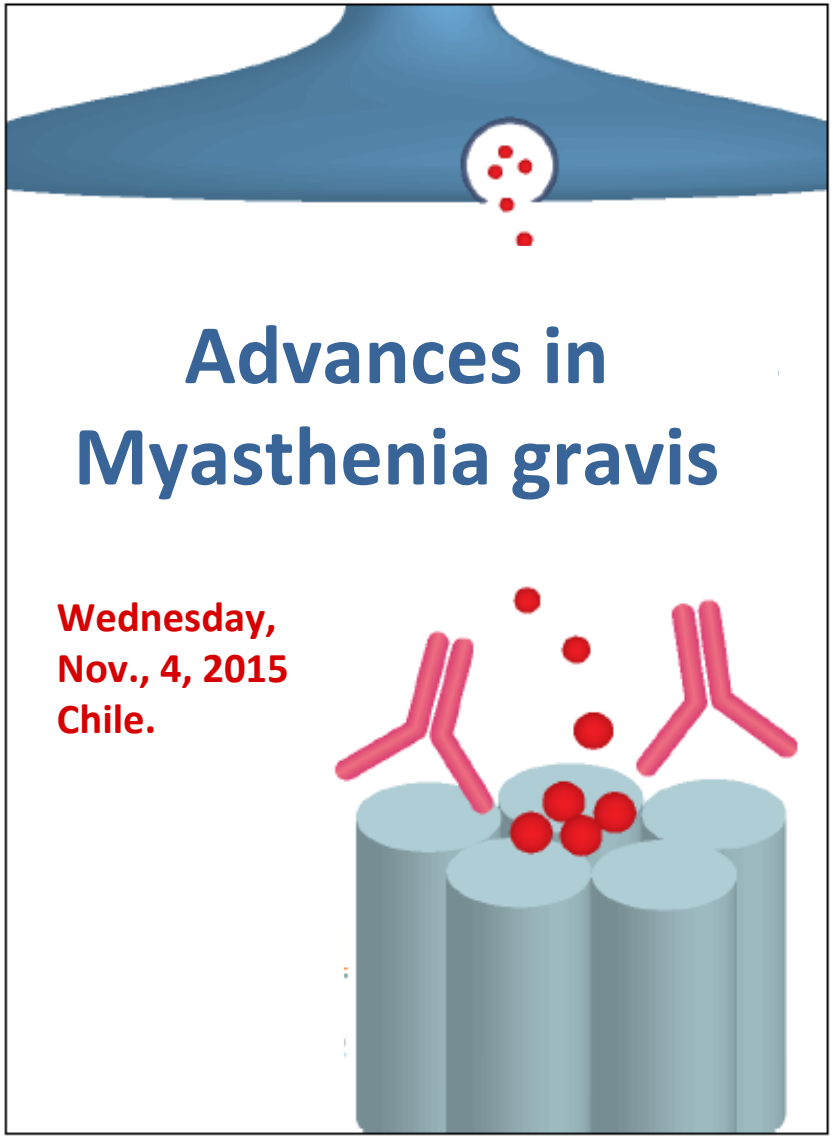
TC 30: MUSCULAR DISORDERS



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ciberer
CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED DE ENFERMEDADES RARAS

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

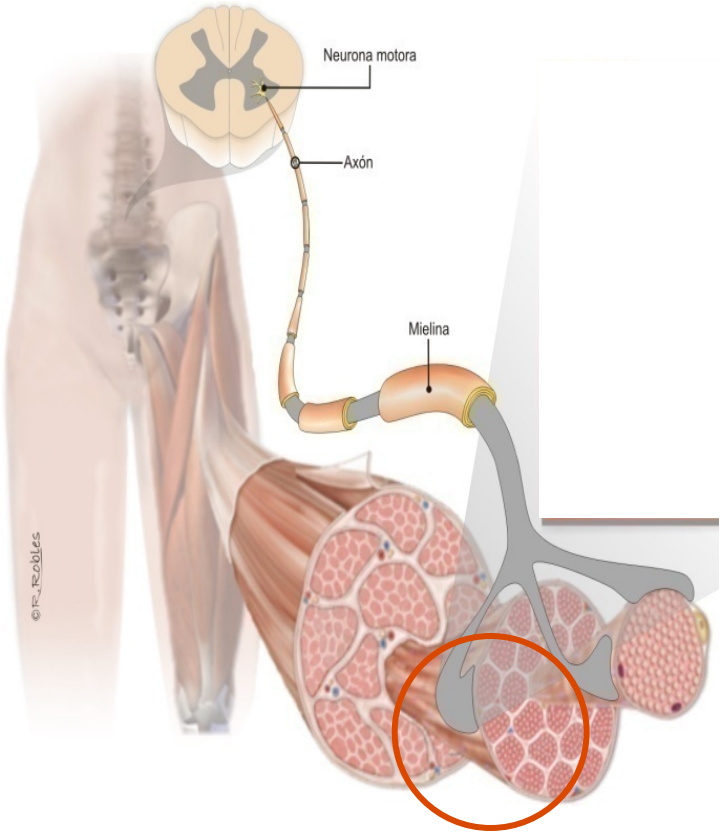
Instituto de Salud Carlos III

Disclosure

- I.Illa has received research funds from Grifols and received speaking fees and travel grants from Grifols, Genzyme and Pfizer.
- I. Illa provided expert testimony to Alexion, UCB and Grifols.

Myasthenia

- **1934:** Acetylcholinesterase inhibitors improved MG. [NMJ]
- **1936 :** Patient with thymoma improvement after thymectomy.
- **1973.** MG is an autoimmune disease. Description of antibodies to AChR. Treatment.



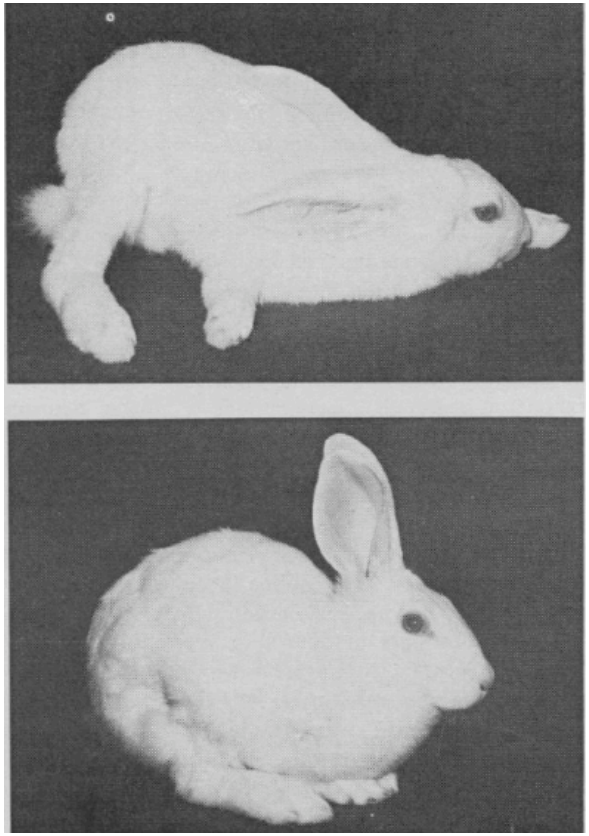
AUTOIMMUNE ERA

Science

AAAS

Autoimmune Response to Acetylcholine Receptor

Abstract. *Injection of rabbits with acetylcholine receptor highly purified from the electric organ of* Electrophorus electricus *emulsified in complete Freund's adjuvant resulted in the production of precipitating antibody to acetylcholine receptor. After the second injection of antigen, the animals developed the flaccid paralysis and abnormal electromyographs characteristic of neuromuscular blockade. Treatment with the anticholinesterases edrophonium or neostigmine dramatically alleviated the paralysis and the fatigue seen in electromyography.*



Patrick J, Lindstrom J.
Science. 1973 May 25;180(4088):871-2.

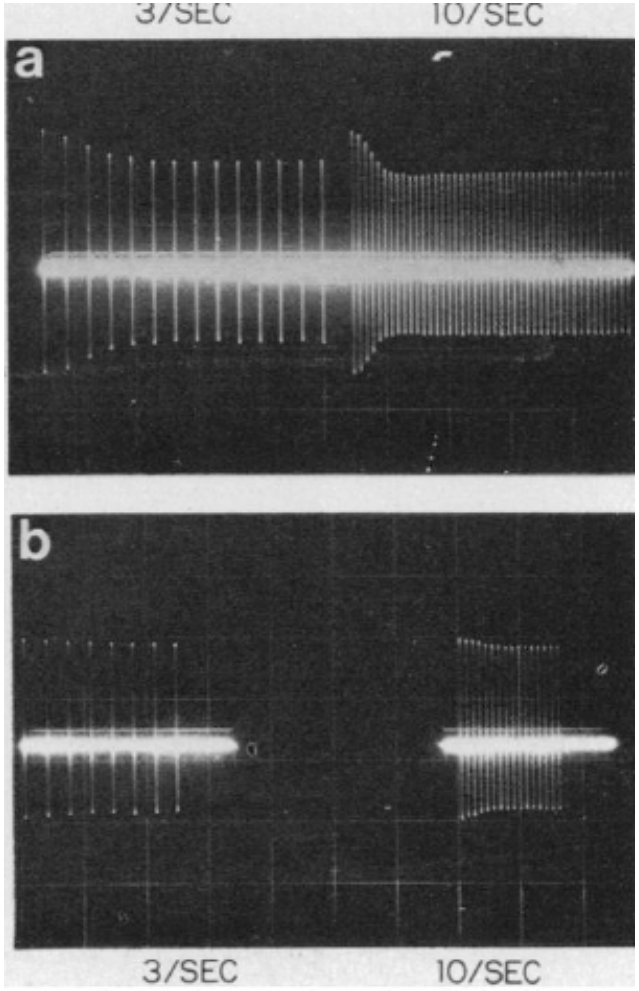
PASSIVE TRANSFER

Science

AAAS

Myasthenia Gravis: Passive Transfer from Man to Mouse

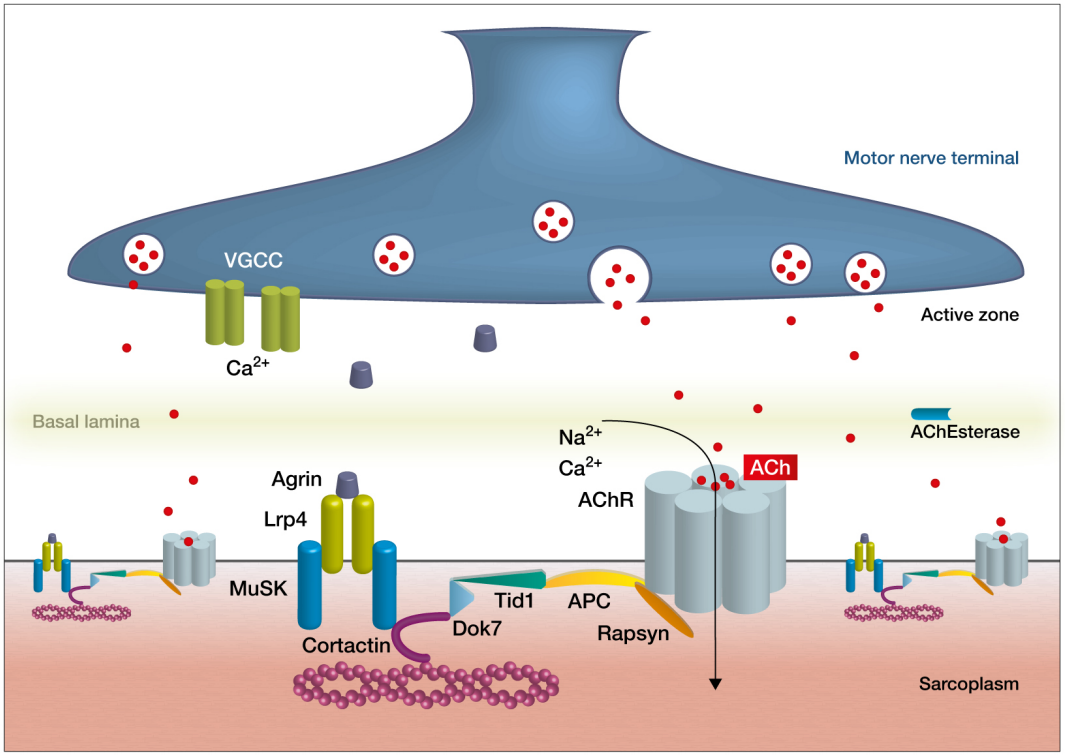
Abstract. *Daily injections into mice of an ammonium sulfate–precipitated immunoglobulin fraction of serum from patients with myasthenia gravis were carried out for up to 14 days. The mice showed reduced amplitudes of miniature endplate potentials and reduced numbers of acetylcholine receptors at the neuromuscular junctions. Some mice showed typical decremental responses on repetitive nerve stimulation, with reversal by neostigmine. This represents the first evidence of a circulating factor in the serum of patients with myasthenia gravis which on passive transfer reproduces features of the disease in experimental animals.*



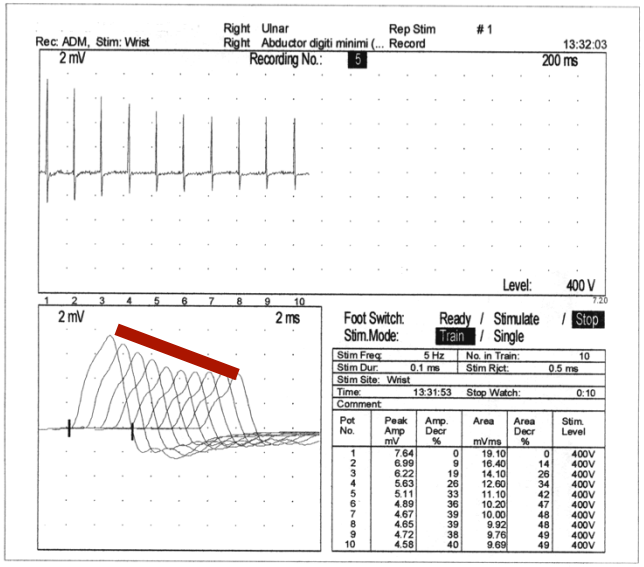
Science. 1975 Oct 24;190(4212):397-9.
Toyka KV, Brachman DB, Pestronk A, Kao I..

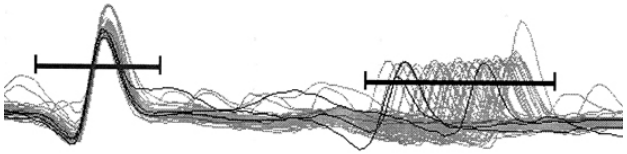
MYASTHENIA GRAVIS

Myasthenia Gravis is an **autoimmune** disease caused by antibodies to proteins of the postsynaptic neuromuscular junction.



MG Diagnosis

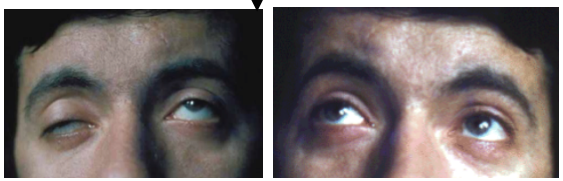




SFEMG - Jitter

- Clinical evaluation
- EMG
- Pharmacologic test
- Antibody test (AchR, MuSK..)

TENSILON test



MESTINON test

MYASTHENIA GRAVIS: A DISEASE OF THE OLD AND THE VERY OLD

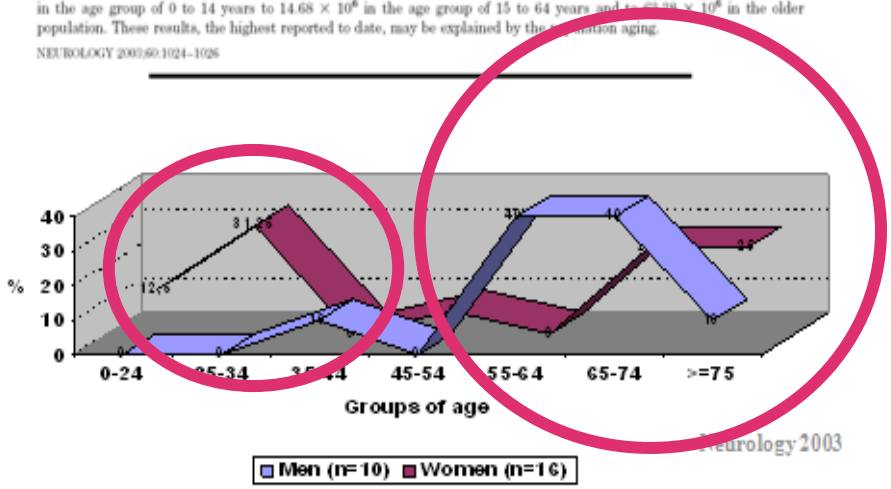
Myasthenia gravis

A higher than expected incidence in the elderly

J.M. Aragonès, MD; I. Bolíbar, MD; X. Bonfill, MD, PhD; E. Bufill, MD; A. Mummany, MD; F. Alonso, MD; and I. Illa, MD, PhD

Abstract—This 10-year (1991 to 2000) prospective study of MG in the county of Osona (Barcelona, Spain) reveals an annual incidence rate of 21.27 cases per million inhabitants (95% CI 13.89 to 31.16). Incidence increased from 5.03 × 10^6 in the age group of 0 to 14 years to 14.68 × 10^6 in the age group of 15 to 64 years and to [illegible] × 10^6 in the older population. These results, the highest reported to date, may be explained by the [illegible]ation aging.

NEUROLOGY 2003;60:1024–1026



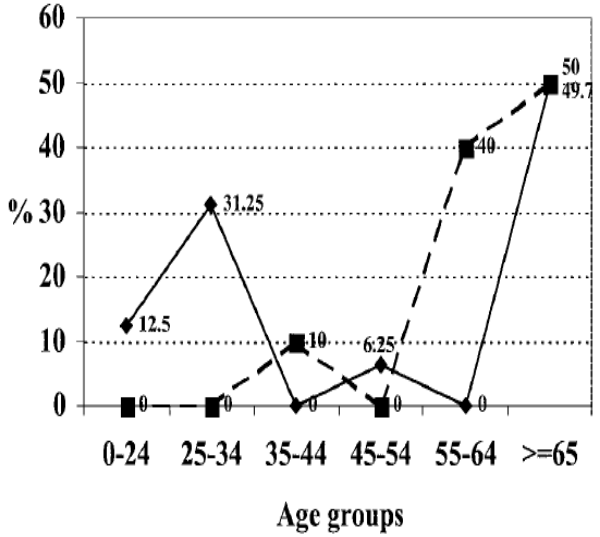


Figure. Percentage distribution of the diagnosed cases of MG (from 1991 to 2000) by age group and sex. —■— = men (n = 10); —◆—; = women (n = 16).

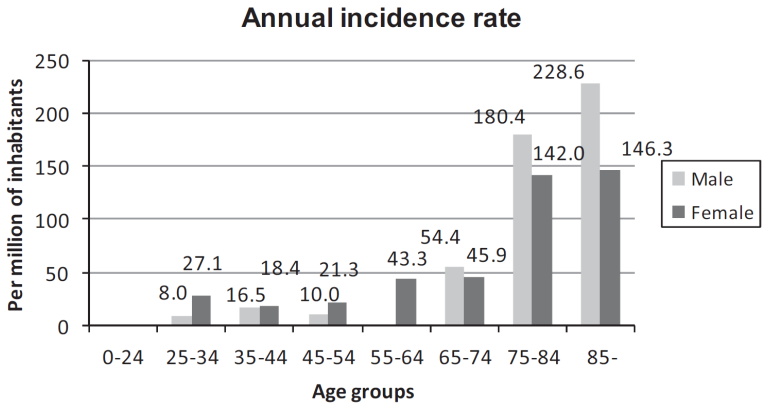
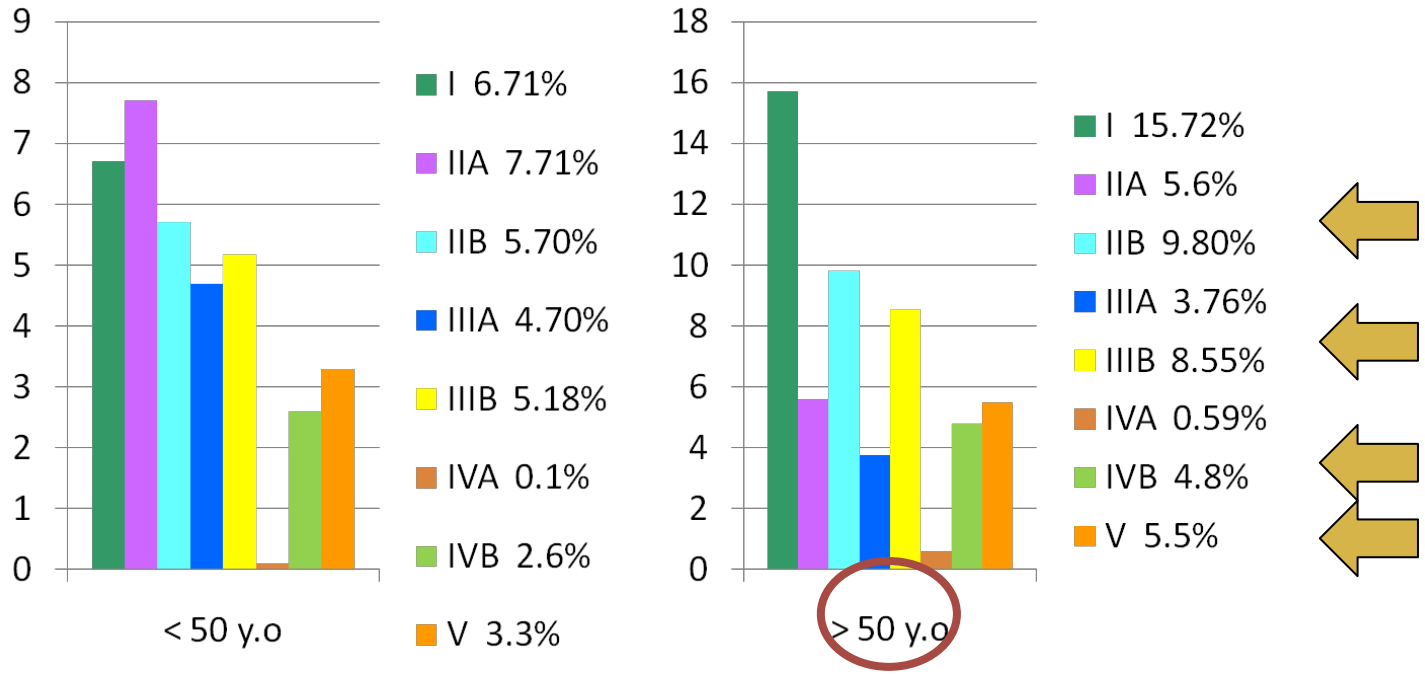


Figure 1. Myasthenia gravis annual incidence between 2001 and 2010 per million inhabitants.

Aragones et al JAGS 2014

NMD-ES Spanish registry 1.150 patients with MG



ORIGINAL ARTICLE

Myasthenia gravis: descriptive analysis of life-threatening events in a recent nationwide registry

NMD.ES
NEUROMUSCULAR DATABASE SPAIN

A. Ramos-Fransi[a,*], R. Rojas-García[a,b,c,*], S. Segovia[a], C. Márquez-Infante[d], J. Pardo[e], J. Coll-Cantí[f], I. Jericó[g] and I. Illa[a,b,c] Myasthenia NMD-ES Study Group[†]

European Journal of Neurology 2015, **0:** 1–6

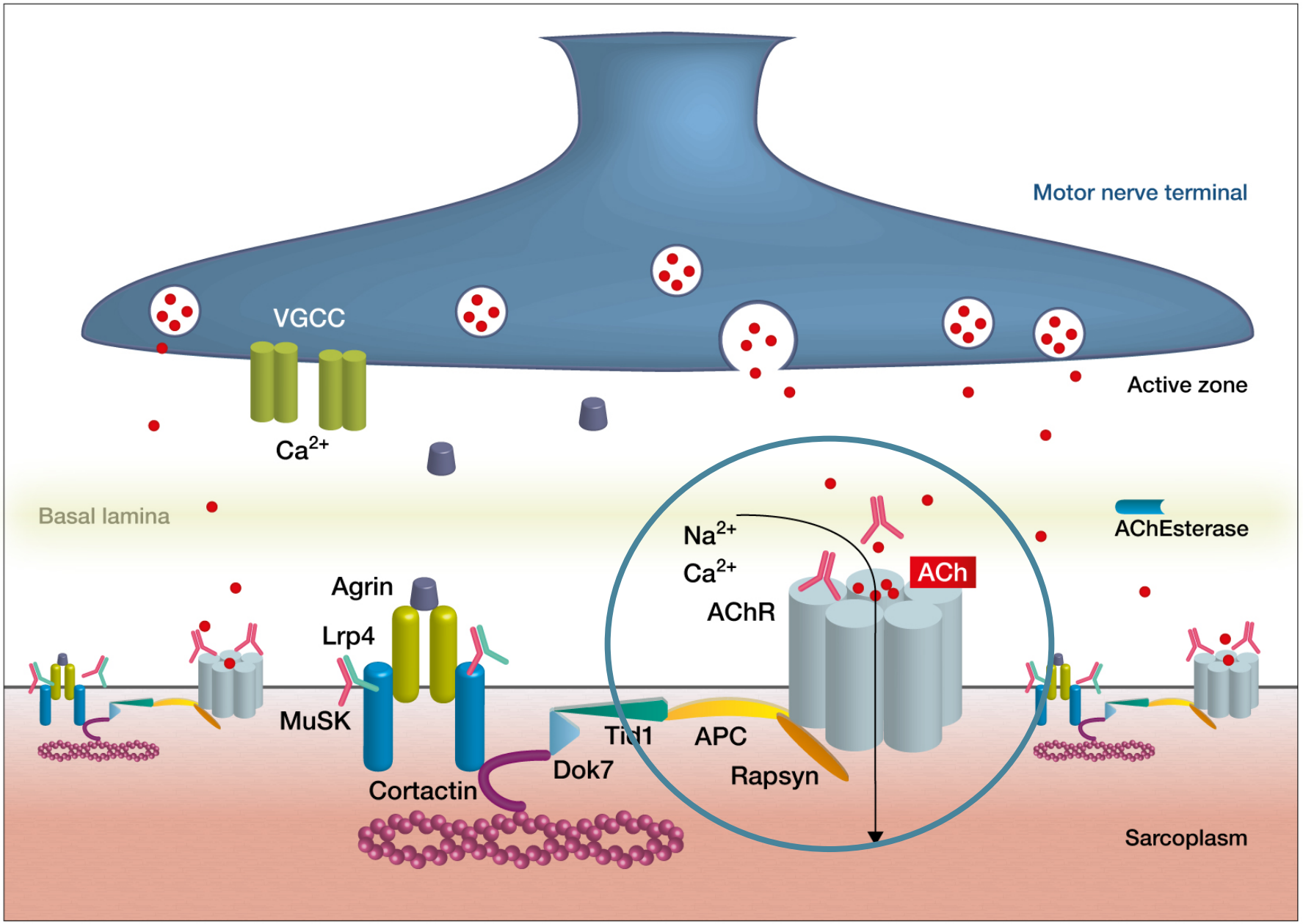
Table 2 Life-threatening events features

Clinical features of the 62 patients with LTE (number, %)	
Gender	
Women	27 (43.5)
Men	35 (56.5)
Age	
EoMG (<50 years old)	20 (32.3)
LoMG	42 (67.7)
MGFA	
IV B	30
V	32
Factors related to the 65 LTE (number, %)	
None	37 (56.9)
Infection	18 (27.7)
Reduction of IS dose	3 (4.6)
Commencement of steroid treatment	1 (1.5)
Use of other drugs	1 (1.5)
Thymoma recurrence with pleural implant	1 (1.5)
Psychological stress	3 (4.6)
Surgery	1 (1.5)
Treatment of the 65 LTE (number, %)	
IgIV 5 days	65 (100)
Single course	48 (73.8)
Re-treatment with IgIV	11 (16.9)
Re-treatment with PLEX	6 (9.2)
Duration of the LTE (median days)	
Time to weaning (MGFA V)	12 days (3–176)
EOMG	54 days
LOMG	9.5 days ($P = 0.019$)
Time to removal of the feeding tube (MGFA IVB)	13 days (1–434)
EOMG	47.5 days
LOMG	11.5 days (n.s.)

Conclusions: The percentage of LTEs in MG patients was low, particularly amongst those previously diagnosed and treated for the disease. The significant percentage of treatment-resistant LTEs indicates that more effective treatment approaches are needed for this vulnerable sub-population.

MG Diagnosis. **Antibody tests**

- Over 80% of patients with generalized MG have Ab. to acetylcholine receptor (AChR) [AChR+MG].
- Ab. to another NM-junction protein, the muscle specific kinase (MuSK), are found in a proportion of AchR negative M.G. patients (0% -50%) [MuSK +MG].
- The remaining M.G. patients are referred as seronegative myasthenia gravis [LRP-4, SN-MG].



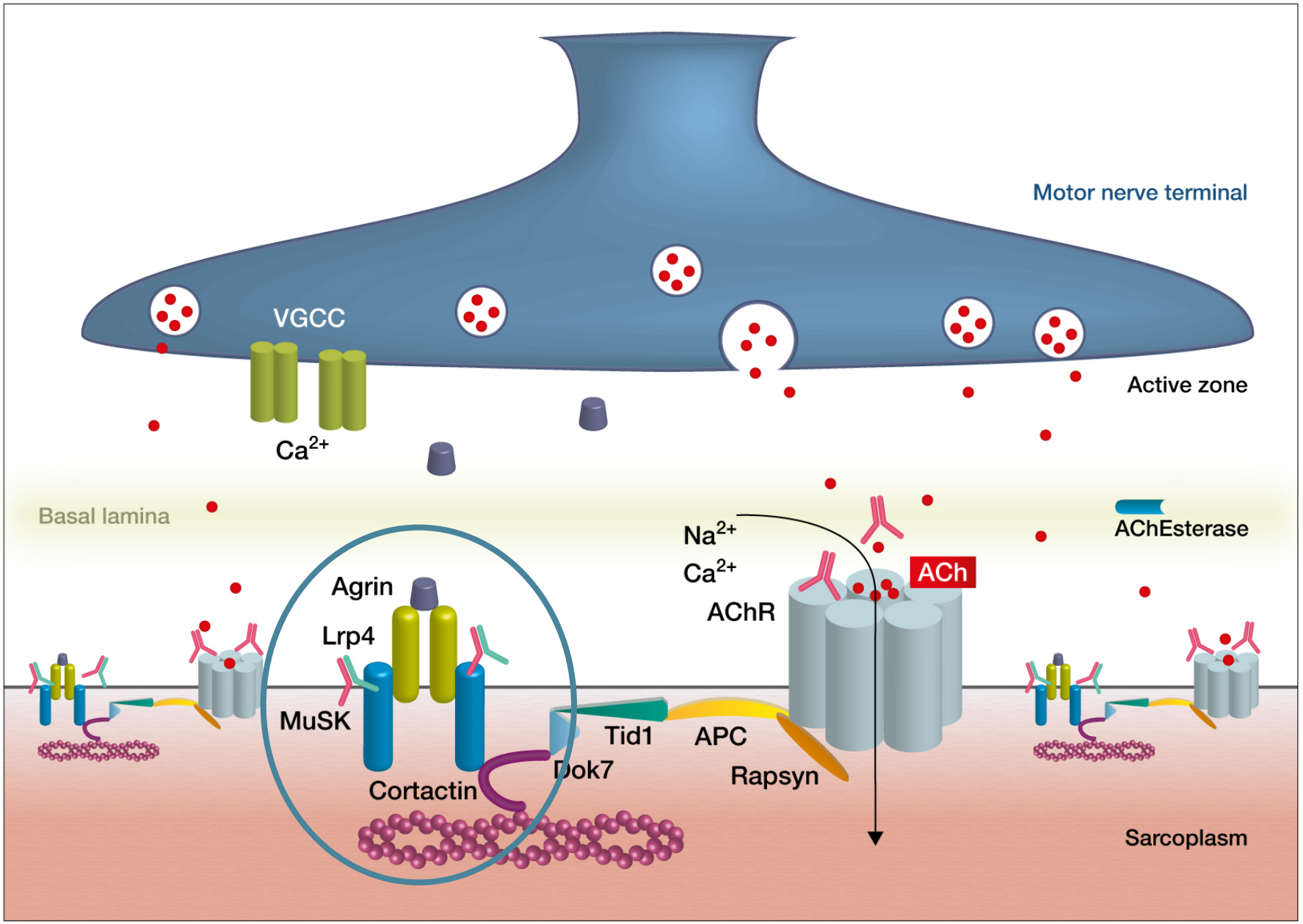
IMMUNOPATHOGENESIS

ACHR MODULATION

COMPLEMENT BINDING

ACHR BLOCK

- **Understanding the mechanisms of action of the autoantibodies is important for the design of new drugs. Exemple: RCT with an anti-complement biological agent.**



NATURE CLINICAL PRACTICE NEUROLOGY JULY 2007 VOL 3 NO 7

Jordi Díaz-Manera, Ricard Rojas-García, Eduard Gallardo, Cándido Juárez, Alejandro Martínez-Domeño, Sergi Martínez-Ramírez, Josep Dalmau, Rafael Blesa and Isabel Illa*

BIOMARKER

Table 1 Comparison of patients with myasthenia gravis associated with antibodies to acetylcholine receptors and muscle-specific tyrosine kinase.

Patient work-up	AChR-MG	MuSK-MG	Comments
Symptoms			
Limb weakness	++	+	Bulbar weakness greater than limb weakness in MuSK-MG
Bulbar weakness	+	++	Bulbar weakness greater than limb weakness in MuSK-MG
Ocular symptoms	++	+	NA
Facial and **[Au: or, or?]** lingual atrophy	+/–	+	NA
Respiratory failure	+	++	Higher incidence of respiratory failure in MuSK-MG than in AChR-MG
Treatment response			
Response to pyridostigmine	80–90%	30–50%	Worsening of symptoms in MuSK-MG is described and might confuse the diagnosis
Electrodiagnostic tests			
Repetitive nerve stimulation in limb muscles	70–80%	35–50%	Higher sensitivity in facial muscles than in limb muscles
Repetitive nerve stimulation in facial muscles	80–90%	80%	Higher sensitivity in facial muscles than in limb muscles
Single-fiber electromyogram in limb muscles	95%	15–50%	NA
Single-fiber electromyogram in orbicular oculi	95–99%	72%	NA
Thymus pathology			
Hyperplasia	65%	10–15%	NA
Thymoma	10%	One case published	NA

Abbreviations: +/– might be present; +, present; ++, very frequent; AChR-MG, myasthenia gravis associated with antibodies to acetylcholine receptor; MuSK-MG, myasthenia gravis associated with antibodies to muscle-specific tyrosine kinase; NA, not applicable.

NEW BIOMARKER

Autoimmunity Reviews 13 (2014) 1003–1007

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Cortactin autoantibodies in myasthenia gravis

Eduard Gallardo [a], Eugenia Martínez-Hernández [a], Maarten J. Titulaer [b], Maartje G. Huijbers [c], Maria Angeles Martínez [h], Alba Ramos [a], Luis Querol [a], Jordi Díaz-Manera [a], Ricard Rojas-García [a], Christopher R. Hayworth [d], Jan J. Verschuuren [c], Rita Balice-Gordon [d], Josep Dalmau [e,f,g], Isabel Illa [a,*]

[a] Neuromuscular Diseases Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autonoma de Barcelona, Barcelona, Spain
[b] Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands
[c] Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands
[d] Department of Neuroscience, University of Pennsylvania, PA, USA
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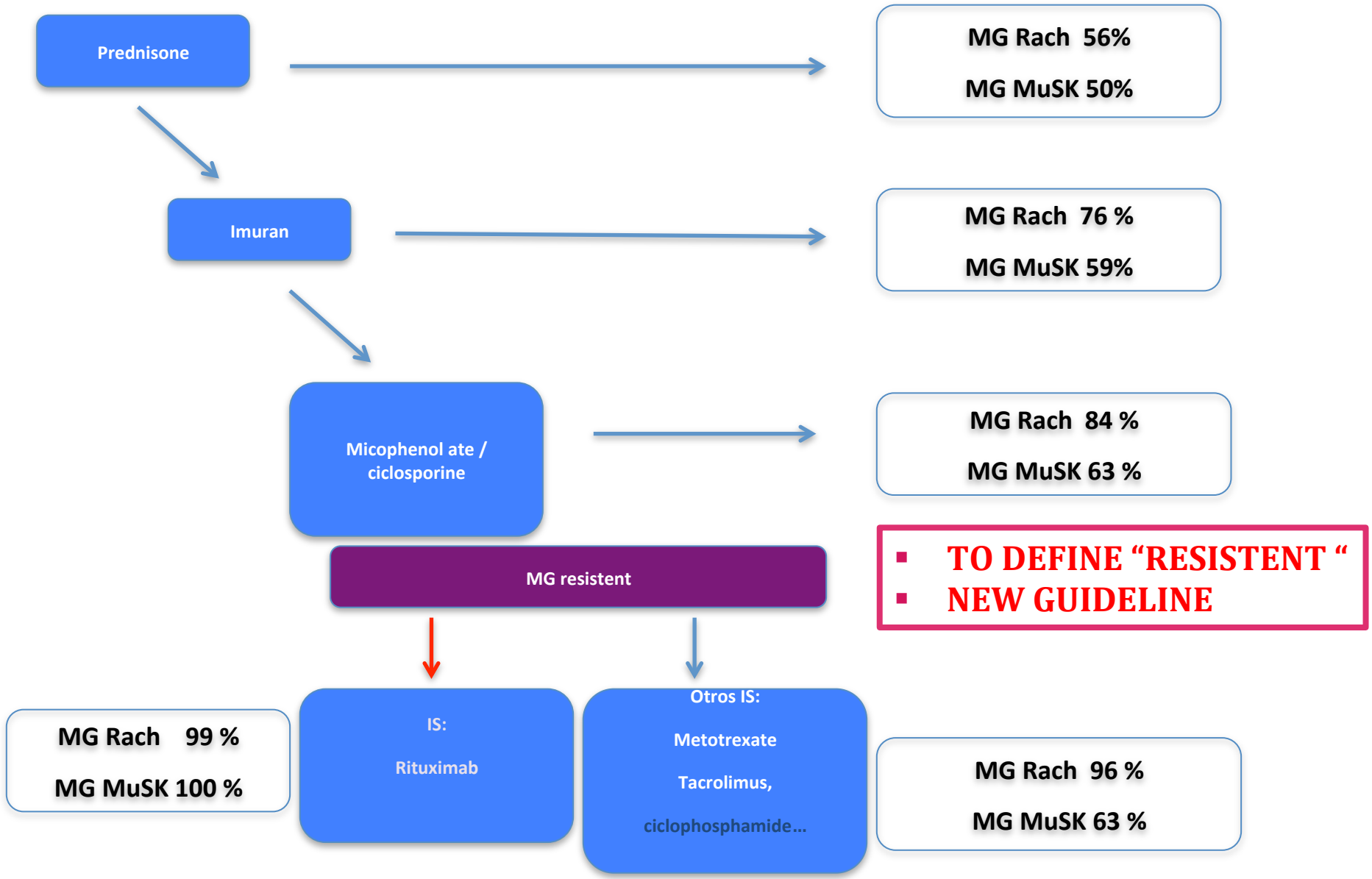
[f] Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
[g] Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain
[h] Department of Immunology, Hospital de la Santa Creu i Sant Pau, Universitat Autonoma de Barcelona, Barcelona, Spain

- Cortactin antibodies in seronegative MG (SNMG) indicate an immune process impairing the endplate.
- Cortactin antibodies can be a diagnostic tool combined with clinical and electrophysiological studies in SNMG.
- Cortactin antibodies in SNMG indicate an autoimmune disease supporting immunomodulatory treatment.

GOAL OF TREATMENT

MINIMAL MANIFESTATIONS / REMISSION

Therapeutic Algorithm

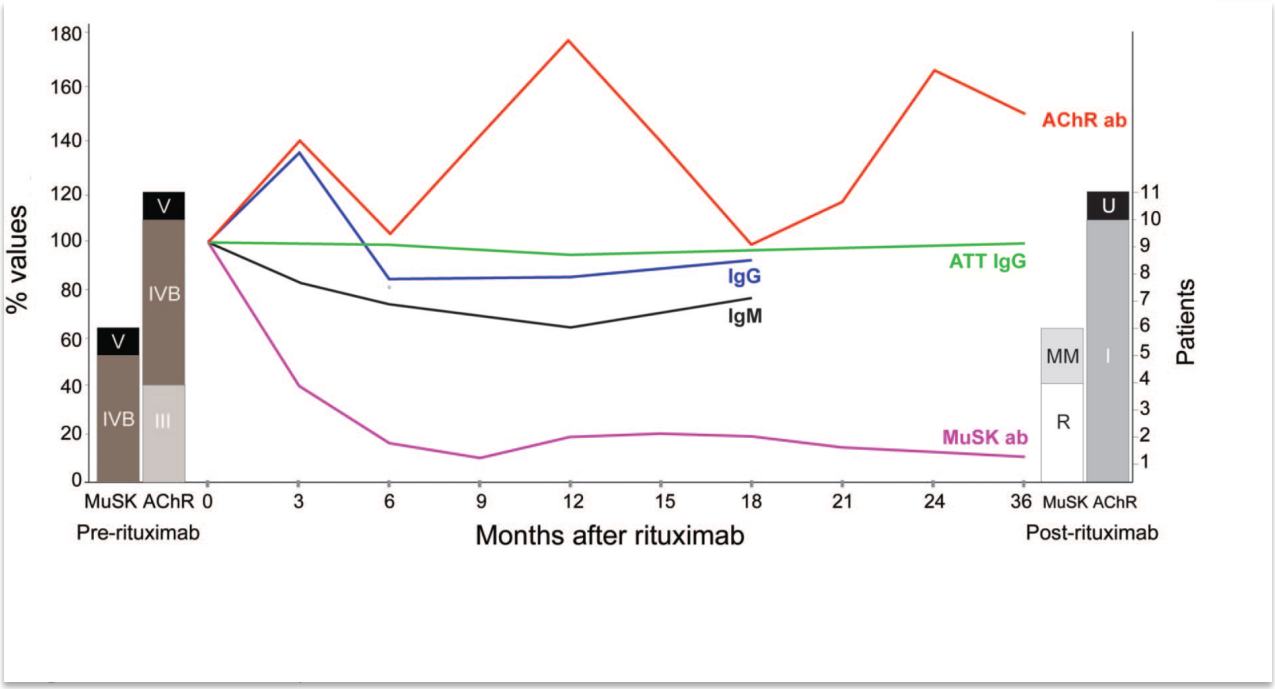


Long-lasting treatment effect of rituximab in MuSK myasthenia

J. Díaz-Manera, MD
E. Martínez-Hernández, MD
L. Querol, MD
R. Klooster, PhD
R. Rojas-García, MD, PhD
X. Suárez-Calvet
J.L. Muñoz-Blanco, MD
C. Mazia, MD
K.R. Straasheijm
E. Gallardo, PhD
C. Juárez, MD, PhD
J.J. Verschuuren, MD
I. Illa, MD, PhD

Correspondence & reprint requests to Dr. Illa: iilla@santpau.cat

Clinical and serologic evolution after treatment with rituximab



Conclusion: In view of the long-lasting benefit observed in MuSK+MG patients, we recommend to use rituximab as an early therapeutic option in this group of patients with MG if they do not respond to prednisone.

Neurology® 2012;78:189–193

Key messages

- MG is an heterogeneous disease : clinically , immunologically and in response to treatment .
- The number of patients poorly responsive to IS drugs is higher in the MuSK-MG group than in the ACRh-MG or seronegative groups.
- Rituximab should be considered in MG refractory to other drugs especially IgG4 MuSK +.
- Further research is essential in order to have new clinical markers and new treatments, more specific and with less adverse event

REFERENCES I

1.- Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol. 2009 May;8(5):475-90.

2.- Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Fundation of America. Myasthenia Gravis Recomendations for clinical research standards. Neurology 2000;55:16-23.

3.- Vincent A, Bowen J, Newsom-Davis J, McConville J. Seronegative generalised myasthenia gravis: clinical features, antibodies, and their targets. Lancet Neurol. 2003 Feb;2(2):99-106.

4.- Aragonès JM, Bolíbar I, Bonfill X, Bufill E, Mummany A, Alonso F, Illa I. Myasthenia gravis: a higher than expected incidence in the elderly. Neurology 2003;60(6):1024-1026.

5.- Evoli, A., Tonali, P.A., Padua, L., Monaco, M.L., Scuderi, F., Batocchi, A.P., Marino, M., Bartoccioni, E., 2003. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain 126, 2304–2311.

6.- Diaz-Manera, J., Rojas-Garcia, R., Gallardo, E.,et al 2007. Antibodies to AChR, MuSK and VGKC in a patient with myasthenia gravis and Morvan's syndrome. Nat. Clin. Pract. Neurol. 3, 405–410.

6.- Querol L, Illa I. Myasthenia gravis and the neuromuscular junction. Curr Opin Neurol 2013;26(5):459-65.

REFERENCES II

8 .- Sanders DB, Evoli A. Immunosuppressive therapies in myasthenia gravis. Autoimmunity 2010;43(5-6):428-35.

9.- Díaz-Manera J, Rojas García R, Illa I. Treatmet strategies for myasthenia gravis: an update. Expert Opin Pharmacother 2012;13(13):1873-1883.

10.- Jurado J, Javidfar J, Newmark A, et al. Minimally invasive thymectomy and open thymectomy: outcome analysis of 263 patients. *Ann Thorac Surg* 2012; 94: 974-81; discussion 981-2.

11.- Diaz-Manera, J., Martinez-Hernandez, E.,. *et al.* 2012. Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology, 78***:** 189-93.

12.- Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 2012;12:CD002277.

13.- Barth D, Nabavi Nouri M, Ng E, New P, Bril V. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology 2011;76:2017-2023.Ç

14.- Ramos-Franci A, Rojas-Garcia R, Segovia S et al. Myasthenia Gravis: descriptive analysis of life-Threatening events in a recent worldwide registry. European J Neurol 2015:1-6.