

Introducción a la Neuroinmunología

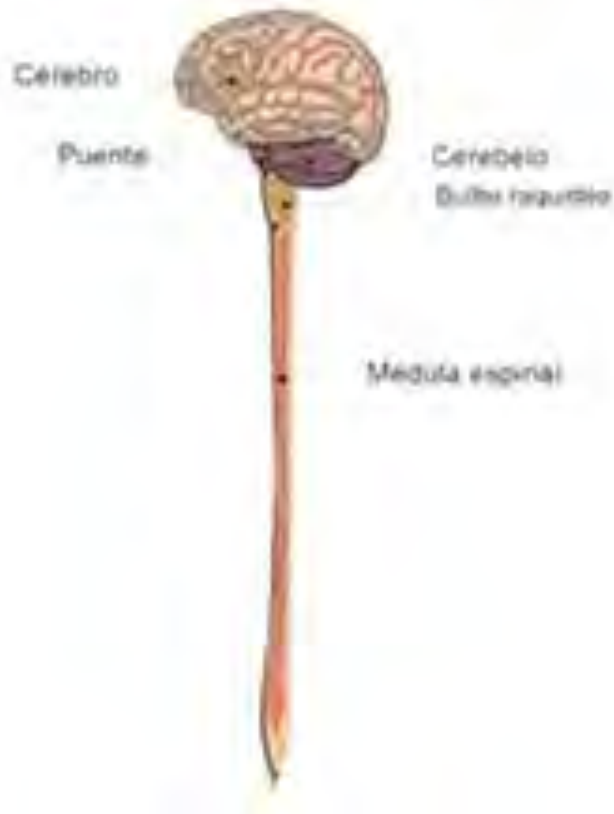
Curso Universitario Trienal de Clínica
Médica – Medicina Interna

Dr. Mariano Marrodan
Neuroinmunología
Fleni

Conflictos de interés

- No tengo conflictos de interés vinculados a esta presentación.

Sistema Nervioso Central (S.N.C)

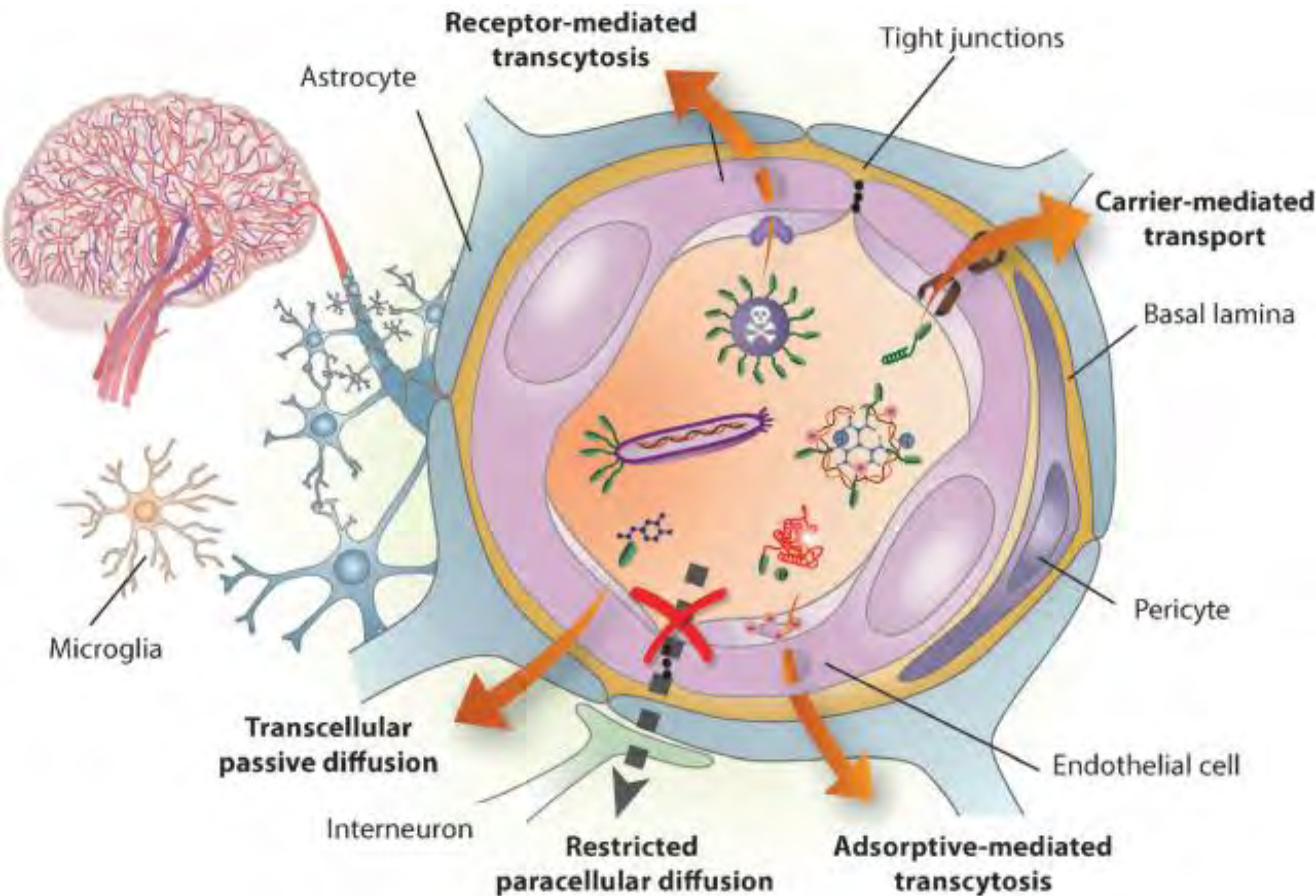


- ESCLEROSIS MÚLTIPLE
- NMOSD
- Otras enf desmielinizantes
- Vasculitis (primarias o secundarias)
- Encefalitis autoinmunes
- Síndromes paraneoplásicos

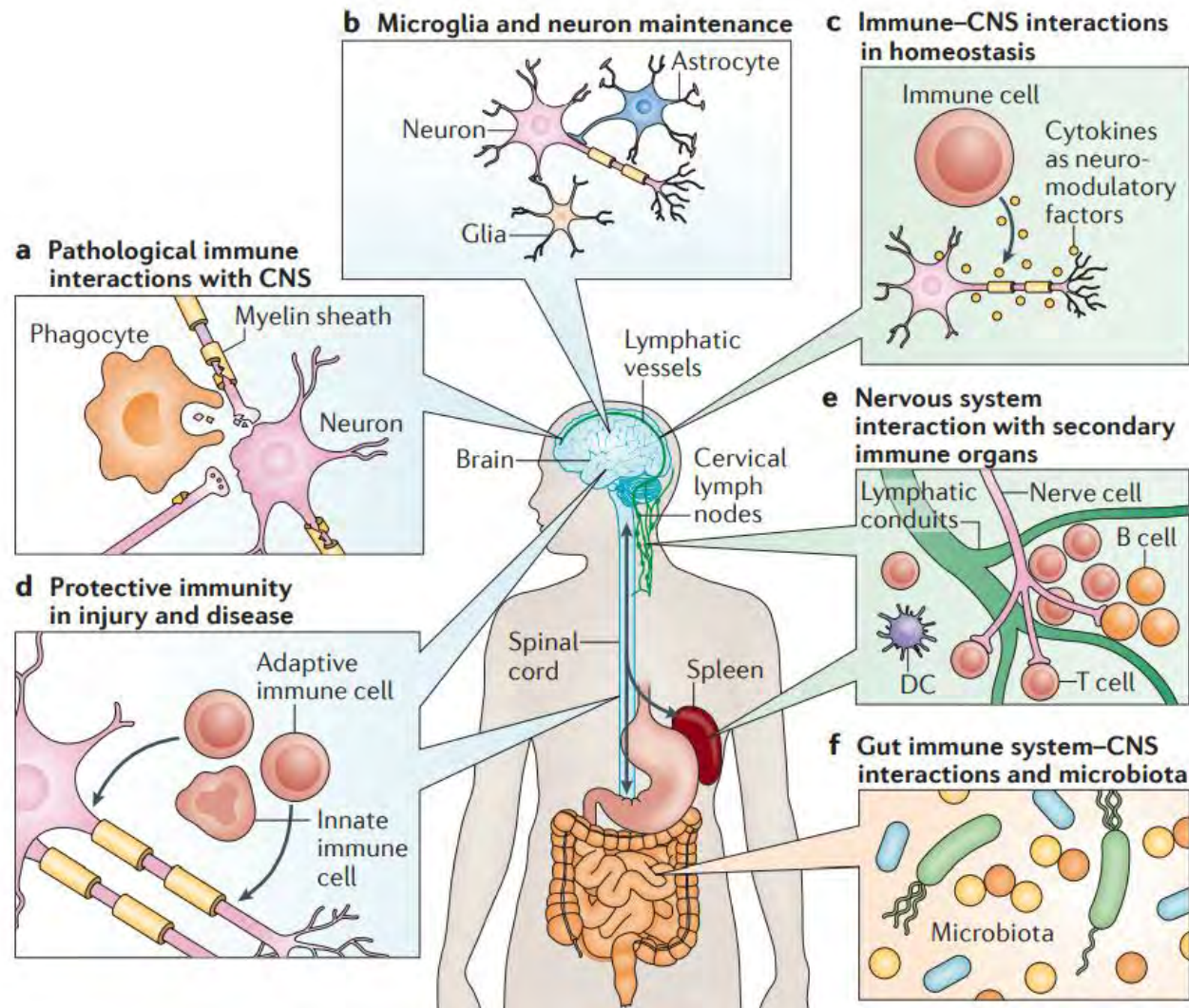
Sistema Nervioso Periferico (S.N.P)



- Sme de Guillain Barré
- Polineuropatía desmielinizante crónica inflamatoria
- Otras neuropatías inmunomediadas
- Miastenia Gravis
- Miositis

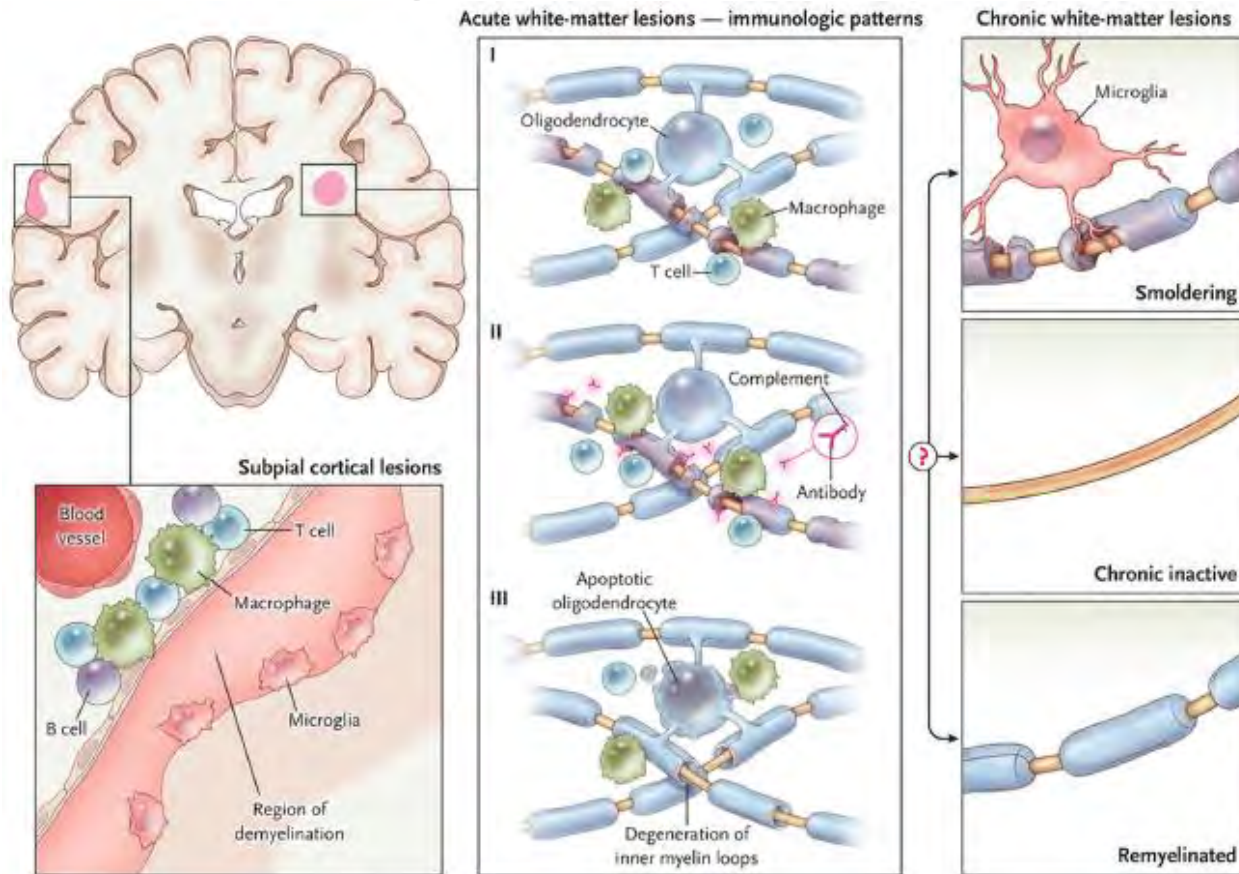


Más allá de los linfocitos



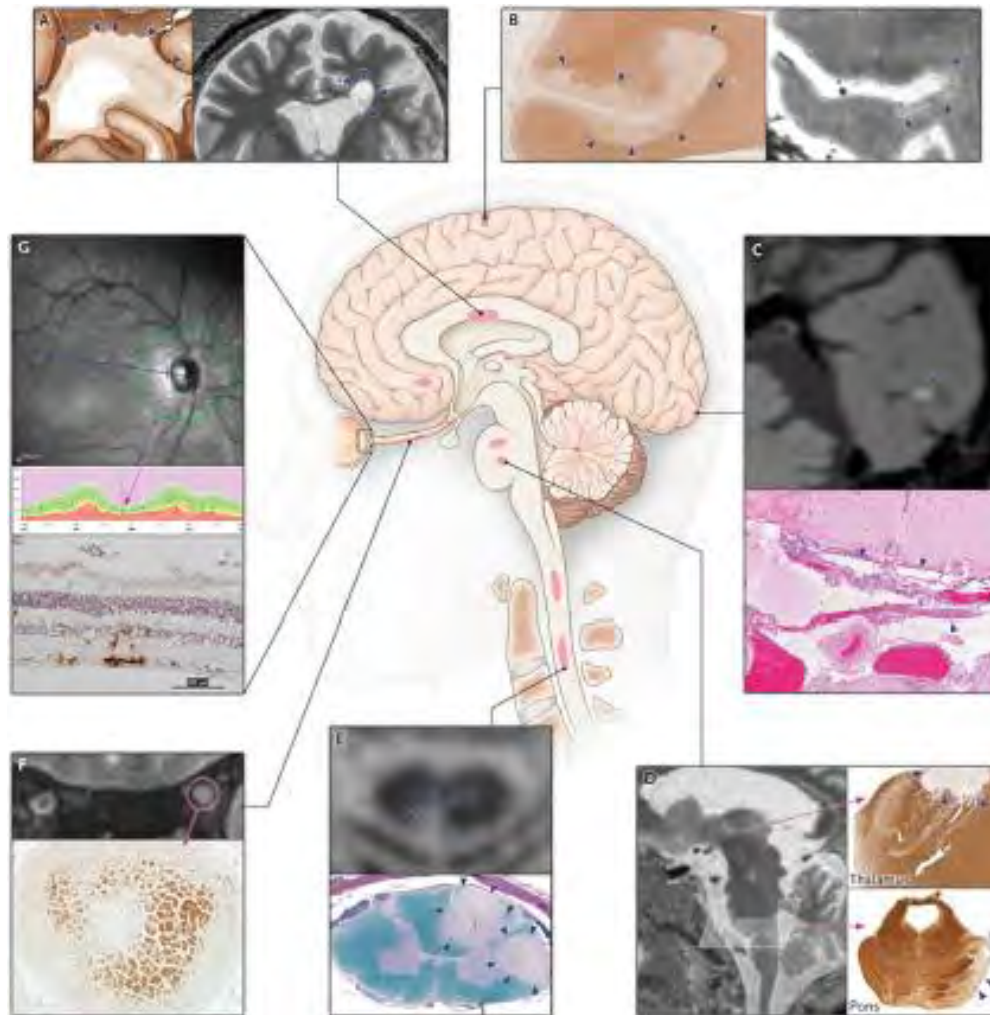
Esclerosis Múltiple (EM)

Fisiopatología → Autoinmune



- Ruptura de barrera hemato-encefálica (BHE)
- Infiltrado inflamatorio
- Mutaciones genéticas comunes
- Producción intratecal de inmunoglobulinas (Bandas oligoclonales)
- Respuesta satisfactoria a drogas inmunosupresoras

Correlación tisular



Reich et al, NEJM 2018

Epidemiología

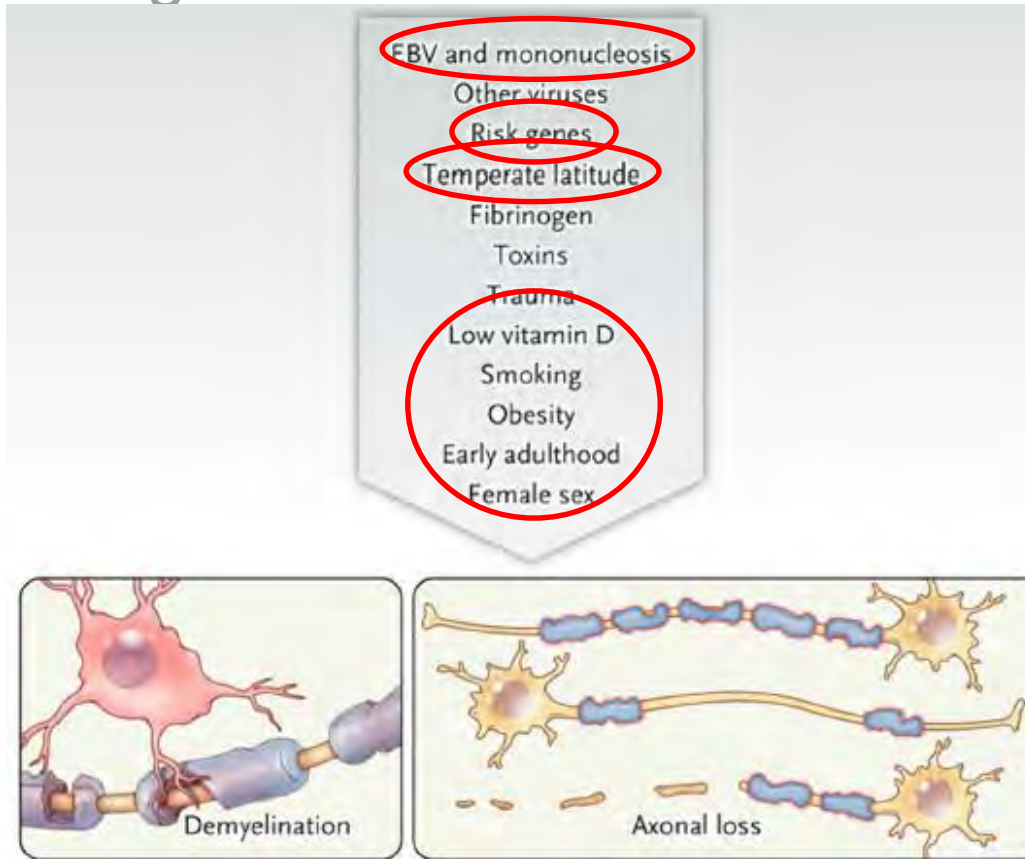


Figura extraída y modificada de Reich et al, NEJM 201

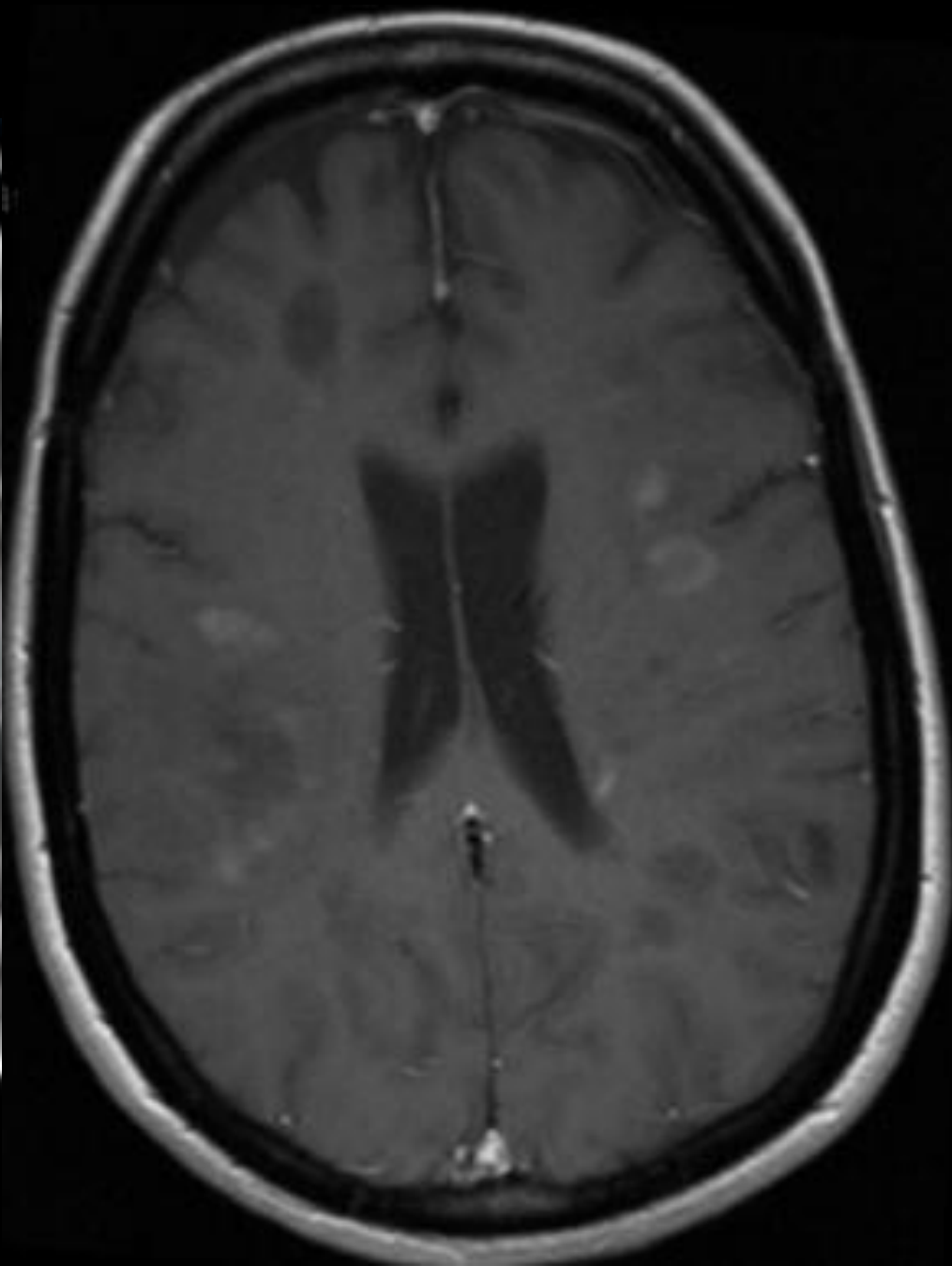
Manifestaciones clínicas

Variadas

- Disminución de agudeza visual uni o bilateral
- Compromiso de pares craneales
- Trastornos esfintereanos
- Debilidad focal, unilateral, paraparesia
- Trastornos sensitivos
- Ataxia

Definiciones importantes

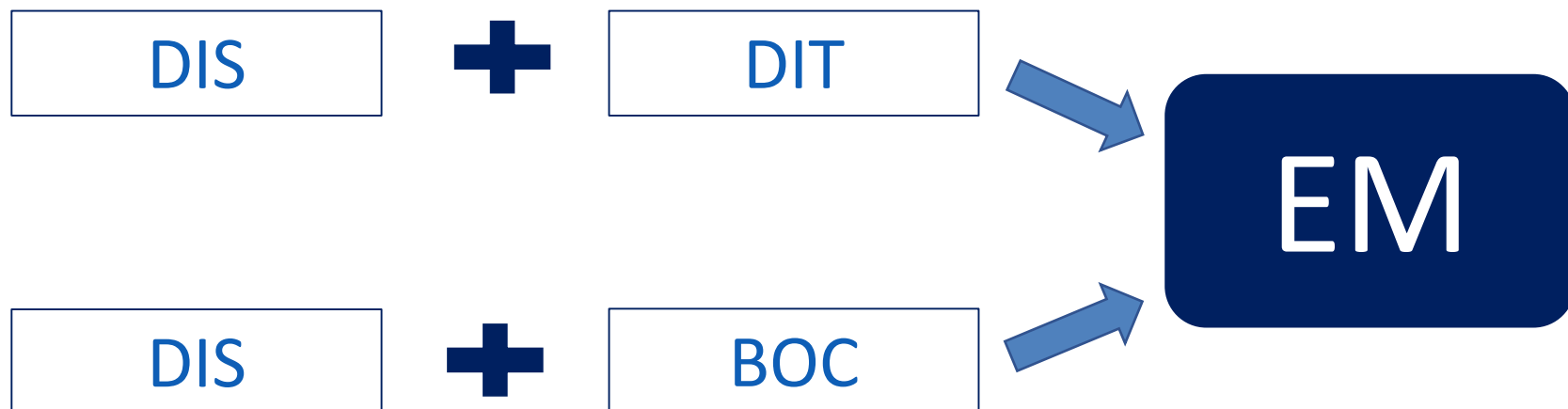
- Brote: signos o síntomas típicos de un evento desmielinizante del SNC durante al menos 24 h, sin fiebre ni infección concomitante, actual o pasado; para síntomas paroxísticos, los mismos deben ser recurrentes a lo largo de al menos 24 h
- Diseminación en tiempo (DIT): enfermedad activa a través del tiempo (al menos 1 mes)
- Diseminación en espacio (DIS): afectación de múltiples áreas del SNC (periventricular, yuxtacortical/cortical, infratentorial y médula)
- Pseudobrote: Reaparición de síntomas previamente presentados (antecedente de brote) a partir de intercurencia clínica, generalmente infecciosa. -Fenómeno de **Uhthoff**



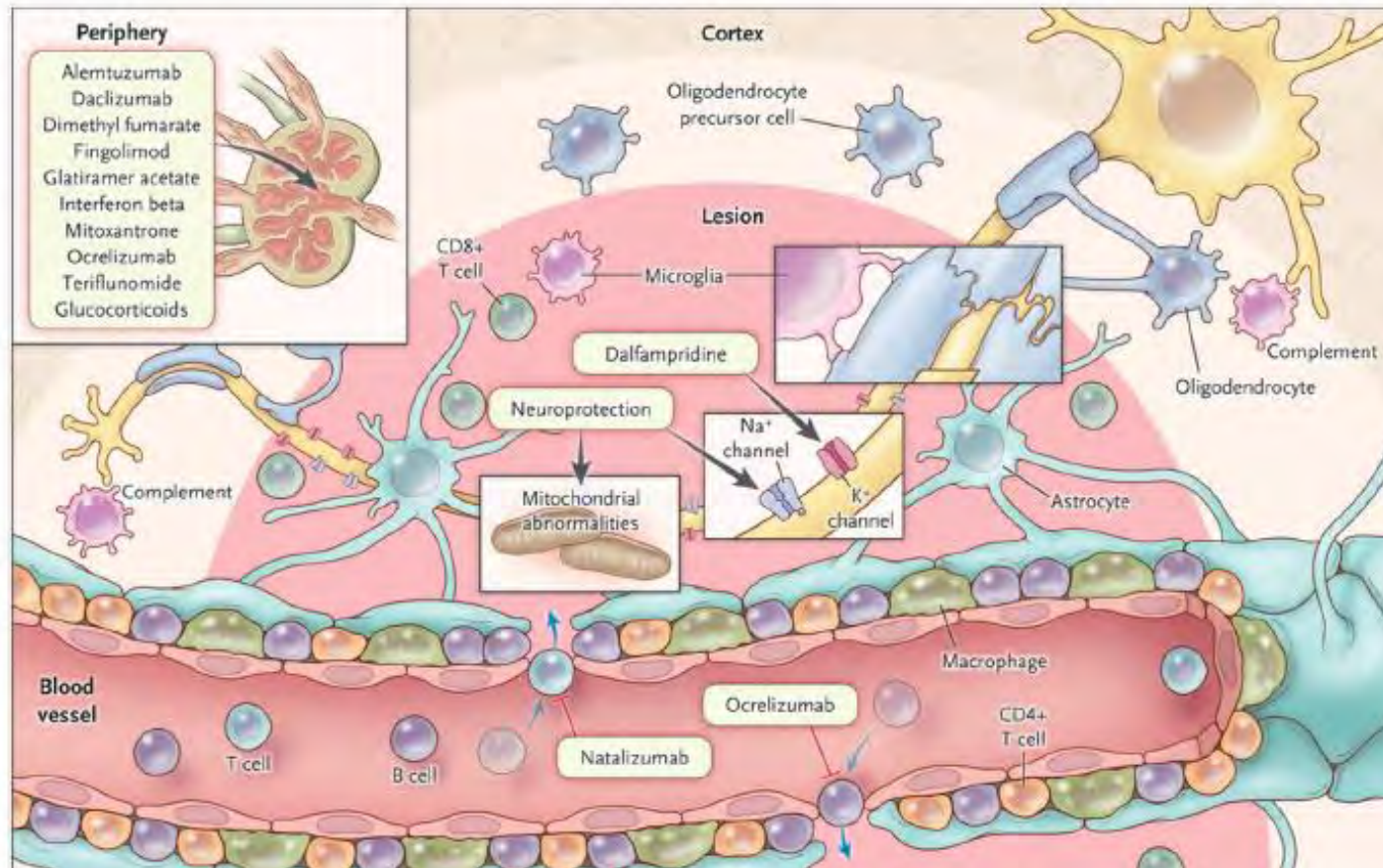
LCR

- Estudio Físico químico ligeramente normal.
Pueden encontrarse hipercelularidad mononuclear leve (menor a 50c/mm^3) o hiperproteinorraquia
- Síntesis intratecal de inmunoglobulinas (IgG) – Bandas oligoclonales** (Método más S y E: isoelectroenfoque en suero y LCR pareados).
 - BOC tipo II o III son sugestivas de EM en el contexto adecuado





EM, Tratamiento



Tratamientos modificadores del curso natural de la EM

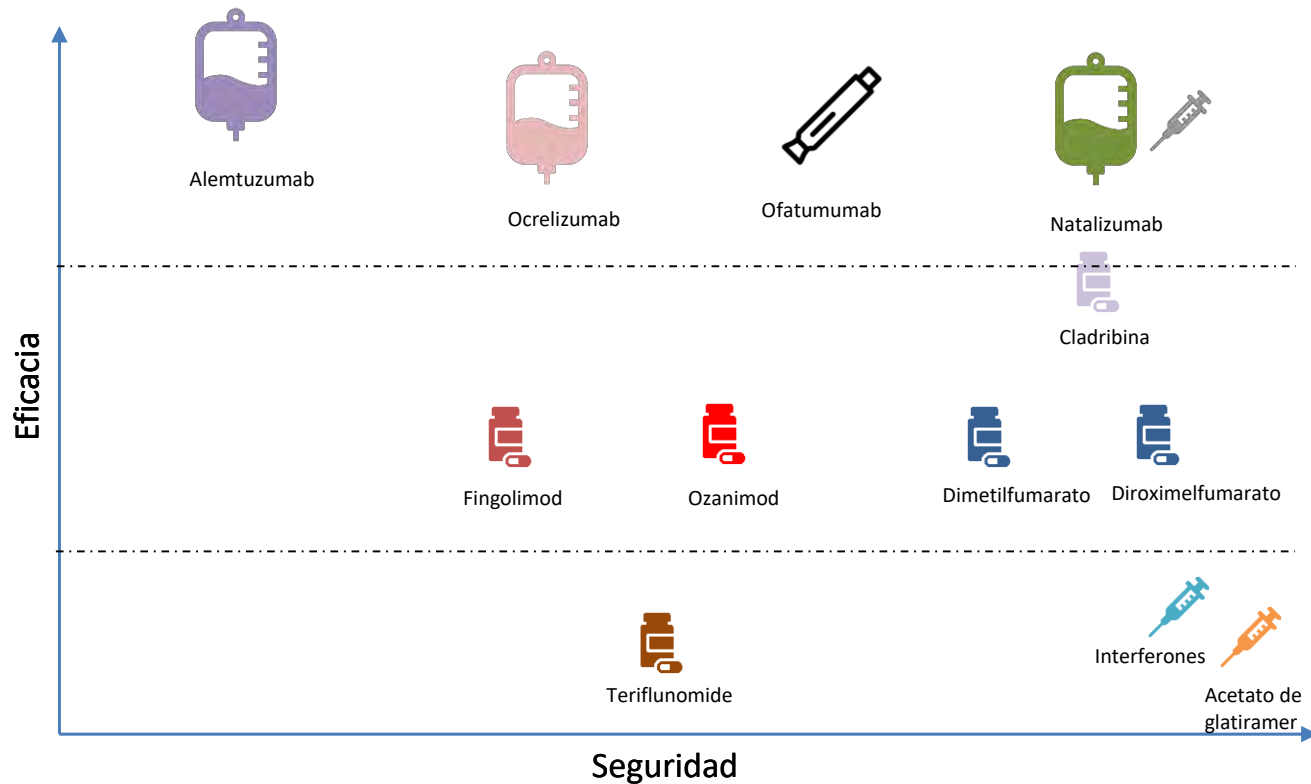
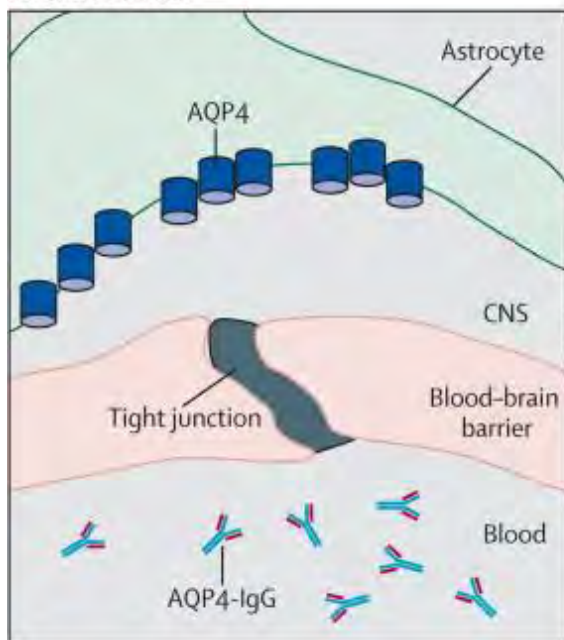
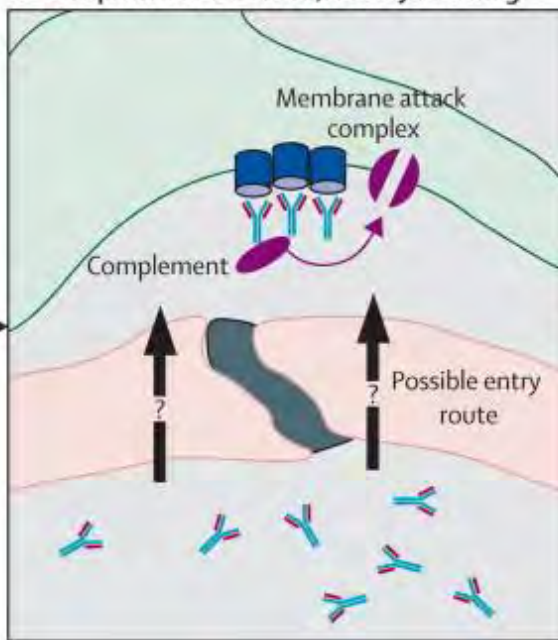
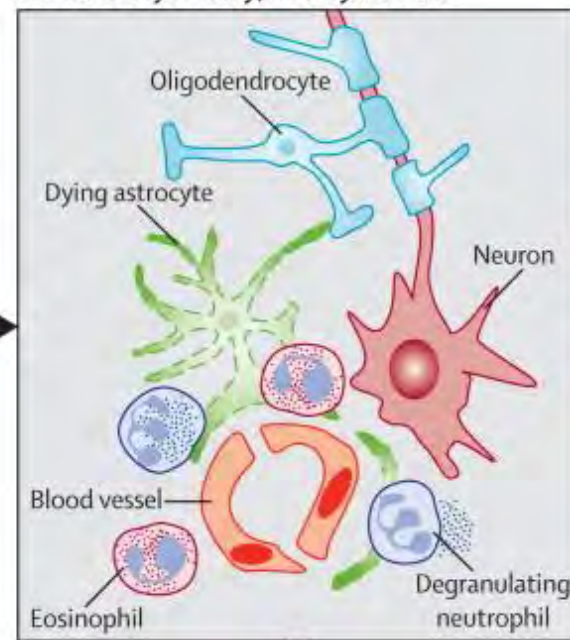
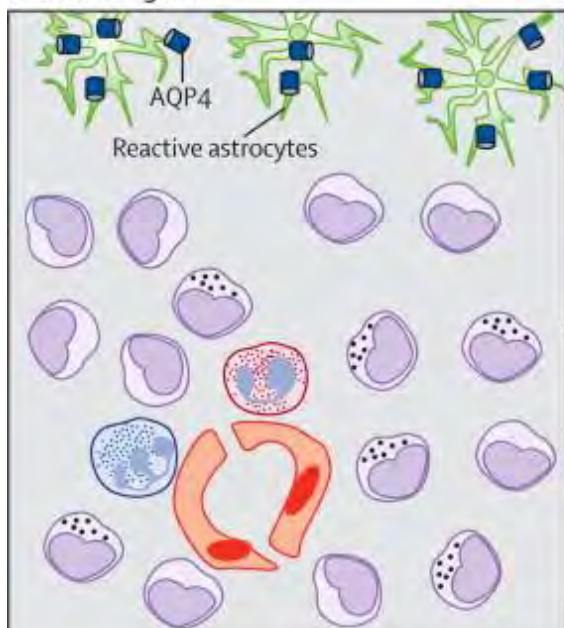
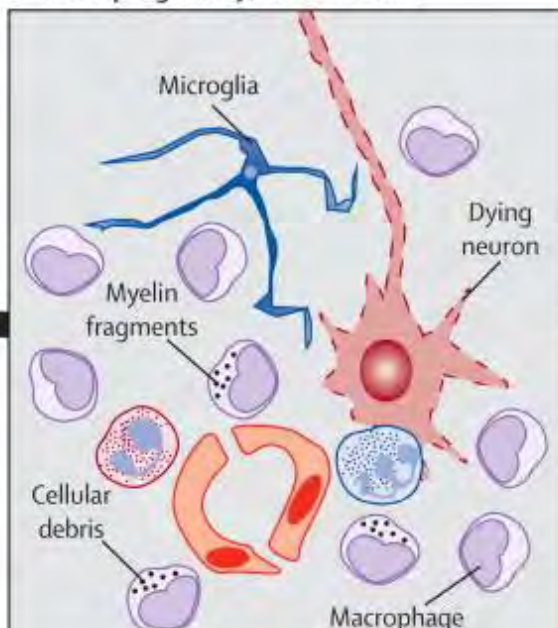
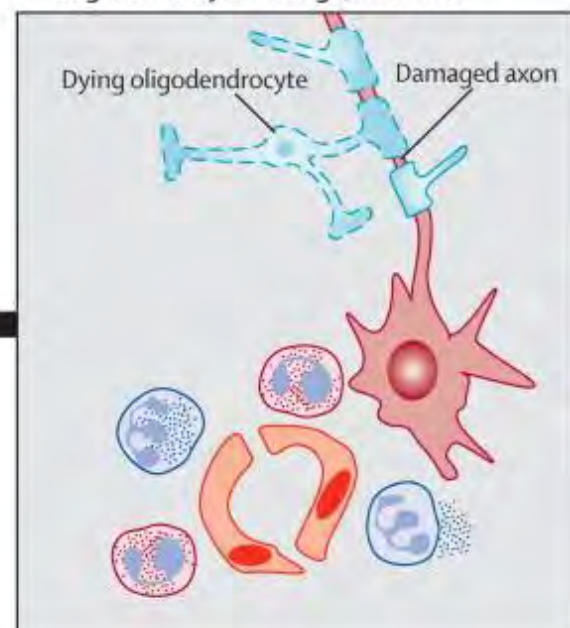


Grafico realizado a partir de datos de Samjoo IA et al, J Effect Clin Research 2022

Neuromielitis óptica: Introducción

- Enfermedad desmielinizante idiopática del SNC
- Menos frecuente que la EM, 1 a 2 cada 100.000
- Afecta el NO y la ME
- Más frecuente en mujeres
- La edad de inicio: 40 años
- El 80 al 90% forma recidivante, primer recaída entre el primer y tercer año desde el inicio.



A Normal CNS**B Complement activation; astrocyte damage****C Granulocyte entry; astrocyte death****F Reactive gliosis****E Macrophage entry; neuron death****D Oligodendrocyte damage; axon loss**

Clínica: en comparación con la EM

El déficit neurológico adquirido es más marcado

Los síntomas empeoran en varios días y duran más tiempo

La recuperación ocurre en semanas o meses

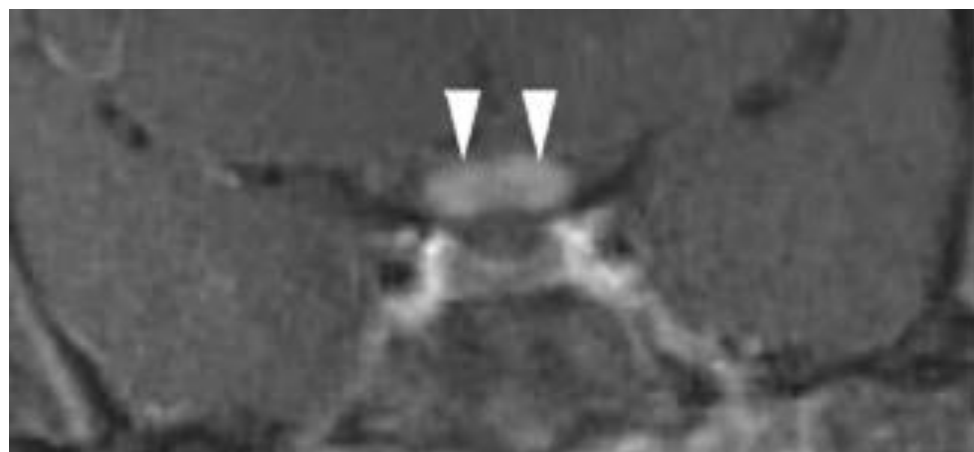
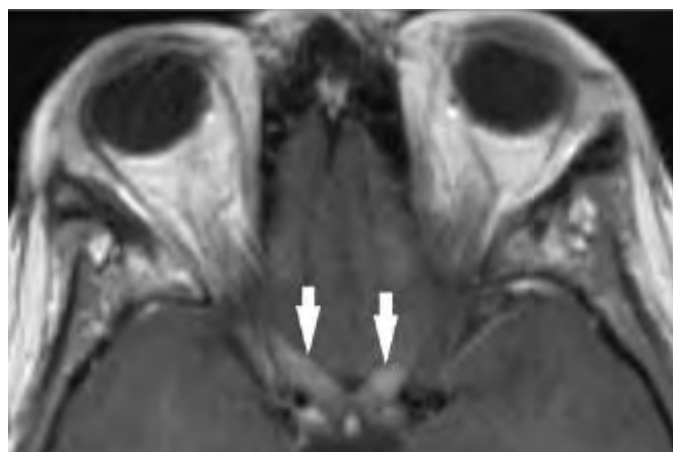
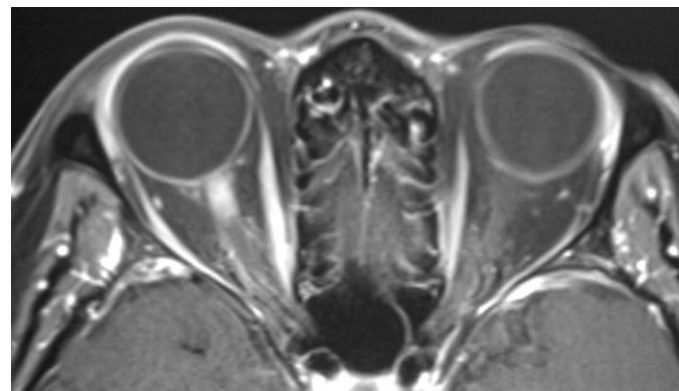
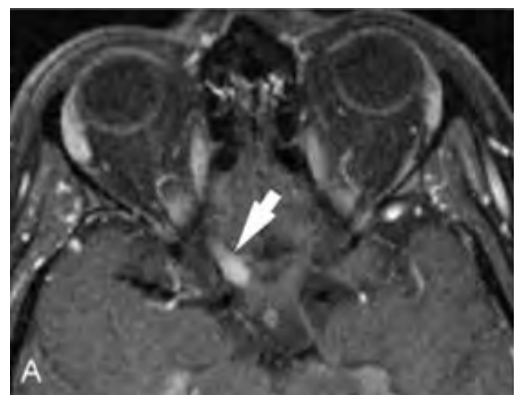
La discapacidad se incrementa rápidamente con las recaídas

Luego de 5 años el 50% de los pacientes tienen ceguera en uno o ambos ojos y requieren asistencia para deambular

La afección del NO suele ser atípica, puede ser bilateral o rápidamente secuencial, muy dolorosa, con pérdida severa de la AV y sin mejoría en las primeras 3 semanas

	Typical	Atypical
Age	Young adult	Age >50 years or <12 years
Ethnic origin	White	African, Asian, or Polynesian descent
Laterality	Unilateral symptoms	Bilateral simultaneous or rapidly sequential
Pain	Mild periocular pain; worse on eye movement	Severe periocular pain waking patient from sleep, painless visual loss, pain persisting longer than 2 weeks
Vision	Mild to moderated uniocular visual loss followed by spontaneous improvement	Severe visual loss (worse than 6/60 or 20/200), no recovery starting within 3 weeks of onset, progression of visual loss for more than 2 weeks
Appearance	Normal or swollen optic disc	Severe optic disc swelling, macular star (neuroretinitis), optic disc haemorrhages, anterior—posterior segment inflammation, marked retinal exudates

Magnetic Resonance Imaging of Optic Neuritis in Patients With Neuromyelitis Optica Versus Multiple Sclerosis



Mielitis

La mielitis suele generar paraplejía severa, pérdida de sensibilidad por debajo del nivel de la lesión y disfunción vesical

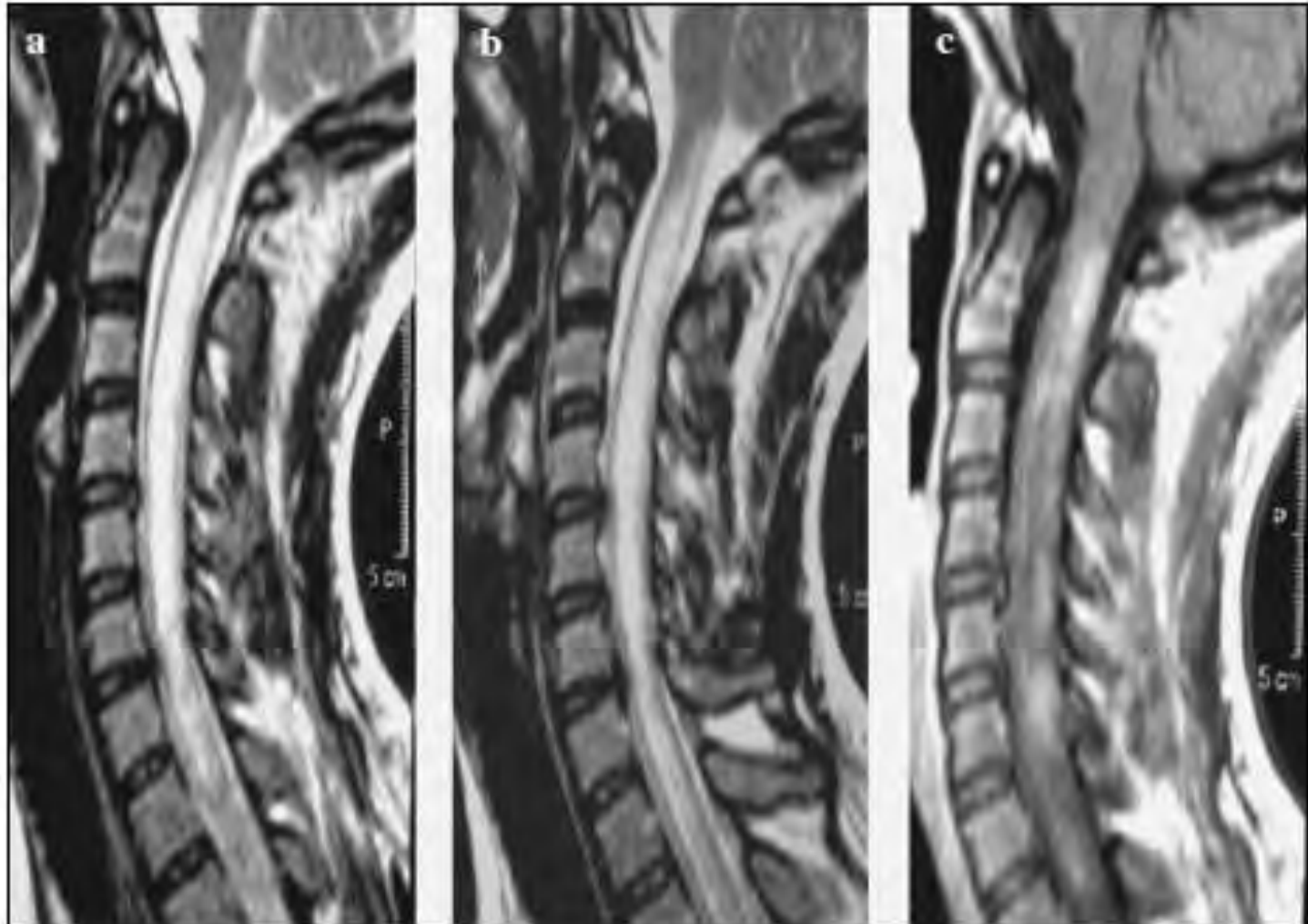
Las lesiones cervicales pueden extenderse hasta el tronco del encéfalo dando náuseas, vómitos e incluso paro respiratorio

Espasmos paroxísticos dolorosos y Lhermitte

Las lesiones medulares son longitudinalmente extendidas, abarcando tres o más segmentos con profuso realce con cte

M. Filippi • M.A. Rocca

MR imaging of Devic's neuromyelitis optica

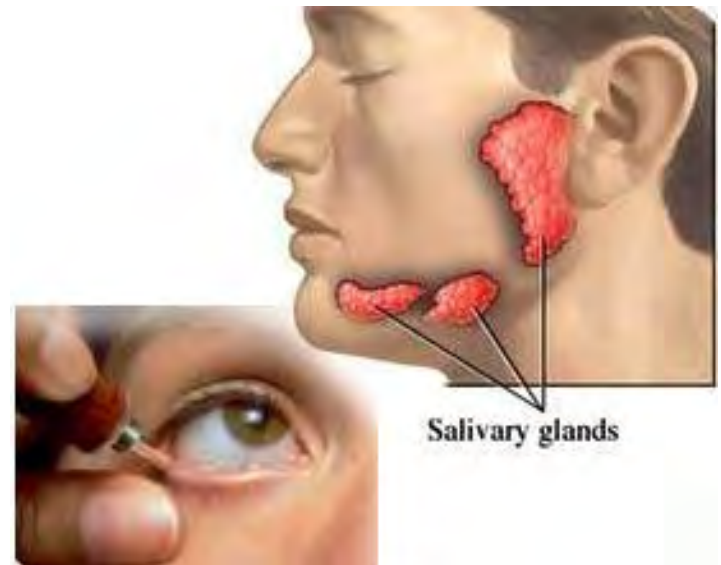


Patología asociada

Muchos pacientes con NMO presentan otras EAI asociadas: enfermedad tiroidea, lupus eritematoso sistémico, y síndrome de Sjogren



Más frecuente aún es el hallazgo de anticuerpos no-órgano específicos, como ANA, o los anticuerpos SSA, en ausencia de síntomas o signos clínicos de enfermedad AI sistémica.



Estudios complementarios

Inicialmente la RMN de encéfalo suele ser normal. Durante el transcurso de la enfermedad, hasta el 60% de los pacientes pueden desarrollar lesiones encefálicas no típicas de EM

RMN de columna y NO alteradas según compromiso

LCR suele presentar linfocitosis y 15-30 % BOC (+)

La detección anti-NMO tiene una sensibilidad mayor al 75% y una especificidad mayor al 90%

Table 1 **NMOSD diagnostic criteria for adult patients**

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses^a

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

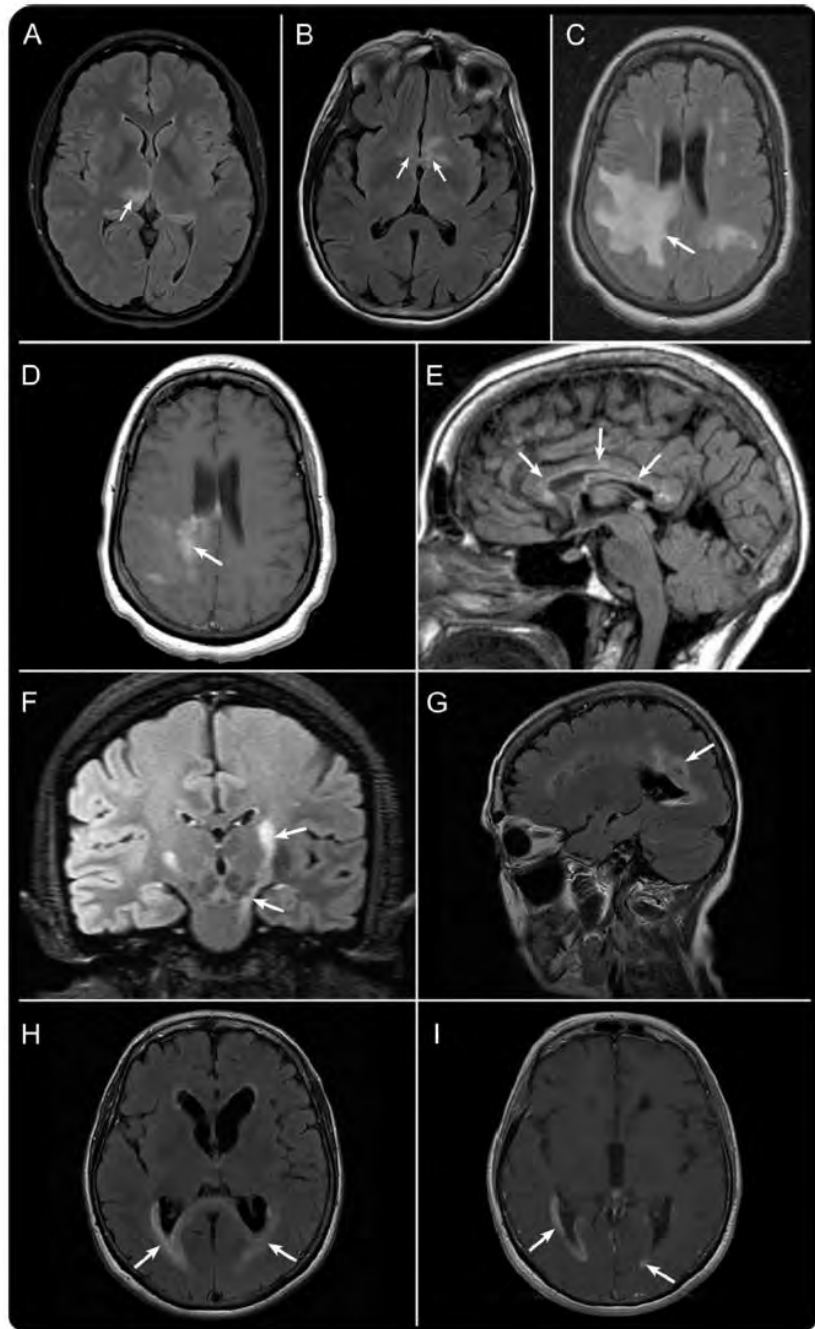
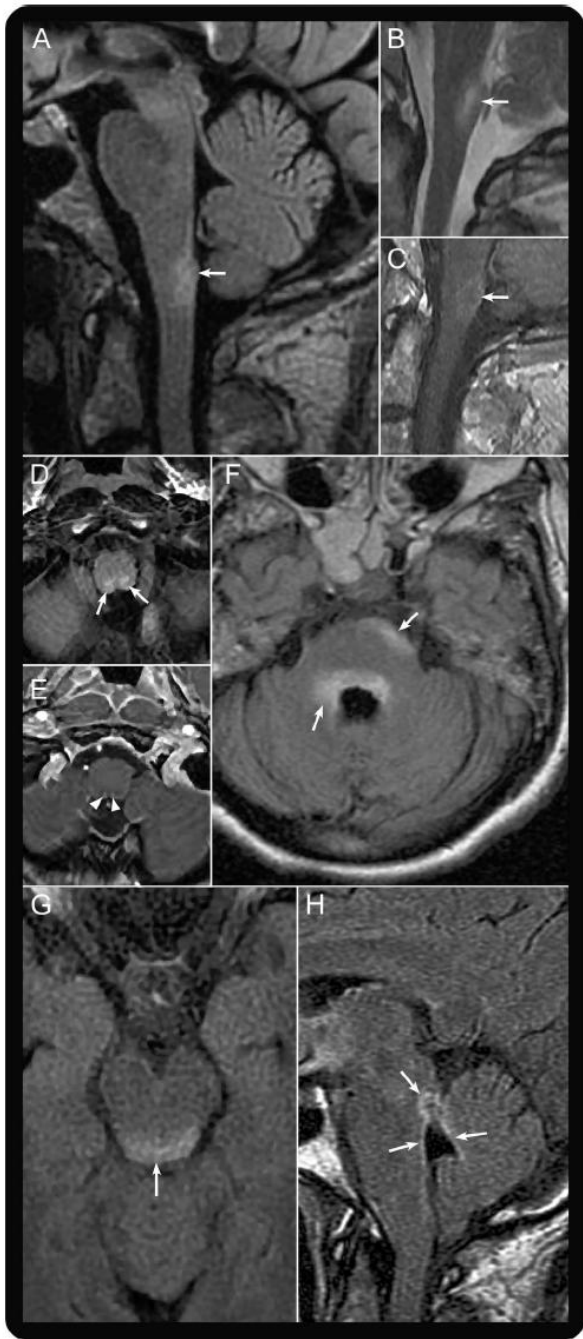
1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
 - a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
 - b. Dissemination in space (2 or more different core clinical characteristics)
 - c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses^a

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over $>1/2$ optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥ 3 contiguous segments (LETM) OR ≥ 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated perpendymal brainstem lesions (figure 2)



MRI characteristics of neuromyelitis optica spectrum disorder

An international update



Table Comparison of characteristic MRI findings between NMOSD and MS

	NMOSD	MS
Spinal cord	Longitudinally extensive lesion (≥ 3 vertebral segments)	Short, often multiple lesions
	Central/gray matter involvement	Peripheral/asymmetrical/often posterior
	T1 hypointensity common on acute lesions	T1 hypointensity rare
Optic nerve	Long-length/posterior-chiasmal lesions	Short-length lesions
Brain	Periependymal lesions surrounding the ventricular system (wide-based along the ependymal lining)	Dawson fingers (perpendicular to ventricles)/S-shaped U-fiber lesions, inferior lateral ventricle and temporal lobe lesions
	Hemispheric tumefactive lesions	Cortical lesions
	Lesions involving corticospinal tracts	Perivenous lesions
	"Cloud-like" enhancing lesions	Ovoid or ring/open-ring enhancing lesions
Others	Normal-appearing tissue involvement may be limited to lesional tracts and associated cortex	Normal-appearing white matter manifests tissue damage using special MRI techniques
	Lesional myo-inositol reduced on MRS	Lesional N-acetyl-aspartate reduced on MRS

MOGAD

Glicoproteína asociada a Mielina del Oligodendrocito

Mismo subgrupo de pacientes.

Neuritis óptica recurrente (también pueden dar LETM) antiAQP4 negativa

Buena respuesta a corticoides

Requerimiento de inmunosupresión a largo plazo.

MOGAD

Presentación:

NO bilateral recurrente, unilateral, papilitis

MTA, LETM, mielitis de menos de 2 segmentos

Otras: cerebelitis, encefalitis

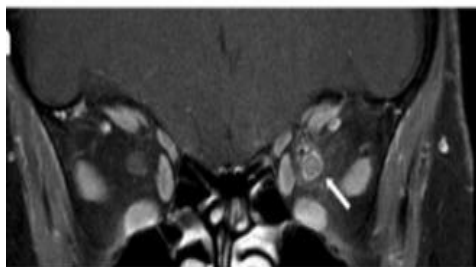
LCR: Pleocitosis moderada, BOC 10%

La recuperacion completa en el primer El 70% recurrentes.

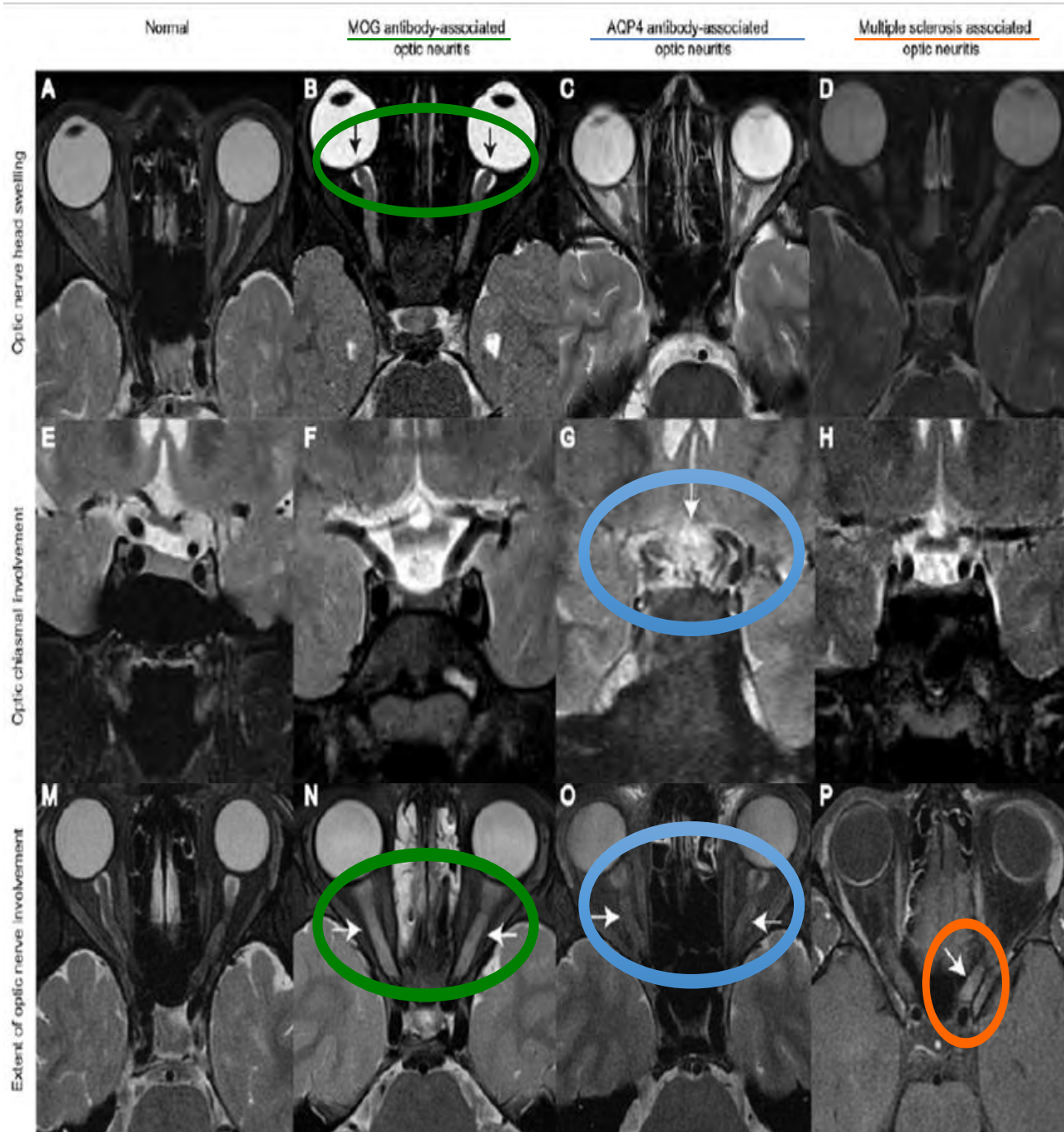
Tiempo a la 2 recaída 5 meses

45% secuela post episodio

40% asociado a infección previa



Realce perineural atípico de EM y de NMO (40%)

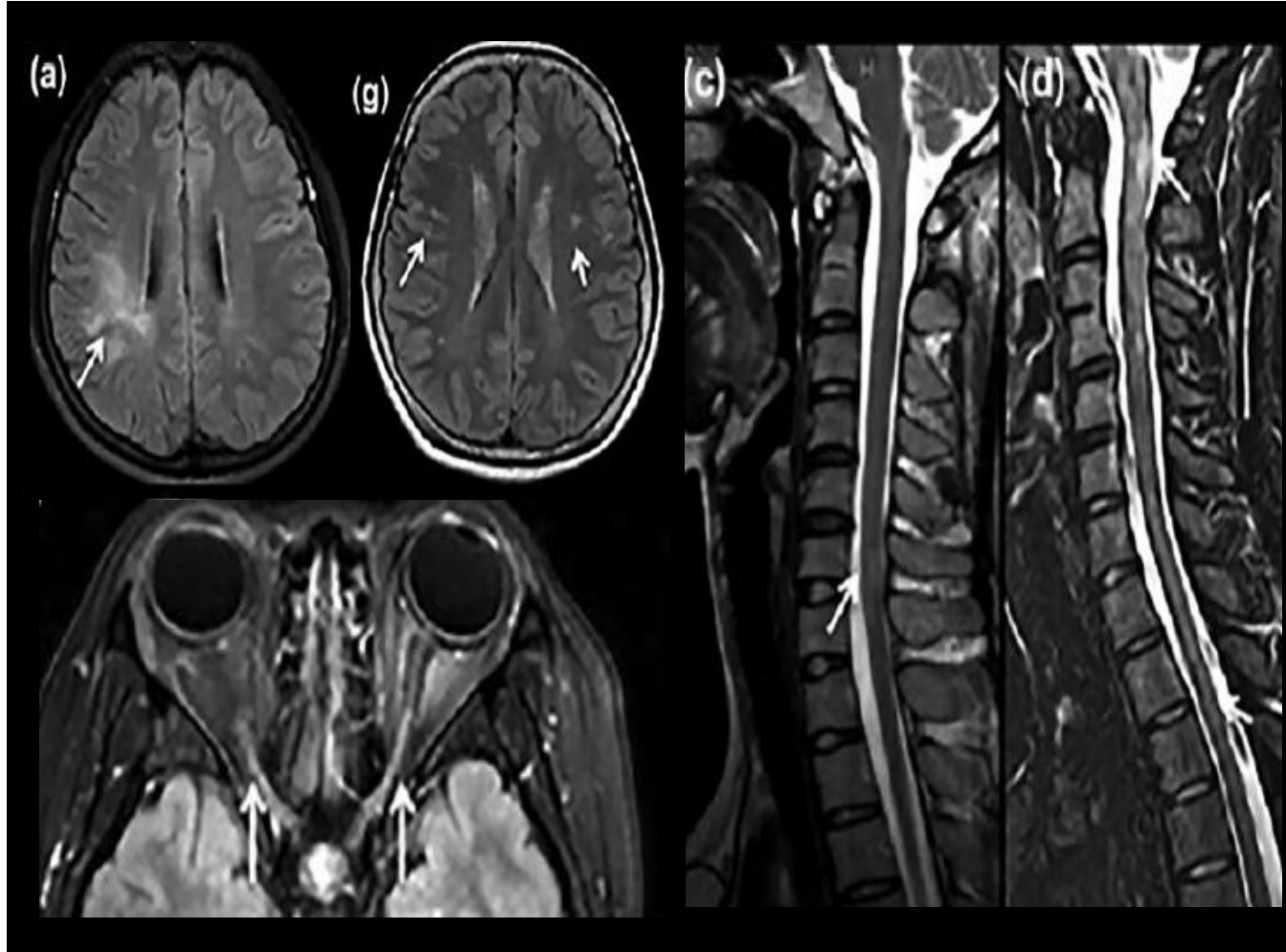


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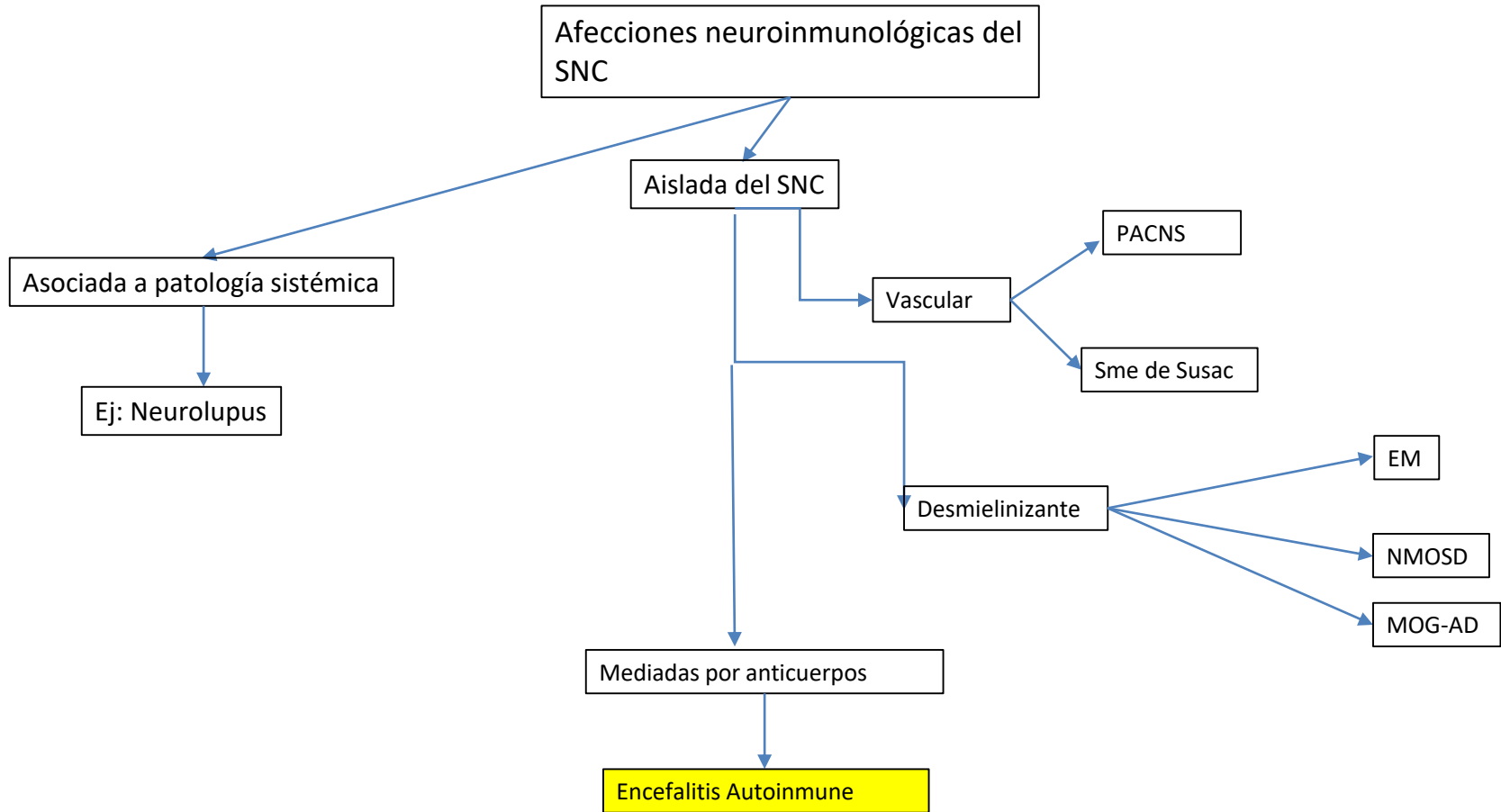
Ramanathan, MS

The clinical spectrum associated with myelin oligodendrocyte glycoprotein antibodies (anti-MOG-Ab) in Thai patients

Compromiso extenso de NO, sin quiasma



Feature	Disease ^a		
	MS	AQP4-Ab-associated NMOSD	MOG-Ab-associated disease
Clinical presentation	Optic neuritis, myelitis, brainstem or cerebellar syndrome, cognitive dysfunction and symptoms caused by involvement of other brain regions typically involved in MS	Optic neuritis, myelitis, area postrema syndrome, brainstem syndrome, narcolepsy or acute diencephalic syndrome, cerebral syndrome with NMOSD-typical brain lesions	ADEM-like (ADEM, MDEM, ADEM–optic neuritis, encephalitis), or opticospinal (optic neuritis, myelitis) or brainstem encephalitis
Female:male ratio	3:1	8–9:1	1–2:1
Age at onset	20–30 years	>40 years	More often in childhood than adulthood
Prevalence (per 100,000)	80–300	1–4	1–4
Disease course	Relapsing–remitting or chronic progressive	More often recurrent than monophasic	Monophasic and recurrent (recurrence often presents as optic neuritis)
Brain MRI findings ^{117,154}	Multiple focal white matter lesions, ovoid lesions adjacent to the body of the lateral ventricles, Dawson fingers and T1 hypointense lesions	No brain lesions or lesions atypical of MS and/or lesions in the brainstem and/or pons	ADEM-like, no brain lesions or lesions atypical of MS (fluffy lesions or three lesions or fewer)
Spinal MRI findings	Short-segment (<3 vertebral segments) lesions	Long-segment (>3 vertebral segments) lesions	Long-segment (>3 vertebral segments) lesions involving the lumbar segment and conus
Optic neuritis	More often unilateral than bilateral	Bilateral or unilateral, severe and often recurrent	Bilateral or unilateral, sparing of the optic chiasm and often recurrent
CSF OCBs	Common (>90% of patients)	Rare (<10% of patients)	Rare (<10% of patients)
CSF pleocytosis	Moderate (<50% of patients)	Common (>70% of patients)	Common (>70% of patients)
Neuropathology	Demyelination, axonal injury and astrogliosis	Astrocytopathy	Oligodendrocytopathy
Risk of future disability	High, owing to disease progression	High, owing to poor recovery from attacks and a high relapse rate	Low, owing to good recovery from attacks; in a subset of patients, recovery from the initial attack is poor
Treatment	Immunomodulatory, immunosuppressive	Immunosuppressive	Immunosuppressive



Encefalitis autoinmune

Definiciones: Encefalitis Autoinmune (EA)

- Familia de procesos patológicos estrechamente relacionados que comparten procesos clínicos superpuestos características y hallazgos de neuroimagen en SNC.¹
- Base inmunomediada
 - Anticuerpos específicos
 - Fenómenos paraneoplásicos
 - Cambios radiológicos
- Fenomenología clínica variable → límbica y “extra-límbica”
- Múltiples clasificaciones.
 - Según topografía de los targets antigénicos²
 - Intracelulares (Hu, CV2, Ma, GAD)
 - De superficie (NMDAr, LGI1, GABAr, AMPAr, GluR1-5...)

1. Grauss F et al, J Neurol 2010

2. Kelley BP, et al, AJNR 2018

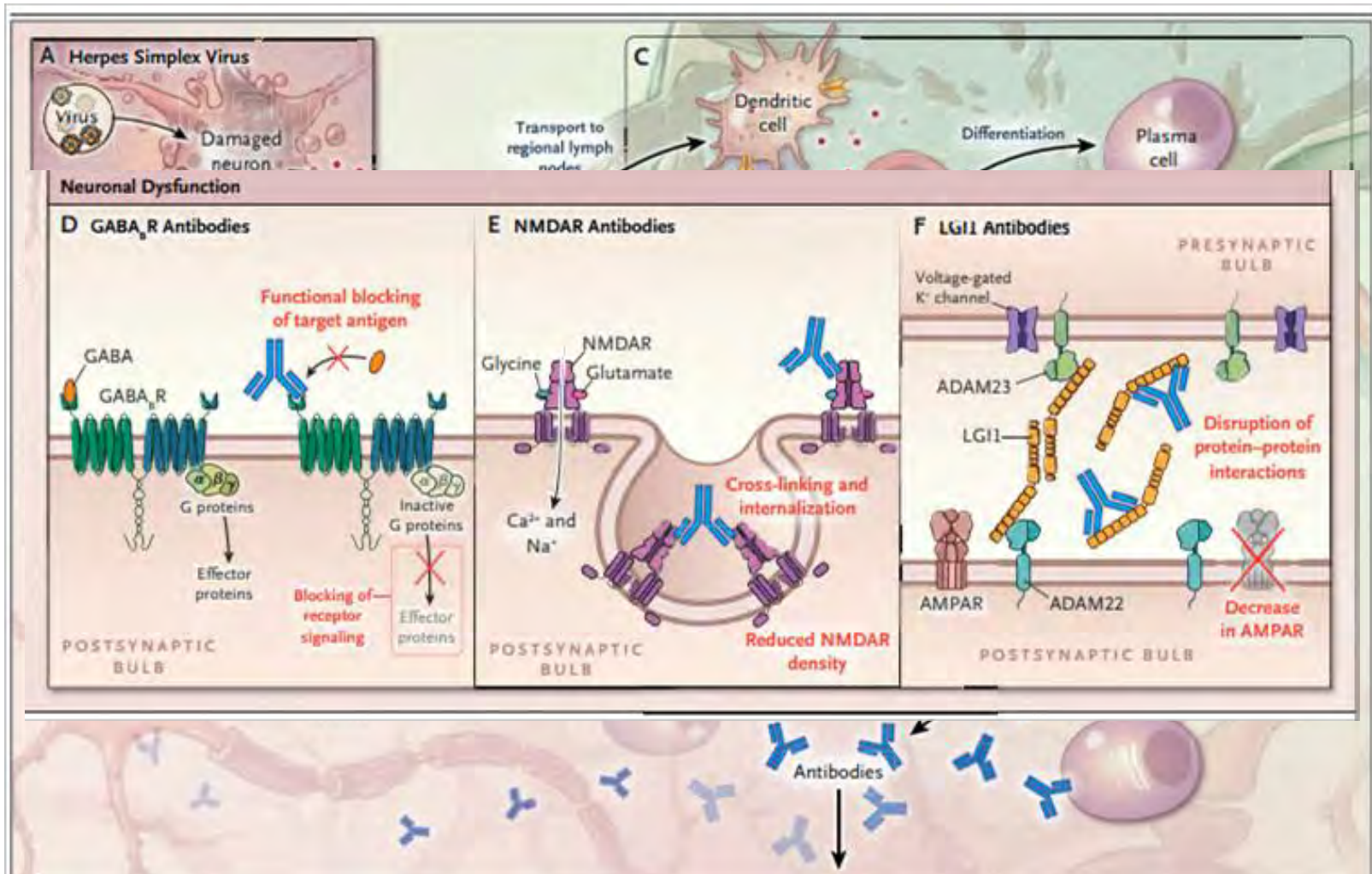
Table 1

Cell-surface targeting autoantibodies in encephalitis

Cell-surface target antigens	Associated diseases (characteristic symptoms)	Refs.
(1) Neurotransmitter receptors		
NMDAR (GluN1)	Anti-NMDAR encephalitis (psychosis, seizure, autonomic instability; teratoma-associated)	[6,7]
AMPA	LE (seizure, psychosis)	[39]
mGluR1	Cerebellar ataxia (Hodgkin's disease associated)	[3,4]
mGluR5	LE, Ophelia syndrome	[58]
GABA _A R	Encephalitis (seizure, thymoma-associated)	[40,41,59]
GABA _B R	LE	[60]
Glycine R	PERM, stiff-person syndrome	[61,62]
Dopamine-2 R	Basal ganglia encephalitis (movement and psychiatric features)	[19,20*]
(2) Transmembrane proteins		
CASPR2	Encephalitis, peripheral nerve hyperexcitability (NMT)	[31,63]
DNER	Paraneoplastic cerebellar degeneration	[64]
DPPX (DPP6)	Encephalitis (diarrhea)	[42*,65]
DCC	NMT associated with thymoma	[9,66]
IgLON5	Abnormal sleep movements, tauopathy	[67,68]
Neurexin-3α	Encephalitis	[25]
(3) Secreted protein		
LGI1	Anti-LGI1 encephalitis (LE, facio-brachial dystonic seizures, hyponatremia)	[9,31,32]

LE, limbic encephalitis; PERM, progressive encephalomyelitis with rigidity and myoclonus; NMT, neuromyotonia.

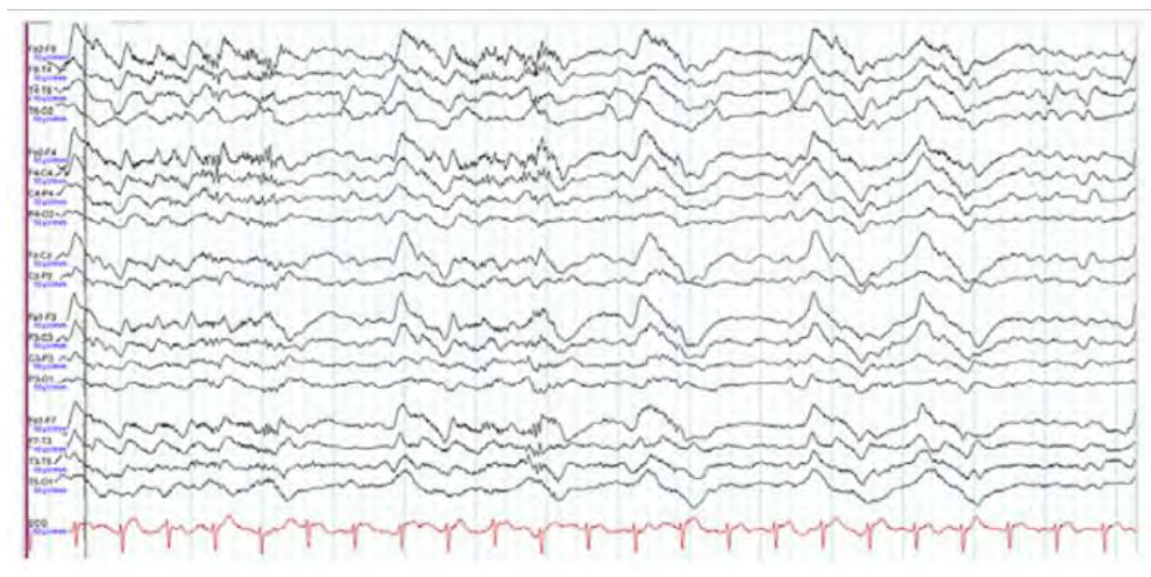
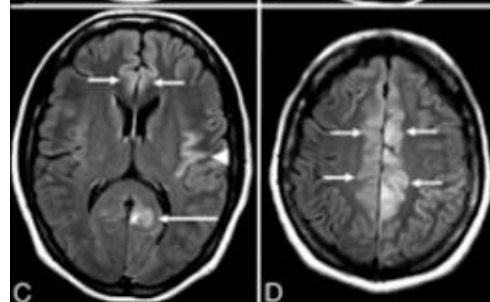
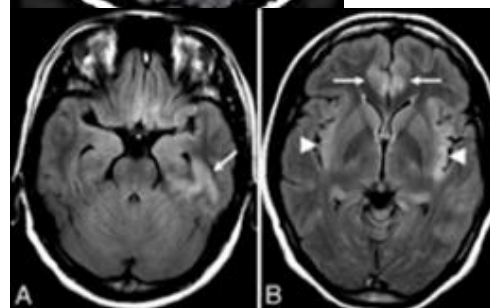
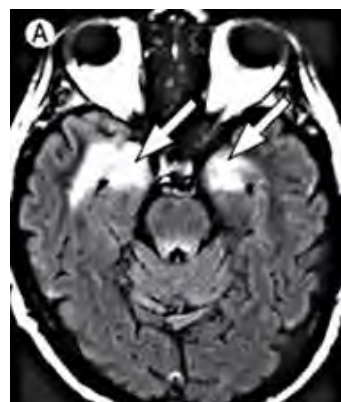
Other neuronal autoantibody targets reported include DPP10, ADAM23, CSMD1, ODZ1, and TMEM132A, although their pathogenic roles remain unclear due to the limited cases [9].

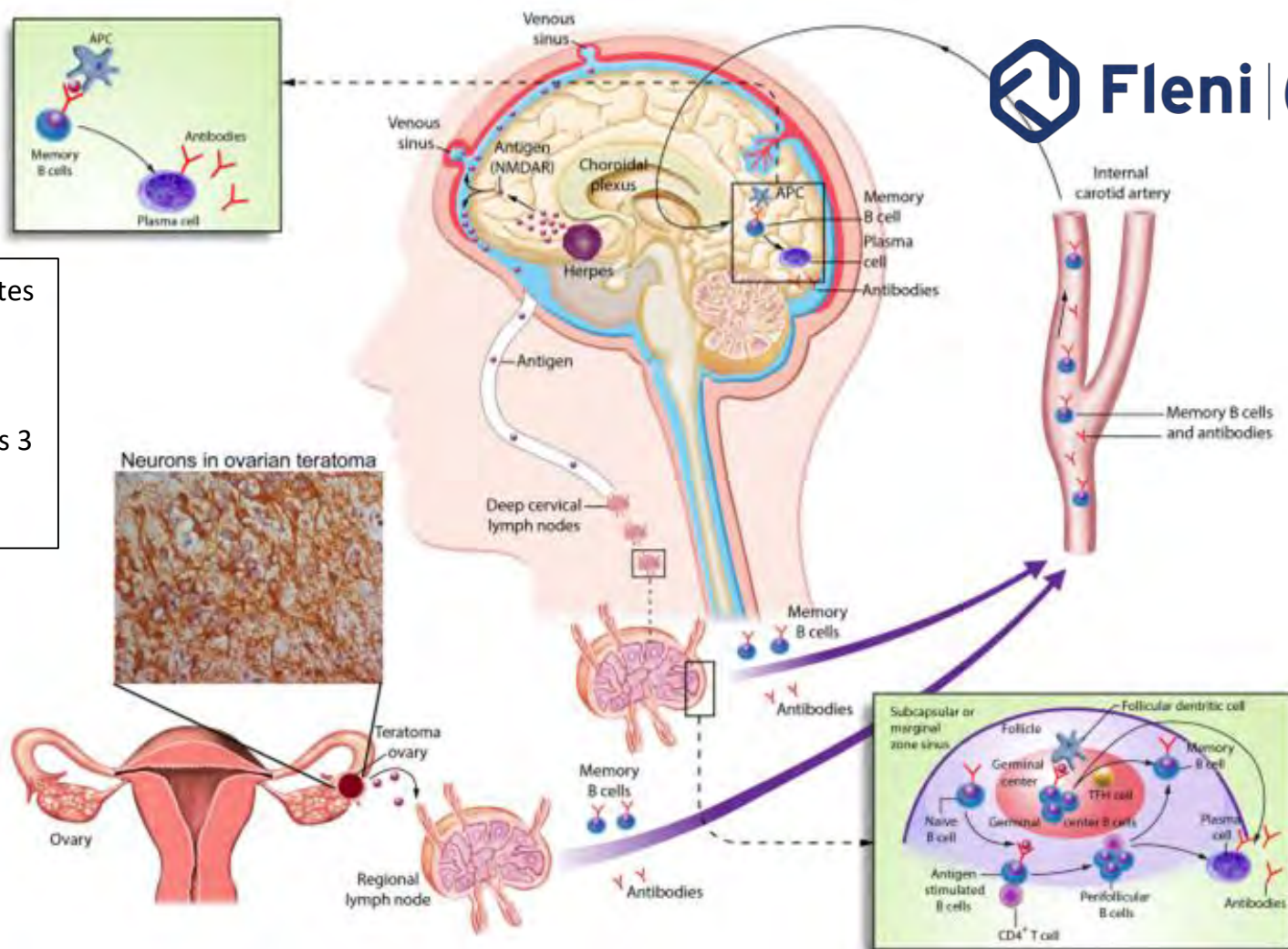


Abordaje diagnóstico Encefalitis Autoinmune

Encefalitis autoinmune *posible*:

1. Inicio **subagudo** (menos de 3 meses) de trastornos en la memoria de trabajo (corto plazo), alteración del estado mental (cambios en el nivel de conciencia, letargia, cambios de personalidad) o síntomas psiquiátricos
2. Al menos 1 de los siguientes
 - a. Hallazgos de **déficit focal** en SNC
 - b. **Crisis comiciales** no explicadas por otras causas
 - c. Pleocitosis en LCR (**>5 c/mm³**)
 - d. Cambios en **RMN** sugestivos de encefalitis
3. Exclusión de otras causas→?



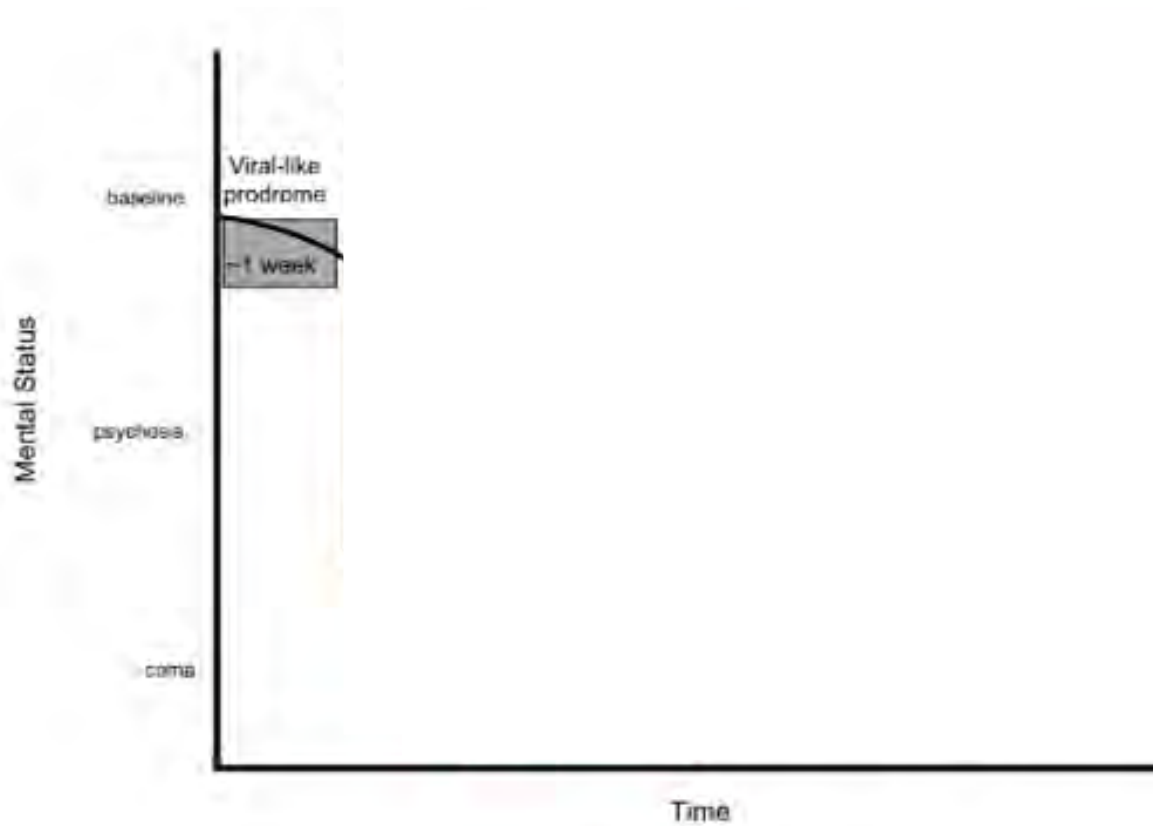


Hasta 27% de los pacientes post encefalitis por HSV puede desarrollar EA mediada por Ac. antiNMDAR dentro de los 3 meses de presentado el cuadro infeccioso

Epidemiología

- Pacientes jóvenes (<45 años)
- Predominancia femenina 4-8:1 (menos evidente en niños)
- Hasta el 58% de las mujeres adultas (<45a) pueden tener teratoma ovárico oculto (<23% de mujeres >45 años y <5% de los chicos tienen tumor oculto)

Manifestaciones clínicas



Estudios complementarios. LCR

- Único test específico: anticuerpos anti-NMDAr (subunidad GluN1) en **LCR**
→ CBA
 - Los títulos no se relacionan precisamente con el curso de la enfermedad
- LCR (FQ): anormal hasta en el 95% de los casos (pleocitosis mononuclear +/- hiperproteinorraquia). *BOC* + (II o III) hasta 67%
 - Elevados dosajes de CXCL13, TNF- α , IL-6, IL-10, YKL-40 (microglía activada) y Fas and FasL

Criterios diagnósticos. NMDAr-E

- Definitiva:
 - Cualquier síntoma típico + **anticuerpo positivo en LCR**
 - Exclusión de otras causas.

Tratamiento

- Tratamiento temprano y agresivo: Corticoides EV, inmunoglobulinas o plasmaféresis
- Escalar rápidamente tratamiento a segunda línea: Rituximab o ciclofosfamida. (10 días)
- En caso de no respuesta (4 semanas), considerar agregar tocilizumab o bortezomib.
- Podría utilizarse también azatioprina, micofenolato o metotrexato como mantenimiento

Nosadini M et al, Exp Rev Neuroth 2015
Lancaster E, J Clin Neurol 2016

Table 2. Main clinical features associated with antibodies to neuronal cell surface proteins and synaptic receptors

Antibody	Main Presenting Symptoms	Main Syndrome	MRI FLAIR/T2 Sequences	PET	Frequency of Cancer	Types of Cancer
NMDA receptor	Psychiatric (adults); seizures, dyskinesias (children)	NMDA receptor encephalitis (57, 89, 309)	Normal or transient non-region specific changes	Increased frontal and temporal FDG uptake; decreased occipital FDG uptake	Overall 40%; 58% in women 18-45 yr	Teratoma*
AMPA receptor	Memory loss	Limbic encephalitis (137, 181)	Hyperintense signal highly restricted to medial temporal lobes	FDG uptake in temporal lobes	65%	Thymoma, SCLC, other
GABAB receptor	Memory loss, seizures	Limbic encephalitis with early and prominent seizures (138, 158, 186)	Hyperintense signal highly restricted to medial temporal lobes	FDG uptake in temporal lobes	50%	SCLC
LGI1	Memory loss, FBD seizures	Limbic encephalitis (11, 323)	Hyperintense signal highly restricted to medial temporal lobes	Basal ganglia and temporal FDG uptake	5-10%	Thymoma
CASPR2	Sleep disorder, neuromyotonia	Morvan; limbic encephalitis (154, 159, 321)	Normal or hyperintense signal in medial temporal lobes	Unknown	Overall 20%. In Morvan syndrome (20-50%)	Thymoma†
GABAA receptor	Seizures	Encephalitis with refractory seizures, status epilepticus (252, 298)	Hyperintense signal in multiple cortical and subcortical areas	Unknown	25%	Thymoma, other
DPPX	Confusion, diarrhea, hyperplexia	Encephalitis, hyperekplexia (21, 33, 311)	Normal or non-region specific changes	Unknown	<10%	Lymphoma

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Dopamine-2 receptor	Lethargy, psychiatric symptoms, abnormal movements, gait disturbance	Basal ganglia encephalitis (55)	Hyperintense signal in basal ganglia	Unknown	0%	n/a
mGluR5	Memory loss	Encephalitis (187)	Normal or hyperintense signal in various brain regions	Unknown	A few cases described	Hodgkin disease
Neurexin-3 α	Confusion, seizures	Encephalitis (119)	Normal	Unknown	0%	n/a
IgLON5	Sleep disorder	NREM and REM sleep disorder, and brain stem dysfunction (104, 273)	Normal	Unknown	0%	n/a
DNER (Tr)	Gait instability	Cerebellar ataxia (27, 66)	Normal or cerebellar atrophy	Unknown	>90%	Hodgkin disease
P/Q-type VGCC	Gait instability	Cerebellar ataxia (114, 219)	Normal or cerebellar atrophy	Unknown	>90%‡	SCLC
mGluR1	Gait instability	Cerebellar ataxia (293)	Normal or cerebellar atrophy	Unknown	30 pacs en cohorte europea 40% recuperación incompleta	Hodgkin disease
Glycine receptor	Muscle rigidity, spasms	PERM, stiff-person syndrome (42, 214)	Normal or non-region specific changes	Unknown		Thymoma, lung, Hodgkin
Amphiphysin	Rigidity, spasms	Stiff-person, encephalomyelitis (256)	Normal or non-region specific changes	Unknown	>90%	Breast cancer, SCLC

Hasta 40 psicosis o DCRE

Dalmau J, J Neurophysiol 2017

Spatola M et al, AAN virtual meeting 2021

Encefalopatías Paraneoplásicas

Asociadas a anticuerpos contra antígenos intracelulares

- Grupo sindromático diverso (encefalitis límbica, degeneración cerebelosa, SOMA)
 - Prevalencia estimada (0.37-0.82/100.000 personas x año)
- Tasa de respuesta variable.
- Pobre pronóstico. Tumores pequeños /incipientes / de difícil diagnóstico
- Diferencia con anticuerpos de superficie (FP no vinculada a la disfunción de un receptor sino al daño producido por las Células T en las neuronas target). Fenotipo menos específico

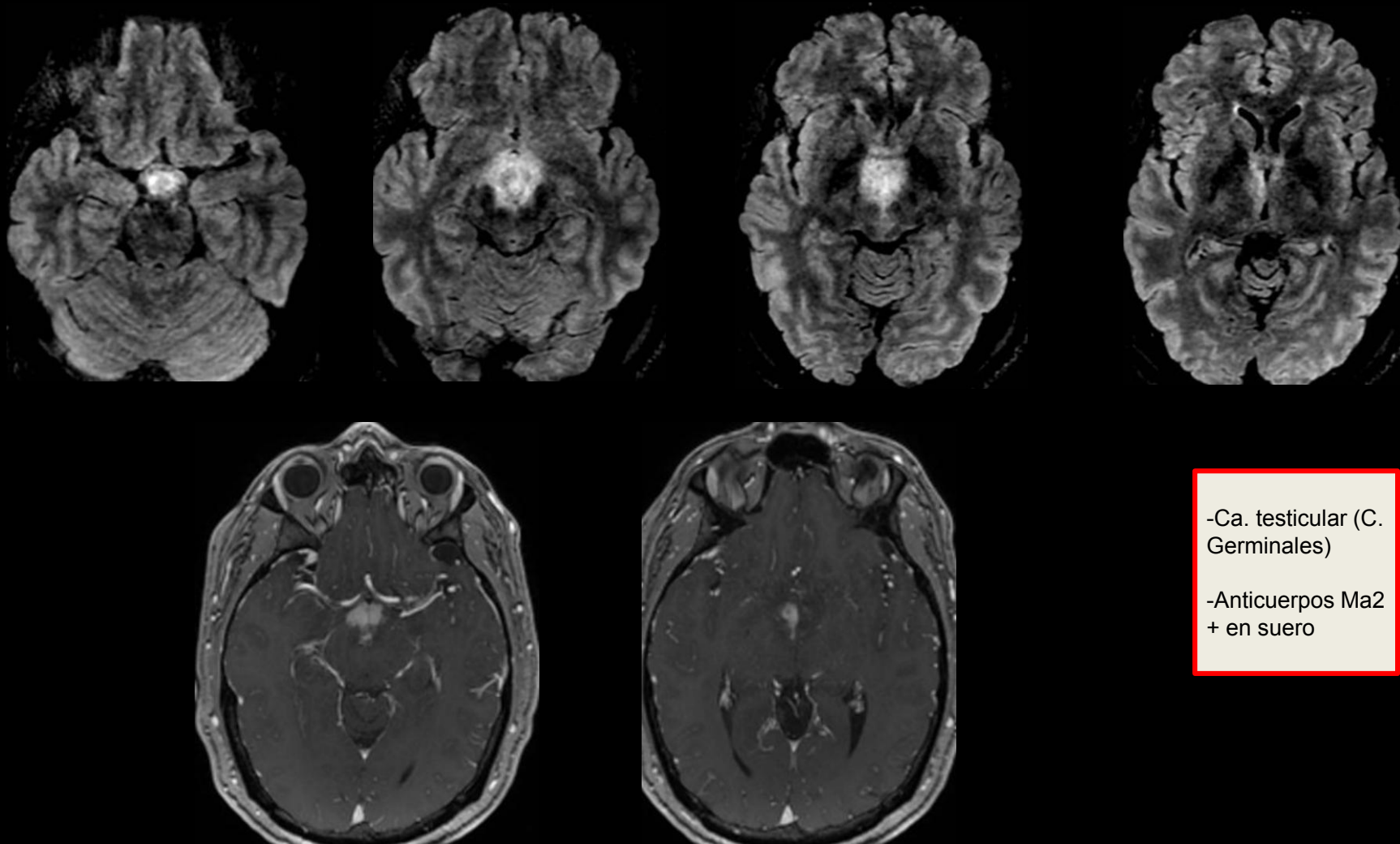
TABLE 8-2 Classic Paraneoplastic Disorders With Antibodies to Intracellular Antigens^a

Antibody (and Alternative Name) and Antigen	Patient Demographics	Clinical Syndromes	Tumors
PCA-1 (Yo) Target cdr2, a cytoplasmic protein expressed in brain and in tumors	Almost all female, young adult to elderly	Cerebellar degeneration	More than 90% have breast, ovarian, or female reproductive tract cancers
PCA-2 Bind a cytoplasmic protein in neurons, especially cerebellar neurons	Limited number of cases reported	Cerebellar degeneration is most common, but other syndromes reported in association with other antibodies	Small cell cancers
CRMP-5 CRMP-5 is a neuronal protein critical for growth cone function	Men and women, older adults	Dementia, ataxia, myelopathy, chorea, seizures, cranial neuropathies, peripheral neuropathy, retinopathy, often multifocal; significant overlap with other paraneoplastic markers	Lung cancer, thymoma
PNMA-1 (Ma) Target PNMA-1 and PMNA-2, expressed in brain/ testes and also in tumors	Males and females, middle aged	Encephalitis, cerebellar ataxia, ophthalmoplegia, dementia	High risk of diverse tumors (eg, lung, breast, colon, renal)
PNMA-2 (Ma2) (also known as Ta) Target PNMA-2	Mostly males (median age 34 years) with fewer females (median age 64 years)	Brainstem encephalitis (with involvement of ocular and other bulbar muscles) is most characteristic; encephalitis, cerebellar degeneration also reported	Young men with Ma2 often have germ cell tumors

Inmunoteapia temprana y agresiva

Tasa de respuesta variable

Dosaje de Ac en suero!



-Ca. testicular (C. Germinales)

-Anticuerpos Ma2
+ en suero

Pendientes

Vasculitis (aislada del SNC y sistémica)

Sme de Susac

Enfermedad por anticuerpos anti GAD

Miopatias inflamatorias

Impacto reumatológico de las enfermedades sistémicas

LES

Sarcoidosis

SSJ

Bechet