TRASTORNOS DE LA TRANSMISION NEUROMUSCULAR ASPECTOS CLINICOS Y PATOLOGICOS

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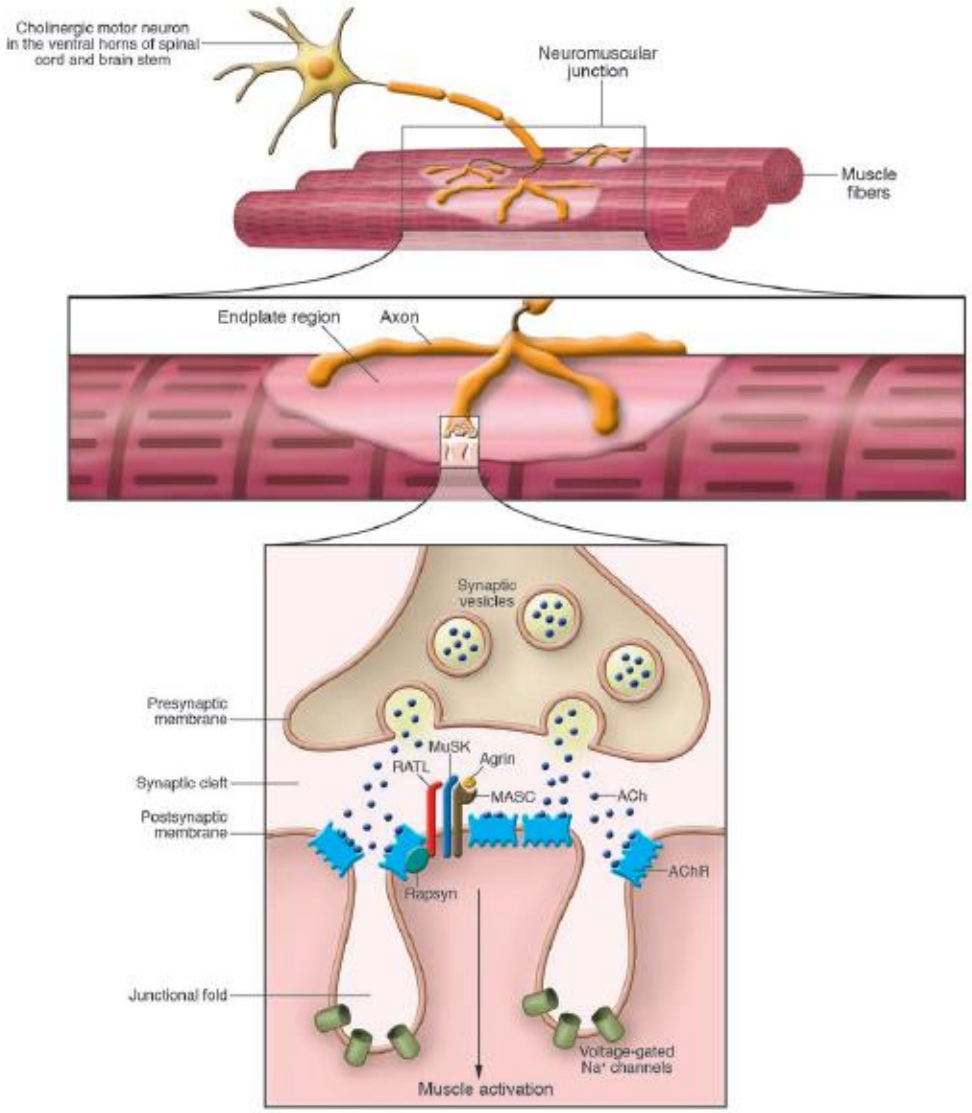
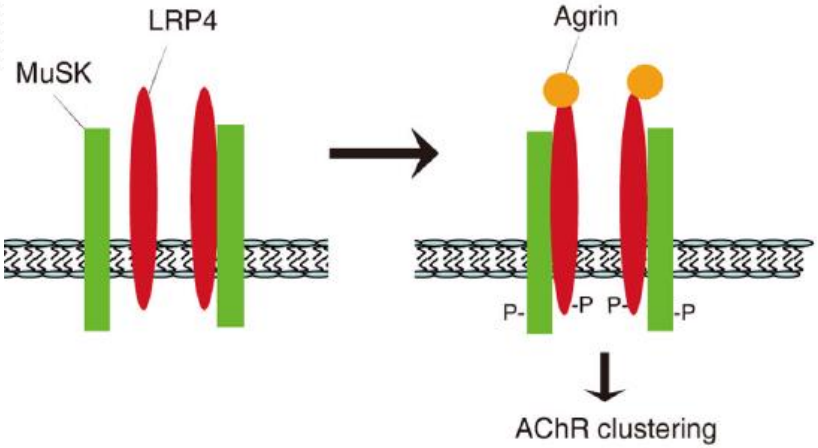
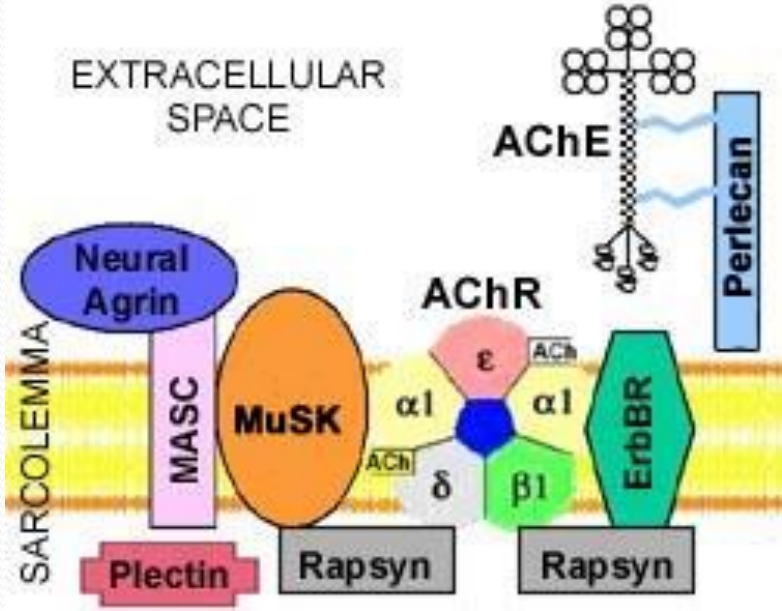
Objetivos

- Revisión clínica
  - Fisiopatológico
  - Diagnóstico
  - Tratamiento

TRANSMISION NEUROMUSCULAR







FISIOLOGIA DE LA TRANSMISION NEUROMUSCULAR

Potencial de acción se despolariza la membrana

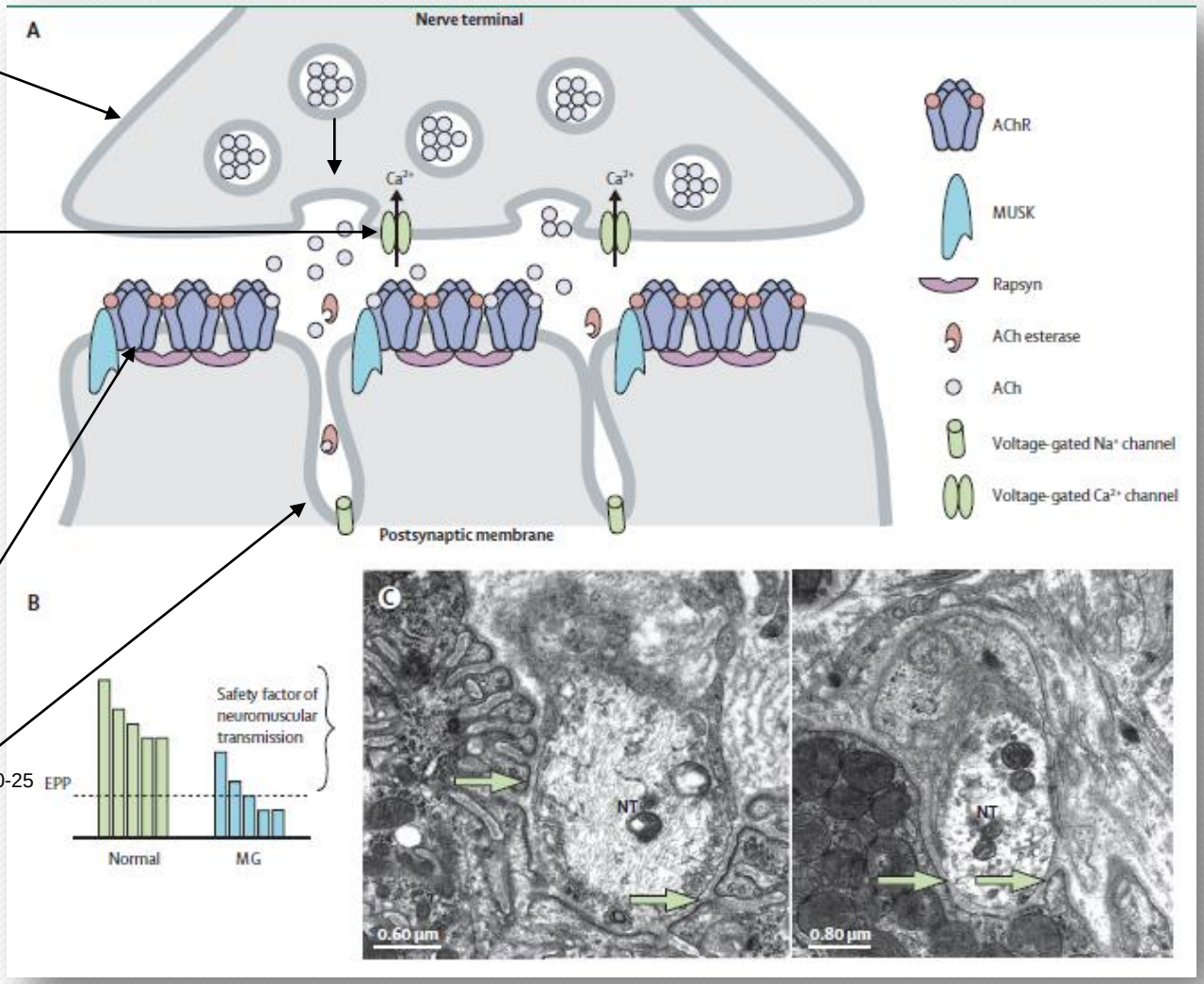
Apertura de canales de Ca.

Fusión de vesículas con la membrana y liberación de Ach.

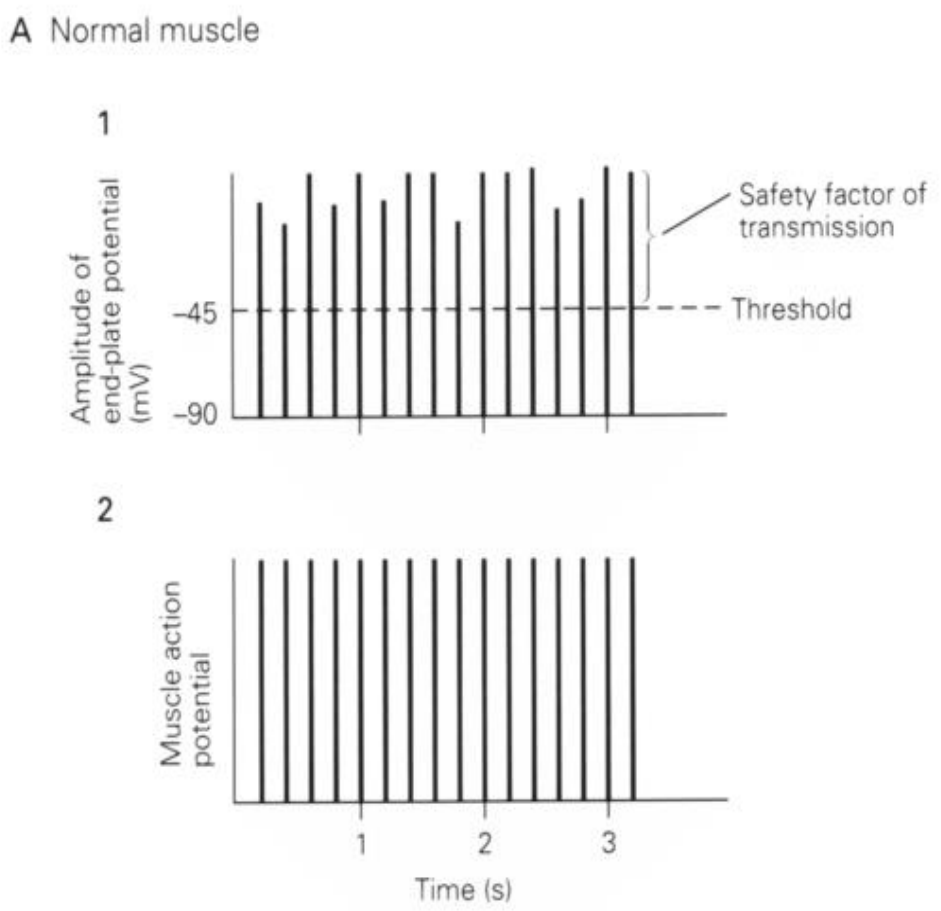
La unión de 2 moléculas de Ach con el R permite la entrada de Na.

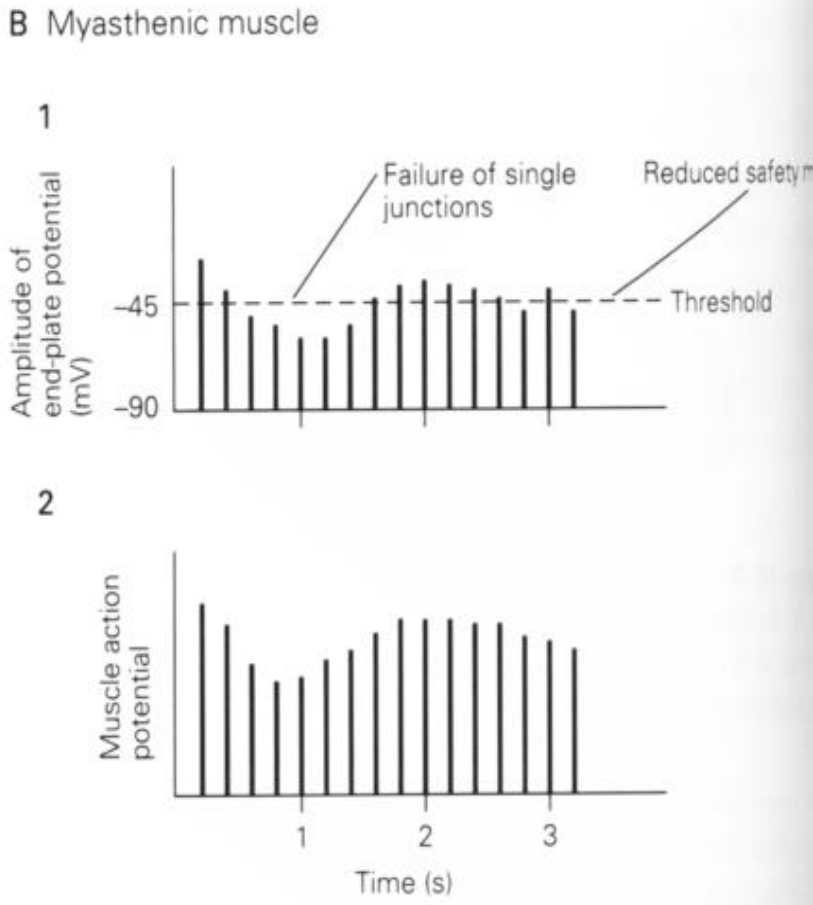
Se genera EPP que abre los canales de NaVD.

PA 80 mV



FISIOPATOLOGIA DE LA TRANSMISION NEUROMUSCULAR





Enfermedades de la unión neuromuscular

PRESINAPTICAS

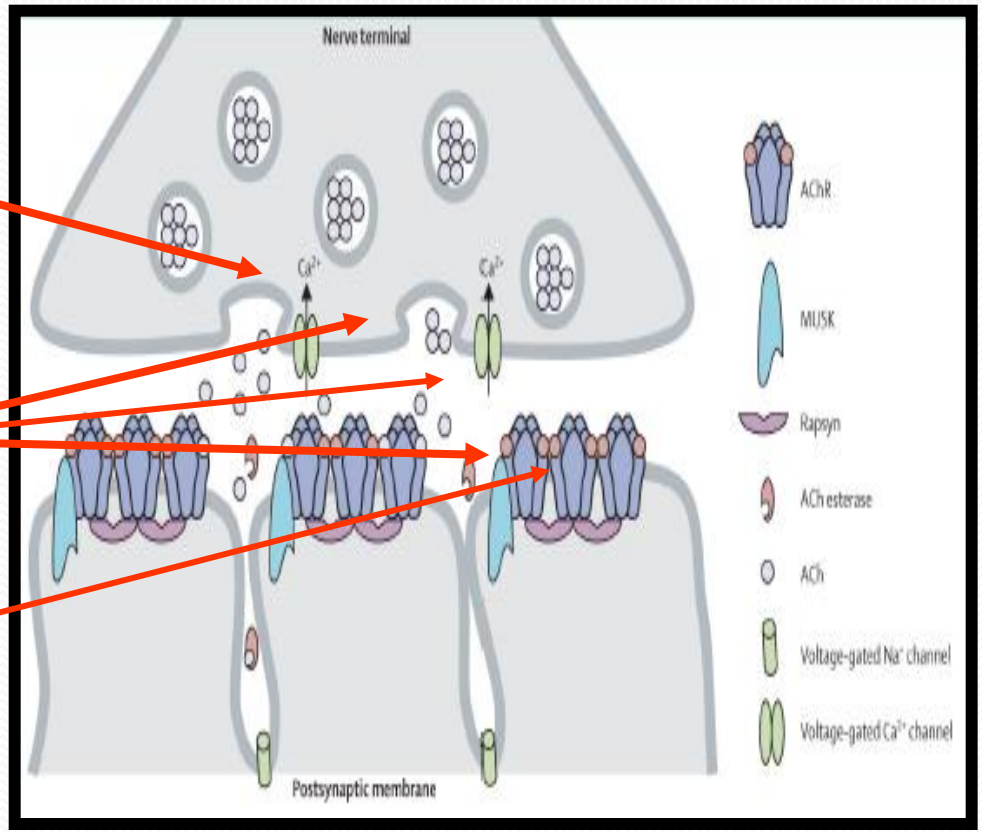
- Síndrome de Eaton Lambert

SINAPTICAS

- Síndromes Miasténicos congénitos

POSTSINAPTICAS

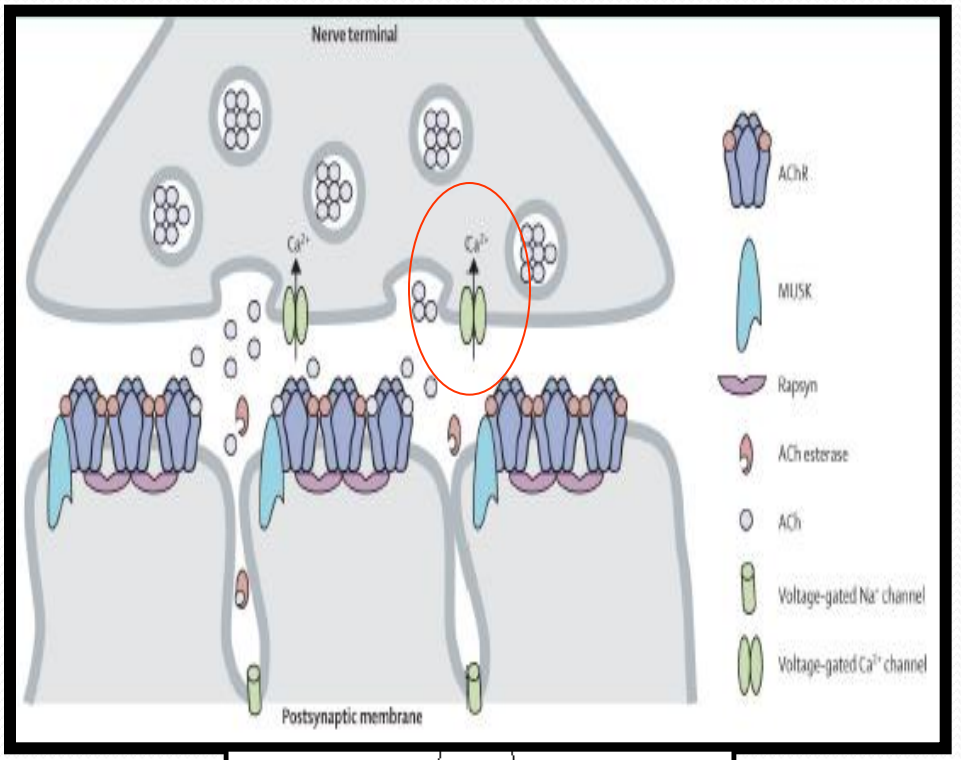
- Miastenia gravis

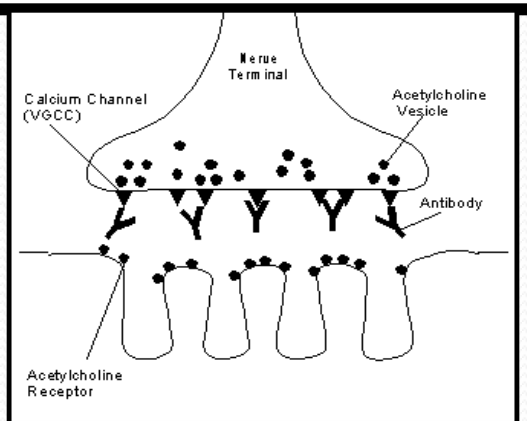


Síndrome de Eaton Lambert

- Inmune: Ac. Canal de calcio VD (p/q)+ 85%
- Incidencia 0,48/1.000.000
- Adultos Varon 4:1

- 50% es paraneoplásico*
  - Microcítico pulmón (85 %)
  - Adenocarcinoma próstata u ovario.
  - Linfomas.
  - Tumores Gastrointestinales.
  - Timomas.
  - Leucemias.
  - 90% en 2 años siguientes del LEMS

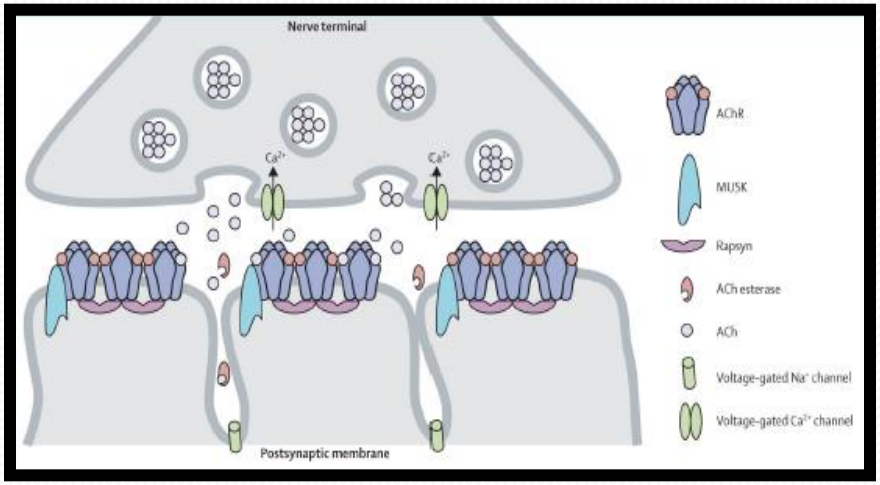


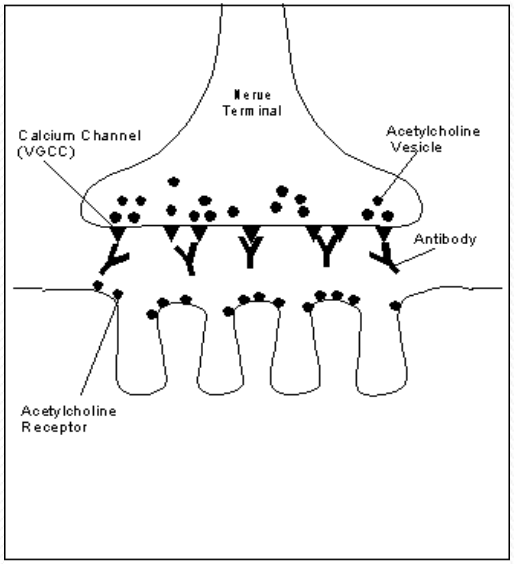


Síndrome de Eaton Lambert

- Debilidad mas proximal de MMII.
- Arreflexia.
- Curso ascendente.
- Afectación ocular (< 25%) y bulbar leves.
- Parestesias transitorias.
- Dolor muscular, rigidez.
- Disautonomia (se asocia mas a neoplasias):
  - Boca seca, ojo seco, gusto metálico
  - Estreñimiento, hipotensión ortostática.
  - Disfunción eréctil.

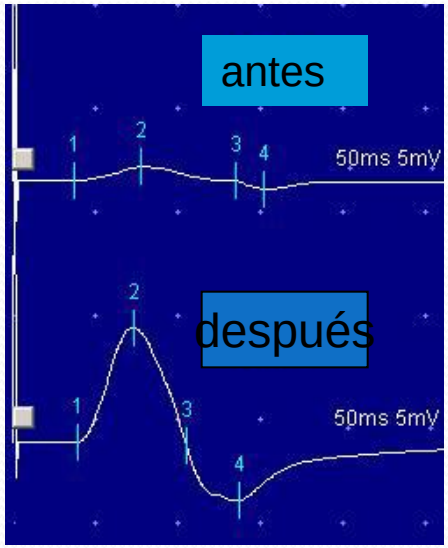
- Signo clínico mas típico es la <u>facilitación</u> :
  - mejoría de la fuerza tras breve ejercicio intenso o recuperación de RMC.

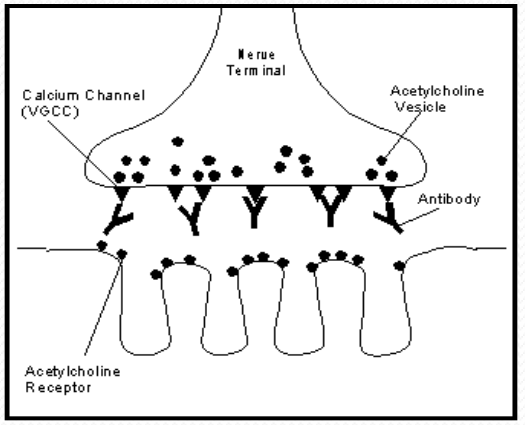


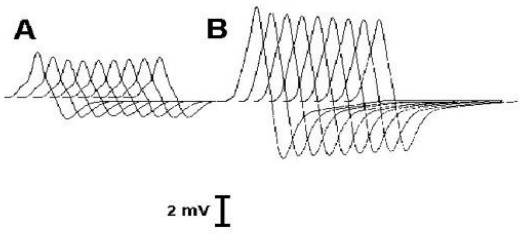


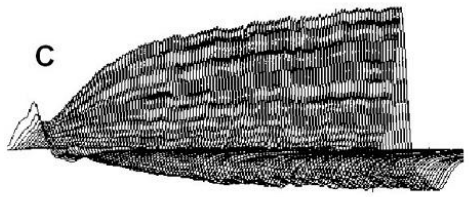
Voltage-Gated Calcium Channel (VGCC) Antibody Assay

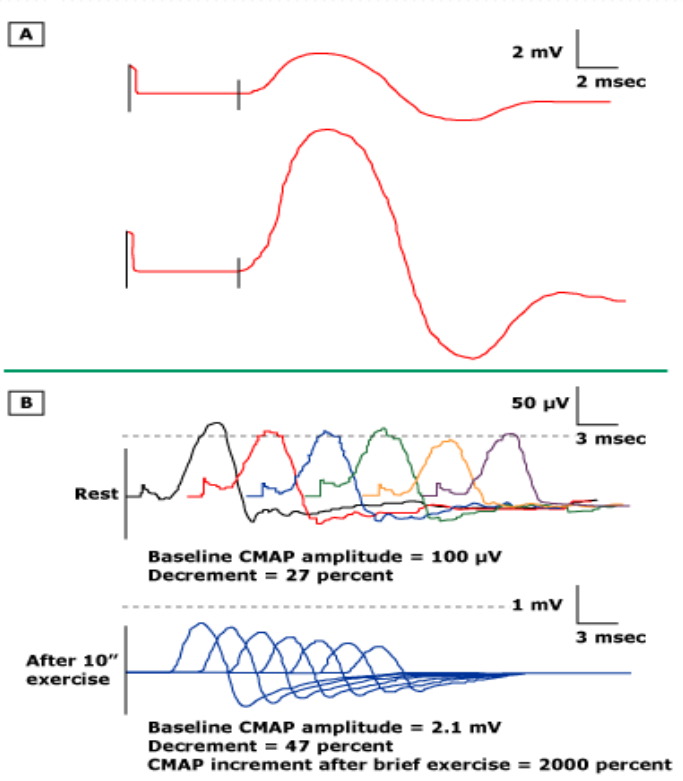
Estudio de la facilitación con EMG











Tratamiento sintomático LEMS
3,4 diaminopirina

- Hasta la fecha disponible en forma de base como formula magistral. Desde 2002 disponible en forma de sal en comprimidos de 10 mg.
- Perfil toxicológico y de bioequivalencia ha sido establecido entre ambas.
- 6 RCT frente a placebo con un total de 56 pacientes
- Dosis entre 20-100 mg/dia (40-80).
- Recomendado en Guia de EFNS como tratamiento sintomatico de primera linea en LEMS

- BASE

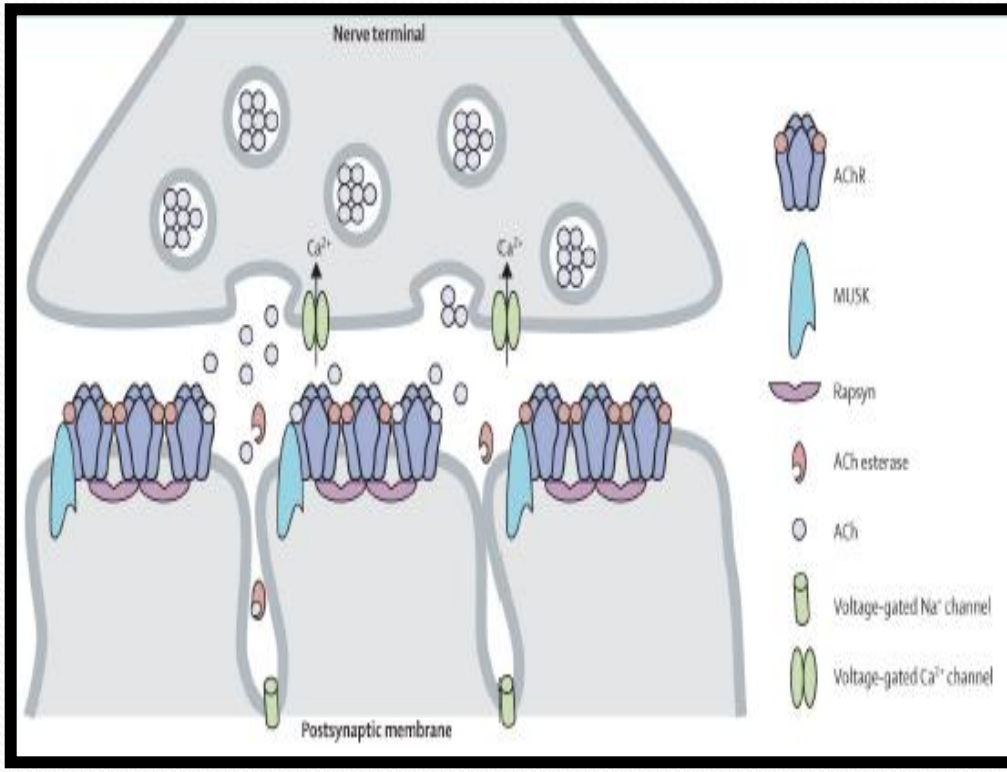
- Parestesias
- Sensación de calor
- Insomnio
- Cefalea
- Fatiga
- Crisis epilépticas en 2 de los 56 pacientes con dosis > 100 mg/dia
- Potencialmente arritmógena.

- SAL

- Parestesias, nauseas, vomitos, diarrea, dolor abdominal, fatiga, perdida de peso, palpitaciones.

Síndromes miasténicos congénitos

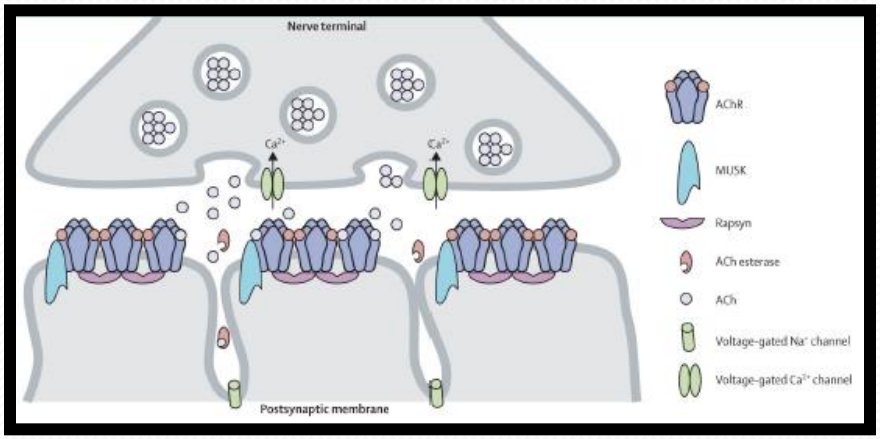
- Presentes desde la infancia (adultos).
- Debilidad muscular e hipotonia.
- AR. (CL –AD)
- Sindromes
  - Presinapticos
  - Sinapticos
  - Postsinapticos



Sindromes MC presinápticos

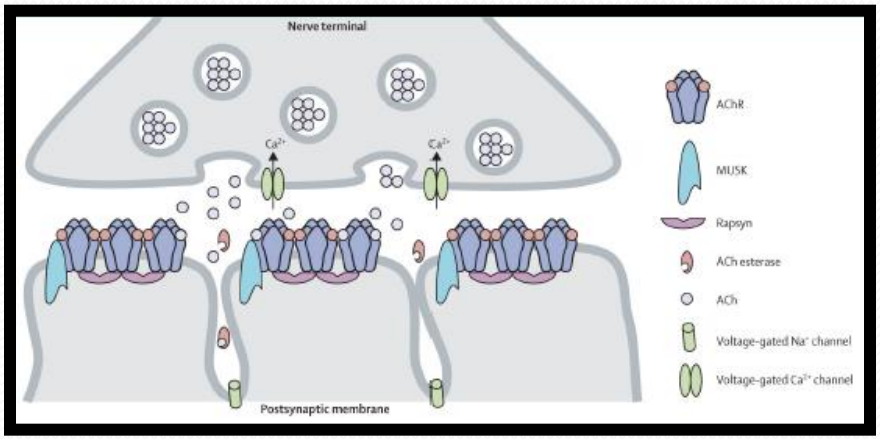
- Son los menos frecuentes

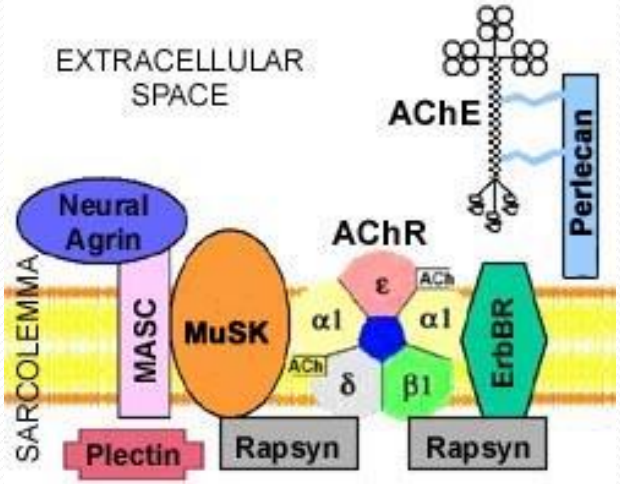
1. Mutaciones de la colinacetiltransferasa (CHAT)que interviene en la resintesis de AC.
2. Eaton Lambert “like”
3. Disminucion del numero de vesiculas de Ach.
4. Disminucion de la liberacion de quanta de acetilcolina



Síndromes sinápticos

1. Carencia de acetilcolinesterasa sináptica (mutaciones en el gen COLQ, que codifica la estructura proteica de la cola de esta enzima.
   - Aumenta la Ach en sinapsis
   - No respuesta a AC (empeoran).
   - Respuesta favorable a efedrina.

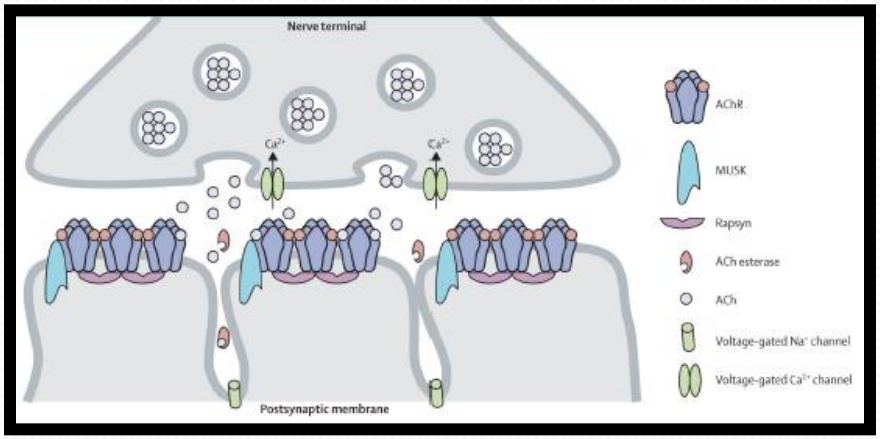




Síndromes postsinápticos

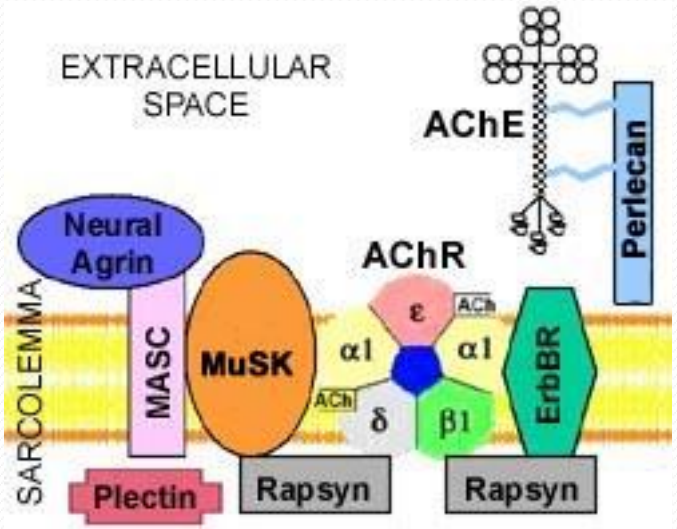
- Son los mas comunes.

1. Anomalías Cinéticas
   a) Canales lentos (Fluoxetina, Quinidina)
   b) Canales rápidos (AC+3,4D).
2. Deficit de receptores (AC+3,4D)
3. Alteracion del gen de la rapsina (AC+3,4D).

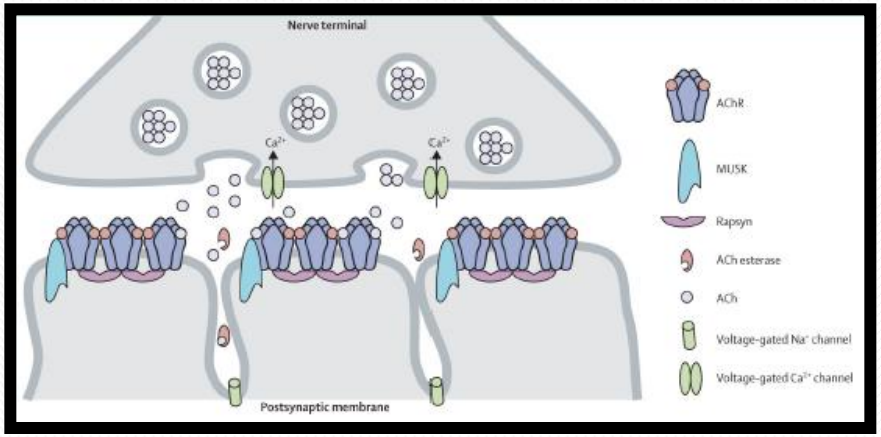


Síndromes miasténicos congénitos

- Otros



- Mutaciones en el gen MUSK.
- Deficit de plectina
- Dok-7 miastenia
- Mutacion en el canal de sodio SCN4A
- Miastenia transitoria neonatal (AARA +)



Published in final edited form as:
Neurotherapeutics. 2007 April ; 4(2): 252–257.

THE THERAPY OF CONGENITAL MYASTHENIC SYNDROMES

Andrew G. Engel

Table 1

Classification of CMS Based on Site of Defect*

	Index cases
Presynaptic (8%)	
Choline acetyltransferase deficiency**	13
Paucity of synaptic vesicles and reduced quantal release	1
Congenital Lambert-Eaton-like	2
Other presynaptic defects	3
Synaptic space (14%)	
Endplate AChE deficiency**	35
Postsynaptic (73%)	
Primary kinetic defect ± AChR deficiency**	52
Primary AChR deficiency ± minor kinetic defect**	92
Rapsyn deficiency**	36
Na channel myasthenia**	1
Plectin deficiency	1
Synaptopathy (5%)	
Dok-7 myasthenia**	12
Total	**248**

* Classification based on cohort of CMS patients investigated at the Mayo Clinic between 1988 and 2006. A single case of a CMS related to defect in MuSK has been reported by Chevessier et al.[14]

** Genetic defect detected

Miastenia Gravis Autoinmune

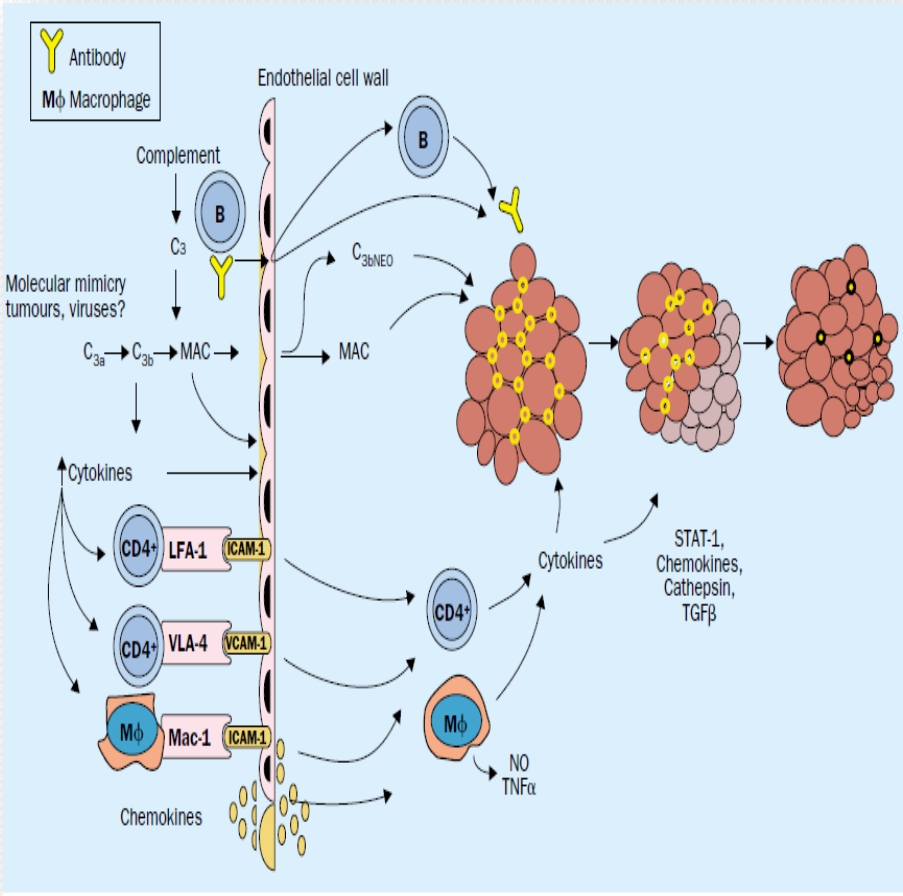
- Es una enfermedad autoinmune con anticuerpos contra la membrana postsináptica de la unión neuromuscular (+ 80 % formas generalizadas)
  - Anticuerpos contra Receptor de Acetilcolina
  - AntiMUSK
  - Anti LRP-4
- Cuando la MG se presenta antes de los 19 años se denomina Miastenia Gravis Juvenil (MGJ).
  - Prepuberal
  - Puberal
  - Postpuberal/adulta
- La MGJ comparte muchas características con la forma adulta, pero también presenta algunas diferencias.

Miastenia Gravis Autoinmune

- Es una enfermedad bien conocida:
  - Modelos experimentales de la enfermedad
  - Conocimiento de los mecanismos básicos de fisiología de la TNM.
  - Conocimiento de la patogenia de la enfermedad.
  - Conocimiento de la autoinmunidad.

Patogenia de la MG RAC+

- Cumple los criterios de enfermedad mediada por anticuerpos:
  - Los Ac están presentes en la UNM (IgG1 e IgG3
  - Ac de pacientes causan síntomas de MG cuando se inyectan a ratones.
  - La inmunización de animales con RAC reproduce la enfermedad.
  - Tratamientos que eliminan anticuerpos reducen la severidad de la enfermedad.



PATOGENIA. TIMO Y MIASTENIA GRAVIS

- TIMO ES EL ORGANO CENTRAL PARA DESARROLLAR Y CONTROLAR LA INMUNOTOLERANCIA.
- TIMO CONTIENE TODOS LOS ELEMENTOS NECESARIOS EN LA PATOGENESIS DE LA MG:
  - 1 CELULAS MIOIDES QUE EXPRESAN RAC.
  - 2 CELULAS PRESENTADORAS DE ANTIGENO Y LINFOCITOS T
- CENTROS GERMINALES LOS LINFOCITOS B INTERACTUAN CON LINFOCITOS T (HELPER) PARA PRODUCIR ANTICUERPOS.

M. Okumura et al.: Thymectomy for Myasthenia Gravis

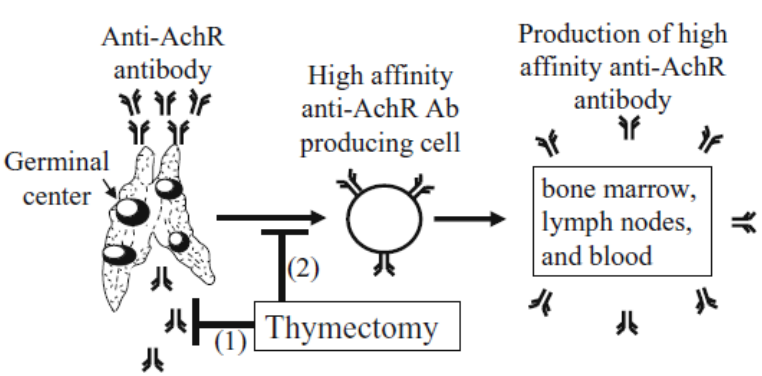


Fig. 1. Hypothetical role of the thymus in myasthenia gravis patients without a thymoma. Thymectomy terminates anti-acetylcholine receptor (*anti-AchR*) antibody (*Ab*) production by the thymus and the provision of high affinity anti-AchR antibody-producing cells to peripheral organs

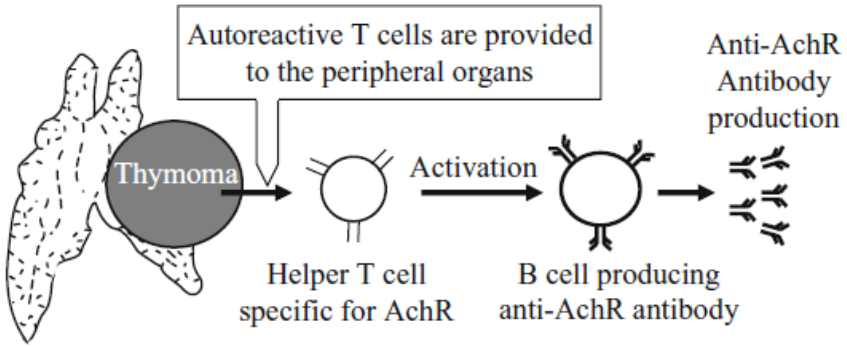
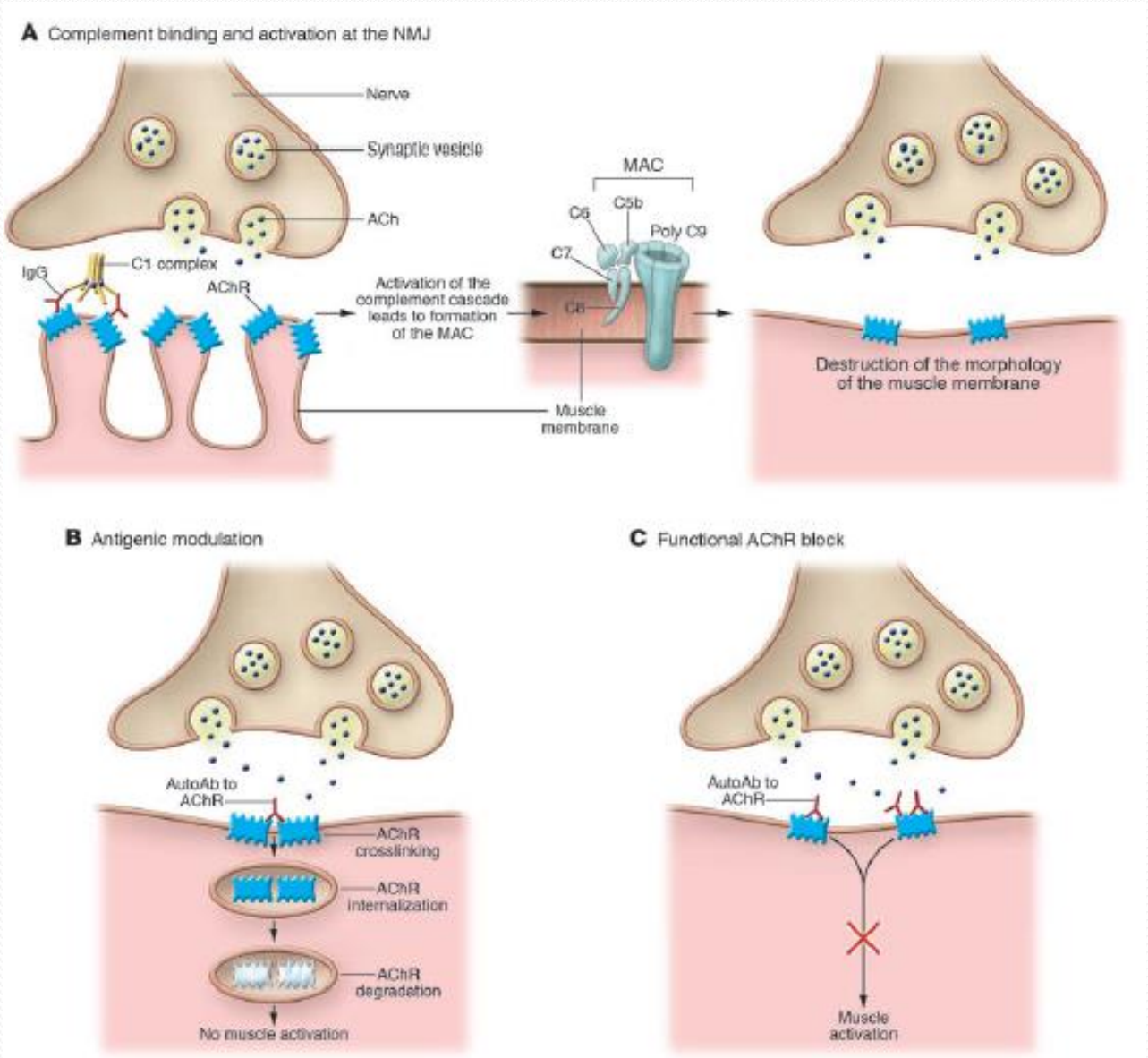


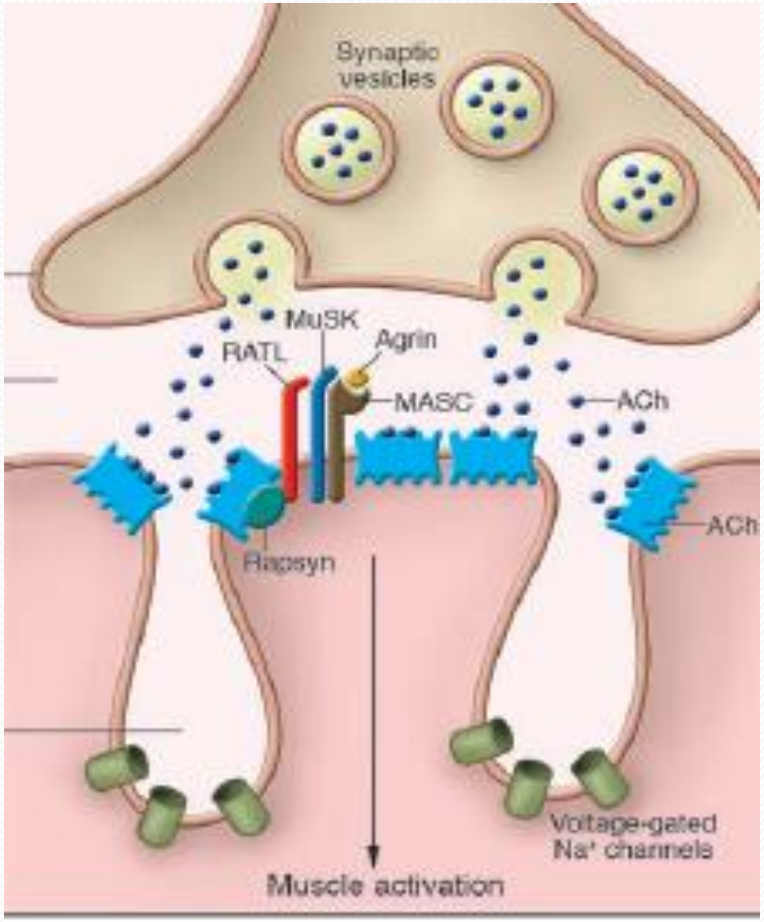
Fig. 2. Hypothetical role of a thymoma in myasthenia gravis. A thymoma produces helper T cells specific for AchR and provides them to the periphery. These helper T cells activate B cells to produce anti-AchR antibodies

Patogenia de la MG RAC+



Patogenia de la MG MusK+

- Los Ac son de clase IgG4 (diferentes a los RAC que son IgG1 e IgG3) NO ACTIVAN EL COMPLEMENTO.
- La densidad de los RAC esta conservada.
- La EAMG por MusK produce una reducción de los MEPP (menor nº de RAC funcionantes).
- Inhiben la agregación de RAC inducida por la agrina.



Epidemiologia

- La prevalencia MGAse sitúa en 20/100.000 (0,5-20/100.000)
- La incidencia MGA oscila en un rango entre 3-30/1.000.000.

- No existen datos precisos de incidencia/prevalencia de MGJ, pero hay diferencias geográficas, siendo mas frecuente en poblaciones orientales.
- Hasta un 50 % de todos los casos de MG en China se presentan en la infancia , la mayoría con síntomas oculares, con un pico de presentación entre los 5-10 años.
- En caucásicos se describe un inicio prepuberal inferior al 10% de todos los casos.

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 63.38×10^6 in the older population. These results, the highest reported to date, may be explained by the population aging.

NEUROLOGY 2003;60:1024–1026

Table *Number of cases and annual incidence rates of MG observed during 10-year (1991–2000) prospective study according to groups of sex and age*

Groups	No. of cases	Person–years	Annual incidence*
Total	26	1,222,212	21.27
Sex			
Men	10	600,725	16.65
Women	16	621,487	25.74
Age, y†			
Total			
0–14	1	198,783	5.03
15–64	12	817,406	14.68
≥65	13	208,388	62.38
Men			
0–14	0	96,610	0.00
15–64	5	417,580	11.97
≥65	5	89,390	55.93
Women			
0–14	1	92,400	10.82
15–64	7	411,700	17.00
≥65	8	121,550	65.82

* Per 10^6 inhabitants.
† Using available official data of the study area from the census of 1991 and 1996 and from projected population for the 2000. When specified by sex, only 1996 census population was used.

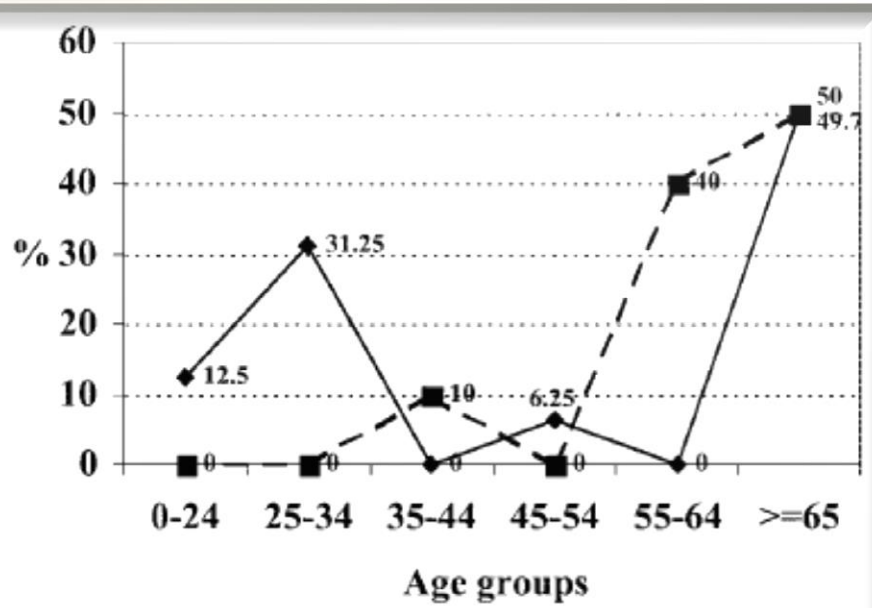


Figure. Percentage distribution of the diagnosed cases of MG (from 1991 to 2000) by age group and sex. —■— = men (n = 10); —◆—; = women (n = 16).

Juvenile Myasthenia Gravis: A Paediatric Perspective

Maria F. Finnis and Sandeep Jayawant

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Autoimmune Diseases
Volume 2011, Article ID 404101, 7 pages

TABLE 1: Comparisons of prepubertal and postpubertal features of JMG.

	Prepubertal	Pubertal	Postpubertal/ adult
Male : female ratio	M = F	F > M 4.5 : 1	F > M 4.5 : 1

Muscle Nerve **37:** 141–149, 2008

LIFETIME COURSE OF MYASTHENIA GRAVIS

DAVID GROB, MD,[1] NORMAN BRUNNER, MD,[1] TATSUJI NAMBA, MD,[1] and MURALI PAGALA, PhD[2]

[1] Department of Medicine, Maimonides Medical Center, Brooklyn, New York
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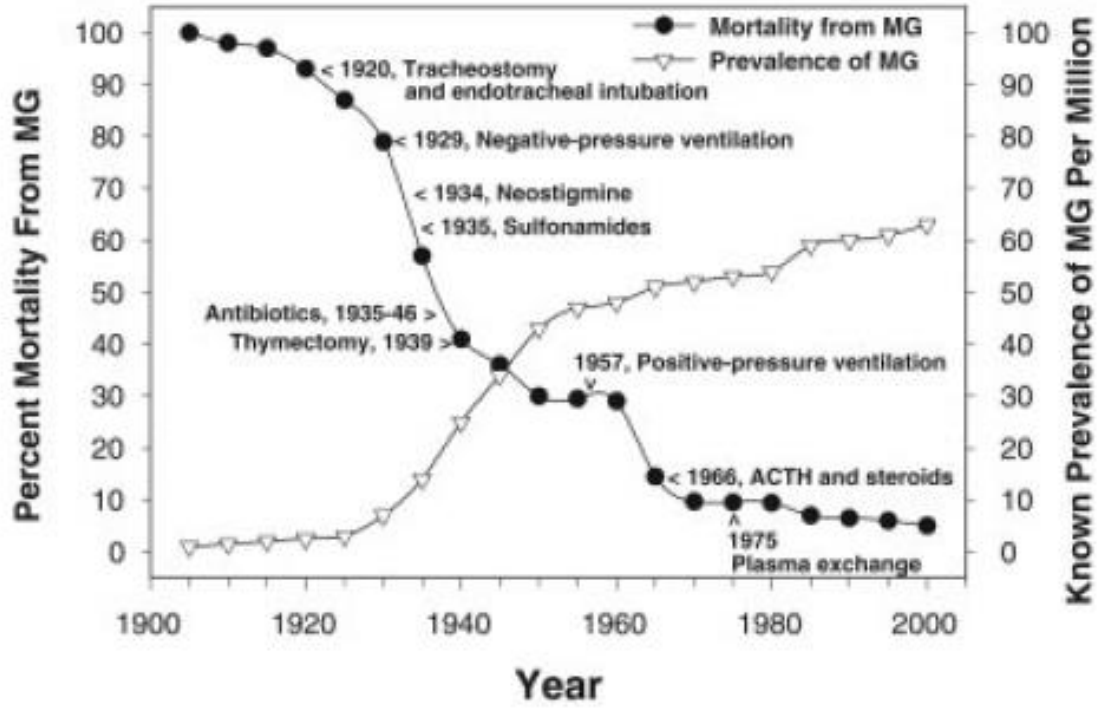


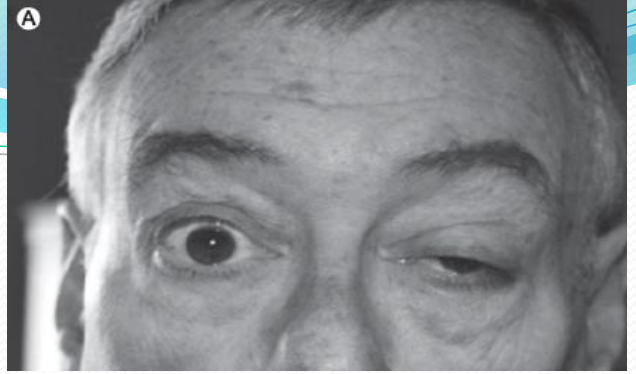
FIGURE 1. Known prevalence and mortality from MG during 1900 to 2000.

Manifestaciones clínicas

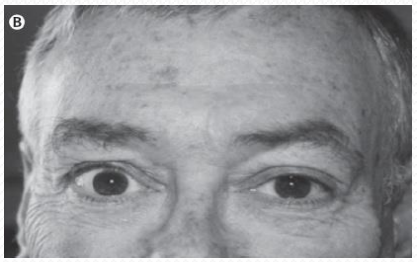
Síntomas de la enfermedad

- Los síntomas de la MG están causados por una debilidad muscular característica que empeora con el uso del musculo afectado.
- La debilidad muscular por fatigabilidad es un síntoma y un signo que se puede explorar.
- Diferenciarlo de “Fatiga” o “Cansancio”.
- Es un dato muy sugerente de alteración de TNM.
- Puede verse en otras enfermedades NM.
- De forma característica en la MG es fluctuante.
- Puede afectar a diferentes grupos musculares.

Debilidad de MOE



- La debilidad de la musculatura ocular (ptosis y/o diplopía fluctuante) esta presente al inicio de la MG hasta en un 85-90% de pacientes,



- Las formas "oculares puras" al inicio representan el 18-59%. Un 80 % de ellas progresaran a formas generalizadas.

- En la MGJ la forma mas habitual de presentación es la PTOSIS , asociada frecuentemente con
  - Oftalmoplejia unilateral o asimétrica,
  - Estrabismo (puede causar (AMBLIOPIA)

Table 1: Comparisons of prepubertal and postpubertal features of JMG.

	Prepubertal	Pubertal	Postpubertal/ adult
Ocular presentation			
Caucasian	40% [7]	9–16% [12]	28% [6]
Chinese	75% [6]		

Debilidad de la musculatura bulbar

- Puede presentarse como inicio hasta en el 15% de casos en la forma adulta.
- En la MGJ estos síntomas aparecen cuando la enfermedad se generaliza
  - Disartria por debilidad lingual, bucal o palatal (habla nasal)
  - Disfagia
  - Debilidad en masticación con mayor debilidad para el cierre de la mandíbula.
- Existe riesgo de asfixia/aspiración y de infecciones pulmonares,
- La ausencia en ocasiones de síntomas oculares puede sugerir otros diagnósticos (ENM).
- La debilidad de la musculatura facial no es infrecuente, hay que explorarla, manifestándose con debilidad para cerrar los parpados con fuerza o inflar las mejillas.

Debilidad de extremidades y otros músculos

- La debilidad de extremidades puede ser la forma de presentación entre un 9-20% de casos en las formas adultas.
  - Se presenta preferentemente de forma simétrica y proximal.
  - Se ha descrito una forma clínica con distribución clínica de la debilidad que simula una distrofia de cinturas (LGMD) hasta en un 3% de casos.
  - Puede haber también una afectación con predominio distal en el 3 % de casos o focal.
- Puede haber afectación de musculatura del cuello flexora>extensora .
- La insuficiencia respiratoria aislada puede ser una forma de presentación en 1-2% de casos.
- Esfínter vesical.

Acta Neurol Scand 2003: 108: 209–210
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ACTA NEUROLOGICA
SCANDINAVICA
ISSN 0001-6314

Distal myasthenia gravis – frequency and clinical course in a large prospective series

Werner P, Kiechl S, Löscher W, Poewe W, Willeit J. Distal myasthenia gravis – frequency and clinical course in a large prospective series. Acta Neurol Scand 2003: 108: 209–210. © Blackwell Munksgaard 2003.

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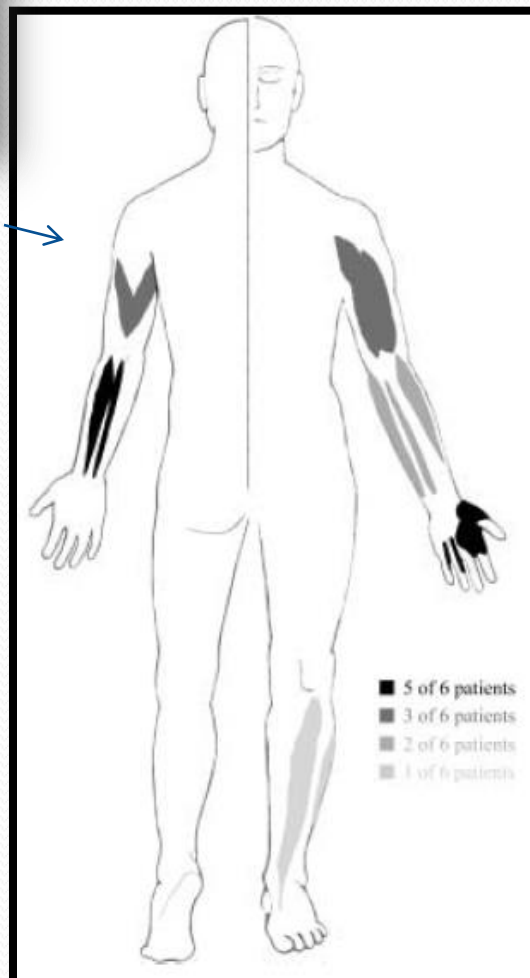

Distal myasthenia gravis.

Clasificación de la MG

- Osserman
- MGFA
  - Clase I
  - Clase II a, II b
  - Clase III a, III b
  - Clase IV a, IV b
  - Clase V
- QMG score (quantitative MG score)
- QOLQ (quality of life questionnaire)

Clasificación de la MG. MGFA

Table 1 *MGFA Clinical Classification*

Class I	Any ocular muscle weakness May have weakness of eye closure All other muscle strength is normal
Class II	Mild weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class III	Moderate weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class IV	Severe weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IVa:	Predominantly affecting limb and/or axial muscles May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Quantitative MG score

Table 2 *Quantitative MG score for disease severity*

Test item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision on lateral gaze right or left (circle one), seconds	61	11–60	1–10	Spontaneous	
Ptosis (upward gaze), seconds	61	11–60	1–10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz. water (½ cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)	
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30–49	Dysarthria at 10–29	Dysarthria at 9	
Right arm outstretched (90 deg sitting), seconds	240	90–239	10–89	0–9	
Left arm outstretched (90 deg sitting), seconds	240	90–239	10–89	0–9	
Vital capacity, % predicted	≥80	65–79	50–64	<50	
Rt-hand grip, kgW					
Men	≥45	15–44	5–14	0–4	
Women	≥30	10–29	5–9	0–4	
Lt-hand grip, kgW					
Men	≥35	15–34	5–14	0–4	
Women	≥25	10–24	5–9	0–4	
Head lifted (45 deg supine), seconds	120	30–119	1–29	0	
Right leg outstretched (45 deg supine), seconds	100	31–99	1–30	0	
Left leg outstretched (45 deg supine), seconds	100	31–99	1–30	0	
				Total QMG score (range, 0–39) _____	

Subtipos de MG

1. MGJ. Edad de inicio < 19 años
2. Edad de inicio temprano < 40 años.
3. Edad de inicio tardío > 40 años.
4. MG con timoma.
5. MG MUSK positiva.
6. MG seronegativa (AARA y MUSK).
7. MG ocular.

1. MGJ. Edad inicio < 19 años

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Table 1: Comparisons of prepubertal and postpubertal features of JMG.

	Prepubertal	Pubertal	Postpubertal/ adult
Male : female ratio	M = F	F > M 4.5 : 1	F > M 4.5 : 1
Ocular presentation			
Caucasian	40% [7]	9–16% [12]	28% [6]
Chinese	75% [6]		

HLA DRw9 poblaciones orientales
HLA DQ8 y DR3 poblaciones caucásicas
HLADR5 descendientes africanos.

Muscle Nerve **39:** 423–431, 2009

JUVENILE MYASTHENIA GRAVIS

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Table 1. Symptoms at presentation and progression.

Investigators	Year	Subset	*n*	Onset range (years)	At presentation				Ocular only
					I	IIA	IIB	III/IV	
Lindner et al.	1997		79		7	36	25	11	9%
Rodriguez et al.	1983		149	1–16	14	24	108	3	9%
Evoli et al.	1998		133	1.5–20	23	47	38	25	17%
		Evoli (young cohort)	19	1.5–9.2	5	4	2	8	26%
		Evoli (older cohort)	114	>9.3 (M), >8.9 (F)	18	43	36	17	16%
Batocchi et al.	1990		59	1–17	11	20	28		19%
		Batocchi (pre)	26	<12	8	8	10		31%
		Batocchi (post)	33	13–17	3	12	18		9%
Morita et al.	2001		18	1–12	4	5		9	22%
Ashraf et al.	2006		77	0.5–25	23	40	12	2	30%
Snead et al.	1980		32		20	12			63%
Mullaney et al.	2000		25	0.9–16	14	11			56%
Wong et al.	1992		101	1–15	72	17		12	71%
Raksadawan et al.	2002		27	0.25–10	25			2	93%
Compilation			**700**	**0.25–25**	**213**		**487**		**44%**

1. MGJ. Edad inicio < 19 años

Table 1: Comparisons of prepubertal and postpubertal features of JMG.

	Prepubertal	Pubertal	Postpubertal/ adult
Male : female ratio	M = F	F > M 4.5 : 1	F > M 4.5 : 1
Patients with AChR antibodies detected in generalised disease	50–71% [1, 2]	68–92% [1, 2]	80–90%

Los datos en las formas de MGJ oculares puras son controvertidos .

En las MGA oculares puras la positividad esta alrededor del 50%

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Table 3. Anti-AChR status.

Investigators	Year	Subset	*n* tested	Anti-AChR$^+$	Anti-AChR$^+$ (%)
Ashraf et al.	2006		14	11	79%
Evoli et al.	1998		133	124	93%
		Evoli (young cohort)	19	14	74%
		Evoli (older cohort)	114	110	96%
Andrews et al.	1994		95	75	79%
		Andrews (prepubertal)	14	7	50%
		Andrews (peripubertal)	25	17	68%
		Andrews (postpubertal)	56	51	91%
Zhang et al.	2007		197	127	64%
Morita et al.	2001		11	9	82%*
Lindner et al.	1997		42	34	81%
Batocchi et al.	1990		40	35	88%
		Batocchi (pre)	26	8	31%
		Batocchi (post)	33	3	9%
Snead et al.†	1980		17	9	53%
Compilation			**532**	**415**	**78%**

2.Edad inicio temprano < 40 años

- Son más frecuentemente mujeres (ratio 4:1). Pico en los 30 años.
- Los AARA (IgG1 e IgG3) positivos hasta en un 90 % de los casos.
- No suele ser frecuente la presencia de anticuerpos contra otros componentes musculares.
- Suelen haber otros anticuerpos organoespecificos, y pueden presentar otras enfermedades autoinmunes, siendo la mas frecuente las tiroideas.
- El timo suele presentar una hiperplasia que se evidencia en mas del 80% de los casos, que contiene células B, T y células plasmáticas, así como células miodes que expresan RAC. Por tanto están todos los componentes necesarios para que se desarrolle una respuesta inmune contra el RAC. Patogenesis intratimica.

3.Edad inicio tardío > 40 años

- Son más frecuentes en hombres (ratio 1:3). Pico en los 65 años.
- Pueden presentar un curso clínico más severo que las formas tempranas, siendo las remisiones espontaneas raras.
- Los AARA pueden ser negativos hasta en un 40%. Además de los AARA estos pacientes pueden tener anticuerpos frente a otras proteínas del musculo estriado (titina y el receptor de rianodina). La presencia de estos anticuerpos antimúsculo particularmente el receptor de rianodina se ha asociado con formas generalizadas más severas, o debilidad predominantemente orofaringea y con frecuentes crisis miasténicas.
- El timo suele ser normal o presenta atrofia. El mecanismo de autosensibilizacion no está claro planteándose la posibilidad de que pudieran existir células timomatosas ocultas y suprimidas por reacciones inmunes antitumor.

4. MG con timoma

- Presente entre un 10-15% de pacientes.
- Presenta por igual en mujeres que en hombres.
- Puede ocurrir en cualquier edad con un pico de incidencia a la edad de 50 años.
- Es muy raro en la MGJ y mas en la prepuberal.

- La hiperplasia timica es el hallazgo mas frecuente en las timectomias (73-89%) de MGJ > 10 años.
  - MGJ <9,2 años HT tras TX en un 33 % (n 3)
  - MGJ 9,3-20 años HT tras TX en un 84 %

Muscle Nerve **39:** 423–431, 2009

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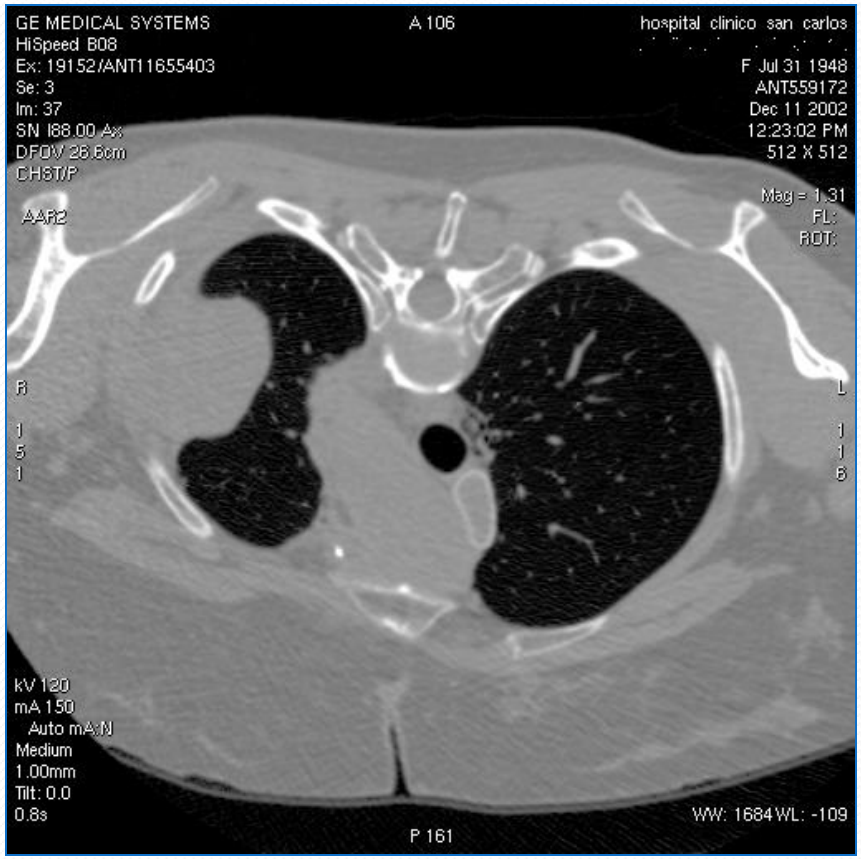
Table 2. Thymic pathology.

Investigators	Thymectomy	Thymic hyperplasia	Thymoma	Thymic hyperplasia of those undergoing thymectomy*
Ashraf et al.	11	8	1	73%†
Evoli et al.	105	84	4	80%
Evoli et al. (younger)	9	3	0	33%
Evoli et al. (older)	96	81	4	84%
Rodriguez	85	66	2	77%
Wong et al.	12	6	4	50%
Morita et al.	4	4	0	100%
Batocchi et al.	43	38	1	88%‡
Snead et al.	7	3	0	43%
Mullaney et al.	14	9	0	64%
Compilation	**281**	**218**	**12**	**78%**

4. MG con timoma

- La forma de presentación suele ser más severa siendo habitual la debilidad generalizada y la afectación bulbar.
- El pronóstico suele ser similar a las formas de inicio tardías.
- Títulos elevados de AARA.
- Suelen presentar anticuerpos anti titina.
- Pueden presentar de forma adicional otros anticuerpos asociados a síndromes paraneoplásicos (anticanal de K o Ca voltaje de pendientes, anti HU, anti decarboxilasa del acido glutámico …).
- A pesar de la timectomia suelen precisar inmunosupresion crónica.

Timoma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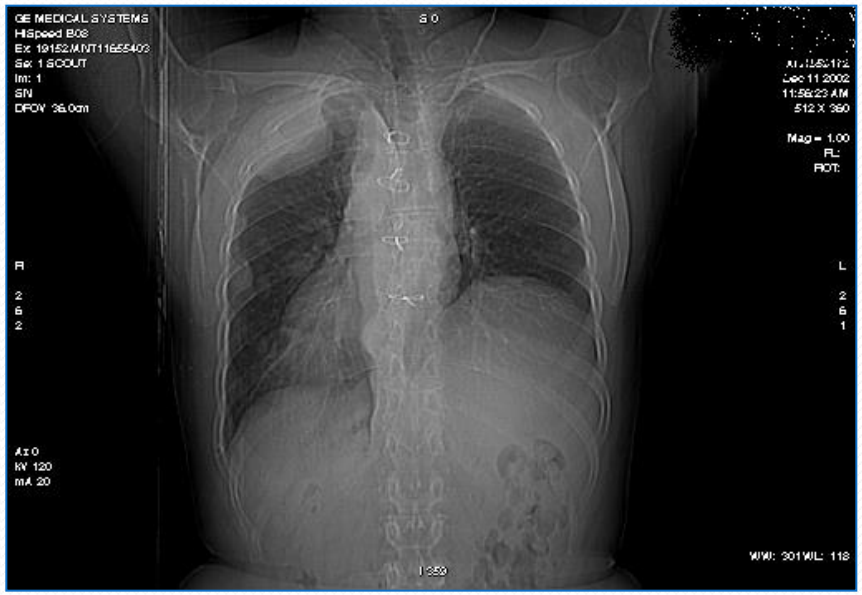
GE MEDICAL SYSTEMS
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Mag = 1.00
FL:
ROT:
R
L
kV 120
mA 20
WW: 301 WL: 118

TUMORES TIMICOS Y MIASTENIA GRAVIS RECIDIVAS A LARGO PLAZO

Prieto C[1*], Vázquez M[1*], Eimil M[1*], Gómez A[1**], Trancho FH[1**], Martín C[1***],Vela A[2*], Pérez Antón JA[2**], Martín J[2***], Guerrero Sola A[1*2*]

[1]**Hospital Clínico San Carlos de Madrid**: * Neurología, ** Cirugía Torácica, ***Anatomía Patológica.

MATERIAL Y METODOS

- Pacientes con diagnostico de MG en seguimiento desde el año 1990 hasta el año 2004 diagnosticados de Timoma con TAC torácico como parte del protocolo habitual en el estudio de la Miastenia (11 casos)
- Pacientes remitidos de Cirugía Torácica con diagnostico de Timoma para evaluación de posible enfermedad neuromuscular (4 casos)
- Se identifican un total de 15 pacientes con Timoma de un total de 146 (10.2 %)

RESULTADOS
DATOS CLÍNICOS

- El diagnóstico de MG y Timoma fue simultáneo en 9 casos (64.2 %)
- El diagnóstico de Timoma precedió al de MG en 3 casos (21.4 %)
  - Intervalo de tiempo entre 1 y 4 años. (1 caso mas).
- El diagnóstico de MG precedió al de Timoma en 2 casos (14.2 %)
  - Intervalo de tiempo entre 4 y 5 años. ***

RESULTADOS
DATOS CLÍNICOS

- Recidiva en 3 pacientes (21.4 %) con diseminación pleural:
  - Los tres son mujeres con edades al diagnóstico de 31, 31 y 47 años.
  - El tiempo transcurrido para la recidiva fue de 1, 10 y 19 años desde QX

Caso	Tiempo	Masaoka	WHO
Caso 4	19 años	I	AB
Caso 2	10 años	IV	AB
Caso 9	1 año	IV	B3

- Presentaron reagudización de la MG en relación con el diagnóstico de recidiva tumoral, sin cambios significativos en títulos de AARA.

5. MG MUSK positiva

- Un 15 % de pacientes con MG generalizada son AARA -.
- Un 40 % de estos presentan anticuerpos anti-MUSK (M>V). Edad temprana.
- MGJ MUSK+ es muy infrecuente, con marcado predominio en niñas
- En algunos MGJ AARA+ tras timectomia se produce seroconversión a MUSK+. (esto no se ha visto en adultos.)
- Pueden presentar formas clínicas similares a las que tienen AARA+,.
- Otros con datos clínicos atípicos con debilidad muscular selectiva de musculatura facial, bulbar (esofágica superior), paraespinal, y respiratoria (crisis mas frecuentes), a veces con marcada atrofia muscular y relativa preservación de la musculatura ocular.
- Peor respuesta a IgIV que a plasmaferesis.
- Pueden presentar una mayor sensibilidad a los anticolinesterasicos, pudiendo presentar un empeoramiento o falta de respuesta.
- No se conoce como se produce la sensibilización pero es probable que no esté implicado el timo
- MUSK son anticuerpos principalmente IgG4, que no activan el complemento.

6. MG seronegativa

- AARA y MUSK negativos.
- Se han detectado hasta en un 66 % de estos pacientes AARA de baja afinidad del tipo IgG1, que tiene capacidad para activar el complemento.
- Los pacientes responden al tratamiento inmunosupresor e incluso a la timectomia.
- El timo suele presentar hiperplasia y presencia de centros germinales similares a los AARA positivos.

- Anticuerpos anti-LRP4 + 9,2% de AARA-y MUSK -

7. MG ocular pura

Table 1: Comparisons of prepubertal and postpubertal features of JMG.

	Prepubertal	Pubertal	Postpubertal/ adult
Male : female ratio	M = F	F > M 4.5 : 1	F > M 4.5 : 1
Patients with AChR antibodies detected in generalised disease	50–71% [1, 2]	68–92% [1, 2]	80–90%
Ocular presentation			
Caucasian	40% [7]	9–16% [12]	28% [6]
Chinese	75% [6]		
Progression of OMG to generalised MG	8–15% [17, 18]	23–43% [16, 19]	79% [8]

7. MG ocular pura

- Si la debilidad queda limitada a la MOE a los 2 años del inicio hay un 90% de probabilidad de que no se generalice.
- Hasta un 50 % de pacientes tiene AARA positivos. Los títulos altos no predicen la generalización. AntiMusk se presentan raramente.
- La inmunopatogenesis puede ser similar a las formas generalizadas.
- La mayor susceptibilidad de los MOE puede derivar de diferencias en la morfología y fisiología de la UNM.
  - Los MOE tiene hendiduras sinápticas menos prominentes, menos RAC postsinapticos y unidades motora pequeñas, sujetas a frecuencias de descarga elevadas.
  - Otro posible factor relevante es la escasa expresión de los reguladores del complemento en sus membranas musculares, que las puede hacer más vulnerables a la acción del complemento.

Pronóstico de la MGJ

- En la MGJ se presentan índices de remisión espontánea mayores que en la MGA.)
  - MGJ 15-34 %
  - Prepuberal 42-60 %

Diagnostico

	Details
Bedside	
Edrophonium test	Reliable in patients with ptosis/extraocular weakness
Ice-pack test	Used only when assessing improvement in ptosis
Electrophysiological	
Repetitive nerve stimulation	75% of generalised MG, <50% of ocular MG
Single-fibre electromyography	Highly sensitive (95–99%), but not specific
Immunological (autoantibodies)	
Anti-AChR (binding)	85% of generalised MG, 50% of ocular MG
Anti-MUSK	40% of AChR-negative generalised MG
Low-affinity anti-AChR	66% of AChR and MUSK-negative generalised MG
Anti-titin	95% of thymomatous MG, 50% of late-onset, non-thymomatous MG
Anti-ryanodine receptor	70% of thymomatous MG (more severe disease)
Other	
CT scan or MRI of chest	Obtain in all patients after diagnostic confirmation of MG
Thyroid function testing	..

AChR=acetylcholine receptor. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase.

Table 2: **Diagnostic tests for MG**

PERGAMON

Neuromuscular Disorders 16 (2006) 459–467

www.elsevier.com/locate/nmd

A systematic review of diagnostic studies in myasthenia gravis

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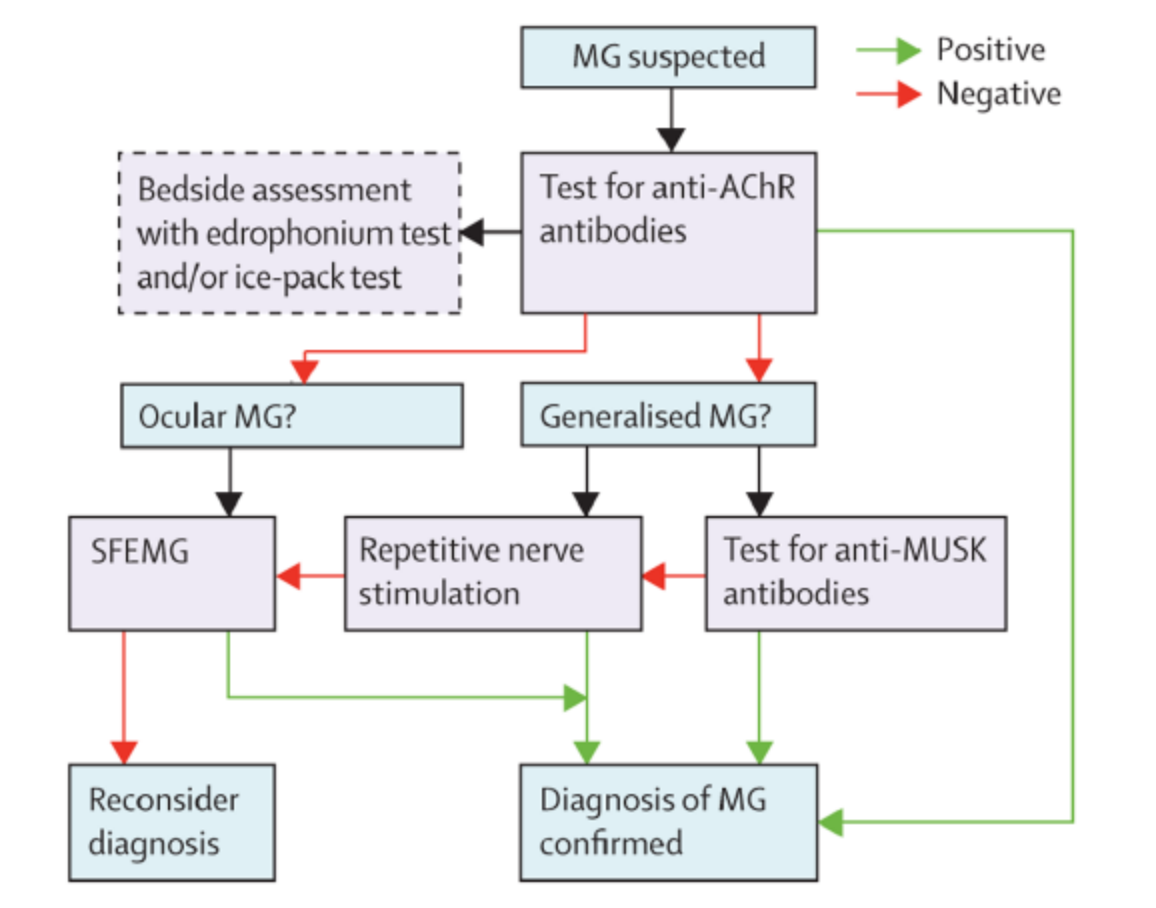
Received 29 March 2006; received in revised form 5 May 2006; accepted 9 May 2006

Abstract

We performed a systematic review to identify studies that reported the accuracy of tests for the diagnosis of myasthenia gravis. We identified 20 studies of reasonable, although variable, methodological quality upon which to base estimates of the accuracy of the ice test, rest test, Tensilon test, acetylcholine receptor antibodies, repetitive nerve stimulation and single fiber electromyography for the diagnosis of myasthenia gravis. After examining inter-study heterogeneity for each diagnostic modality, we calculated pooled estimates of sensitivity and specificity as well as positive and negative likelihood ratios. Results are reported separately for ocular and generalized myasthenia. Studies that have examined the performance of anti-acetylcholine receptor antibody testing and single fiber electromyography were generally of better quality than those that examined other diagnostic modalities. We suggest that caution should be exercised in the interpretation of the diagnostic performance of these tests given the methodological limitations of the studies upon which test performance is based.

Esquema diagnostico



Reconsiderar el diagnostico ante presentaciones clínicas dudosas, y diagnósticos basados en predomino de síntomas sobre signos.

Considerar posibilidad de errores en resultados de test.

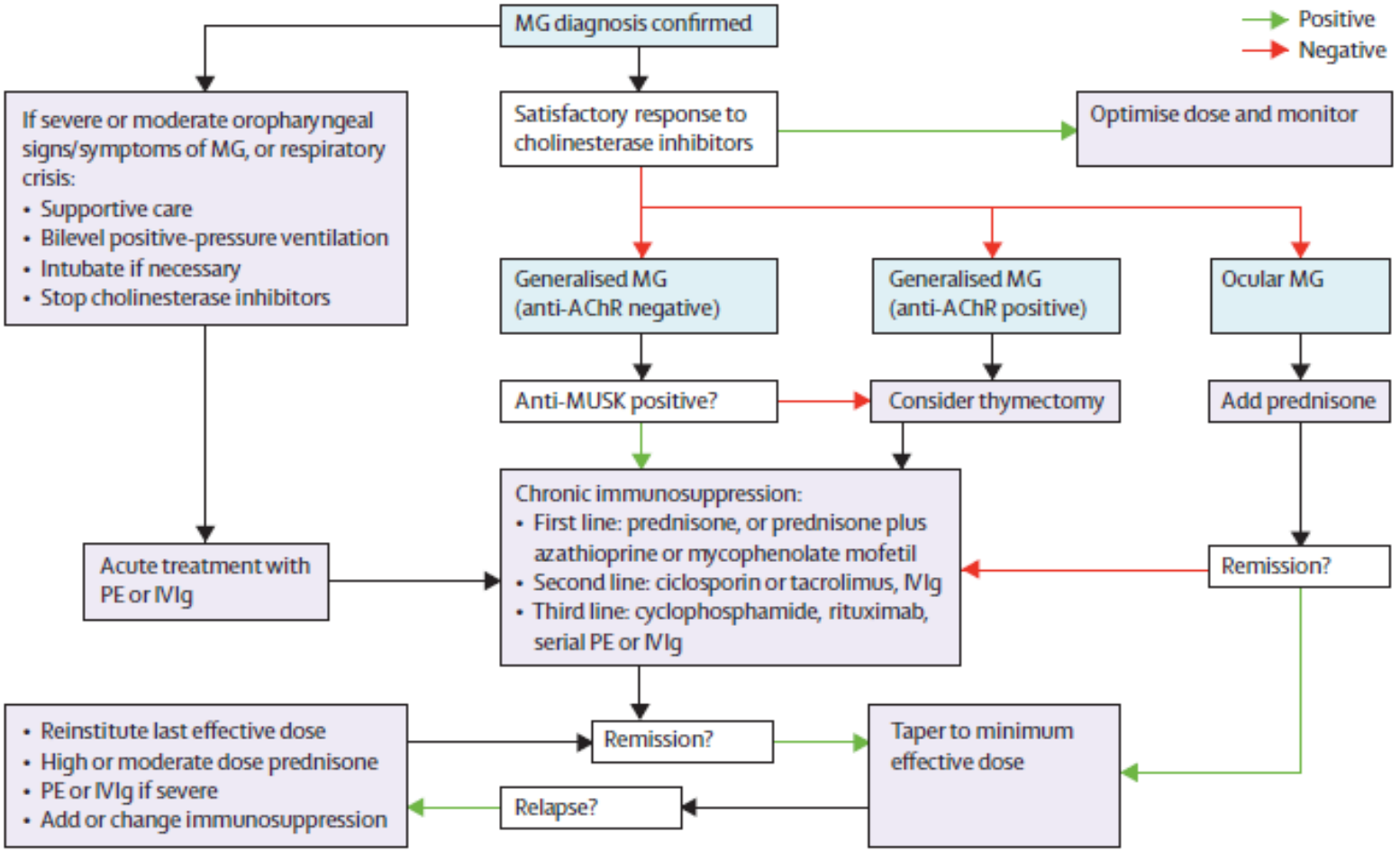
Tratamiento farmacológico

	Initial dosing and frequency	Comments
Symptomatic therapy		
Pyridostigmine[4,99]	30–90 mg every 4–6 h	Causes worsening in some MUSK MG patients
Short-term immune therapies		
Plasma exchange[100–102]	4–6 exchanges on alternate days	Treatment of choice in myasthenic crisis
Intravenous immunoglobulin[103,104]	1–2 g/kg (over 2–5 days)	Use in patients with exacerbating MG
AChR immunoadsorption[105–107]	Not established	Might offer more efficient/safer alternative to plasma exchange
Long-term immune therapies		
Prednisone[108–111]	0·75–1·0 mg/kg daily; or 60–100 mg on alternate days (gradual escalation); or 20–40 mg daily for ocular MG	First-line immune therapy; short-term use of high doses; frequent side-effects
Azathioprine[112–115]	2–3 mg/kg daily	First-line steroid-sparing
Mycophenolate mofetil[116–120]	2–2·5 g daily in divided twice daily doses	First-line steroid-sparing? Widely used in USA
Ciclosporin[121,122]	4–6 mg/kg daily in divided twice daily doses	Steroid-sparing in patients intolerant of or unresponsive to azathioprine or mycophenolate mofetil
Tacrolimus[123–126]	3–5 mg daily	Steroid-sparing in patients intolerant of or unresponsive to azathioprine, mycophenolate mofetil, or ciclosporin
Cyclophosphamide[127–129]	500 mg/m^2 or 4x50 mg/kg	Use in refractory/severe MG
Rituximab[130–132]	2x1000 mg intravenously (separated by 2 weeks)	Use in refractory/severe MG

AChR=acetylcholine receptor. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase.

Table 4: **Treatment options and management of MG**

Esquema terapéutico

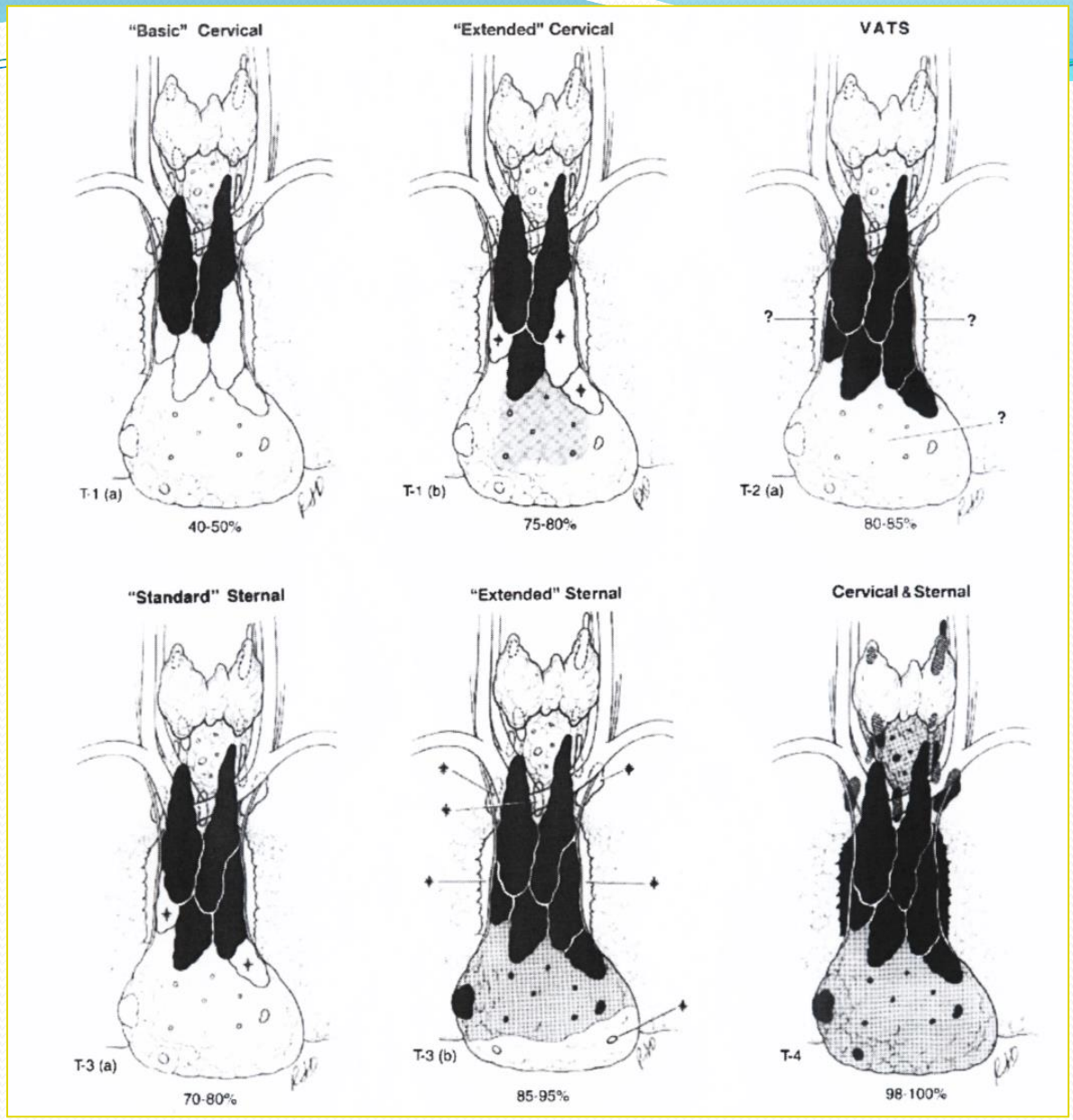


Timectomia

Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Gronseth GS, Barohn RJ. Neurology 2000.

- 21 articulos (1953-1998).
- Pacientes con TX doble probabilidad de estar en remision libre de medicacion.
- Pacientes con TX 1,6 veces mas probable de estar asintomatico.
- Pacientes con TX 1,7 veces mas probable que mejoren.
- Ningun estudio muestra influencia negativa de la TX.
- Las formas oculares puras no se benefician de la TX.
- El pronostico de los TX jovenes no fue diferente del grupo total.
- Las formas mas leves (Ossermann 1-2) menor beneficio
- Las formas mas severas (Ossermann 2b-4) 3,7 veces mas probable la remision

- Recomendable en el primer año de evolucion.


"Basic" Cervical
T-1 (a)
40-50%
"Extended" Cervical
T-1 (b)
75-80%
VATS
?
?
?
T-2 (a)
80-85%
"Standard" Sternal
T-3 (a)
70-80%
"Extended" Sternal
T-3 (b)
85-95%
Cervical & Sternal
T-4
98-100%

Maria F. Finnis and Sandeep Jayawant

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Thymectomy	Recommended to increase remission rates in postpubertal, seropositive children. Not recommended in prepubertal children	Hennessey et al., 2011 [30] Rodriguez et al., 1983 [31] Tracy et al., 2009 [32] Lindner et al., 1997 [20]

Remisiones 60% timectomias

Timectomia

Response of thymectomy: clinical and pathological characteristics among seronegative and seropositive myasthenia gravis patients. Guillermo GR, Tellez-Zenteno JF, Weder-Cisneros N, et al. Acta Neurologica Scandinavica. 2004.

- RAC+ remisión o mejoría en 3 años tras TX del 51% de los pacientes.
- RAC- remisión o mejoría en 3 años tras TX del 57% de los pacientes.

Muscle-Specific Receptor Tyrosine Kinase Antibody Positive Myasthenia Gravis Current Status. Shin Joong Oh, MD. Distinguished Professor of Neurology, The University of Alabama at Birmingham, The Veterans Affairs Medical Center, Birmingham, Alabama, USA. J Clin Neurol 2009;5:53-64.

Table 7. Improvement rate and rate of thymic hyperplasia

Series	Patient	Thymecomty	Improvement	Thymic hyperplasia
Evoli et al.	37	15	None	0
Zhou et al.	10	6		1/6 (17%)
Lavmie et al.	17	9	4; 2 CSR, 2 PR,	7/17 (41%), thymoma in 2
Ohta et al.	23	23		6/23 (26%)
Kostera-Pruszozyk	4	4	2; 1 CSR; 1 PR	2/3 (67%)
Saunders	12	7	0*	
Nemoto	4	4		1/1
Evoli et al.	57	17	0	1; thymoma
Pasnoor et al.	53	18	7; 1 CSR; 3 PR	

*Followed for 8 months. No improvement.
CSR: complete stable remission, PR: pharma cological remission.

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

J Neuroimmunol. 2008 September 15; 201-202: 80–84. doi:10.1016/j.jneuroim.2008.05.031.

The MGTX Experience: Challenges in Planning and Executing an International, Multicenter Clinical Trial

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ENSAYOS CLINICOS

- ACTIVOS

- Trasplante de células madre hematopoyéticas autólogas en MG refractaria. FASE I
- Eficacia de Metotrexate en MG. FASE II
- Eficacia y seguridad de Tacrolimus en MG. FASE III
- Rituximab en MG refractaria- FASE I,II *
- Estudio comparativo de dos estrategias de disminucion de esteroides (MYACOR). FASE IV.

- FINALIZADOS

- Eculizumab en MG refractaria. FASE II.

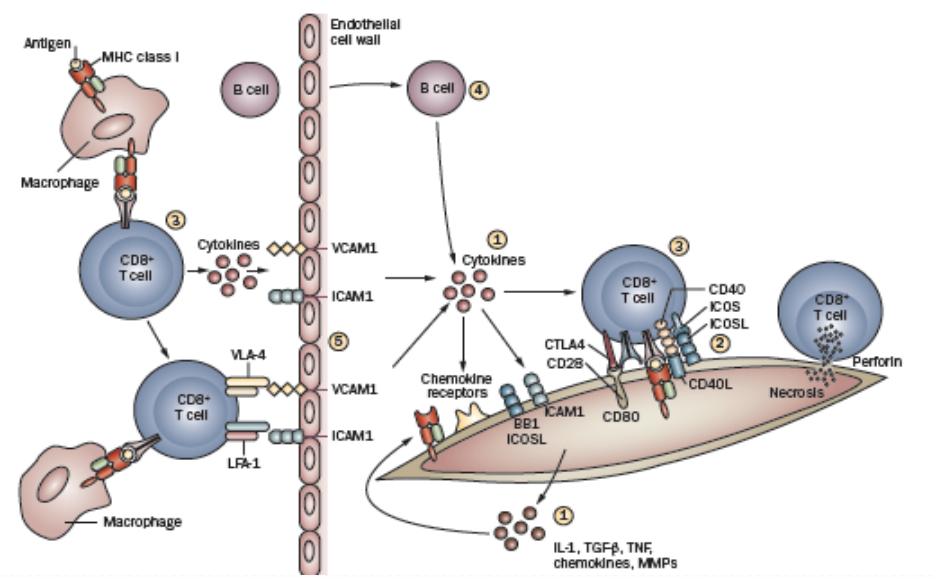
- PROXIMOS

- Evaluación de Belimumab en MG. FASE II

Posibles futuras terapias

Anticuerpos Monoclonales

- RITUXIMAB (anti CD20 células B)
- BELIMUMAB (Anti factor de crecimiento de células B.)
  - BAFF y APRIL
- ALEMTUZUMAB (Anti señalización de células T).
- NATALIZUMAB ((anti moléculas de adhesión).
- ECULIZUMAB (anti proteína del complemento C5).
- FINGOLIMOD (anti migración células) T.
- DACLIZUMAB (antagonista del receptor IL2).
- EFALIZUMAB Y ALEFACEPT (anti moléculas co-estimuladoras de las proteinas de membrana de linfocitos LFA-1 LFA-3)
- Inhibidores del TNF (INFLIXIMAB, ADALIMUBAB, ETANERCEPT).



Células Madre Hematopoyéticas

Fase I

- Hematopoietic Stem Cell Therapy for Patients With Refractory Myasthenia Gravis
- This study is currently recruiting participants.
- Verified by Northwestern University, November 2009
- First Received: January 18, 2007 Last Updated: November 18, 2009

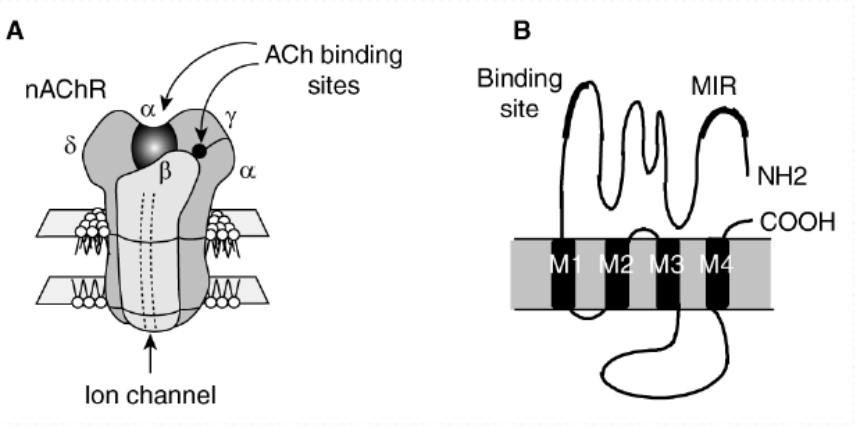
- MG may be neonatal, congenital, or autoimmune. Neonatal MG arises from transplacental transfer of ACh receptor antibodies from a mother with autoimmune MG to the fetus. Neonatal MG resolves with post delivery clearance of maternal antibodies. Congenital MG results from a genetic defect in the ACh receptor. Patients with congenital MG do not have ACh receptor antibodies. Both neonatal and congenital MG are excluded from this study. Autoimmune MG, which is the most common form of MG, affects approximately 25,000 Americans. Like most autoimmune diseases, it is associated with particular HLA genotypes, has a female predominance, and environmental factors involved in breaking tolerance to the ACh receptor are unknown. Patients with refractory and severe autoimmune MG will be considered candidates for this study.
- The purpose of this study is to assess the toxicity/feasibility (phase I) of autologous hematopoietic stem cell transplantation for refractory myasthenia gravis.

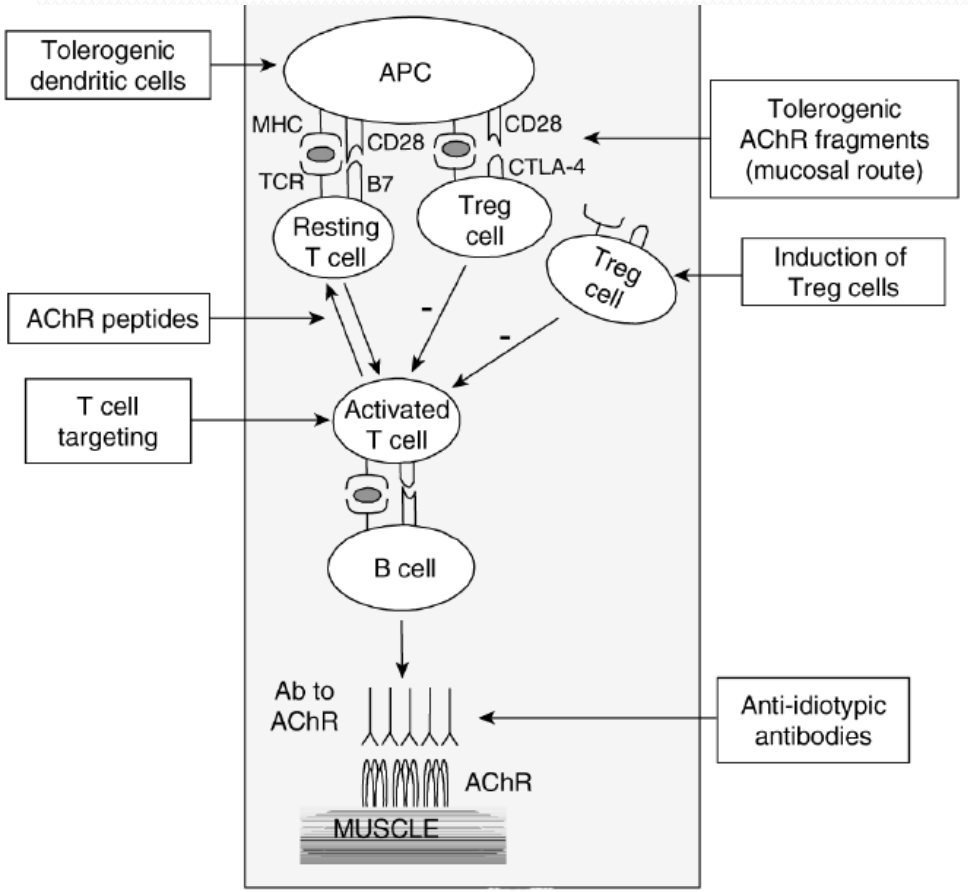
Posibles futuras terapias

Vacunas

Different methods of vaccination used in experimental models of myasthenia gravis: putative mechanisms of action.

Vaccines	Route	Species	Mechanism of action	Effects observed
Native AChR	Mucosal	Rats		Prevention
Denatured AChR	Intradermal	Rabbits		Ongoing
AChR recombinant fragments	Mucosal (nasal and oral)	Rats	Shift Th1 to Th2/Th3 Downregulation of costimulatory molecules	Ongoing
AChR peptides	Oral	Rabbits Mice	Anergy	Prevention Prevention and ongoing
AChR peptides	Intraperitoneal	Mice	Anergy, apoptosis Downregulation of IL-2, IFN-γ, IL-10	Prevention and ongoing
Altered peptides	Oral	Mice	CD4+CD25+ Upregulation of IL-10, TGF	Ongoing
Dendritic cells treated with IL-10	Intraperitoneal	Rat	Downregulation of costimulatory molecules	Ongoing
Dendritic cells pulsed with AChR	Subcutaneous	Rat	Reduced expression of BAFF	Prevention
Anti-Vβ5.1 antibodies	Intraperitoneal	SCID mice	Shift Th1 to Th2 Deletion of Vβ5.1$^+$ cells	Biological parameters

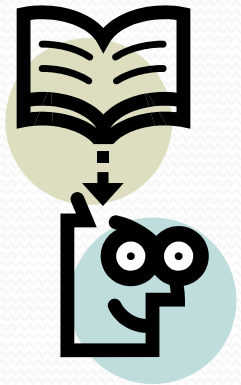




Conclusiones

- Las ETNM son un grupo de enfermedad bien tipificadas.
- El diagnostico adecuado depende de su conocimiento experiencia clínica y la correcta valoración de las pruebas diagnosticas (no sobrevalorarlas). En casos dudosos replantear el diagnostico.
- Existen numerosas alternativas terapéuticas (escalones). Es fundamental conocer el tiempo y forma de actuación de los fármacos utilizados para que el tratamiento sea mas exitoso
- El conocimiento de la patogenia y de modelos experimentales facilita la aplicación y ensayo de nuevos tratamientos.

Gracias por su atención



TIMECTOMIA EN LA MIASTENIA GRAVIS: EVOLUCIÓN Y PRONÓSTICO

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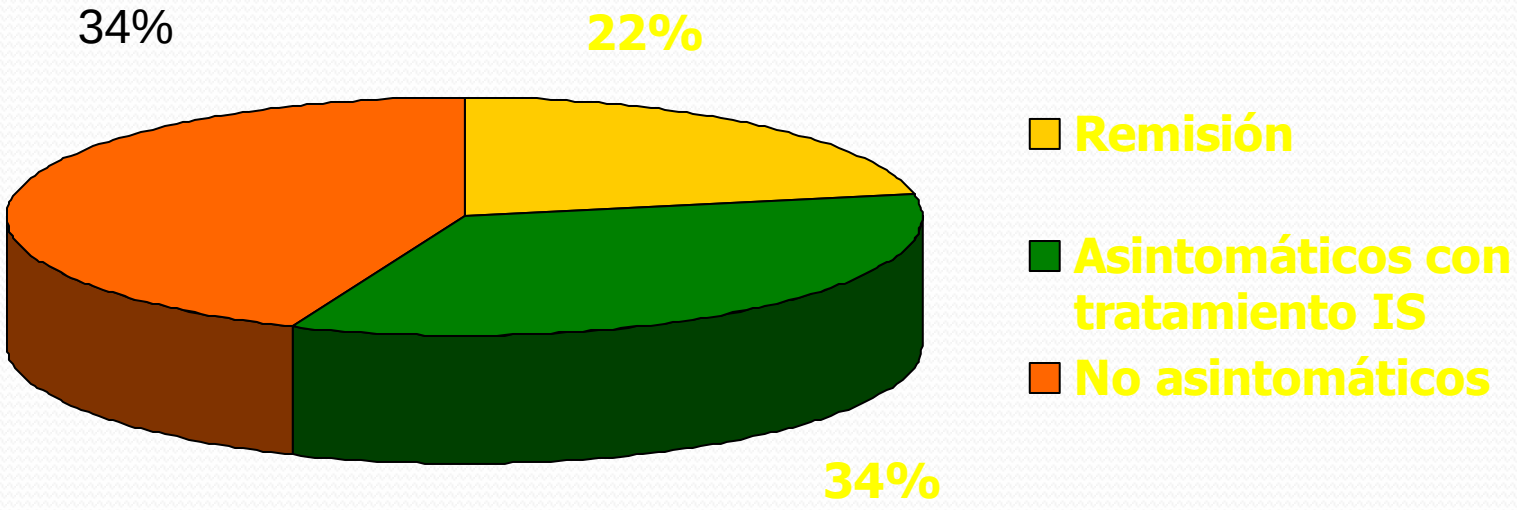
Hospital Clínico San Carlos. Madrid.

Material y métodos

- **Diseño: estudio retrospectivo de cohortes.**
- **Población de estudio: pacientes diagnosticados de MG entre los años 1975 y 2000 en el HCUSC.**
- **n = 107 pacientes.**
- **Mediana de seguimiento: 65 meses.**

Resultados (IX)



Evolución tras la timectomía

Esteroides

- En estudios observacionales (4) 442 pacientes un 73% presentan marcada mejoría o remisión que puede tardar en aparecer entre 4 y 16 semanas.
- Dosis altas 0,7-1 mg/kg/dia (1/3 posible empeoramiento entre los 4-10 dias, dura pocos dias, puede haber crisis).
- Reducir dosis lentamente tras remisión a una pauta a días alternos y dosis mínima eficaz.

- Pauta ascendente 20 mg/DA hasta 60-80 mg/DA

Azatioprina

- Interfiere con la proliferación de células T y B.
- El inicio de la respuesta puede demorarse entre 4 y 12 meses, con un máximo efecto entre los 2-24 meses.
- En 4 estudios (1 RCT) se demuestra beneficio entre 70-90% de pacientes, con mejor resultado cuando se usa en combinación con esteroides.
- Recomendable el inicio simultaneo con esteroides cuando sea previsible la necesidad de IS a largo plazo con inicio de 50 mg dia y aumento 50 mg semanales hasta 2-3 mg/kg/dia (o según actividad enzimatica)
- Déficit de TPMT (11% población es heterocigoto y 0,3% homocigoto) riesgo de mielosupresion.
- 15-20% reacción idiosincrasica pseudocatarral, gastrointestinal, pancretitis. Hepatitis. Leucopenia.
- Controles hematologicos y de transaminasas. Riesgo de cancer.

Micofenolato

- Es un bloqueador de la síntesis de purinas.
- Inhibe proliferación de células T y B.
- Dosis habitual 1000 mg/dia (3000 mg/dia vigilar hemograma por riesgo de mielosupresion).
- 2 RCT no han mostrado beneficio adicional sobre 20 mg de prednisona/dia
  - Estadio leve de los pacientes.
  - Mejor respuesta de la esperada a la dosis de prednisona.
  - Corta duración de los estudios.

Ciclosporina

- Inhibe la proliferacion de celulas T, se bloquea la sintesis de IL2 esenciales en la funcion de CD4.
- Estudios retrospectivos y 1 RCT
- En pacientes con mala respuesta a AZA o intolerantes.
- Dosis de inicio entre 4-6 mg/kg (en 2 dosis) con mantenimiento entre 3-4 mg/kg.
- Efectos adversos: HTA, nefrotoxicidad, hirsutismo, temblor, anemia, hipertrofia gingival.

Tacrolimus

- Mecanismo de acción similar a la ciclosporina.
- Estudios abiertos y 1 RCT (no ciego).
- Respuesta mas positiva en pacientes con anticuerpos antirreceptor de rianodina.
- Dosis entre 3-5 mg/dia .
- Perfil de menor toxicidad que ciclosporina, pero exige los mismos controles.

Ciclofosfamida

- Es un agente alquilante con efecto inmunosupresor.
- 3 estudios en pacientes con MG refractarias presentan respuestas positivas a tratamiento con pulsos IV.
  - 500 mg/m2

    De Feo LG, Schottlender J, Martelli NA, Molfino NA. Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. Muscle Nerve 2002;26:31–36.

  - 50 mg/kg/4 dias

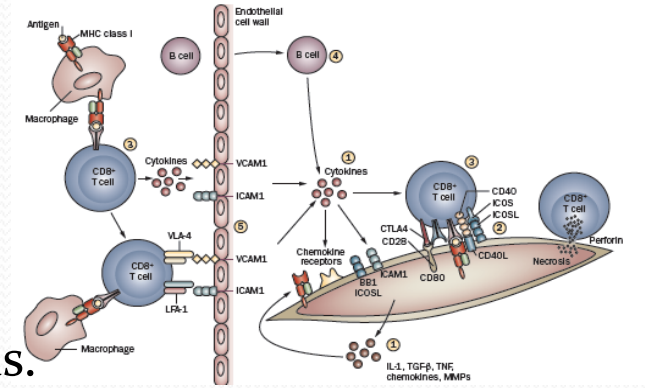
    Drachman DB, Jones RJ, Brodsky RA. Treatment of refractory myasthenia: “rebooting” with highdose cyclophosphamide. Ann Neurol 2003;53:29–34.

    Drachman DB, Adams RN, Hu R, Jones RJ, Brodsky RA. Rebooting the immune system with highdose cyclophosphamide for treatment of refractory myasthenia gravis. Ann N Y Acad Sci 2008;1132:305–14

Posibles futuras terapias

- Los avances en biotecnología han favorecido la aparición de nuevos fármacos en inmunoterapia, como los anticuerpos monoclonales que modifican la respuesta inmune.

  - Pueden inhibir o deplecionar de forma selectiva a células B o T
  - Factores de crecimiento.
  - Moléculas de transducción.
  - Citokinas
  - Moleculas de adhesión y co-estimuladoras.



Rituximab

- Ac. Monoclonal anti CD20 de las celulas B.
- Evidencia de eficacia en MG refractarias (tambien en MUSK+).
- 375 mg/m2/semana/4 semanas.
- Respuesta al retratamiento.
- Vigilancia, control de efectos adversos.
- Riesgo de LMP.

Posibles futuras terapias

Vacunas

- La vacuna se refería tradicionalmente al preparado utilizado para generar una inmunización protectora contra agentes infecciosos (viruela).
- Actualmente esa definición se ha extendido para incluir la administración de antígenos para conseguir la tolerancia o “apagar” la respuesta inmune antigénica especifica que permita prevenir o tratar enfermedades autoinmunes.
- Las enfermedades autoinmunes afectan a un 5 % de la población occidental, lo que conlleva una importante morbilidad y coste sociosanitario.
- El objetivo en inmunoterapia (vacuna) seria la supresión de la respuesta inmune sin afectar al resto del sistema inmune.

Clinical subtypes of myasthenia gravis

	Age at onset (years)	Thymic histology	Muscle autoantibodies	HLA associations	Comments
Early onset	<40	Hyperplasia	AChR	DR3-B8, DR9 (in Asians)	Male:female ratio=1:3
Late onset	>40	Normal	AChR, titin, ryanodine receptor	DR2-B7	Anti-titin and ryanodine-receptor antibodies associated with severe disease
Thymoma	40–60 (usually)	Neoplasia	AChR, titin, ryanodine receptor, KCNA4	None identified	Might be associated with other paraneoplastic disorders
MUSK	<40 (most patients)	Normal	MUSK	DR14-DQ5	Marked female predominance; selective oropharyngeal, facial, respiratory weakness in some patients
Seronegative (generalised)	Variable	Hyperplasia in some	Antibodies against clustered AChR in 66%	None identified	Unidentified autoantigen in those without low-affinity antibodies?
Ocular	Adult in USA and Europe; childhood in Asia	Unknown	AChR in 50%	Bw46 (in Chinese patients)	Low-affinity AChR antibodies?

AChR=acetylcholine receptor. KCNA4=voltage-gated K^+ channel subfamily A member 4. MUSK=muscle-specific receptor tyrosine kinase.

Meriggioli and Sanders

Ensayos Clínicos Activos

Exercise for Stable Myasthenia Gravis
This study is currently recruiting participants.
Verified by Baltimore VA Medical Center, January 2010
First Received: January 12, 2010 No Changes Posted

Purpose

Generalized fatigue in myasthenia gravis results in physical deconditioning that reduces fitness and increases risk of obesity, hypertension, elevated cholesterol and type 2 diabetes. This study will examine how active and fit are 30 individuals with chronic, generalized myasthenic subjects.
This study will also determine whether a 3 month home exercise program with aerobic, resistive, and pulmonary training can improve physical activity, strength, fitness, lung function and reduce cardiovascular disease risk.

Prednisona

Fase III

- Efficacy of Prednisone In the Treatment of Ocular Myasthenia (EPITOME')
- This study is not yet open for participant recruitment.
- Verified by Emory University, October 2009
- The purpose of this study is to evaluate the efficacy and tolerability of prednisone in patients diagnosed with ocular myasthenia.

Reducción de Prednisona (P+Aza)

Fase IV

- Study Comparing Two Tapering Strategies of Prednisone in Myasthenia Gravis (MYACOR)
- This study is currently recruiting participants.
- Verified by Assistance Publique - Hôpitaux de Paris, September 2009
- First Received: September 29, 2009 No Changes Posted .

  Purpose Pathology - Generalized myasthenia gravis (MG) is cause of muscle weakness that can have a significant impact on daily life activity but can also be, when respiratory or bulbar muscles are involved, life-threatening.
- Rationale - Additionally to thymectomy, which indication of is still debated in absence of thymoma, the long-term treatment of generalized myasthenia gravis includes usually prednisone and azathioprine. However, the most used scheme for prescribing and tapering corticosteroid in MG resulted in a very important cumulative dose of prednisone. Indeed, at twelve month, more than 50 percent of patients are still daily treated with at least 18 mg of prednisone and the proportion of patients who are in remission and no longer taking prednisone is very low (Palace and NEWSOM Davis, Neurology 1998). Prolonged corticosteroid therapy is accompanied with various and major side effects, hypertension, osteoporosis, weight gain, glaucoma. Therefore, tapering, eventually discontinuing, prednisone earlier is a relevant therapeutic goal.
- For this reason, the investigators will compare to the standard one, a strategy consisting of a rapid decrease in corticosteroid.
- Objective - To assess whether, in patients with generalized MG requiring a long-term treatment with corticosteroids and azathioprine, that the strategy of rapid tapering allows discontinuing more rapidly the prednisone for equivalent efficacy than the classical strategy.

Methotrexate

Fase II

- Methotrexate in Myasthenia Gravis
- This study is currently recruiting participants.
- Verified by University of Kansas, May 2009
- First Received: December 23, 2008 Last Updated: May 4, 2009

- Myasthenia gravis is a rare neuromuscular disorder characterized by weakness and fatigability of ocular, bulbar, and extremity musculature. The specific aim of this study is to determine if oral methotrexate is an effective therapy for myasthenia gravis (MG) patients who are prednisone dependent. Patients will be randomized to receive either methotrexate or placebo and those who are entered onto this trial will have symptoms and signs of the disease while on prednisone therapy.
- The hypothesis is that adding methotrexate therapy in these patients will improve the MG manifestations so that the prednisone dose can be reduced and clinical measures of MG severity will improve.

Rituximab

Fase II

- Rituximab for the Treatment of Refractory Inflammatory Myopathies and Refractory Myasthenia Gravis (FORCE)
- This study is currently recruiting participants.
- Verified by Assistance Publique - Hôpitaux de Paris, December 2007
- First Received: October 16, 2008 No Changes Posted

- The traditional treatment of inflammatory myopathies (IM) and generalized myasthenia gravis (MG) is immunosuppressive therapy, usually beginning with corticosteroids. However, up to 70% of treated patients show an incomplete response, including 10 - 30% who are unresponsive. Corticosteroids and other immunosuppressive therapies presented also many side effects. We propose to evaluate in a pilot, open, prospective, multicentric, phase II study, the interest of rituximab in the treatment of patients with primary IM associated with specific AAb (anti-synthetase and anti-SRP AAbs), or MG (with anti-AchR AAbs), refractory to conventional therapies. Twenty fourth patients with primary IM (12 with anti-synthetase, 12 with anti-SRP AAbs), and 12 with MG will be included in the study

Pharmacodynamic Study of CK-2017357 in Patients With Generalized Myasthenia Gravis

This study is currently recruiting participants.
Verified by Cytokinetics, December 2010
First Received: December 28, 2010 Last Updated: December 29, 2010

Purpose The primary objective of this early-stage clinical study is to demonstrate an effect of single doses of CK-2017357 on measures of skeletal muscle function and fatigability in patients with generalized myasthenia gravis (MG).

Timectomía con prednisona

Fase III

- Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy
- This study is currently recruiting participants.
- Verified by University of Alabama at Birmingham, November 2009
- First Received: February 21, 2006 Last Updated: November 9, 2009.
- Purpose The purpose of this trial is to determine if thymectomy combined with prednisone therapy is more beneficial in treating non-thymomatous myasthenia gravis than prednisone therapy alone.

The Role of the Thymus in Myasthenia Gravis

This study is currently recruiting participants.
Verified by Charite University, Berlin, Germany, December 2010
First Received: April 12, 2010 Last Updated: December 20, 2010

Purpose Although the association between thymic hyperplasia / thymoma and autoimmune myasthenia gravis has been known for some time, the question of causality remains uncertain. Recent research findings indicate, however, that especially in myasthenia patients with thymomas a non-physiological export of naive CD4 + T-cells can take place by the tumour and this could possibly play an important role in the pathogenesis of myasthenia gravis. The investigators want to analyse the functionality and specificity of t-cells generated in thymomas as well as the effect of thymectomy on the immune system.

Ensayos completados

Eculizumab

Fase II

- Safety and Efficacy Study of Eculizumab in Patients With Refractory Generalized Myasthenia Gravis
- This study is currently recruiting participants.
- Verified by Alexion Pharmaceuticals, February 2010.
- The purpose of this study is to determine whether eculizumab is safe and effective in the treatment of patients with generalized myasthenia gravis despite treatment with various immunosuppressants, such as prednisone, methotrexate, Cellcept, cyclosporine, and cyclophosphamide, that are currently available.

Rituximab

Fase I-II

- A Pilot Trial of Rituxan in Refractory Myasthenia Gravis
- This study is ongoing, but not recruiting participants.
- First Received: January 14, 2008 Last Updated: June 20, 2008
- Myasthenia gravis is a disease that happens because the immune system attacks the nervous system. The damage is caused by antibodies produced by B lymphocytes. These antibodies damage a special part of the muscle that helps transmit impulses from nerves to muscles to allow muscles to work properly. This damage results in symptoms of myasthenia gravis. Participants are being asked to participate in this research study because their myasthenia gravis has either failed to respond to treatments commonly used in the disease, or they have had bad side-effects from such treatments.
- This is a research study of a drug called Rituximab. Rituximab, also called Rituxan, is a mouse antibody that has been changed to make it similar to a human antibody. Antibodies are proteins that can protect the body from foreign invaders, such as bacteria and viruses, by binding to substances called antigens. Rituxan works by binding to a protein, called the CD20 protein. Rituxan helps to destroy white blood cells that produce antibodies in the body, called B-lymphocytes. It is a treatment given through a vein in the participant's arm over a period of approximately 4-6 hours. It has been approved by the Food and Drug Administration (FDA) for use in patients with a form of cancer of the lymph glands called Non-Hodgkin's Lymphoma (NHL). Rituximab is not approved for their myasthenia gravis.
- Treatment with Rituximab is being tried in this research study because Rituximab decreases B lymphocytes. There is preliminary evidence that Rituximab helps some patients with chronic and otherwise difficult to treat myasthenia gravis.
-

Inmunoglobulina frente PF

Fase III

- Efficacy and Safety Study of GB-0998 for Treatment of Generalized Myasthenia Gravis
- This study is currently recruiting participants.
- Verified by Benesis Corporation, June 2009
- First Received: August 10, 2007 Last Updated: June 4, 2009
- Purpose This randomized controlled, multi-center study will carry out to assess the efficacy of GB-0998 compared to plasmapheresis in the treatment of the generalized Myasthenia Gravis based on the changes in Quantitative Myasthenia Gravis score (QMG score) as primary endpoint, and in addition, to assess the safety of GB-0998

Micofenolato

Fase III

- Mycophenolate Mofetil in Myasthenia Gravis
- This study has been completed.
- First Received: January 31, 2006 Last Updated: April 24, 2007.

Purpose This is a prospective, multi-center, double-blind, placebo-controlled trial to determine the efficacy and safety of mycophenolate mofetil (MM) in combination with prednisone as the initial form of immunosuppression in patients with acquired myasthenia gravis (MG).

Micofenolato

Fase III

- A Study to Assess the Effect of CellCept (Mycophenolate Mofetil) and Reduced Corticosteroids in Controlling Symptoms of Myasthenia Gravis
- This study has been completed.
- First Received: May 19, 2008 Last Updated: May 23, 2008.
- Purpose The efficacy and safety of CellCept (1g po, bid for 36 weeks) will be assessed in patients with myasthenia gravis receiving prednisone, or other corticosteroids. During the study, patients will undergo gradual corticosteroid dose reduction, if they respond to treatment. The anticipated time on study treatment is 3-12 months, and the target sample size is 100-500 individuals.

Micofenolato Vs Azatioprina

- Trial of Mycophenolic Acid Versus Azathioprine in the Treatment of Corticosteroid-refractory Myasthenia Gravis (Myfortic)
- This study is ongoing, but not recruiting participants.
- First Received: October 16, 2009 .
- Purpose This is an randomized, double-blind, double-dummy trial, and the objective is to compare the efficacy and safety of Mycophenolic acid (MA) and Azathioprine (AZA), immunosuppressive drugs, in myasthenia gravis patients. This prospective study will enroll 40 myasthenia gravis (MG) patients who are poor controlled under prior steroid therapy. All subjects should be randomly assigned to MA group and AZA group that will receive routine pyridostigmine and prednisolone in combination with MA or AZA.
-

Micofenolato

Fase III continuacion

- A Continuation Study to Assess the Effect of CellCept in Patients With Myasthenia Gravis.
- This study has been completed.
- First Received: December 5, 2006 Last Updated: May 22, 2008 .
- Purpose This 2 arm study will provide optional continuation of double-blind treatment with CellCept or placebo, in patients with myasthenia gravis who have achieved good symptom control in study WX17798. Patients who have completed 36 weeks of treatment in study WX17798, with stable prednisone dosing for the last 4 weeks, can continue on blinded treatment with CellCept (1g bid) or placebo until the database for WX17798 is locked and unblinded. The anticipated time on study treatment is 3-12 months, and the target sample size is 100-500 individuals.

Tacrolimus

Fase III

- FK506 Phase 3 Study: a Study for Steroid Non-Resistant Myasthenia Gravis (MG) Patients
- This study has been completed.
- First Received: March 29, 2006 Last Updated: July 9, 2008.
- Purpose The purpose of the study is to investigate the efficacy and safety for steroid non-resistant MG patients in a double blind, placebo controlled study.

Tacrolimus

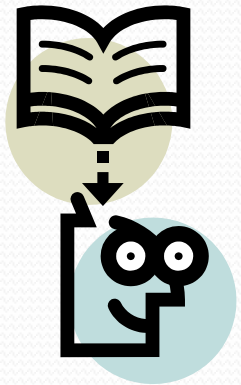
Fase III

- An Open Study for Steroid Resistant, Non-Thymectomized MG Patients
- This study has been completed.
- First Received: March 29, 2006 Last Updated: June 2, 2009.
- The purpose of the study is to investigate the efficacy and safety for steroid resistant, non-thymectomized MG patients.

CONCLUSIONES

- La MG es una enfermedad de origen autoinmune .
- Es una enfermedad tratable con una buena respuesta clínica en la mayoría de los casos.
- Se dispone de un numero de fármacos cada vez mayor que actúan sobre el sistema inmune.
- Es recomendable utilizar los nuevos fármacos mientras no se disponga de mayor experiencia y evidencia en segunda o tercera línea.
- Los AM pueden ofrecer alternativas actuales en los casos mas refractarios, aunque la experiencia es limitada.
- Los estudios controlados y doble ciego son necesarios pero plantean problemas en su diseño y evaluación que condicionan su interpretación.

Gracias por su atención



Different methods of vaccination used in experimental models of myasthenia gravis: putative mechanisms of action.

Vaccines	Route	Species	Mechanism of action	Effects observed
Native AChR	Mucosal	Rats		Prevention
Denatured AChR	Intradermal	Rabbits		Ongoing
AChR recombinant fragments	Mucosal (nasal and oral)	Rats	Shift Th1 to Th2/Th3 Downregulation of costimulatory molecules	Ongoing
AChR peptides	Oral	Rabbits Mice	Anergy	Prevention Prevention and ongoing
AChR peptides	Intraperitoneal	Mice	Anergy, apoptosis Downregulation of IL-2, IFN-γ, IL-10	Prevention and ongoing
Altered peptides	Oral	Mice	CD4+CD25+ Upregulation of IL-10, TGF	Ongoing
Dendritic cells treated with IL-10	Intraperitoneal	Rat	Downregulation of costimulatory molecules	Ongoing
Dendritic cells pulsed with AChR	Subcutaneous	Rat	Reduced expression of BAFF	Prevention
Anti-Vβ5.1 antibodies	Intraperitoneal	SCID mice	Shift Th1 to Th2 Deletion of Vβ5.1^{+} cells	Biological parameters

Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity

Matthew N Meriggioli, Donald B Sanders

Acquired myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction in which patients experience fluctuating skeletal muscle weakness that often affects selected muscle groups preferentially. The target of the autoimmune attack in most cases is the skeletal muscle acetylcholine receptor (AChR), but in others, non-AChR components of the neuromuscular junction, such as the muscle-specific receptor tyrosine kinase, are targeted. The pathophysiological result is muscle endplate dysfunction and consequent fatigable muscle weakness. Clinical presentations vary substantially, both for anti-AChR positive and negative MG, and accurate diagnosis and selection of effective treatment depends on recognition of less typical as well as classic disease phenotypes. Accumulating evidence suggests that clinical MG subgroups might respond differently to treatment. In this Review, we provide current information about the epidemiology, immunopathogenesis, clinical presentations, diagnosis, and treatment of MG, including emerging therapeutic strategies.

Lancet Neurol 2009; 8: 475–90

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Introduction

Acquired myasthenia gravis (MG) is a prototypical, antibody-mediated autoimmune disorder of the neuromuscular junction (NMJ).[1] In most cases, it is caused by pathogenic autoantibodies directed towards the skeletal muscle acetylcholine receptor (AChR).[2] In diagnosis and treatment of MG, and an increasing longevity of the population in general. Incidence varies widely from 1·7 to 10·4 per million, depending on the location of study,[8] and has been reported to be as high as 21 per million in Barcelona, Spain.[9] The occurrence of MG is influenced by sex and age: women are affected

Figure 1: **The normal NMJ and pathophysiology of MG**

(A) Components of the NMJ. In the normal NMJ, ACh is released from the nerve terminal following a nerve action potential, and interacts with the AChR on t postsynaptic membrane. Voltage-gated Ca^{2+} channels allow the influx of Ca^{2+} into the nerve terminal, which facilitates the release of ACh. Voltage-gated Na^{+} on the postsynaptic membrane serve to propagate the muscle action potential on depolarisation. Acetylcholinesterase scavenges and hydrolyses unbound A MUSK initiates clustering of the cytoplasmic protein rapsyn and AChRs, and is believed to maintain normal postsynaptic architecture. (B) Effect of the loss of functional AChRs in MG. Conceptual representation of EPP amplitudes after repeated nerve stimulation. EPP amplitude is reduced in MG, narrowing the safe of neuromuscular transmission. With repeated stimulations, the EPP amplitude falls below threshold (indicated by the dotted line) for muscle fibre activation resulting in neuromuscular transmission failure. (C) Electron micrographs of endplate regions from mice with experimental MG, showing lysis and altered morphology of the postsynaptic membrane. A normal endplate region is shown in the left panel. An endplate region from a myasthenic mouse showing loss normal endplate morphology due to complement-mediated lysis is shown in the right panel. Postsynaptic membranes are indicated by the arrows. ACh=acetylcholine. AChR=ACh receptor. EPP=endplate potential. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase. NMJ=neuromuscu junction. NT=nerve terminal. Panel C modified with permission from Lippincott Williams & Wilkins.[43]

***Figure 4*: Treatment flowchart**

Management of MG must be individualised, but this general approach is suitable for most patients. Thymectomy is usually considered in early-onset, anti-AChR-positive MG. Pre-operative immunosuppression (PE or IVIg with or without steroids) might be required, particularly in patients with oropharyngeal or respiratory weakness, but some patients can successfully undergo thymectomy without prior treatment. If a thymoma is discovered, thymothymectomy is a requisite component of early disease management. A course of PE/IVIg can be considered at initiation of chronic immunosuppression to hasten onset of clinical response. AChR=acetylcholine receptor. IVIg=intravenous immunoglobulin. MG=myasthenia gravis. MUSK=muscle-specific receptor tyrosine kinase. PE=plasma exchange.

that are currently used in MG patients, and present the results of their use in more than 1000 patients with MG seen at our two centers. Immunosuppressive treatment was considered along with, or as an alternative to thymectomy in MG patients with disabling weakness, not adequately controlled with anticholinesterase drugs. Overall, 82% of our patients received immunosuppressants for at least 1 year, with frequencies varying according to disease severity, from 93-95% of those with thymoma or MuSK antibodies to 72% in ocular myasthenia. Prednisone was used in the great majority of patients, azathioprine was the first-choice immunosuppressant; mycophenolate mofetil and cyclosporine were used as second-choice agents. All clinical forms of MG benefited from immunosuppression: the rate of remission or minimal manifestations ranged from 85% in ocular myasthenia to 47% in thymoma-associated disease. Treatment was ultimately withdrawn in nearly 20% of anti-AChR positive early-onset patients, but in only 7% of thymoma cases. The risk of complications appears to depend on drug