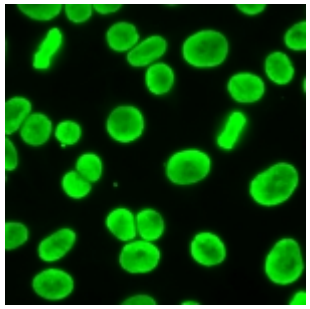
Hospital Universitario Ramón y Cajal
SaludMadrid
Comunidad de Madrid

Aportación de la inmunología al diagnóstico de las enfermedades neuromusculares



ÁNGELA CARRASCO SALAYERO
F.E.A. INMUNOLOGÍA
17 DE MARZO 2016

Síndromes Miastenicos

Los Síndromes Miasténicos consisten en grupos de enfermedades donde se encuentra **alterada la transmisión neuromuscular.**

Dicho defecto puede ser ***congénito*** (genéticos de la unión neuromuscular) ó ***adquirido*** (autoinmune o tóxica)

Síndrome Miasténicos Congénitos

Defectos Presinápticos

- En la **síntesis o almacenamiento** de Acetilcolina
- Disminución en el **número de vesículas** sinápticas

Defectos Sinápticos

- **Deficiencias** de acetil-colinesterasa

Defectos Postsinápticos

- SM Congénito por canales lentos (autosómico dominante)
- SM Congénito por canales rápidos (autosómico recesivo)
- Deficiencia primaria de los receptores de Acetil Colina
- Deficiencia de Plectina, (miopatías)

Síndrome Miastenicos Adquiridos

- **Síndrome Miasténico de Lambert-Eaton**
- Botulismo
- Intoxicación por órgano fosforados
- Intoxicación por Magnesio
- Crisis colinérgicas
- **Miatenia Gravis**

Miastenia Gravis

Es una enfermedad ***autoinmune*** causada por el **fallo** en la **transmisión** neuromuscular produciendo debilidad muscular, debida a la presencia de **anticuerpos** frente al receptor de acetilcolina (anti-AChR).

Se considera enfermedad ***autoinmune humoral*** mediada por **células B** (debido a la producción de autoanticuerpos),

Los mecanismos de ***autotolerancia y modulación*** de estos anticuerpos donde las **células T** desempeñan un importante papel a través de la síntesis de diferentes mediadores como las citocinas.

J Neurol
21 January 2016

Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society

Nico Melzer[1] · Tobias Ruck[1] · Peter Fuhr[2] · Ralf Gold[3] · Reinhard Hohlfeld[4] · Alexander Marx[5] · Arthur Melms[6] · Björn Tackenberg[7] · Berthold Schalke[8] · Christiane Schneider-Gold[3] · Fritz Zimprich[9] · Sven G. Meuth[1] · Heinz Wiendl[1]

MG

- Trastorno autoinmune con diferentes características inmunogeneticas
- Síndrome Pareneoplásico asociado a tumor del TIMO

1. Early-onset MG (EOMG)
2. Late-onset MG (LOMG)
3. Thymoma-associated MG (TAMG)
4. Anti-musk-Ab associated MG (MAMG)
5. Ocular MG (OMG)
6. Seronegative MG (SNMG)

Epidemiologia/Inmunología / Factores genéticos

Table 1 Features of different subtypes of MG

	Early-onset MG (EOMG)	Late-onset MG (LOMG)	Thymoma-associated MG (TAMG)	Anti-MuSK-Ab-associated MG (MAMG)	Ocular MG (OMG)	"Seronegative" MG (SNMG)
Estimated frequency	20 %	45 %	10–15 %	6 %	15 %	4 %
Disease-course and manifestation	Generalized, disease maximum within the first 3 years	Generalized, disease maximum within the first 3 years	Generalized, more scarcely—complete remission is possible	Generalized, fasciopharyngeal focus	Ocular	Generalized
Age at disease onset	≤45 (50, 60) years[a]	>45 (50, 60) years[a]	Any age (primarily 40–60 years)	Any age (primarily Younger patients)	Any age	Any age
Male: female ratio	1:3	5:1	1:1	1:3	1:2	n. a.
HLA-association (caucasians)	B8 A1 DR3 (strong) DR16 DR9 (less strong)	B7 DR2 (less strong) Anti-titin-ab$^-$ with DR7 Anti-titin-ab$^+$ with DR3	DR7 (less strong) A25 (less strong)	DR14 (strong)	n. a.	n. a.
(Auto-)antibodies	**Anti-AChR-ab**	**Anti-AChR-ab** Anti-Titin-ab Anti-RyR-ab Anti-IL12-ab Anti-IFNα-ab	**Anti-AChR-ab** Anti-Titin-ab Anti-RyR-ab Anti-IL12-ab Anti-IFNα-ab Anti-IFNω-ab	**Anti-MuSK-ab**	**Anti-AChR-ab** (50–70 %)	**Anti-LRP4-ab** **Anti-Argin-ab**
Typical thymus pathology	lymphofollicular hyperplasia (LFH)	Atrophy, involution	Thymoma Type A 5 % Type AB, B1–3 92 %	Usually normal	No systematic data	No systemic data
Response to thymectomy	good when performed within the first 1–2 years after diagnosis	No systematic data	Often poor	Poor	No systematic data	No systematic data
Response to immunotherapy	+++	+++	+(+)	+(+)	+++	+(+)

n. a. not applicable

[a] Currently there is no agreement in the literature regarding the age differentiating EOMG from LOMG [20, 104]

MG Tratamientos

- Tratamientos **sintomáticos** que facilitan la trasmisión neuromuscular
- Tratamientos de **reducción** de anticuerpos.
- Estrategias de **tratamientos inmunoterapeuticos** para terapia de mantenimiento
- Terapias experimentales, **anticuerpos monoclonales** trasplante de células stem..

MG - Patógena

EA mediada por Auto-anticuerpos frente al receptor nicotínico ACh de los músculos estriados

PRE-Sináptico: **Síndrome Miasteniforme Lambert-Eaton**

Ac. anti-VGCC y Ac. anti-SOX

Paraneoplásico asociado cáncer de pulmón de célula pequeña

POST-Sináptico: **Miastenia Gravis**

Ac. anti-AChR, anti-MuSK, anti-LRP-4, anti-musculo estriado, Titina, Cortactin

MG – Fisiopatología

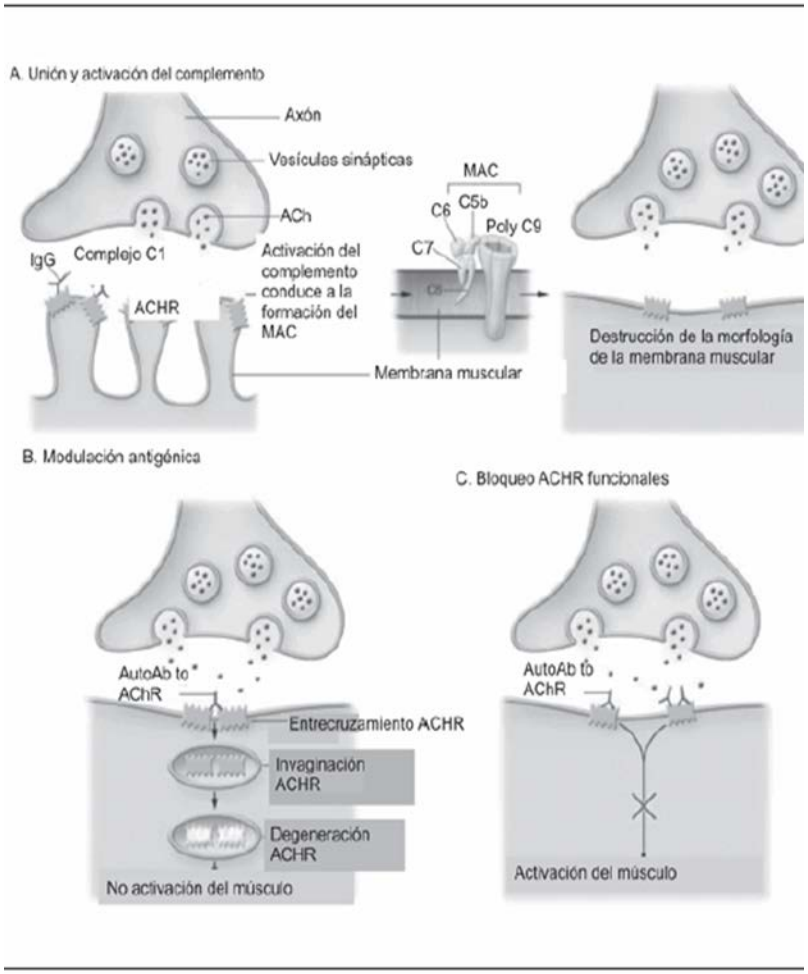
Los **anti AChR** en MG alteran la trasmisión neuromuscular por

1) **Bloqueo** funcional de los receptores de ACh.

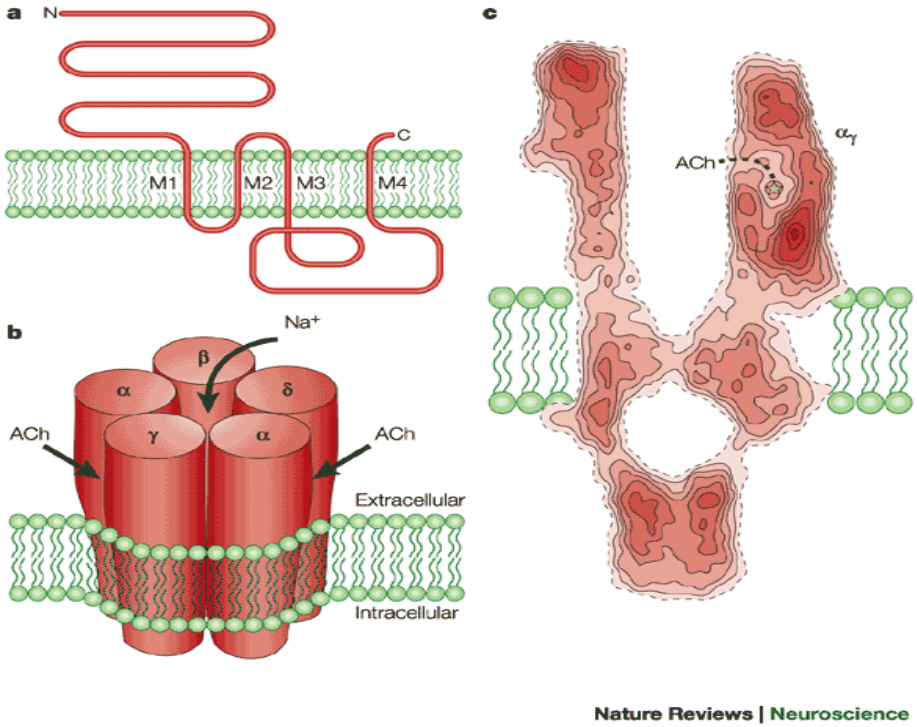
2) **Unión al antígeno** y activando al complemento y formación de **MAC**

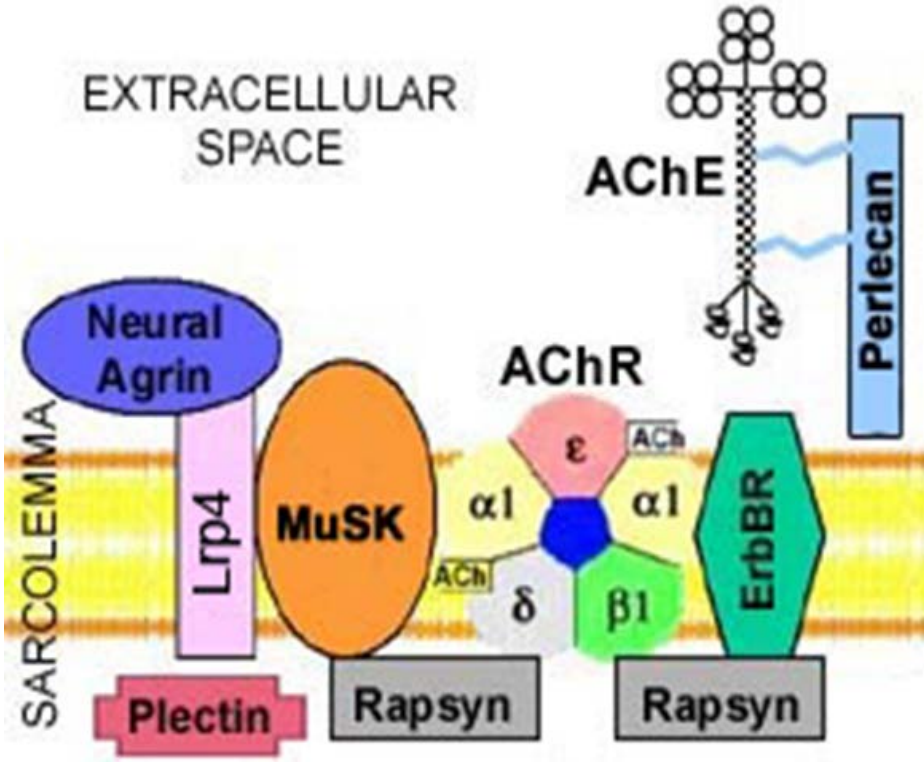
3) **Degradación de los AChR** uniéndose a dos antígenos (AChR) lesión celular (modulación antigénica.)

El daño tisular es considerado la lesión primaria en la MG.



MG - Patogenia





Ac. anti-AChR

Principalmente clase **IgG isotipo IgG1 / IgG3**

Se han descrito **IgM e IgA**, siempre junto a titulos altos los de clase IgG. Aparecen con **enfermedad de larga duración** y mayor severidad

Se dirigen hacia la **unidad α del AChR** siendo afectadas en menor medida el resto de unidades (β, δ, γ – recién nacido/musculo denervado, ε- adulto)

60% de los Ab se dirigen frente a un **epítopo conformacional** ubicado en la unidad α, entre los aminoácidos 67-76.

Ac. anti-MuSK / Ac. anti-Lrp4

MuSK (Tirosinkinasa musculo especifica)
Lrp4 proteína **clave** para la activación del MuSK

aLrp4 (IgG1)
Impiden la unión del la agrina al MuSK
Activan el complemento daño directo de la M.Posinaptica

aMusk (IgG4)
Se une a la zona extracelular del AChR impidiendo ensamblaje funcionamiento del complejo

NO activan complemento

Group II: Antibodies against cell surface and perisynaptic antigens

Antibody (synonym)	Antigen (calculated mass monomer, UniProt)	Preference of expression	Antigen function	Associated clinical syndromes	Frequently associated tumors	Common serological tests	References
Anti-AChR	Muscle-type nicotinic acetylcholine receptor (α1: 55 kDa)	Skeletal muscle (motor endplate of the neuromuscular junction), thymus	Ionotropic neurotransmitter receptor, ligand-gated ion channel (cation current), involved in fast synaptic cholinergic transmission at neuromuscular junctions	Myasthenia gravis	Thymoma (15%)	CBA, RIA, ELISA	Leite et al. (2008, 2010), Lindstrom et al. (1976), Vincent and Newsom-Davis (1985) and Vrolix et al. (2010)
Anti-MuSK	Muscle-specific receptor tyrosine kinase (97 kDa)	Skeletal muscle (motor endplate of the neuromuscular junction)	Key role in the formation and maintenance of neuromuscular junctions (synaptogenesis), including Agrin-mediated postsynaptic AChR clustering	Myasthenia gravis	Thymoma (occasionally)	CBA	Guptill et al. (2011), Hoch et al. (2001), Ito et al. (2013), McConville et al. (2004) and Vincent and Leite (2005)
Anti-Lrp4	Low-density lipoprotein receptor-related protein 4 (212 kDa)	Skeletal muscle (motor endplate of the neuromuscular junction)	Receptor for Agrin, mediates Agrin-induced activation of MuSK leading to postsynaptic AChR clustering and other postsynaptic specializations	Myasthenia gravis	-	CBA	Higuchi et al. (2011), Pevzner et al. (2012) and Zhang et al. (2012)

Abbreviations: AGNA, anti-glial nuclear antibody; ANNA, anti-neuronal nuclear antibody; CBA, cell-based assay; CDR, cerebellar degeneration-related antigen; CNS, central nervous system; ELISA, enzyme-linked immunosorbent assay; kDa, kiloDalton; Nova, neuro-oncological ventral antigen; PCA, Purkinje cell cytoplasmic autoantibody; PNMA, paraneoplastic Ma antigen; RIA, radioimmunoassay; SCLC, small-cell lung cancer; TBA, tissue-based assay; VGKC, voltage-gated potassium channel.

[a]Well-characterized onconeuronal paraneoplastic antibodies; >95% tumor association (Graus et al., 2004).

Group 1a: Antibodies against intracellular nuclear and cytoplasmic antigens

Antibody (synonym)	Antigen (calculated mass monomer, UniProt)	Preference of expression	Antigen function	Associated clinical syndromes	Frequently associated tumors	Common serological tests	References
Anti-Sox1 (AGNA)	Sry-like high mobility group box protein 1 (39 kDa)	Nuclei of Bergmann glia in the cerebellar Purkinje cell layer	Transcription factor, involved in neurogenesis	Lambert-Eaton myasthenic syndrome, sensory/sensorimotor neuropathy, cerebellar syndrome	SCLC	TBA, immunoblot	Graus et al. (2005), Sabater et al. (2008b, 2013), Titulaer et al. (2009) and Tschernatsch et al. (2010)
Anti-Titin	Titin (3816 kDa)	Skeletal and cardiac sarcomere	Part of the contractile machinery in striated muscle	Myasthenia gravis	Thymoma (39%)	TBA, immunoblot	Romi et al. (2005) and Suzuki et al. (2011)

Abbreviations: AGNA, anti-glial nuclear antibody; ANNA, anti-neuronal nuclear antibody; CBA, cell-based assay; CDR, cerebellar degeneration-related antigen; CNS, central nervous system; ELISA, enzyme-linked immunosorbent assay; kDa, kiloDalton; Nova, neuro-oncological ventral antigen; PCA, Purkinje cell cytoplasmic autoantibody; PNMA, paraneoplastic Ma antigen; RIA, radioimmunoassay; SCLC, small-cell lung cancer; TBA, tissue-based assay; VGKC, voltage-gated potassium channel.

[a]Well-characterized onconeuronal paraneoplastic antibodies; >95% tumor association (Graus et al., 2004).

Multiple Sclerosis and Related Disorders (2014) 3, 303–320

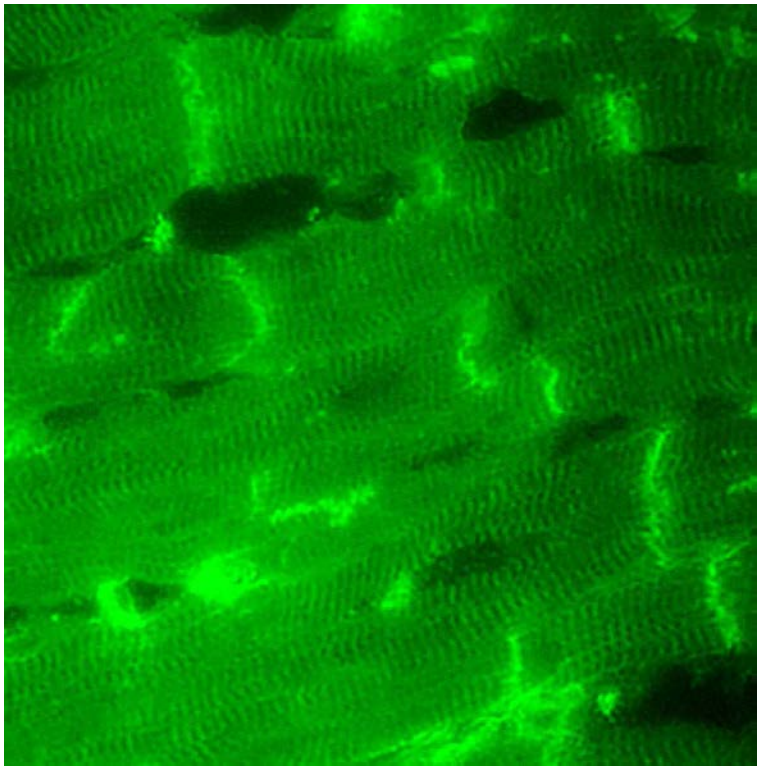
Ac. anti-musculo estriado

Reactividad cruzada en tejidos musculares y cardiacos

NO específicos para la MG (miocarditis)

Se dirigen frente a varias **proteínas musculares;** Actina, miosina(α,β) **titina** ryanodina ,actinina..

IFI Músculo esquelético



AC Anti-TITINA

Proteína filamentosa de M.Estriado de PM alto(3000 kD)

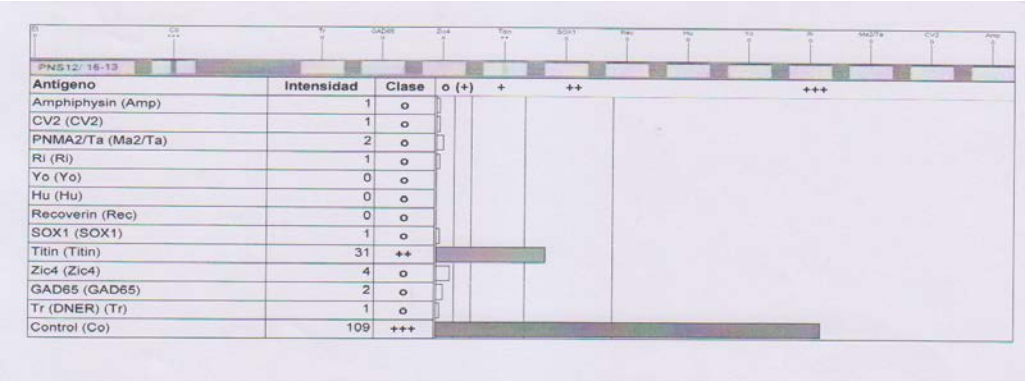
Se encuentra en el **sarcómero** muscular, cardíaco ó esquelético.

La **región inmunogénica** esta en un fragmento de30 KD

Reacción **cruzada con los epítopes** AChR

Se relaciona con la severidad de la MG

Aparecen en un **80%** con **TIMOMA**



PNS12/ 16-13

Antigeno	Intensidad	Clase
Amphiphysin (Amp)	1	o
CV2 (CV2)	1	o
PNMA2/Ta (Ma2/Ta)	2	o
Ri (Ri)	1	o
Yo (Yo)	0	o
Hu (Hu)	0	o
Recoverin (Rec)	0	o
SOX1 (SOX1)	1	o
Titin (Titin)	31	++
Zic4 (Zic4)	4	o
GAD65 (GAD65)	2	o
Tr (DNER) (Tr)	1	o
Control (Co)	109	+++

AC Anti-Cortactin (Anti-CTTN)

Cortactin

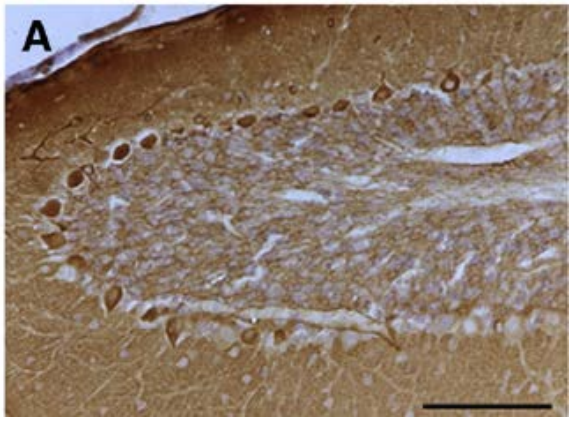
- Proteína de baja densidad 62 KDa (Tipo IgG1)
- Localizada en la **unión neuromuscular** AChR
- Estimulación de la sinapsis, **agrin / Musk**

Ab –Cortactin en SNMG (19,7%)

- **Bloquean** la unión de la Ach con le Receptor
- Mediado por **complemento**, perjudican la placa final
- **Inhiben** la interacción de **agrin-LP4-MuSK**
- ELISA, Inmunoblot
- herramienta de diagnostico con estudios clínicos y electrofisiológicos
- **Ac Cortactin en SNMG** indican enfermedad autoinmune (

Cortactin autoantibodies in myastemia gravis . Eduard Gallardo and col. Autoimmunity Reviews 2014

Síndrome de Miasteniforme Lambert – Eaton (SMLE)



Respuesta autoinmune contra canales de calcio (VGCC)

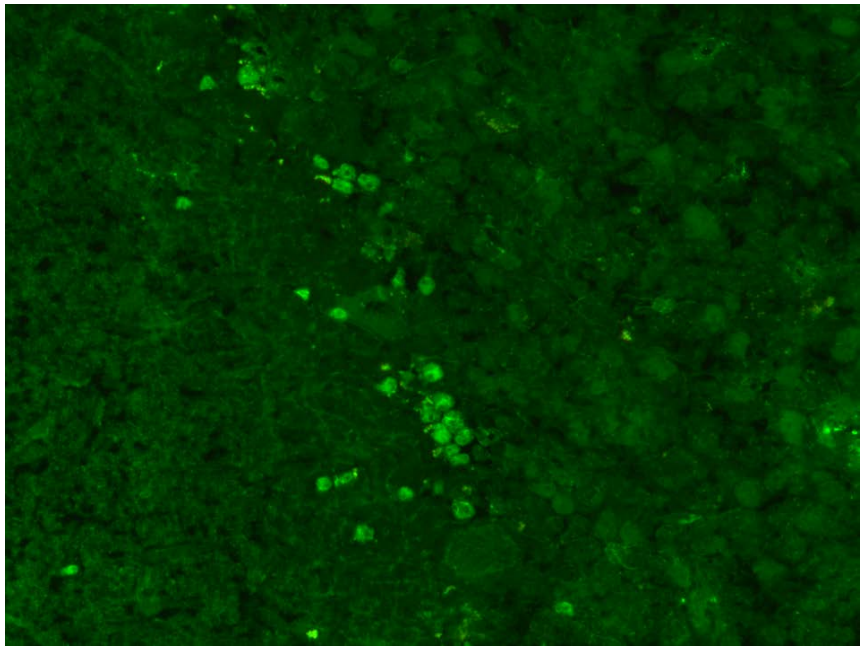
Anti-VGCC se unen a los antígenos *extracelulares y* dirigidos contra el tipo P/Q de los canales calcio , **expresado en la estructura molecular** del cerebelo, citoplasma de la células de Purkinje y capa granular

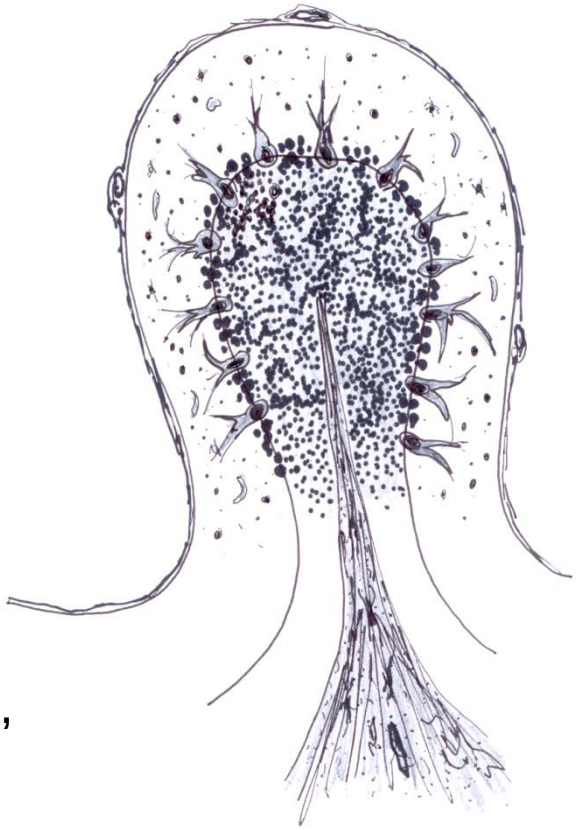
Disminución de liberación de ACh

Mas frecuente en hombres que en mujeres (5:2)

Se **asocia a neoplasia** (SNP)

Anti-SOX1(AGNA)





IFI núcleo de las células de glia de Bergman,
Alrededor de la CP
Se asocia a CPCP

Diagnostico

Clínico: debilidad y cansancio muscular variable SIN afectación sensitiva, de los reflejos o de las funciones cerebrales

Farmacológico: mejoría de la debilidad muscular después de la administración de la medicación anticolinérgica.

Serológico: presencia de **Abs**

Electrofisiológico: evidencia de defecto en la transmisión neuromuscular.

Diagnostico serológico

RIA - “Gold Standard”

nAChR marcado con I^{125}-α-bungarotoxina

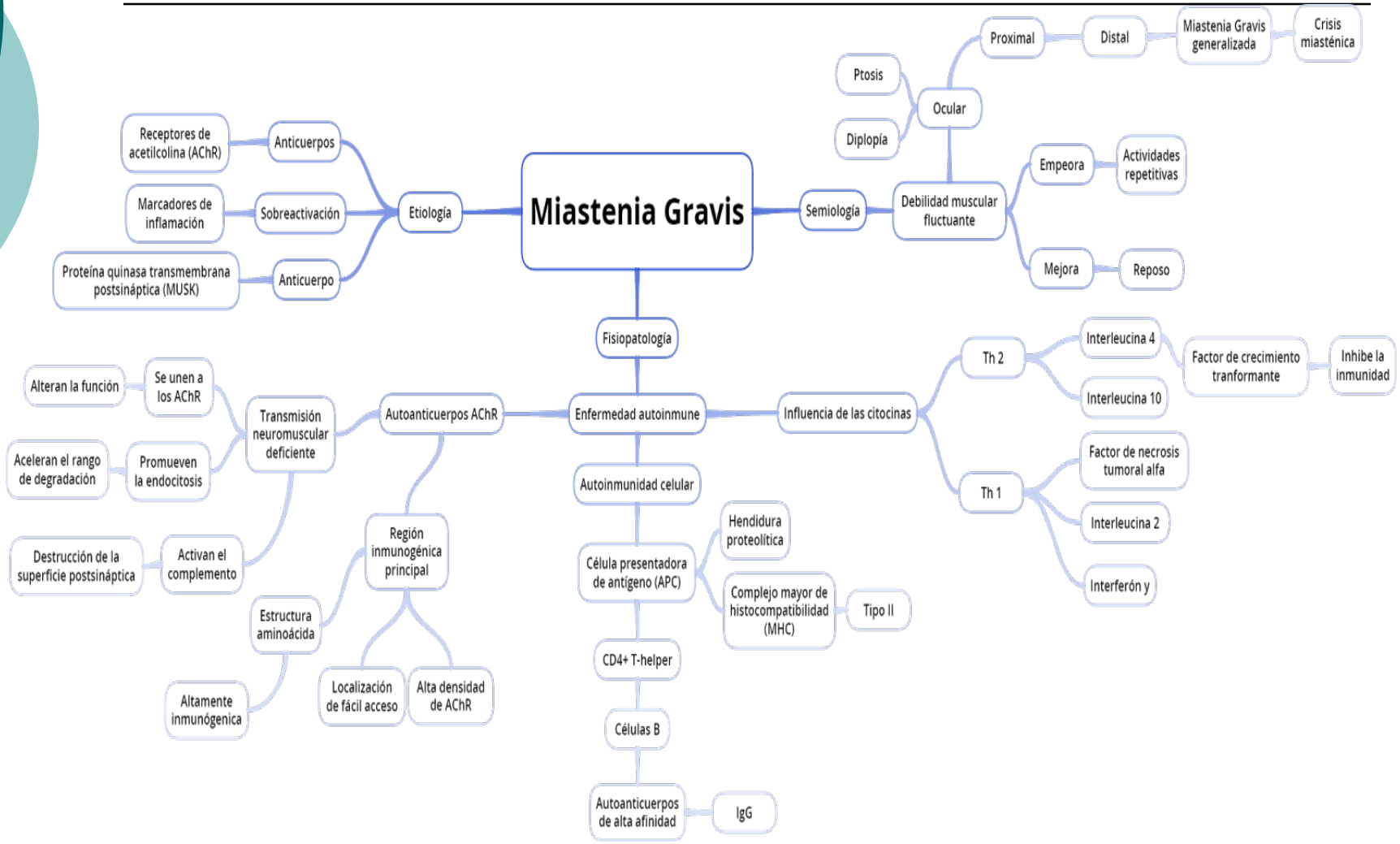
anti-VGCC, I^{125}-conotoxina

ELISA AChR, SOX, Musk, Cortactin

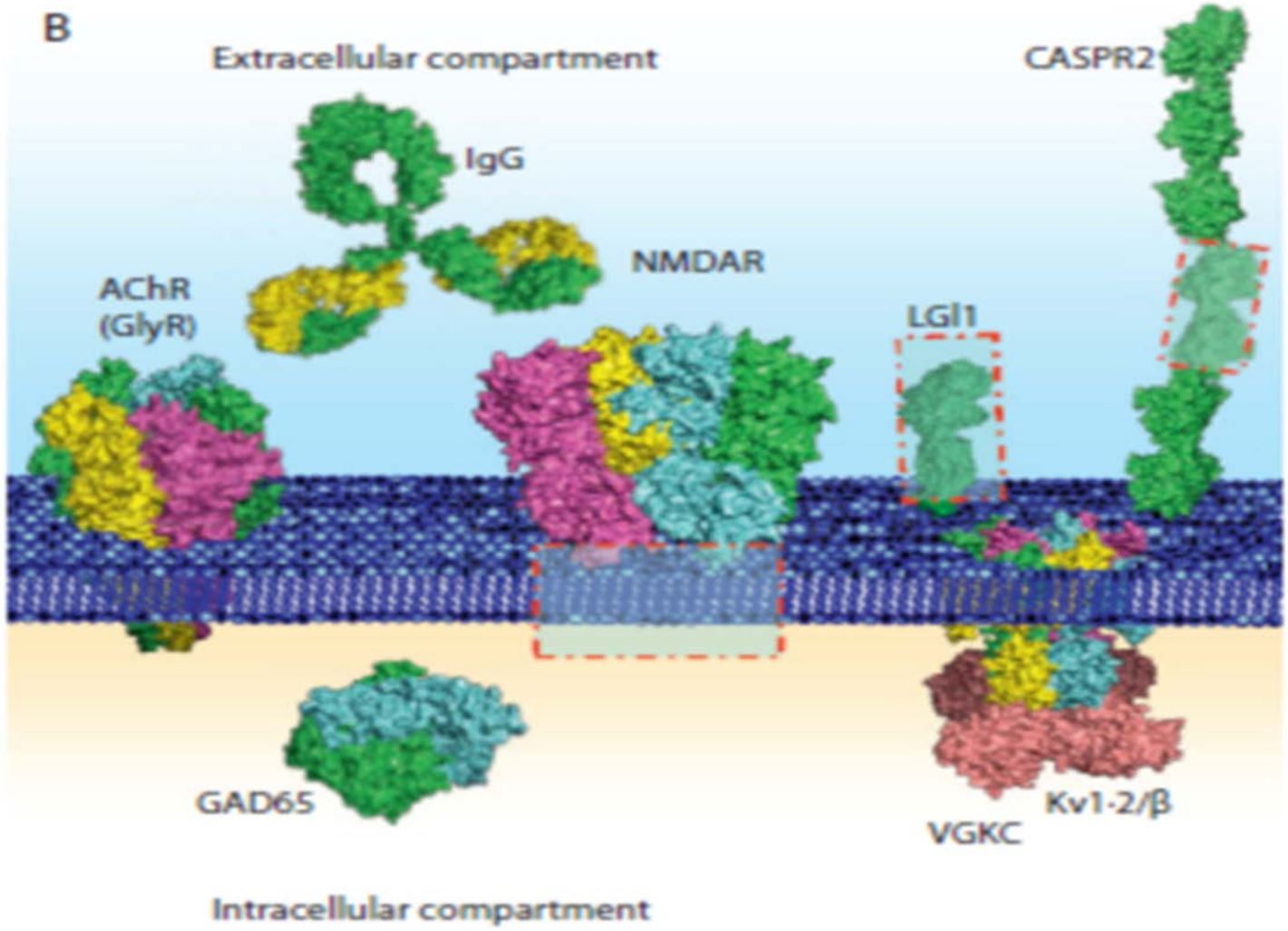
IFI . Musculo estriado, SOX

Inmunoblot : Titina , Cortactin

Miastenia Gravis



Síndromes de Hiperexcitabilidad



Antígenos de superficie y sinápticos

Group II: Antibodies against cell surface and perisynaptic antigens

Anti-LGI1	Leucine-rich glioma-inactivated protein 1 (64 kDa)	Mainly in neuron cell bodies throughout the CNS, weakly in neuropil	(learning and memory) Secreted glycoprotein in a transsynaptic complex, regulates presynaptic Kv1 channels (VGKC) and postsynaptic AMPARs	Limbic encephalitis, hyponatremia, myoclonus (tonic seizures, facio-brachial dystonic seizures), Morvan's syndrome	Thyroid, lung, renal cell, ovary, thymoma (<20%)	TBA, CBA, (VGKC-RIA)	Andrade et al. (2011), Irani et al. (2010a, 2011, 2012, 2013 and Lai et al. (2010)
Anti-CASPR2	Contactin-associated protein 2 (148 kDa)	Mainly in the CNS neuropil and juxtaparanodes, weakly or not in neuron cell bodies	Cell-adhesion molecule, mediates juxtaparanodal Kv1 channel (VGKC) clustering on myelinated axons	Morvan's syndrome, neuromyotonia, limbic encephalitis	Thymoma (<20%)	TBA, CBA (VGKC-RIA)	Balint et al. (2013), Irani et al. (2010a, 2012, Lancaster et al. (2011a) and Vincent and Irani (2010)

Group 1b: Antibodies against intracellular synaptic antigens

Anti-GAD65	Glutamic acid decarboxylase (65 kDa)	Mainly in GABAergic inhibitory neurons and pancreatic islet β-cells; presynaptic vesicle-associated protein	Catalyzes the decarboxylation of glutamate to the inhibitory neurotransmitter γ-	Stiff-person syndrome, cerebellar syndrome, limbic encephalitis, epilepsy	SCLC, non-SCLC, thymus, colon, pancreas, renal cell, breast (occasionally)	TBA, immunoblot, RIA, ELISA, CBA	Honnorat et al. (2001), Malter et al. (2010), McHugh et al. (2007), Murinson and

Abbreviations: AGNA, anti-glial nuclear antibody; ANNA, anti-neuronal nuclear antibody; CBA, cell-based assay; CDR, cerebellar degeneration-related antigen; CNS, central nervous system; ELISA, enzyme-linked immunosorbent assay; kDa, kiloDalton; Nova, neuro-oncological ventral antigen; PCA, Purkinje cell cytoplasmic autoantibody; PNMA, paraneoplastic Ma antigen; RIA, radioimmunoassay; SCLC, small-cell lung cancer; TBA, tissue-based assay; VGKC, voltage-gated potassium channel.

[a]Well-characterized onconeuronal paraneoplastic antibodies; >95% tumor association (Graus et al., 2004).

Multiple Sclerosis and Related Disorders (2014) 3, 303–320

Anti-GAD65: anti- glutamato descarboxilasa

Proteína sináptica.

Antígeno localizado en el terminal presináptico intracelular.

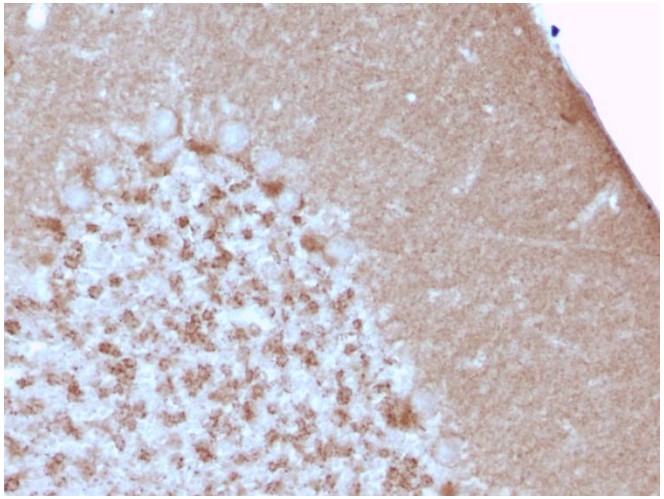
Respuesta **inmune celular e humoral**

Diana antigénica relacionada con la síntesis de GABA

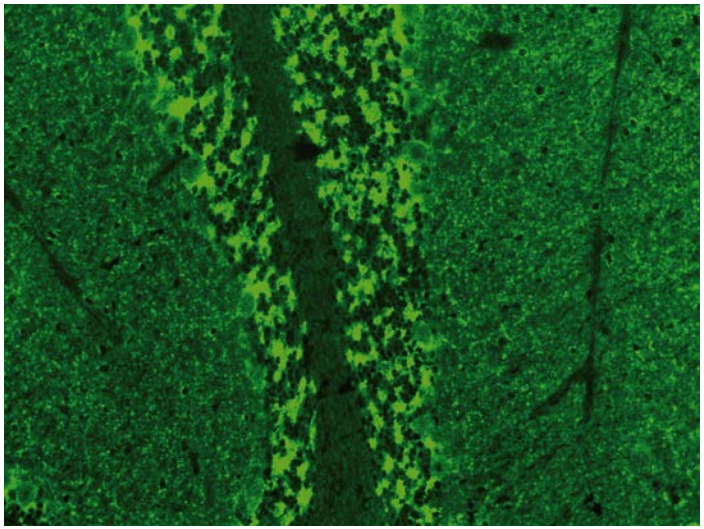
Pacientes , SPS, Ataxia cerebelo, Encefalitis límbica, Estatus epilépticos

No se detecta **tumo**r

Se detecta en títulos elevados > 2000



IFI Patrón Granular en capa molecula

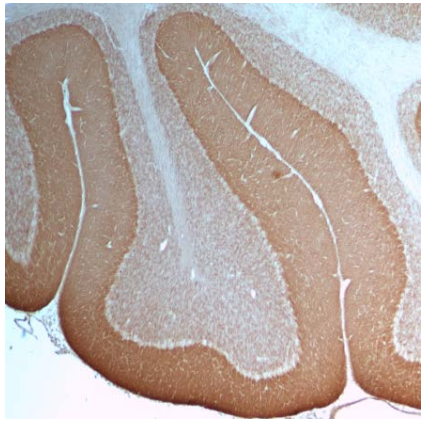


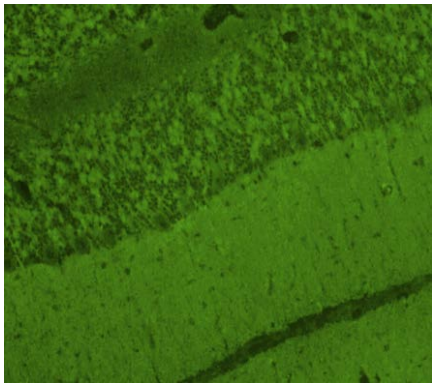
Current Treatment Options in Neurology (2013) 15:150–168

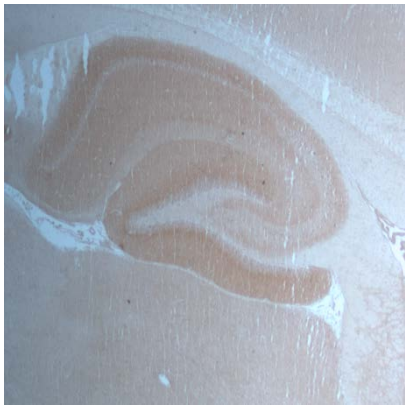
Anticuerpos anti-VGKC

Tabla 1 Espectro clínico asociado a la detección de anticuerpos anti-CKVD

LGI1	Encefalitis límbica, hiponatremia, movimientos tipo mioclónicos (crisis facio-braquio-distónica o crisis tónicas)
Caspr2	Encefalitis, neuromiotonía, síndrome de Morvan, neuropatía dolorosa
Anticuerpos anti-CKVD con antígeno no caracterizado	Neuropatía periférica asociada a trabajadores de matadero porcino Dolor neuropático Encefalitis en niños Encefalopatía epiléptica refractaria inducida por fiebre (FIRES) Demencia rápidamente progresiva Enfermedad de Creutzfeldt-Jakob Epilepsia







Fermo O et al. *Autoimmune encephalitis mimicking Creutzfeldt-Jakob disease*. Neurol Clin Pract. 2014.
Viaccoz A, Honnorat J. Paraneoplastic Neurological Syndromes: General Treatment Overview. Curr Opin Neurol. 2013.

Anti LGI1: leucine-rich glioma inactivated1

Proteína neuronal rica en **leucina**

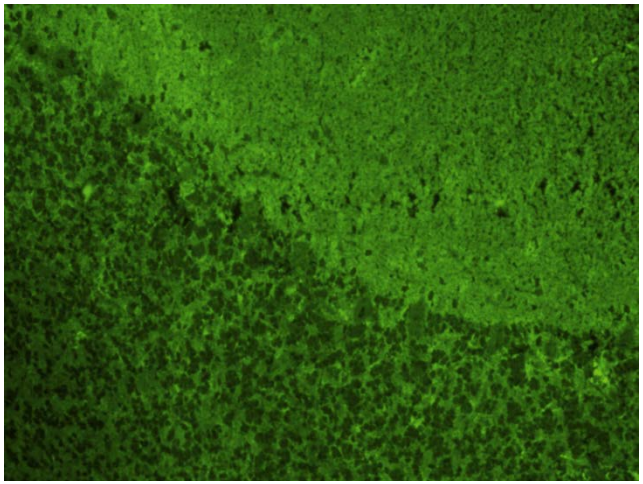
Control de la excitabilidad sináptico

Epilepsia autosómica dominante

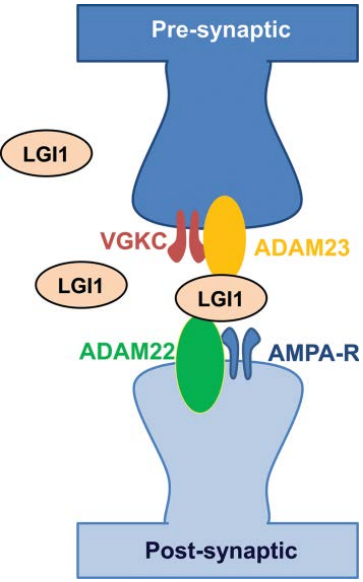
Encefalitis límbica clásica.

Recidiva poco frecuente

Asociación a tumores <10% Timoma

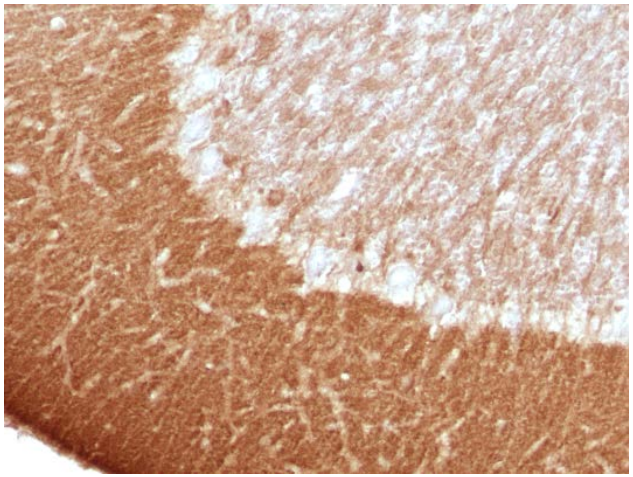


IFI zona molecular, hipocampo y cerebelo

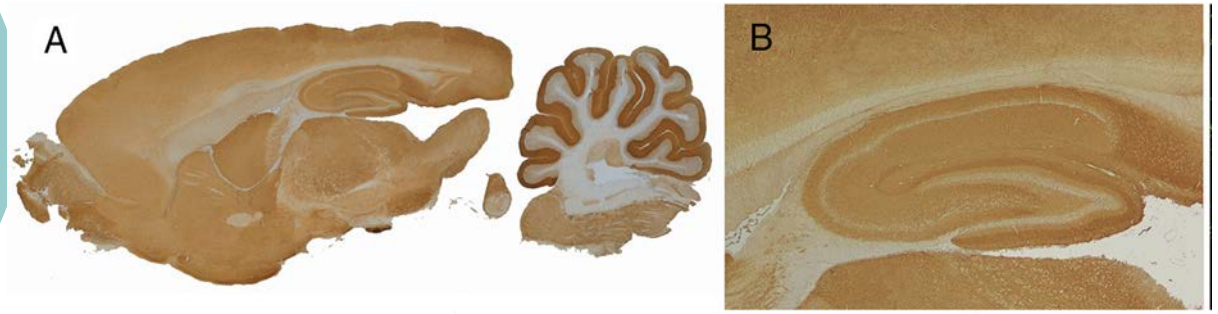


Espectro clínico y valor diagnóstico de los anticuerpos contra el complejo proteico asociado a canales de potasio

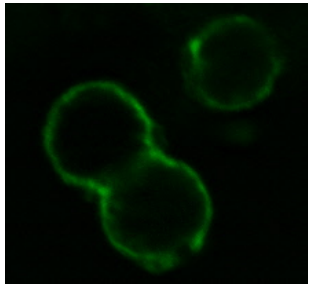
M.T. Montojo et al



Anti- CASPR2: contactin- associated protein-like 2



HEK2 contactina



Proteína en superficie neuronal de regiones del cerebro y región yuxtaparanodal de axones mielinizados

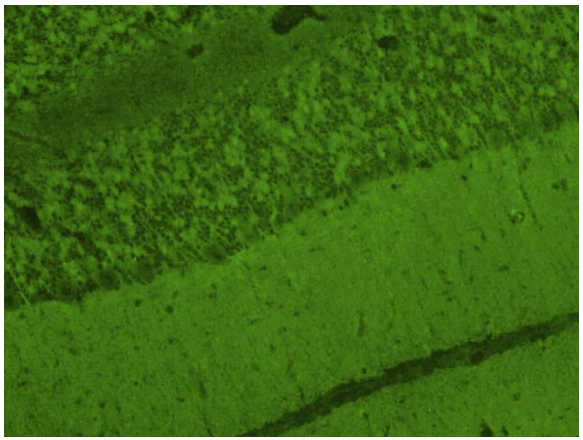
Mutaciones CNTNAP2 (gen codificador): Esquizofrenia, psicosis, autismo

Coexistencia con Ac AchR, GAD65,MuSK.

Tumor <40% timomas.

Riesgo de **reciviva** (encefalitis)

Zona molecular de cerebelo



Lancaster E, *The Diagnosis and Treatment of Autoimmune Encephalitis*. JCN. 2016.

Josep Dalmau et al. : anti-DPPX (Ann neurol. 2013)

Encefalitis con: hiperexcitabilidad, temblor y myoclonus

Antígeno "diana"

Dipeptidyl amino peptidase- like protein 6 (DPPX)

Una subunidad reguladora de Kv4.2 de canales de potasio de la superficie de las neuronas

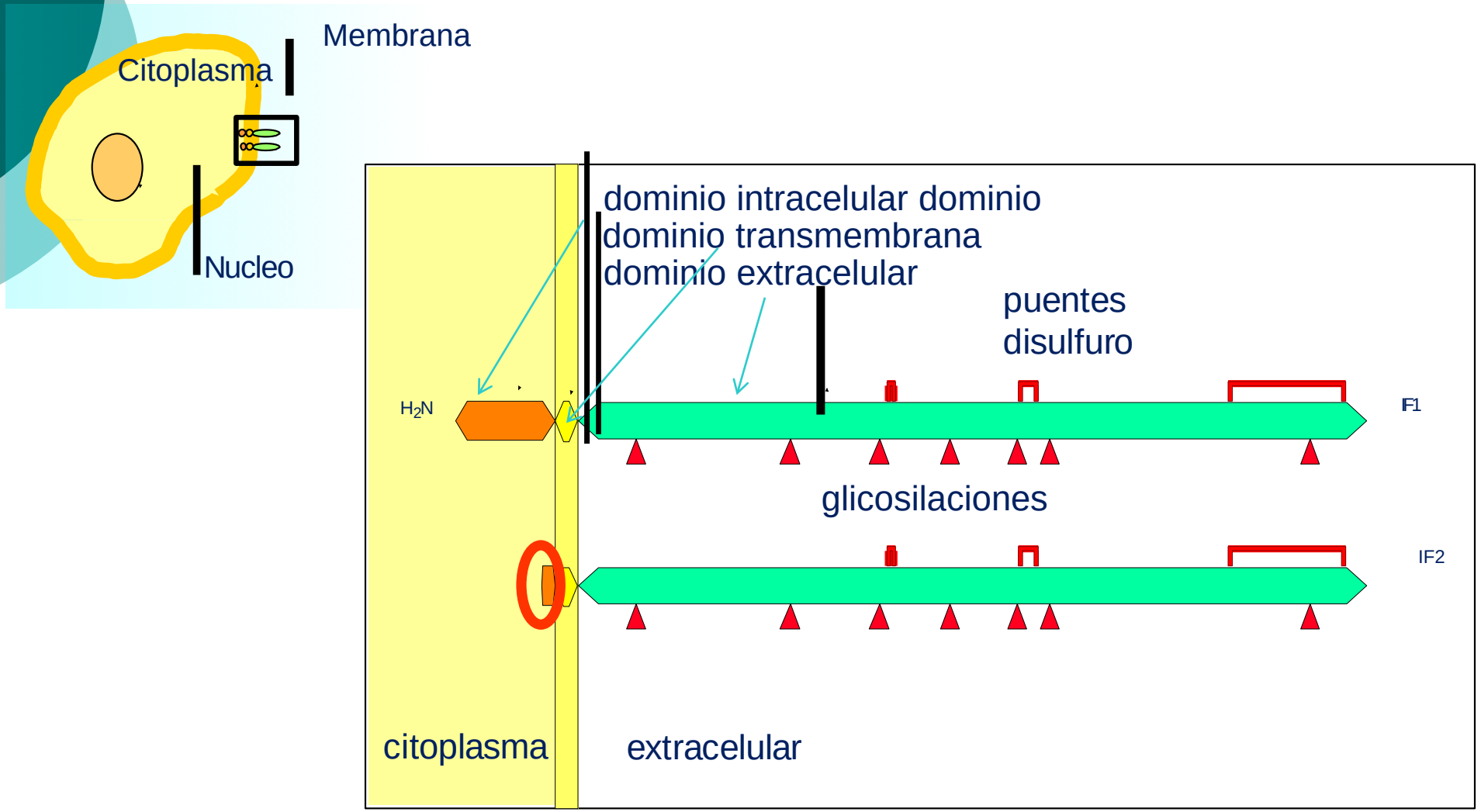
Encephalitis and Antibodies to Dipeptidyl-Peptidase–Like Protein-6, a Subunit of Kv4.2 Potassium Channels

Anna Boronat, BS,[1] Jeffrey M. Gelfand, MD,[2] Nuria Gresa-Arribas, PhD,[1] Hyo-Young Jeong, PhD,[3] Michael Walsh, MD,[4] Kirk Roberts, MD,[5] Eugenia Martinez-Hernandez, MD,[6] Myrna R. Rosenfeld, MD, PhD,[1,7] Rita Balice-Gordon, PhD,[8] Francesc Graus, MD,[1] Bernardo Rudy, PhD,[3] and Josep Dalmau, MD, PhD[1,7,9]

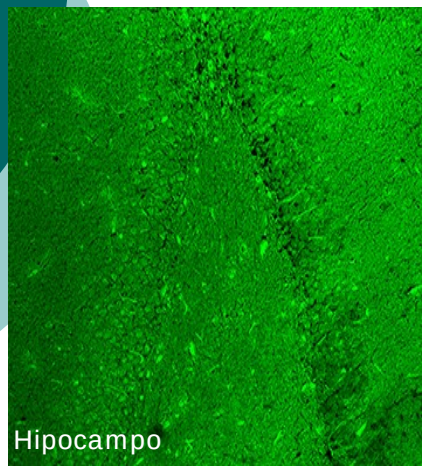
Objective: To report a novel cell surface autoantigen of encephalitis that is a critical regulatory subunit of the Kv4.2 potassium channels.
Methods: Four patients with encephalitis of unclear etiology and antibodies with a similar pattern of neuropil brain immunostaining were selected for autoantigen characterization. Techniques included immunoprecipitation, mass spectrometry, cell-base experiments with Kv4.2 and several dipeptidyl-peptidase–like protein-6 (DPPX) plasmid constructs, and comparative brain immunostaining of wild-type and *DPPX*-null mice.
Results: Immunoprecipitation studies identified DPPX as the target autoantigen. A cell-based assay confirmed that all 4 patients, but not 210 controls, had DPPX antibodies. Symptoms included agitation, confusion, myoclonus, tremor, and seizures (1 case with prominent startle response). All patients had pleocytosis, and 3 had severe prodromal diarrhea of unknown etiology. Given that DPPX tunes up the Kv4.2 potassium channels (involved in somatodendritic signal integration and attenuation of dendritic back-propagation of action potentials), we determined the epitope distribution in DPPX, DPP10 (a protein homologous to DPPX), and Kv4.2. Patients' antibodies were found to be specific for DPPX, without reacting with DPP10 or Kv4.2. The unexplained diarrhea led to a demonstration of a robust expression of DPPX in the myenteric plexus, which strongly reacted with patients' antibodies. The course of neuropsychiatric symptoms was prolonged and often associated with relapses during decreasing immunotherapy. Long-term follow-up showed substantial improvement in 3 patients (1 was lost to follow-up).
Interpretation: Antibodies to DPPX are associated with a protracted encephalitis characterized by central nervous system hyperexcitability (agitation, myoclonus, tremor, seizures), pleocytosis, and frequent diarrhea at symptom onset. The disorder is potentially treatable with immunotherapy.

ANN NEUROL 2013;73:120–128

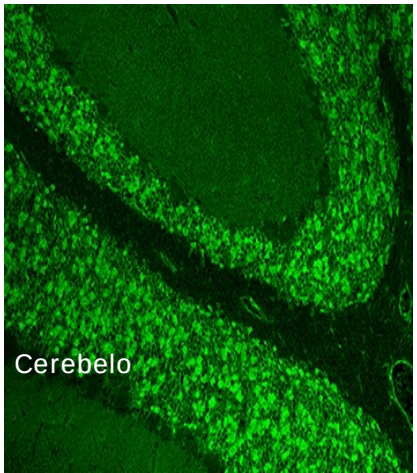
DPPX: Proteína transmembrana de tipo II



Anti-DPPX(=DPP6,dipeptidil-peptidase-like protein 6)

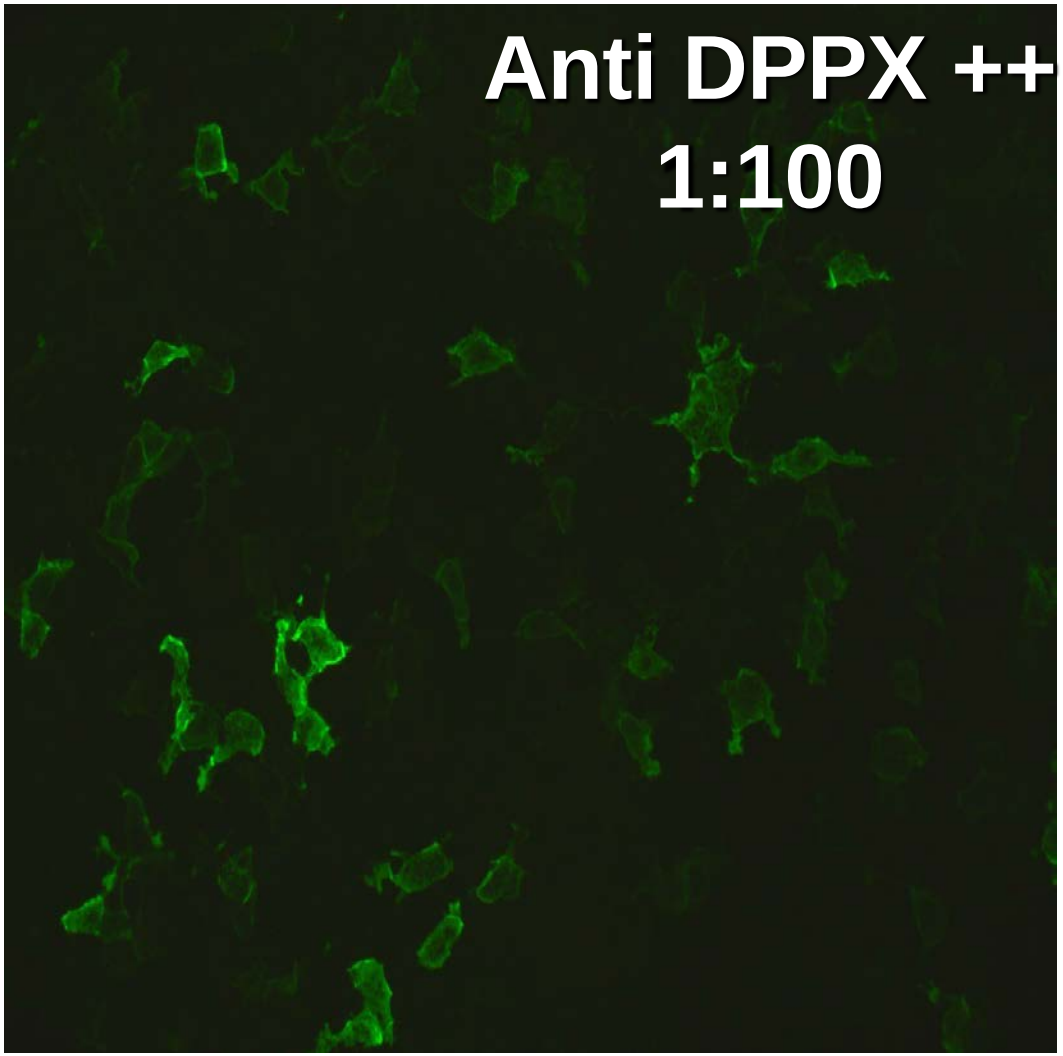


Fluorescencia granular del Estrato Molecular del Cerebelo, Estrato lúcido del Hipocampo.



Antígeno	
Peso Molecular	98 kDa (humano,Isoforma DPPX- L)
Expresión	Cerebelo, Membrana Celular
Función	Proteína de membrana, funciones reguladoras correspondientes a los Canales de Potasio Kv4.2.
Clínica	
Enfermedad	Encefalitis Autoinmune
Síntomas	Inquietud física, Confusión, Convulsiones, Temblores,
Tumos asociado	Ataques Ninguno descrito
Caracterización	
Publicación	Boronat A, Ann Neural 2013 73(1):102-128
Método	Inmunoprecipitación

Anti-DPPX (=DPP6, dipeptidil-peptidase-like protein 6)

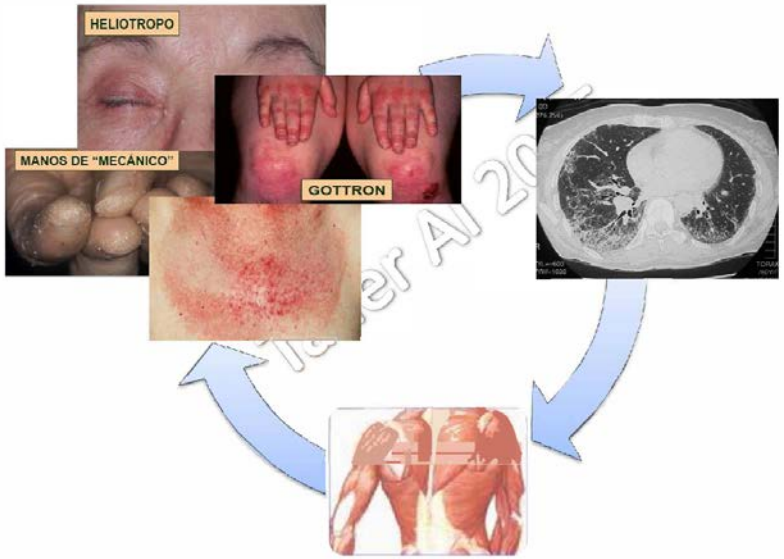


Miopatías Inflamatorias Idiopáticas (MII)

- Afectan a **musculatura estriada**
- **Naturaleza inflamatoria:** Dermatomiositis, Polimiositis, Miositis con cuerpos de inclusión (MCI)
- **Enfermedades sistémicas**
- Se pueden **asociar a cáncer** y presencia de **autoanticuerpos** específicos asociado a enfermedades autoinmunes MSA

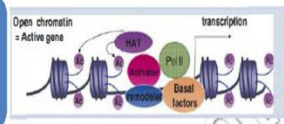
MIOPATÍAS AUTOINMUNES

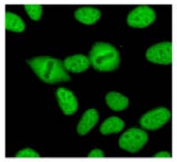
MSA CLÁSICOS
50%



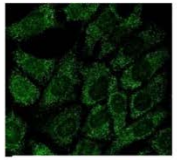
ANTICUERPOS ESPECÍFICOS DE MIOSITIS ***CLÁSICOS*** (MSA)

Mi2

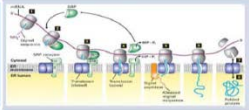


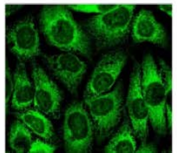


Aminoacil-tRNA-Sintetasa



SRP





MSA CLÁSICOS +
NUEVOS
80%

Table 1. Myositis-specific autoantibodies, target autoantigens, and clinical associations

Autoantibody	Target autoantigen	Clinical associations	Frequency, percentage	
			Adults	JDM
Anti-ARS	Amino-acyl-tRNA synthetase	Anti-synthetase syndrome	Overall: 30-40	Overall: 1-3
- Jo-1	- Histidyl	Myositis	Jo-1: 15-20	
- PL7	- Theronyl	Interstitial lung disease	PL7: <5	
- PL12	- Alanyl	Raynaud phenomenon	PL12: <5	
- OJ	- Isoleucyl	Arthritis	OJ: <5	
- EJ	- Glycyl	Mechanic's hands	EJ: <5	
- KS	- Asparaginyl	Fever	KS: <5	
- Ha	- Tyrosyl		Ha: <1	
- Zo	- Phenylalanyl		Zo: <1	
Anti-Mi-2	Nucleosome remodeling deacetyalse complex (NuRD)	DM	<10	4-10
Anti-p155/140	Transcriptional intermediary factor 1 gamma (TIF1-γ)	JDM: DM and ulceration Adults: DM and malignancy	13-21	22-29
Anti-p140	Nuclear matrix protein 2 (NXP2)	JDM: DM and calcinosis Adults: DM and ILD	<5	23
Anti-SAE	Small ubiquitin-like modifier activating enzyme (SAE)	DM	<5	<1
Anti-CADM-140	Melanoma differentiation-associated gene 5 (MDA5)	CADM and ILD	50-73 CADM (not in Caucasians)	Not known
Anti-SRP	Signal recognition particle (SRP)	Necrotizing myopathy	5-10	<3
Anti-200/100	Unknown 100- and 200-kDa proteins	Necrotizing myopathy	<10 necrotizing myopathy	Not known

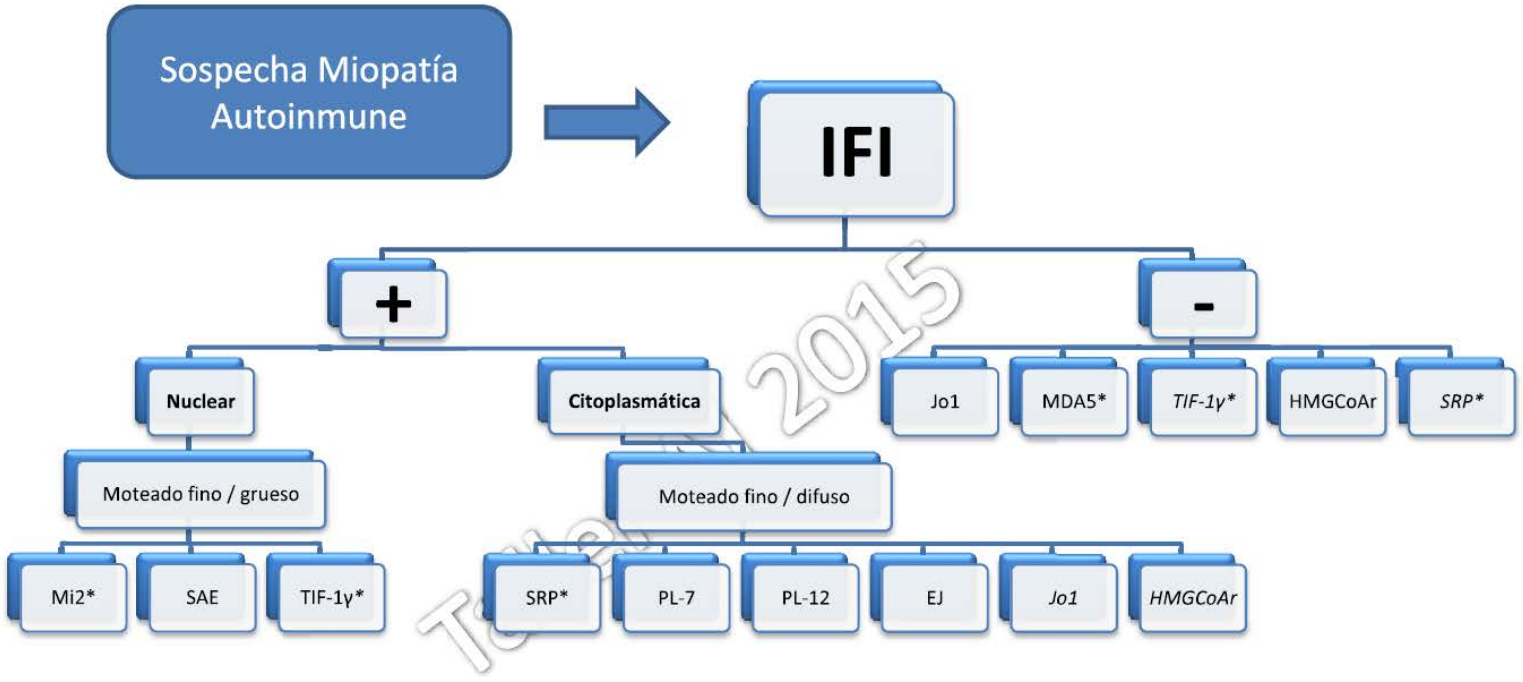
ARS, amino-acyl-tRNA synthetase; CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease; JDM, juvenile dermatomyositis.

MSA : antígenos específicos de miositis

- En las MII se detectan MSA dirigidos frente a proteínas intracelulares claves en el procesamiento DNA/RNA/proteínas ⇒ *implicación patogénica*

- Estos MSA correlacionan con el fenotipo clínico/pronóstico/ respuesta terapéutica ⇒ *marcador clínico*

- La validación de la eficacia diagnostica de estos MSA precisan del desarrollo de ensayos comerciales aplicables a la *rutina clínica*



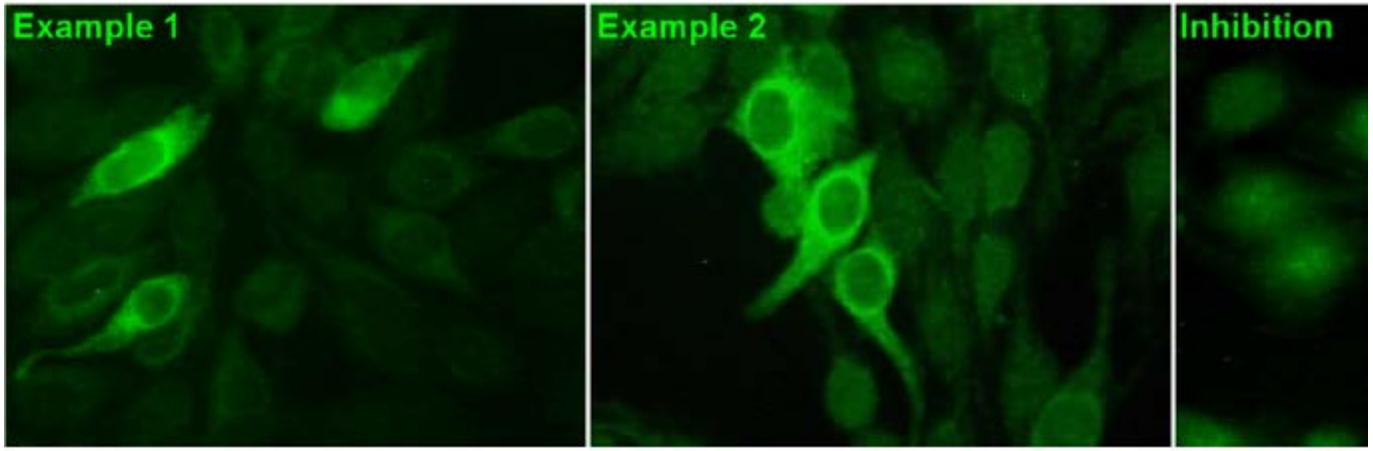
Propuesta de algoritmo diagnóstico para Miopatías Autoinmunes basado en los resultados obtenidos en el Taller de AI 2015

Drouot *et al. Arthritis Research & Therapy* 2014, **16**:R39
http://arthritis-research.com/content/16/1/R39

arthritis research&therapy

RESEARCH ARTICLE Open Access

Exploring necrotizing autoimmune myopathies with a novel immunoassay for anti-3-hydroxy-3-methyl-glutaryl-CoA reductase autoantibodies



anti-HMGCR autoantibodies in indirect immunofluorescence on HEp-2 cells.

MIOTOXICIDAD relacionada con las ESTATINAS

- **Clínica: (SINAM) Statin necrotizing autoimmune myopathy**

Statin-related myotoxicity phenotype classification [8].

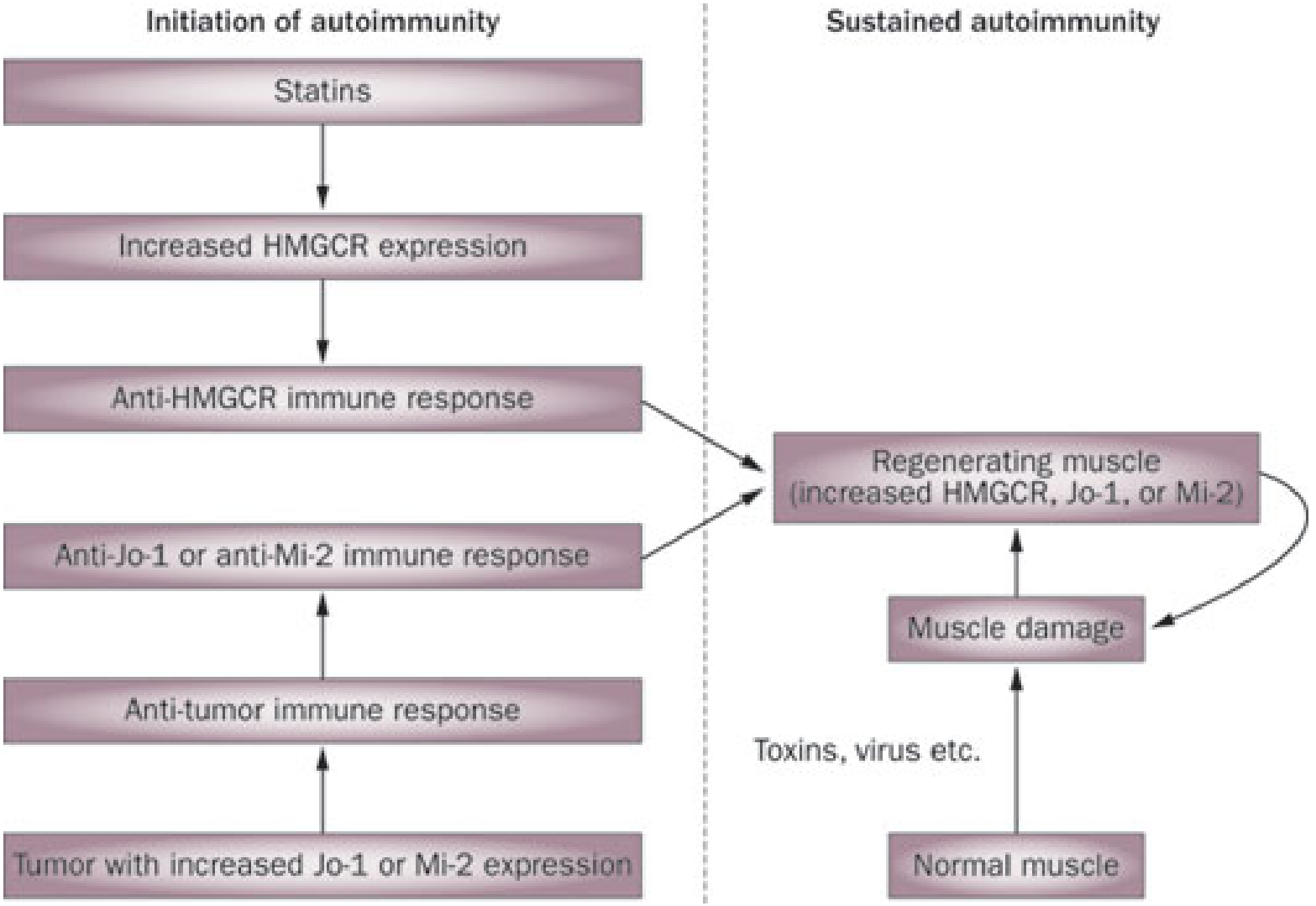
Classification	Phenotype	Definition	Incidence
SRM 0	CK elevation < 4 X ULN	No muscle symptoms	1.5–26%
SRM 1	Myalgia, tolerable	Muscle symptoms without CK elevation	0.3–33%
SRM 2	Myalgia, intolerable	Muscle symptoms, CK < 4 X ULN	0.1–1/1,000
SRM 3	Myopathy	CK 4 to 10 X ULN +/− muscle symptoms	5/100,000 Patient-years
SRM 4	Severe myopathy	CK 10 to 50 X ULN, muscle symptoms	0.11%
SRM 5	Rhabdomyolysis	CK > 10 X ULN with muscle symptoms and renal impairment; Or CK > 50 X ULN	0.1–8.4/100,000 Patient –years
SRM 6	Autoimmune-mediated necrotizing myositis	HMGCR antibodies, incomplete resolution upon discontinuation	~2/million per year

SRM statin-related myotoxicy, CK creatine kinase, ULN upper limit of normal.

SINAM: 2/millón por año

Anti-HMGCoAR

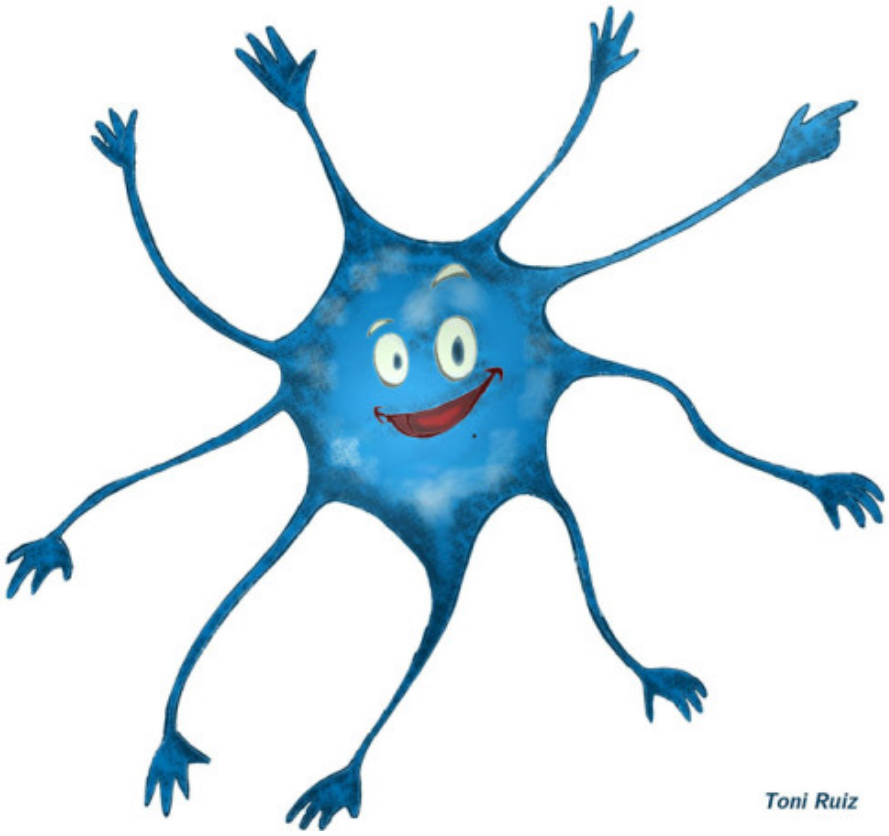
Anti-3hidroxi-3-metilglutaril coenzima A reductasa.



Estatinas
Miopatía necrotizante
anti-HMGoAR (Anti-3hidroxi-3-metilglutaril coenzima A reductasa)

- Miotoxicidad y Miopatía necrotizante
- Presencia de Anti- HMGCR
- Miopatía necrotizante autoinmune se asocia a la presencia de anticuerpos contra la partícula de señal de reconocimiento (SRP)
- NO se asocian con otros anticuerpos específicos de miositis
- Se correlaciona con niveles altos de CPK
- Útiles en el seguimiento

GRACIAS



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