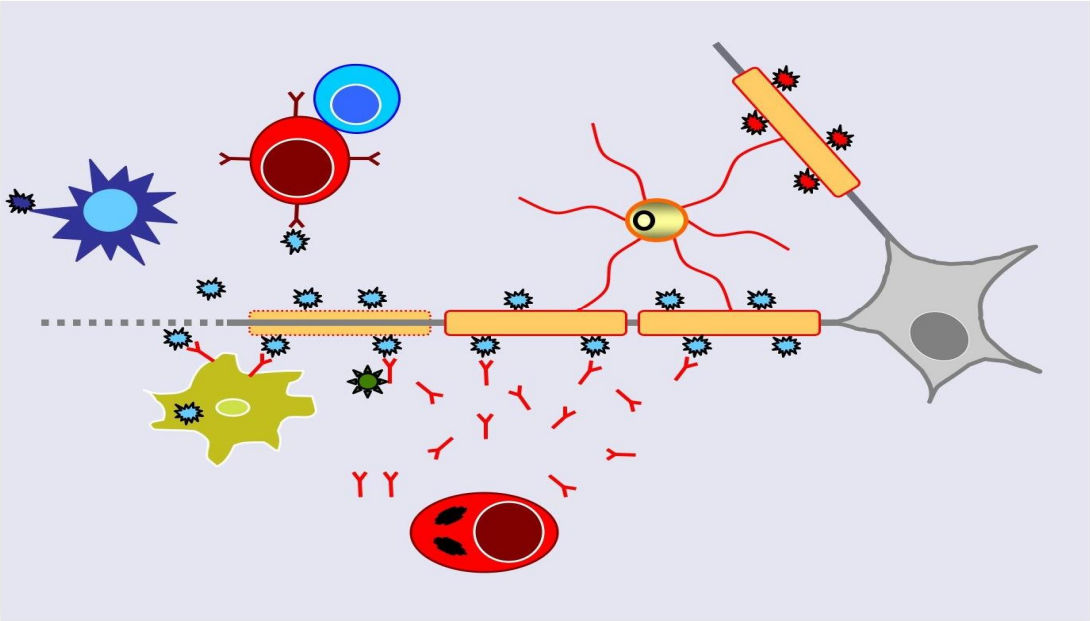

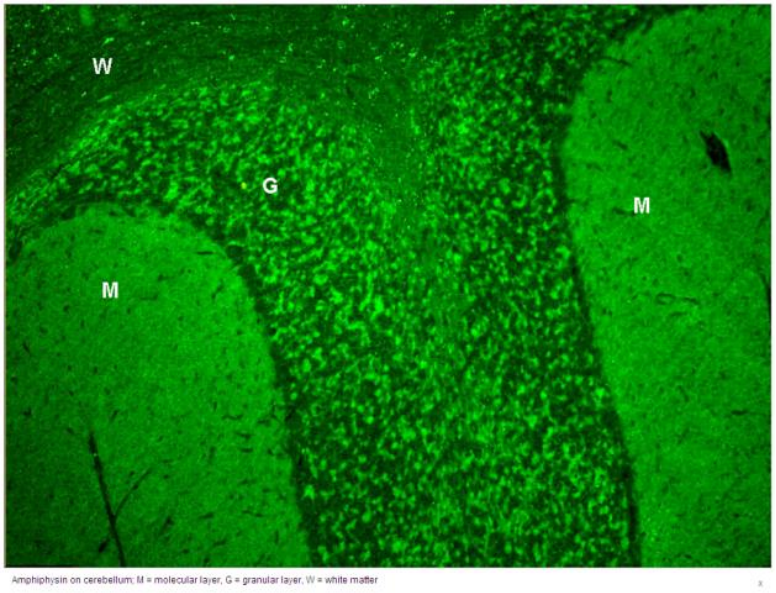

Amphiphysin on cerebellum; M = molecular layer, G = granular layer, W = white matter

Les pathologies neurologiques auto-immunes : quand un anticorps fait perdre la tête

CORATA Rouen 2018

Francis Corazza
Service d'immunologie, LHUB-ULB

Pathologies neurologiques autoimmunes

- **Pathologies du Système Nerveux Central**
- Pathologies Neuromusculaires
- Pathologies du Système Nerveux Péripherique

Pathologies neurologiques autoimmunes

Pathologies centrales

- Ac anti proteines onconeuronales
- Ac anti récepteurs/protéines de surfaces
    - Encephalomyelites
    - Encéphalites limbiques
- Neuromyelite optique
- Encephalite de Hashimoto
- PANDAS (Paediatric Autoimmune Disorders Associated with Streptococcus infections)
- Manifestations neurologiques centrales des pathologies autoimmunes systémiques (Lupus, Granulomatoses, vasculites

Pathologies Neuromusculaires : Ac anti Rec. Acethyl Choline, Anti MUSK, Anti VGCC

- Syndromes myasthéniques
- Lambert Eaton

Pathologies neurologiques autoimmunes

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- Lambert Eaton

Polyneuropathies périphériques autoimmunes

Syndrome Guillain Barré	
AIDP (90%)	?
AMAN (10%)	GM1, GM1b, GD1a
AMSAN	GM1, GM1b, GD1a
Miller Fisher (ophtalmoplégie, ataxie, areflexie)	GQIb, GT1a
Neuropathies paranéoplasiques (sensitive subaiguë de Denny Brown)	Hu, CV2
CIDP	?
MMN	GM1
Neuropathies vasculaires (vasculites)	ANCA, aPL,
Neuropathies / gammopathies monoclonales	Anti-MAG, myelin

Polyneuropathies périphériques autoimmunes

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Pathologies neurologiques centrales autoimmunes

Concept ancien

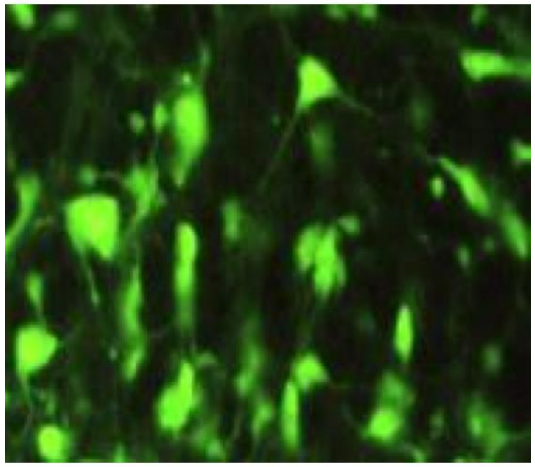
Paraneoplasiques

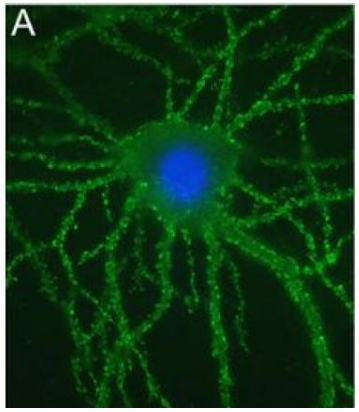
- Anti-Hu
- Anti-Yo
- Anti-CV2
- Anti-Ma2

Non paraneoplasiques

- Anti-VGKC
- Anti-VGCC

mais 20 à 60% de cancers





Concept récent

Antigènes intracellulaires

- Anti-Hu
- Anti-Yo
- Anti-CV2
- Anti-Ma2
- Anti-Zic4é

Antigènes onco-neuronaux

Marqueurs indirects

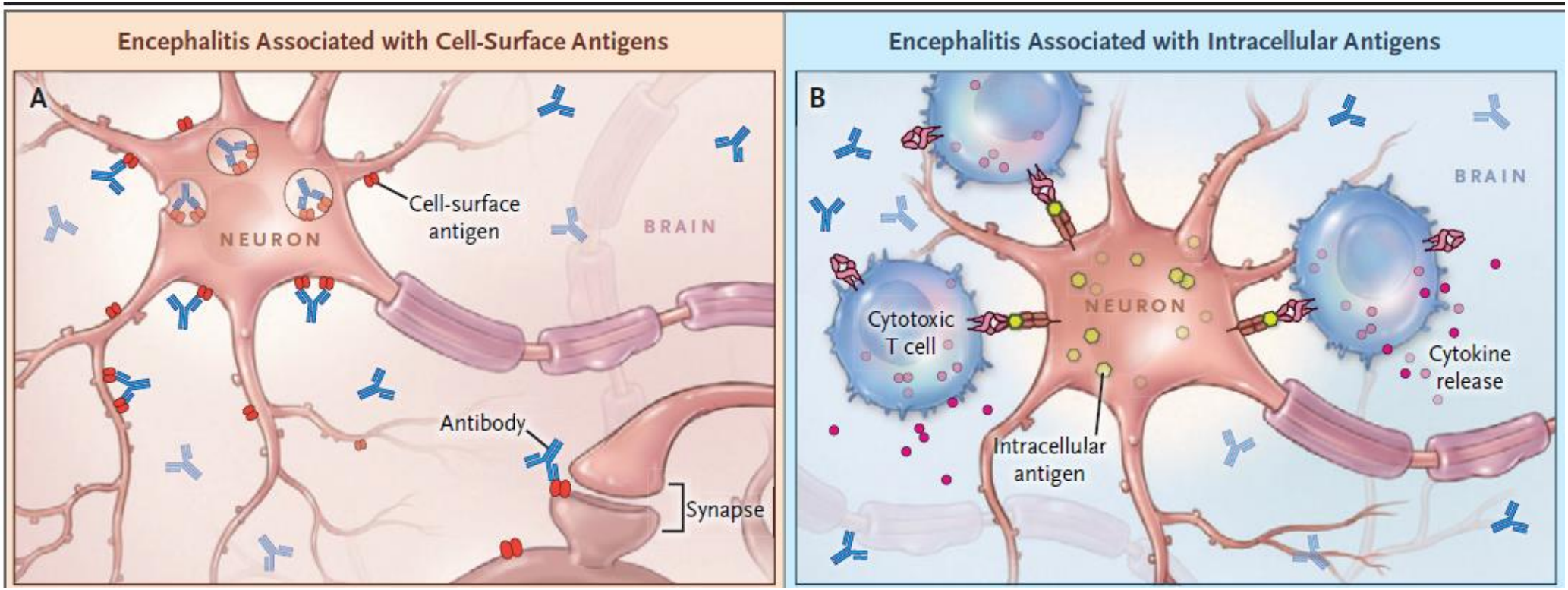
Antigènes membranaires

- Anti-NMDAR
- Anti-VGKC
- Anti-AMPAR
- Anti-GABAR

Rôle pathologique direct

Peuvent être paraneoplasiques ou non

Deux mécanismes physiopathologiques distincts



Pathologies neurologiques autoimmunes

Ac dirigé contre un antigène neuronal intracytoplasmique

Non pathogène

Marqueur secondaire

Destruction neuronale / Immunité cellulaire

Lesions peu réversibles

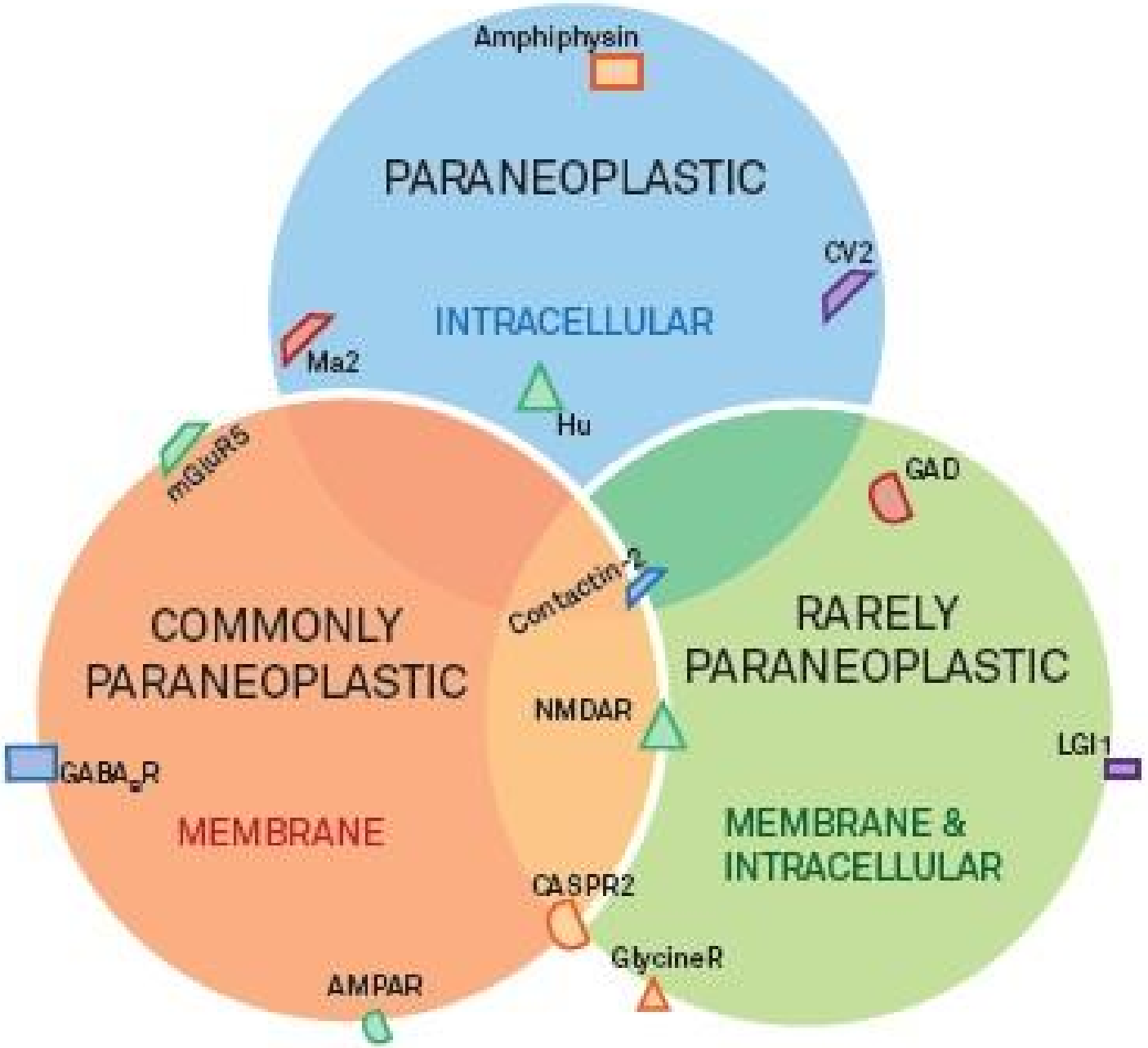
Ac dirigé contre un récepteur membranaire

Rôle pathogène direct

Effet fonctionnel de l'Ac sur le récepteur

Généralement pas de destruction Neuronale

Tableau réversible: efficacité du traitement


Amphiphysin
PARANEOPLASTIC
CV2
INTRACELLULAR
Ma2
Hu
mGluR5
GAD
Contactin-2
COMMONLY
PARANEOPLASTIC
RARELY
PARANEOPLASTIC
NMDAR
LGI1
GABA$_B$R
MEMBRANE
MEMBRANE &
INTRACELLULAR
CASPR2
GlycineR
AMPAR

= pathologies rares !!!

Only 979 patients with definite PNS collected
By the PNS Euronetwork consortium between 2000 and 2008
(11 countries, 22 centers)

Table 3. Onconeural Antibody Profile in the PNS Euronetwork Database

Antibody	Patients, No. (%)[a] (N=979)
Hu	380 (38.8)
Yo	131 (13.4)
Ri	50 (5.1)
CV2	59 (6.0)
Tr	17 (1.7)
Amphiphysin	33 (3.4)
Ma or Ta	44 (4.5)
VGCC	39 (4.0)
VGKC	10 (1.0)
Atypical	30 (3.1)
Other	67 (6.8)
None	179 (18.3)
Unknown	14 (1.4)

Table 4. Tumor Types in the PNS Euronetwork Database

Tumor Type	Patients, No. (%) (n=899)
Small cell lung cancer	345 (38.4)
Ovary	94 (10.5)
Breast	87 (9.7)
Non–small cell lung cancer	71 (7.9)
Non-Hodgkin lymphoma	31 (3.4)
Hodgkin lymphoma	27 (3.0)
Thymoma	24 (2.7)
Prostate	23 (2.6)
Metastasis from unknown primary	18 (2.0)
Colorectal	16 (1.8)
Esophagus or gastric	16 (1.8)
Testicular	15 (1.7)
Kidney or bladder	11 (1.2)
Neuroblastoma	7 (0.8)
Merkel carcinoma	6 (0.7)
Melanoma	4 (0.4)
Other	104 (11.6)

Giometto et al, Arch Neurol, 2010;67:330-335

Pathologies neurologiques centrales autoimmunes

	Paraneoplasique	Non- Paraneoplasique
Antigène intracellulaire	Anti- Hu, Ri, CRMP5 Tr	
Antigène membranaire		

Encephalites autoimmunes

	Syndrome	Diagnostic assay	Frequency of cancer	Main type of cancer
Antibodies against intracellular antigens				
Hu (ANNA1)[8]*	Limbic encephalitis	Western blot	>95%	Small-cell lung carcinoma
Ma2[9]	Limbic encephalitis†	Western blot	>95%	Testicular seminoma
GAD[10]	Limbic encephalitis‡	Radioimmunoassay	25%§	Thymoma, small-cell lung carcinoma
Antibodies against synaptic receptors				
NMDA receptor[11]	Anti-NMDA receptor encephalitis	Cell-based assay	Varies with age and sex	Ovarian teratoma¶
AMPA receptor[12]	Limbic encephalitis	Cell-based assay	65%	Thymoma, small-cell lung carcinoma
$GABA_B$ receptor[13]	Limbic encephalitis	Cell-based assay	50%	Small-cell lung carcinoma
$GABA_A$ receptor[14]	Encephalitis	Cell-based assay	<5%	Thymoma
mGluR5[15]	Encephalitis	Cell-based assay	70%	Hodgkin's lymphoma
Dopamine 2 receptor[16]	Basal ganglia encephalitis	Cell-based assay	0%	..
Antibodies against ion channels and other cell-surface proteins				
LGI1[17]	Limbic encephalitis	Cell-based assay	5–10%	Thymoma
CASPR2[18]	Morvan's syndrome‖ or limbic encephalitis	Cell-based assay	20–50%	Thymoma**
DPPX[19]	Encephalitis††	Cell-based assay	<10%	Lymphoma
MOG[20]‡‡	Acute disseminated encephalomyelitis	Cell-based assay	0%	..
Aquaporin 4[21]‡‡	Encephalitis	Cell-based assay	0%	..
GQ1b[22]	Bickerstaff's brainstem encephalitis	ELISA	0%	..

***Lancet Neurol* 2016; 15: 391ï 404**

Principaux anticorps / Ag / tableau neurologique

Antibody	Antigen	Associated syndromes and symptoms	Most common tumours
Onconeural antibodies (Well characterized, paraneoplastic antibodies Tumour in >90%)			
Anti-Hu (ANNA-1)	HuD	encephalomyelitis, limbic encephalitis, cerebellar degeneration, brain stem encephalitis, multi-segmental myelitis, sensory neuronopathy, sensory-motor neuropathy, autonomic neuropathy	lung cancer (85%), mostly SCLC, neuroblastoma, prostate carcinoma
Anti-Yo (PCA-1)	CDR2, CDR62	paraneoplastic cerebellar degeneration	ovarian, breast cancer
Anti-CV2/CRMP5	CRMP5	encephalomyelitis, polyneuropathy, optic neuritis, limbic encephalitis, choreatic syndromes, cerebellar degeneration	SCLC, thymoma
Anti-Ta/Ma2*	MA-proteins	limbic encephalitis, rhombencephalitis, m>>f	testicular cancer
Anti-Ri (ANNA-2)	NOVA-1	opsoclonus-myoclonus syndrome, rhombencephalitis, cerebellar degeneration, myelitis, jaw dystonia, laryngospasm	breast, ovarian carcinoma, SCLC
Anti-amphiphysin	AMPHIPHYSIN	stiff-person syndrome, limbic encephalitis, rhombencephalitis, cerebellar degeneration, polyneuropathy	breast cancer, SCLC
Anti-recoverin	RECOVERIN	retinopathy	SCLC
Anti-SOX-1 (AGNA)	SOX-1	Non syndrome-specific	sensitivity 67%, specificity 95% for SCLC in LEMS
Partially characterized onconeural antibodies (antigen not characterized or positive predictive value for tumour unknown)			
Anti-Tr (PCA-Tr)	DNER	cerebellar degeneration	Hodgkin-lymphoma, non-Hodgkin-lymphoma
Anti-Zic4	ZIC1-4	cerebellar degeneration	SCLC
PCA-2	280 kD	encephalitis, Lambert-Eaton-myasthenic syndrome, polyneuropathy	SCLC
ANNA-3	170 kD	neuropathy, cerebellar degeneration, limbic encephalitis	SCLC

Syndromes neurologiques paraneoplasiques

Table 1. Classical and non-classical paraneoplastic syndromes and diagnostic criteria [4].

Classical syndrome	Non-classical syndrome
Central nervous system	
Encephalomyelitis	Brain stem encephalitis
Limbic encephalitis	Optic neuritis
Subacute cerebellar degeneration	Myelitis/necrotizing myelopathy
Opsoclonus–myoclonus syndrome	Stiff-person syndrome and variants
Peripheral nervous system	
Subacute sensory neuronopathy	Distal-symmetric sensorimotor neuropathy
Chronic intestinal pseudo-obstruction	Polyradiculoneuropathy (acute/chronic)
	Multiplex mononeuropathy
	Pure autonomic neuropathies
Neuromuscular junction and muscle	
Lambert–Eaton myasthenic syndrome	Myasthenia gravis
Dermatomyositis	Neuromyotonia

Diagnostic criteria	Well-characterized onconeural antibodies	Partially characterized onconeural antibodies/no cancer	No antibodies/high cancer risk	Cancer detected
Classical syndrome	Definite	Possible	Possible	Definite
Non-classical syndrome	Definite	Possible	Not applicable	Possible (definite if improving after cancer treatment)

2013 British Society for Immunology, *Clinical and Experimental Immunology*, **175:** 336–348

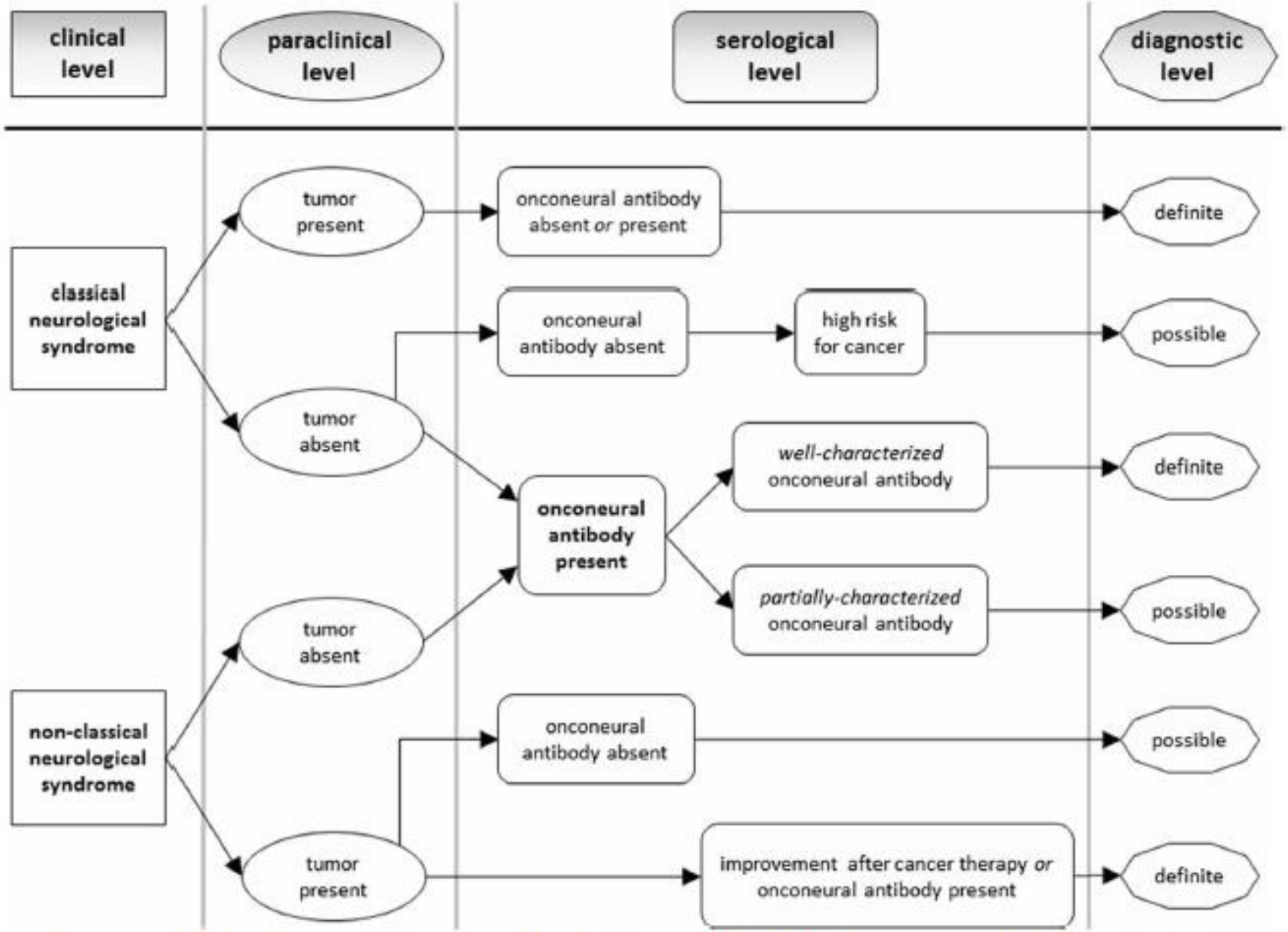


Fig. 1 Algorithm assessing the various levels of diagnostic evidence of the neurological syndromes suspected to be paraneoplastic, in accordance with the 2004 international consensus-based criteria (modified from [2])

Un peu de confusion…

- Un même anticorps peut être associé à des tableaux cliniques différents
- Un même tableau clinique peut s'observer avec des Ac différents
- La plupart des syndromes paranéoplasiques précèdent le diagnostic de cancer parfois de plusieurs années (→ 5ans)
- L'absence d'Ac n'exclu pas un syndrome paranéoplasique (ex opsoclonus-myoclonus/neuroblastome)
- Un patient peut présenter plusieurs Ac (CRMP5, Hu et Zic4)
- Des anticorps peuvent être présents sans symptomes neurologiques

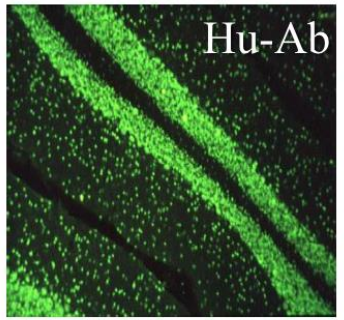
Tableau clinique/Anticorps

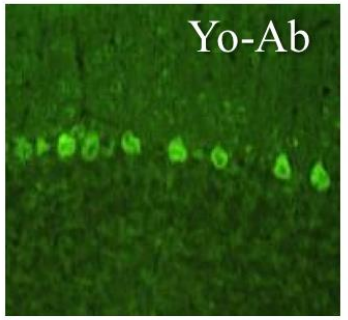
	Amphiphysin	CV1.2	Hu	Yo	Cv2	Ri	Ma2/Ta	Tr	VGKC LGI1	VGKC CASPR1	VGKC complex	NMDA	AMPAR	GLU-R1	GABAr	GAD	nAChR (α3)	DPPX	Iglon 5	Glu-R5
Acquired neuromyotonia										Yes										
painful neuropathy										Yes										
Morvan syndrome (limbic encephalitis and neuromyotonia)										Yes	Yes									
Rare tumors (eg, thymoma, small cell lung cancer)																				
Hyponatremia									Yes											
Myoclonic movements									Yes											
Stiff-person syndrome	Yes															yes				
Paraneoplastic encephalomyelitis (PEM)	Yes	Yes	Yes		Yes		Yes													
Diencephalic encephalitis	yes						Yes													
Brainstem encephalitis	yes		Yes			Yes	Yes													
Myelitis	yes					Yes														
Cerebellar degeneration/ataxia		Yes			Yes											yes				
Sensory neuronopathy (SN)	Yes		Yes		Yes															
Chorea		Yes		Yes	Yes															
Optic neuritis		Yes																		
Peripheral neuropathy		Yes																		
opsoclonus-myoclonus			Yes			Yes														
Subacute cerebellar degeneration			Yes	Yes	Yes	Yes	Yes													
enteric neuropathy (gastrointestinal [GI] dysmotility)			Yes	Yes	Yes						Yes									
Sensorimotor neuropathy	Yes				Yes															
Optic neuropathy (retinitis, optic neuritis, uveitis					Yes															
Jaw dystonia						Yes														
Atypical parkinsonism							Yes													
Neuromyotonia (Isaac syndrome											Yes									
Undulating myeloma											Yes									
Cramp-fasciculation syndrome											Yes									
Limbic encephalitis	Yes		Yes		Yes		Yes		Yes	Yes	Yes	yes	yes		yes	yes				
Psychoses (eg, hallucinations, delusions, paranoia)												yes	yes							
Paranoia												yes								
Memory issues, cognitive impairment												yes						Yes		
Limbic encephalitis (with early prominent seizures)															yes			yes		
Limbic encephalitis, agitation/psychiatric disturbances ()													yes							
Seizures												yes	Yes							
Dyskinesia, movement disorders												yes								
Catatonic phase												yes								
Autonomic neuropathy (hypoventilation, tachycardia, hypertension, hyperthermia)			Yes		Yes							yes					yes			
Speech and language dysfunction												yes								
not reported in children													yes							
Agitation													yes					Yes	Yes	
Sleep disorders																			Yes	
Diarrhea																		Yes		
Association à Hodgkin								Yes												Yes
Hyperrekplexia																		Yes		

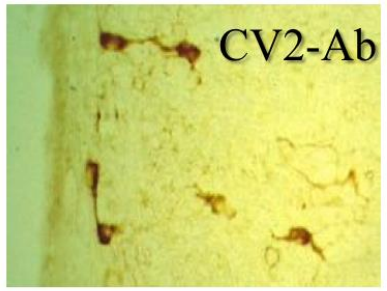
Main onco-neural antibodies associated with PNS

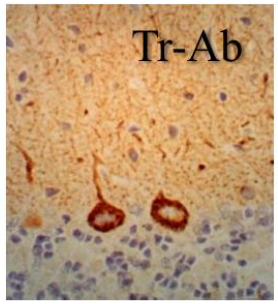
(Graus et al, JNNP 2004;75:1135-1140)

Antibodies	Main associated neurological syndromes	Cancer
Hu-Ab	Sensory neuronopathy Encephalomyelitis Chronic gastrointestinal pseudoobstruction Cerebellar ataxia Limbic encephalitis	SCLC
Yo-Ab	Subacute cerebellar ataxia	Ovary, breast, uterus
CV2-Ab	cerebellar ataxia Sensory-motor neuropathy Uveitis, retinopathy Encephalomyelitis	SCLC, thymoma
Ri-Ab	Opsomyoclonus Cerebellar ataxia	Breast, SCLC
amphiphysin-Ab	Stiff-person syndrome Sensory neuronopathy Encephalomyelitis	Breast, SCLC
Tr-Ab	Cerebellar ataxia	Hodgkin's disease
Ma2-Ab	Limbic encephalitis	Testicular







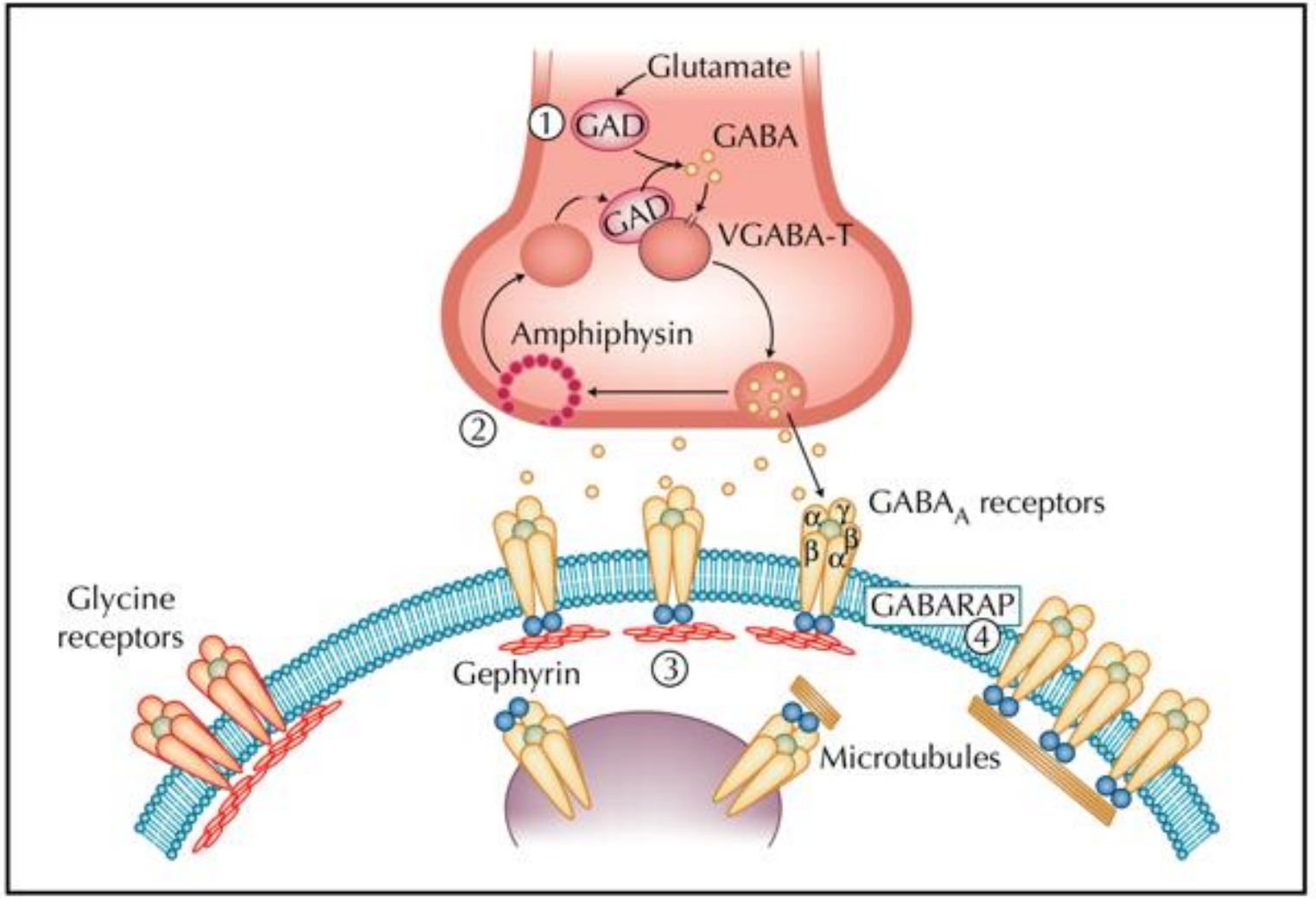


specificity 99 % ; sensitivity 50 %

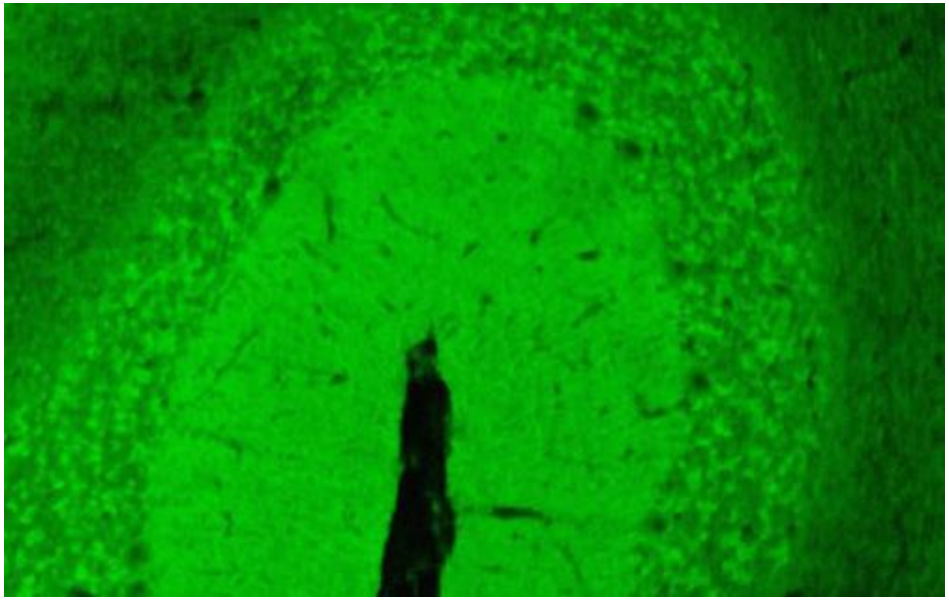
Stiff person syndrome

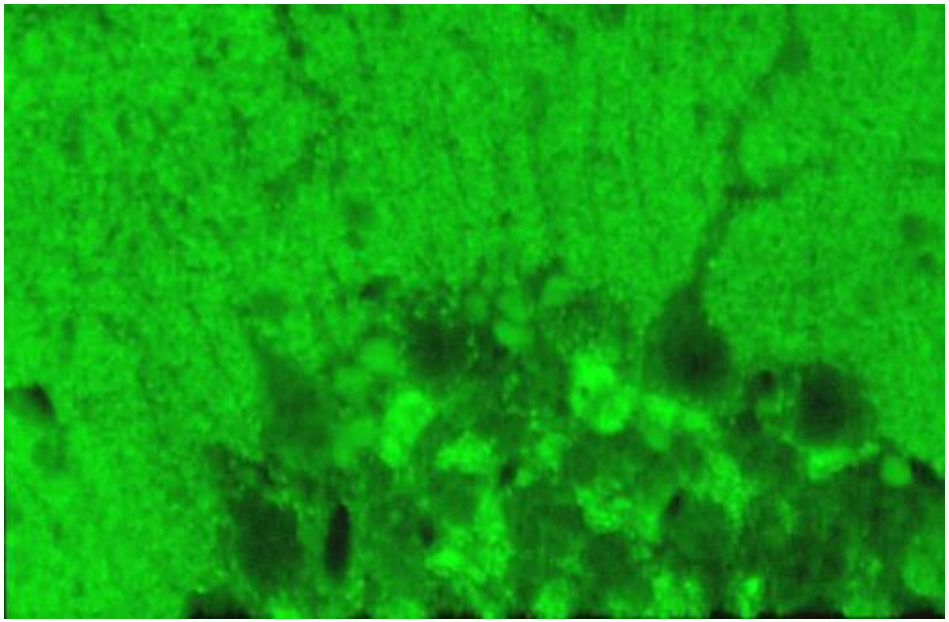
Patient rigid in moderate opisthotonos, with arms

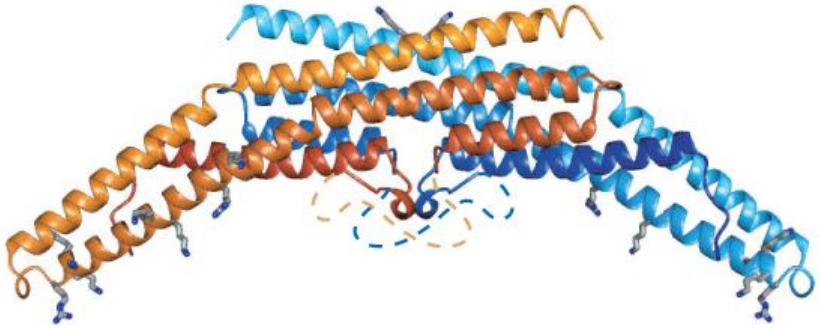
Stiff Man Syndrome

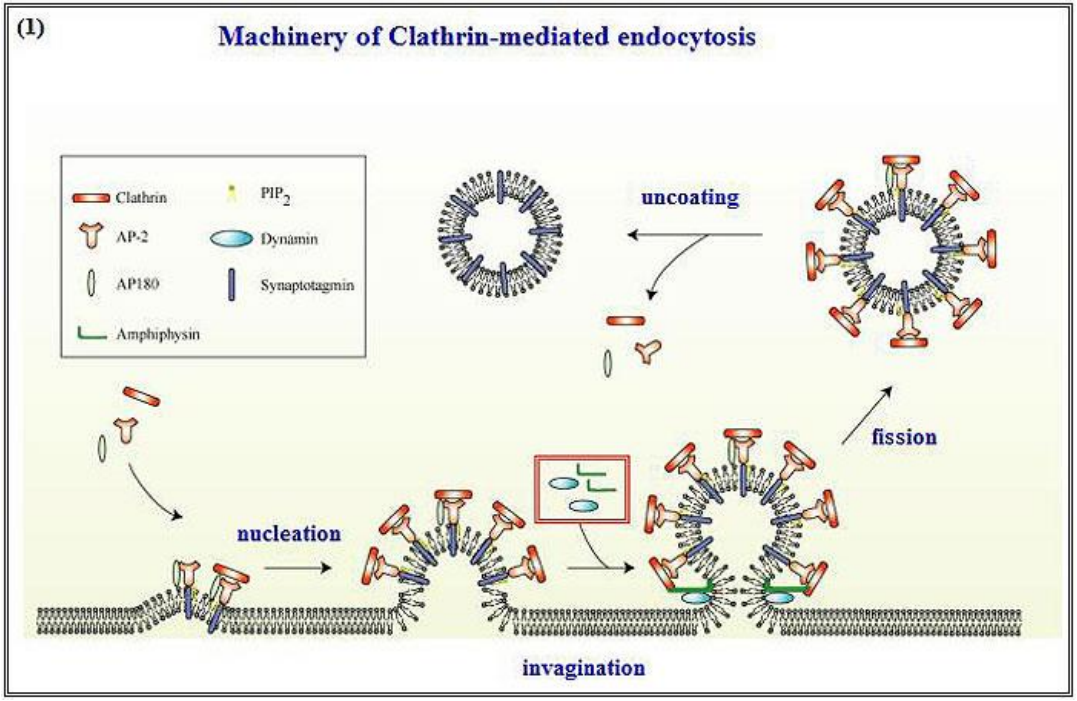


Anti Amphiphysine



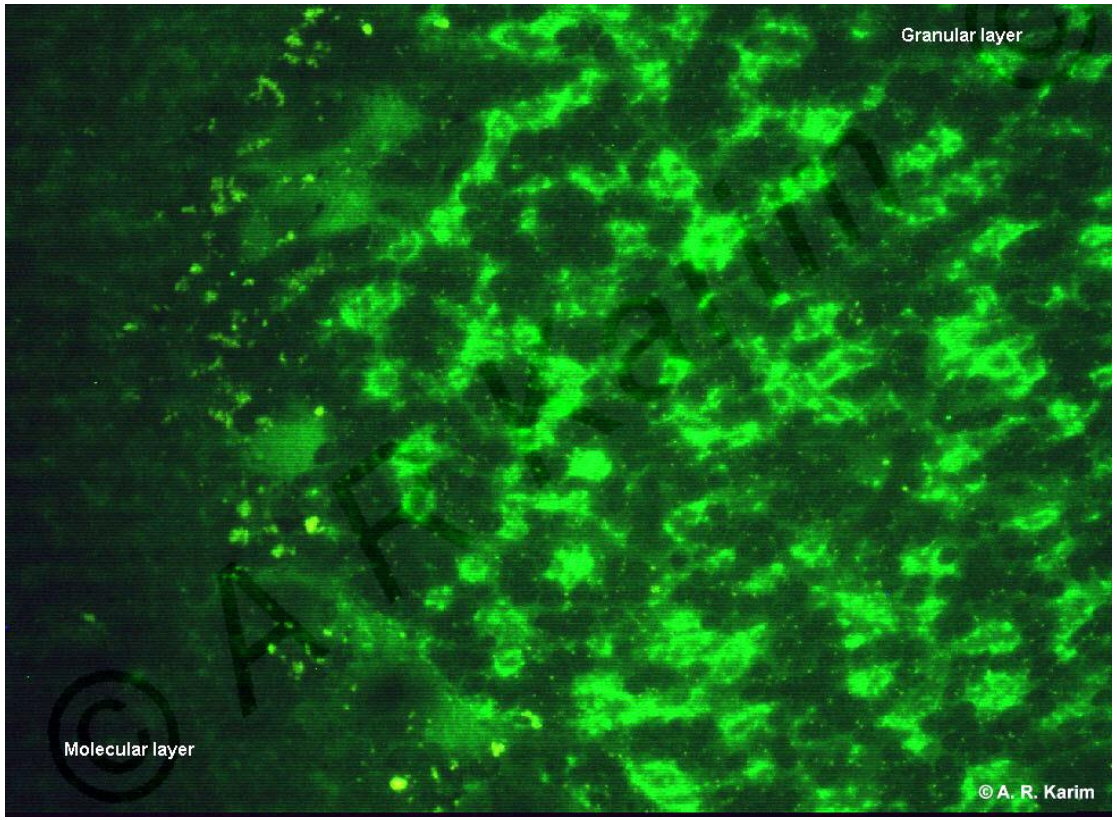






Amphiphysin belongs to the BAR (Bin-Amphiphysin-Rsvsp) family proteins. There are two isoforms, amphiphysin I and II. Amphiphysin I is the antigen recognized by anti-amphiphysin antibodies that occur in paraneoplastic neurological syndromes. Amphiphysin I is a presynaptic protein that play a key role in clathrin-mediated endocytosis of synaptic vesicles released in the presynaptic terminals.

Anti-GAD



Higher magnification of the granular cells showing GAD reactivity

GAD65 : neurotransmission
GAD67 autres fonctions neuronales
Enzyme produisant le GABA

GAD antibody on primate pancreas (Islet cell antibody has similar distribution). The target antigens are GAD 67 and GAD 65.

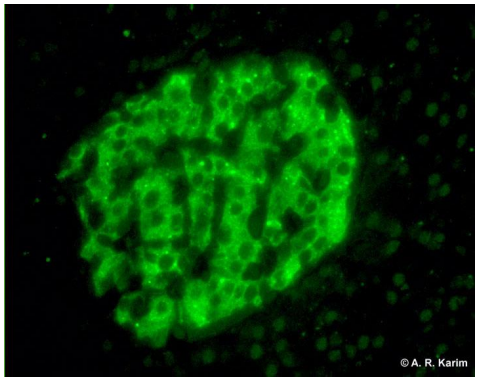
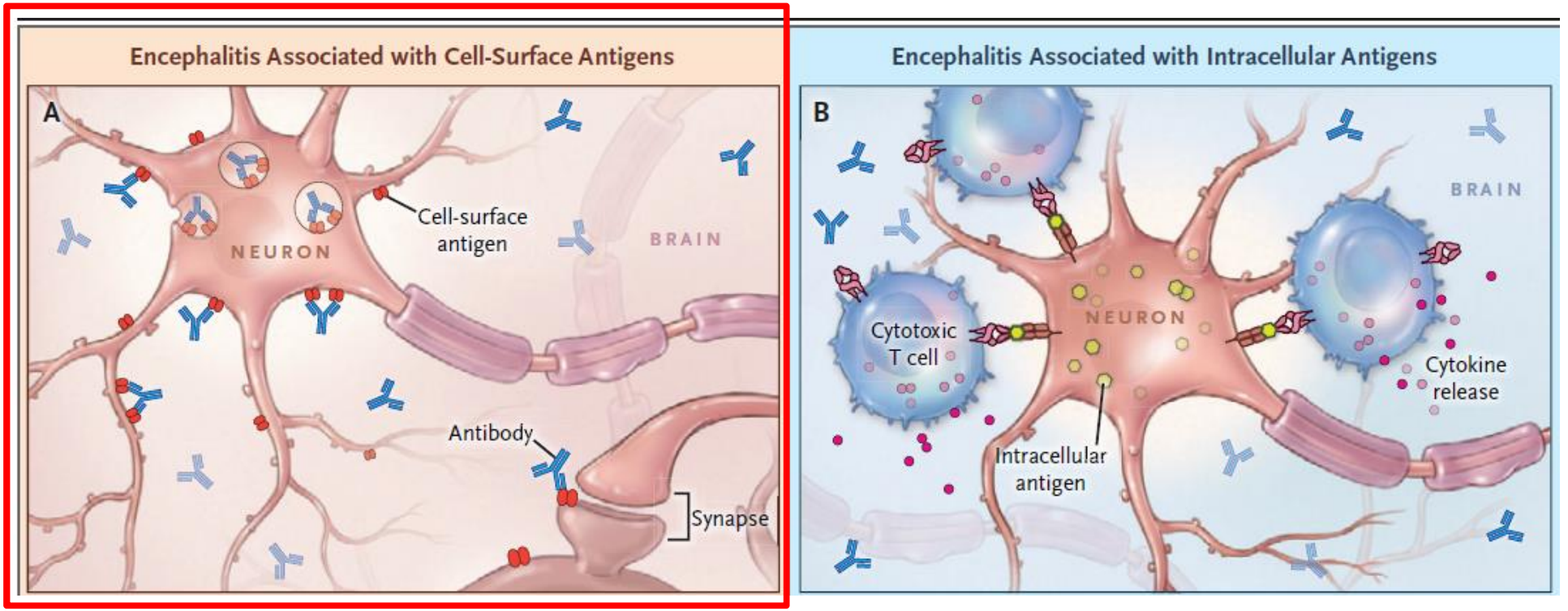
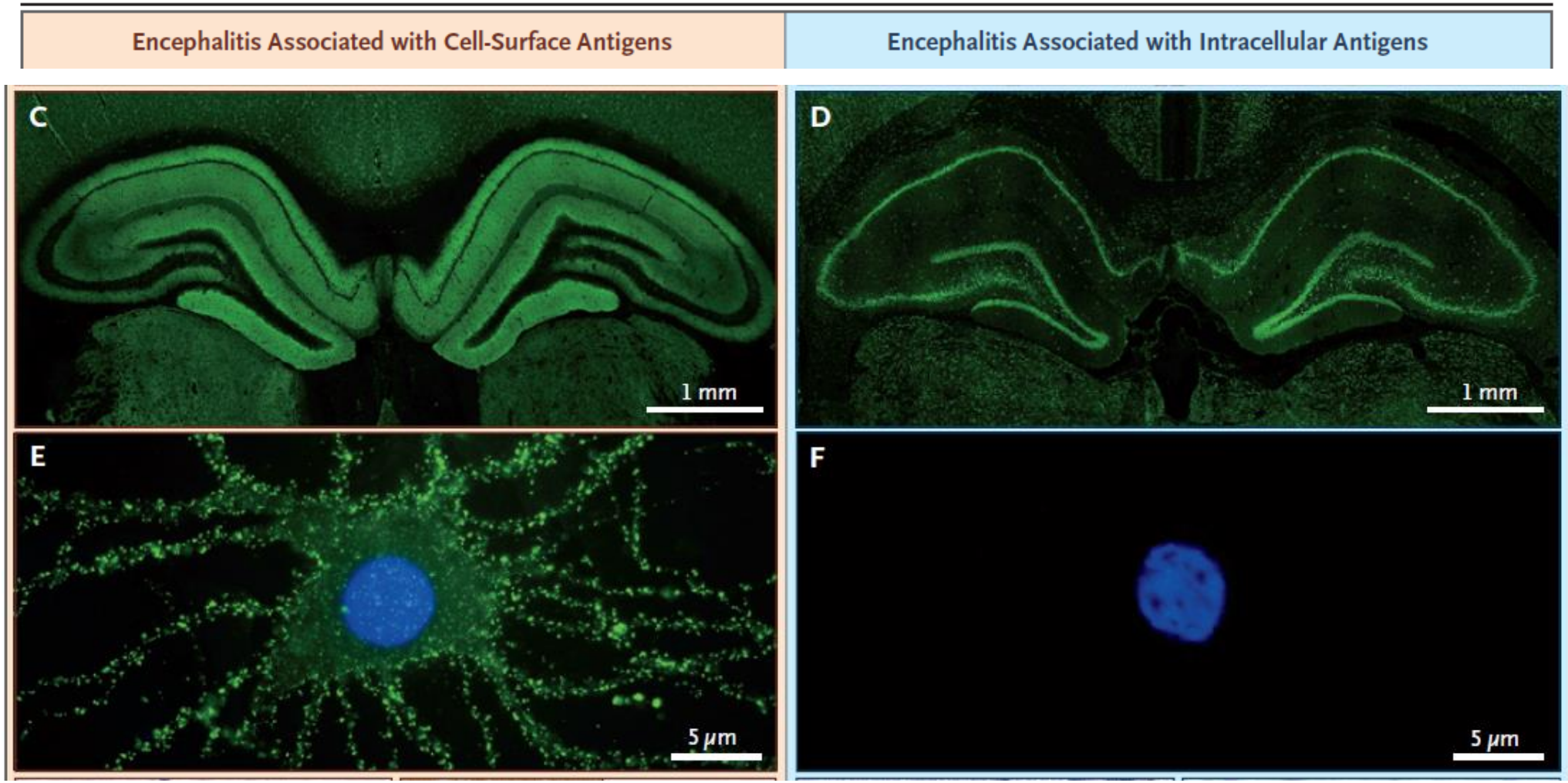


Tableau clinique en fonction de la cible antigénique

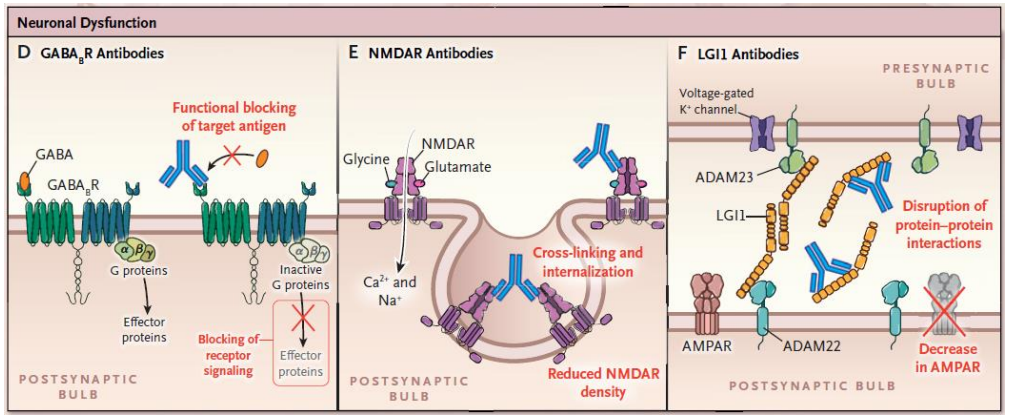


NEJM 2018


Encephalitis Associated with Cell-Surface Antigens
Encephalitis Associated with Intracellular Antigens
C
1 mm
D
1 mm
E
5 μm
F
5 μm

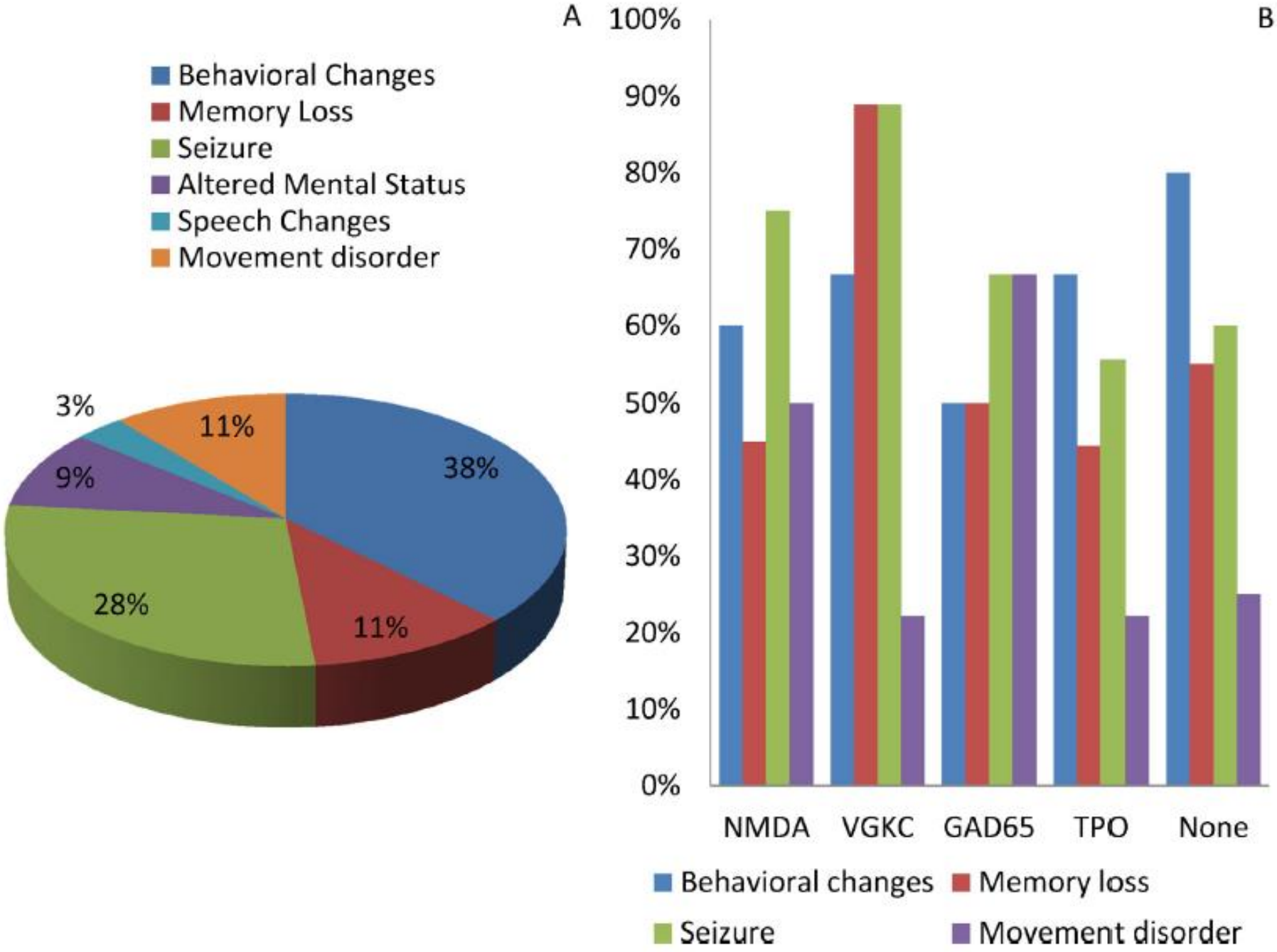
NEJM 2018

Anticorps dirigés contre les protéines de surface, des récepteurs ou des canaux ioniques

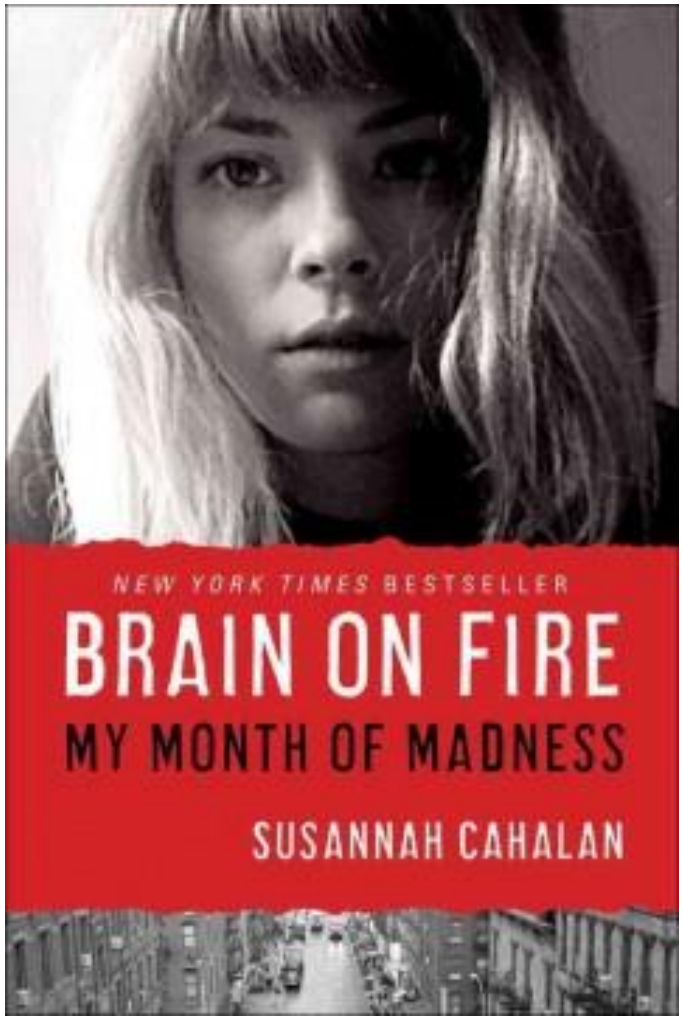


- Tableau clinique prédominant :
  - Troubles du comportement
  - Psychose
  - Crises E
  - Troubles cognitifs et de mémoire
  - Mouvements anormaux
  - Dysautonomie
  - Altération de la conscience
- Pas d'autre manifestations systémiques >< Lupus
- Atteint tous les ages
- Récupération complète si traitement précoce

- Effet pathogène direct des anticorps

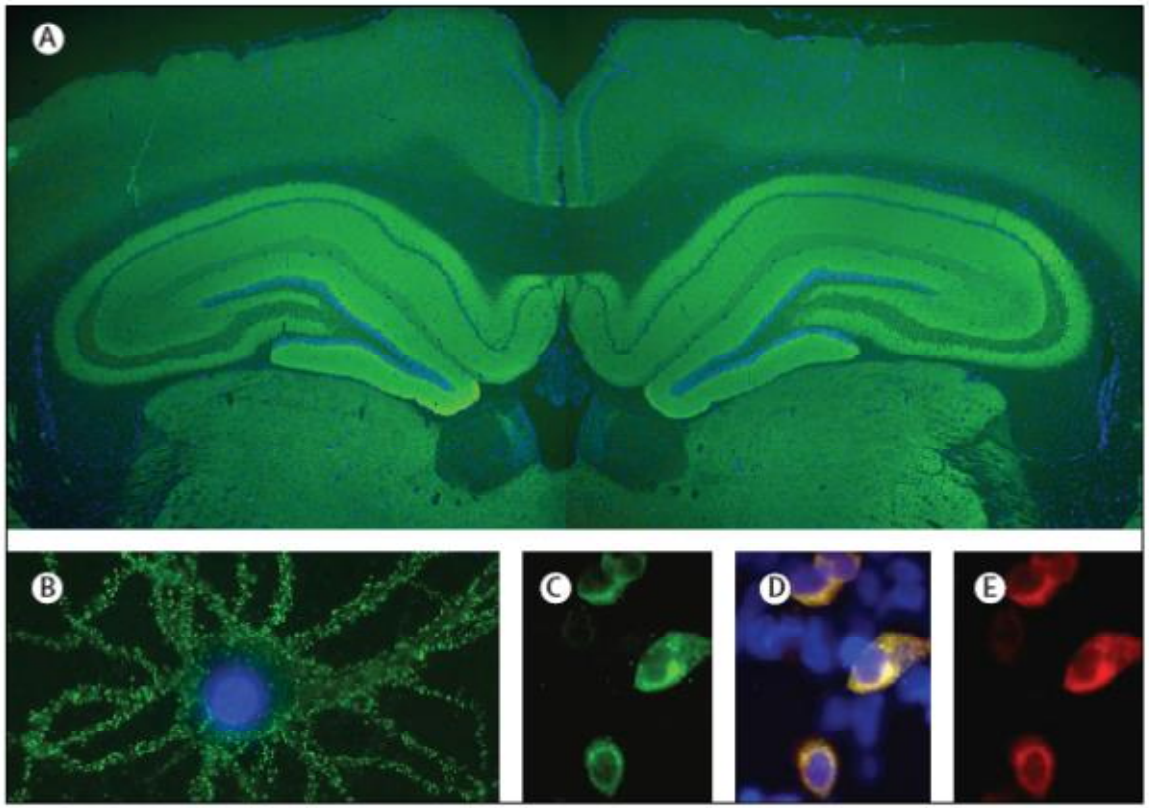

A
Behavioral Changes
Memory Loss
Seizure
Altered Mental Status
Speech Changes
Movement disorder
38%
11%
28%
9%
3%
11%
B
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
NMDA
VGKC
GAD65
TPO
None
Behavioral changes
Memory loss
Seizure
Movement disorder

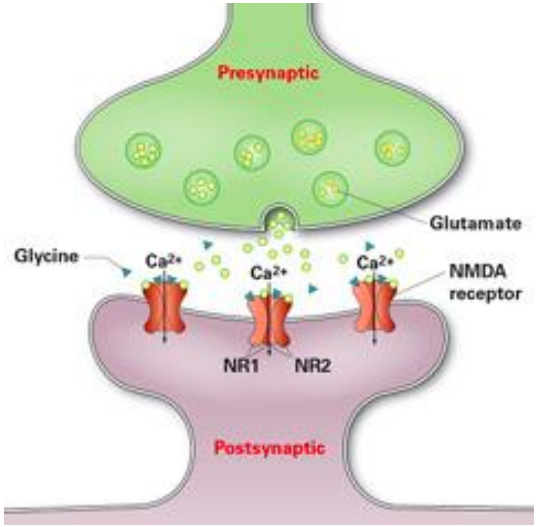
Encéphalite limbique



In April 2009, Susannah Cahalan, a 24-year-old reporter for the New York Post, woke up strapped to a bed in a hospital room. She had no clear memory of the previous few weeks, though her medical records showed that she'd been psychotic and violent before lapsing into a profound catatonia. Her doctors had ordered a battery of blood tests and brain scans, but they revealed nothing. It took the brilliant neurologist Souhel Najjar, MD, to find the cause: Cahalan had a rare disease that caused her immune system to attack her brain. In her new book, Brain on Fire, Cahalan chronicles her terrifying ordeal and the desperate search for a cure. We asked her to walk us through her journey.

Ac anti-Glutamate récepteur





Auto-Ac et encephalites limbiques

- Ac dirigés contre cible intracellulaire
  - Hu, Ma2, CV2, Amphiphysine
  - GAD
- Ac dirigé contre protéine (récepteur) membranaire
  - Glutamate rec :
    - Rec ionotropes: NMDA (Ca++), AMPAR (Na+/K+)
    - Rec Metabotropes: mGLUR1 (deg. Cerebelleuses)
  - VGKC (Kv1,Kv2,é LGI1, CASPR2
  - $GABA_B$ Rec
  - GlyR
- Cible inconnue : 40%
  - Ac reconnaissant « Neuropil » limbique (+/-30%)
  - Pas dêanticorps

32% Ac découvert Í Ac suspecté

Encéphalite limbique

Å désorientation,

Å agitation,

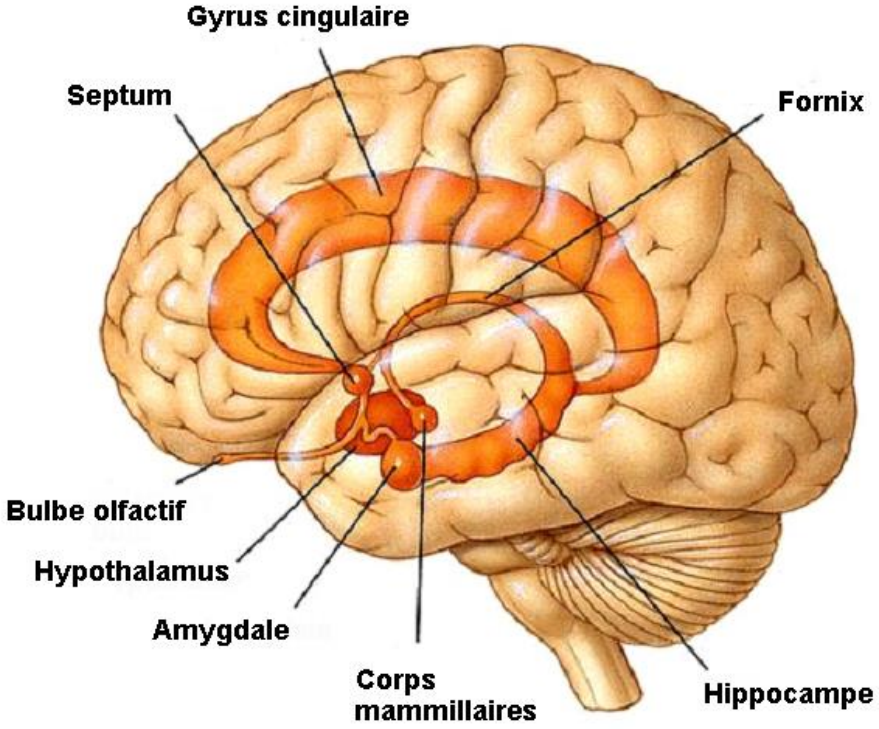
Å Perte de mémoire à court terme,

Å Epilepsies temporales,

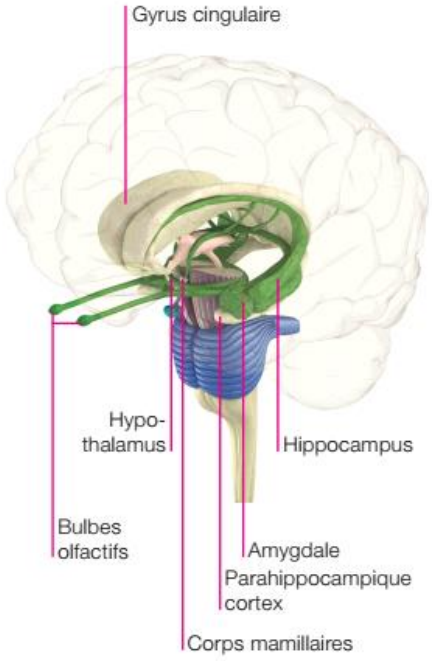
Å Troubles du sommeil,

Å Hallucinations

Système limbique

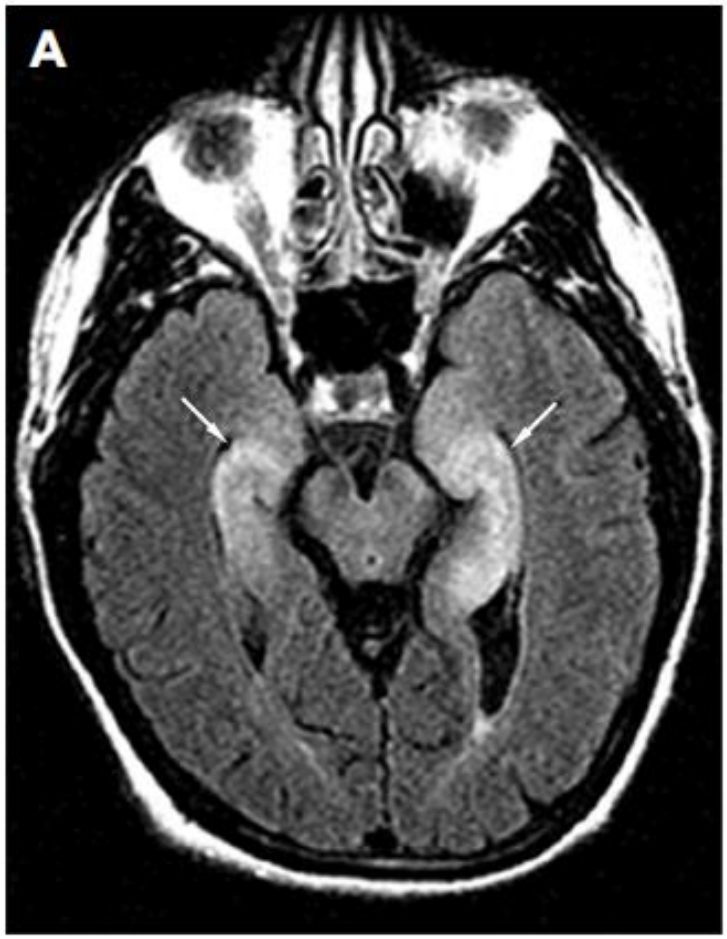


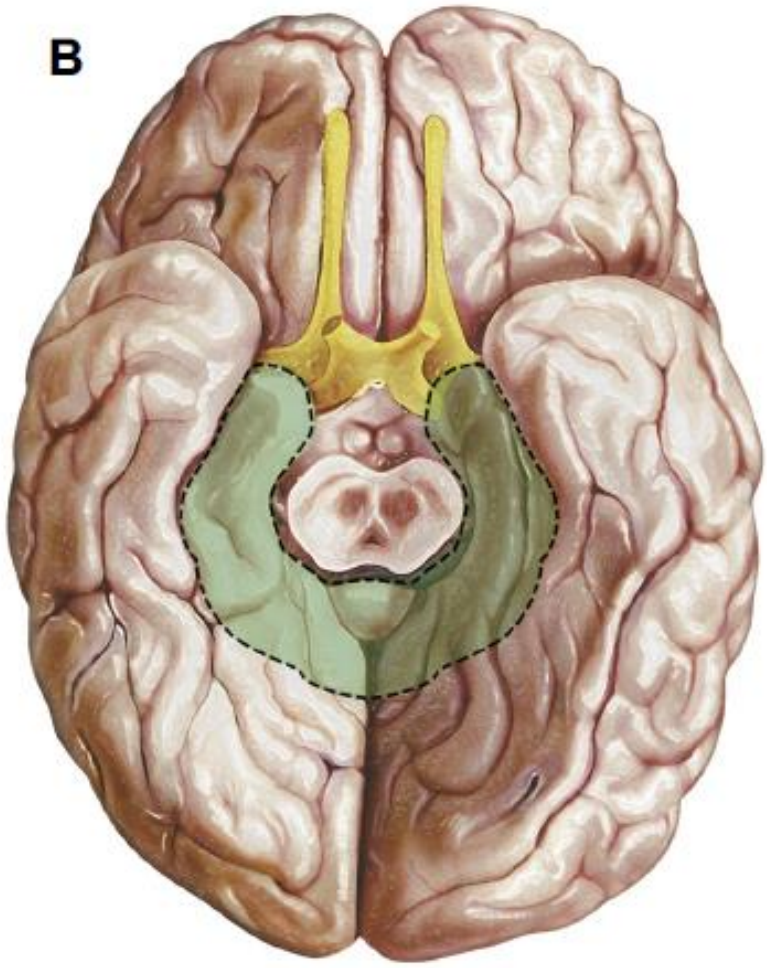
Amygdale : L'amygdale joue un rôle important dans l'apprentissage, la mémorisation et la gestion des émotions. De plus l'amygdale coordonne la réponse corporelle à la peur et à l'agression.
Gyrus Parahippocampique : Zone corticale adjacente à l'hippocampe participant à la visualisation des scènes et des lieux.
Hypothalamus : principal lien entre le système nerveux et le système hormonal.
Bulbes olfactifs : Faisceau de cellules nerveuses sensorielles allant de la cavité nasale à l'intérieur du cerveau. Ils traitent partiellement les informations relatives à l'odorat avant qu'elles ne soient conscientes.
Corps mamillaires : petit amas de cellules nerveuses qui relaient les signaux au thalamus, contribuant ainsi à la vigilance et à la construction de la mémoire -
Gyrus cingulaire Partie du cortex limbique située au-dessus du corps calleux



Olfaction
Mémoire
Emotions
Contrôle endocrinien

Encéphalite limbique

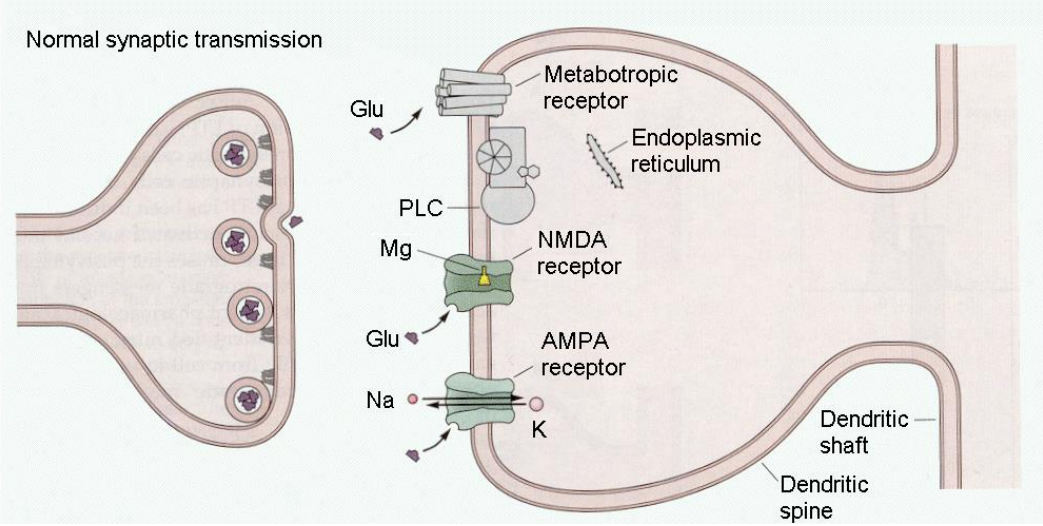




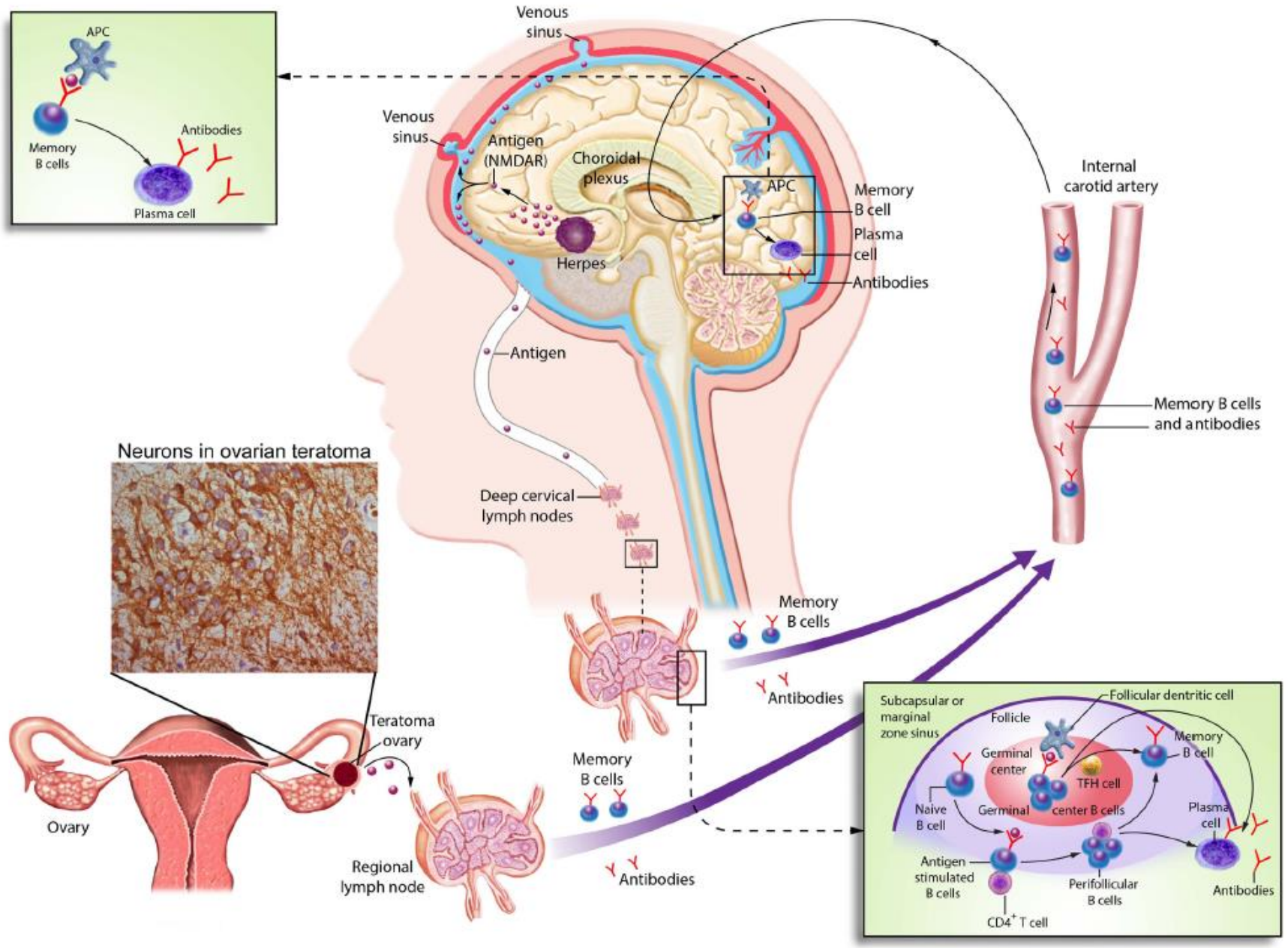
Physiol Rev • VOL 97 • APRIL 2017

Récepteurs glutamate

- Récepteurs ionotropes
  - Récepteurs NMDA (Ca++) tétramère 2NR1/2NR2
  - Récepteurs AMPA (Na+/K+) hétérotétramère GluR1, GluR2, GluR3, GluR4.
- Récepteurs métabolotropes au glutamate:
  - Homodimères (mglu1, mglu… mglu8)



Encephalite à Ac anti NMDAR



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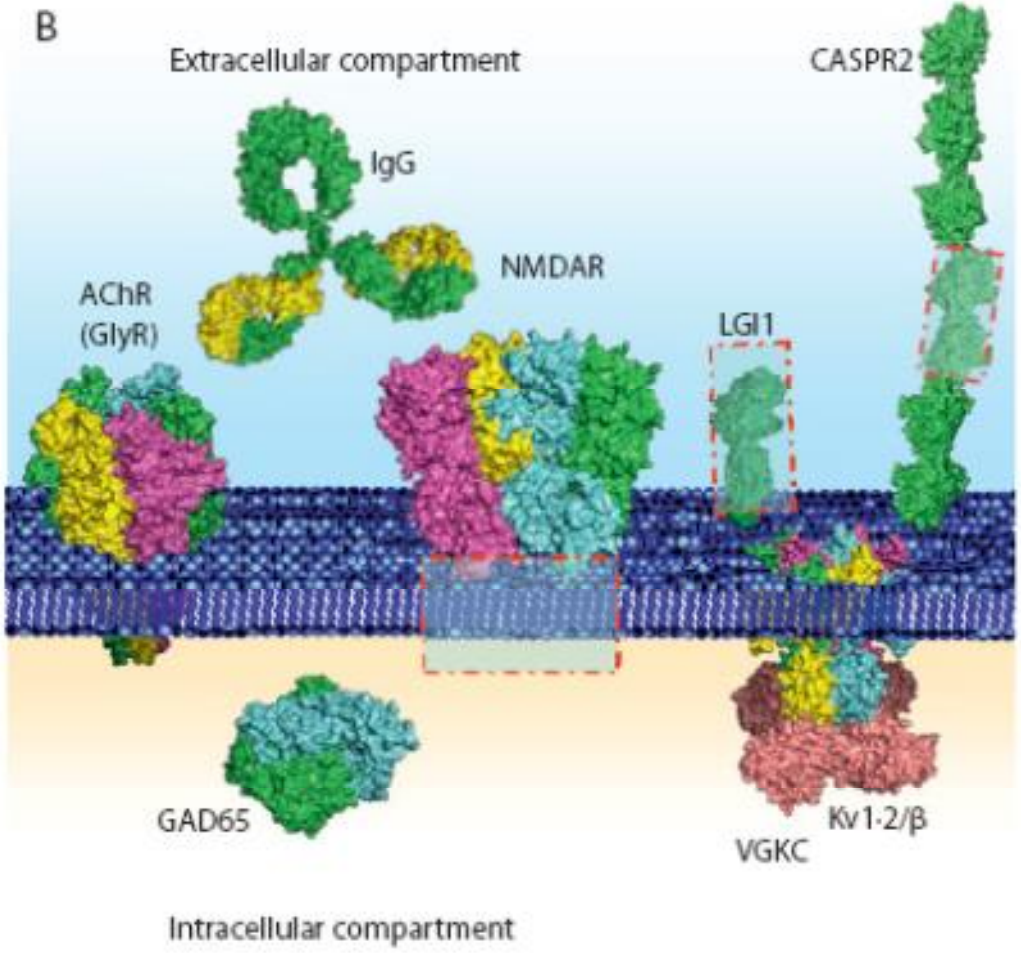
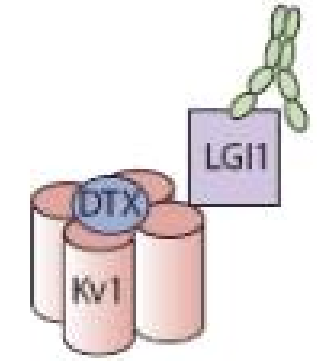
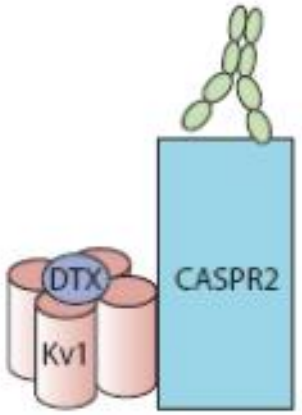
Anticorps Anti VGKC
(Voltage Gated K channels)







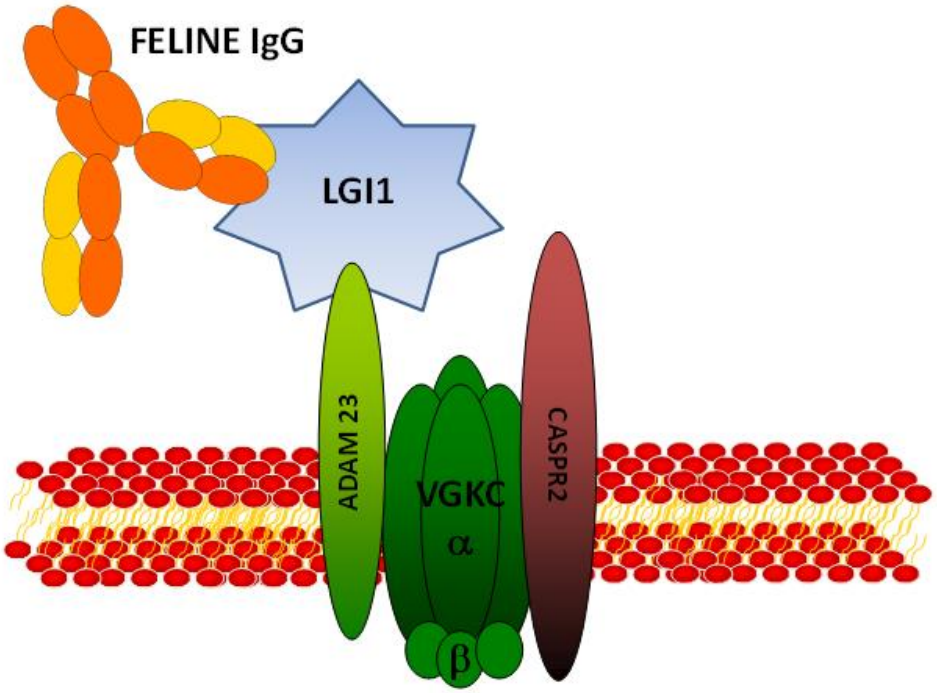
DTX = Dendrotoxine (< mamba vert)

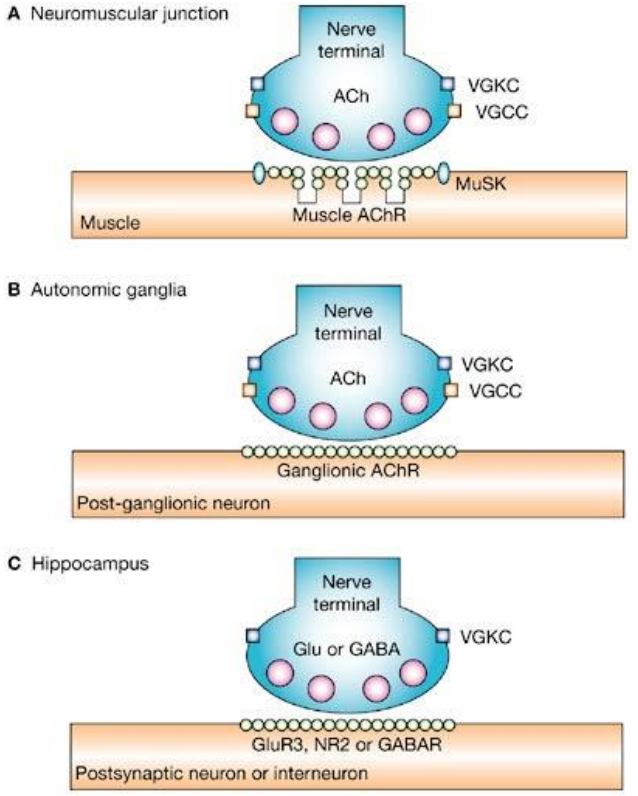
RIA: test incluant l'ensemble du complexe

Anti VGKC : associations

- Neuromyotonie — CASPR2
- Syndrome de Morvan — LGI1/CASPR2
- Encéphalite limbique — LGI1
- Opsonus Myoclonus (également Hu, Ri)

Anti VGKC


FELINE IgG
LGI1
ADAM 23
VGKC
α
β
CASPR2


A Neuromuscular junction
Nerve terminal
ACh
VGKC
VGCC
MuSK
Muscle AChR
Muscle
B Autonomic ganglia
Nerve terminal
ACh
VGKC
VGCC
Ganglionic AChR
Post-ganglionic neuron
C Hippocampus
Nerve terminal
Glu or GABA
VGKC
GluR3, NR2 or GABAR
Postsynaptic neuron or interneuron


KODAK 05 EPP 01
KODAK 05 EPP 01
KODAK 05 EPP 01
KODAK 05 EPP 01

Ac anti- Ag de surface / Néo

	% cas paraneoplasiques	Tumeurs
Å NMDAR	9-55%	Teratome ovarien
Å AMPAR	70%	Po, Thym, sein
Å GABA R	60%	SCLC
Å LGI1	<20%	SCLC, thymome
Å CASPR2	<10%	Thymome

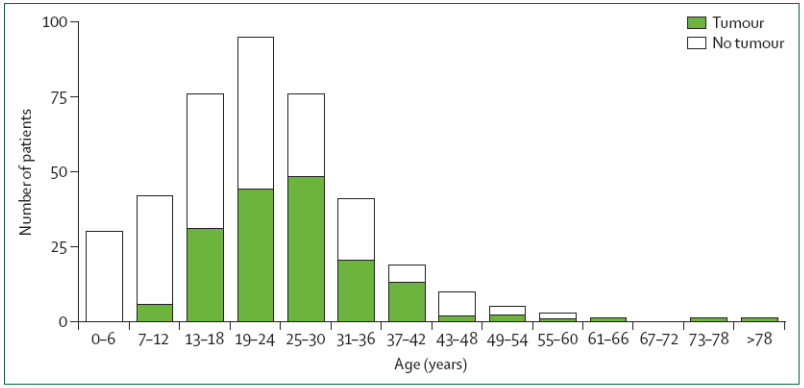
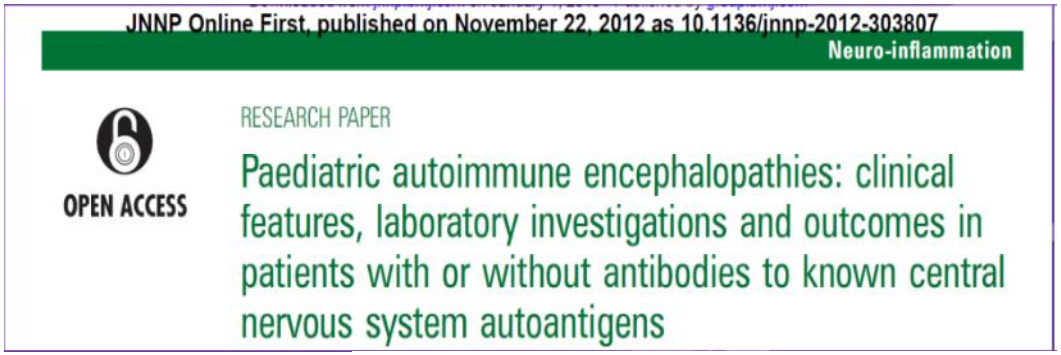


Figure 2: Distribution of patients by age and presence or absence of tumours
Data are for 400 patients with anti-NMDAR encephalitis.

Lancet Neurol 2011; 10: 63–74

Encéphalies autoimmunes en pédiatrie



NMDAR ï 13/48
VGKC-complex ï 7/48
Glycine receptor ï 1/48

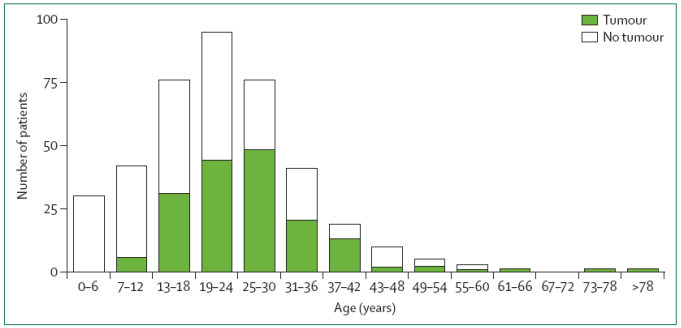


Figure 2: Distribution of patients by age and presence or absence of tumours
Data are for 400 patients with anti-NMDAR encephalitis.

Anti-GM1 antibodies
- In cryptogenic partial epilepsy (6%)

GluR3 antibodies
- Mainly in Rasmussens encephalitis

NMDAR antibodies
- 140 patients identified in the first 2 years in the UK
- 26% of female patients aged 15 to 45 with unexplained new-onset epilepsy (*Arch Neurol* 2009; 66:458)

GABAA antibodies
- in severe epilepsy, encephalitis and status (Petit-Pedrol M et al, *Lancet Neurol* 2014 Mar)

Encéphalies autoimmunes en pédiatrie

NMDAR ï 13/48
VGKC-complex ï 7/48
Glycine receptor ï 1/48

Anti-GM1 antil
- In cryp
GluR3 antiboc
- Mainly
NMDAR antib
- 140 pa
- 26% of
ne
GABAA antibc
- in seve
status (Petit-P

JNNP Online First, published on November 22, 2012 as 10.1136/jnnp-2012-303807
Neuro-inflammation

OPEN ACCESS

RESEARCH PAPER

Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens

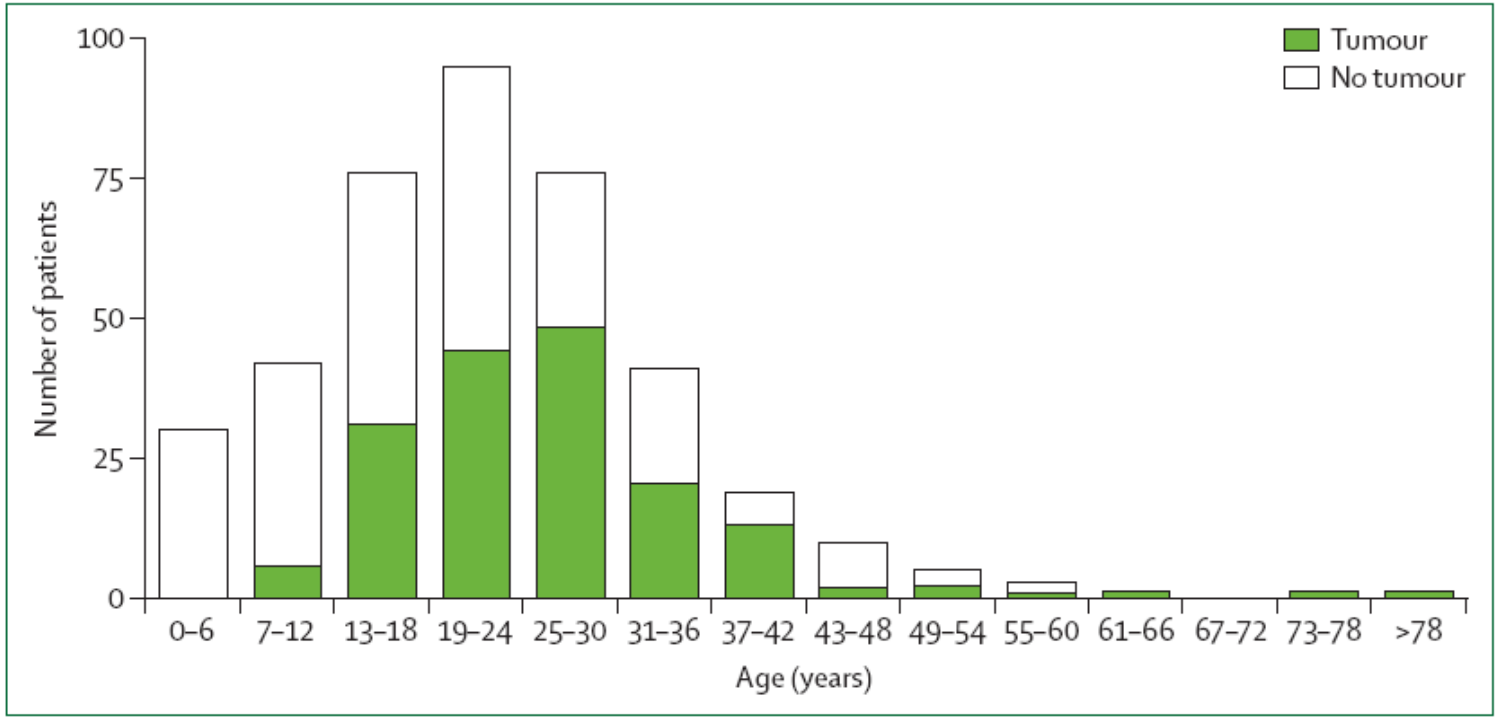


Figure 2: **Distribution of patients by age and presence or absence of tumours**
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Stratégie recherche Ac anti-Neurones

Immunofluorescence indirecte
(cervelet primate +/- syst limbique)

Négatif

Discussion avec clinicien

Faible suspicion clinique

STOP

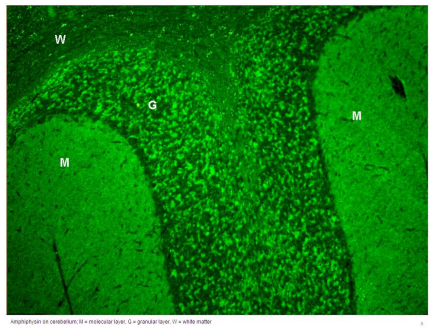
Forte suspicion clinique

Anti-NMDAR, AMPAR
VGKC (LGI1, CASPR2),
AQ4

selon présentation

Cell based assays
(cellules transfectées)

Positif



Marquage du Neuropile
(couche moléculaire)

selon pattern

Ac anti-neurones
Anti-Hu, Ri, Yo,
CV2, Ma2,
Amphiphysine

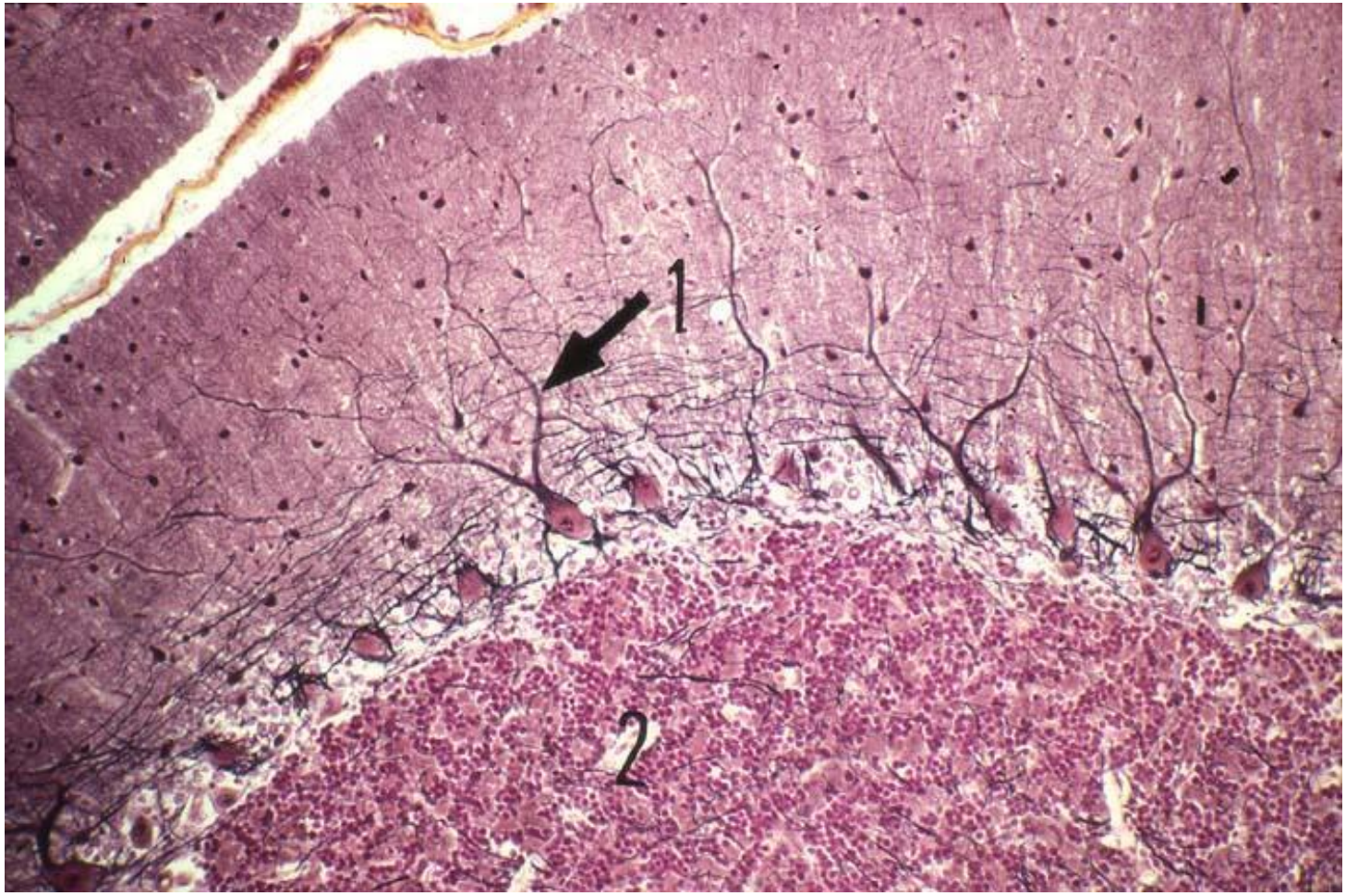
Immunoblot

Pattern immunofluorescence indirecte

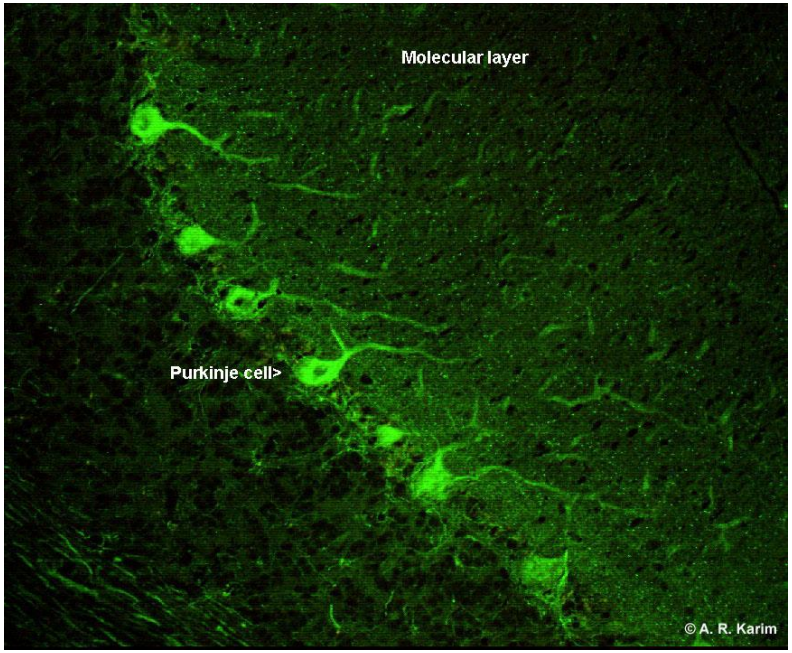
- Cytoplasme Purkinije → Yo (PCA1) ou mGluR1
- Noyaux neurones (exclure ANA) → Hu, Ri
- Cytoplasme et dendrites → PCA2
- Couche granulaire (cytopl) → GAD
- Couche moléculaire et granulaire → NMDA, AMPA, Amphiphysine
- Couche moléculaire → VGKC, GABA

Histologie du cervelet

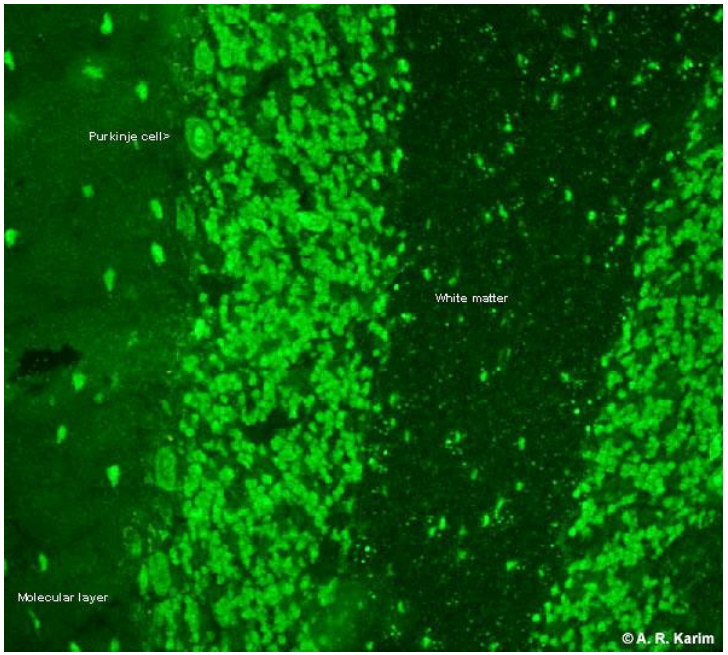
outil de screning



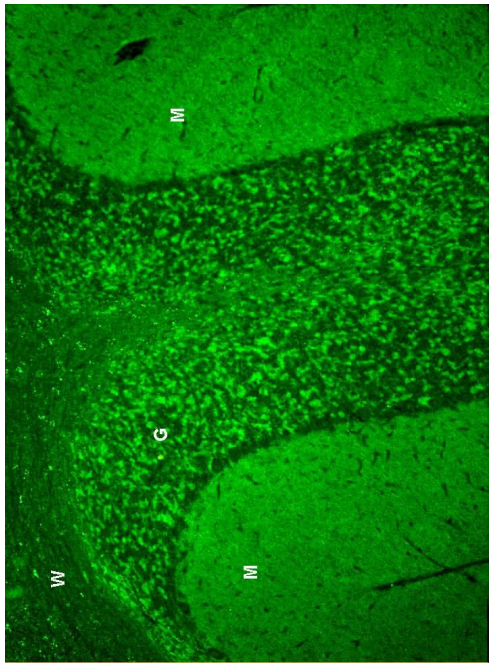
Anti-Tr



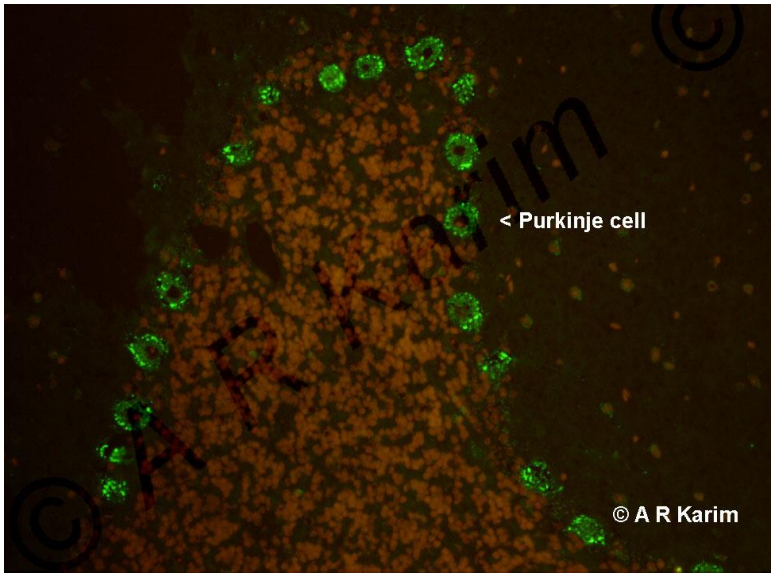
Anti-Hu



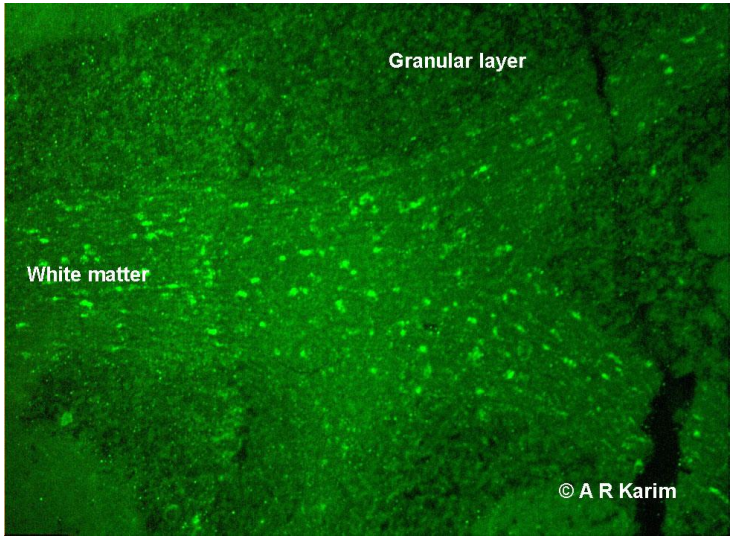
Anti-Amphyphisine



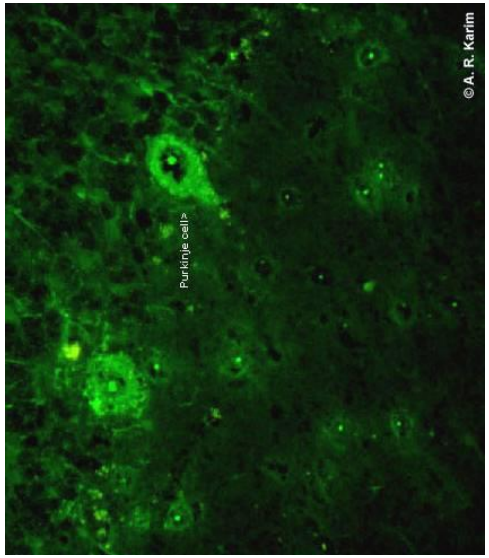
Anti-Yo



Anti-CV2



Anti-Ma1/Ma2/Ma3



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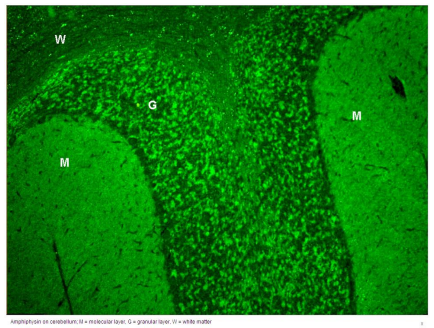


Marquage du Neuropile
(couche moléculaire)

selon pattern

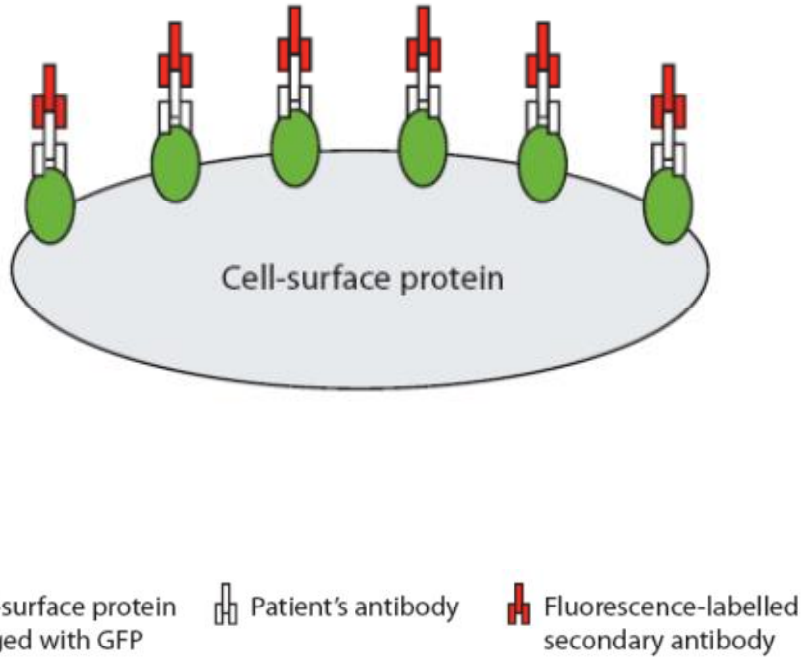
Ac anti-neurones
Anti-Hu, Ri, Yo,
CV2, Ma2,
Amphiphysine

Immunoblot

Cell based assays

Human Embryonic Kidney cells

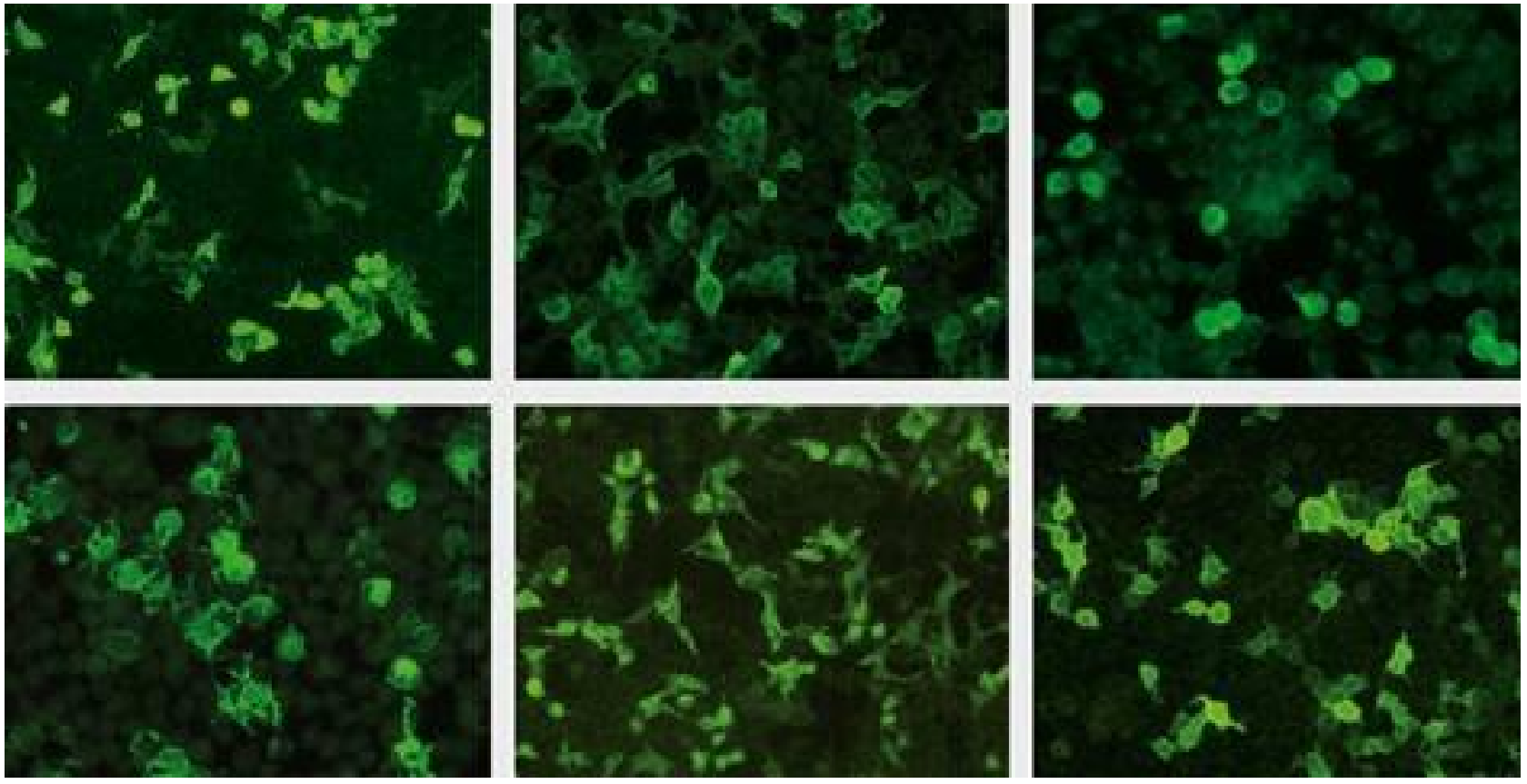
Cellule transfectée avec gène du la protéine spécifique → Exprimée en surface



Cell Based Assays

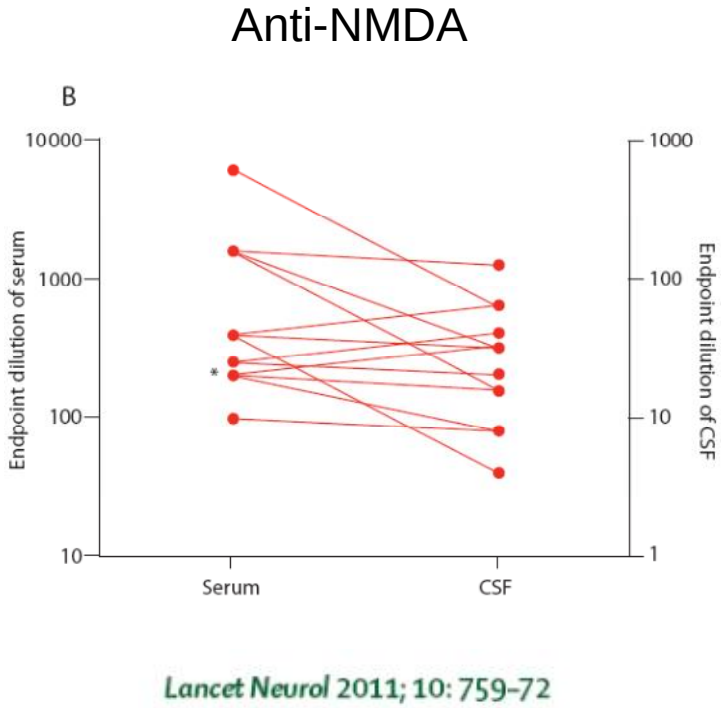
Transfected HEK 293 cells

Anti-Neuropil antibodies



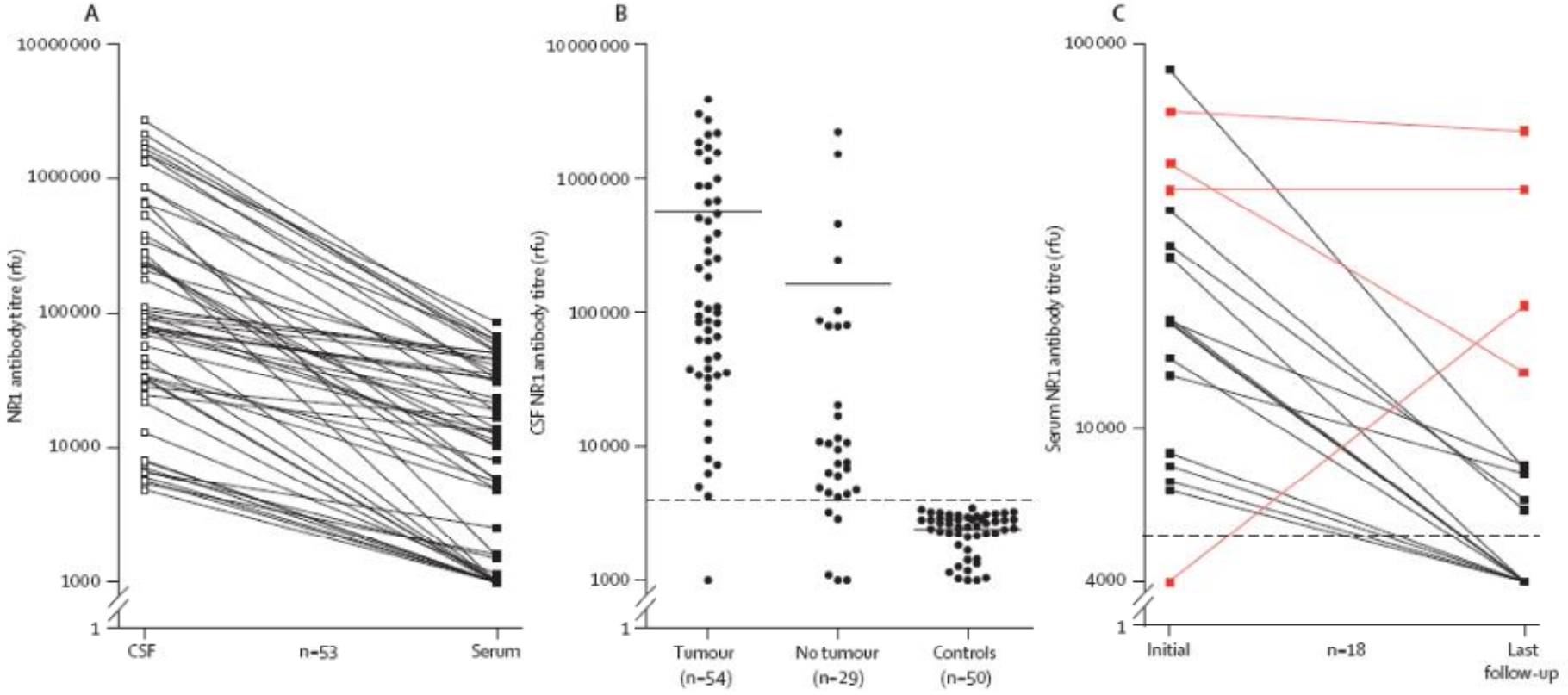
Serum ou LCR ?

- Serum:
  - Hu, Yo, Ma, CV2, Amphiphysine,
  - LG1, CASPR2
  - Recoverine
- LCR :
  - NMDAR
- Serum (et LCR):
  - VGKC, AMPAR, $GABA_BR$



Lancet Neurol 2011; 10: 759–72

Ac anti NMDAR



Dalmau, Philadelphia

***Figure 3*: Analysis of NR1 antibody titres**

In 53 patients with anti-NMDA-receptor encephalitis, antibody titres were higher in CSF than in serum (A). In 83 patients with anti-NMDA-receptor encephalitis (54 with tumour, 29 without tumour) and 50 controls (B), those with tumours had higher titres than those without (Wilcoxon rank, $p<0{\cdot}0001$) and controls ($p<0{\cdot}0001$). Six patients (one with tumour, five without tumour) had very low ELISA readings that overlapped with the signal given by negative controls. These six patients had low antibody titres; in contrast, the 50 controls were negative. Solid lines indicate the mean of the titres in each group. The dotted line indicates three SD above the mean value given by background signal of negative controls. Follow-up of serum antibody titres (C) in 14 representative patients who had neurological improvement (black lines) and four who did not (red lines); the second time-point is the sample obtained at the last follow-up (median 5·6 months, range 2–83 months). The dotted line indicates three SD of the mean value given by background signal of 50 negative control sera. Similar results were obtained by ELISA with NR1–NR2 heteromers (data not shown). Values in A, B, and C are given in relative fluorescence units (rfu) from the ELISA reader, and plotted in a logarithmic scale.

	VGKC-complex-Ab; mainly LGI1-Abs	VGKC-complex-Ab; mainly CASPR2-Abs	Anti-NMDAR encephalitis	AMPAR-Ab limbic encephalitis	$GABA_BR$-Ab limbic encephalitis	GAD-Ab limbic encephalitis	GlyR-Ab-associated disorders
Common symptoms	Predominantly limbic encephalitis with amnesia, seizures, psychiatric disturbance; faciobrachial dystonic seizures might predate the obvious cognitive involvement	Morvan's phenotype with confusion, amnesia, insomnia, autonomic dysfunction, neuromyotonia, and pain	Multistage cortico-subcortical encephalopathy including psychiatric manifestations, dyskinesias, seizures, mutism, reduction in consciousness; occasionally limbic encephalitis	Typical limbic encephalitis (amnesia, seizures); psychosis can dominate	Limbic encephalitis with prominent seizures	Temporal lobe epilepsy with mild cognitive involvement	Combinations of startle (hyperekplexia), stiffness, rigidity, brainstem disturbance, cognitive involvement rare but sometimes seizures
Differential diagnoses	Wernicke-Korsakoff syndrome, infective encephalitis (especially HSV), drug or toxin overdose, Creutzfeldt-Jakob disease, Hashimoto's encephalopathy, non-convulsive status epilepticus	Motor neuron disease, prion diseases (fatal familial insomnia), hereditary neuromyotonia (eg, Kv1.1 mutations), heavy metal (gold, mercury, or manganese) poisoning, phaeochromocytoma	Encephalitis lethargica, PANDAS, Sydenham's chorea, infective encephalitis (eg, rabies), neuroleptic malignant syndrome, Kleine-Levin syndrome, non-convulsive status epilepticus, Hashimoto's encephalopathy, neuropsychiatric lupus, porphyria	As for LGI1	As for LGI1	As for LGI1	Stiff person syndrome, tetanus, hereditary startle disease
Main known target‡	VGKC-complex-associated LGI1 Abs more frequent than CASPR2 Abs	VGKC-complex-associated CASPR2	NMDAR (mainly NR1 subunit)	GluR1/2	$GABA_BR1$	GAD	GlyRα1
Localisation	Strong in hippocampal neuropil	Ubiquitous but strong in hippocampal and cerebellar neuropil	High in hippocampal neuropil	Widespread in CNS but high in hippocampus	Widespread in CNS but high in hippocampus	Widespread in CNS on inhibitory interneurons	Inhibitory interneurons in spinal cord and brainstem
Antibodies	IgG4>IgG1	IgG4>IgG1	IgG1 predominantly	Not well described	IgG1 mainly	IgG1 mainly	IgG1 mainly
CSF intrathecal synthesis	Variable intrathecal synthesis	Insufficient data	Almost always intrathecal synthesis, which can be considerable (eg, >20 fold)	Intrathecal synthesis	Intrathecal synthesis	Intrathecal synthesis reported	Intrathecal synthesis reported
Tumour association or other pathology	Tumours very rare in patients with LGI1-Abs	Not invariable; thymoma principally, small-cell lung cancer or other rarer tumours	Ovarian (or other) teratomas in ≤50%	In about 50% of cases (thymoma, lung, breast)	Thymoma and lung	Very uncommon but can occur	Typically non-paraneoplastic, one thymoma
Disease course	Often monophasic without need for continuing immunosuppression	Can be treatment-responsive or have spontaneous improvement, but prognosis confounded by tumour when present	Responds well to early immunotherapies and early tumour removal but non-paraneoplastic cases can be chronic and tend to relapse	Responds to treatments but relapses common	Responds to treatments	Usually chronic disorders and role of long-term immunosuppression not yet clear	In case reports, immunotherapy led to substantial improvement

VGKC=voltage-gated potassium channel. Ab=antibody. LGI1=leucine-rich glioma inactivated 1. NMDAR=NMDA receptor. AMPAR=AMPA receptor. $GABA_BR$=GABA type B receptor. GAD=glutamic acid decarboxylase. GlyR=glycine receptor. HSV=herpes simplex virus. PANDAS=pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. CASPR2=contactin associated protein 2.

Table 1: **CNS antibody-associated disorders in adults**

Auto-anticorps : méthodes

	iIHC*	Western Blot	RIA	ELISA	CBA
Limbic encephalitis					
Onconeural antibodies (anti-Hu, Ma1/2, CV2, amphiphysin)	+	+	..	..	..
GAD antibodies	+	+	+	+	..
VGKC-complex antibodies (LGI1, CASPR2, Contactin-2)†	+	..	+	..	+
NMDAR antibodies‡	+	..	..	+	+
AMPAR antibodies	+	..	..	..	+
$GABA_BR$ antibodies	+	..	..	..	+
Faciobrachial dystonic seizures					
VGKC-complex antibodies (LGI1)†	+	..	+	..	+
Progressive cortico-subcortical encephalopathy					
NMDAR antibodies	+	..	..	+	+
Rapidly progressive abnormal behaviour resembling acute psychosis					
AMPAR antibodies; NMDAR antibodies	+	..	..	..	+
Morvan's syndrome					
VGKC-complex antibodies (LGI1, CASPR2)†	+	..	+	..	+
Stiff person syndrome complex					
GAD antibodies	+	+	+	+	..
GlyR antibodies	..	..	..	..	+
Amphiphysin antibodies	+	+	..	..	..

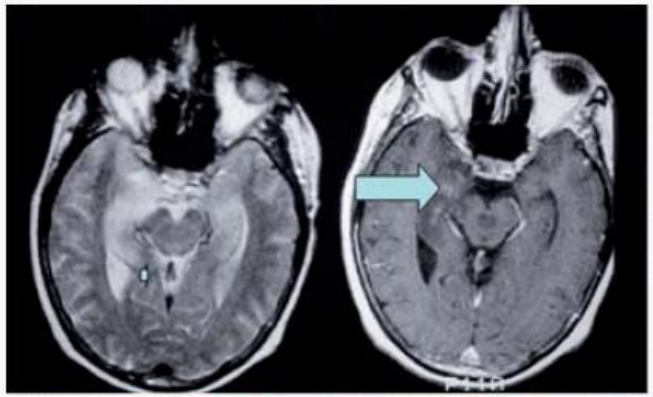
Lancet Neurol 2011; 10: 759–72

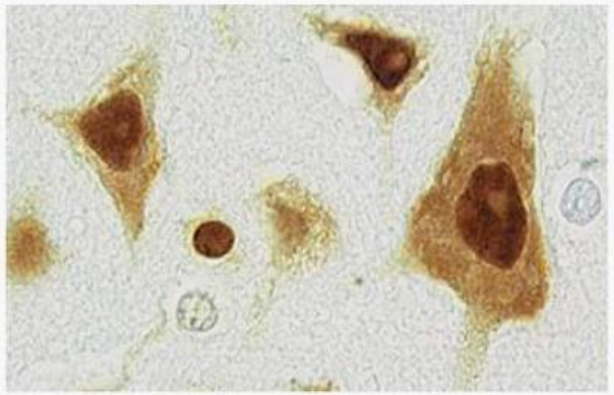
Techniques dôinvestigation biologique

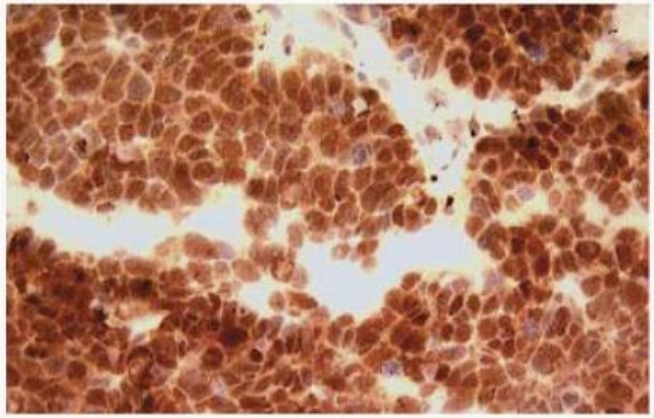
- Immunofluorescence indirecte: screening
  - Coupe de cervelet, dôhippocampe (système limbique)
  - Coupe de nerf sciatique
- Identification
  - Immunodots
  - Cellules transfectées (pour récepteurs membranaires)
  - ELISA (anti-GAD, anti-MAG, ..)

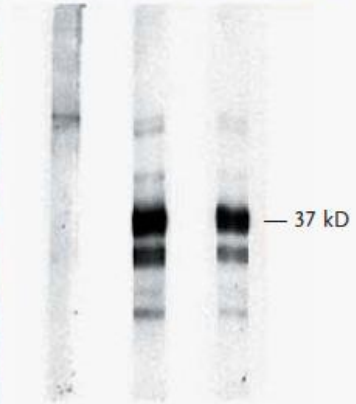
Merci

Patient rigid in moderate opisthotonos, with arms








— 37 kD
Normal serum
Patient's serum
Patient's tumor

Autoimmune encephalitis screen

Serum sample from patient is screened on transfected HEK cells for the detection of the following antibodies:-

Glutamate receptor type:

NMDA (see below), AMPA1 and AMPA2

Voltage-gated potassium channel associated proteins:

Leucine-rich glioma inactivated protein 1 (LGI1) and
Contactin-associated protein 2 (CASPR2)
DPPX

GABA receptors 1 (GABARB1)

Syndrome / cible antigénique

	Syndrome	Relevant antibodies
CNS	Subacute cerebellar degeneration 25%	Hu, Yo, CV2/CRMP5, Ri, Tr*, amphiphysin, VGCC
	Encephalomyelitis 6%	Hu, CV2/CRMP5, amphiphysin
	Limbic encephalitis 10%	Hu, Ma2, CV2/CRMP5, Ri, amphiphysin NMDAR, Lgi1§, CASPR2§, GABA(b)-, AMPA-, mGluR5, glyR§, GAD§
	Opsoclonus-myoclonus syndrome (adults) 2%	Ri, Hu, Ma/Ta, NMDAR
	Retinopathy 1%	Hu, CV2/CRMP5, recoverin
	Stiff-person syndrome 1%	amphiphysin, glyR§, GAD§

Quelques définitions

- **Syndrome de Morvan** : maladie neuro-musculaire rare, auto-immune, caractérisée par la présence de nombreuses fasciculations douloureuses. Elle se traduit par des contractions musculaires du visage et de la langue, des faiblesses et des crampes dans les muscles principalement dans les membres inférieurs. Associé à hyponatrémie. Video

- **myoclonus (myoclonies)** : contractions musculaires rapides, involontaires, de faible amplitude, d'un ou plusieurs muscles.

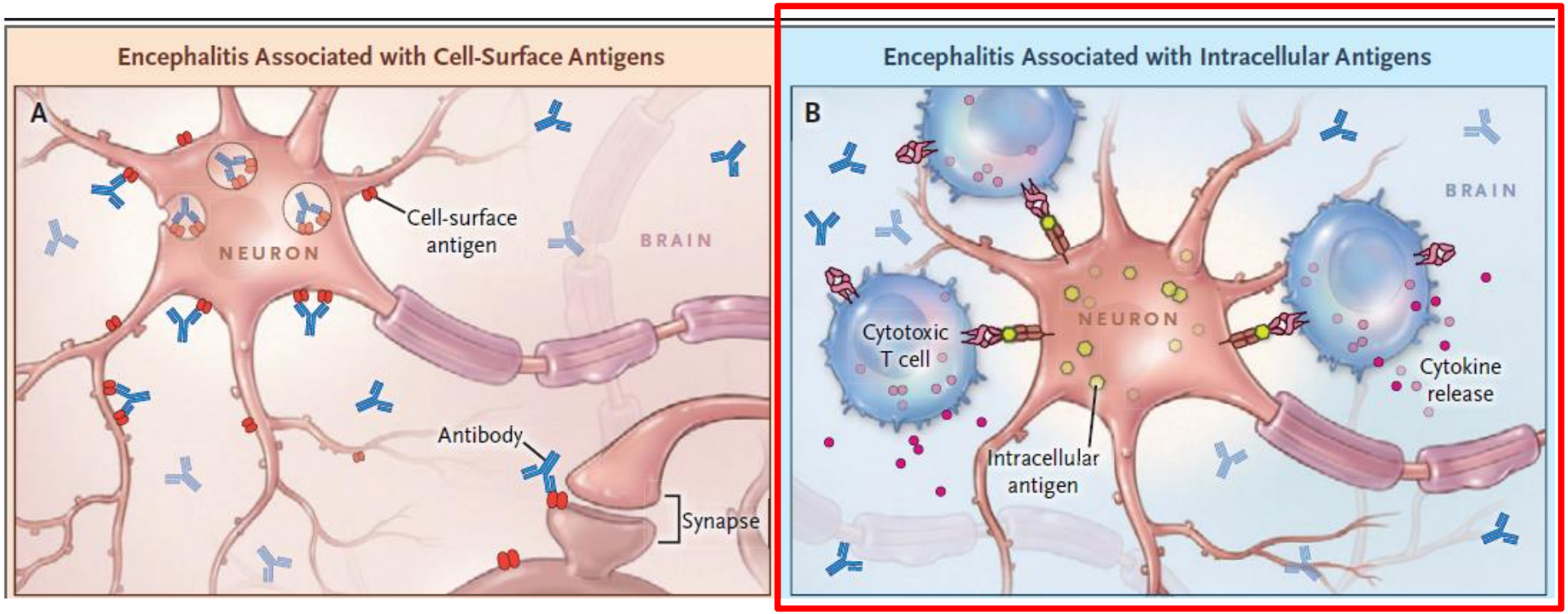
- **Opsoclonus** : mouvements oculaires conjugués, involontaires, arythmiques, multidirectionnels. Video

- **Encéphalite limbique** : survenue aiguë ou subaigue de troubles mnésiques, d'un syndrome confusionnel et/ou de crises d'épilepsie. Le début est parfois plus insidieux se manifestant par des signes d'allure psychiatriques avec anxiété, dépression, hallucinations.

- **Dysautonomie** : sub-occlusion intestinale, fièvre, hypersialorhée voire hypoventilation conduisant à une hospitalisation en réanimation.

- Stiff Person Syndrome

Tableau clinique en fonction de la cible antigénique

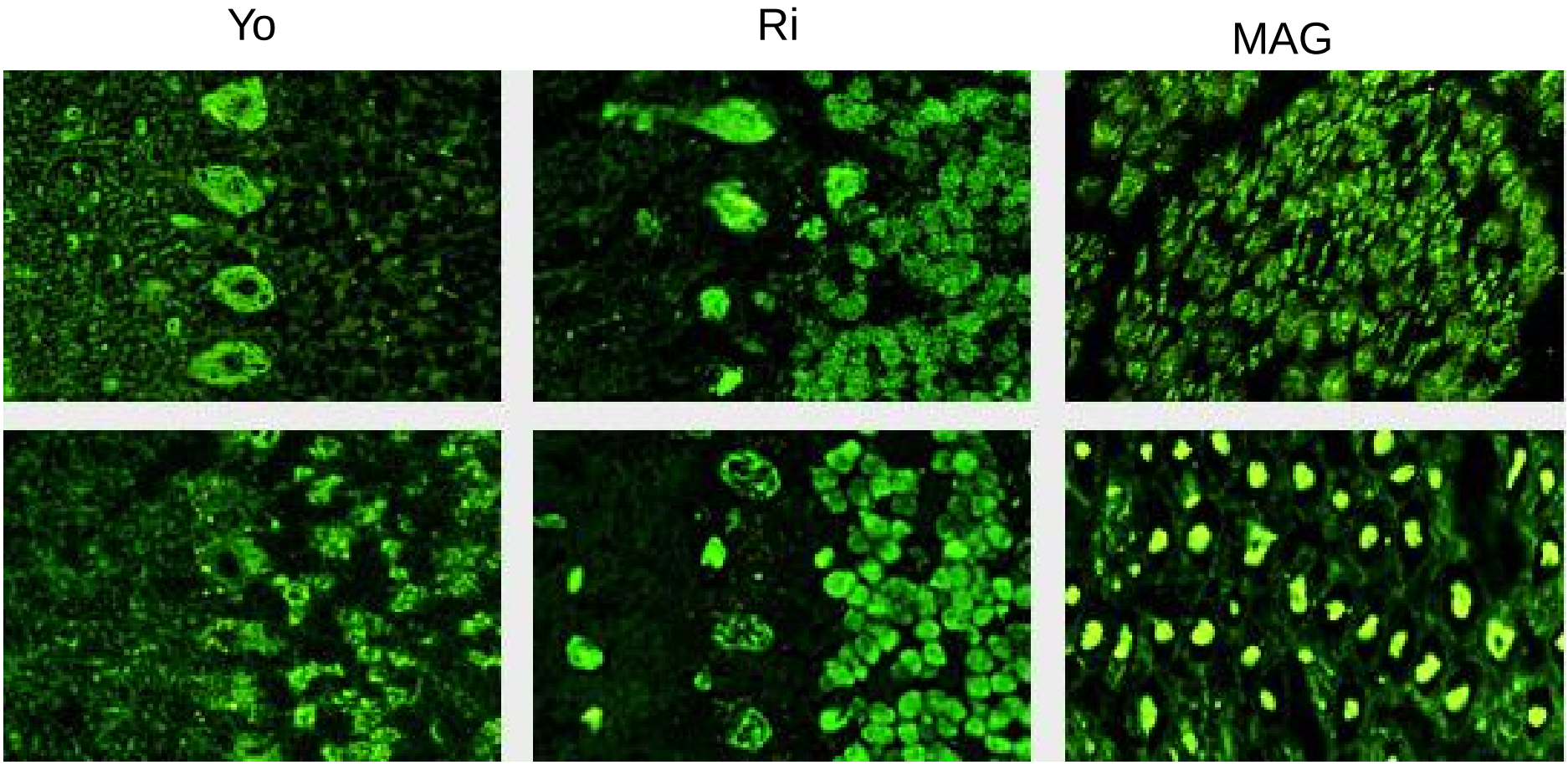


Anticorps dirigés contre antigènes neuronaux ou des cellules gliales

- Dégénerescence cerebelleuse
- Neuromyelite optique
- Stiff person syndrome

- Rarement associé aux symptomes d'encephalite

Antikörper (gegen)	Ergebnis	0 (+)	+	++	+++
Amphiphysin	neg.				
CV2	neg.				
PNMA2/Ta	neg.				
Ri	neg.				
Yo	neg.				
Hu	neg.				
Recoverin	neg.				
SOX1	neg.				
Titin	neg.				


Yo
Ri
MAG
GAD
Hu
Myelin

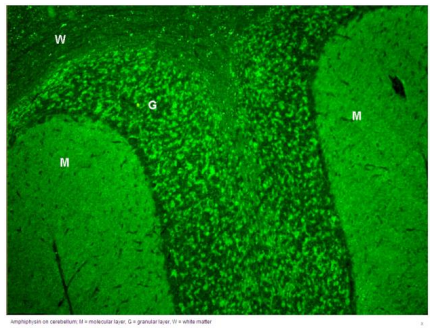
Stratégie recherche Ac anti-Neurone

Immunofluorescence indirecte
(cervelet primate +/- hippocampe/amygdale)

Négatif

Discussion avec clinicien

Positif



Ac anti-neurones
Anti-Hu, Ri, Yo,
CV2, Ma2,
Amphiphysine

Immunoblot

Anti-NMDAR, AMPAR
VGKC (LGI1, CASPR2),

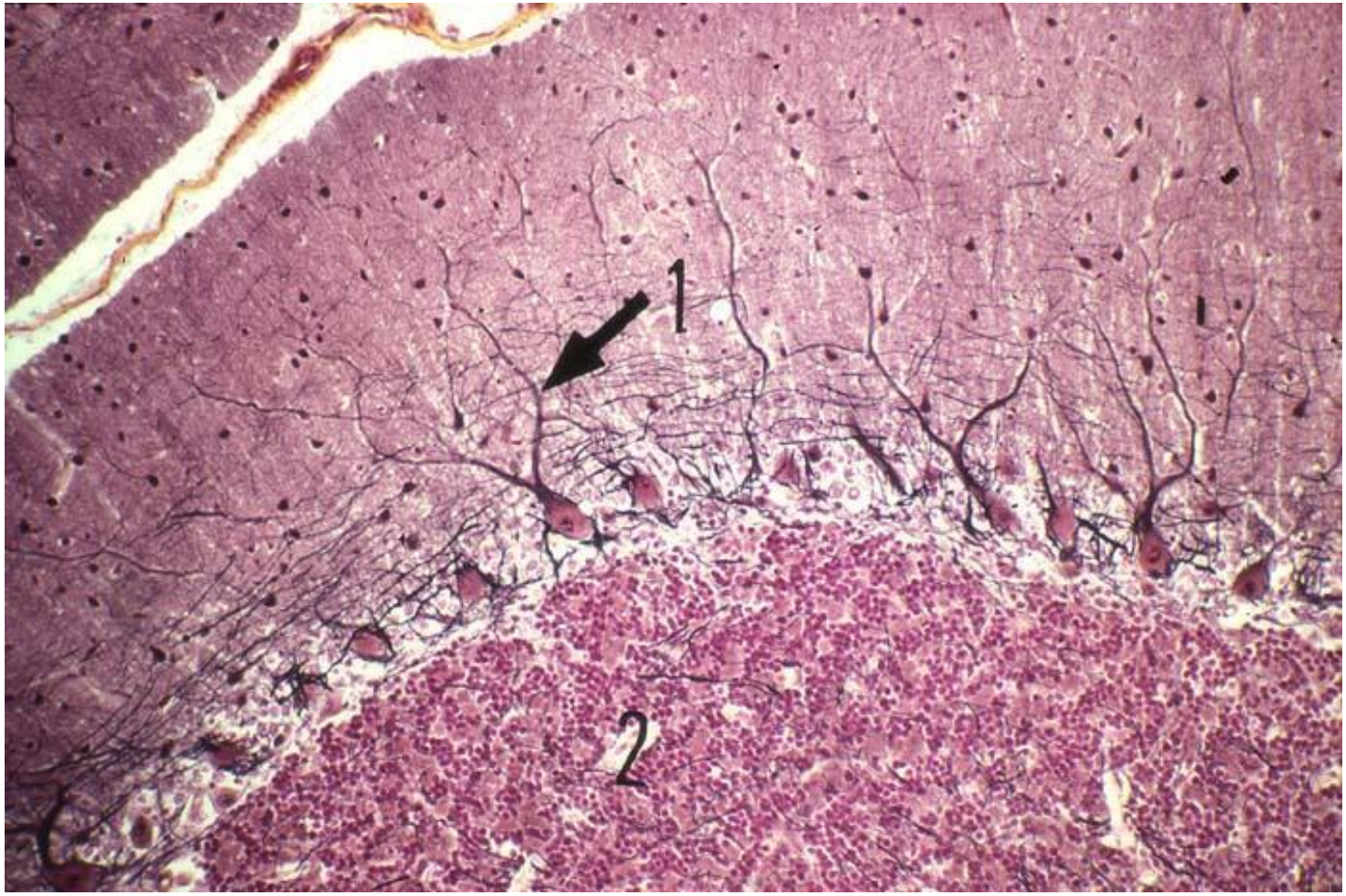
Specific
Cell based assays
(cellules transfectées)

Pattern immunofluorescence indirecte

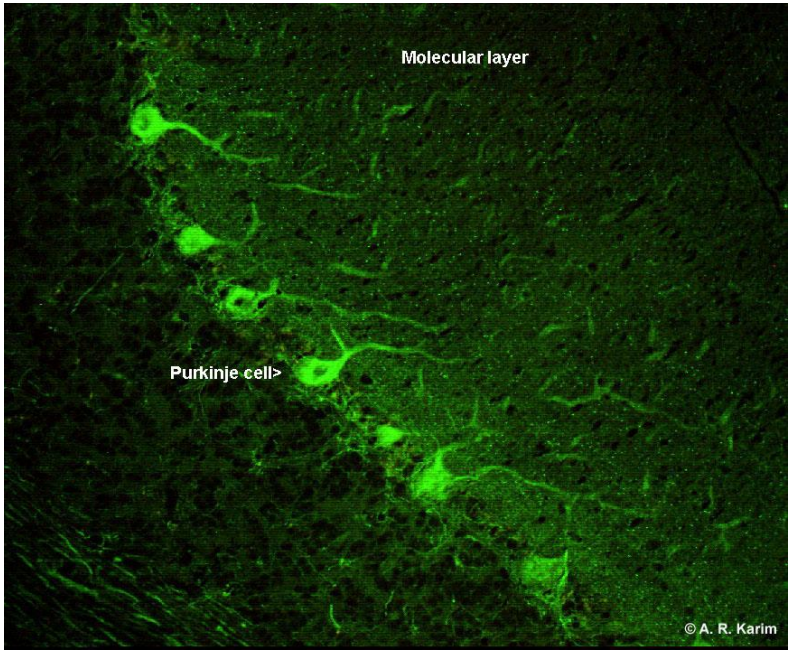
- Cytoplasme Purkinije → Yo (PCA1) ou mGluR1
- Noyaux neurones (exclure ANA) → Hu, Ri
- Cytoplasme et dendrites → PCA2
- Couche granulaire (cytopl) → GAD
- Couche moléculaire et granulaire → NMDA, AMPA, Amphiphysine
- Couche moléculaire → VGKC, GABA

Histologie du cervelet

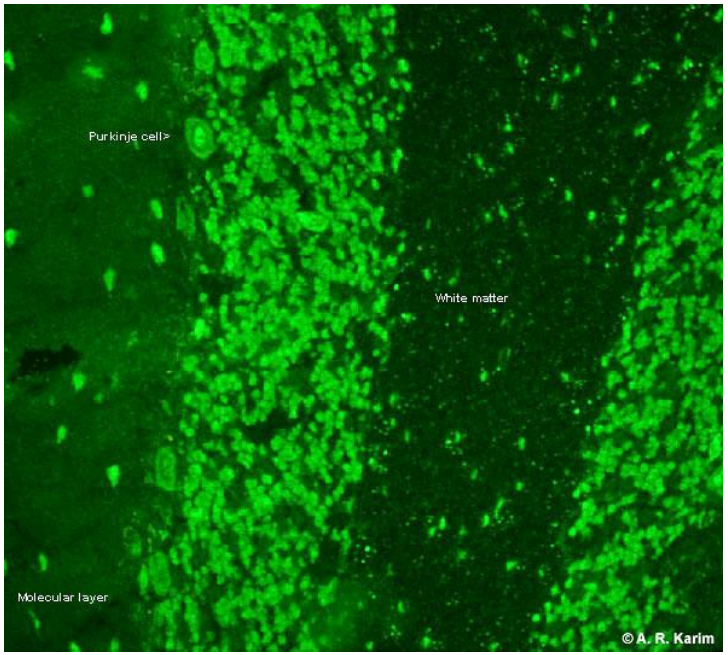
outil de screning



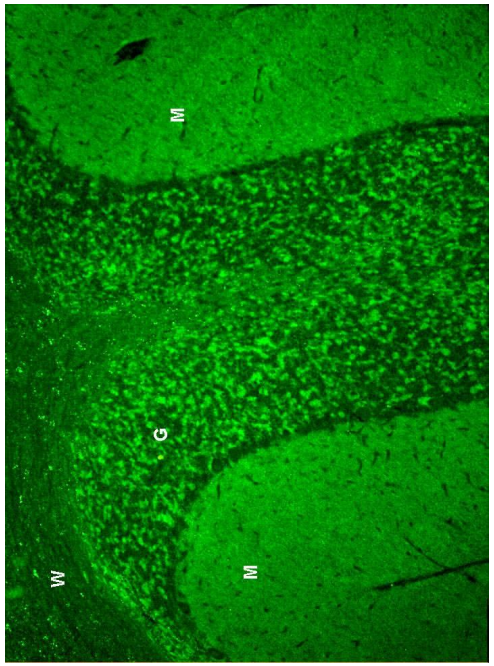
Anti-Tr



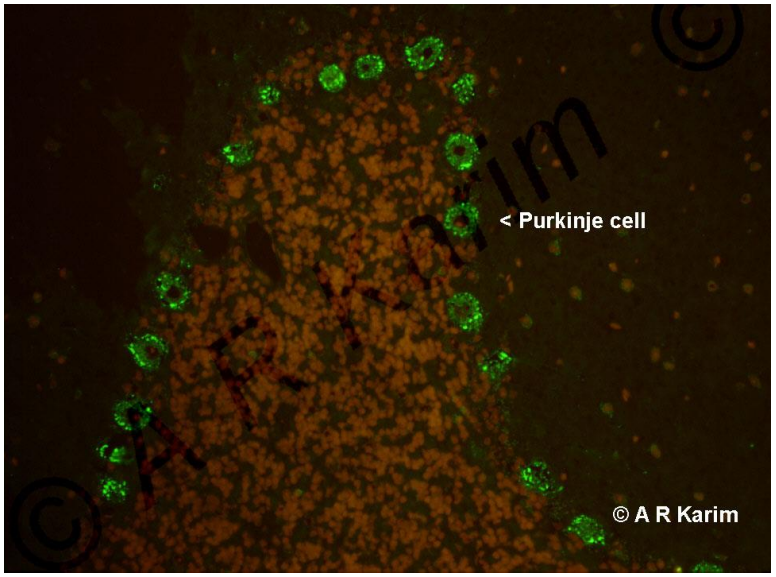
Anti-Hu



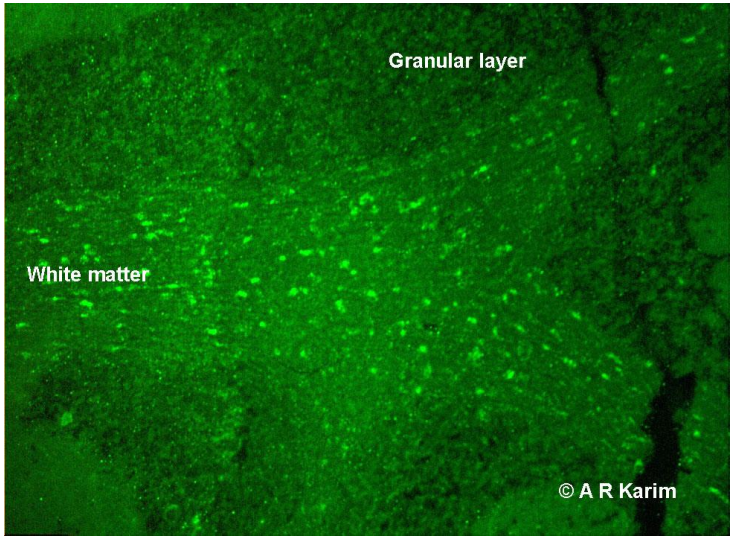
Anti-Amphyphisine



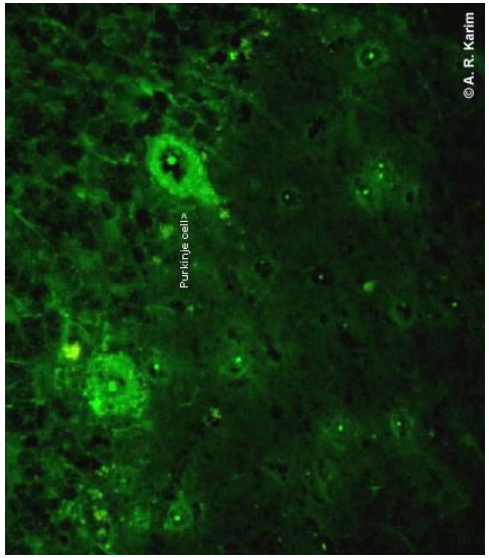
Anti-Yo



Anti-CV2



Anti-Ma1/Ma2/Ma3



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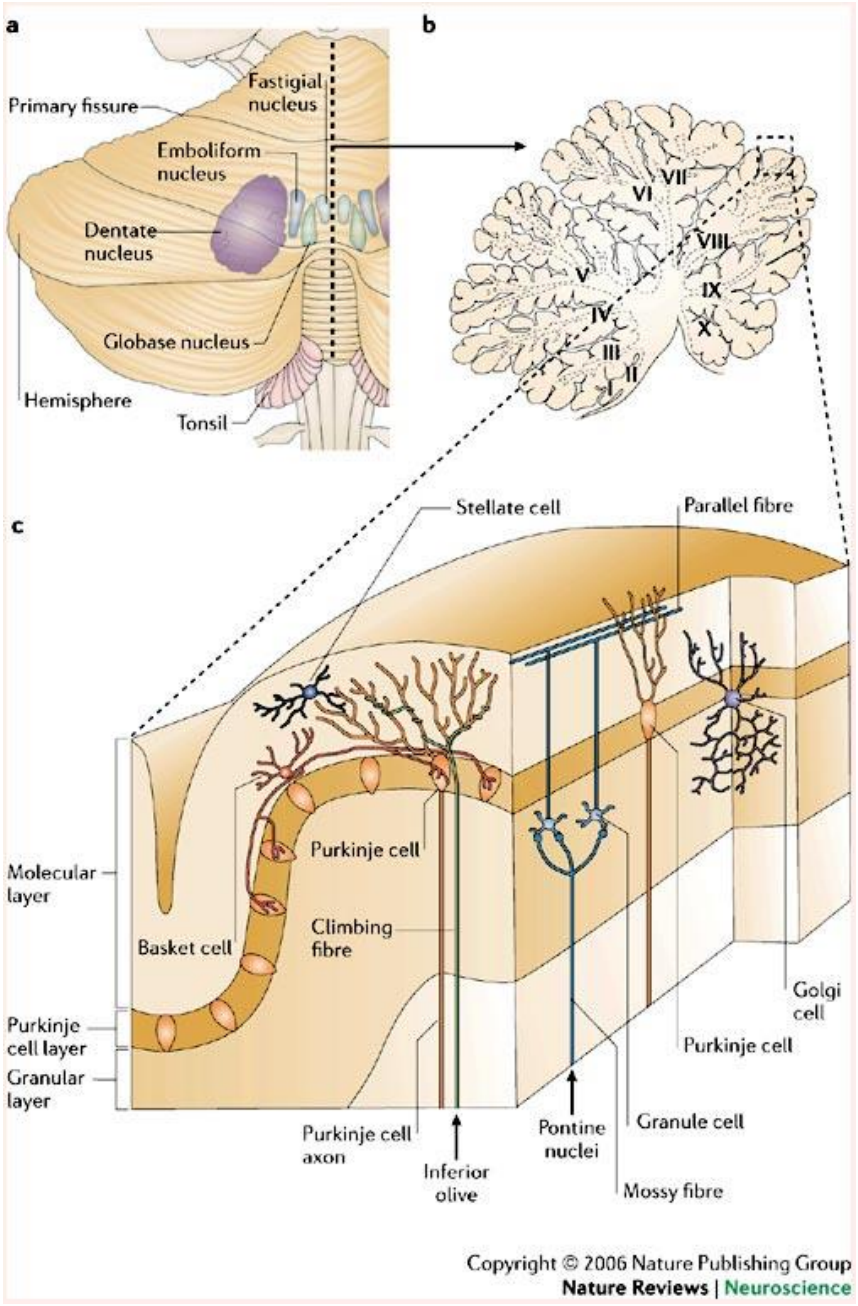
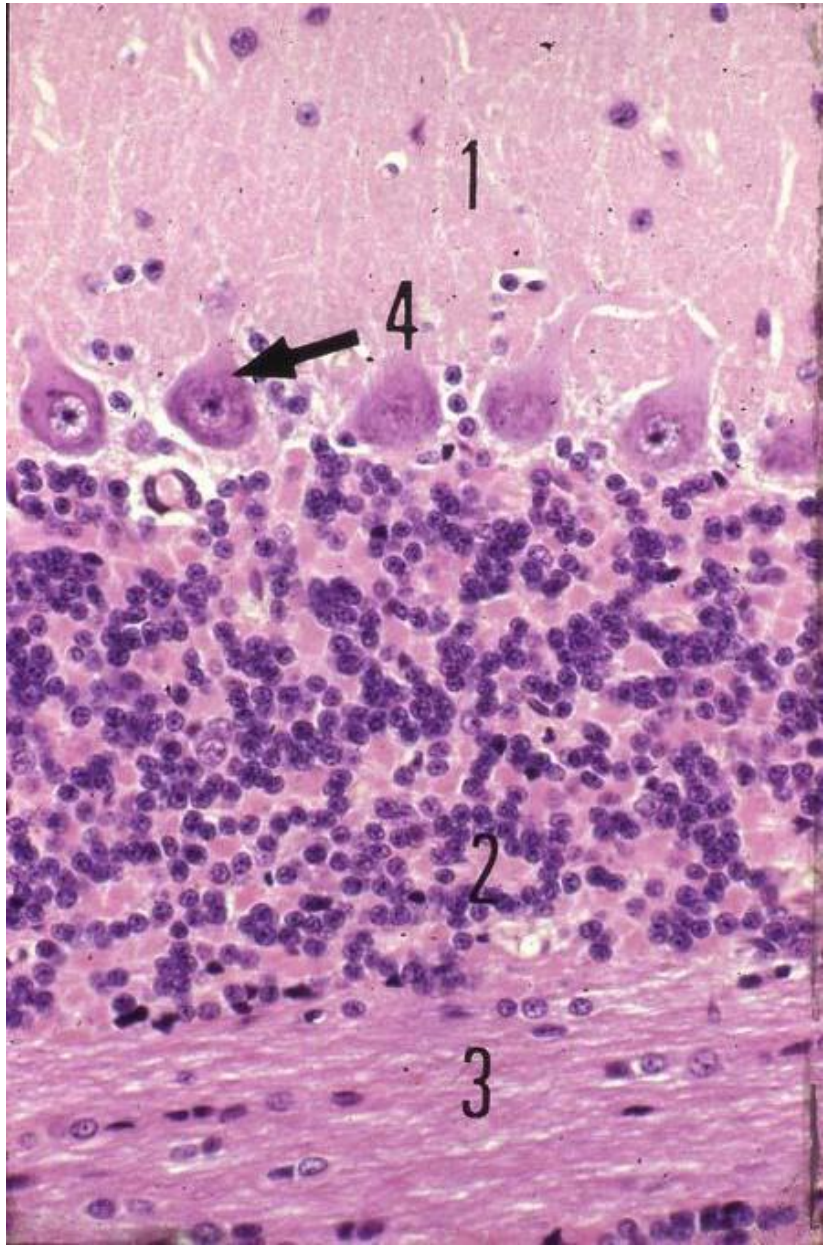
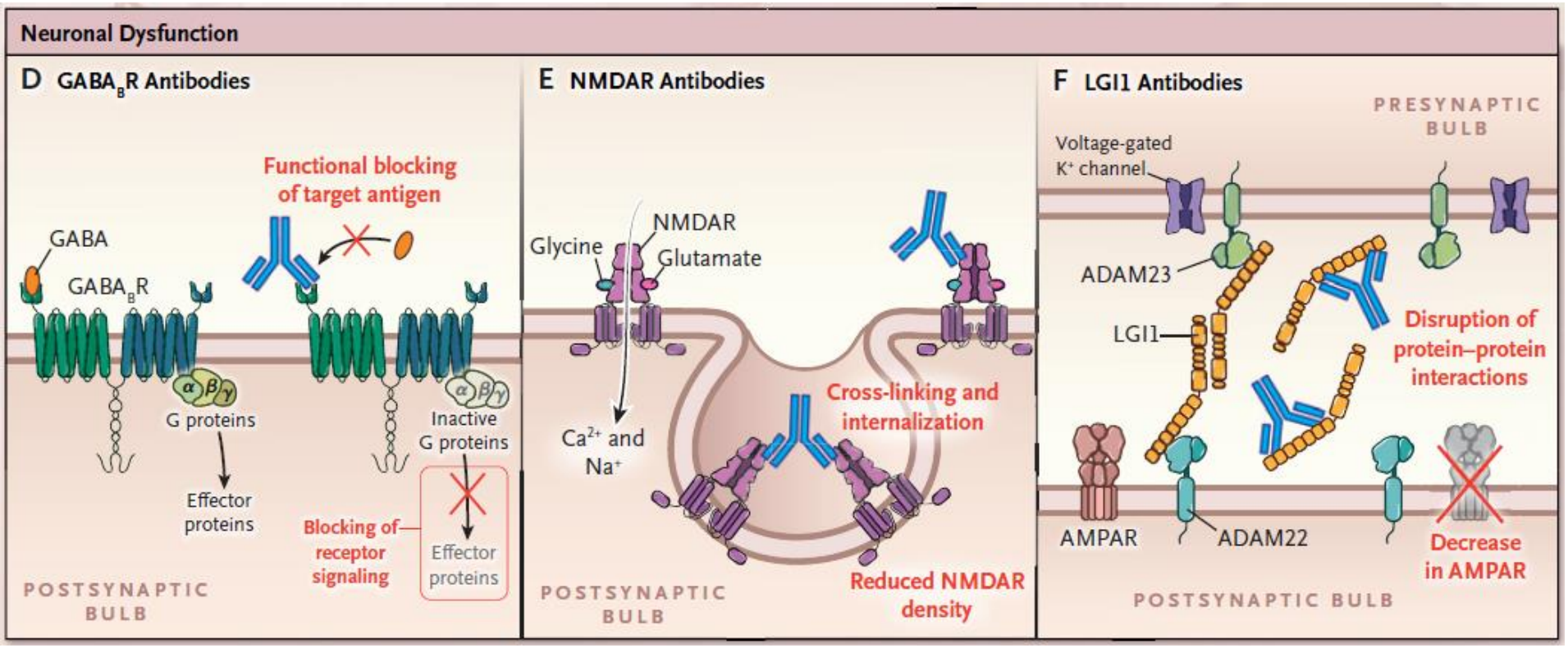
PNMA2/Ta	neg.				
Ri	neg.				
Yo	neg.				
Hu	neg.				
Recoverin	neg.				
SOX1	neg.				
Titin	neg.				

Histologie du cervelet





Mécanismes physiopathologiques



PAVAL / Paraneoplastic Autoantibody Evaluation, Serum

Always performed

Immunofluorescence (IFA)
- Anti-Neuronal Nuclear Ab, Type 1
- Anti-Neuronal Nuclear Ab, Type 2
- Anti-Neuronal Nuclear Ab, Type 3
- Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1), Serum
- Purkinje Cell Cytoplasmic Ab Type 1
- Purkinje Cell Cytoplasmic Ab Type 2
- Purkinje Cell Cytoplasmic Ab Type Tr
- Amphiphysin Ab
- CRMP-5-IgG

Enzyme-Linked Immunosorbant Assay (ELISA)
- Striational (Striated Muscle) Ab*

Radioimmunoprecipitation (RIA)
- P/Q-Type Calcium Channel Ab
- N-Type Calcium Channel Ab
- ACh Receptor (Muscle) Binding Ab*
- AChR Ganglionic Neuronal Ab
- Neuronal Voltage-Gated Potassium Channel Complex (VGKC) Autoantibody, Serum

If ACh Receptor (Muscle) Binding Ab is >0.02 nmol/L or Striational Ab is ≥1:60

ACh Receptor (Muscle) Modulating Ab and CRMP-5-IgG Western Blot**

IFA pattern suggests Amphiphysin Ab

Amphiphysin Western Blot**

IFA pattern suggests NMO-IgG

NMO-IgG Assay**

IFA pattern suggests GAD65 Ab

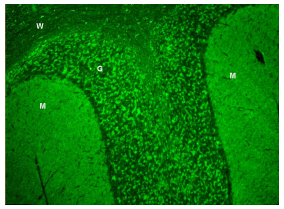
GAD65 Ab Assay**

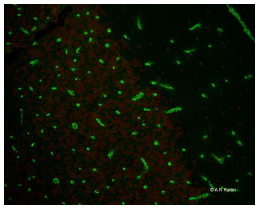
IFA pattern suggest CRMP-5-IgG or client requests

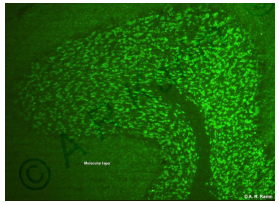
CRMP-5-IgG Western Blot**

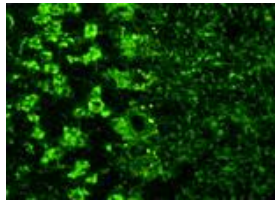
IFA pattern indeterminate

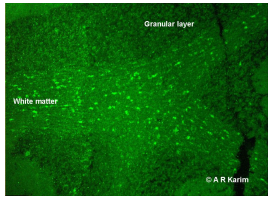
Paraneoplastic Autoantibody Western Blot**



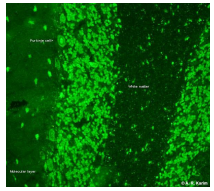




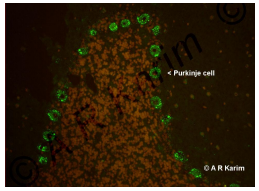




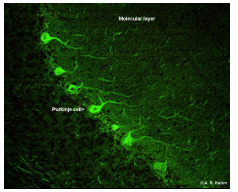
ANNA1 (Hu)



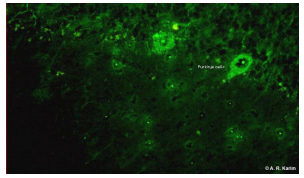
PCA1,2 (Yo)

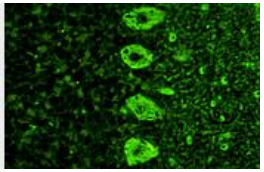


Tr



Ma(1,2,3)

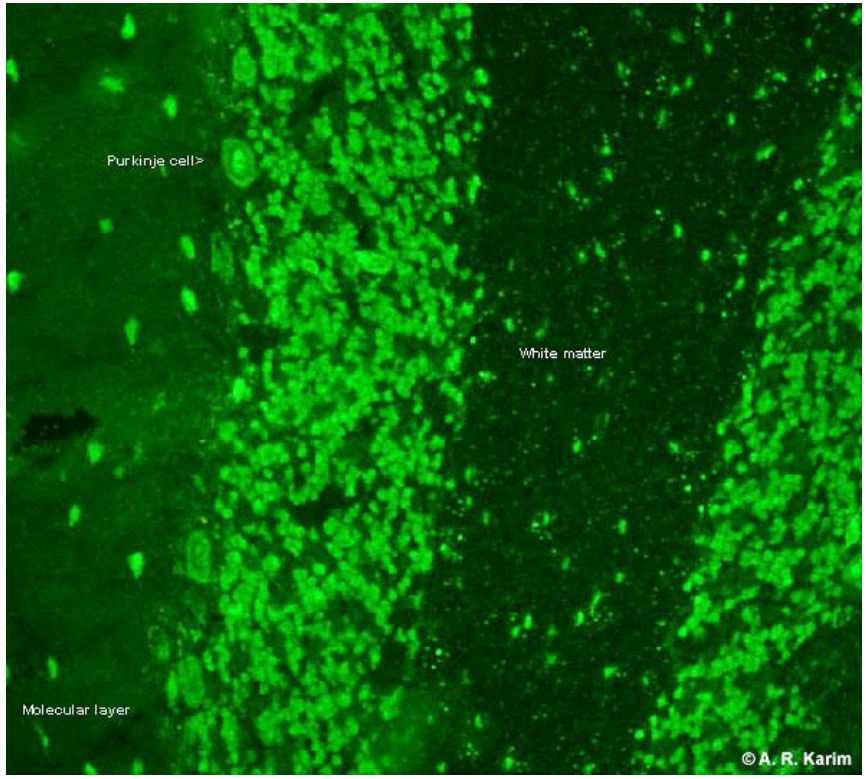




Syndromes cerebelleux

syndromes paraneoplasiques

Ri (ANNA2) antibodies



Rare antibodies (IgG)

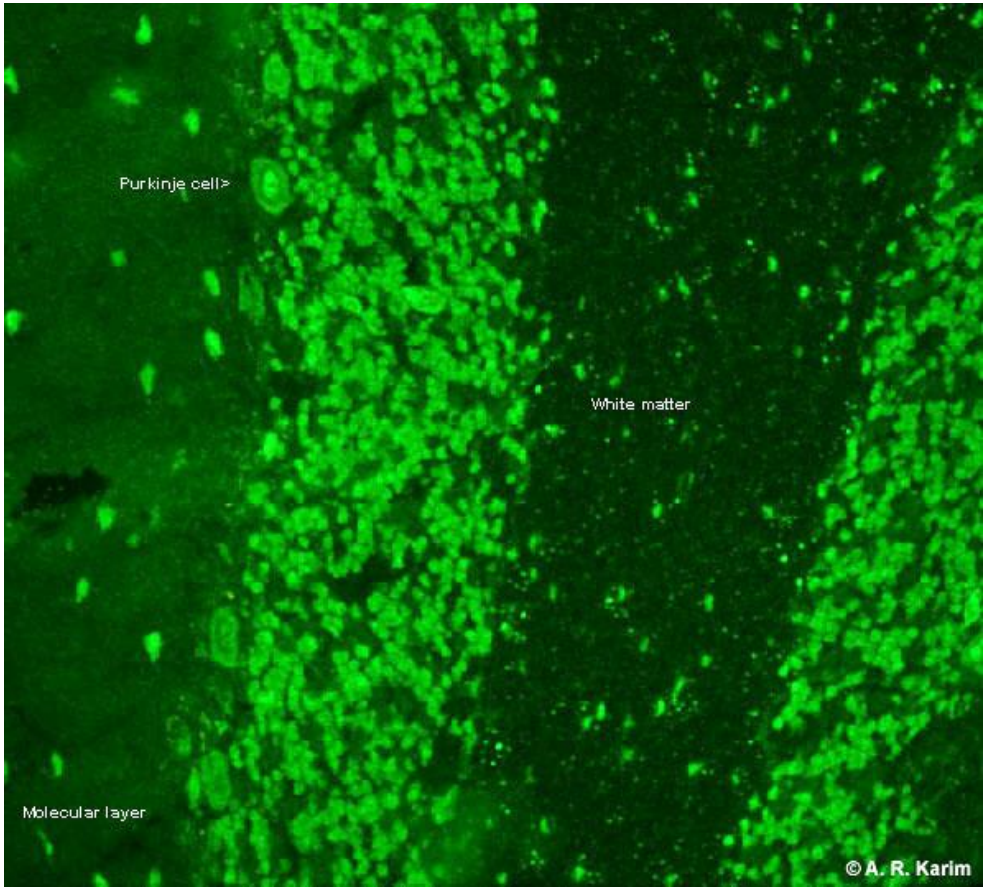
Similar staining pattern as anti-Hu antibody

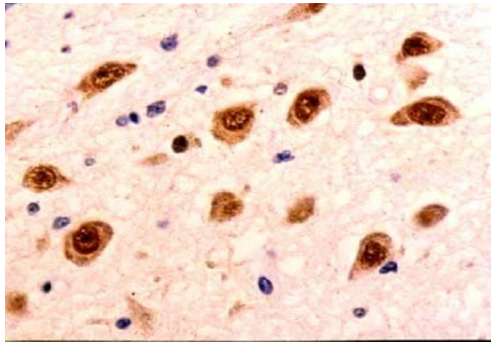
Antibody binds to CNS but not PNS neurones (myenteric neurones stain negative)
A high intensity signal at both 55 and 80 kDa on a Western blot would confirm Ri specificity.

Neurological syndrome: Cerebellar degeneration, opsoclonus/myclonus

Associated tumours: Breast, gynaecological and small cell lung carcinoma

Anti Hu (ANNA1) antibodies





Hu antibody binds to the granular and Purkinje neurones

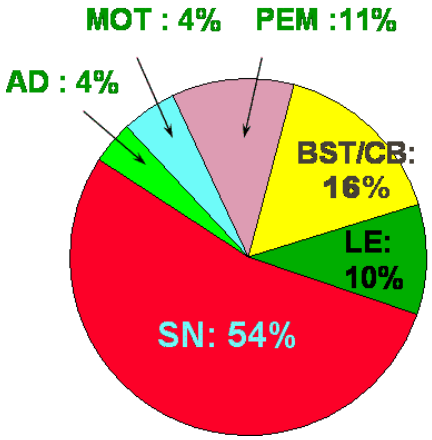
This is the most commonly occurring paraneoplastic neurological antibody.

Neurological syndrome: Cerebellar ataxia, encephalomyelitis, sensory neuropathy

Associated tumour: Small cell lung carcinoma and neuroblastoma

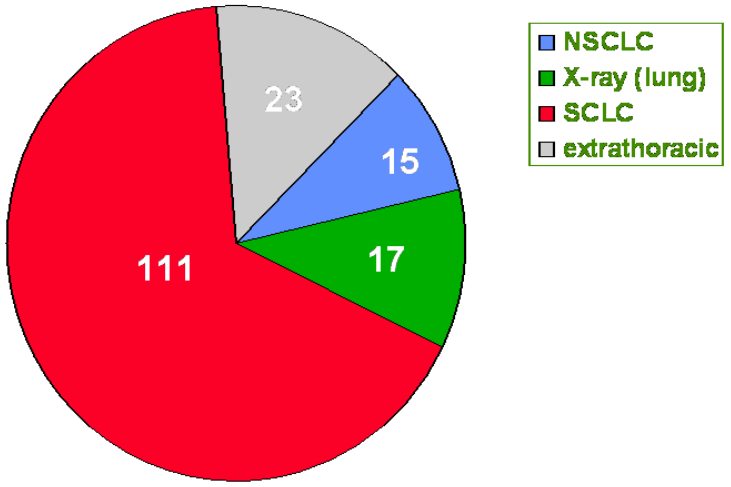
Anti Hu (ANNA1) antibodies

Initial syndrome in 200 patients with Hu-Ab



- SN: Sensory neuropathy (108)
- MOT: Motor weakness (9)
- AD: Autonomic dysfunction (8)
- PEM: Multifocal (22)
- LE: Limbic encephalitis (20)
- BST: Brainstem dysfunction (12)
- CB: Cerebellar syndrome (21)

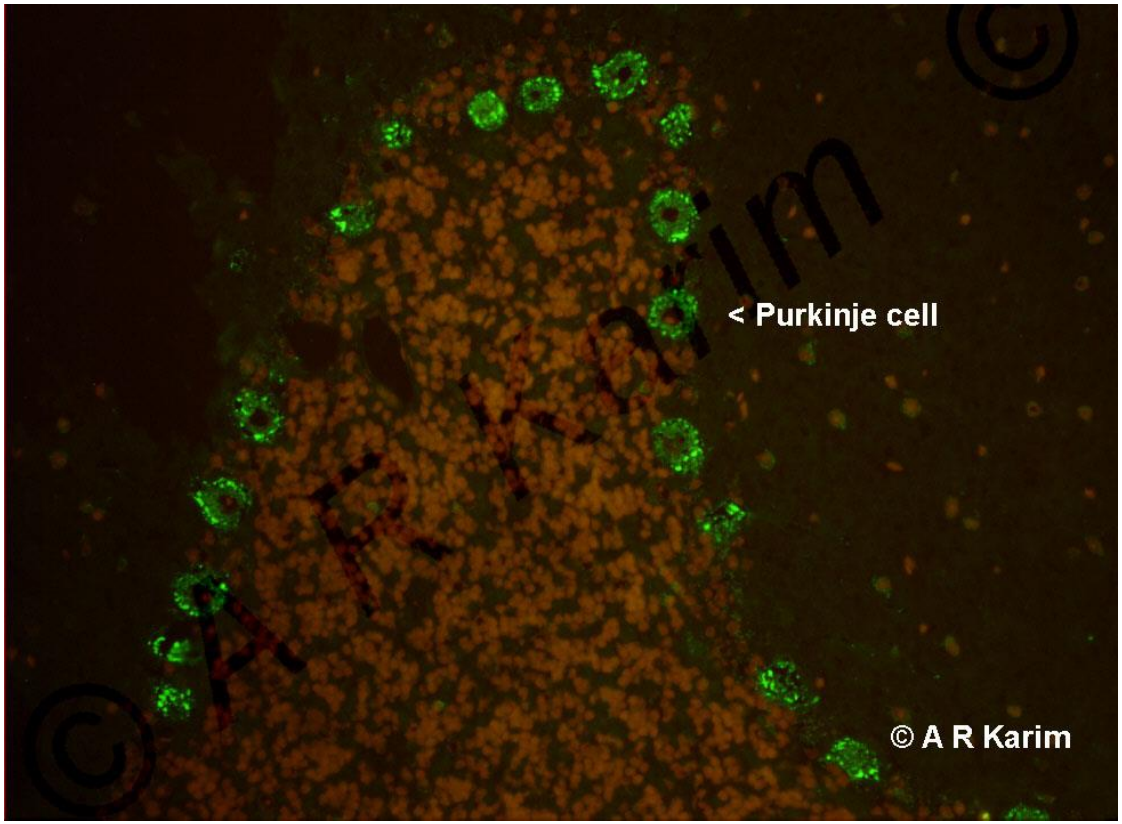
Location and histologic tumor diagnosis in 167 anti-Hu-positive patients



SCLC: small-cell lung carcinoma; NSCLC: Non-SCLC

Patients with paraneoplastic syndromes and anti-Hu antibodies may develop concurrent antibodies to other onconeuronal antigens. They include, anti-CV2 (CRMP5), anti-amphiphysi, anti-Ri, anti-VGCC, or anti-Zic4 antibodies.

Yo (PCA-1) antibodies

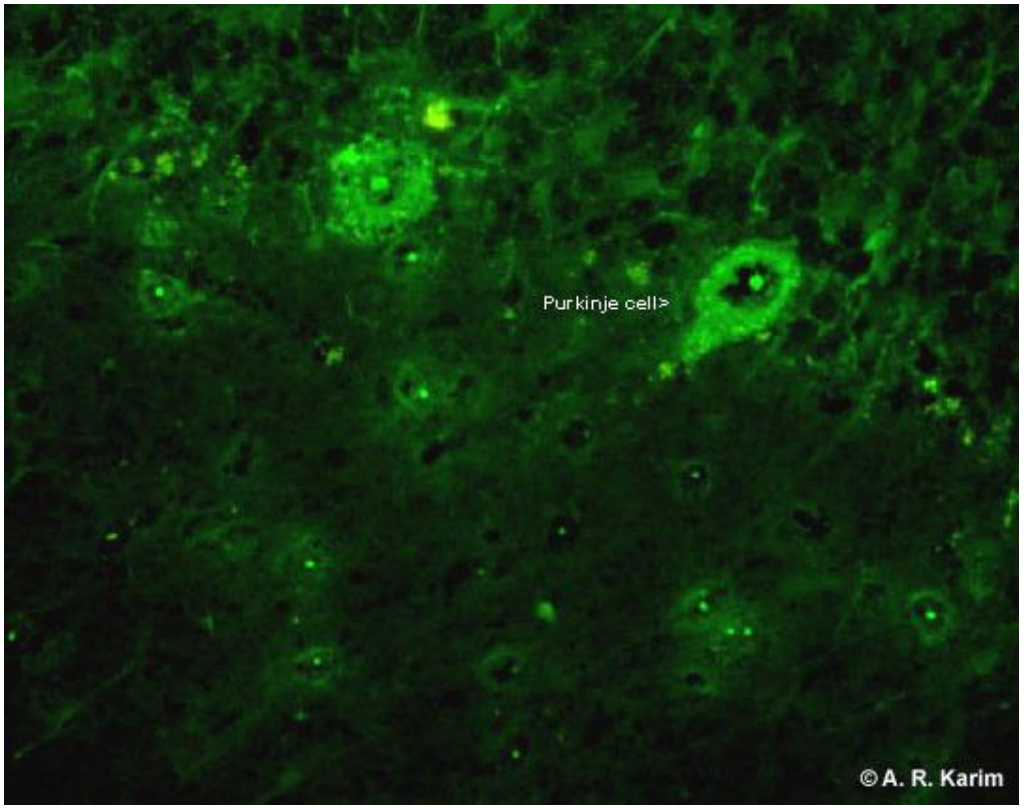


Yo antibody (also known as Purkinje cell antibody type 1 (PCA-1)) reacts with primate cerebellum with coarse granular staining of the Purkinje cell cytoplasm. This reaction must be confirmed with Western blot/line blot.
Clinical indication: Cerebellar degeneration

Associated tumours: Breast and ovarian carcinomas. With only few exceptions PCA are found exclusively in female patients.

Ma antibodies

similar pattern of distribution on the cerebellum. All three antibodies can coexist with each other and this i



Tumour: Ma1: Various tumours. Ma2 usually found in younger males with testicular tumour.

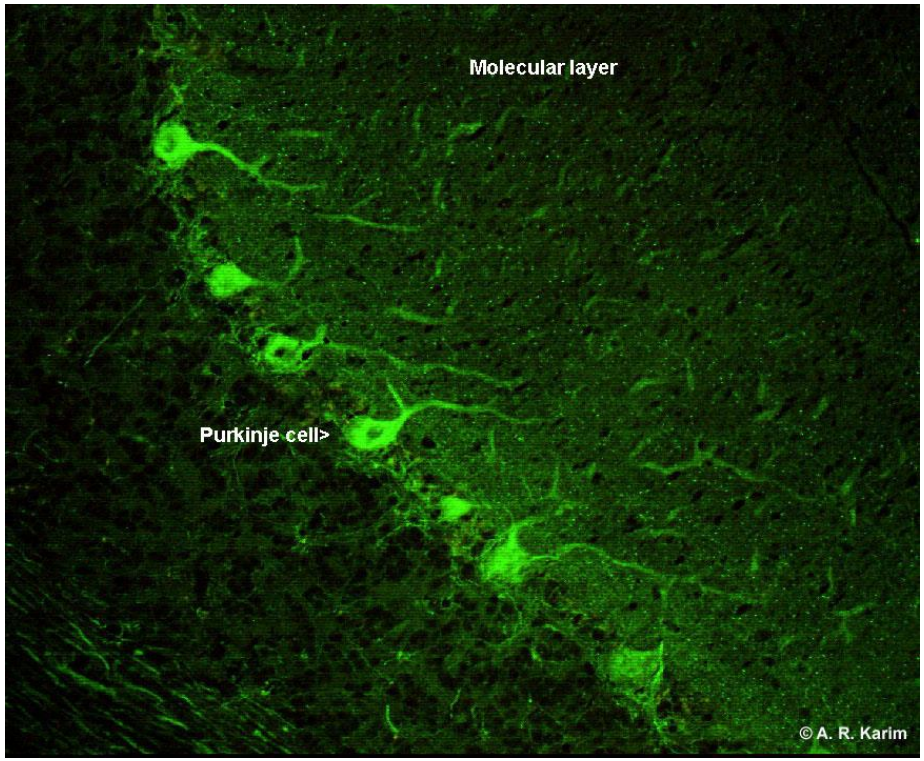
Syndrome: Ma1: Brainstem/cerebellar syndrome. Ma2; Brainstem, cerebellar, limbic signs.

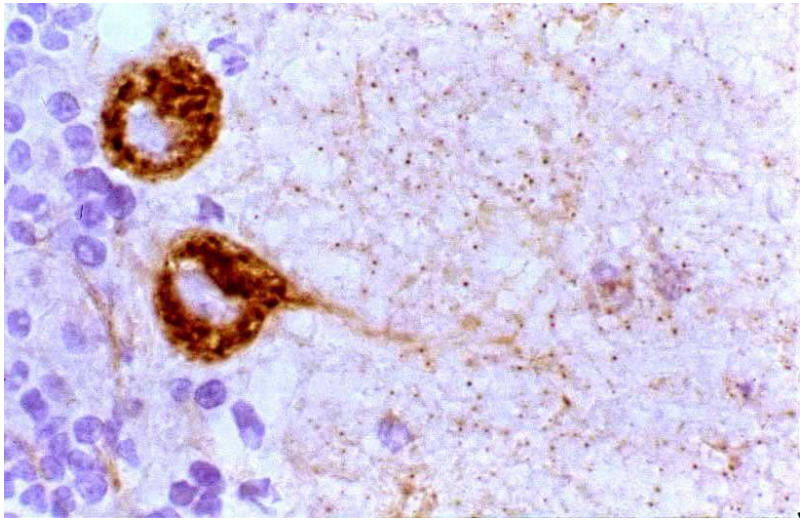
Cerebellum: Ma is located in nucleoli of the molecular and Purkinje neurones. Nucleolar ANA must be eliminated as it produces similar pattern as Ma. This type of distribution can also be seen with non Ma sera of undetermined significance

Tumour: Ma1: Various tumours. Ma2 usually found in younger males with testicular tumour.

Syndrome: Ma1: Brainstem/cerebellar syndrome. Ma2; Brainstem, cerebellar, limbic signs.

Tr antibodies





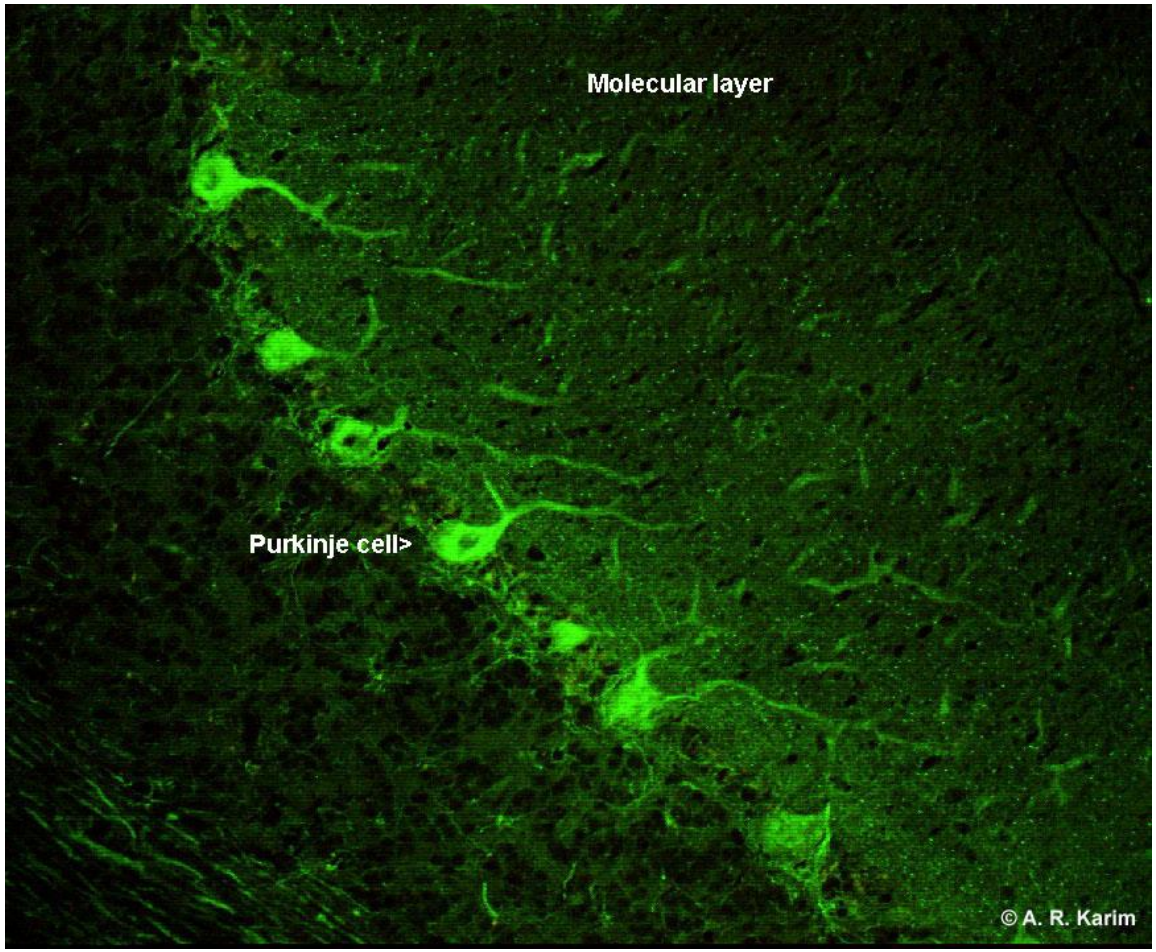
Primate cerebellum: Anti-Tr IgG stains the cytoplasm of Purkinje cells together with the dendrites. In the molecular layer, punctate (dotted) pattern further distinguishes from Yo. The staining in the Purkinje cells is finer than that of anti-Yo antibodies. The identification of Tr is based on immunocytochemical distribution alone, as no common band has been identified by Western blot analysis.

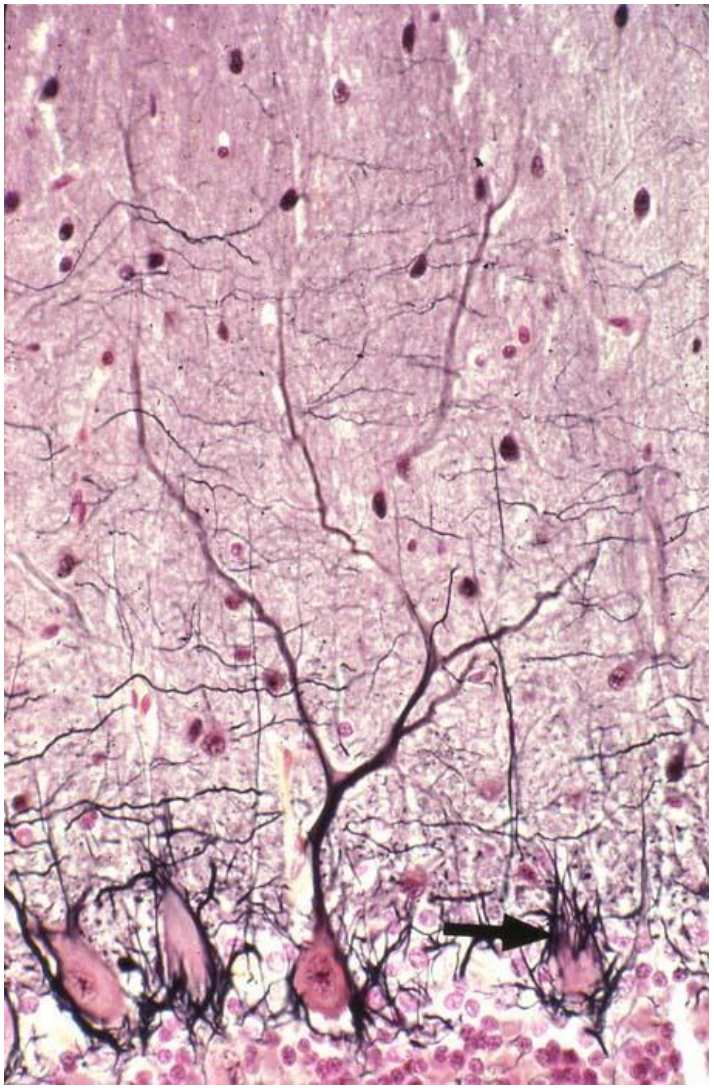
Associated tumour: Hodgkin's disease

Neurological syndrome: Cerebellar degeneration

There are several antibodies (for example, Yo, PCA-2 and Tr) which have different specificities yet react with Purkinje cell cytoplasm thus producing a similar immunofluorescence distribution pattern. For this reason it can be difficult to differentiate between them by immunofluorescence alone. Alternative methods (such as Western blot) must be employed to confirm specificity of the antibody.

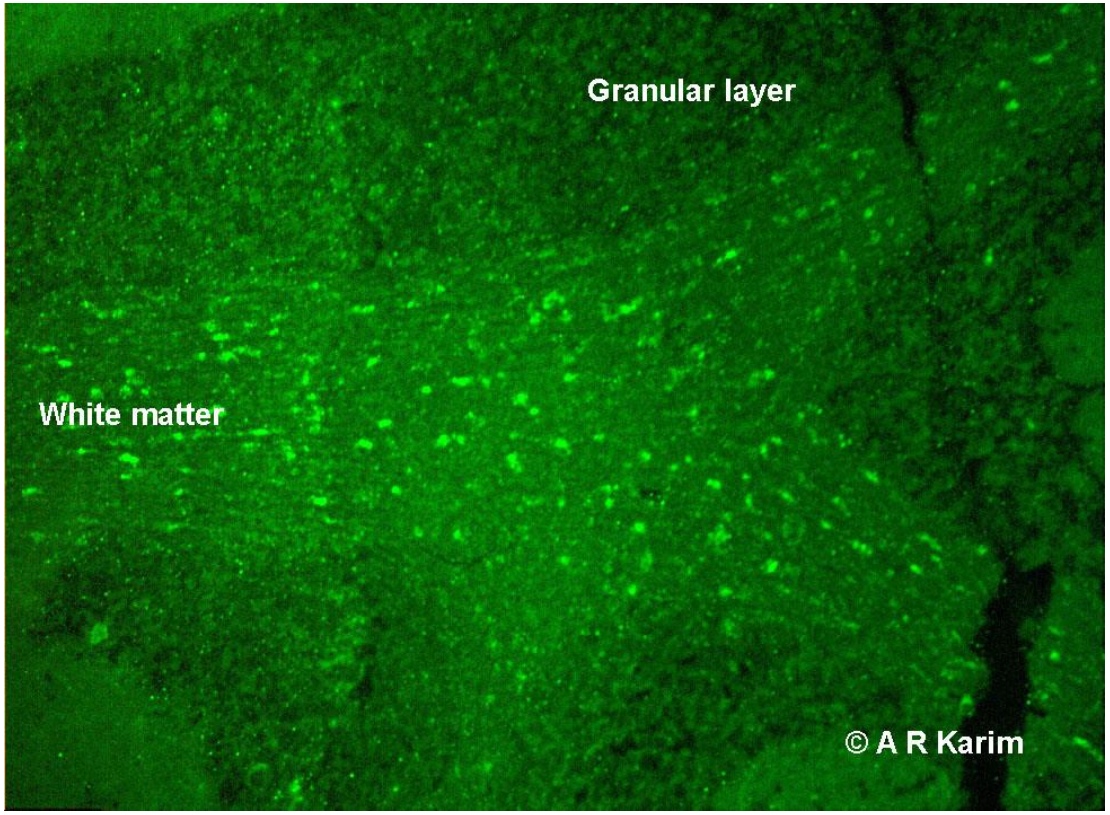
Tr antibodies





Confirmatory test:
Not available. Antibody not detected by immunoblot

CV2/CRMP5 antibodies



CV2/CRMP5 is a 66 kDa protein found in the cytoplasm of oligodendrocytes in the white matter When this antibody was first described, it was called CV2 and now it also known by its antigenic protein (collapsing response mediator protein 5; i.e CRMP5)

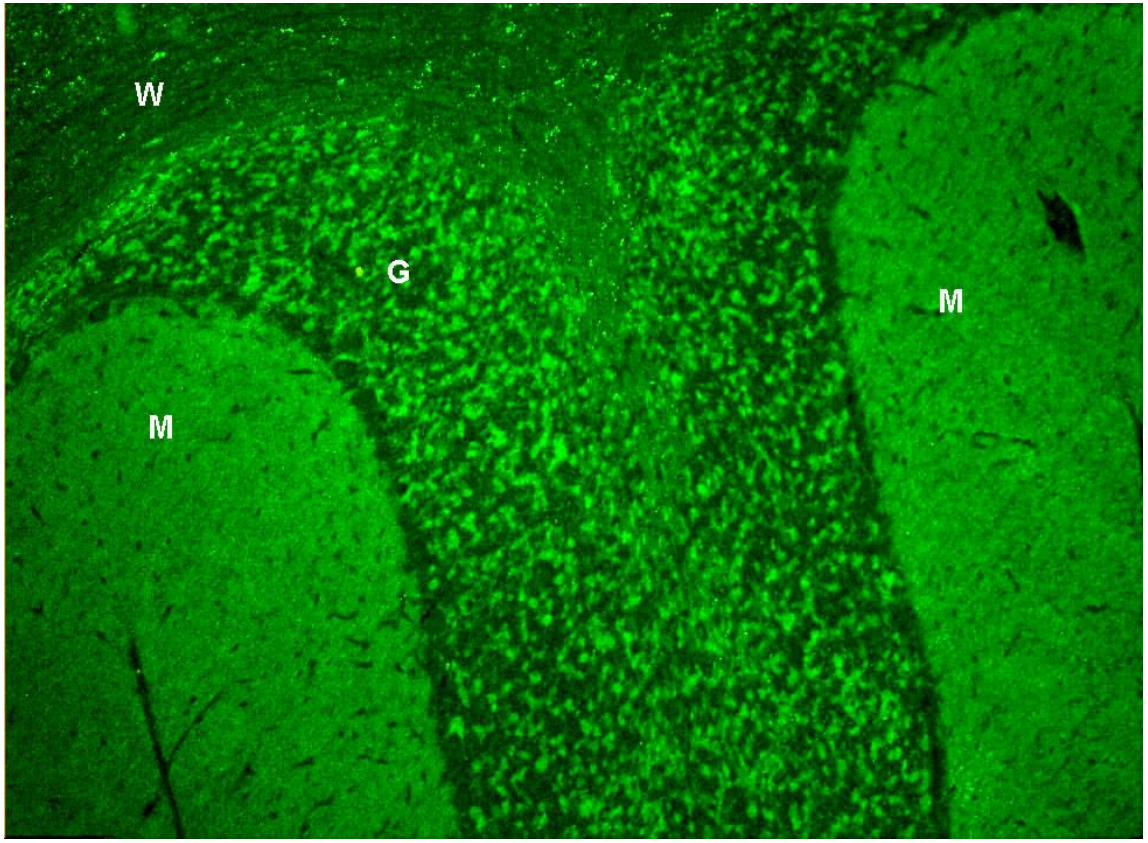
Clinical conditions: Paraneoplastic encephalomyelitis/sensory neuropathy

Associated tumours: Thymoma, small cell lung carcinoma.

Stiff person syndrome

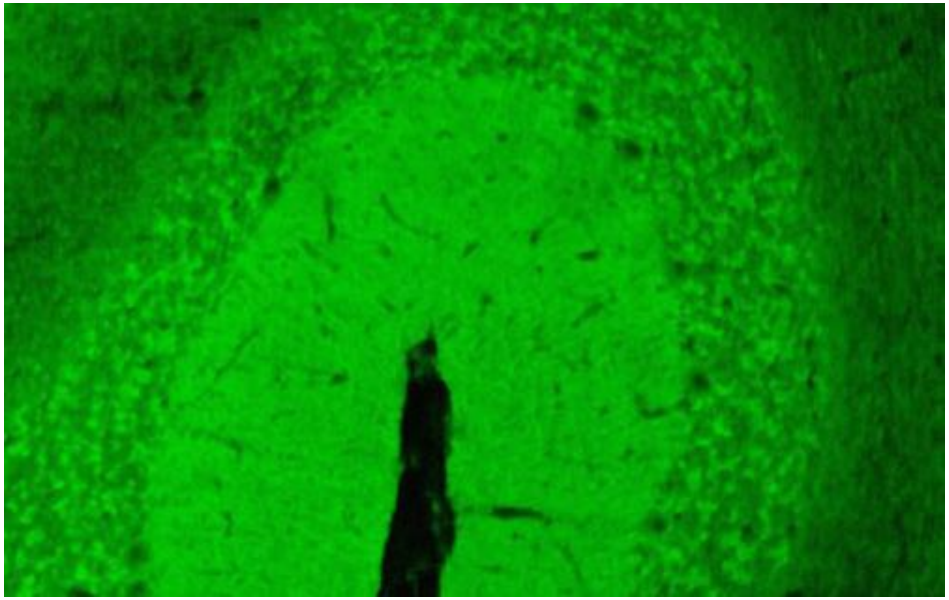
Patient rigid in moderate opisthotonos, with arms

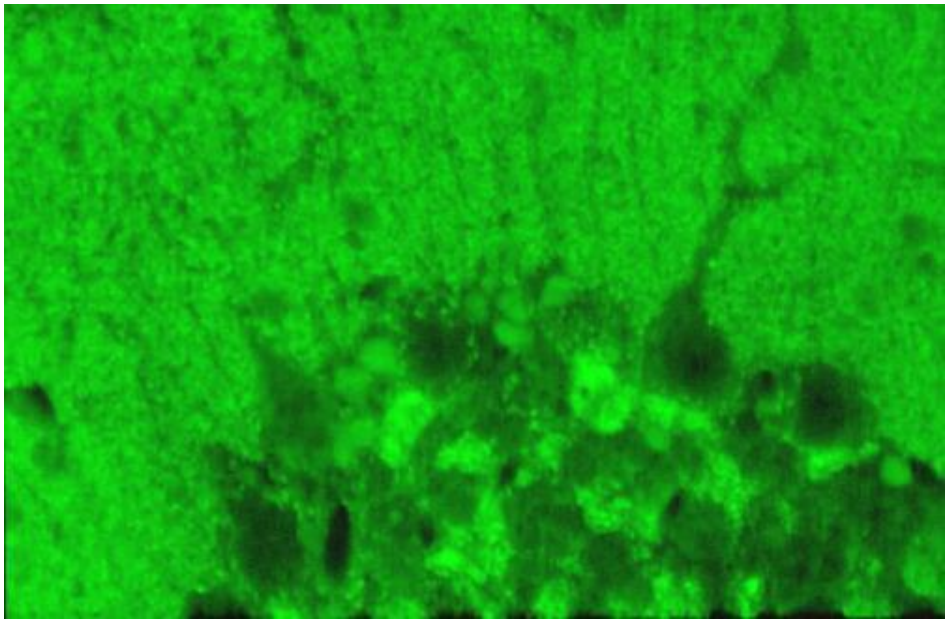
Anti Amphiphysine

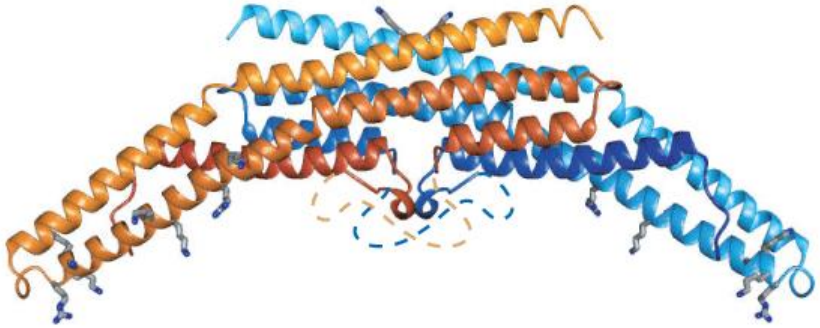


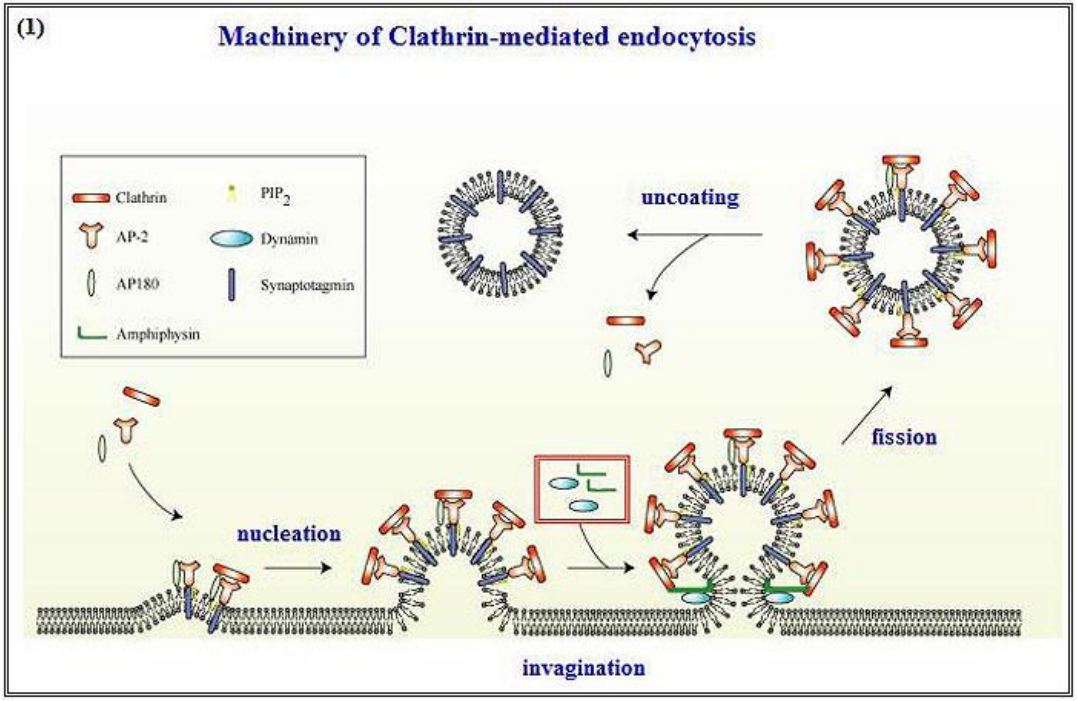
Amphiphysin (128 kDa dimeric, synaptic protein) is found in cerebellar presynaptic nerve terminals.
The cell processes in the molecular layer are stained more intensely than the nerve terminals in the granular layer. The pattern in the granular layer resembles that of GAD.
Amphiphysin can also coexist with Hu, CV2 or PCA-2.
Clinical conditions: Stiff person's syndrome (5%), paraneoplastic encephalomyelitis.
Associated tumours: Most common malignancies are small cell lung carcinoma and breast cancer

Anti Amphiphysine



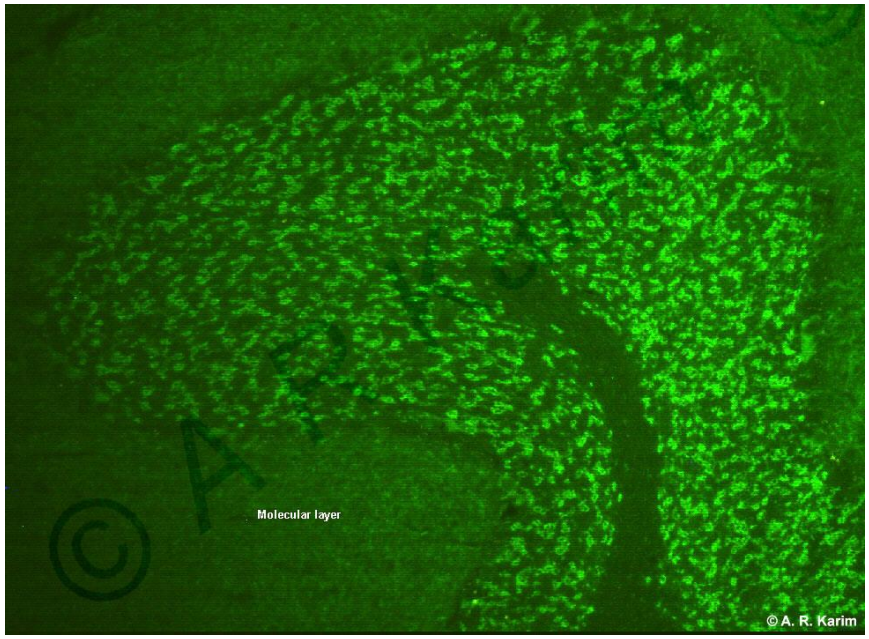


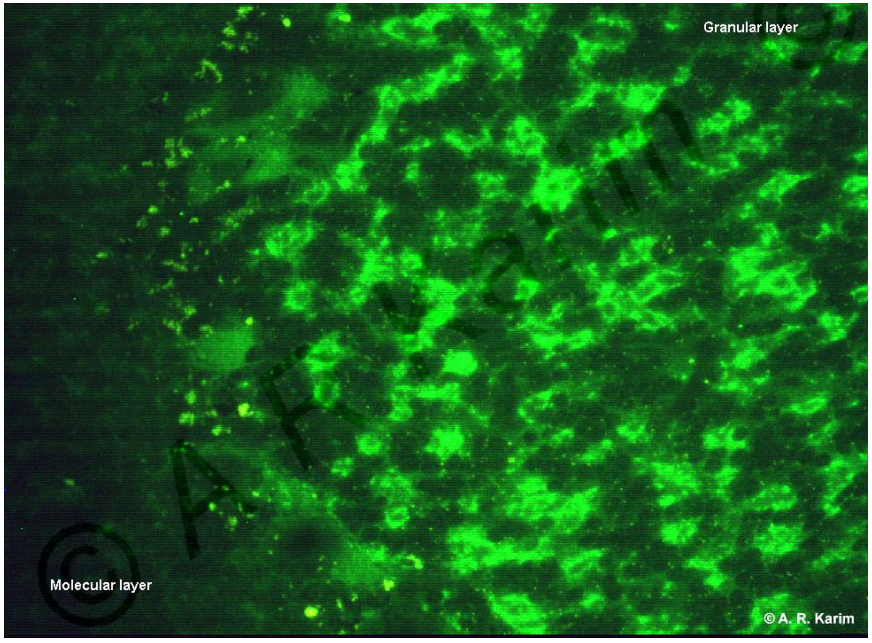




Amphiphysin belongs to the BAR (Bin-Amphiphysin-Rsvsp) family proteins. There are two isoforms, amphiphysin I and II. Amphiphysin I is the antigen recognized by anti-amphiphysin antibodies that occur in paraneoplastic neurological syndromes. Amphiphysin I is a presynaptic protein that play a key role in clathrin-mediated endocytosis of synaptic vesicles released in the presynaptic terminals.

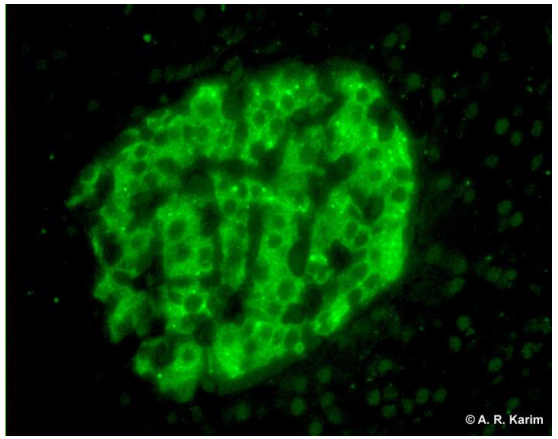
Anti GAD



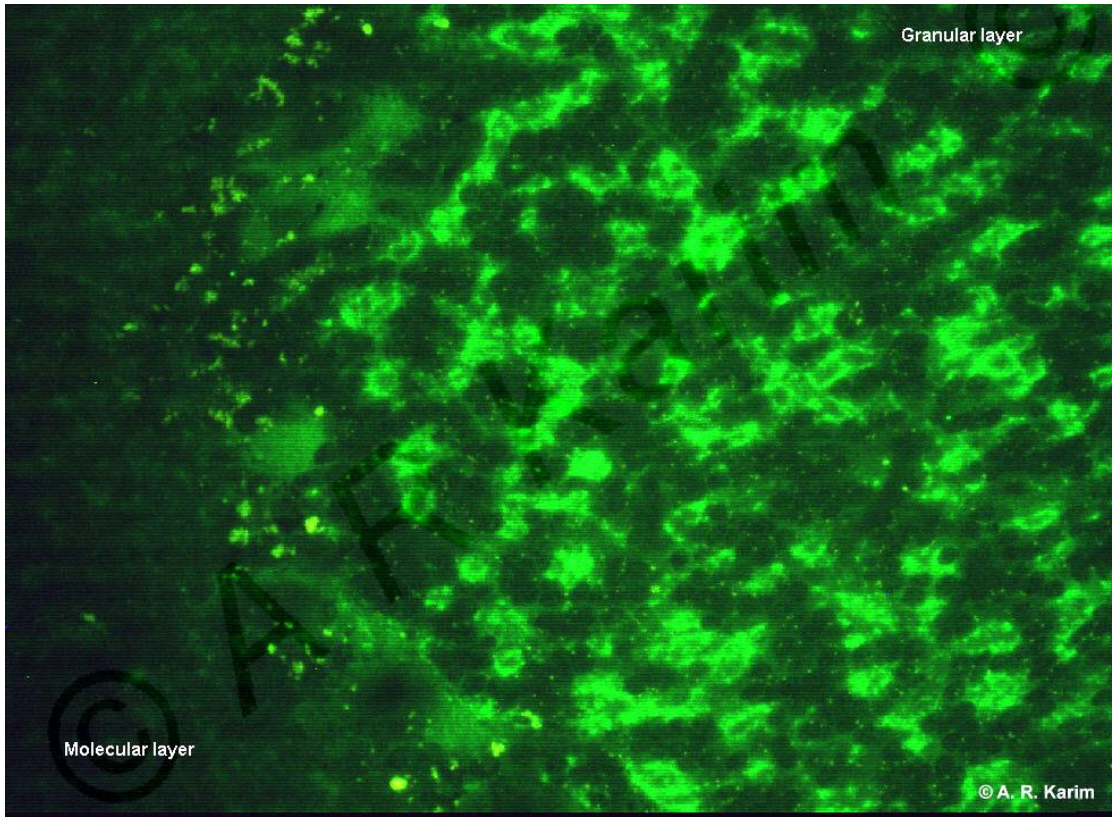


Low magnification: GAD staining the granular layer in the primate cerebellum. In contrast to amphiphysin there is a lack of staining in the molecular layer.

Neurological syndrome: Stiff personôs syndrome or diffuse hypertonia. GAD has also been reported in cerebellar ataxia, epilepsy and myoclonus.
Tumour associated: Breast, colon, small cell lung carcinoma



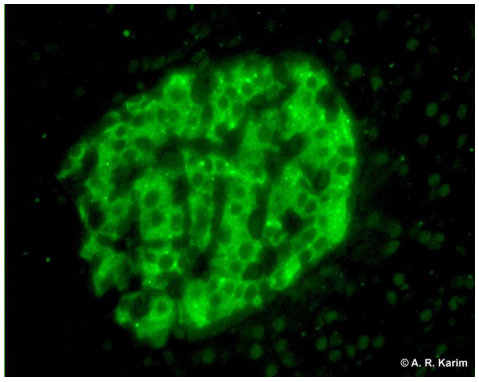
Anti-GAD



Higher magnification of the granular cells showing GAD reactivity

GAD65 : neurotransmission
GAD67 autres fonctions neuronales
Enzyme produisant le GABA

GAD antibody on primate pancreas (Islet cell antibody has similar distribution). The target antigens are GAD 67 and GAD 65.

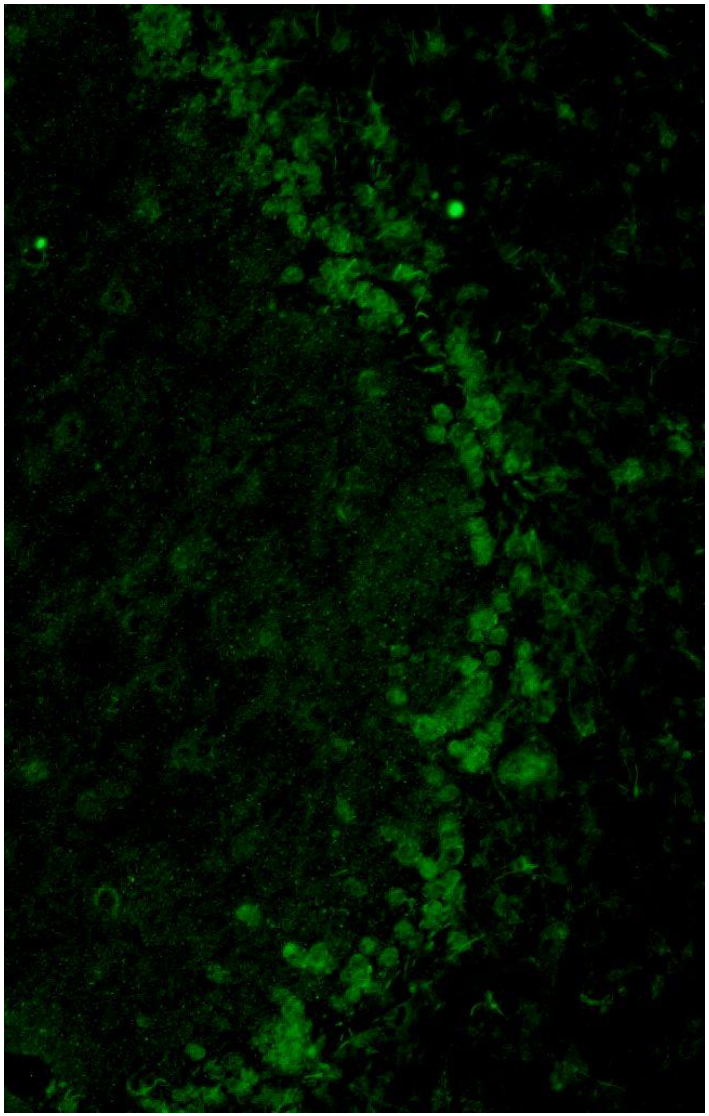


Anti-GAD

Table 2
Comparison of immune responses to GAD in SPS and diabetes.

	SPS	Type 1 diabetes
Autoantibody levels	Moderate to very high [9,43]	Low to moderate [43]
Frequency		
anti-GAD65	70%+ [7,9]	60% [40]
anti-GAD67	50–60% [7,9]	12% [40], cross-reactive
Immunofluorescence +ve		
Pancreas	GAD65 only [40]	GAD65 & other reactants [40]
Brain	GAD65, 67, others [40]	Minimal if any reactivity [38]
Enzyme inhibition +ve	60% [7,43]	Rare, 2% [7]
Western blotting +ve	GAD65 only [9,38]	Rare, <10% [49]
B Cell epitopes		
GAD67, conformational	(see text)	(see text)
GAD65, linear	C-terminal [2,38,46]	C-terminal (rare) [45a,46]
GAD65, linear	N-terminl, aa 4–22 [43,46–49]	None ascertained
GAD67, conformational	GAD67 specific	GAD67or 65
IgG isotypes, subtypes	IgG1 (IgG4, IgE)	IgG1
T cell epitopes	aa 81–171, 313–403	aa 161–243, 473–555
Serum transfer to animals	Yes [44]	No [44]
Associated autoimmune diseases	Thyrogastric cluster [22,23]	Thyrogastric cluster [22,23]

Anti-glial nuclear antibody (AGNA) antibodies (SOX1)



Recent emergence of another antibody directed against the Bergmann glia of the Purkinje cell layer of cerebellum has been described in patients with PNS (usually **Lambert Eaton myasthenic syndrome**) associated with SCLC. The target for this antibody is SOX1 protein.

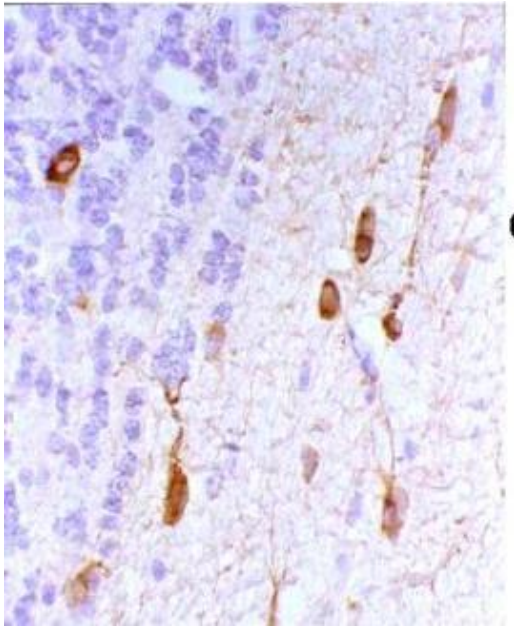
Both SOX1 and SOX2 are targets for the AGNA, with higher positivity seen against SOX1

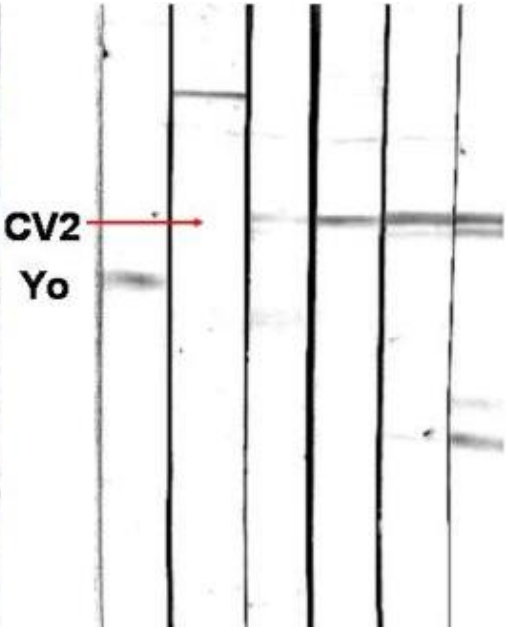
Immunofluorescence shows characteristic staining of the nuclei of Bergmann glia.

CV2/CRMP5 antibodies

Neurological syndromes (click here)	%
Peripheral neuropathy	59.6
Cerebellar ataxia	51.1
Ocular involvement (optic neuritis/uveitis)	17
Limbic encephalitis	14.9
Myasthenic syndrome	10.6
Gastroparesia	10.6
Chorea	8.5
Dysautonomia	4.3
Opsoclonus	2.1

Immunohistochemistry on paraformaldehyde fixed rat brainstem and cerebellum sections. The typical staining is that of oligodendrocytes. Additionnaly, the neuropile may be stained





Panel 6: Diagnostic criteria for Hashimoto's encephalopathy

Diagnosis can be made when all six of the following criteria have been met:

1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
2. Subclinical or mild overt thyroid disease (usually hypothyroidism)
3. Brain MRI normal or with non-specific abnormalities
4. Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies*
5. Absence of well characterised neuronal antibodies in serum and CSF
6. Reasonable exclusion of alternative causes

*There is no disease-specific cutoff value for these antibodies (detectable in 13% of healthy individuals).[100]

Panel 7: Criteria for autoantibody-negative but probable autoimmune encephalitis

Diagnosis can be made when all four of the following criteria have been met:

1 Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms

2 Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)

3 Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:
- MRI abnormalities suggestive of autoimmune encephalitis*
- CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both*
- Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)

4 Reasonable exclusion of alternative causes

*Some inherited mitochondrial and metabolic disorders can present with symmetric or asymmetric MRI abnormalities and CSF inflammatory changes resembling an acquired autoimmune disorder.[102]

Table 2 | Ion channel targets of autoantibodies in the brain.

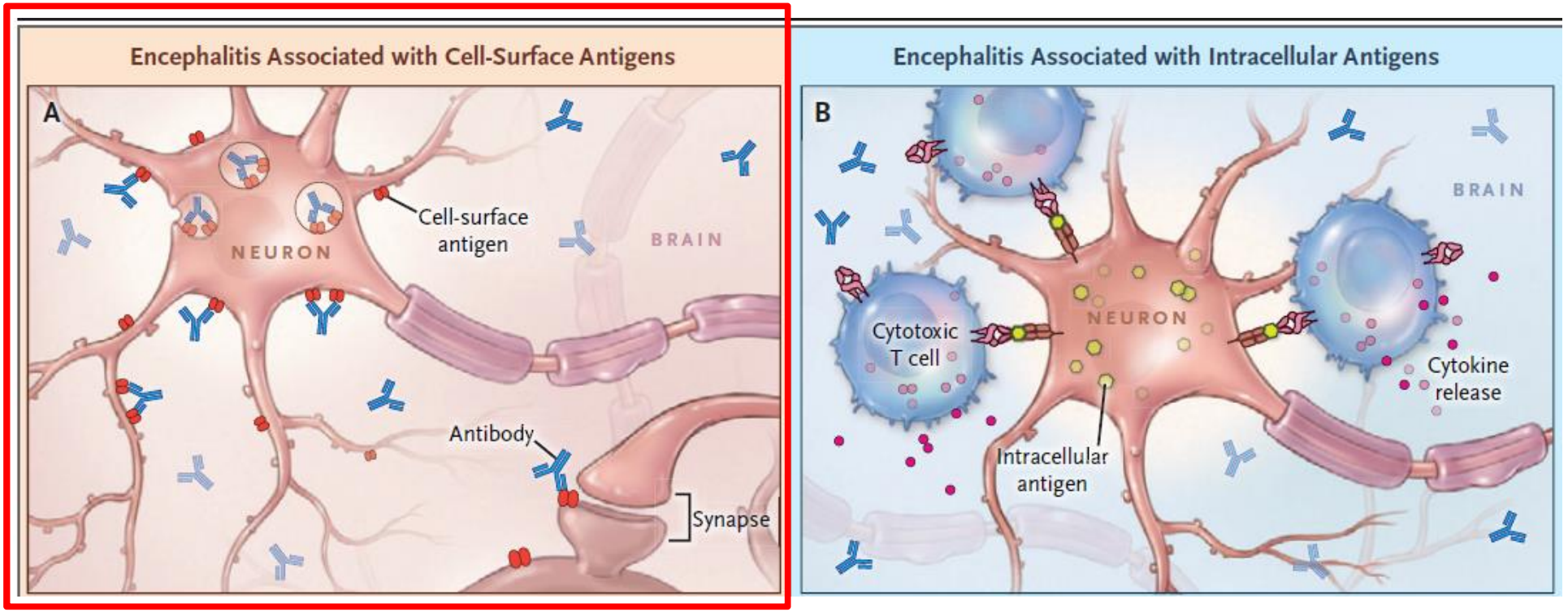
Targeted antigen	Disease(s)	Subunit/associated protein	Reference
Potassium channel/VGKC-complex	Limbic encephalitis, Morvan's syndrome, Schizophrenia	LG1 or Caspr2 LG1 or Caspr2	Irani et al. (2010, 2011), Lai et al. (2010) Irani et al. (2011), Zandi et al. (2011), Steiner et al. (2013)
NMDAR	Encephalitis, Schizophrenia	NR1	Dalmau et al. (2011), Zandi et al. (2011), Steiner et al. (2013)
AMPAR	Limbic encephalitis		Vincent et al. (2011)
Glutamic acid decarboxylase	Limbic encephalitis, Stiff person syndrome		Vincent et al. (2011), Graus et al. (2010)
Muscarinic AChR	Schizophrenia	M1; M2	Borda et al. (2002, 2004)
Nicotinic AChR	Schizophrenia	α7	Chandley et al. (2009)
$GABA_BR$	Limbic encephalitis		Vincent et al. (2011)
Glycine-R	Progressive encephalomyelopathy		Hutchinson et al. (2008)

Antigen	Demographics	Clinical Phenotypes	Paraclinical Findings	Tumor Association	Outcome
LGI 1	65% male Age range 30–80 years (median: 60 years)	Limbic encephalitis Faciobrachial dystonic seizures	Hyponatremia (distinctive feature) CSF: usually normal, occasional OCB MRI: medial temporal lobe increase of FLAIR signal (80%)	Rare	Good outcome; relapses uncommon Good response to immunotherapy but absent or poor response with regular AED in faciobrachial dystonic seizures
Caspr2	85% male Age range 46–77 years (median: 60 years)	Neuromyotonia Morvan syndrome Limbic encephalitis Idiopathic ataxia	MRI: medial temporal lobe increase of FLAIR signal (40%) in limbic encephalitis EMG: spontaneous muscular hyperactivity in neuromyotonia	Thymomas, SCLC (uncommon)	Good outcome but can be complicated by tumor
NMDA receptor	80% female Age range from months to 85 years (median: 21 years)	Psychiatric symptoms, memory and language deficits, seizures, movement disorder, autonomic instability, and decreased level of consciousness	CSF: lymphocytosis (70%) in the early stages and OCBs later (52%) EEG: generalized slowing, occasional epileptiform discharges in early stages MRI: normal or mild signs of inflammation (cortical or subcortical)	Teratoma (40%)	Good outcome with timely immunotherapy (± tumor removal) Cognitive and behavioral sequelae may persist
AMPA receptor	90% female Age range 38–78 years (median: 60 years)	Limbic encephalitis (prominent psychiatric manifestations, sometimes isolated)	CSF: lymphocytosis with occasional raised protein and OCBs MRI: medial temporal lobe increase of FLAIR signal (90%)	SCLC, thymoma, or breast cancer (70%)	Tendency to relapse (50%), even in the absence of tumor
GABA B receptor	50% female Age range 24–75 years (median: 62 years)	Limbic encephalitis (prominent seizures)	CSF: lymphocytosis with occasional raised protein and OCBs MRI: medial temporal lobe increase of FLAIR signal (about 66%)	SCLC (50%)	Good outcome. Relapses are rare

Continued

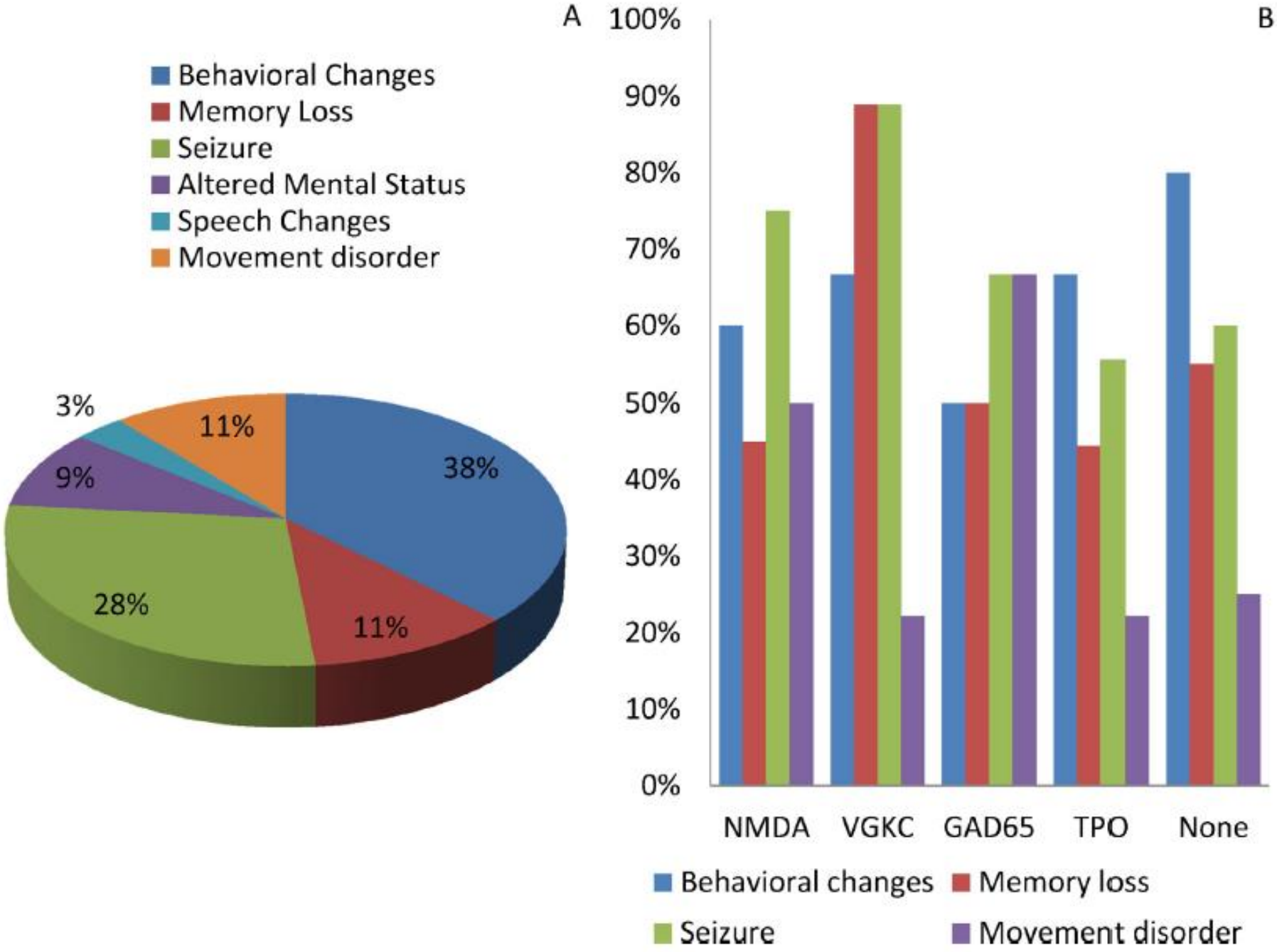
Antigen	Demographics	Clinical Phenotypes	Paraclinical Findings	Tumor Association	Outcome
Glycine receptor	60% male Age range from months to 70 years (median: 46 years)	Progressive encephalomyelitis, rigidity, and myoclonus Classic and variant Stiff-man syndrome	CSF: usually normal, occasional mild lymphocytosis MRI: normal EMG: continuous muscle activities in the agonist and antagonist muscles	Thymoma, Hodgkin lymphoma (rare)	Good outcome; frequent relapses with immunotherapy taper

Tableau clinique en fonction de la cible antigénique

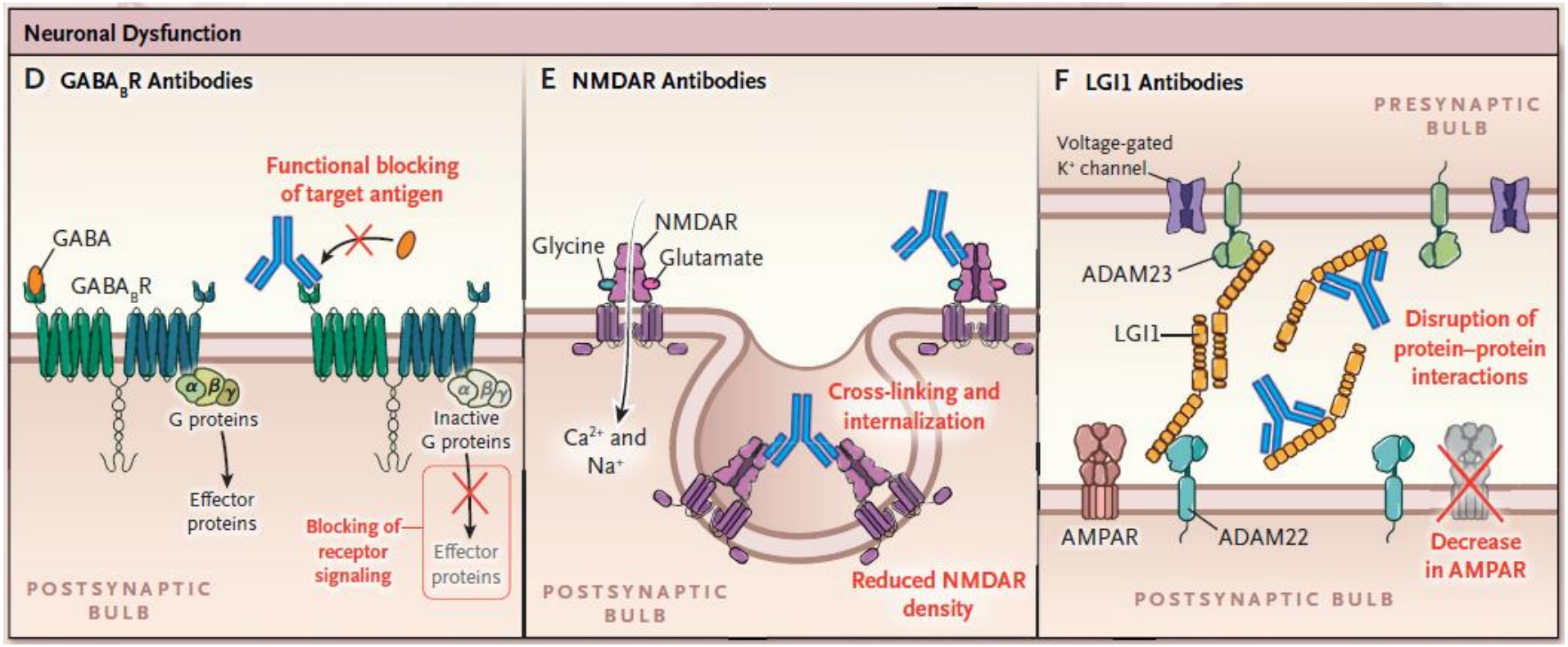


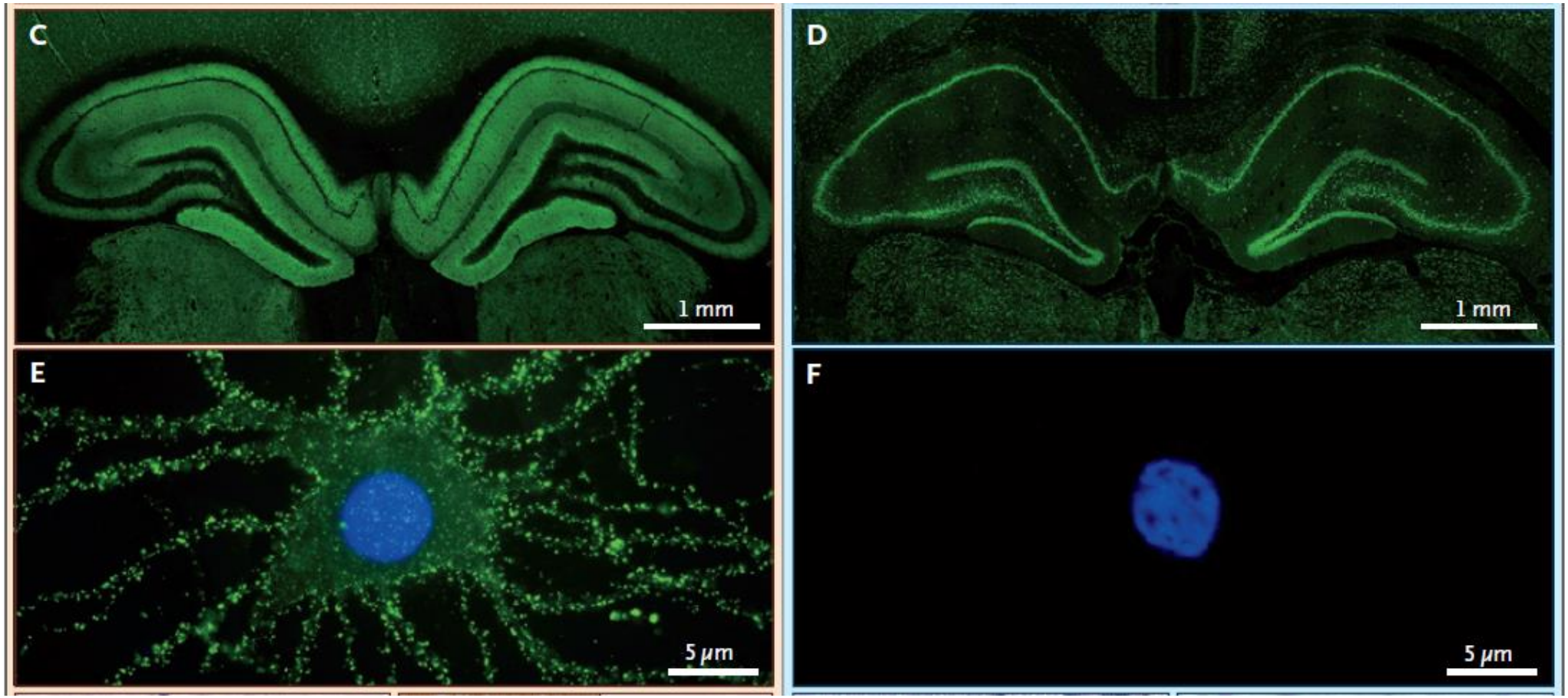
Anticorps dirigés contre les protéines de surface, des récepteurs ou des canaux ioniques

- Tableau clinique prédominant :
  - Troubles du comportement
  - Psychose
  - Crises E
  - Troubles cognitifs et de mémoire
  - Mouvements anormaux
  - Dysautonomie
  - Altération de la conscience
- Pas d'autre manifestations systémiques >< Lupus
- Atteint tous les ages
- Récupération complète si traitement précoce
- Effet pathogène direct des anticorps

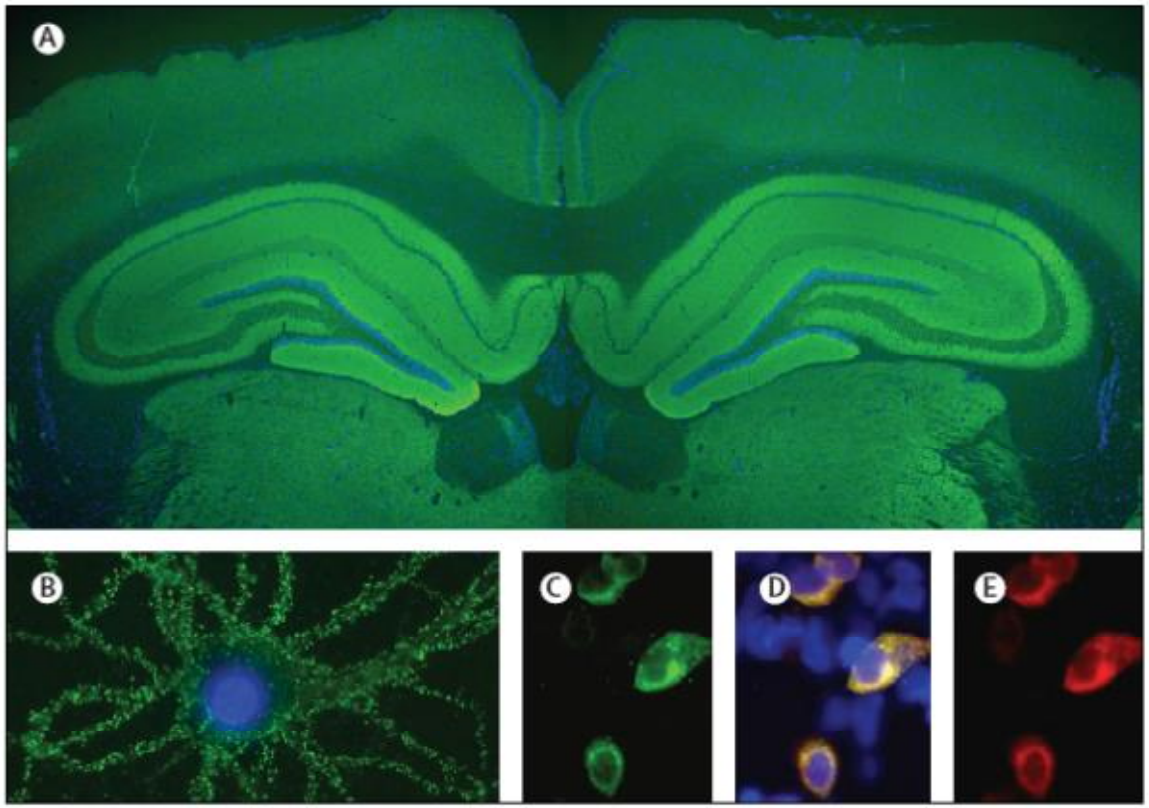

A
Behavioral Changes
Memory Loss
Seizure
Altered Mental Status
Speech Changes
Movement disorder
38%
11%
28%
9%
3%
11%
B
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
NMDA
VGKC
GAD65
TPO
None
Behavioral changes
Memory loss
Seizure
Movement disorder

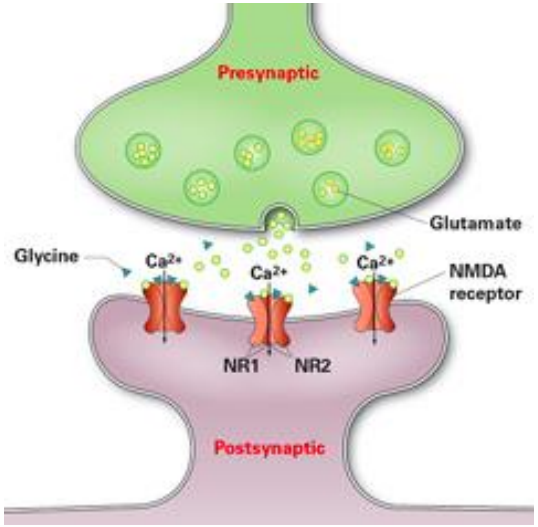
Mécanismes physiopathologiques




Encephalitis Associated with Cell-Surface Antigens
Encephalitis Associated with Intracellular Antigens
C
1 mm
D
1 mm
E
5 μm
F
5 μm

Ac anti-Glutamate récepteur





Autoimmune encephalitis screen

Serum sample from patient is screened on transfected HEK cells for the detection of the following antibodies:-

Glutamate receptor type:

NMDA (see below), AMPA1 and AMPA2

Voltage-gated potassium channel associated proteins:

Leucine-rich glioma inactivated protein 1 (LGI1) and
Contactin-associated protein 2 (CASPR2)
DPPX

GABA receptors 1 (GABARB1)

Ac anti- Ag de surface / Néo

	% cas paraneoplasiques	Tumeurs
Å NMDAR	9-55%	Teratome ovarien
Å AMPAR	70%	Po, Thym, sein
Å GABA R	60%	SCLC
Å LGI1	<20%	SCLC, thymome
Å CASPR2	<10%	Thymome

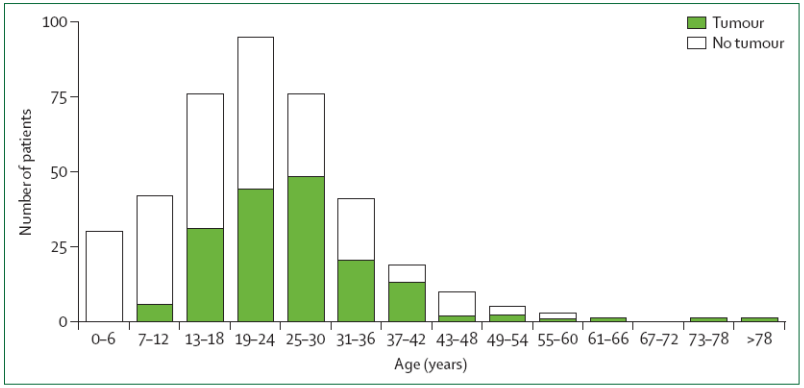


Figure 2: Distribution of patients by age and presence or absence of tumours
Data are for 400 patients with anti-NMDAR encephalitis.

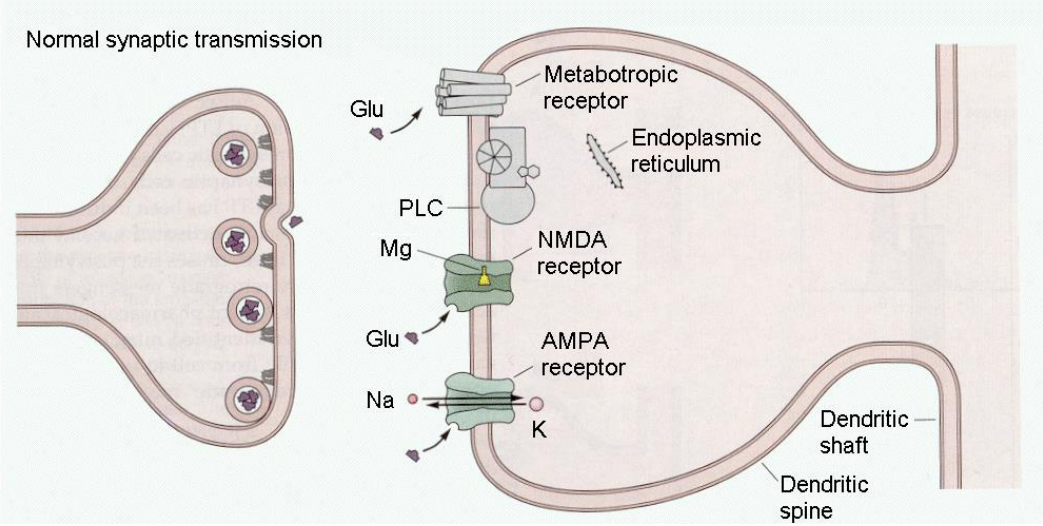
Lancet Neurol 2011; 10: 63–74

Table 1. Clinical and Immunologic Features and Antibody Effects of Antibody-Mediated Encephalitis.*

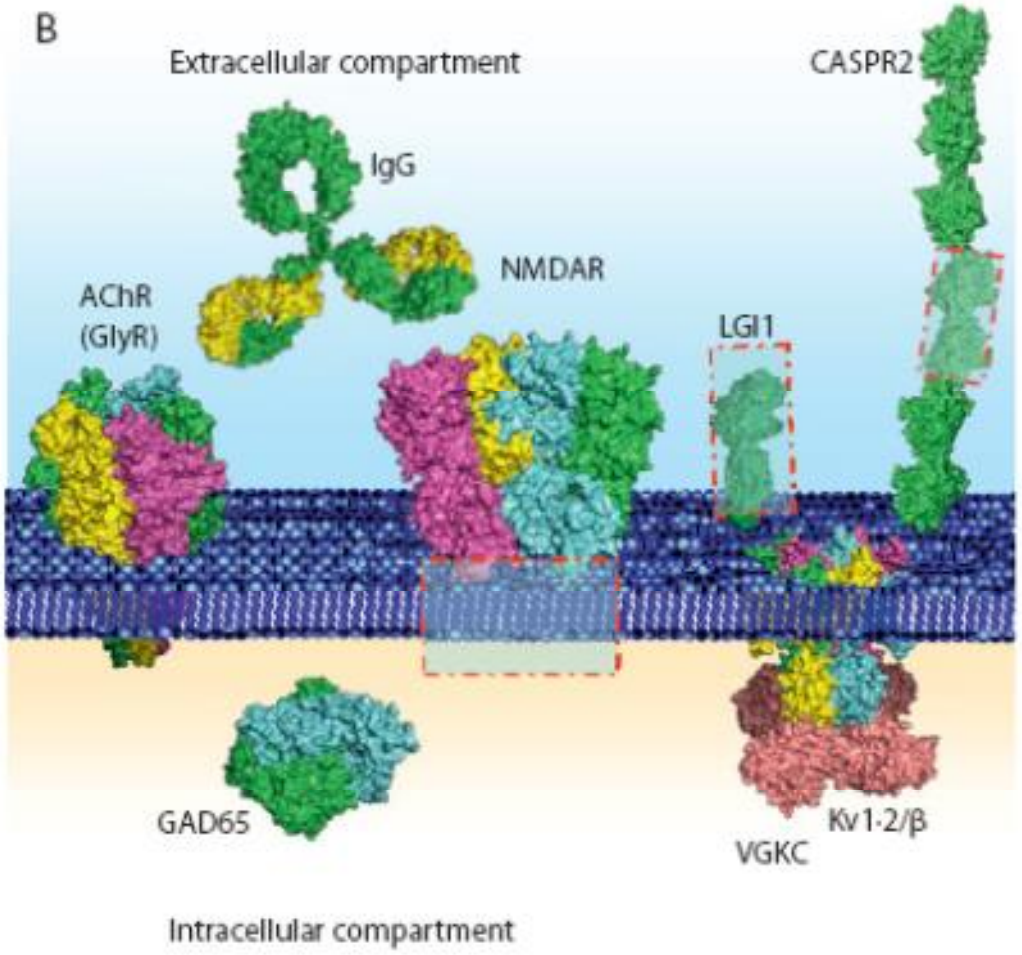
Antibody (No. of Patients)†	Median Age (Range); Male:Female Ratio	Main Clinical Features on Presentation	Main Syndrome	Findings on MRI (% of Patients)‡	Frequency of Cancer (% of Patients)	Predominant IgG Class	In Vitro Antibody Effects
NMDAR (>1500)	21 yr (2 mo–85 yr); 1:4	Children: seizures, dyskinesias; adults: behavioral changes, psychiatric symptoms	NMDAR encephalitis	Normal findings (70) or nonspecific changes	Varies with age and sex; ovarian teratoma in women 18–45 yr old (58)§	IgG1	Internalization of NMDAR, disruption of NMDAR interaction with ephrin-B2 receptor
AMPAR (80)	56 yr (23–81); 1:2.3	Confusion, memory loss; in rare cases, psychiatric symptoms	Limbic encephalitis	Increased signal in medial temporal lobes (67)	SCLC, thymoma, or breast cancer (56)	IgG1	Internalization of AMPARs
$GABA_BR$ (80)	61 yr (16–77); 1.5:1	Seizures, memory loss, confusion	Limbic encephalitis, prominent seizures	Increased signal in medial temporal lobes (45)	SCLC (50)	IgG1	Blocking of agonist effect of baclofen on $GABA_BR$
LGI1 (400)	64 yr (31–84); 2:1	Memory loss, faciobrachial dystonic seizures, hyponatremia	Limbic encephalitis	Increased signal in medial temporal lobes (83)	Thymoma (<5)	IgG4	Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease in postsynaptic AMPAR
CASPR2 (120)	66 yr (25–77); 9:1	Memory loss, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, neuropathic pain	Limbic encephalitis¶‖	Increased signal in medial temporal lobes (67)	Varies with the syndrome (<5 overall)**	IgG4	Alteration of gephyrin clusters in inhibitory synapses
mGluR5 (11)	29 yr (6–75); 1.5:1	Confusion, psychiatric symptoms	Encephalitis	Normal findings in 5 of 11 patients	Hodgkin's lymphoma in 6 of 11 patients	IgG1	Decrease in density of surface mGluR5
D2R (25)	6 yr (2–15); 1:1	Parkinsonism, dystonia, psychiatric symptoms	Basal ganglia encephalitis	Increased signal in basal ganglia (50)	No associated cancer	Unknown	Receptor internalization and decrease in D2R surface density
DPPX (45)	52 yr (13–76); 2.3:1	Confusion, diarrhea, weight loss	Encephalitis, myoclonus, tremors, hyperekplexia¶	Normal findings or nonspecific changes (100)	B-cell neoplasms (<10)	IgG4	Decrease in density of surface DPPX and Kv4.2
$GABA_AR$ (70)	40 yr (2 mo–88 yr); 1:1	Seizures, confusion, behavioral changes	Encephalitis, frequent status epilepticus	Cortical and subcortical FLAIR signal abnormalities involving two or more brain regions (77)	Thymoma (27)	IgG1	Selective reduction of $GABA_AR$ at synapses
Neurexin-3α (6)	44 yr (23–57); 2:4	Confusion, seizures	Encephalitis	Normal findings in 4 of 6 patients	No associated cancer	Unknown	Decrease in density of surface neurexin-3α and total number of synapses in neurons undergoing development

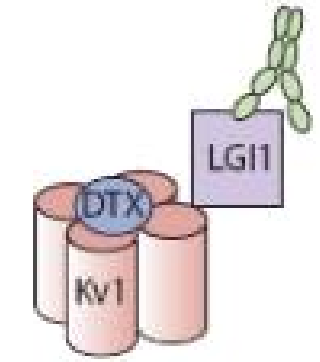
Récepteurs glutamate

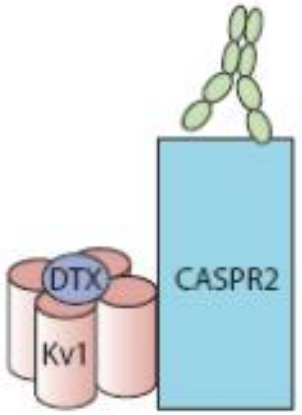
- Récepteurs ionotropes
  - Récepteurs NMDA (Ca++) tétramère 2NR1/2NR2
  - Récepteurs AMPA (Na+/K+) hétérotétramère GluR1, GluR2, GluR3, GluR4.
- Récepteurs métabolotropes au glutamate:
  - Homodimères (mglu1, mglu… mglu8)



Anticorps Anti VGKC







DTX = Dendrotoxine (< mamba vert)

RIA: test incluant l'ensemble du complexe

Anti-VGKC: cible = protéines associées au VGKC

- Kv1.1, Kv1.2, Kv1.6 — 3%
- LGI1 — 80%
- CASPR2
- Contactin2 et autres — ?

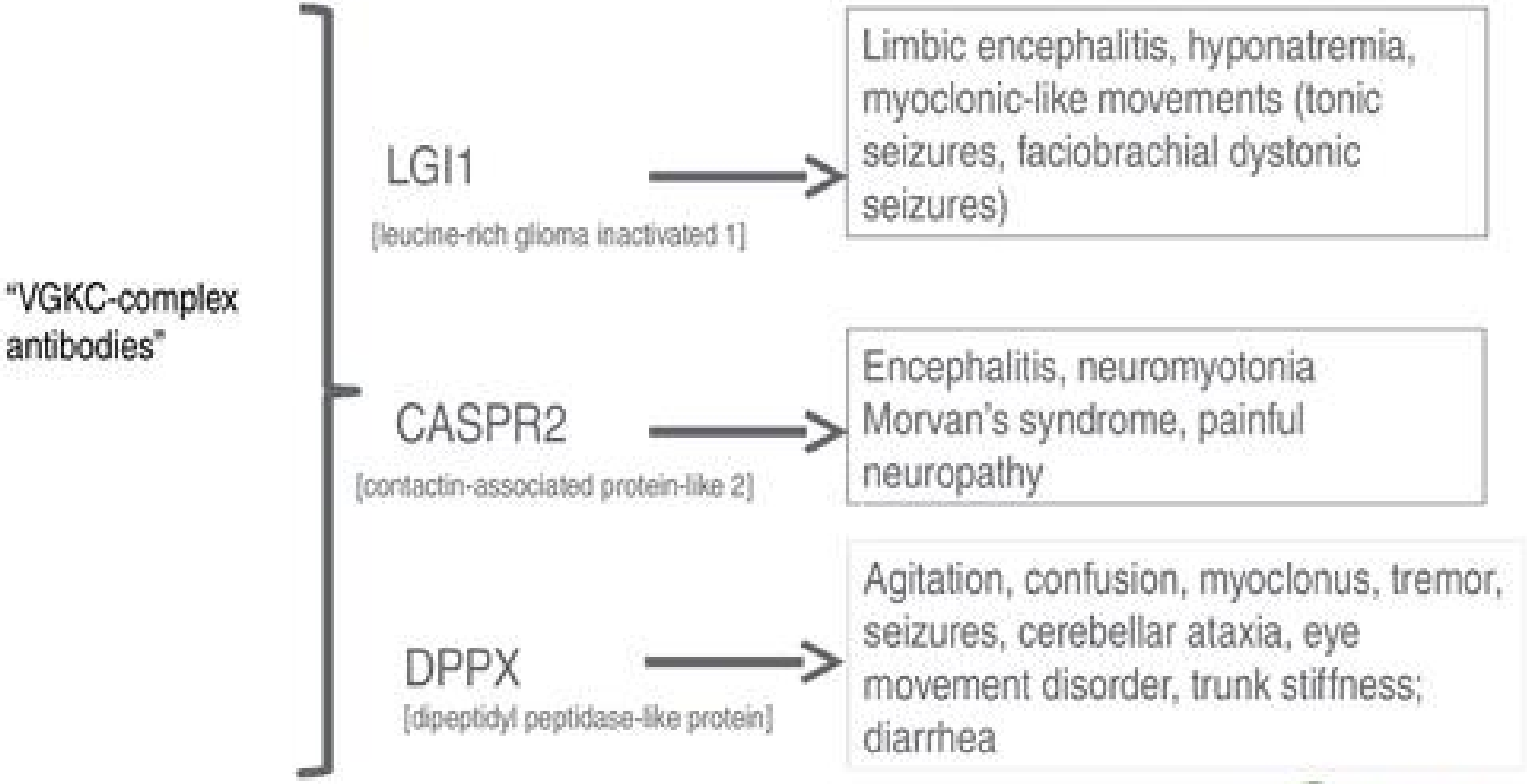
Formes d'encéphalites plus indolentes que NMDA-encephalites

Anti VGKC : associations

- Neuromyotonie — CASPR2
- Syndrome de Morvan — LGI1/CASPR2
- Encéphalite limbique — LGI1

Antibodies against voltage-gated potassium channels (VGKC)

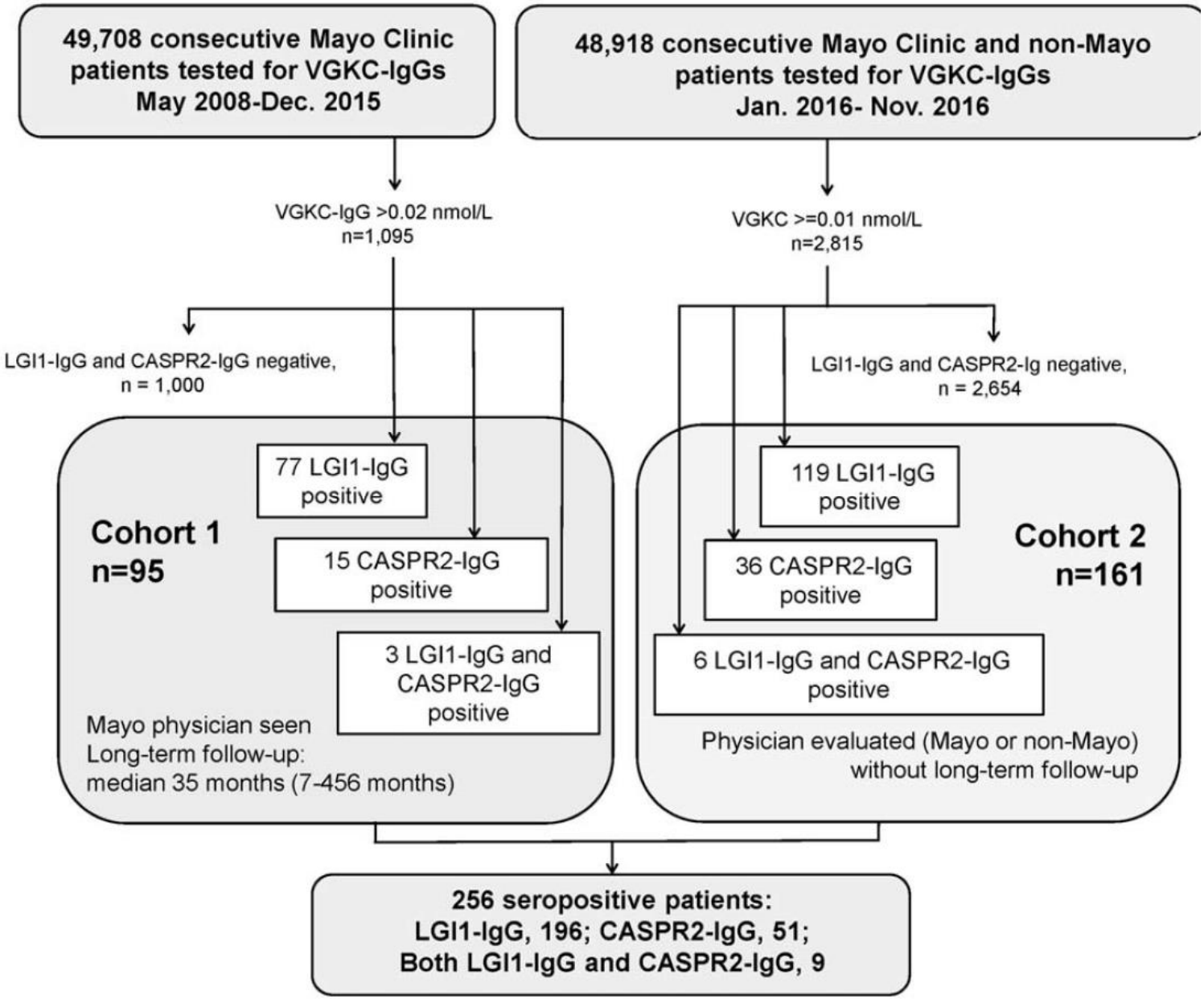
80% of Anti-VGKC antibodies target LGI1 and CASPR2!



Rosenfeld M et al., Neurology: Clin Practice 2012; Sarosh et al., Brain, 2013; Tobin et al., Neurol 2014.

Quest Diagnostics

Anti-VGKC



ANN NEUROL 2017;82:79–92

Anti-VGKC

TABLE 1. Serological Demographics

Characteristic	LGI1-IgG Positive, n = 196	CASPR2-IgG Positive, n = 51	Both Positive, n = 9	Significant *p* values, LGI1 vs CASPR2
Male, No. (%)	115 (59)	40 (74)	6 (67)	0.014
Age, yr, median [range]	65 [17–89]	66 [29–82]	64 [21–76]	
VGKC-IgG, nmol/l serum, median [range]	0.33 [0.02–5.14]	0.1 [0.00–0.45]	0.31 [0.03–0.66]	<0.001
Central manifestations alone, No. (%)	145/179 (81)	21/44 (47)	2/8 (25)	<0.00001
Peripheral manifestations alone, No. (%)[a]	13/179 (7)	17/44 (39)	3/8 (38)	<0.00001
Both central and peripheral manifestations, No. (%)	21/179 (12)	6/44 (14)	3/8 (38)	
VGKC tissue-based IFA positive, serum, No. (%)	77/173 (45)	14/49 (29)	1/9 (11)	0.049
VGKC tissue-based IFA positive, CSF, No. (%)	58/83 (70)[b]	8/10 (80)[c]	0/3	
CSF IFA positive; serum negative, No. (%)	16/96 (17)	4/35 (11)	N/A	
CSF CBA positive, No. (%)	24/38 (63)	5/6 (83)	0/1	

[a]Peripheral involvement was more common in Cohort 1 (patients with detailed long-term follow-up; Table 3).
[b]IFA was more sensitive for CSF than serum ($p < 0.0002$).
[c]IFA was more sensitive for CSF than serum ($p < 0.003$).
CBA = transfected cell-based IFA; CSF = cerebrospinal fluid; IFA = tissue-based immunofluorescence assay; N/A = information not available; VGKC = voltage-gated (Kv1) potassium channel complex.

Reflex testing for #83380 Paraneoplastic Autoantibody Evaluation, Serum

Always performed

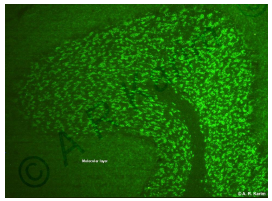
Immunofluorescence (IFA)
- #83381 Anti-Neuronal Nuclear Ab, Type 1
- #83382 Anti-Neuronal Nuclear Ab, Type 2
- #83137 Anti-Neuronal Nuclear Ab, Type 3
- #83383 Purkinje Cell Cytoplasmic Ab Type 1
- #83138 Purkinje Cell Cytoplasmic Ab Type 2
- #83076 Purkinje Cell Cytoplasmic Ab Type Tr
- #83386 Amphiphysin Ab
- #83077 CRMP-5-IgG

IFA pattern suggests GAD65 Antibody

#81596 GAD65 Ab Assay is performed at an additional charge.

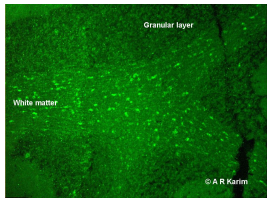
IFA pattern suggests or client requests

#83107 CRMP-5-IgG Western Blot is performed at an additional charge.



IFA pattern indeterminate

#83108 Paraneoplastic Autoantibody Western Blot is performed at an additional charge.



Always performed

Enzyme-Linked Immunosorbant Assay (ELISA)
- #8746 Striational (Striated Muscle) Ab

Radioimmunoprecipitation (RIA)
- #81185 P/Q-Type Calcium Channel Ab
- #81184 N-Type Calcium Channel Ab
- #8338 ACh Receptor (Muscle) Binding Ab
- #84321 AChR Ganglionic Neuronal Ab

If Calcium Channel Antibody P/Q-Type is >0.02 nmol/L or N-Type is >0.03 nmol/L

#83107 CRMP-5-IgG Western Blot is performed at an additional charge.

If ACh Receptor (Muscle) Binding Antibody is >0.02 nmol/L or Striational Antibody is ≥1:60

#83378 ACh Receptor (Muscle) Modulating Ab and #83107 CRMP-5-IgG Western Blot are performed at an additional charge.

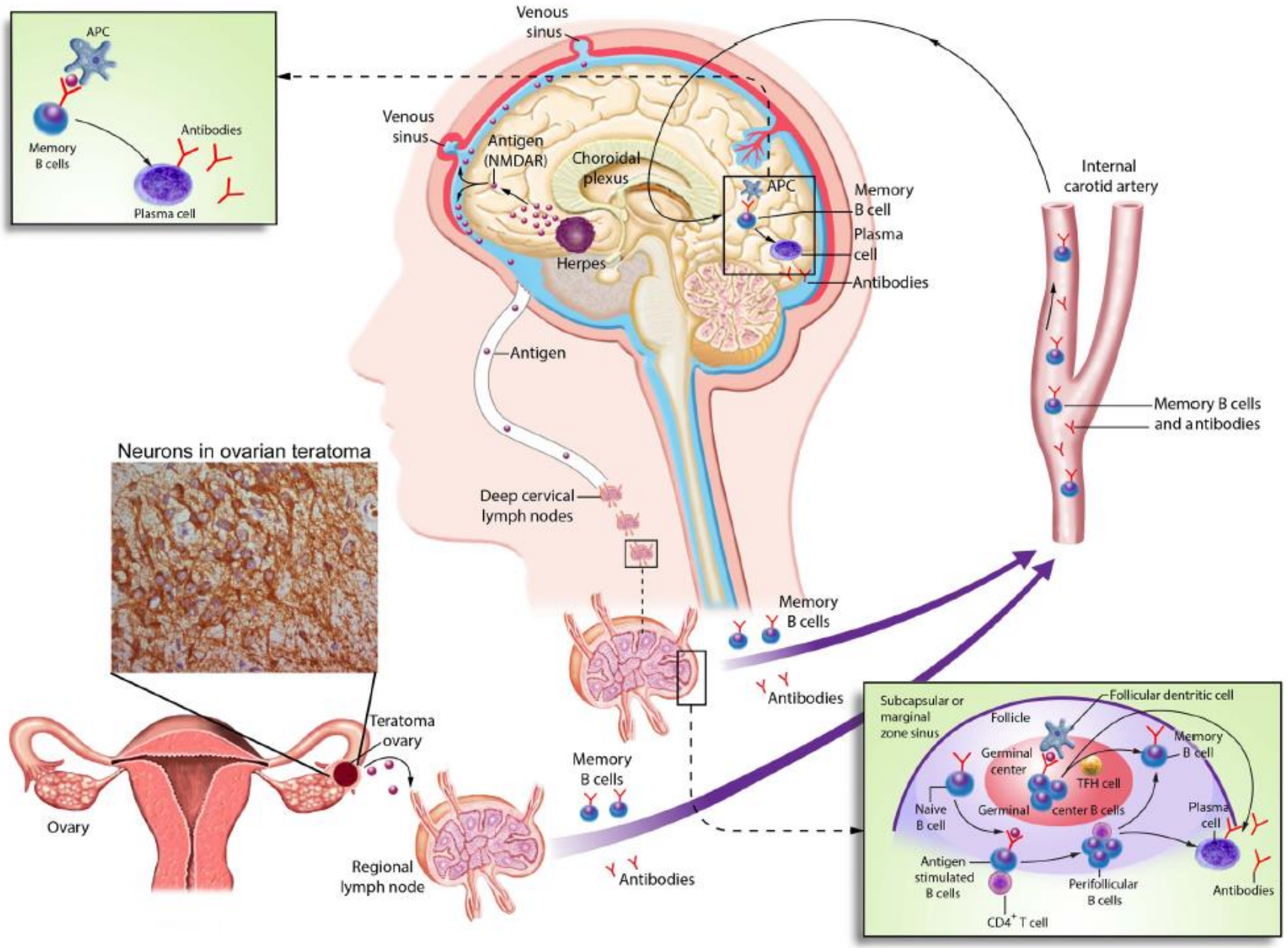
If ACh Recptor (Muscle) Modulating Antibody is ≥40% loss or Mayo's laboratory has requested a second specimen

#83379 ACh Receptor (Muscle) Blocking Ab is performed at an additional charge.

If ACh Ganglionic Neuronal Antibodies are ≥0.02 nmol/L

#83107 CRMP-5-IgG Western Blot is performed at an additional charge.

Encephalite à Ac anti NMDAR



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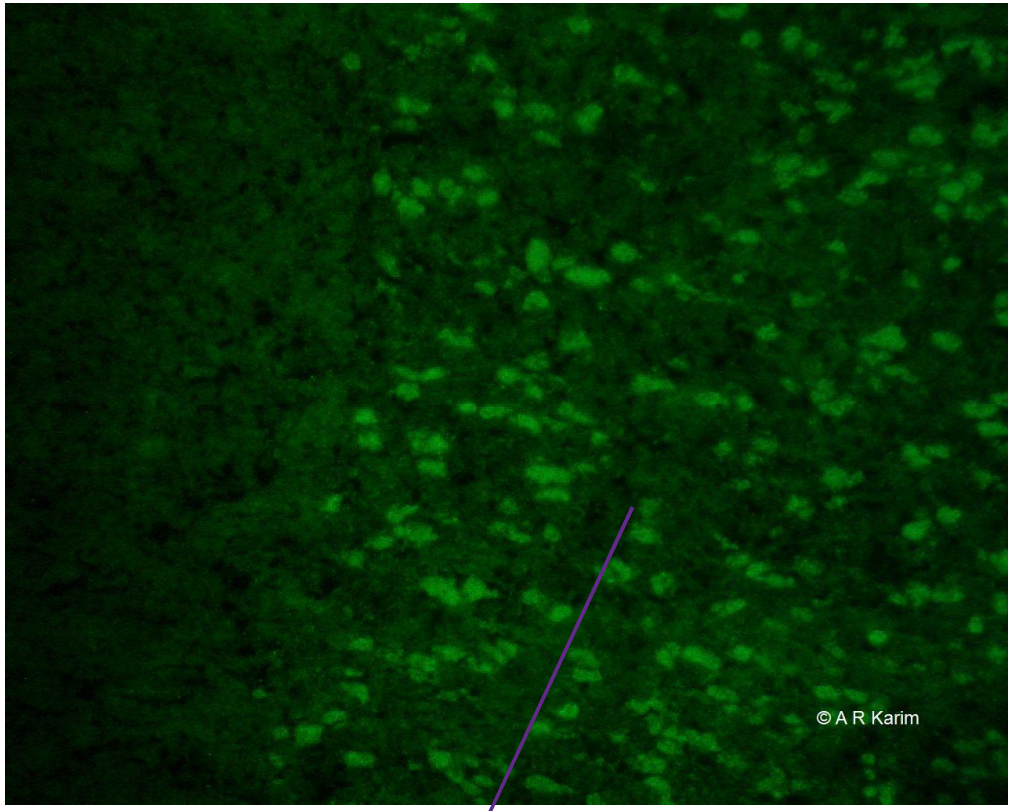
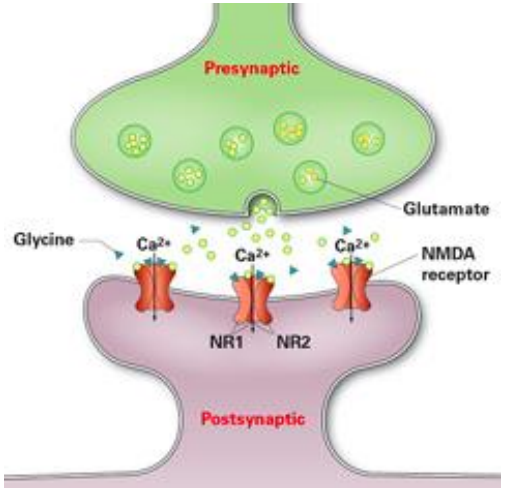
Anti-NMDA



Couche granulaire du cervelet

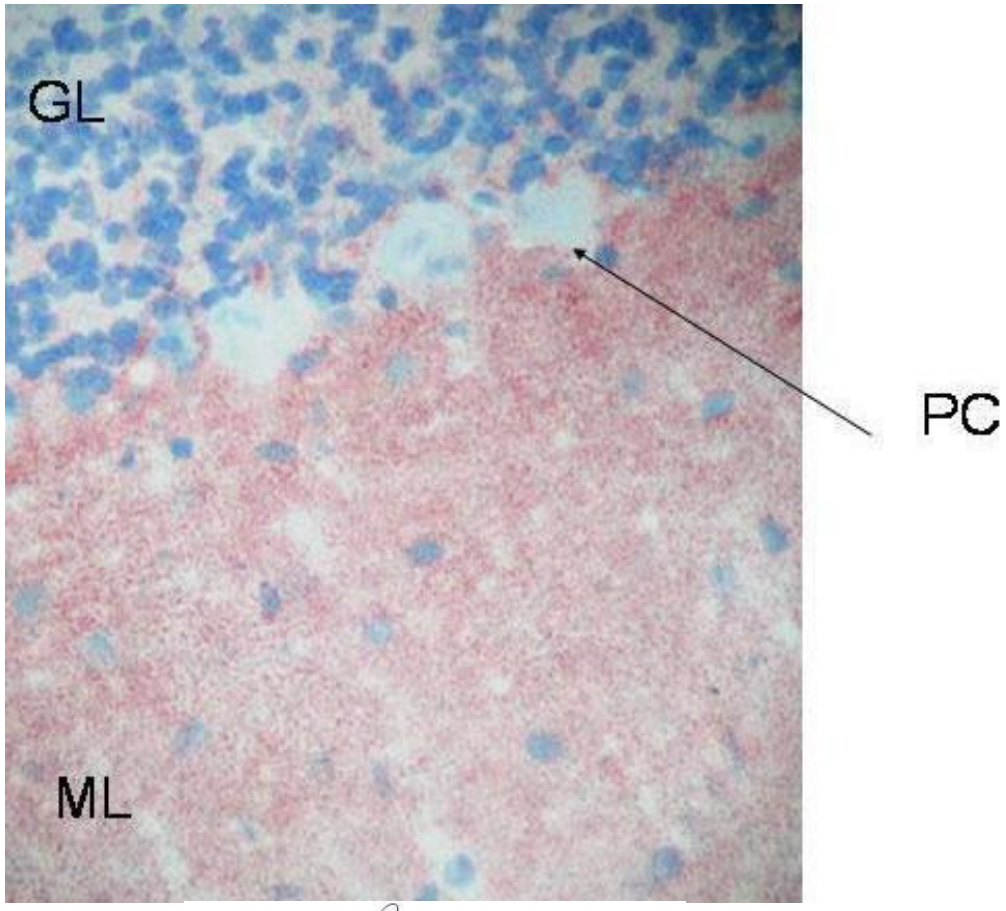
NMDAR antibody is associated with treatable limbic encephalitis and its target is the NMDA receptor which comprises four NR units, with each of the subunit has a molecular size of 100 kDa and together they form an ion channel/receptor. NMDAR antibody binds to the neuropils in the molecular layer of the hippocampus as well as the granular layer of the cerebellum

Tumours: Ovarian teratoma (56%, young women).
Syndrome: Limbic encephalitis



Forme la plus fréquente :
1% des admissions de jeunes à l'USI

Anti VGKC



Patients with VGKC antibodies may have associated myasthenia gravis with or without acetylcholine receptor antibodies, or may have acetylcholine receptor antibodies without myasthenia gravis. Other thymoma-related antibodies (eg. Interferon alpha, IL-12) may be present. Acquired neuromyotonia has been reported in patients following bone marrow transfer, with systemic sclerosis and with other autoimmune diseases.

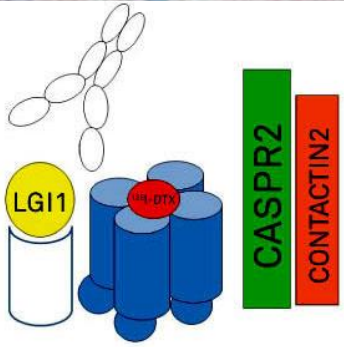
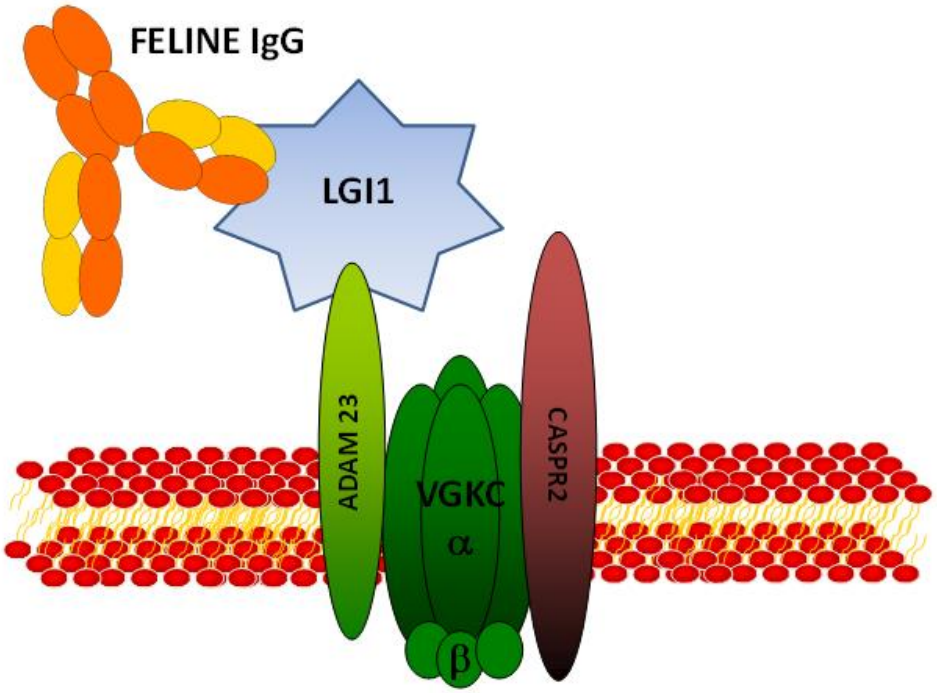
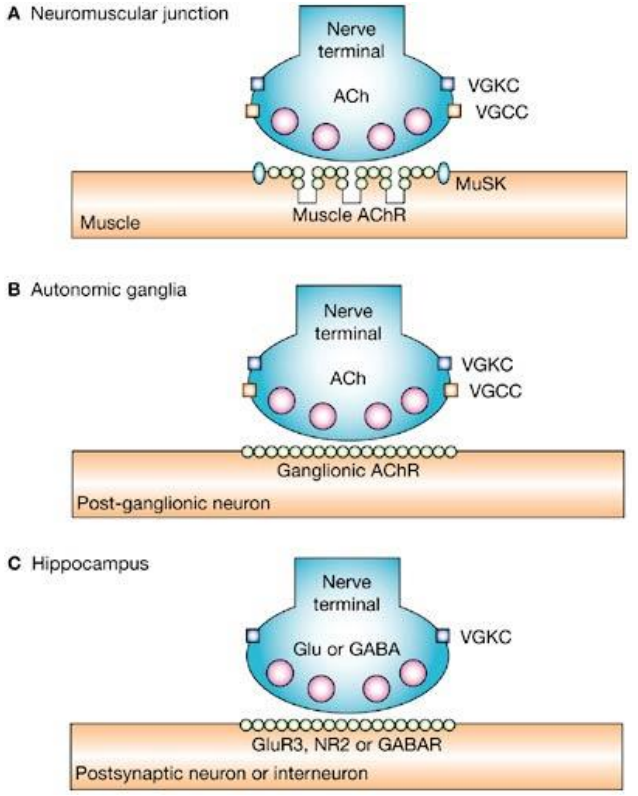


Fig 2. The VGKC-complex. leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2) and contactin-2 are tightly associated with VGKCs in mammalian brain membranes and are co-immunoprecipitated in the radioimmunoassay. These proteins are commonly targeted by the patient antibodies (white).[125]I-DTX = radioiodinated dendrotoxin, a Kv1 antagonist.

High titres of VGKC antibodies may be detected by immunohistochemistry showing characteristic staining of molecular layer of the cerebellum.

Anti VGKC


FELINE IgG
LGI1
ADAM 23
VGKC
α
β
CASPR2

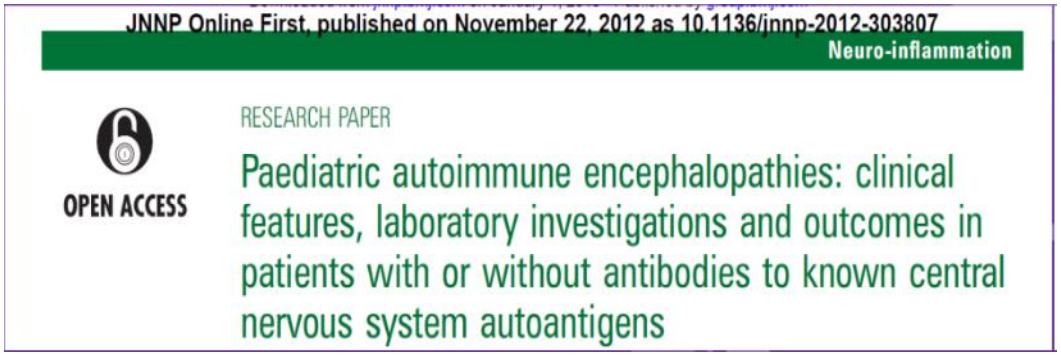

A Neuromuscular junction
Nerve terminal
ACh
VGKC
VGCC
MuSK
Muscle AChR
Muscle
B Autonomic ganglia
Nerve terminal
ACh
VGKC
VGCC
Ganglionic AChR
Post-ganglionic neuron
C Hippocampus
Nerve terminal
Glu or GABA
VGKC
GluR3, NR2 or GABAR
Postsynaptic neuron or interneuron


KODAK 05 EPP 01
KODAK 05 EPP 01
KODAK 05 EPP 01
KODAK 05 EPP 01

Table 1. A Comparison of NMDA-receptor Antibody Positive and VGKC-complex Antibody Positive Cases of Limbic Encephalitis (LE): Clinical Features, Investigation Results, and Antigenic Targets

	VGKC-complex Antibody LE (usually LGI1 antibody)	**NMDAR-antibody**
Gender ratio (male:female)	2:1	1:3
Age	Usually >50 years old	Usually <50 years old
Target antigen	LGI1 >> CASPR2	NR1 subunit of NMDAR
Tumor associated?	Rarely (<10%). If so, small cell lung cancer and thymoma.	Ovarian teratoma (20-50%), others rarely
Clinical features	Amnesia, disorientation and seizures	Psychiatric features, amnesia, disorientation and seizures; progress to movement disorder, dysautonomia and central hypoventilation
Distinctive clinical features	Faciobrachial dystonic seizures, often preceding the amnesia	Movement disorder (tyically choreoathetoid), usually starting 10 to 20 days after the psychiatric features
Blood tests (other than antibody)	Hyponatremia (in around 60%)	Nil
MRI	Bilateral hippocampal high signal (in around 60%)	Often normal. Occasionally, non-specific high signal or medial temporal lobe high signal
CSF	Most commonly normal	Early lymphocytic pleocytosis and later oligoclonal bands
Immunotherapy regime	Usually good response to 2 immunotherapies (steroids plus IVIg/Plasma exchange)	Slow response; often requires >3 immunotherapies

Encéphalies autoimmunes en pédiatrie



NMDAR ï 13/48
VGKC-complex ï 7/48
Glycine receptor ï 1/48

Anti-GM1 antibodies
- In cryptogenic partial epilepsy (6%)

GluR3 antibodies
- Mainly in Rasmussens encephalitis

NMDAR antibodies
- 140 patients identified in the first 2 years in the UK
- 26% of female patients aged 15 to 45 with unexplained new-onset epilepsy (*Arch Neurol* 2009; 66:458)

GABAA antibodies
- in severe epilepsy, encephalitis and status (Petit-Pedrol M et al, *Lancet Neurol* 2014 Mar)

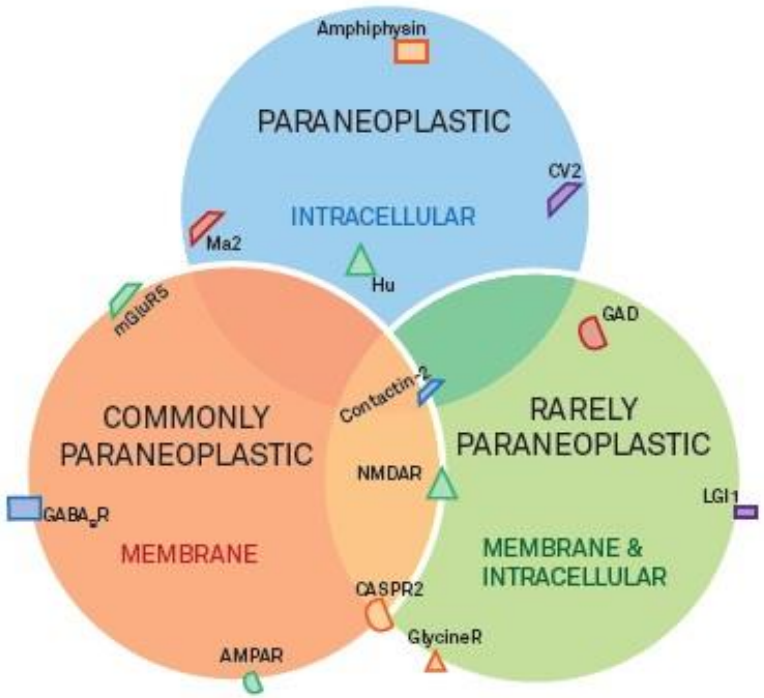
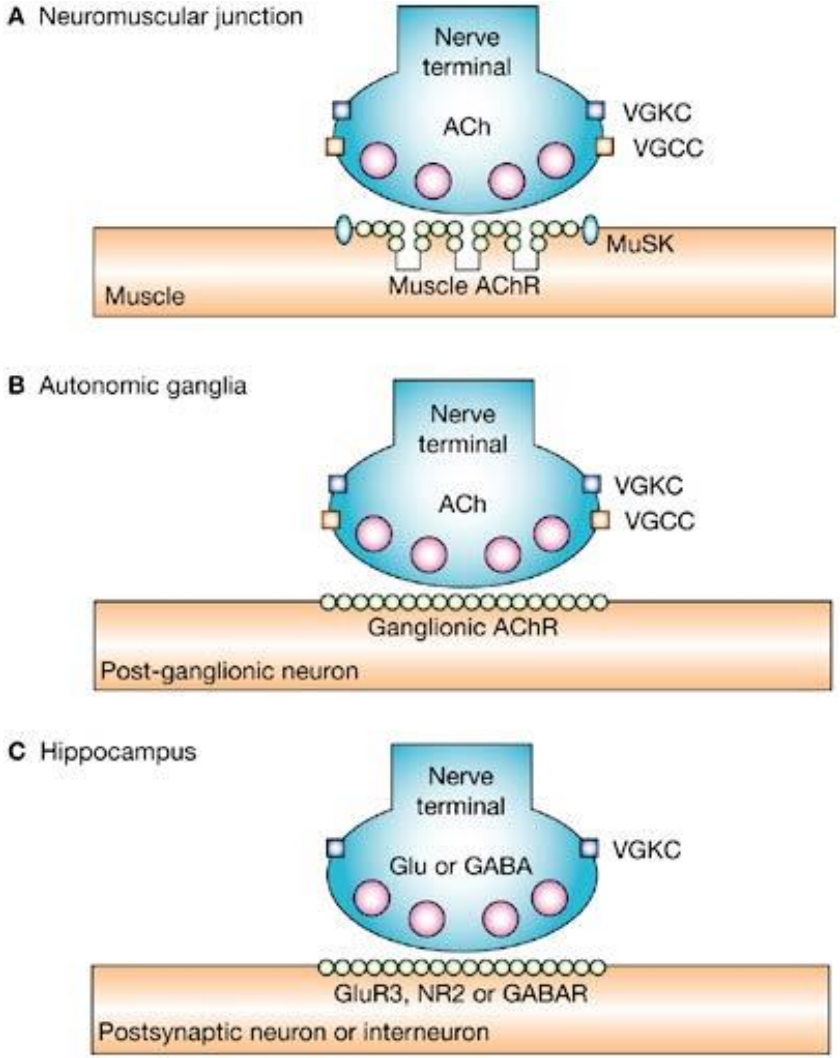
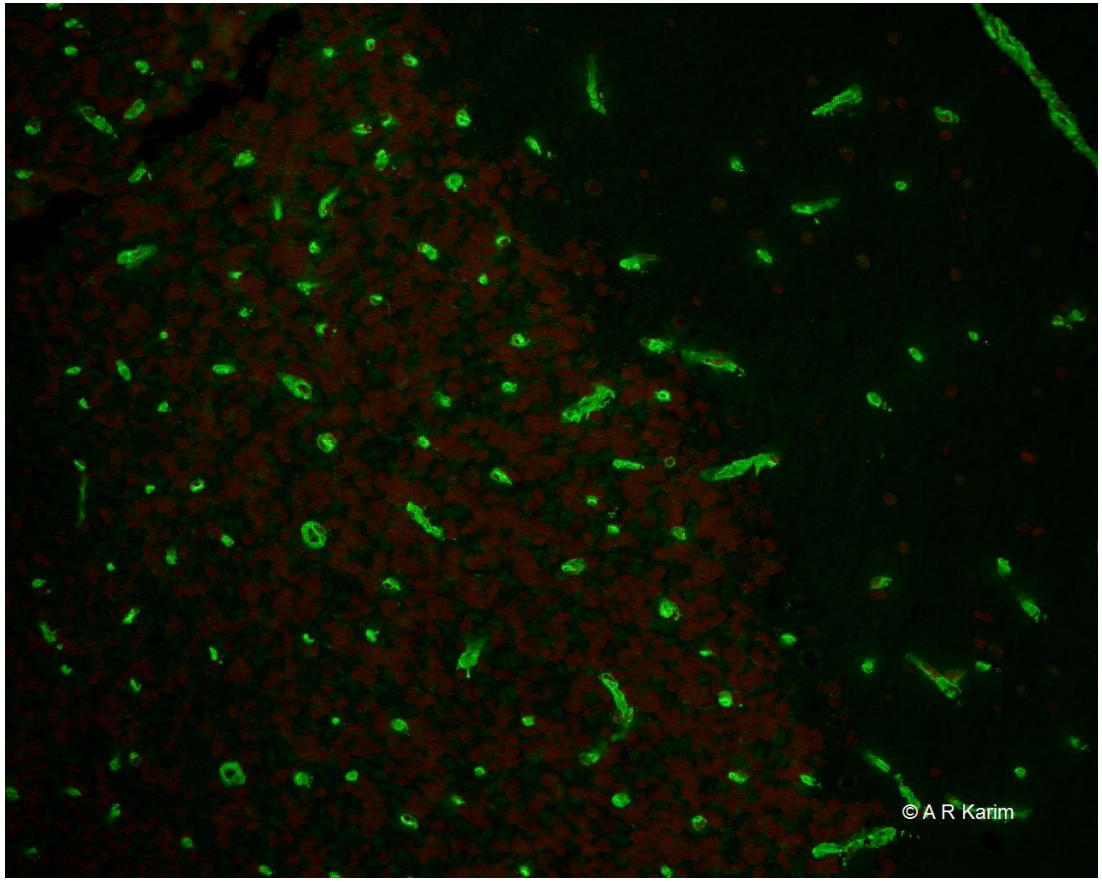


Fig 1. Antibody targets associated with non-paraneoplastic and paraneoplastic syndromes. Although most commonly associated with intracellular antibodies, paraneoplastic syndromes may also be caused by membrane antibodies. Hence, even in the presence of membrane antibodies, a search for an underlying malignancy should be considered.
LGI1: leucine-rich glioma inactivated 1; GAD: glutamic acid decarboxylase

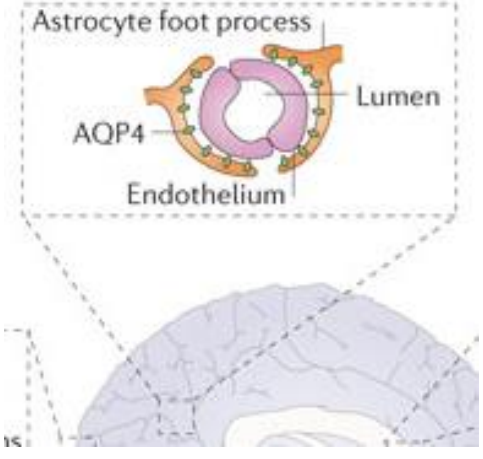


NMO (aquaporin 4) antibodies

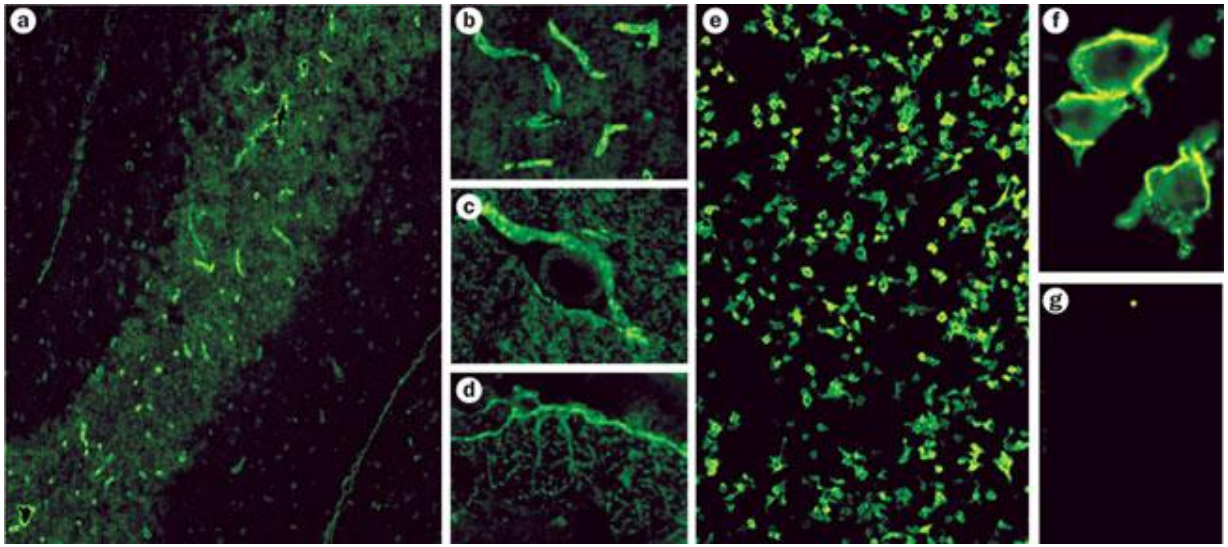


Neuromyelitis optica (NMO) associated antigen, a water channel protein, known as aquaporin 4 (AQP4) is found both in the central and peripheral tissues. Detection of AQP4 antibody is clinically useful in differentiating between NMO and other optic neuritis or myelitis. Unlike multiple sclerosis, a patient with AQP4 antibody can benefit from plasmapheresis and immunosuppression.

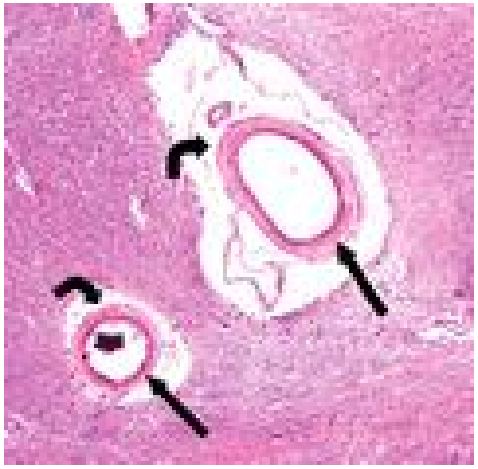
On cerebellum, AQP4 is found in the juxtaposed pial membrane, microvessels in the white matter, molecular layer and granular layer.

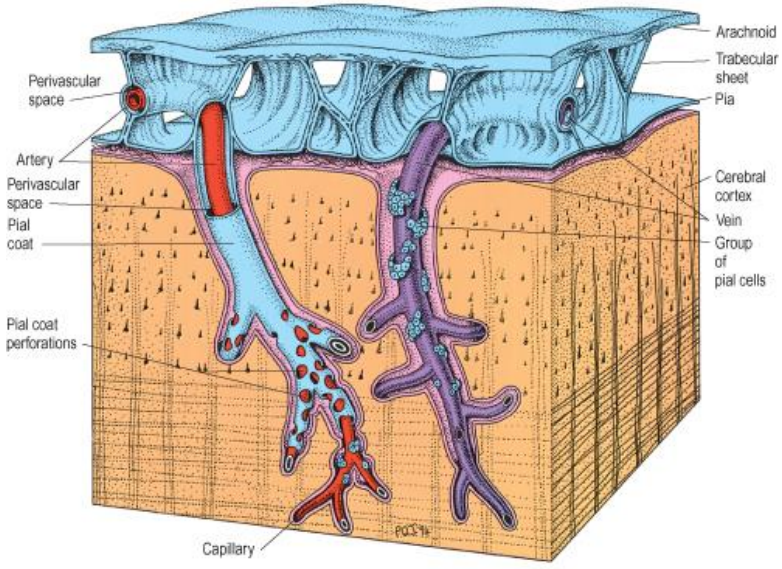


AQ4 : espaces de Virchow Robin

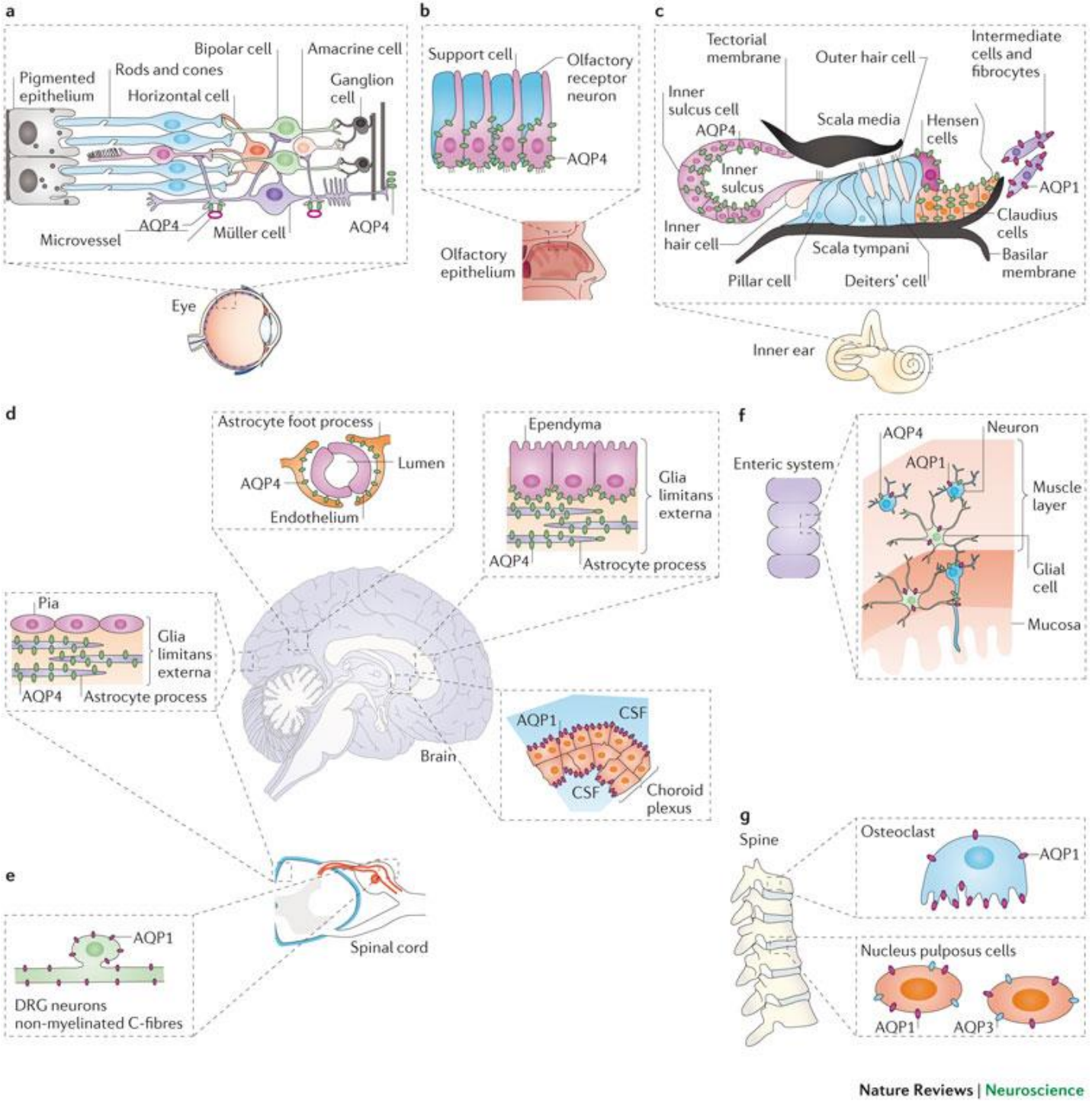


Binding of serum AQP4-Ab to adult mouse cerebellum as demonstrated by immunohistochemistry. Magnified images show staining of **b** | the microvasculature, **c** | the Virchowï Robin spaces and **d** | the pia mater. **eï g** | Binding of serum AQP4-Ab to the surface of cultured human embryonic kidney (HEK293) cells transfected with human full length AQP4 (panel e; see panel f for higher magnification) or nontransfected control cells (panel g), as demonstrated by immunocytochemistry. Bound IgG was visualized using a goat anti-human IgG secondary antibody labeled with fluoresceinisothiocyanate. Abbreviations: Ab, antibodies; AQP4, aquaporin-4.



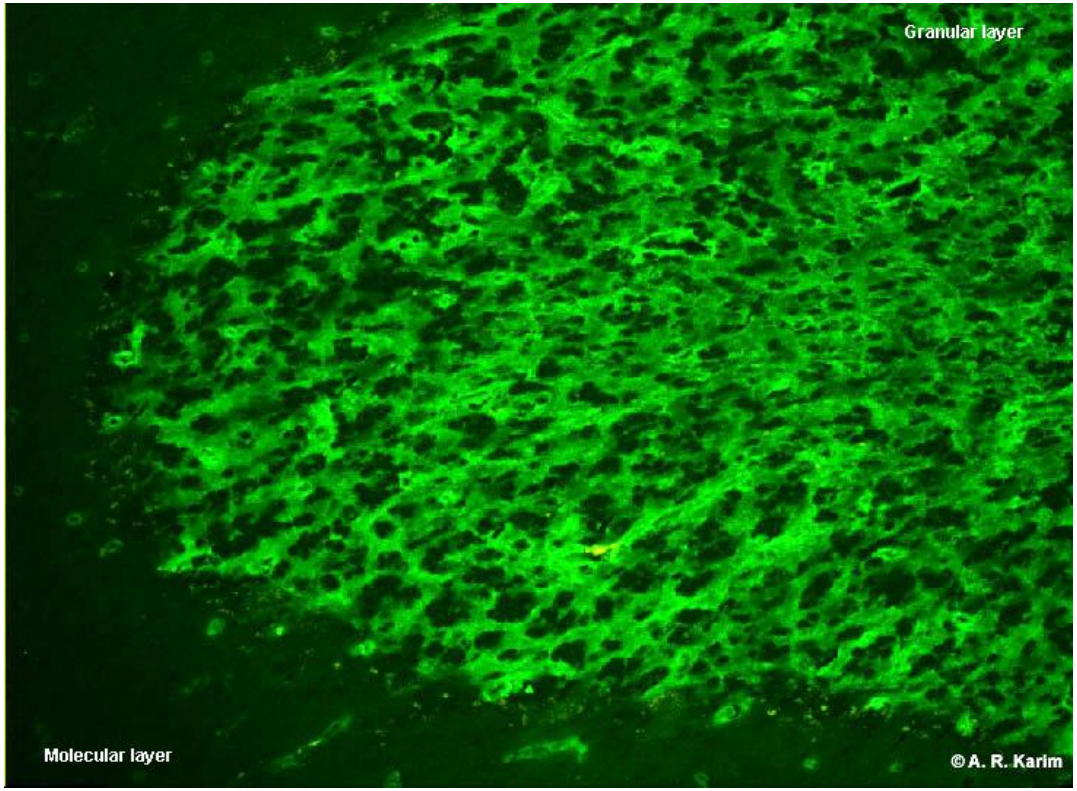


Localisation de Aquaporine 4

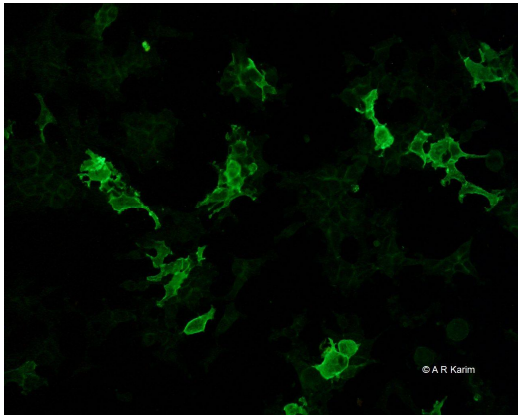


Nature Reviews | Neuroscience

NMO (aquaporin 4) antibodies



Often, AQP4 antibody is also associated with the staining of the cytoplasm of the granular cells: Such reactivity is also found in the CSF.



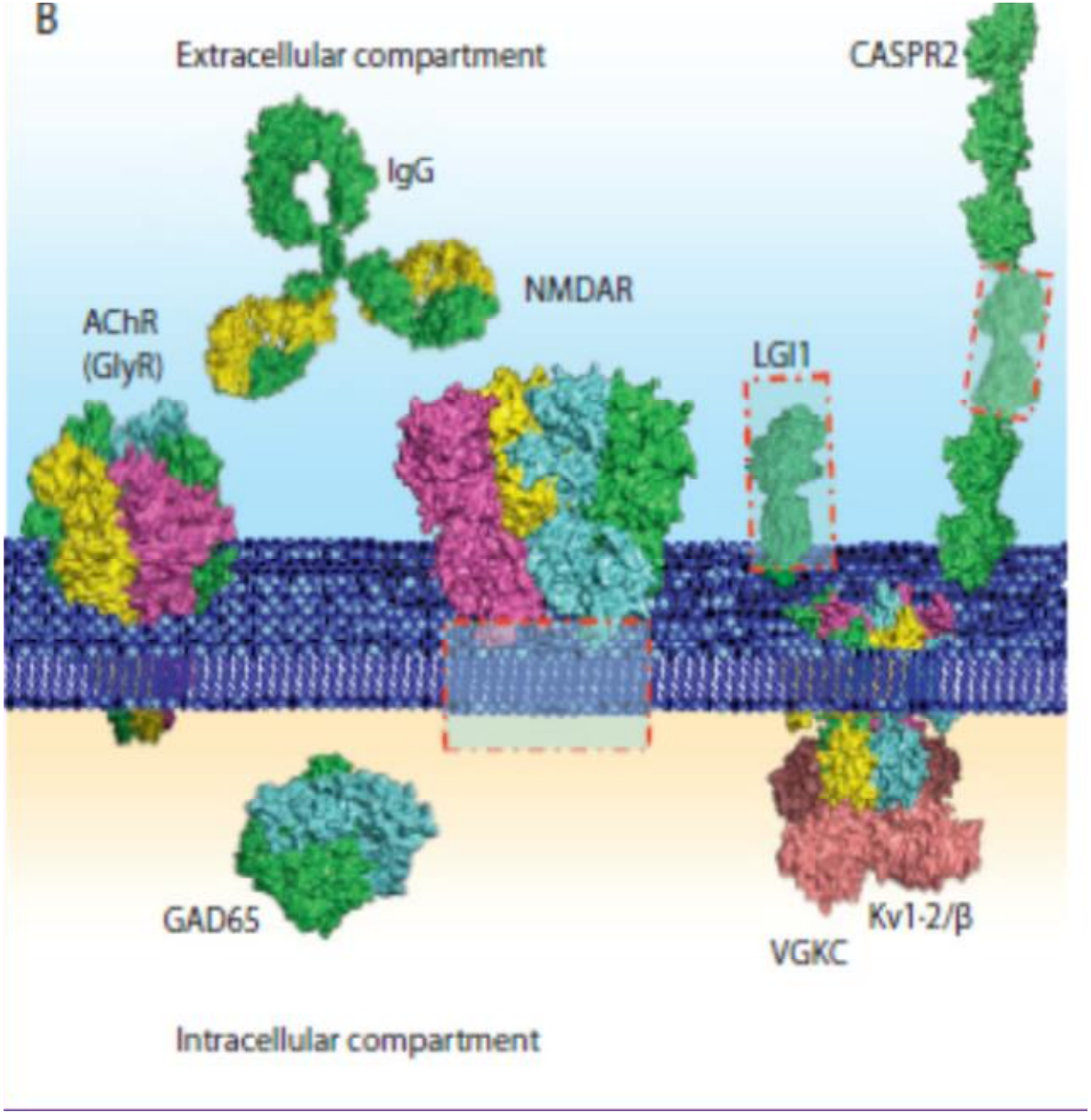
Clinical: Neuromyelitis optica (also known as Devic's disease, ~65%) is an immune-mediated demyelinated disorder of the optic nerve and spinal cord. The disorder resembles multiple sclerosis (MS) and the two cannot be distinguished from one another.

VGKC-complex encephalitis

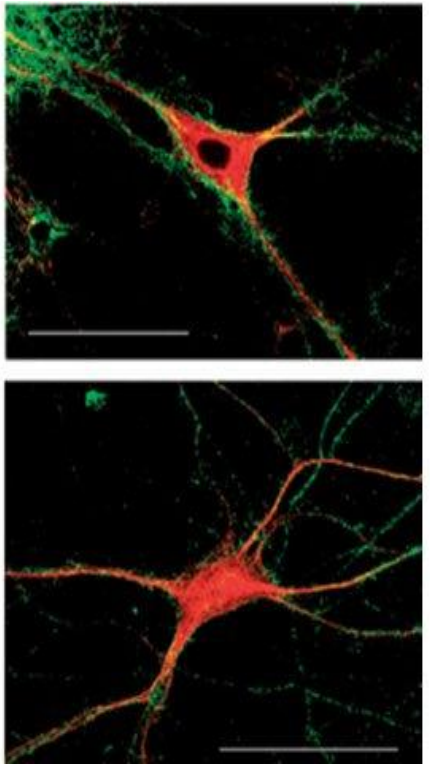
Manifestation (n=72) No. (%)

- Cerebral cortex 54 (75)
- Hypothalamic 27 (38) ï Hyponatraemia 36%
- Dyssomnia 19 (26)
- Extrapyramidal 15 (21)
- Cranial nerve/brainstem 14 (19)
- Myoclonus 21 (29)
- Autonomic 24 (33)
- Hyperhidrosis 7 (10)
- Somatic peripheral nerve 18 (25)

Encéphalites limbiques



	Lgi1 (n = 55)	Caspr2 (n = 19)	Caspr2 versus Lgi1 (uncorrected P-values)*
Male:female	37 : 18	16 : 3	NS
Amnesia	47	10	0.002
Confusion/disorientation	41	8	0.009
Seizures	49	10	0.0004
MRI medial temporal lobe high signal	31	5	0.03
Hyponatraemia	34	2	<0.0001
Neuromyotonia	2	10	<0.0001
Pain	6	7	0.031
Insomnia	4	6	0.017
Other sleep disorder	12	0	0.028
Any dysautonomia	8	6	NS
Active tumour (thymoma)	0	6 (5)	0.0002
Weight loss	2	6	0.003
Death	1	4	0.016
Final diagnosis			
Limbic encephalitis	49	7	<0.0001
Morvan's syndrome	2	3	NS
Neuromyotonia only	1	7	0.0002
Epilepsy only	1	2	NS
Other	2	0	NS
Morvan's syndrome or neuromyotonia	3	10	<0.0001



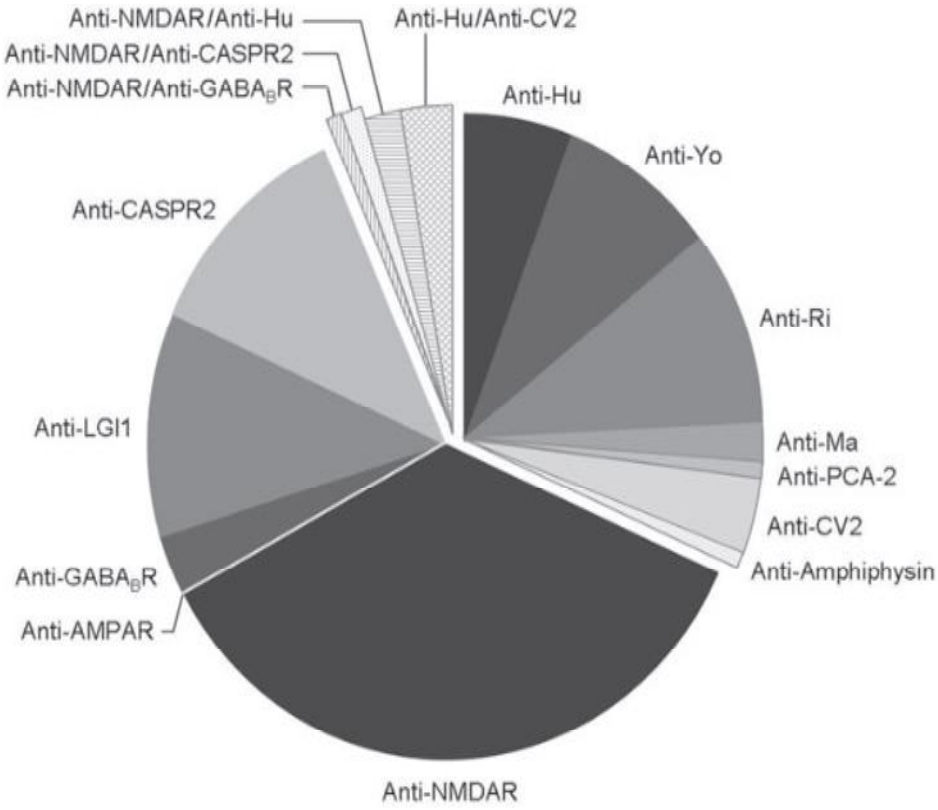
Lg1: encéphalite limbique
Caspr2: Neuromyotonie

The Frequency of Autoimmune *N*-Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project

Mary S. Gable,[1] Heather Sheriff,[1] Josep Dalmau,[2,3] Drake H. Tilley,[4] and Carol A. Glaser[1]

2007-2011

- 761 patients with unidentified encephalitis
- Enterovirus ï 30
- HSV ï 7
- VZV ï 5
- WNV ï 5
- **NMDAR - 32**



Encéphalite limbique à Ac anti-NMDAR

Stage 1 (10-20 days)

Å Psychosis

Å Seizures

Å Confusion

Å Amnesia

Stage 2

Å Involuntary movements

Å Altered consciousness

Å Autonomic features

Role in excitatory neurotransmission:

- NMDA
- AMPA

Role in inhibitory neurotransmission:

- GABA
- Glycine

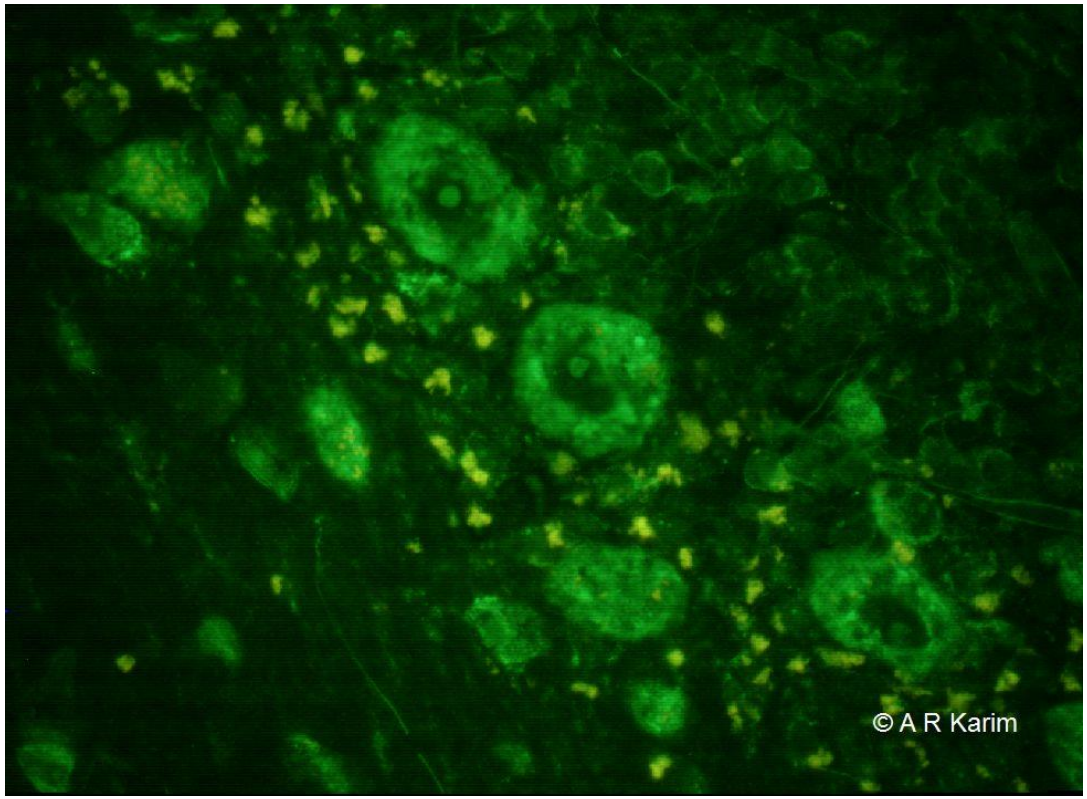
Role in axoglial interactions:

- Caspr2
- Contactin-2

Role under investigation:

- **Lgi1 (localisation to synapses and elsewhere)**

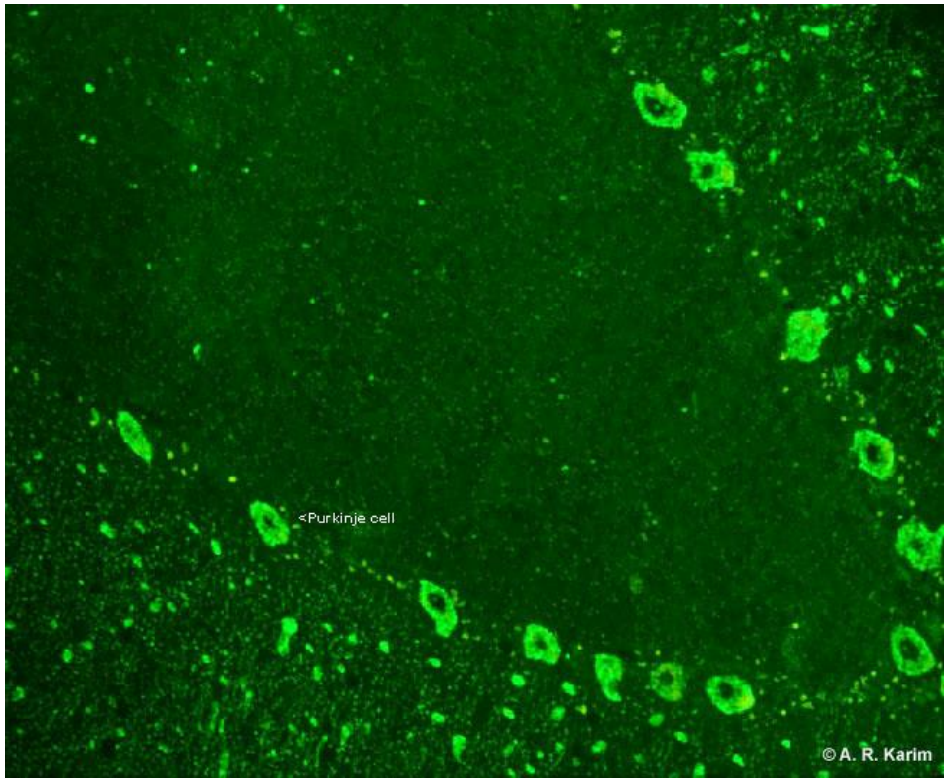
Non-Ma nucleolar antibody



This rare nucleolar antibody which reacts with cerebellar neurones and closely resembles Ma2 pattern. Extensive testing did not show any reactivity against stomach, kidney, liver, ovary, testis and ANA. Granular staining in the cytoplasm of HEp2 resembled ribosomal antibody but this was not ribosomal P. This antibody also reacted with peripheral neurones of the stomach but was negative for all the characterised paraneoplastic antibodies. The serum also tested negative against AChR, RF, ENAS, ANCA and TTG.

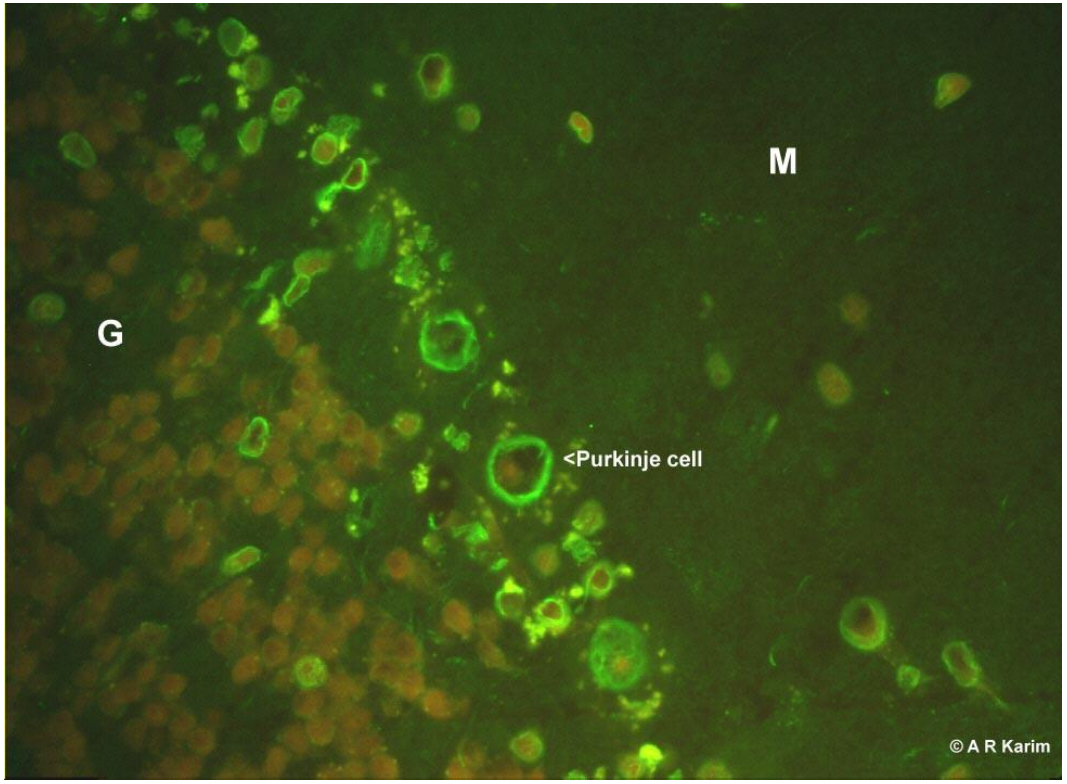
Conclusion: This is a rare antibody of undetermined significance which reacts with epitopes of primate liver and cerebellum generalised severe muscle weakness (unable to walk) and aches

Purkinje cell cytoplasm antibody (Yo/Tr type staining)



Human IgG autoantibody to primate cerebellum. This type of distribution can be mistaken for Yo antibody. The peripheral neurones were also spared.

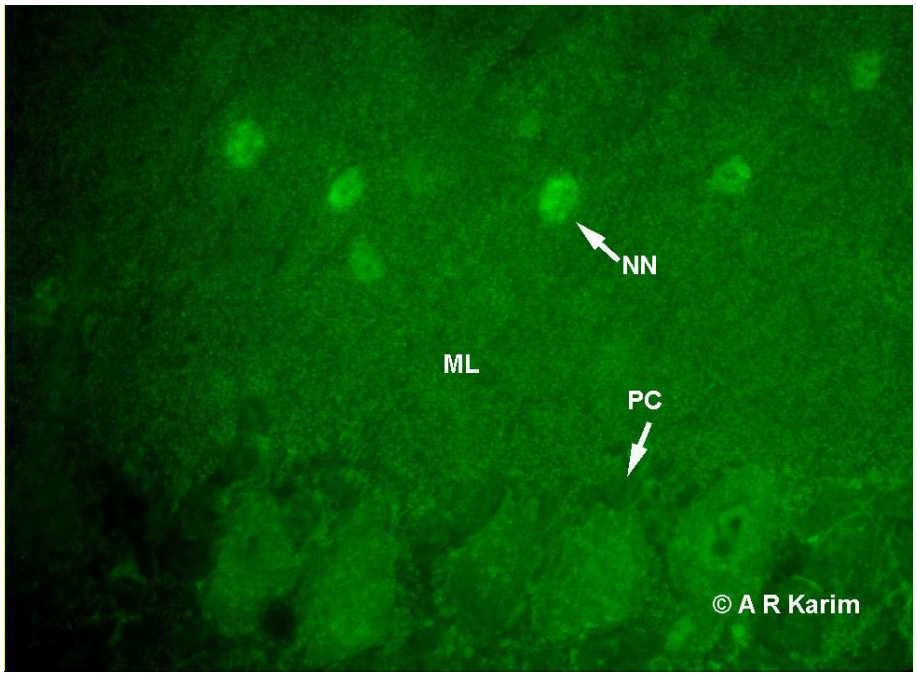
Neuronal nuclei rim

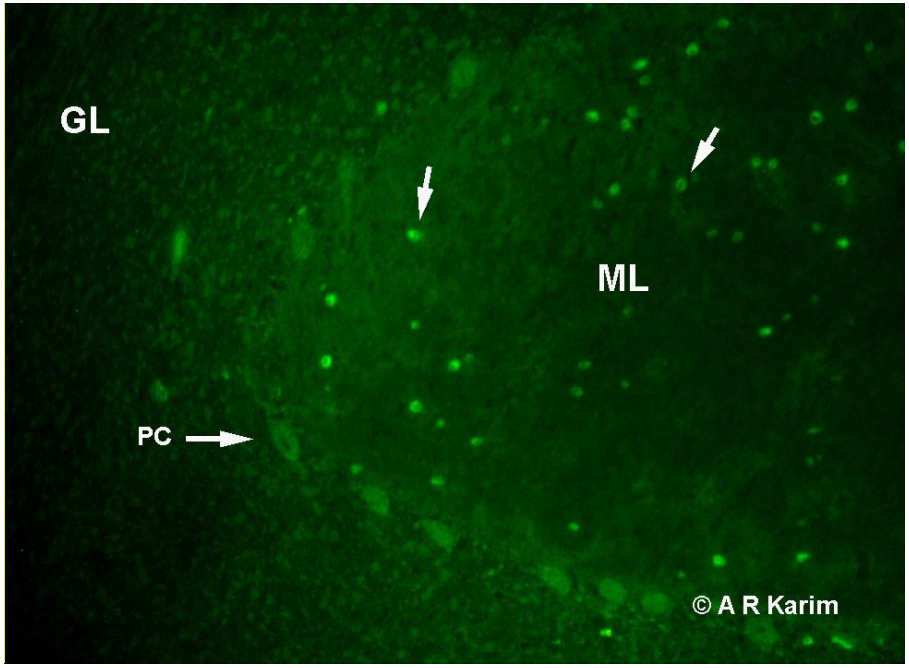


Primate cerebellum showing human IgG binding to the rims of the neuronal nuclei of the Purkinje layer (G is the granular and M is the molecular layer).

Clinical significance: Unknown.

Molecular layer specific antibody

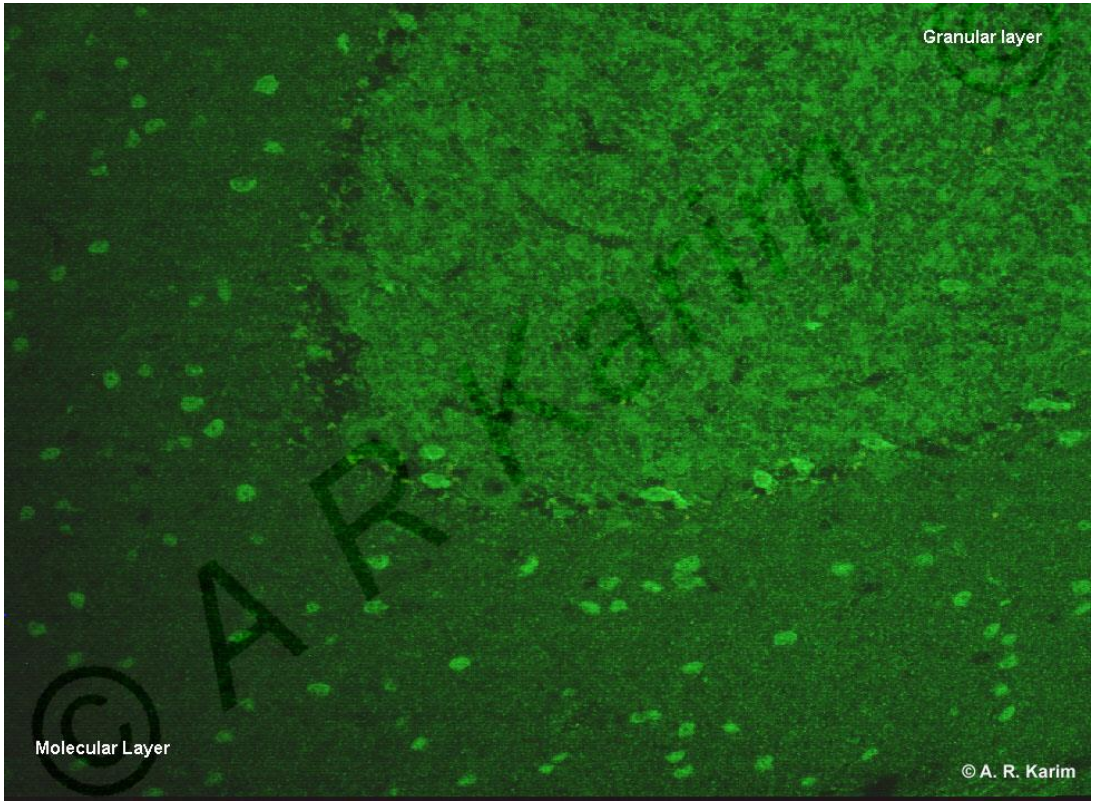




Primate cerebellum showing intense staining of neuronal nuclei (arrows) in the molecular layer (ML). There is no substantial staining of the Purkinje cells (PC) or granular layer (GL) neurones.

At a higher magnification, generalised speckled staining of the molecular layer appears similar to that seen with **amphiphysin**, The neuronal nuclei (NN) give the impression of being masked with the speckled staining.

Masking of Hu by anti-mitochondrial antibodies



This is an example of mitochondrial antibody masking Hu (ANNA1) reactivity that was only revealed when testing by Western blot. It is important to eliminate other antibodies particularly when there is excessive staining as seen here.

Table 1 Classical and non-classical paraneoplastic neurological syndromes

Syndromes of the central nervous system
Encephalomyelitis
Limbic encephalitis
Brainstem encephalitis
Subacute cerebellar degeneration
Opsoclonus-myoclonus*
Optic neuritis†
Cancer associated retinopathy†
Melanoma associated retinopathy†
Stiff person syndrome
Necrotising myelopathy‡
Motor neuron diseases‡
Syndromes of the peripheral nervous system
Subacute sensory neuronopathy
Acute sensorimotor neuropathy
Guillain-Barré syndrome‡
Brachial neuritis‡
Subacute/chronic sensorimotor neuropathies*
Neuropathy and paraproteinaemia†
Neuropathy with vasculitis‡
Autonomic neuropathies
Chronic gastrointestinal pseudo-obstruction
Acute pandysautonomia‡
Syndromes of the neuromuscular junction and muscle
Myasthenia gravis†
Lambert-Eaton myasthenic syndrome‡
Acquired neuromyotonia‡
Dermatomyositis‡
Acute necrotising myopathy‡

Classical syndromes are underlined.
*Associated with onconeural antibodies only with particular tumour types.
†Syndromes not included in the present recommendations.
‡Neurological syndromes not associated with known onconeural antibodies.

Syndromes neurologiques paraneoplasiques

Formes classiques
= forte probabilité de cancer

Formes non classiques
= faible probabilité de cancer

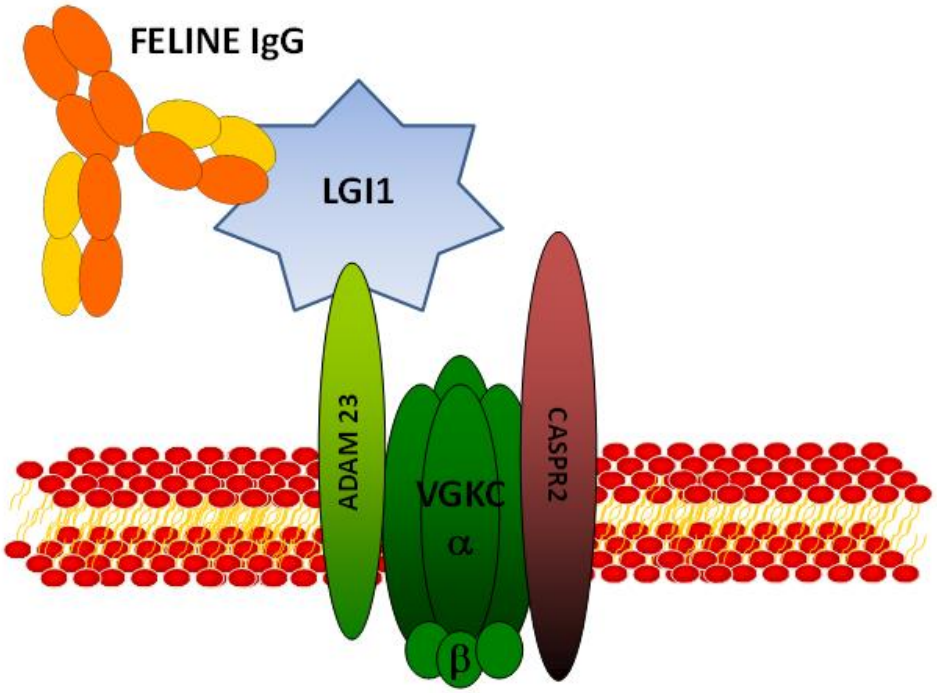
Auto-anticorps : méthodes

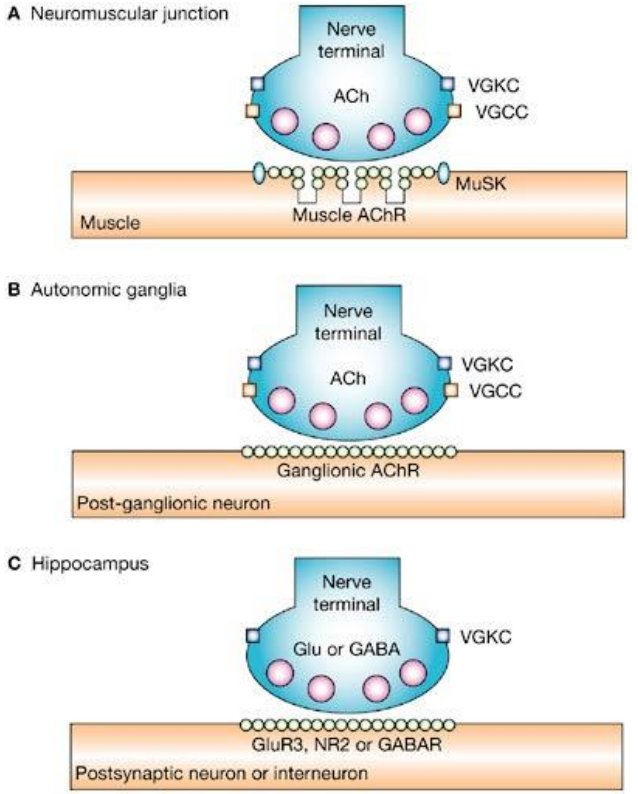
	iIHC*	Western Blot	RIA	ELISA	CBA
Limbic encephalitis					
Onconeural antibodies (anti-Hu, Ma1/2, CV2, amphiphysin)	+	+	..	..	..
GAD antibodies	+	+	+	+	..
VGKC-complex antibodies (LGI1, CASPR2, Contactin-2)†	+	..	+	..	+
NMDAR antibodies‡	+	..	..	+	+
AMPAR antibodies	+	..	..	..	+
$GABA_BR$ antibodies	+	..	..	..	+ → Envoyé en Allemagne
Faciobrachial dystonic seizures					
VGKC-complex antibodies (LGI1)†	+	..	+	..	+
Progressive cortico-subcortical encephalopathy					
NMDAR antibodies	+	..	..	+	+
Rapidly progressive abnormal behaviour resembling acute psychosis					
AMPAR antibodies; NMDAR antibodies	+	..	..	..	+
Morvan's syndrome					
VGKC-complex antibodies (LGI1, CASPR2)†	+	..	+	..	+
Stiff person syndrome complex					
GAD antibodies	+	+	+	+	..
GlyR antibodies	..	..	..	..	+ → Envoyé en Allemagne
Amphiphysin antibodies	+	+	..	..	..

Lancet Neurol 2011; 10: 759–72

Anti VGKC

Prolonge la dépolarisation des neurones moteurs





Anti-VGKC: cible = protéines associées au VGKC

- Kv1.1, Kv1.2, Kv1.6 — 3%
- LGI1
- CASPR2

  80%
- Contactin2 et autres — ?

Anti VGKC : associations

- CASPR2 : Neuromyotonie et EL paraneoplasiques (thymome, SCLC)

- LGI1/CASPR2 : Syndrome de Morvan

- LGI1 : Encéphalite limbique non paranéoplasique

Table 1. Clinical and Immunologic Features and Antibody Effects of Antibody-Mediated Encephalitis.*

Antibody (No. of Patients)†	Median Age (Range); Male:Female Ratio	Main Clinical Features on Presentation	Main Syndrome	Findings on MRI (% of Patients)‡	Frequency of Cancer (% of Patients)	Predominant IgG Class	In Vitro Antibody Effects
NMDAR (>1500)	21 yr (2 mo–85 yr); 1:4	Children: seizures, dyskinesias; adults: behavioral changes, psychiatric symptoms	NMDAR encephalitis	Normal findings (70) or nonspecific changes	Varies with age and sex; ovarian teratoma in women 18–45 yr old (58)§	IgG1	Internalization of NMDAR, disruption of NMDAR interaction with ephrin-B2 receptor
AMPAR (80)	36 yr (23–81); 1:2.3	Confusion, memory loss; in rare cases, psychiatric symptoms	Limbic encephalitis	Increased signal in medial temporal lobes (67)	SCLC, thymoma, or breast cancer (56)	IgG1	Internalization of AMPARs
$GABA_BR$ (80)	61 yr (16–77); 1.5:1	Seizures, memory loss, confusion	Limbic encephalitis, prominent seizures	Increased signal in medial temporal lobes (45)	SCLC (50)	IgG1	Blocking of agonist effect of baclofen on $GABA_BR$
LGI1 (400)	64 yr (31–84); 2:1	Memory loss, faciobrachial dystonic seizures, hyponatremia	Limbic encephalitis	Increased signal in medial temporal lobes (83)	Thymoma (<5)	IgG4	Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease in postsynaptic AMPAR
CASPR2 (120)	66 yr (25–77); 9:1	Memory loss, insomnia, dysautonomia, ataxia, peripheral-nerve hyperexcitability, neuropathic pain	Limbic encephalitis¶‖	Increased signal in medial temporal lobes (67)	Varies with the syndrome (<5 overall)**	IgG4	Alteration of gephyrin clusters in inhibitory synapses
mGluR5 (11)	29 yr (6–75); 1.5:1	Confusion, psychiatric symptoms	Encephalitis	Normal findings in 5 of 11 patients	Hodgkin's lymphoma in 6 of 11 patients	IgG1	Decrease in density of surface mGluR5
D2R (15)	6 yr (2–15); 1:1	Parkinsonism, dystonia, psychiatric symptoms	Basal ganglia encephalitis	Increased signal in basal ganglia (50)	No associated cancer	Unknown	Receptor internalization and decrease in D2R surface density
DPPX (45)	32 yr (13–76); 2.3:1	Confusion, diarrhea, weight loss	Encephalitis, myoclonus, tremors, hyperekplexia¶	Normal findings or nonspecific changes (100)	B-cell neoplasms (<10)	IgG4	Decrease in density of surface DPPX and Kv4.2
$GABA_AR$ (70)	40 yr (2 mo–88 yr); 1:1	Seizures, confusion, behavioral changes	Encephalitis, frequent status epilepticus	Cortical and subcortical FLAIR signal abnormalities involving two or more brain regions (77)	Thymoma (27)	IgG1	Selective reduction of $GABA_AR$ at synapses
Neurexin-3α (6)	14 yr (23–57); 2:4	Confusion, seizures	Encephalitis	Normal findings in 4 of 5 patients	No associated cancer	Unknown	Decrease in density of surface neurexin-3α and total number of synapses in neurons undergoing development

* Data are from a review of studies.[1] ADAM denotes a disintegrin and metalloproteinase; AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2 contactin-associated protein–like 2; D2R dopamine 2 receptor; DPPX dipeptidyl-peptidase–like protein 6; GABA γ-aminobutyric acid; $GABA_AR$ GABA type A receptor; $GABA_BR$ GABA type B receptor; LGI1 leucine-rich, glioma-inactivated 1; mGluR5 metabotropic glutamate receptor 5; NMDAR *N*-methyl-D-aspartate receptor; and SCLC small-cell lung cancer.

† The number of patients is the approximate number reported.

‡ Data on brain abnormalities are based on T_2-weighted MRI of the head with fluid-attenuated inversion recovery (FLAIR). Unless otherwise indicated, MRI showed normal features or nonspecific changes.

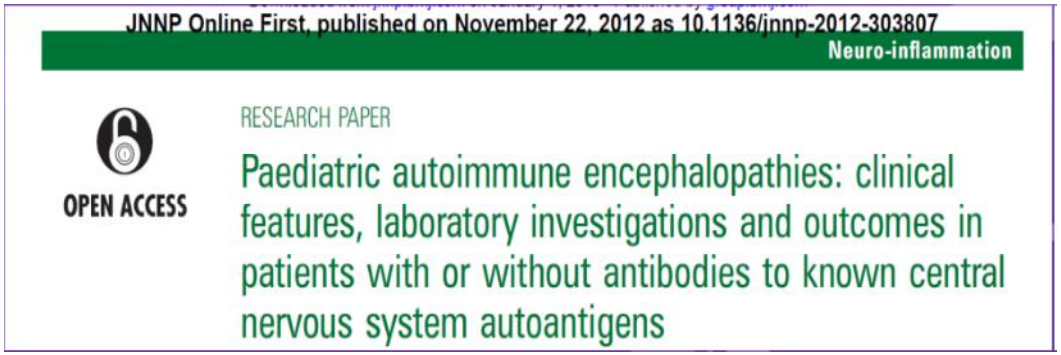
§ The association with teratoma is sex- and age-dependent. Young women frequently have an ovarian teratoma, but the presence of a tumor is uncommon in children and young men.

¶ Most patients have progressive symptoms over a period of more than 3 months.

‖ CASPR2 antibodies are frequently associated with Morvan's syndrome, a chronic disorder characterized by neuromyotonia, cognitive deterioration, sleep dysfunction (agrypnia excitata), and autonomic features.

** The frequency of an underlying tumor in patients with CASPR2 antibodies varies according to the syndrome; although patients with limbic encephalitis rarely have an underlying tumor (but if they do, the type of tumor may vary from patient to patient), 40% of patients with Morvan's syndrome have an underlying thymoma.

Encéphalies autoimmunes en pédiatrie



NMDAR ï 13/48
VGKC-complex ï 7/48
Glycine receptor ï 1/48

Anti-GM1 antibodies
- In cryptogenic partial epilepsy (6%)

GluR3 antibodies
- Mainly in Rasmussens encephalitis

NMDAR antibodies
- 140 patients identified in the first 2 years in the UK
- 26% of female patients aged 15 to 45 with unexplained new-onset epilepsy (*Arch Neurol* 2009; 66:458)

GABAA antibodies
- in severe epilepsy, encephalitis and status (Petit-Pedrol M et al, *Lancet Neurol* 2014 Mar)

Table 3. Syndromes of the central nervous system (CNS) and relevant well-characterized onconeural or neuronal cell-surface antibodies.

	Syndrome	Relevant antibodies
CNS	Subacute cerebellar degeneration	Hu, Yo, CV2/CRMP5, Ri, Tr[†], amphiphysin, VGCC
	25%	
	Encephalomyelitis	Hu, CV2/CRMP5, amphiphysin
	6%	
	Limbic encephalitis	Hu, Ma2, CV2/CRMP5, Ri, amphiphysin
	10%	NMDAR, Lgi1[‡], CASPR2[‡], GABA(b)-, AMPA-, mGluR5, glyR[‡], GAD[‡]
	Opsoclonus–myoclonus syndrome (adults)	Ri, Hu, Ma/Ta, NMDAR
	2%	
	Retinopathy	Hu, CV2/CRMP5, recoverin
	1%	
	Stiff-person syndrome	Amphiphysin, glyR[‡], GAD[‡]
	1%	

[†]Tr antibodies are not considered well-characterized but should raise a high suspicion of underlying cancer. [‡]Lgi1: leucine-rich, glioma-inactivated 1; gadolinium (GAD) glycine-receptor antibody associated syndromes are rarely paraneoplastic. VGCC: voltage-gated calcium channel; CV2/CRMP5: collapsing response mediator protein 5; NMDAR: N-methyl-D-aspartate receptor; CASPR2: contactin-associated protein-like 2; GAD: gadolinium; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid; mGluR5: metabotrophic glutamate receptor 5; glyR: α1-glycine receptor; GABA: γ-amino-butyric acid.

Antibody	Antigen	Associated syndromes and symptoms	Most common tumours
Onconeural antibodies (well-characterized, paraneoplastic antibodies tumour in >90%)			
Anti-Hu (ANNA-1)	HuD	Encephalomyelitis, limbic encephalitis, cerebellar degeneration, brain stem encephalitis, multi-segmental myelitis, sensory neuronopathy, sensory motor neuropathy, autonomic neuropathy	Lung cancer (85%), mostly SCLC, neuroblastoma, prostate carcinoma
Anti-Yo (PCA-1)	CDR2, CDR62	Paraneoplastic cerebellar degeneration	Ovarian, breast cancer
Anti-CV2/CRMP5	CRMP5	Encephalomyelitis, polyneuropathy, optic neuritis, limbic encephalitis, choreatic syndromes, cerebellar degeneration	SCLC, thymoma
Anti-Ta/Ma2[†]	MA-proteins	Limbic encephalitis, rhombencephalitis, male>>female	Testicular cancer
Anti-Ri (ANNA-2)	NOVA-1	Opsoclonus–myoclonus syndrome, rhombencephalitis, cerebellar degeneration, myelitis, jaw dystonia, laryngospasm	Breast, ovarian carcinoma, SCLC
Anti-amphiphysin	Amphiphysin	Stiff-person syndrome, limbic encephalitis, rhombencephalitis, cerebellar degeneration, polyneuropathy	Breast cancer, SCLC
Anti-recoverin	Recoverin	Retinopathy	SCLC
Anti-SOX-1 (AGNA)	SOX-1	Non-syndrome-specific	Sensitivity 67%, specificity 95% for SCLC in LEMS
Partially characterized onconeural antibodies (antigen not characterized or positive predictive value for tumour unknown)			
Anti-Tr (PCA-Tr)	DNER	Cerebellar degeneration	Hodgkin lymphoma, non-Hodgkin lymphoma
Anti-Zic4	ZIC1-4	Cerebellar degeneration	SCLC
PCA-2	280 kD	Encephalitis, Lambert–Eaton myasthenic syndrome, polyneuropathy	SCLC
ANNA-3	170 kD	Neuropathy, cerebellar degeneration, limbic encephalitis	SCLC

DNER: delta/notch-like epidermal growth factor-related receptor. [†]In some patients co-existing Ma1 antibodies, in which case brain stem syndromes and non-testicular tumours often predominate. SCLC: small-cell lung cancer; LEMS: Lambert–Eaton myasthenic syndrome (LEMS).

Antigen	NMDA receptor NR1	Lgi1	CASPR2	AMPA receptor	GABA(b) receptor	Glycine receptor α1	mGluR5
Age (median)/gender female : male	0·6–85 (21) 4:1	30–80 (60) 1:2	46–77 (60) 1:4	38–87 (60) 9:1	24–75 (62) 1:1	5–69 (43) 6:5	46, 15 1:1
Clinical syndrome	1. Prodomal syndrome 2. Psychiatric syndrome, seizures, amnesia 3. Movement disorders catatonia, autonomic instability	Limbic encephalitis, tonic or facio-brachial dystonic seizures, myoclonus	Morvan syndrome, encephalitis, neuromyotonia	Limbic encephalitis, psychiatric syndromes	Limbic encephalitis	Encephalomyelitis with rigidity and myoclonus, hyperekplexia, stiff-person syndrome, (retinopathy)	Limbic encephalitis, myoclonus
MRI T2/FLAIR hyperintensities medial-temporal	25% (only 33% abnormal)	>80%	40%	90%	70%	10%	≈ 50%
CSF: pleocytosis or ocb	95% (at onset 80%)	40%	25%	90%	90%	Some ocb	2/2
Tumour	Age-dependent 10–50% ovarian teratomas	<10%† (lung, thymoma)	<20%† (lung, thymoma)	70% (lung, breast, thymoma)	60% (lung)	Rare ≈ 10%	2/2 Hodgkin lymphoma
Miscellaneous	EEG in 90% abnormal, 30% 'extreme delta brush'	Hyponatraemia (60%)	Limbic encephalitis	Common relapses	Prominent seizures and status epilepticus	Few cases known	Only 2 cases known
Estimated relative frequency	55%	30%	4%	4%	5%	2%	<1%

†True tumour incidence unknown; ocb: oligoclonal bands; EEG: electroencephalograph; NMDA: N-methyl-D-aspartate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid; GABA: γ-amino-butyric acid receptor; CASPR2: contactin-associated protein-like 2; Lgi1: leucine-rich, glioma-inactivated 1; mGluR5: metabotrophic glutamate receptor 5.

Anti Ma2 paraneoplastic syndromes

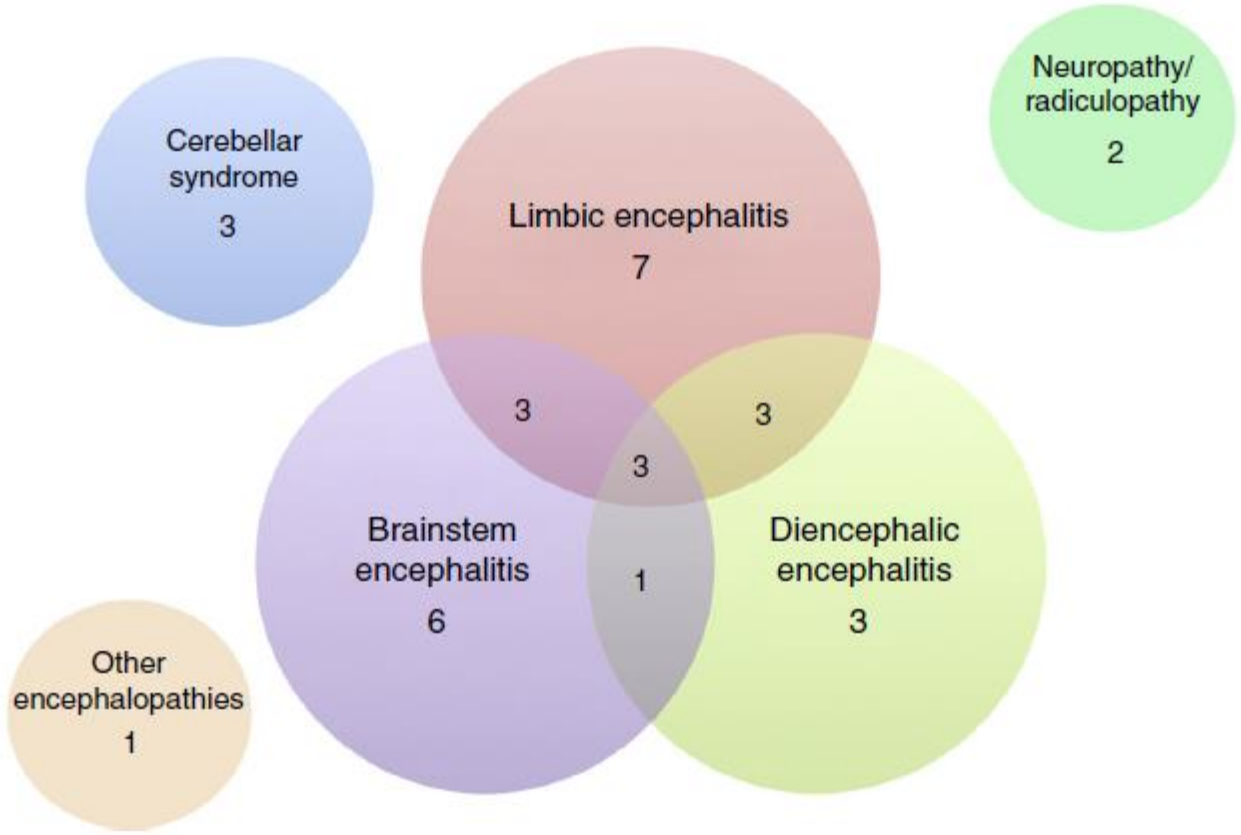


Figure 3 Clinical manifestations in paraneoplastic syndromes associated with anti-Ma and anti-Ma2 in a total of 32 patients. The numbers indicate how many patients were included in each symptom group.

Neurología. 2018;33(1):18—27

Table 3. Paraneoplastic and Other Autoimmune Neurological Disorders Organized by Anatomic Level.[a]

Neuraxis Level	Disorder	Examples of Salient Antibodies
Eye	Autoimmune retinopathy, optic neuropathy	CRMP-5-IgG, NMO-IgG
Cerebral cortex	Limbic encephalitis, encephalitides presenting primarily with seizures or cognitive dysfunction, myoclonus	ANNA-1, VGKC complex Ab, NMDA receptor Ab
Diencephalon	Hypothalamic dysfunction, sleep disorders	Ma1/Ma2 Ab
Basal ganglia	Chorea, dystonia	CRMP-5 IgG
Cerebellum	Cerebellar ataxia/degeneration	PCA-1, P/Q type calcium channel Ab
Brain stem	Brain stem encephalitis, jaw dystonia Stiff-man phenomena (including stiffness, spasms, exaggerated startle, if widespread referred to as progressive encephalomyelitis with rigidity and myoclonus [PERM]), opsoclonus–myoclonus syndrome	ANNA-2, Ma1/Ma2, glycine receptor ab
Cranial nerves	Special senses, bulbar, motor neuropathies	ANNA-1, CRMP-5 IgG
Spinal cord	Myelopathy, myoclonus Stiff-man phenomena	CRMP-5 IgG, NMO-IgG, GAD65 Ab
Peripheral somatic nerves and ganglia	Sensory neuronopathy, sensorimotor neuropathies	ANNA-1, VGKC complex Ab
Neuromuscular junction	Lambert-Eaton syndrome, Myasthenia gravis	P/Q-type calcium channel Ab, muscle AChR Ab
Muscle	Polymyositis dermatomyositis, necrotizing myopathy	Jo1 Ab, SRP-54 Ab
Autonomic and enteric nervous system	Dysautonomias (pandysautonomia or limited dysautonomia, which includes gastrointestinal dysmotilities)	ANNA-1, alpha-3 ganglionic AChR

Abbreviations: AchR, acetylcholine receptor; ANNA, antineuronal nuclear antibody; CRMP5, collapsin-response mediator protein 5; PCA-1, purkinje cell cytoplasmic antibody type 1; VGKC, voltage-gated potassium channel; NMDA, N-methyl-d-aspartate; GABA-B, gamma-aminobutyric acid-B; Jo-1 Abs, anti-histidyl-tRNA synthetase Abs; NMO, neuromyelitis optica; IgG, immunoglobulin G; PERM=progressive encephalomyelitis with rigidity and myoclonus; SRP=signal recognition particle.

[a]Many of these disorders can be multifocal.

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Table 2. Characteristic Findings Among Patients With Neuronal Nuclear or Cytoplasmic Antibodies.[a]

Antibody	Antigen	Oncological Association	Neurological Presentations
ANNA-1	ELAVL (Hu)	Small cell carcinoma	Limbic encephalitis, brain stem encephalitis, autonomic neuropathies, sensory neuronopathy, other peripheral neuropathies
ANNA-2	NOVA 1, 2 (Ri)	Small cell carcinoma, breast adenocarcinoma	Dementia, limbic encephalitis, brain stem encephalitis, myelopathy, peripheral neuropathy
ANNA-3	Unknown	Aerodigestive carcinomas	Brain stem encephalitis, limbic encephalitis, myelopathy, peripheral neuropathy
AGNA	SOX-1	Small cell carcinoma	Neuropathy, Lambert-Eaton syndrome, limbic encephalitis
Ma1, Ma2	PNMA1, PNMA2 (Ma1, Ma2)	Testicular (Ma2); breast, colon, testicular (Ma1)	Limbic encephalitis, hypothalamic disorder, brain stem encephalitis
PCA-1	CDR2	Mullerian adenocarcinoma, breast adenocarcinoma	Cerebellar ataxia, brain stem encephalitis, myelopathy, radiculopathies, peripheral neuropathies
PCA-2	Unknown	Small cell carcinoma	Limbic encephalitis, ataxia, brain stem encephalitis, Lambert-Eaton syndrome, peripheral and autonomic neuropathies
PCA-Tr	Unknown	Hodgkin lymphoma	Cerebellar ataxia
CRMP-5 IgG	CRMP-5	Small cell carcinoma, thymoma	Subacute onset dementia, personality change, aphasia, depression, chorea, ataxia, myelopathy, radiculopathy, neuropathy, Lambert-Eaton syndrome
Amphiphysin IgG	Amphiphysin	Small cell carcinoma, breast adenocarcinoma	Limbic encephalitis, aphasia, other subacute onset dementias, stiff-person phenomena, myelopathy, neuropathy
GAD65 antibody	GAD65	Thymoma; renal cell, breast or colon adenocarcinoma	Stiff-man syndrome, stiff-man phenomena, ataxia, seizures, limbic encephalitis, brain stem encephalitis, ophthalmoplegia, parkinsonism, myelopathy
ZIC-4 antibody	ZIC-4	Small cell carcinoma	Cerebellar ataxia

Abbreviations: AGNA, antiglial/neuronal nuclear antibody; ANNA, antineuronal antibody; CDR, cerebellar degeneration-related protein; ELAVL, embryonic lethal, abnormal vision, Drosophila-like 1; GAD65, 65 kDa isoform of glutamic acid decarboxylase; NOVA, neuro-oncological ventral antigen; PCA, Purkinje cell cytoplasmic antibody; PNMA, paraneoplastic Ma antigen; SOX, sex determining region Y-box 1; ZIC, zinc finger transcription factor; NMDA, *N*-methyl-D-aspartate; NMO, neuromyelitis optica; IgG, immunoglobulin G.

[a]Reproduced with permission from Springer.[5]

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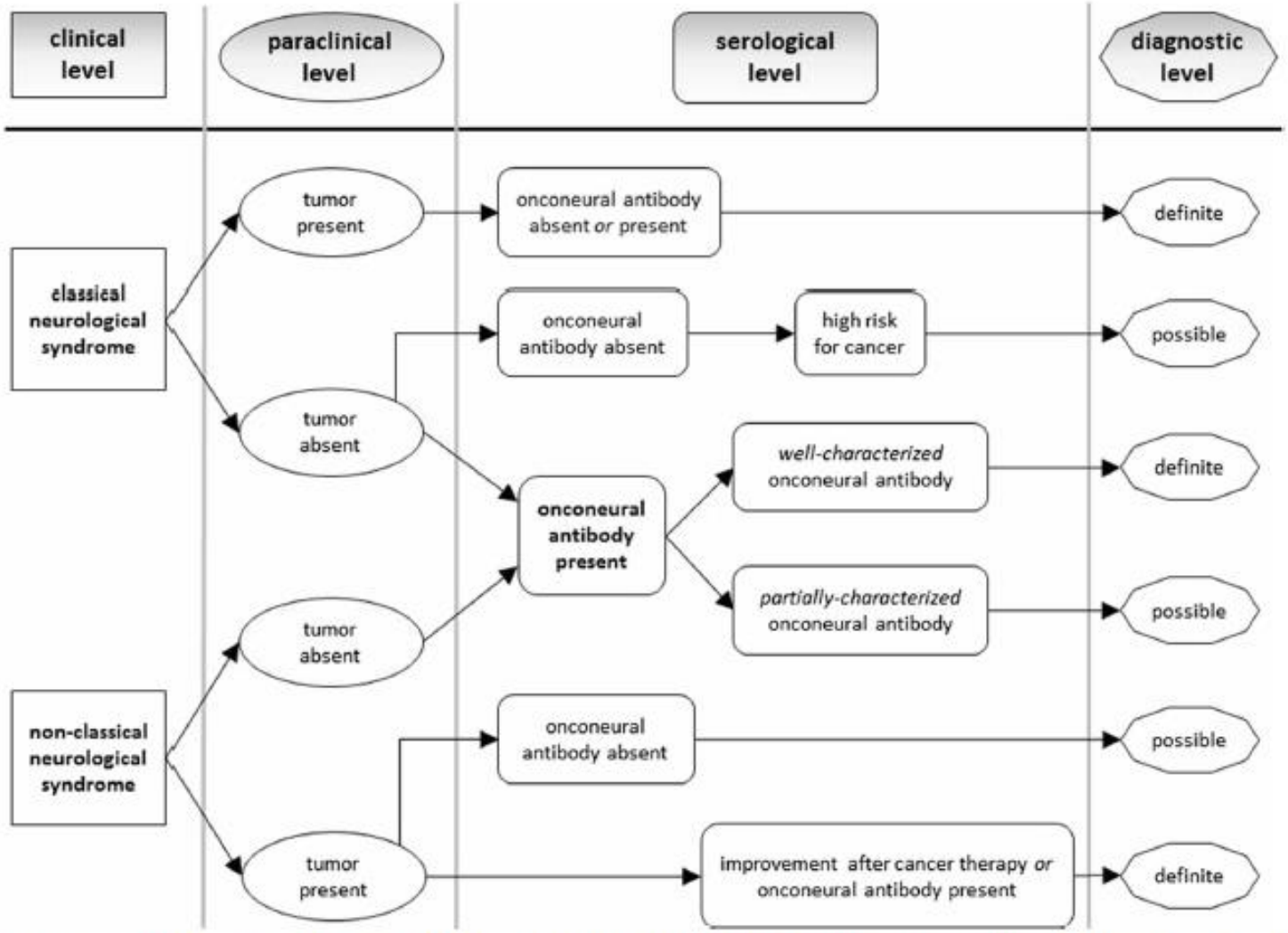


Fig. 1 Algorithm assessing the various levels of diagnostic evidence of the neurological syndromes suspected to be paraneoplastic, in accordance with the 2004 international consensus-based criteria (modified from [2])

(a) "**well-characterized**" onconeural antib
tive predictive value for tumor):
  (a) Anti-Hu (ANNA-1); in paranec
  subacute neuropathy: sensitivity,
  99% [22]
  (b) Anti-Yo (PCA-1); in paraneoplas
  bellar degeneration: sensitivity,
  99% [23]
  (c) Anti-CV2/CRMP5
  (d) Anti-Ta/Ma2
  (e) Anti-Ri (ANNA-2)
  (f) Anti-amphiphisin
  (g) Anti-recoverin
  (h) Anti-SOX-1 (AGNA); for small cel
  ma in Lambert-Eaton myasther
  (LEMS): sensitivity, 67%; specificity
  (i) Anti-Tr/DNER [24]; in paraneoplasti
  generation: sensitivity, 100%; specifi
  (j) Anti-GAD
(b) "**partially characterized**" onconeural a
known positive predictive value for tumo
  (a) Anti-Zic4
  (b) PCA2
  (c) ANNA3

Diagnostics of PNS is performed on serum samples [1, 2], but testing CSF is recommended in cases of dubious seropositivity or seronegativity. Reference laboratories, within the AINI network, are available for further and in depth diagnostic investigations. Diagnostics includes, sequentially, **screening tests on cerebellar tissue**, which yields immunohistochemically defined patterns, and recombinant protein-based **confirmation dot/line blot tests** [1, 2]. In dot/line blots denatured recombinant proteins might generate false positive and even false negative results [26, 27]. Notwithstanding these shortcomings, the trend towards the simplification of PNS diagnostics by using only dot/line blots satisfies the need of large generalist laboratories. Screening tests on cerebellar tissues are less expensive than dot/line blots, but require expertise in interpretation, which usually lacks in the generalist laboratories. Although not explicitly stated [1, 2], it is recommended not to use confirmatory tests without preliminary positive screening tests, which also allows to detect "atypical" antibody responses possibly targeting unknown CNS antigens. The frequency of "atypical" antibodies is around 3% of PNS [3]. They could be further studied for the target antigen identification. There are no guidelines for the clinical management of patients with "atypical" antibodies, but the possibility that they have a PNS should not be overlooked. Antibody reactivities to neuronal nuclei on cerebellar tissue that result negative on dot/line blots are usually due to systemic anti-nuclear antibodies (positive ANA test).

Analogously to other areas of neuroimmunological diagnostics, certified tests in certified large laboratories are replacing in-

Antigens	Neurological diseases	Methods of detection
NMDA-R	NMDA-R encephalitis	CBA, IHC
Lgi1	Limbic encephalitis, FBDS	CBA, IHC
Caspr2	Neuromyotonia, Morvan syndrome	CBA, IHC
Hu (ANNA-1)	Encephalomyelitis, limbic encephalitis, subacute sensory neuronopathy, brainstem, encephalitis, chronic intestinal pseudoobstruction	IIF/IHC, dot/line blot
Yo (PCA-1)	Subacute cerebellar degeneration	IIF/IHC, dot/line blot
Ri (ANNA-2)	Opsoclonus-myoclonus	IIF/IHC, dot/line blot
Tr	Subacute cerebellar degeneration	IIF/IHC, dot/line blot
Amphiphysin	Stiff person syndrome, encephalomyelitis	IIF/IHC, dot/line blot
GAD	Stiff person syndrome; cerebellar ataxia	IIF/IHC, ELISA/RIPA
CV2/CRMP5	Cerebellar degeneration, encephalomyelitis, limbic encephalitis	IIF/IHC, dot/line blot
Ma2	Limbic encephalitis	IIF/IHC, dot/line blot
VGCC	Lambert-Eaton myasthenic syndrome	RIPA
ACh-R	Myasthenia gravis	RIPA
MuSK	Myasthenia gravis	RIPA
Aquaporin-4	NMOSD	CBA
MOG	NMOSD, ADEM	CBA
MAG	IgM paraproteinemic neuropathy	ELISA
GM1, GM2	IgM-associated multifocal motor neuropathy	Dot/line blot, ELISA, TLC
GQ1b, GT1a	Fisher syndrome, Bickerstaff syndrome	Dot/line blot, ELISA, TLC

NMDA-R, N-methyl-D-aspartate receptor; *CBA*, cell-based assay; *IHC*, immunohistochemistry; *IIF*, indirect immunofluorescence Lgi1, leucine-rich, glioma inactivated 1; *FBDS*, faciobrachial dystonic seizures; *Caspr2*, contactin associated protein-like 2; *ANNA*, anti-neuronal nuclei antibody; *PCA*, Purkinje cell antibody; *GAD*, glutamic acid decarboxylase; *ELISA*, enzyme-linked immunosorbent assay; *CRMP5*, collapsin response mediator protein 5; *VGCC*, voltage-gated calcium channel; *RIPA*, radioimmunoprecipitation assay; *ACh-R*, acetylcholine receptor; *MuSK*, muscle specific kinase; *MOG*, myelin oligodendrocyte glycoprotein; *NMOSD*, neuromyelitis optica spectrum disorders; *ADEM*, acute disseminated encephalomyelitis; *MAG*, myelin-associated glycoprotein; *TLC*, thin layer chromatography

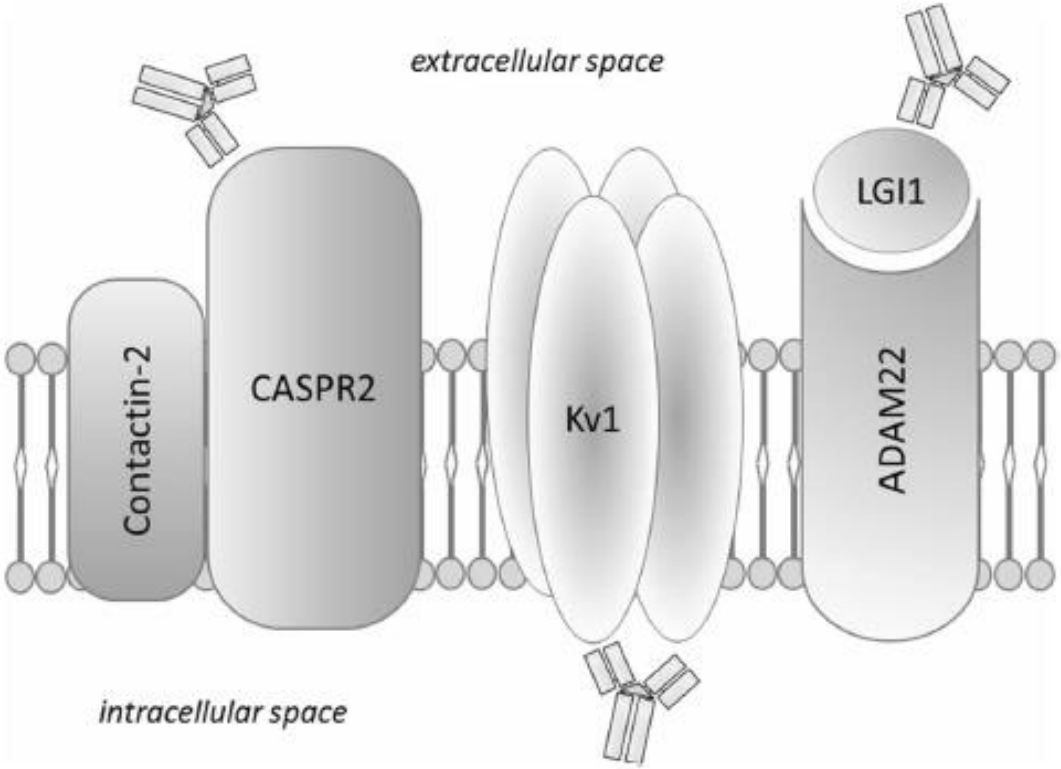
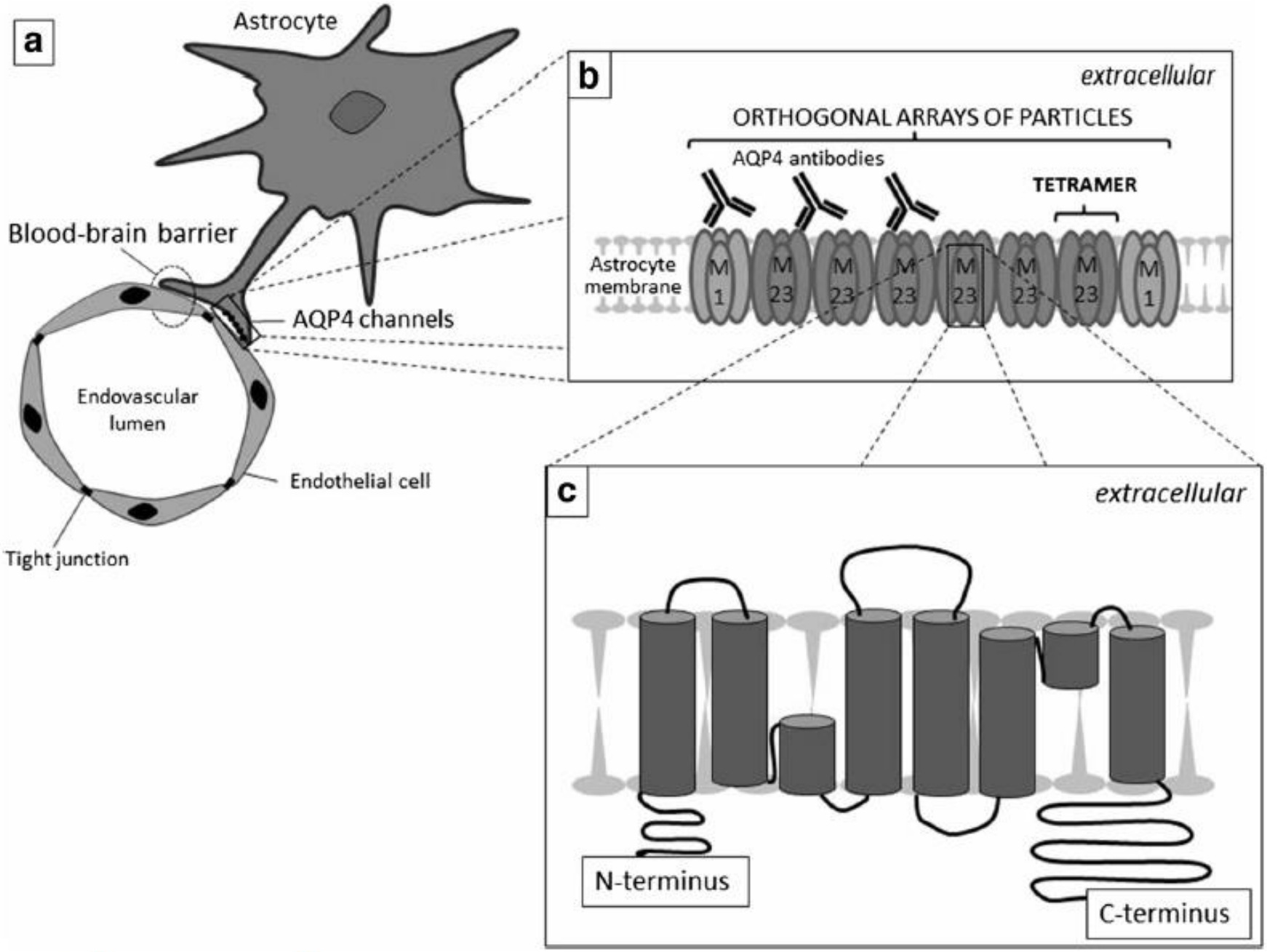


Fig. 1 Molecular organization of the *voltage-gated potassium* (*Kv*) *channel-complex*. Kv channels regulate cell-membrane potential and excitability in neurons and other cell types, with regulatory activity by interacting proteins (LGI1, leucine-rich, glioma inactivated 1) and accessory subunits (CASPR2, contactin-associated protein-like 2; contactin-2; ADAM22, disintegrin and metalloproteinase domain-containing protein 22); autoimmune antibody attacks can target extracellular or intracellular epitopes


a
Astrocyte
Blood-brain barrier
AQP4 channels
Endovascular lumen
Endothelial cell
Tight junction
b
extracellular
ORTHOGONAL ARRAYS OF PARTICLES
AQP4 antibodies
TETRAMER
Astrocyte membrane
M 1
M 23
M 23
M 23
M 23
M 23
M 23
M 1
c
extracellular
N-terminus
C-terminus

Demographic and clinical characteristics of autoimmune encephalitis patients.

Type of antibodies	Number	Age range (years)	Gender	First symptom	MRI T2/FLAIR abnormality (%)	Malignancy	Clinical improvement
NMDA	16	15.5 (2–44)	M 8 F 8	Behavioral changes (43.7%), seizure (31.2%)	43.75	2 (ovarian teratoma)	62.5% (10)
VGKCc	9	55 (45–86)	M 7 F 2	Behavioral changes (33%), seizure (22.2%)	77.8	4 (breast Ca, lymphoma, thymoma, PTCA)	44.4% (4)
GAD	6	39.5 (15–72)	M 4 F 2	Memory loss (40%)	33.3	0	50% (3)
TPO	9	47 (25–74)	M 3 F 6	Behavioral changes (33%)	66.7	0	55.6% (5)
$GABA_B$	3	53 (34–69)	M 1 F 2	Seizures (66%)	66.7	1 (SCC lung)	66.7% (2)
Hu	1	66	M 0 F 1	Memory loss (100%)	0	0	0
No Antibody	20	44 (5–66)	M 13 F 7	Seizure (41%)	70	5 (breast Ca, prostate Ca, pancreatic Ca, ADCA lung, testicular Ca)	65% (13)

VGKCc voltage gated potassium channel complex antibody; NMDA N-methyl-D-aspartate receptor antibody; GAD glutamic acid decarboxylase receptor antibody; $GABA_B$ γ-aminobutyri acid B receptor antibody; M Male; F Female; Ca Cancer; PTCA Papillary thyroid cancer; SCC small cell cancer; ADCA adenocarcinoma; NL Normal.

Table 1. Characteristic Neurological and Oncological Findings Among Patients With Plasma Membrane Protein Antibodies.

Antibody	Antigen	Oncological Association	Neurological Presentation
VGKC complex antibody	LGI1, CASPR2	Small cell lung carcinoma; thymoma; adenocarcinoma of breast, prostate	Limbic encephalitis, amnestic syndrome, executive dysfunction, personality change, disinhibition hypothalamic disorder, brain stem encephalitis, ataxia, extrapyramidal disorders, myoclonus, peripheral, and autonomic neuropathy
NMDA receptor antibody	NR1	Ovarian teratoma	Anxiety, psychosis, seizures, amnestic syndrome, extrapyramidal disorders
AMPA receptor antibody	GluR1,2	Thymic tumors, lung carcinomas, breast carcinoma	Limbic encephalitis, nystagmus, seizures
GABA-B receptor antibody	GABA-B	Small cell lung carcinoma, other neuroendocrine neoplasia	Limbic encephalitis, orolingual dyskinesias
P/Q and N type calcium channel antibody	P/Q and N-type calcium channels	Small cell carcinoma, breast, or gynecological adenocarcinoma	Encephalopathies, myelopathies, neuropathies, Lambert-Eaton syndrome
Muscle AChR antibody	Muscle AChR	Thymoma, thymic carcinoma, lung carcinoma	Myasthenia gravis. Also sometimes observed in paraneoplastic CNS contexts
Neuronal ganglionic AChR antibody	Neuronal ganglionic AChR	Adenocarcinoma, thymoma, small cell carcinoma	Dysautonomia, peripheral somatic neuropathies, encephalopathies.
NMO-IgG	Aquaporin-4	Some reports of thymoma and other solid tumors	Relapsing optic neuritis, transverse myelitis, encephalopathies
Glycine receptor antibody	α1 subunit GlyR	Lymphoma and thymoma reported	Stiff-man syndrome and variants
Metabotropic glutamate receptor 5 antibody	mGluR5	2 patients with Hodgkin lymphoma	Limbic encephalitis

Abbreviations: AchR, acetylcholine receptor; AMPA, alpha-amino-3-hydroxy-5-methyl-4- isoxazole-propionic acid; CASPR, contactin-associated protein; GABA, gamma amino butyric acid; GluR, glutamate receptor; GlyR, glycine receptor; LGI1, leucine-rich, glioma inactivated 1; NMDA, *N*-methyl-D-aspartate; NMO, neuromyelitis optica; VGKC, voltage-gated potassium channel; IGg, immunoglobulin G.
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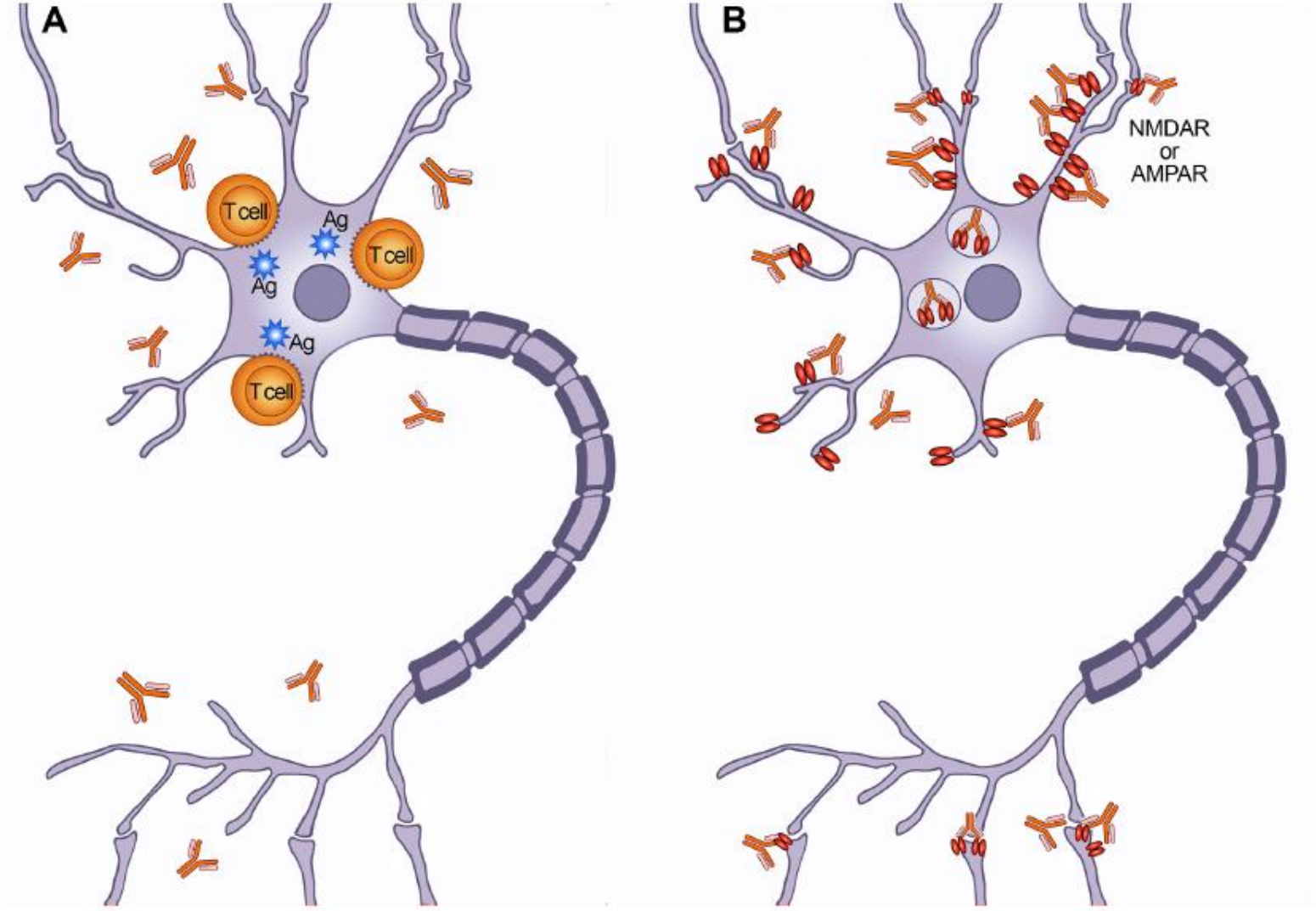
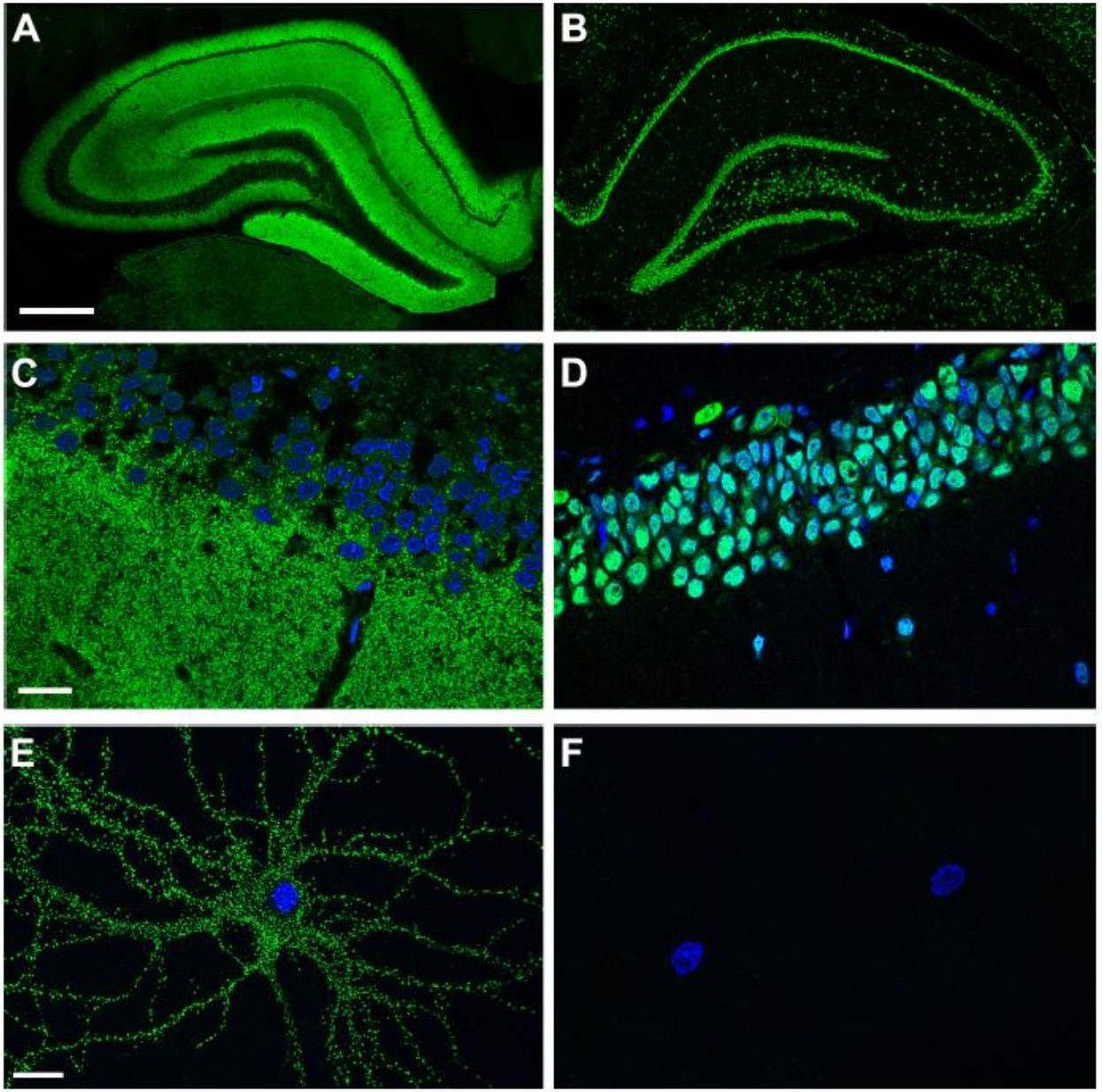

A
Tcell
Ag
Tcell
Ag
Ag
Tcell
B
NMDAR
or
AMPAR


A
B
C
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E
F

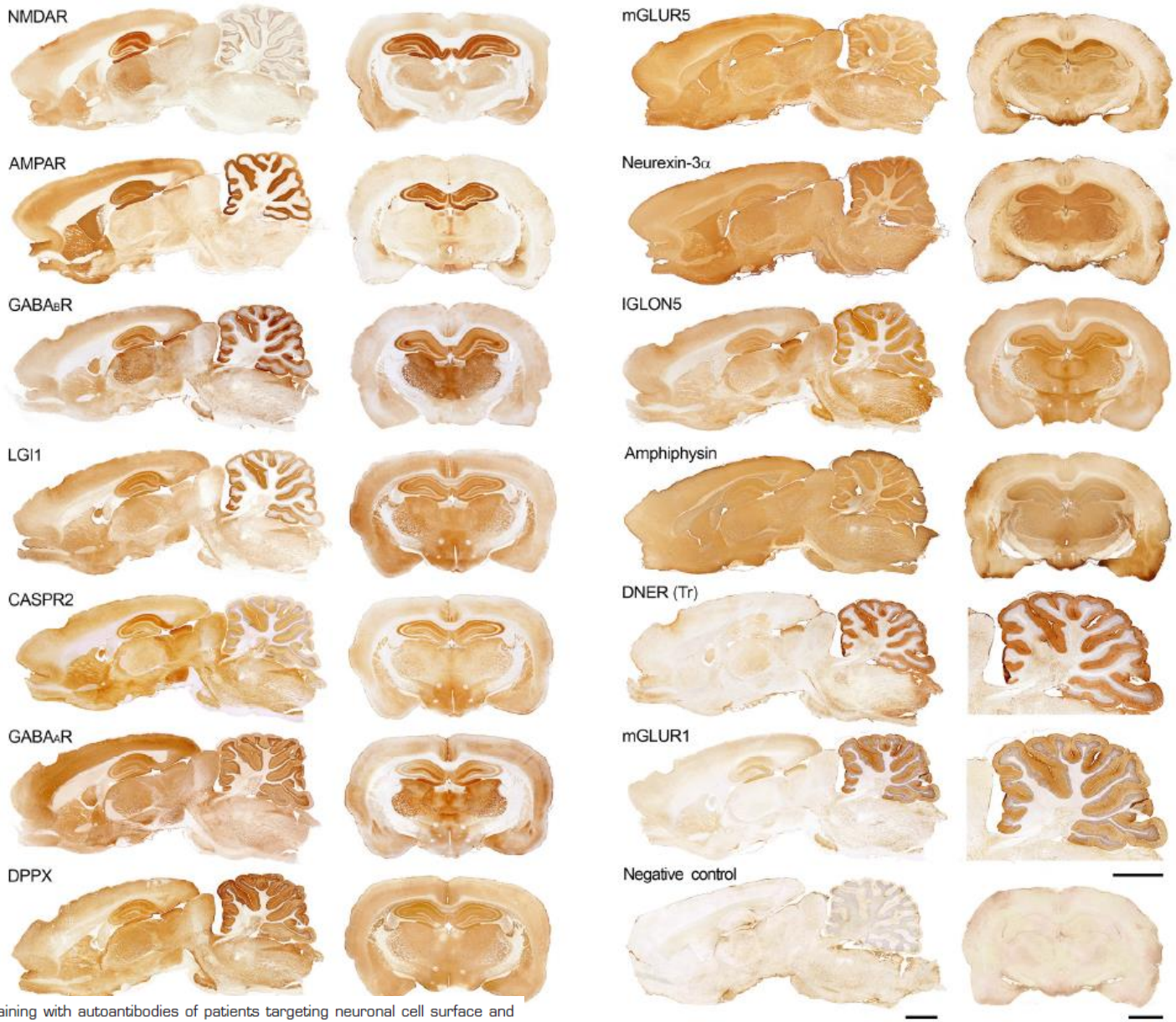


FIGURE 3. Rat brain immunostaining with autoantibodies of patients targeting neuronal cell surface and synaptic proteins. Sagittal and coronal sections of rat brain immunostained with 13 autoantibodies against neuronal cell surface and synaptic proteins. For DNER and mGluR1, which predominantly react with cerebellum, the coronal section has been replaced by a sagittal section of cerebellum. Autoantibodies against VGCC, dopamine 2R, and GlyR with patterns of immunostaining poorly visible with this technique have been excluded. Technique of immunostaining was reported in Ref. 7. All tissue sections have been mildly counterstained with hematoxylin. Scale bars: all panels = 2 mm. [From Dalmau et al. (56).]

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 update	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
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-3α	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 (211, 293)	Normal or cerebellar atrophy	Unknown	A few cases described	Hodgkin disease
Glycine receptor	Muscle rigidity, spasms	PERM, stiff-person syndrome (42, 214)	Normal or non-region specific changes	Unknown	<5%	Thymoma, lung, Hodgkin
Amphiphysin	Rigidity, spasms	Stiff-person, encephalomyelitis (256)	Normal or non-region specific changes	Unknown	>90%	Breast cancer, SCLC

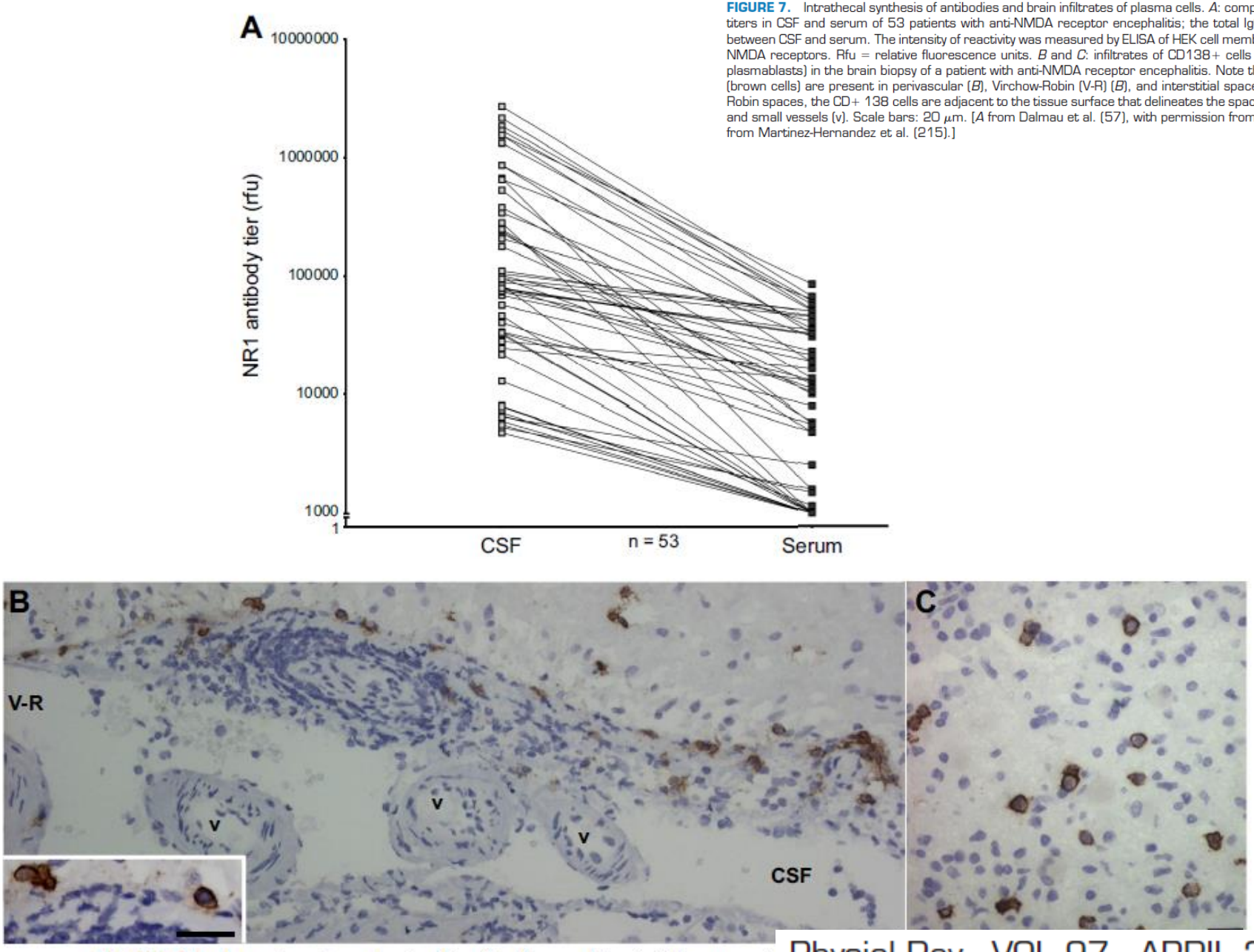
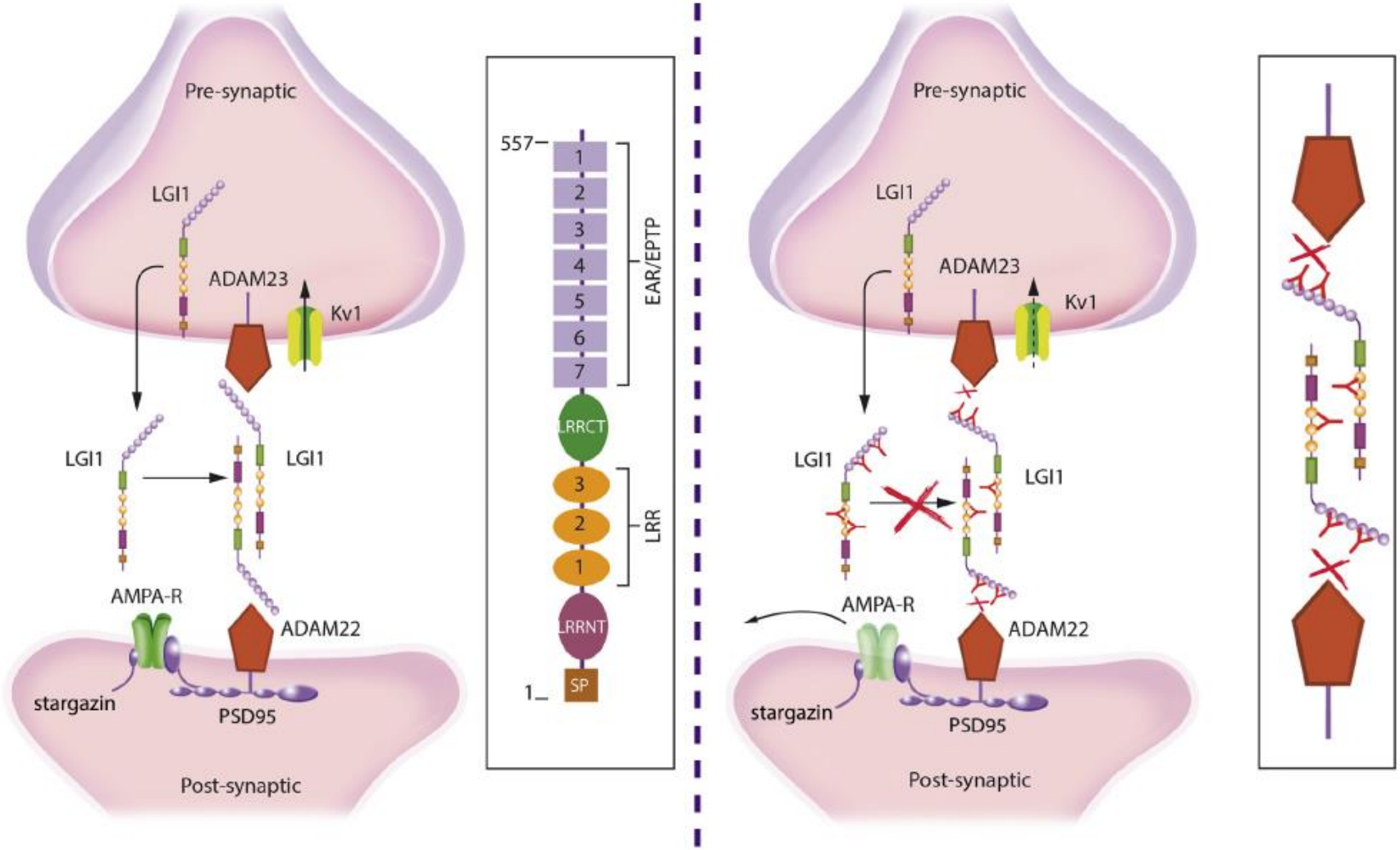
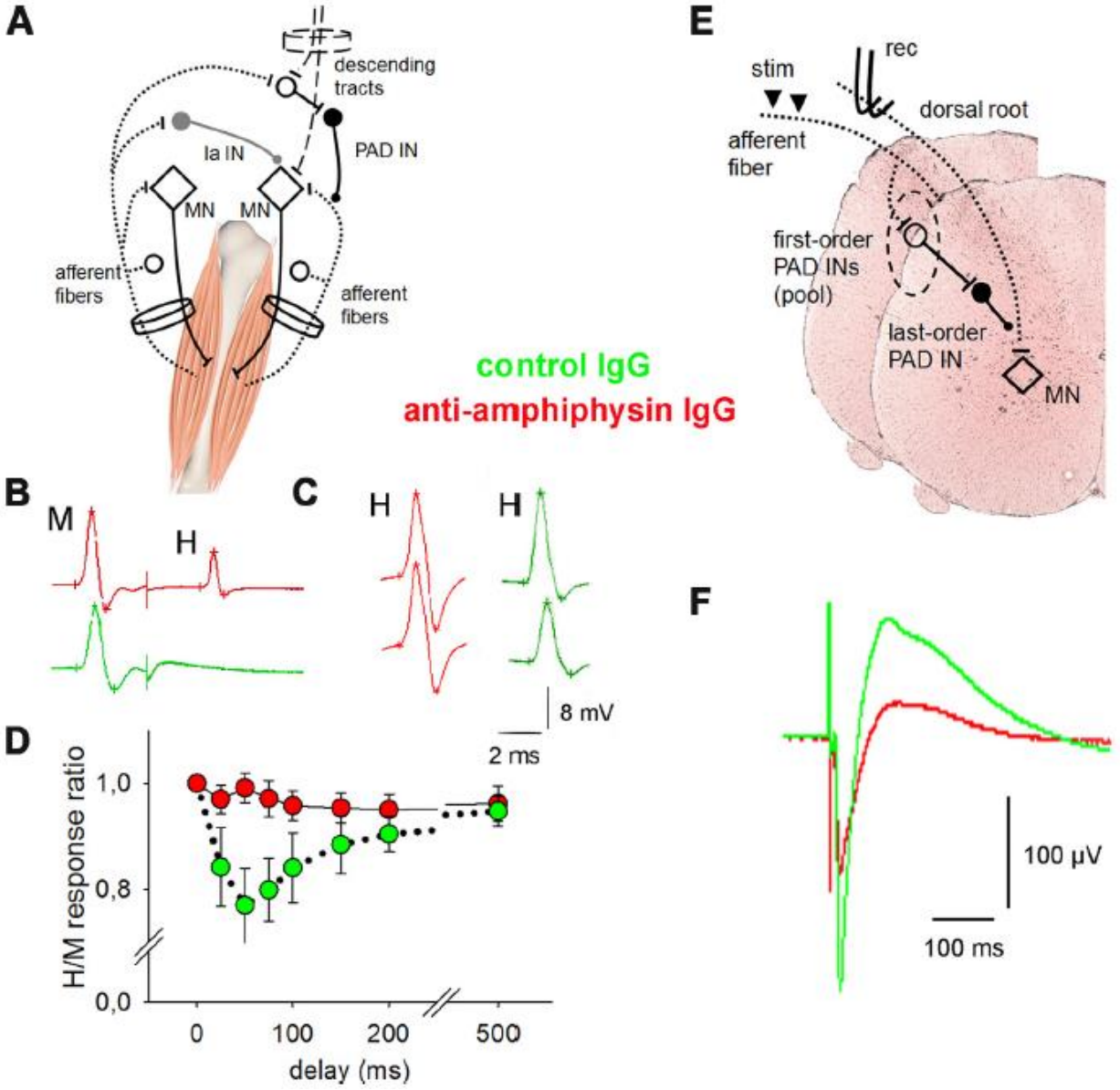


FIGURE 7. Intrathecal synthesis of antibodies and brain infiltrates of plasma cells. *A*: comparison of antibody titers in CSF and serum of 53 patients with anti-NMDA receptor encephalitis; the total IgG was normalized between CSF and serum. The intensity of reactivity was measured by ELISA of HEK cell membranes expressing NMDA receptors. Rfu = relative fluorescence units. *B* and *C*: infiltrates of CD138+ cells (plasma cells and plasmablasts) in the brain biopsy of a patient with anti-NMDA receptor encephalitis. Note that CD+138 cells (brown cells) are present in perivascular (*B*), Virchow-Robin (V-R) (*B*), and interstitial spaces (*C*). In Virchow-Robin spaces, the CD+ 138 cells are adjacent to the tissue surface that delineates the spaces containing CSF and small vessels (v). Scale bars: 20 μm. [*A* from Dalmau et al. (57), with permission from Elsevier. *B* and *C* from Martinez-Hernandez et al. (215).]

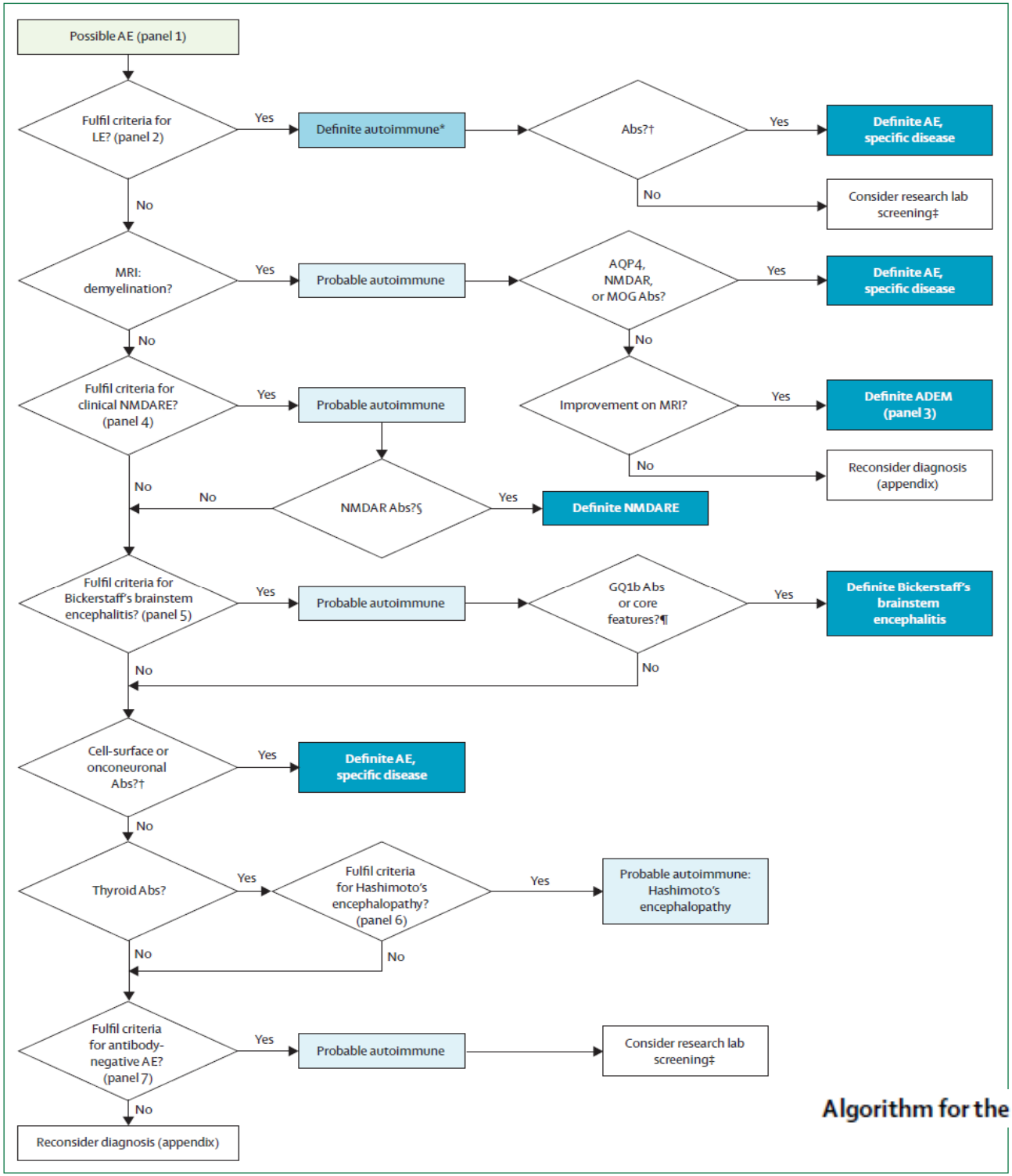

Pre-synaptic
LGI1
ADAM23
Kv1
LGI1
LGI1
AMPA-R
ADAM22
stargazin
PSD95
Post-synaptic
557
1
2
3
4
5
6
7
EAR/EPTP
LRRCT
3
2
1
LRR
LRRNT
SP
1
Pre-synaptic
LGI1
ADAM23
Kv1
LGI1
LGI1
AMPA-R
ADAM22
stargazin
PSD95
Post-synaptic


A
descending tracts
Ia IN
PAD IN
MN
MN
afferent fibers
afferent fibers
control IgG
anti-amphiphysin IgG
B
M
H
C
H
H
8 mV
2 ms
D
H/M response ratio
1,0
0,8
0,0
0
100
200
500
delay (ms)
E
stim
rec
dorsal root
afferent fiber
first-order PAD INs (pool)
last-order PAD IN
MN
F
100 µV
100 ms

	Syndrome	Diagnostic assay	Frequency of cancer	Main type of cancer
Antibodies against intracellular antigens				
Hu (ANNA1)[8]*	Limbic encephalitis	Western blot	>95%	Small-cell lung carcinoma
Ma2[9]	Limbic encephalitis†	Western blot	>95%	Testicular seminoma
GAD[10]	Limbic encephalitis‡	Radioimmunoassay	25%§	Thymoma, small-cell lung carcinoma
Antibodies against synaptic receptors				
NMDA receptor[11]	Anti-NMDA receptor encephalitis	Cell-based assay	Varies with age and sex	Ovarian teratoma¶
AMPA receptor[12]	Limbic encephalitis	Cell-based assay	65%	Thymoma, small-cell lung carcinoma
$GABA_B$ receptor[13]	Limbic encephalitis	Cell-based assay	50%	Small-cell lung carcinoma
$GABA_A$ receptor[14]	Encephalitis	Cell-based assay	<5%	Thymoma
mGluR5[15]	Encephalitis	Cell-based assay	70%	Hodgkin's lymphoma
Dopamine 2 receptor[16]	Basal ganglia encephalitis	Cell-based assay	0%	..
Antibodies against ion channels and other cell-surface proteins				
LGI1[17]	Limbic encephalitis	Cell-based assay	5–10%	Thymoma
CASPR2[18]	Morvan's syndrome|| or limbic encephalitis	Cell-based assay	20–50%	Thymoma**
DPPX[19]	Encephalitis††	Cell-based assay	<10%	Lymphoma
MOG[20]‡‡	Acute disseminated encephalomyelitis	Cell-based assay	0%	..
Aquaporin 4[21]‡‡	Encephalitis	Cell-based assay	0%	..
GQ1b[22]	Bickerstaff's brainstem encephalitis	ELISA	0%	..

GAD=glutamic acid decarboxylase. LGI1=leucine-rich glioma inactivated 1. CASPR2=contactin associated protein 2. DPPX=dipeptidyl-peptidase-like protein-6. MOG=myelin oligodendrocyte glycoprotein. *Amphiphysin or CV2 (CRMP5) antibodies instead of Hu antibodies in a few patients with limbic encephalitis and small-cell lung carcinoma. †Limbic encephalitis frequently associated with hypothalamic and mesencephalic involvement. ‡GAD antibodies occur more frequently in patients with stiff person syndrome and cerebellar ataxia. The association with cancer preferentially occurs in patients with limbic encephalitis. §Tumours found more frequently in men older than 50 years.[23] ¶Ovarian teratoma usually found in young women aged 12–45 years. ||Morvan's syndrome usually has a more chronic clinical course, but might present with predominant cognitive and behavioural symptoms fulfilling criteria of possible autoimmune encephalitis. **Thymoma associated with Morvan's syndrome rather than limbic encephalitis. ††Encephalitis associated with diarrhoea and hyperekplexia. ‡‡Mostly restricted to children.

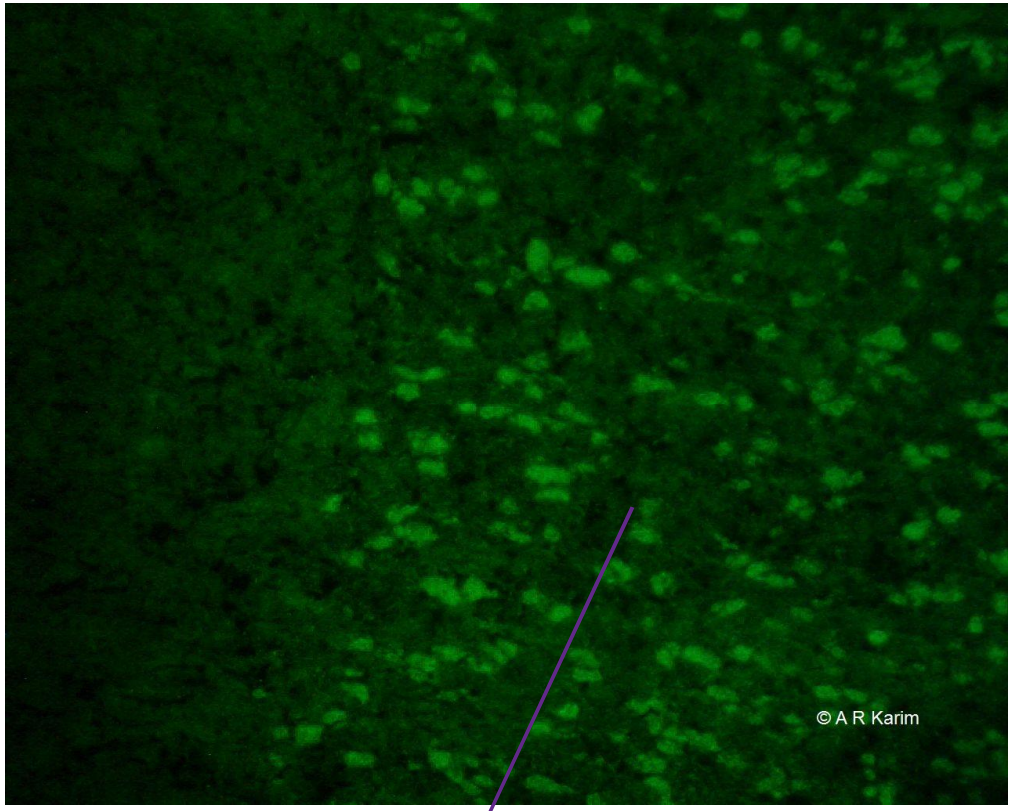
Table: **Antibodies in the diagnosis of autoimmune encephalitis**



Algorithm for the diagnosis of autoimmune encephalitis

Nuclear and cytoplasmic targets
AK5: limbic encephalitis
ANNA-1: limbic encephalitis, sensory neuronopathy, GI dysmotility
ANNA-2: brainstem encephalitis, opsoclonus-myoclonus, laryngospasm, jaw dystonia
ANNA-3: sensory/sensorimotor neuropathies, cerebellar ataxia, myelopathy, brain stem, and limbic encephalopathy
Amphiphysin: SPS, encephalopathy, myelopathy
AGNA: LES, cerebellar degeneration
CRMP-5: chorea, optic neuropathy, peripheral and autonomic neuropathy, retinitis, myelopathy, cerebellar ataxia
GAD65: multifocal, SPS, cerebellar ataxia, encephalitis, autoimmune epilepsy, myelopathy, neuropathy
GFAP: meningoencephalitis, myelitis, bilateral optic disc edema, tremor
GRAF1: cerebellar ataxia
ITPR1: cerebellar ataxia, neuropathy
Ma1 Ma2: limbic encephalitis, diencephalic syndrome, brainstem encephalitis, ataxia
PCA-1: cerebellar degeneration
PCA-2: peripheral neuropathy, cerebellar ataxia, encephalopathy
ZIC4: cerebellar ataxia

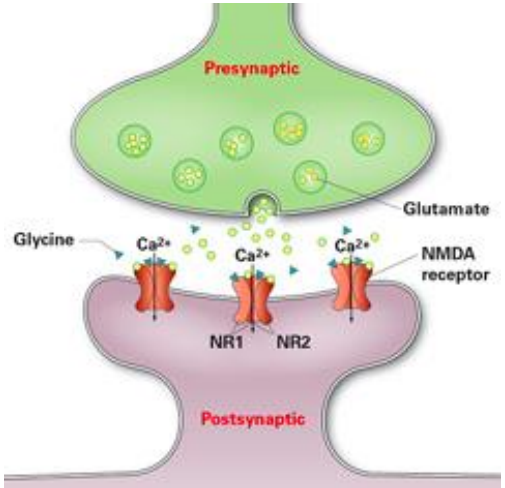
Anti-NMDA



Couche granulaire du cervelet

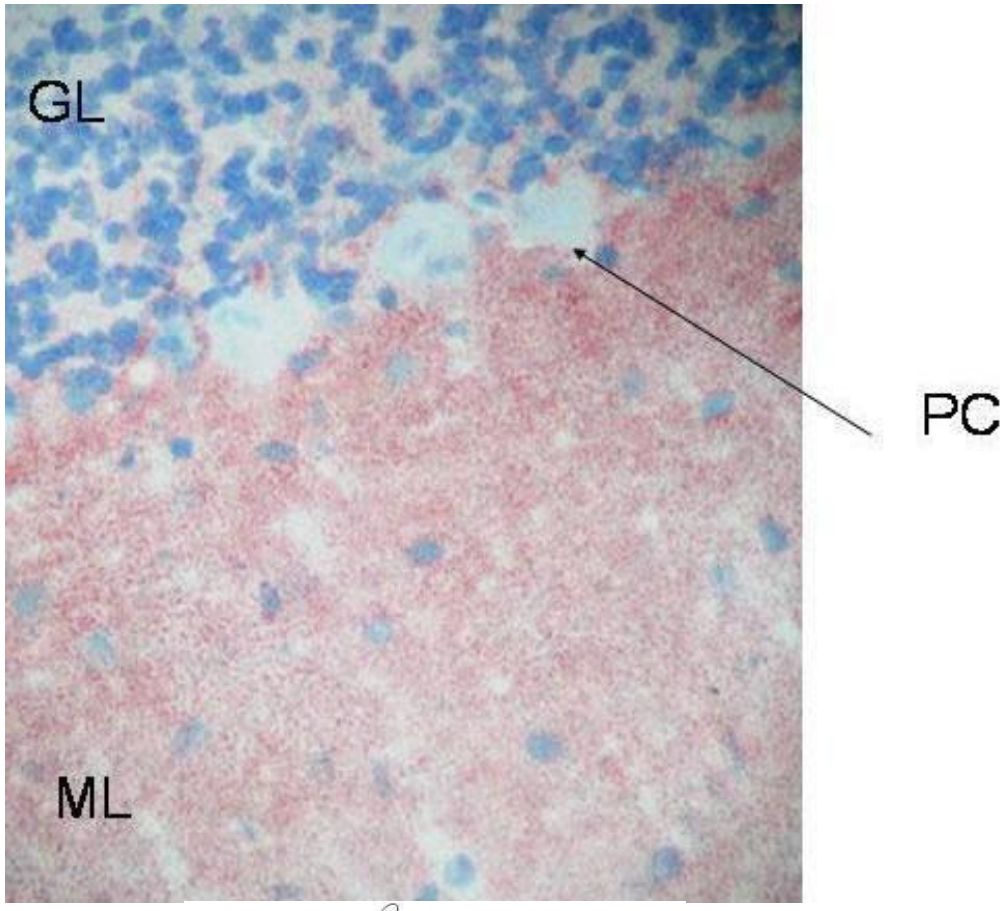
NMDAR antibody is associated with treatable limbic encephalitis and its target is the NMDA receptor which comprises four NR units, with each of the subunit has a molecular size of 100 kDa and together they form an ion channel/receptor. NMDAR antibody binds to the neuropils in the molecular layer of the hippocampus as well as the granular layer of the cerebellum

Tumours: Ovarian teratoma (56%, young women).
Syndrome: Limbic encephalitis



Forme la plus fréquente :
1% des admissions de jeunes à l'USI

Anti VGKC



Patients with VGKC antibodies may have associated myasthenia gravis with or without acetylcholine receptor antibodies, or may have acetylcholine receptor antibodies without myasthenia gravis. Other thymoma-related antibodies (eg. Interferon alpha, IL-12) may be present. Acquired neuromyotonia has been reported in patients following bone marrow transfer, with systemic sclerosis and with other autoimmune diseases.

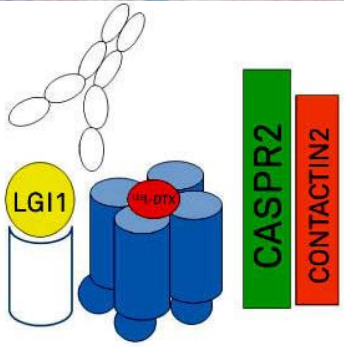


Fig 2. The VGKC-complex. leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2) and contactin-2 are tightly associated with VGKCs in mammalian brain membranes and are co-immunoprecipitated in the radioimmunoassay. These proteins are commonly targeted by the patient antibodies (white).[125]I-DTX = radioiodinated dendrotoxin, a Kv1 antagonist.

High titres of VGKC antibodies may be detected by immunohistochemistry showing characteristic staining of molecular layer of the cerebellum.

Synaptic targets
AChR, muscle type: myasthenia gravis
AChR, α3-ganglionic: dysautonomia, peripheral neuropathy
AQP4: NMOSD
AMPAR: limbic encephalitis
CASPR2: peripheral nerve hyperexcitability (Isaac's syndrome), encephalitis, dysautonomia, neuropathy, Morvan's syndrome
DPPX: severe weight loss, diarrhea, dysautonomia, cardiac arrhythmias, encephalomyelitis
Dopamine 2 R: lethargy, psychiatric symptoms, abnormal movements, gait disturbance
$GABA_AR$: limbic encephalitis, common seizures
$GABA_BR$: limbic encephalitis, seizure predilection, status epilepticus
mGluR1: cerebellar ataxia, dysgeusia
mGluR5: limbic encephalitis, prominent psychiatric symptoms
Glycine receptor: PERM, SPS, optic neuropathy
IgLON5: sleep disorder, chorea, dementia
LGI-1: limbic encephalitis, faciobrachial dystonic seizures, hyponatremia
MOG: ADEM, optic neuritis, transverse myelitis
Neurexin-3: encephalitis
NMDA-R: catatonia, seizures, psychosis, dysautonomia
PCATr: cerebellar ataxia
VGCC: LES, cerebellar ataxia, encephalitis, neuropathy