Update in Myasthenia Gravis

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Assistant professor, UAB Neuromuscular Medicine

2018 Alabama Academy of Neurology Annual Meeting

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Disclosure

- None

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Contents

- Overview of Myasthenia Gravis
- Update in AChR MG
- Update in MuSK MG
- Update in double seronegative MG
- Future direction

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Introduction

- Myasthenia Gravis
  - Antibody mediated autoimmune disorder
  - Post synaptic Neuromuscular Junction
  - Fatigable muscle weakness
  - Mortality and Morbidity

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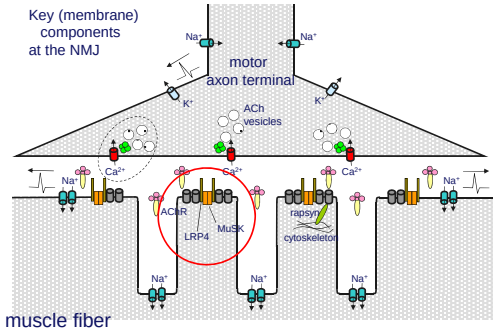
Neuromuscular Junction



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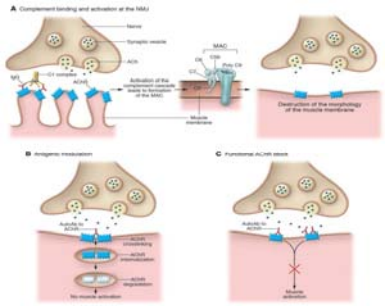
NMJ diagram from Dr. Jaap Plomp

AChR Pathogenesis



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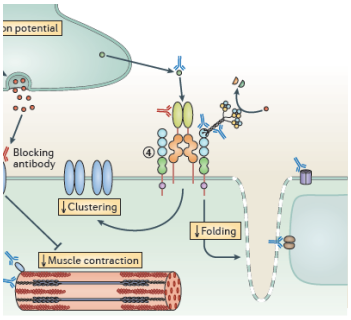
Conti-Fine et al, JCI 2006 Page 7

MuSK Pathogenesis



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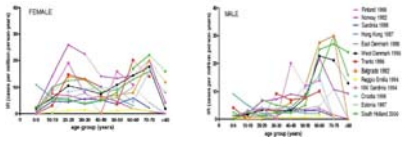
Gilhus et al. Nature reviews. 2016 Page 8

Epidemiology

- Prevalence 1-2/10,000
- F:M 2:1

A systematic review of population based epidemiological studies in Myasthenia Gravis

Aisling S Carr*[1], Chris R Cardwell[2], Peter O McCarron[2] and John McConville[1,3]



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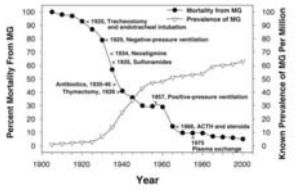
Epidemiology

- Mortality decreased to ~5-10%
- Increasing prevalence
- Recent epidemiologic study is lacking



Grob, Muscle Nerve, 2008

Diagnosis

- If MG is clinically suspected:
  - Antibody testing:
    - AChR binding, blocking and modulating
    - MuSK
  - EMG-RNS
  - SFEMG(if clinically suspected and AB, RNS is negative).

Treatment

- Traditional strategy
  - Acetylcholine inhibitors (Pyridostigmine/Mestinon)
  - Corticosteroids (Prednisone)
  - Immunosuppressant
    - Azathioprine (Imuran)
    - Mycophenolate Mofetil (Cellcept)
    - Cyclosporine
    - Tacrolimus
    - Cyclophosphamide
  - Immunomodulation
    - IVIG
    - Plasma Exchange
  - Thymectomy

Challenges

- Under- and Over-diagnosis
- Delayed diagnosis
- Seronegative MG
- Fluctuation of weakness and fatigue
- Lack of disease specific biomarker
- Treatment refractory MG
- Treatment associated adverse effects
- Autoimmune and none autoimmune comorbidities

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Case 1

- Mr. Rabbit is a 59 yo M and he runs a farm raising cows and rabbits. He has diabetes, hypothyroidism and chronic GI problem. He developed 3 months of double vision, droopy eyelids, trouble chewing swallowing and heaviness in arms and legs. “I can’t work in my farm any more”
- Examination shows fatigable ptosis, more severe on right, double vision with left lateral gaze, weakness in orbicularis oculi. No fatigable weakness in limbs.
- ACHR binding Ab 11.9nmol/L
- CT chest w contrast shows no thymoma or thymic hyperplasia
- Dx: Generalized Myasthenia Gravis with ACHR Ab, without thymoma.

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Case 1 continued,

- He was treated by referring neurologist with mestinon (no benefit), prednisone(rapid taper to 10mg), imuran(50mg daily). None of the treatment was effective.
- His swallowing has worsened, he was given IVIG 1gm/kg x2.
- Last dose of IVIG given a week before the clinic appointment.
- What is the next step?
  - Increase prednisone to 60mg daily
  - Increase imuran to 50mg bid(target to 100mg bid)
  - Referral to thoracic surgery for thymectomy?

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 11, 2016 VOL. 375 NO. 6

Randomized Trial of Thymectomy in Myasthenia Gravis

G.I. Wolfe, H.J. Kaminski, I.B. Aban, G. Minisman, H.-C. Kuo, A. Marx, P. Ströbel, C. Mazia, J. Oger, J.G. Cea, J.M. Heckmann, A. Evoli, W. Nix, E. Ciafaloni, G. Antonini, R. Witoonpanich, J.O. King, S.R. Beydoun, C.H. Chalk, A.C. Barboi, A.A. Amato, A.I. Shaibani, B. Katirji, B.R.F. Lecky, C. Buckley, A. Vincent, E. Dias-Tosta, H. Yoshikawa, M. Waddington-Cruz, M.T. Pulley, M.H. Rivner, A. Kostera-Pruszczyk, R.M. Pascuzzi, C.E. Jackson, G.S. Garcia Ramos, J.J.G.M. Verschuuren, J.M. Massey, J.T. Kissel, L.C. Werneck, M. Benatar, R.J. Barohn, R. Tandan, T. Mozaffar, R. Conwit, J. Odenkirchen, J.R. Sonett, A. Jaretzki, III, J. Newsom-Davis, and G.R. Cutter, for the MGTX Study Group*

ABSTRACT

BACKGROUND

Thymectomy has been a mainstay in the treatment of myasthenia gravis, but there is no conclusive evidence of its benefit. We conducted a multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wolfe at the Department of Neurol-

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Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Prednisone Alone (N = 60)	Thymectomy plus Prednisone (N = 66)
Female sex — no. (%)	39 (65)	50 (76)
Age — yr		
Median	33	32
Range	18–64	18–63
Race or ethnic group — no. (%)†		
Asian	4 (7)	6 (9)
Black	6 (10)	7 (11)
Hispanic	17 (28)	17 (26)
Non-Hispanic white	30 (50)	31 (47)
Other	3 (5)	5 (8)
Therapy at enrollment — no. (%)		
Pyridostigmine	56 (93)	60 (91)
Glucocorticoid	47 (78)	49 (74)
Previous therapy — no. (%)		
Intravenous immune globulin	13 (22)	12 (18)
Plasma exchange	7 (12)	9 (14)
MGFA class — no. (%)‡		
IIa	25 (42)	25 (38)
IIb	14 (23)	18 (27)
III	20 (33)	21 (32)
IV	1 (2)	2 (3)
Duration of disease — yr		
Median	1.14	1.08
Range	0.15–4.38	0.02–4.41
QMG score§	12.35±4.90	11.40±5.12
Prednisone use at baseline		
No. of patients (%)	47 (78)	49 (74)
Dose — mg	42.49±23.52	43.43±28.92

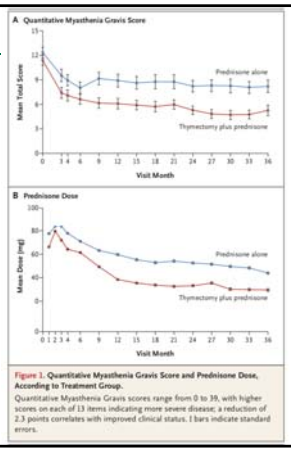

Figure 1. Quantitative Myasthenia Gravis Score and Prednisone Dose, According to Treatment Group.

Quantitative Myasthenia Gravis scores range from 0 to 39, with higher scores on each of 13 items indicating more severe disease; a reduction of 2.3 points correlates with improved clinical status. I bars indicate standard errors.

Thymectomy

- Indicated in thymoma, and AChR MG with or without thymic hyperplasia
- Unclear benefit for MuSK, LRP4 and seronegative MG
- Trans-sternal approach has proven effective, robotic approach is better cosmetically and appears to effectively perform the task
- No cut off for age, however, caution is needed for age over 65(not tested in MGTX trial)
- Recommended early in the course
- Treatment effect can be variable, weeks to years
- Improve disease severity, usage of immunosuppression and remission rate.

Wolfe et al, MGTX trial, 2016

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Back to our Case 1,

- Thymectomy was performed, pathology showing: Benign fibroadipose tissue and lymphoid tissue
- Patient feels improvement in his symptoms, notably better after the surgery. Arm and leg fatigue has resolved, double vision and swallowing difficulties were better. Continues to have mild ptosis.

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Case 1 continued,

- 3 months after the surgery, his symptom worsened again with trouble swallowing and mild shortness of breath.
- He complained of not able to take care of his rabbits.
- Prednisone 60mg daily was continued.
- Imuran was increased to 100mg bid.

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Case 1 continued,

- He started to develop side effects. Blood glucose was high in 300s, A1C 10.8. He started to notice sleep disturbance. He developed fine tremor in his hands.
- What do we do next?
  - He was given 1gm IVIG monthly.
  - Prednisone was tapered down to 40mg and then every other day, Imuran continued 100mg bid
  - Referred to endocrinology for management of DM, positive Anti-GAD Ab.

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Case 1 continued,

- His MG symptoms continued to cause major limitation in his daily activity.
- MG-ADL score measuring the severity of limitation in daily activity was over 10 (0-32).
- He has now tried prednisone, Imuran, IVIG for over 1 year.

->Refractory MG

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Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

James F Howard Jr, Kimiaki Utsugisawa, Michael Benatar, Hiroyuki Murai, Richard J Barohn, Isabel Illa, Saiju Jacob, John Vissing, Ted M Burns, John T Kissel, Srikanth Muppidi, Richard J Nowak, Fanny O'Brien, Jing-Jing Wang, Renato Mantegazza, in collaboration with the REGAIN Study Group*

Lancet Neurol 2017; 16: 976–86
Published Online October 26, 2017
http://dx.doi.org/10.1016/S1474-4422(17)30369-1
This online publication has been corrected.

Summary

Background Complement is likely to have a role in refractory generalised myasthenia gravis, but no approved therapies specifically target this system. Results from a phase 2 study suggested that eculizumab, a terminal complement inhibitor, produced clinically meaningful improvements in patients with anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis. We further assessed the efficacy and safety of eculizumab in this patient population in a phase 3 trial.

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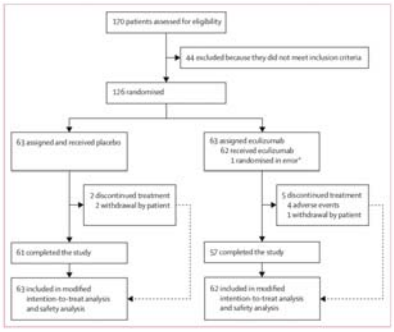
Eculizumab trial



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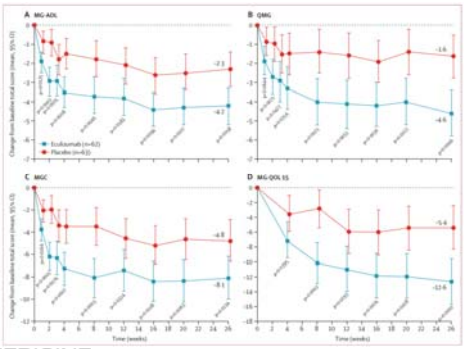
Eculizumab trial



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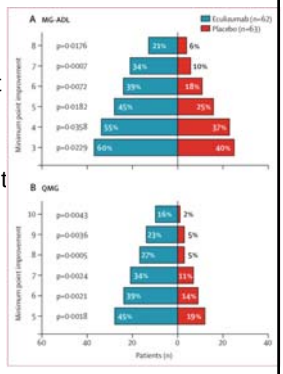
Eculizumab trial

- Significant benefit observed in treatment group compared to placebo group
- Still 40% of the patient did not respond to Eculizumab



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Eculizumab

- First FDA approved treatment for MG.
- Humanized monoclonal antibody binds to complement C5, inhibiting the complement cascade.
- Indication: AChR MG refractory to treatment defined by two or more immunosuppressive therapies, or at least one immunosuppressive therapy with intravenous immunoglobulin or plasma exchange given at least four times per year, for 12 months without symptom control.
- IV infusion; weekly for first month and then bimonthly afterwards.
- Side effects: Potential life threatening Meningococcal infection-> Meningococcus vaccinations(ACYW, B) are needed 2 weeks prior or empiric antibiotic treatment.

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Limitation

- No biomarker available to predict the response to medication
- Significant proportion of the refractory MG patient may not respond to Eculizumab
- Unclear whether the treatment can be terminated in the future
- IV infusion, high cost

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Case 2

- 22 yo AAF with sickle cell disease presented to the ER with 6 months of chronic respiratory failure, 60lbs weight loss, inability to walk and muscle pain.
- Careful examination demonstrated mild ptosis without curtain sign, double vision with fatigue, mild facial weakness and wasting, mild neck flexor weakness, 4/5 proximal arm and leg weakness, and normal sensation.

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Case 2, continued

- RNS demonstrated >10% pathologic decrement.
- Patient was treated with IVIG 2gm/kg with partial improvement.
- Serologic testing for AChR binding/blocking/modulating Ab were negative.
- MuSK Ab came back strong positive.

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Case 2, continued

- How do we approach with her treatment?

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Rituximab as treatment for anti-MuSK myasthenia gravis

Multicenter blinded prospective review

Michael K. Hehir, MD
Lisa D. Hobson-Webb, MD
Michael Benatar, MD, PhD

ABSTRACT

Objective: To evaluate the efficacy of rituximab in treatment of anti-muscle-specific kinase (MuSK) myasthenia gravis (MG).

Methods: This was a multicenter, blinded, prospective review, comparing anti-MuSK-positive patients with MG treated with rituximab to those not treated with rituximab. The primary clinical

- Multicenter review of anti-MuSK positive MG patients
- Minimizing bias by blinding the reviewer from treatment information and obtaining data prospectively.
- Difference in outcome when treated with Rituximab or not (control group)
- MG Status and Treatment Intensity(MGSTI) score used for outcome.

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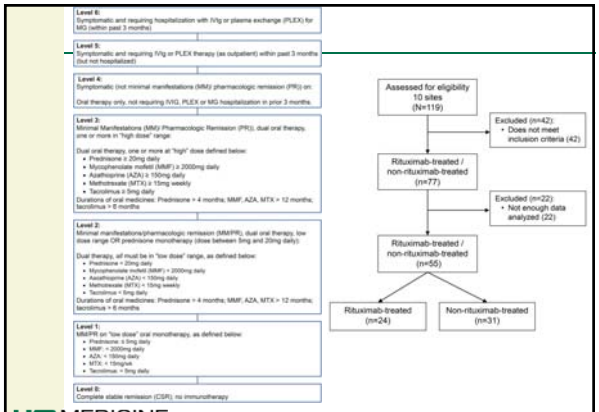

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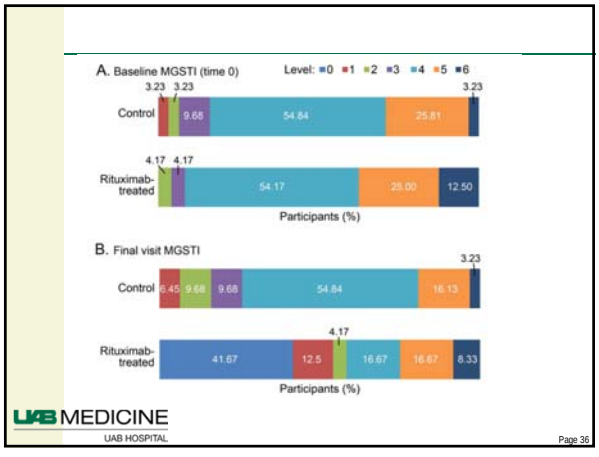

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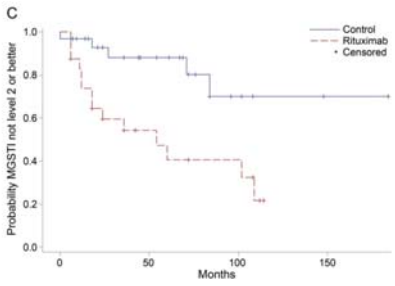
Results



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Back to the case 2,

- Patient was treated with 4 weekly dose of Rituximab 375mg/m^2
- Her symptoms resolved at the following visit
- Continued on prednisone 20mg daily
- Re-evaluation is needed before the next Rituximab dose, especially with potential pregnancy

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Rituximab

- Monoclonal antibody targeting CD20 (plasma B cell).
- Should be considered early in MuSK MG, shown to reduce the dose of prednisone with better symptom control (Hehir et al, blinded prospective review, 2017)
- 375mg/cm2 weekly infusion for 1 week. Dosage can be repeated every 6 months based on symptom recurrence.
- Labs to check: HIV, HCV PCR, Hep B surface/core Ab, TB, VZV IgG(immune status), baseline IgG status, CBC with diff, CD 19/20 count.
- Side effects: severe mucocutaneous reaction, hepatitis reactivation, PML(1 case)
- Growing evidence in the literature showing efficacy in refractory AChR MG, however, recent phase II clinical trial by Nowak et al failed to demonstrate the efficacy(pending publication).

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Case 3

- Mrs. Blister is a 65 yo lady who is a retired therapist. She loves reading and shopping at the mall. She has history of Bechet's disease(since teenager), SLE, inflammatory bowel disease, vasculitis, long term treatment with prednisone and immunosuppressant. She developed chronic waxing and waning weakness of the arm, leg and body. She was told this is from steroid myopathy. Referred for second opinion. She hates looking like "Grandma"
- On examination, she has diplopia, worse in the LLQ. 4/5 strength in proximal leg muscles, waddling gait and stooped posture. Vibration was decreased in both big toes, ankles. Ankle reflexes were diminished.

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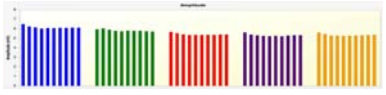
Case 3 continued,

- AChR, MuSK antibodies negative.
- Repetitive nerve stimulation



- Single fiber EMG

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Case 3 continued,

- Treated with increased dose of prednisone and IVIG 1gm/kg in 2 days.
- Double vision and fatigue improved.
- Walk with her back straight up.
- Dx: Double seronegative generalized myasthenia gravis
- Why isn't there an antibody?
  - Antibody we have not identified?
  - Antibody titer is too low for detection?

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Editorial Opinion

Seronegative Myasthenia Gravis—A Vanishing Disorder?

Henry J. Kaminski, MD

With the initial identification in 1976 of antibodies directed toward the acetylcholine receptor (AChR) in the serum of patients with myasthenia gravis (MG),[1] it became clear that upwards of 20% of patients with clinical and electrophysiological evidence of a neuromus-

AChR and MuSK antibodies. Nine of these patients had antibodies directed toward cortactin, and these patients had ocular or mild generalized MG. Among the 17 patients with ocular MG in the double-seronegative MG group, 4 (23.5%) had antibodies to cortactin. A few other individuals had anti-

- Discovery of LRP4/Agrin antibody
- Cell Based Assay detecting AChR antibody more sensitively

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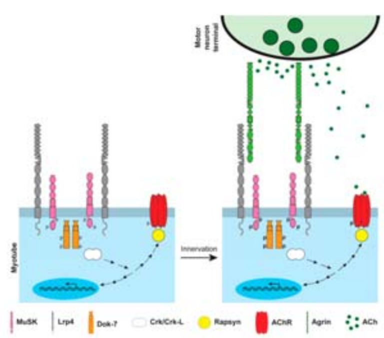
LRP4/Agrin



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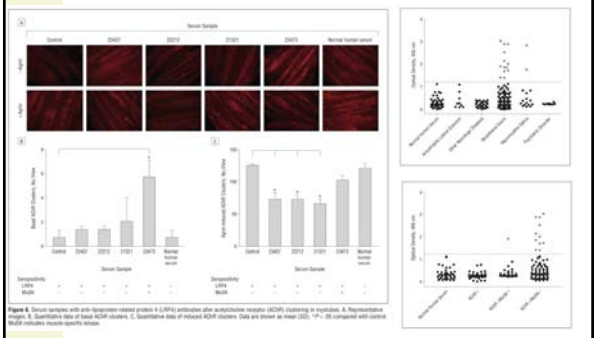
Evidence



Zhang et al. 2012 JAMA Neurology

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LRP4/Agrin

- Nation wide clinical study to characterize LRP4/Agrin (+) MG is ongoing.
- Antibody testing is available through the clinical study and commercial laboratory.
- Advanced our understanding in NMJ physiology and pathology.
- Potential development of targeted treatment.

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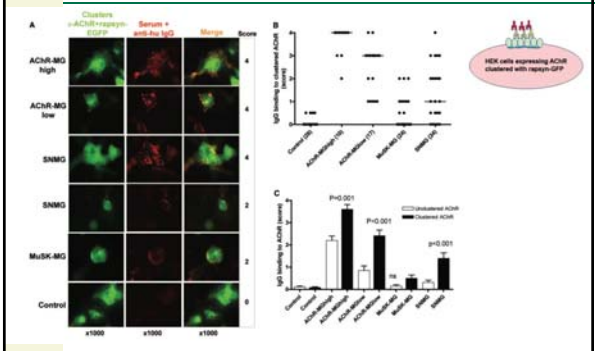
Cell Based Assay



Leite et al, Brain, 2008

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Cell Based Assay

- 14/24 seronegative MG sera showed antibody binding to clustered AChR receptor expressing HEK cell
- Antibodies were predominantly IgG1 and demonstrated complement activation
- Further studies consistently found significant proportion of the double seronegative sample positive for AChR cell based assay

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Lack of Treatment Guidelines

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: Myasthenia Gravis and Related Disorders
REVIEW

Developing treatment guidelines for myasthenia gravis

Donald B. Sanders,[1,a] Gil I. Wolfe,[2,a] Pushpa Narayanaswami,[3,a] and the MGFA Task Force on MG Treatment Guidance[†]

[1]Department of Neurology, Duke University, Durham, North Carolina. [2]Department of Neurology, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, State University of New York, Buffalo, New York. [3]Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Address for correspondence: Donald B. Sanders, Department of Neurology, Duke University, DUMC Box 3403, Durham, NC 27710. Donald.Sanders@duke.edu

A task force of the Myasthenia Gravis Foundation of America recently published a formal consensus statement intended to be a treatment guide for clinicians caring for myasthenia gravis (MG) patients worldwide. Its development was stimulated by the fact that there is generally no accepted standard of care for MG, and no one treatment is best for all MG patients. Also, there are few randomized trials of treatments in current use, and the generalizability of the few trials that have been successful may be difficult. Fifteen international experts in MG participated

Lack of Biomarker

- Antibody Titer?
- Antibody Functional Activity?
- Complement Activation?
- miRNA?
- SFEMG?

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Thank you

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