the release of ACh from nerve terminals. With age the distribution and character of the Ca2+ channels change. The importance of the changes in the distribution of Ca2+ channels is a topic for future research. The work in this poster was a cooperative program between the US and Japan.

Increased Frequency of Circulating Follicular Helper T and CD19+CD27+IgM-CD38+ Antibody-secreting B Cells in Myasthenia Gravis Patients

Y Li, P Chen (Guangzhou, China), C Luo (Dongguan, China), H Wang (Guangzhou, China), W Fang (Brookville, NY), L Qi, C Ou, F Yu, J Deng, H Huang, Z Chen, C Su, W-B Liu (Guangzhou, China)

The MG group from China has an active laboratory research program in addition to their strong clinical research program. This poster examined the composition of immune cells in people with MG compared with healthy controls. They reported that classes of antibody secreting B-cell lymphocytes and T-helper cell lymphocytes (cells that amplify an immune response) are present in higher numbers in the blood of people with MG compared to control subjects. The changes in the white blood cell composition of people with MG may potentiate the immune system in MG.

Comment – This was an excellent meeting in which both clinical and scientific studies were presented. As a long-time MG physician and volunteer for the Myasthenia Gravis Foundation of America (30 years), I have attended a variety of clinical and scientific meetings. The Scientific Sessions of the M/SAB have consistently provided excellent studies on MG. There are larger meetings such as the annual meetings of the Society for Neuroscience or the American Academy of Neurology, but these meetings do not focus on MG. To me the Scientific Sessions of the M/SAB and the International Conferences on Myasthenia Gravis, both of which are sponsored by the MGFA, are the most important international meetings that are devoted to MG.