Les pathologies neurologiques paranéoplasiques autoimmunes, apport du laboratoire

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Syndrome neurologique paranéoplasique

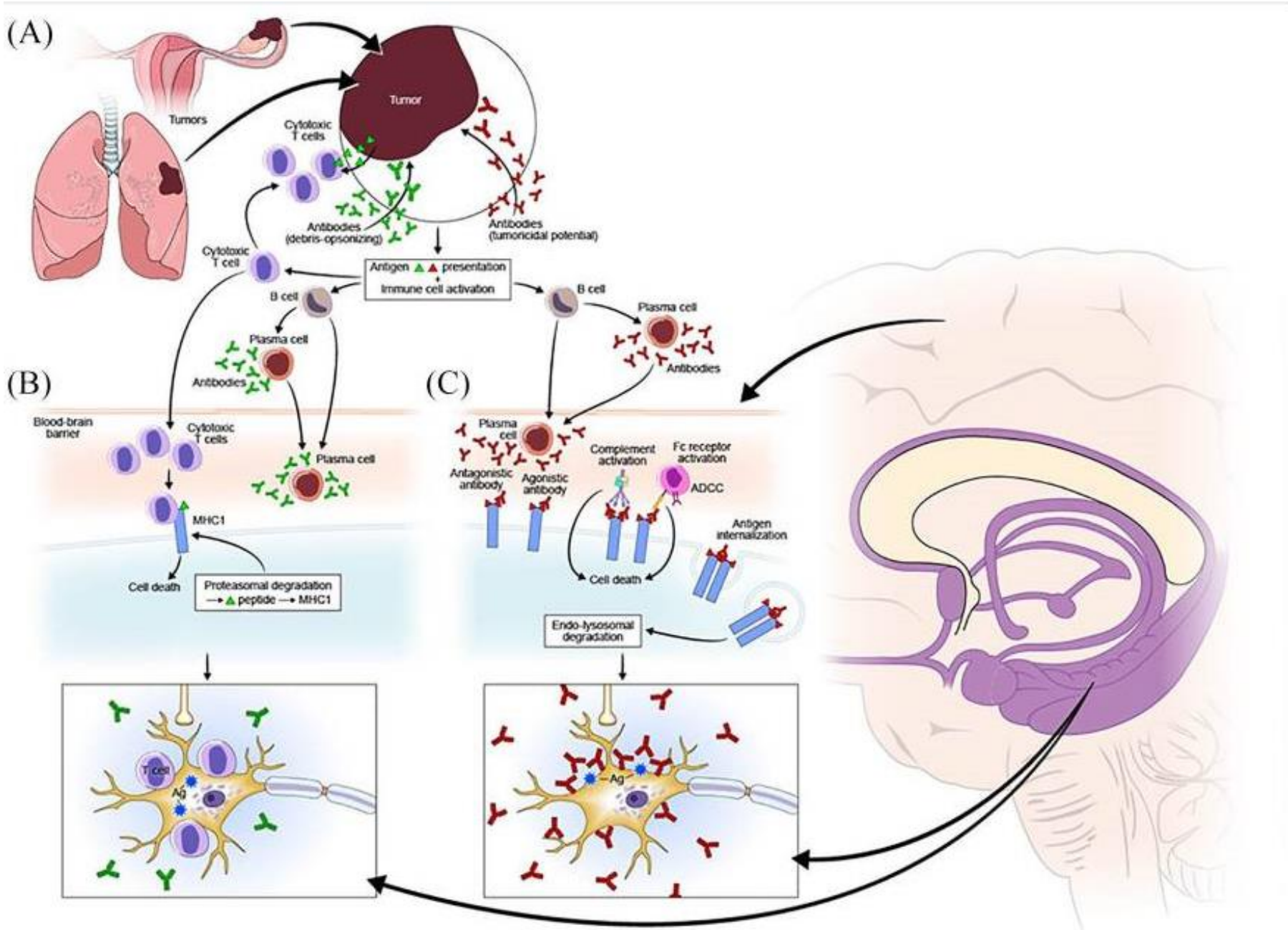
« Syndrome neurologique en rapport avec un cancer mais non causé par le cancer lui-même ou des métastases ni par ses complications iatrogènes, infectieuses, vasculaires ou carentielles »

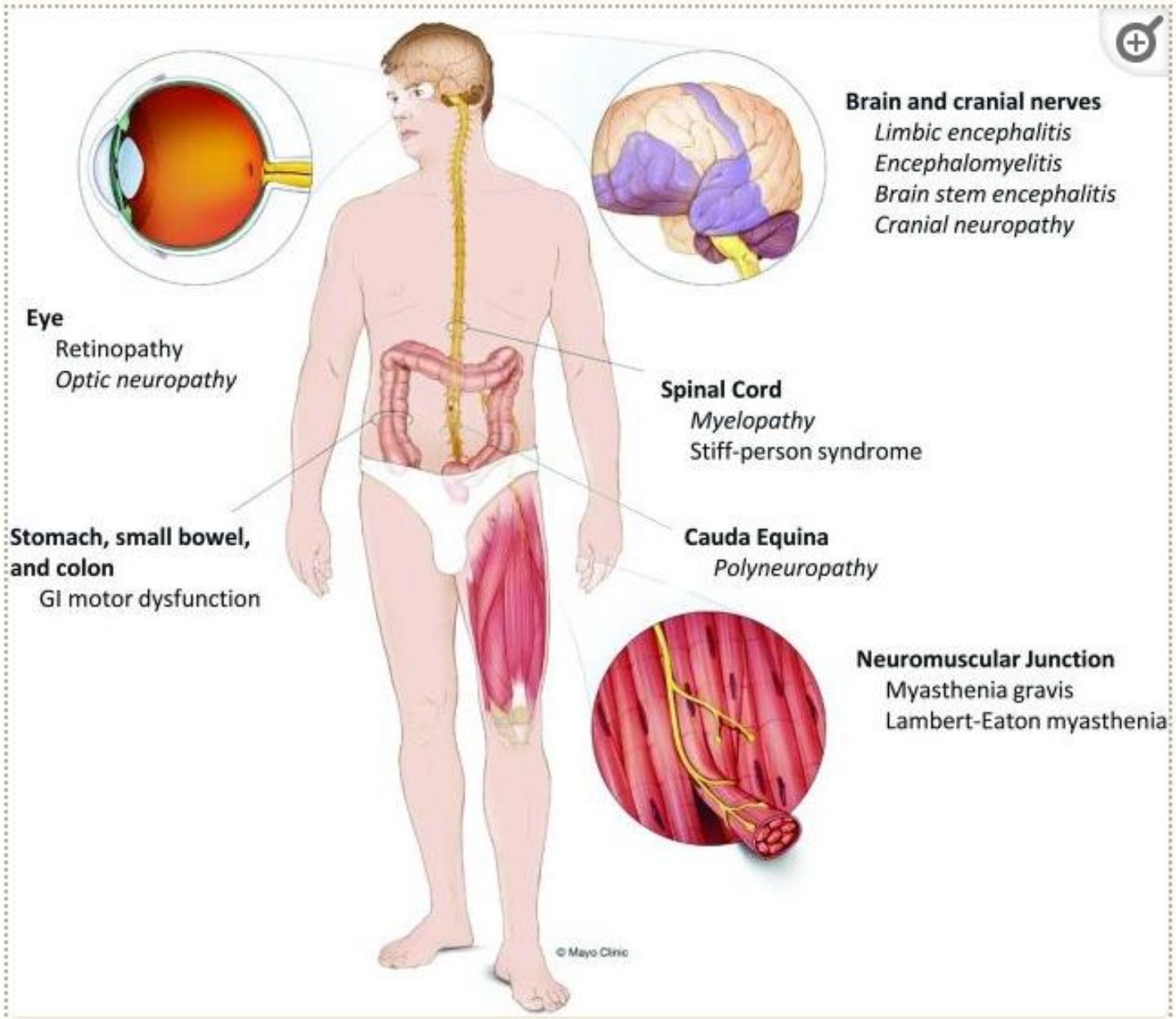
< 1% Cancer; révélateur dans 60% cas

Concept ancien :

Oppeheim : 1888: neuropathie périphérique – cancer pulmonaire

Auché: 1890


(A)
Tumors
Tumor
Cytotoxic T cells
Antibodies (debris-opsonizing)
Antibodies (tumoricidal potential)
Cytotoxic T cell
Antigen presentation
Immune cell activation
B cell
B cell
Plasma cell
Plasma cell
Antibodies
Antibodies
(B)
(C)
Blood-brain barrier
Cytotoxic T cells
Plasma cell
MHC1
Cell death
Proteasomal degradation
peptide
MHC1
Plasma cell
Antagonistic antibody
Agonistic antibody
Complement activation
Fc receptor activation
ADCC
Antigen internalization
Cell death
Endo-lysosomal degradation
T cell
Ag
Ag

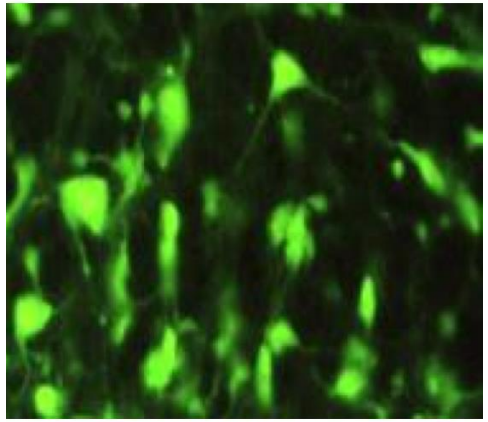

Brain and cranial nerves
Limbic encephalitis
Encephalomyelitis
Brain stem encephalitis
Cranial neuropathy
Eye
Retinopathy
Optic neuropathy
Spinal Cord
Myelopathy
Stiff-person syndrome
Stomach, small bowel, and colon
GI motor dysfunction
Cauda Equina
Polyneuropathy
Neuromuscular Junction
Myasthenia gravis
Lambert-Eaton myasthenia
© Mayo Clinic

Pathologies neurologiques paranéoplasiques autoimmunes centrales

Concept ancien

Paraneoplasiques

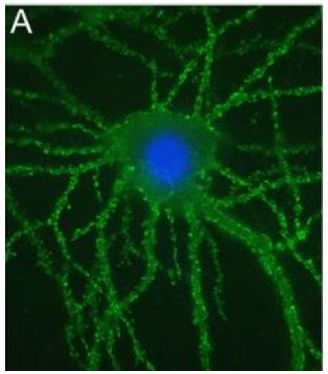
- Anti-Hu
- Anti-Yo
- Anti-CV2
- Anti-Ma2



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-Zic4…

Antigènes onco-neuronaux

Marqueurs indirects

Antigènes membranaires

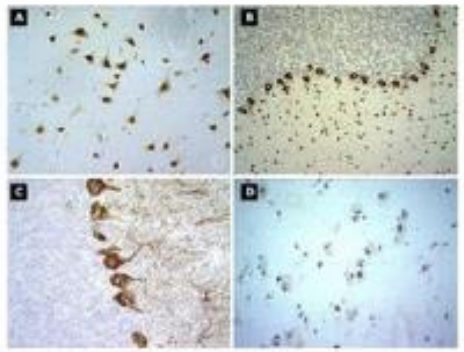
- Anti-NMDAR
- Anti-VGKC
- Anti-AMPAR
- Anti-GABAR

Rôle pathologique direct

Peuvent être paraneoplasiques ou non

Médiation immune: 2 mécanismes

Ac dirigé contre antigène Intracellulaire :
Hu, Yo, CV2/CRMP5, Ri, Tr, Ma, amphiphysin



Ac dirigé contre un antigène de surface membranaire :
LGI1, CASPR2, NMDA-R, AMPA-R, GABA-R, Glycine-R, VGCC

Cancer

Médiation cellulaire cytotoxique

Rôle pathogène direct des Ac

Syndrome neurologique

Mort neuronale → **irréversible**

Immunomodulateurs → **réversible**

Urgence diagnostique et thérapeutique

1

Faire un diagnostic rapide

2

Identifier le cancer sous jacent

3

Traiter le plus vite possible

1 Faire un diagnostic rapide

Recommended diagnostic criteria for paraneoplastic neurological syndromes

F Graus, J Y Delattre, J C Antoine, J Dalmau, B Giometto, W Grisold, J Honnorat, P Sillevis Smitt, Ch Vedeler, J J G M Verschuuren, A Vincent, R Voltz, for the Paraneoplastic Neurological Syndrome Euronetwork

See Editorial Commentary, p 1090

J Neurol Neurosurg Psychiatry 2004;75:1135–1140. doi: 10.1136/jnnp.2003.034447

See end of article for other members of the Paraneoplastic Neurological Syndrome Euronetwork

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Background: Paraneoplastic neurological syndromes (PNS) are defined by the presence of cancer and exclusion of other known causes of the neurological symptoms, but this criterion does not separate "true" PNS from neurological syndromes that are coincidental with a cancer.
Objective: To provide more rigorous diagnostic criteria for PNS.
Methods: An international panel of neurologists interested in PNS identified those defined as "classical" in previous studies. The panel reviewed the existing diagnostic criteria and recommended new criteria for those in whom no clinical consensus was reached in the past. The panel reviewed all reported onconeural antibodies and established the conditions to identify those that would be labelled as "well characterised". The antibody information was obtained from published work and from unpublished data from the different laboratories involved in the study.
Results: The panel suggest two levels of evidence to define a neurological syndrome as paraneoplastic: "definite" and "possible". Each level can be reached combining a set of criteria based on the presence or absence of cancer and the definitions of "classical" syndrome and "well characterised" onconeural antibody.
Conclusions: The proposed criteria should help clinicians in the classification of their patients and the prospective and retrospective analysis of PNS cases.

ARTICLE OPEN ACCESS

Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes

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Paraneoplastic Syndromes	Clinical Feature
Limbic encephalitis	Memory impairment, seizures, behavioral change, neuropsychiatric symptoms, mood and sleep disturbances
Encephalomyelitis	Encephalopathy, myelitis, and peripheral nerve or DRG involvement
Cerebellar degeneration	Ataxia (usually subacute onset), dysarthria, diplopia
Sensory neuronopathy	Asymmetric numbness, paresthesia, sensory ataxia, neuropathic pain
Opsoclonus myoclonus syndrome	Myoclonus and opsoclonus eye movements
Gastrointestinal dysmotility	Gastroparesis, constipation, pseudo-obstruction
Lambert-Eaton myasthenic syndrome	Muscle weakness, fatigue, and autonomic dysfunction and absent deep tendon reflexes
Brainstem encephalitis	Ataxia, vertigo, diplopia, dysphagia, dysarthria
Paraneoplastic myelopathy	Subacute myelopathy, usually tract-specific involvement
Paraneoplastic stiff person syndrome	Muscle spasms and exaggerated startle response
Paraneoplastic chorea	Choreic movements with more extensive nervous system involvement
Poyradiculoneuropathy	Painful asymmetric weakness and numbness, neuropathic pain
Pan dysautonomia	Orthostatic hypotension, dry mouth, incontinence, gastroparesis, and cardiac arrhythmias
Peripheral nerve hyperexcitability	Cramps, myokymia, fasciculation
Myasthenia gravis	Oculobulbar weakness, dysarthria, dysphagia, fatigable proximal limb weakness
Immune-mediated necrotizing myopathy	Proximal weakness with rare respiratory or cardiac involvement
Dermatomyositis	Proximal weakness, skin changes

Phénotypes à haut risque

Phénotypes à risque intermédiaire

- Il n’y a pas de syndrome neurologique exclusivement paranéoplasique
- ET
- Presque tous les syndromes neurologiques peuvent être paranéoplasiques

Recherche des anticorps

Paraneoplastic Syndromes	Associated Antibodies
Limbic encephalitis	ANNA1 (anti-Hu), Ma2, CRMP5 (anti-CV2), mGluR5, ANNA2 (anti-Ri), PCA2, KLHL11, GABAB receptor, AMPAR, LGI1, CASPR2, ANNA3
Encephalomyelitis	ANNA1 (anti-Hu), CRMP5 (anti-CV2), amphiphysin, GFAP
Cerebellar degeneration	PCA1 (anti-Yo), PCA2, PCA-Tr (DNER), mGluR1, ANNA1,2, Zic 4, VGCC (P/Q type), amphiphysin, Ma2, NfL, KLHL11
Sensory neuronopathy	ANNA1 (anti-Hu), amphiphysin, PCA2, CRMP5 (CV2)
Opsoclonus myoclonus syndrome	ANNA2 (anti-Ri), ANNA1 (anti-Hu), Ma2, CRMP5 (anti-CV2), NMDA-R, GluD2
Gastrointestinal dysmotility	ANNA1 (anti-Hu), CRMP5 (anti-CV2), PCA2
Lambert-Eaton myasthenic syndrome	P/Q-type VGCC
Brainstem encephalitis	ANNA2 (anti-Ri), KLHL11, ANNA1 (anti-Hu), Ma2, PCA2, CRMP5 (CV2), amphiphysin, Zic 4
Paraneoplastic myelopathy	ANNA2 (anti-Ri), ANNA1 (anti-Hu), ANNA3, CRMP5 (anti-CV2), Amphiphysin, NfL
Paraneoplastic stiff person syndrome	Amphiphysin, DPPX, GAD65, glycine receptor
Paraneoplastic chorea	CRMP5 (anti-CV2), PDE10A, ANNA1
Poyradiculoneuropathy	CRMP5 (anti-CV2), ANNA1 (anti-Hu), PCA2, and amphiphysin
Pan dysautonomia	ANNA1 (anti-Hu), CRMP5 (anti-CV2), PCA2, ganglionic AChR antibodies
Peripheral nerve hyperexcitability	CASPR2, LGI1, CRMP5 (anti-CV2), Nectrin-1
Myasthenia gravis	AChR binding antibody
Immune-mediated necrotizing myopathy	HMGCR, SRP54
Dermatomyositis	SAE1, TIF1-γ, NXP2

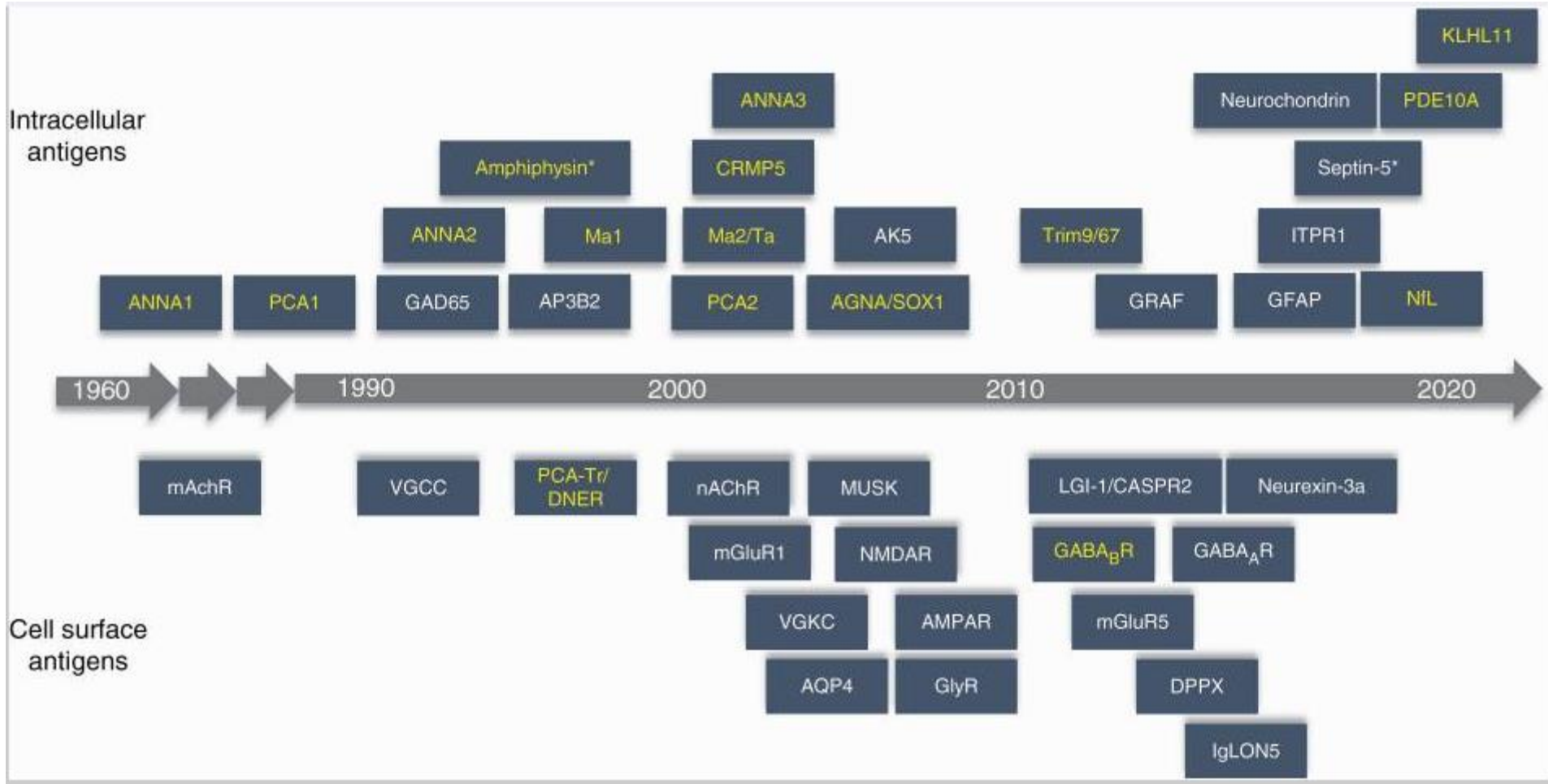

Intracellular antigens
KLHL11
ANNA3
Neurochondrin
PDE10A
Amphiphysin*
CRMP5
Septin-5*
ANNA2
Ma1
Ma2/Ta
AK5
Trim9/67
ITPR1
ANNA1
PCA1
GAD65
AP3B2
PCA2
AGNA/SOX1
GRAF
GFAP
NfL
1960
1990
2000
2010
2020
mAchR
VGCC
PCA-Tr/ DNER
nAChR
MUSK
LGI-1/CASPR2
Neurexin-3a
mGluR1
NMDAR
GABA$_B$R
GABA$_A$R
VGKC
AMPAR
mGluR5
Cell surface antigens
AQP4
GlyR
DPPX
IgLON5

Table 1 High-Risk Antibodies (>70% Associated With Cancer)

Antibody (alternative name)	Neurologic phenotypes	Frequency of cancer (%)	Usual tumors	Sex, age-related, and other specificities
Hu (ANNA-1)[8]	SNN, chronic gastrointestinal pseudo-obstruction, EM, and LE	85	SCLC >> NSCLC, other neuroendocrine tumors, and neuroblastoma	LE is usually nonparaneoplastic in patients aged <18 y[18]
CV2/ CRMP5[30,e17,e40,e41]	EM and SNN	>80	SCLC and thymoma	Patients with an associated thymoma are younger and present more frequently MG and less commonly neuropathy
SOX1[36,e42]	LEMS with and without rapidly progressive cerebellar syndrome	>90	SCLC	Stronger correlation with SCLC than with a particular neurologic presentation
PCA2 (MAP1B) [57,e43,e44]	Sensorimotor neuropathy, rapidly progressive cerebellar syndrome, and EM	80	SCLC, NSCLC, and breast cancer	
Amphiphysin[31,e18]	Polyradiculoneuropathy, SNN, EM, SPS	80	SCLC and breast cancer	Associated antibodies commonly coexist. Patients with isolated antiamphiphysin → women, with breast cancer and SPS
Ri (ANNA-2)[20,26]	Brainstem/cerebellar syndrome, OMS	>70	Breast > lung (SCLC and NSCLC)	Breast cancer in women; lung cancer in men
Yo (PCA-1)[21,e16]	Rapidly progressive cerebellar syndrome	>90	Ovary and breast cancers	Almost all female; in men, antigen expression by tumor should be proven
Ma2 and/or Ma[45,e15,e45]	LE, diencephalitis, and brainstem encephalitis	>75	Testicular cancer and NSCLC	Young men → testicular tumors and isolated Ma2 positivity; older patients → SCLC and both Ma1/2 positivity
Tr (DNER)[22,23]	Rapidly progressive cerebellar syndrome	90	Hodgkin lymphoma	
KLHL11[48-50]	Brainstem/cerebellar syndrome	80	Testicular cancer	Young men

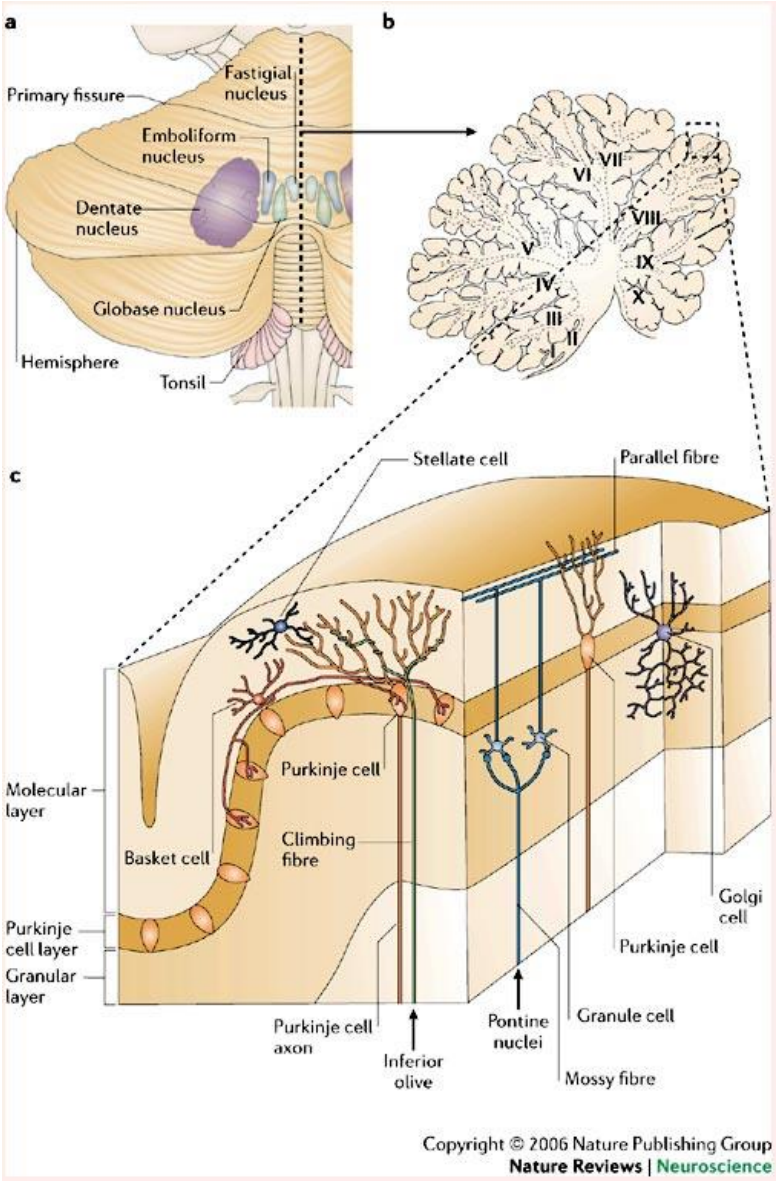
Table 2 Intermediate-Risk Antibodies (30%–70% Associated With Cancer)

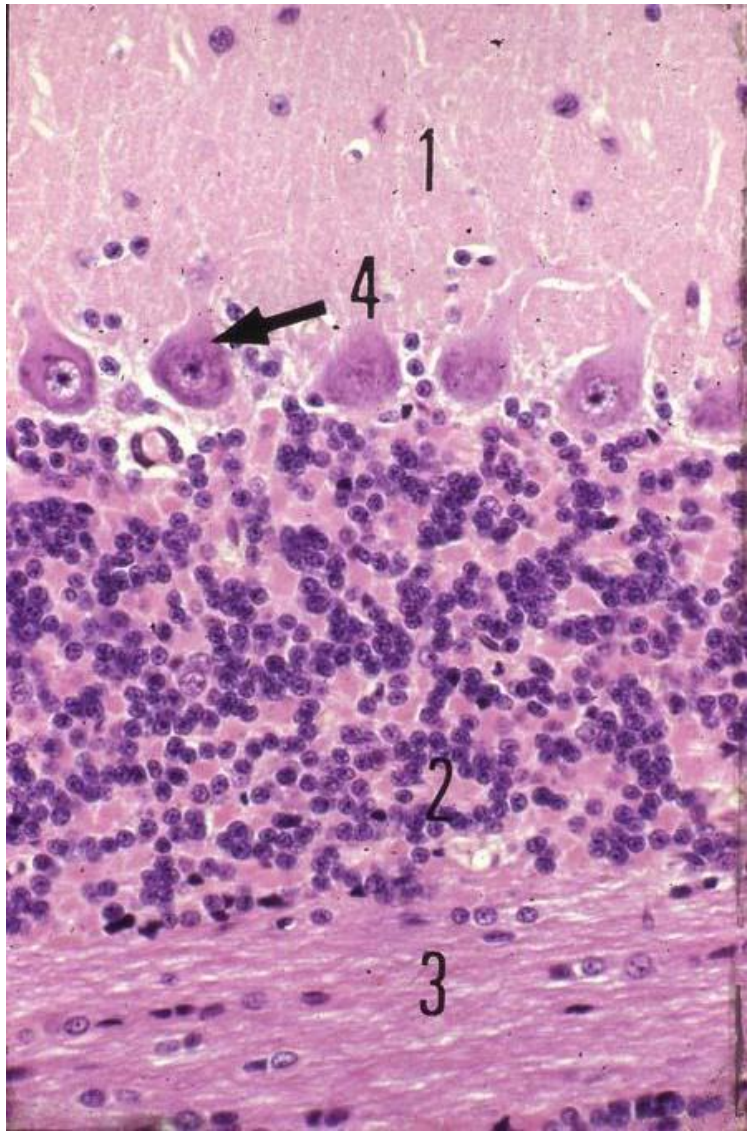
Antibody	Neurologic phenotypes	Frequency of cancer (%)	Usual tumors	Sex, age-related, and other specificities
AMPAR[16,17,e46]	Limbic encephalitis	>50	SCLC and malignant thymoma	Paraneoplastic origin is more likely when other onconeuronal antibodies co-occur
$GABA_BR$[e14,15,e2,e3,e47-e49]	Limbic encephalitis	>50	SCLC	Paraneoplastic cases are more commonly observed in elderly men, smokers, with associated anti-KCTD16 antibodies. Most of young patients are not paraneoplastic
mGluR5[38]	Encephalitis	~50	Hodgkin lymphoma	
P/Q VGCC[e50,e51]	LEMS, rapidly progressive cerebellar syndrome	50 (LEMS; nearly 90 for rapidly progressive cerebellar syndrome)	SCLC	Co-occurrence with N-type VGCC antibodies might be slightly more common in paraneoplastic LEMS[e52-e54]
NMDAR[40,43,44]	Anti-NMDAR encephalitis	38	Ovarian or extraovarian teratomas	Tumor (mostly ovarian teratomas) predominates in female aged between 12 and 45 y (50%). Elderly patients have less frequently tumors (<25%), but usually they are carcinomas. Paraneoplastic cases in children are very rare (<10%)
CASPR2[51,52]	Morvan syndrome	50	Malignant thymoma	CASPR2 should be considered as intermediate-risk antibody only in the setting of Morvan syndrome. When associated with other neurologic syndromes, the risk of cancer is very low.

Techniques d’investigation biologique

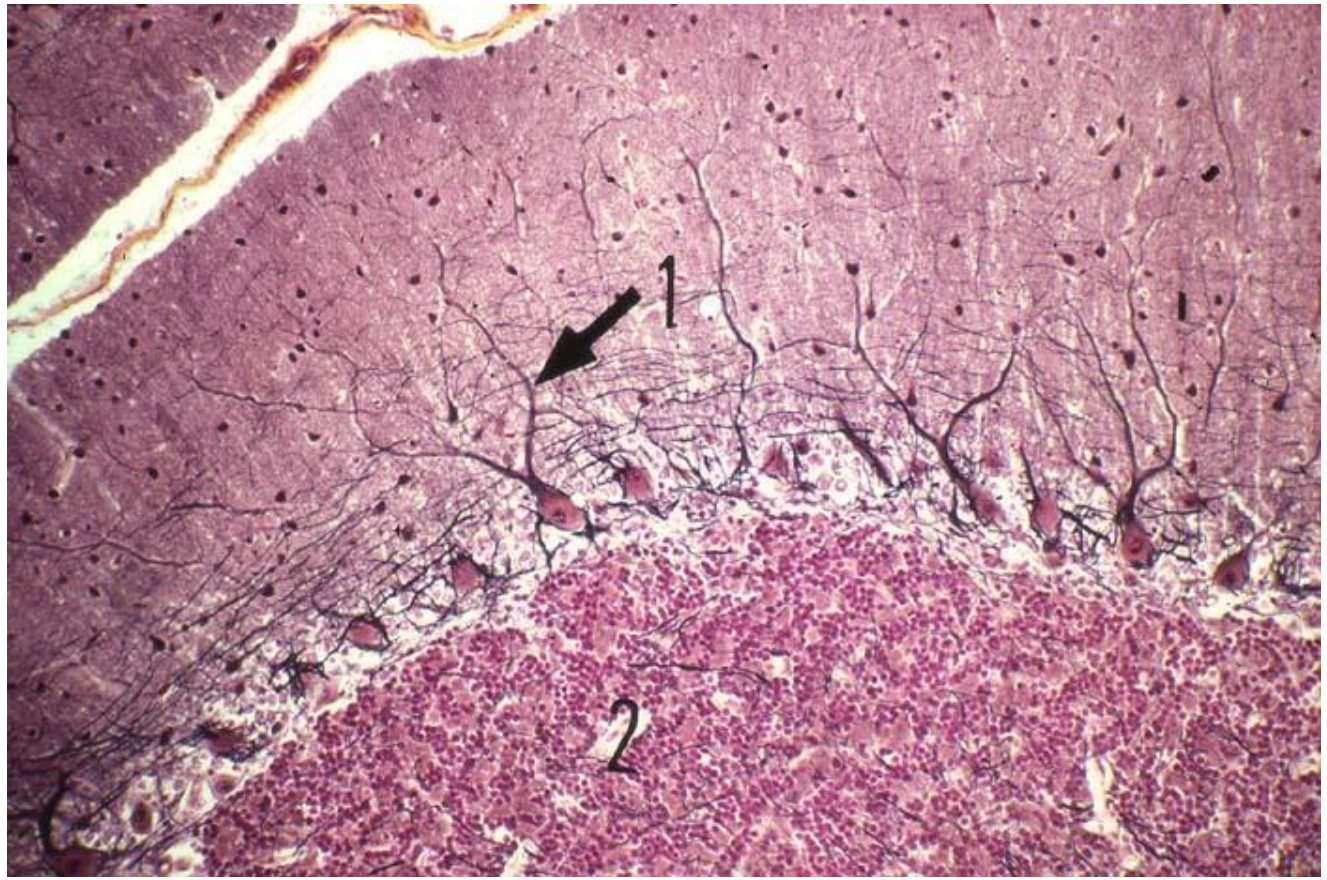
- Immunofluorescence indirecte: screening
  - Coupe de cervelet, d’hippocampe (système limbique)
- Identification
  - Immunodots
  - Cellules transfectées (pour récepteurs membranaires)

Histologie du cervelet



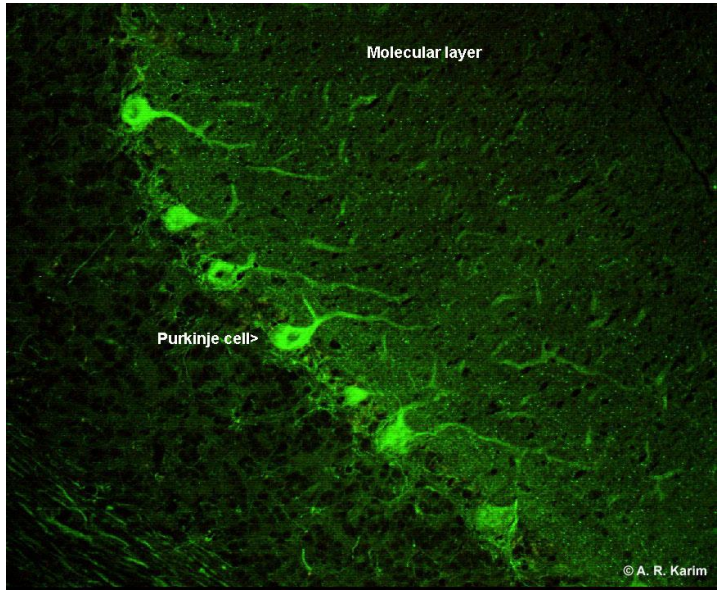


Histologie du cervelet

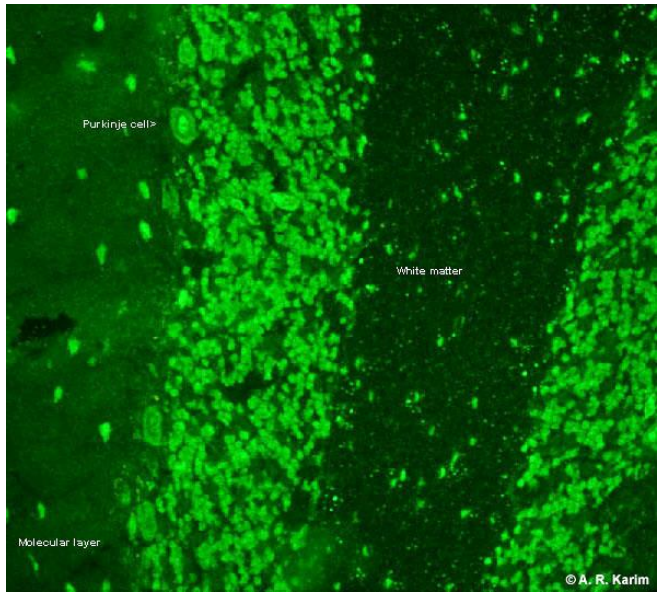


IFI sur coupes de cervelet

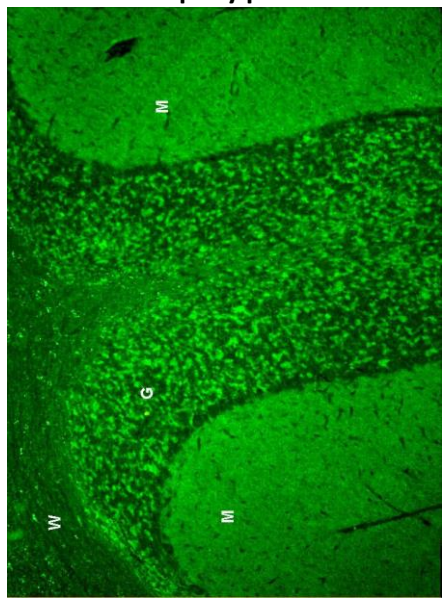
Anti-Tr



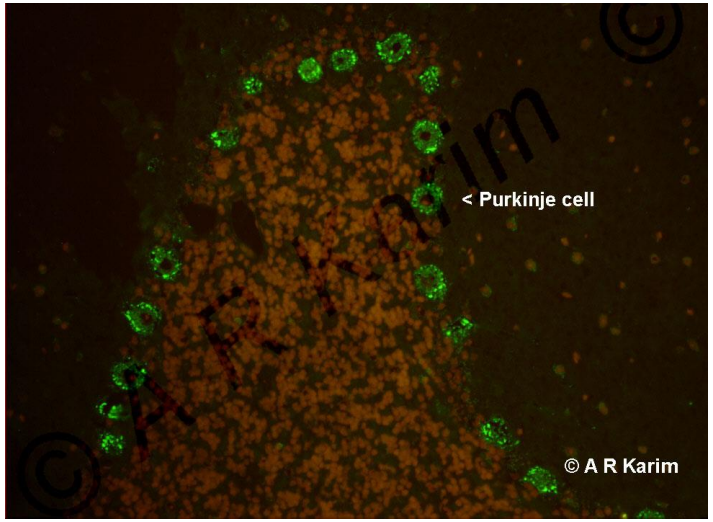
Anti-Hu



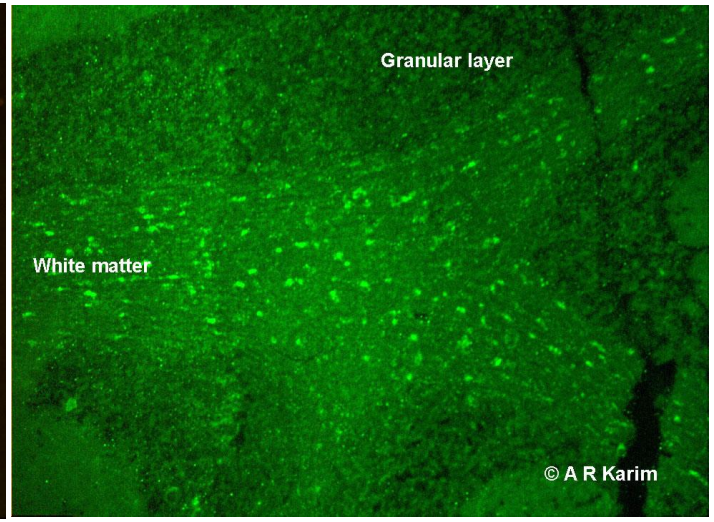
Anti-Amphyphisine



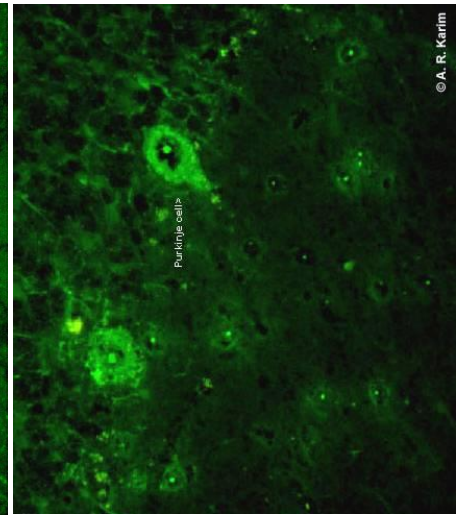
Anti-Yo



Anti-CV2



Anti-Ma1/Ma2/Ma3

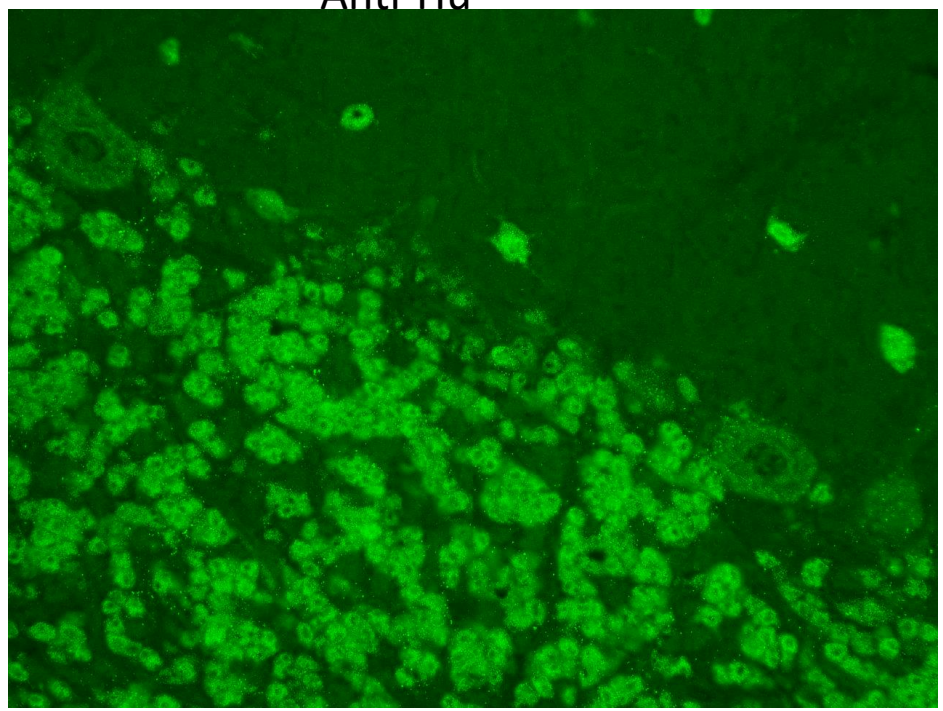


Pattern immunofluorescence indirecte

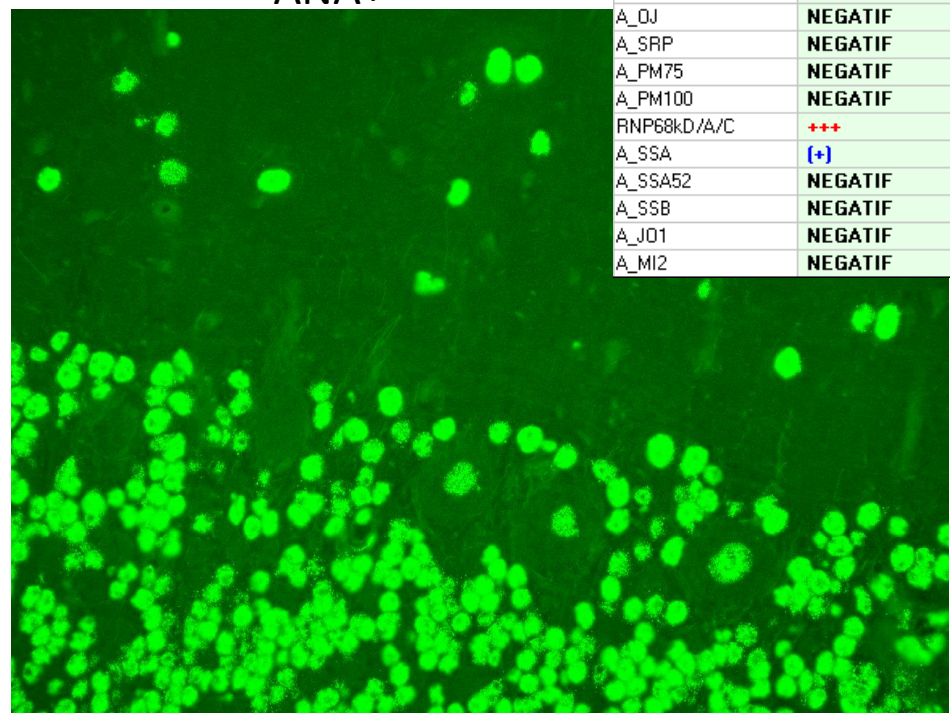
- Cytoplasme Purkinije → Yo (PCA1) ou mGluR1
- Noyaux neurones (exclure ANA) → Hu, Ri
- Cytoplasme et dendrites → PCA2
- Couche granulaire (cytopl) → GAD
- Couche moléculaire et granulaire → NMDA, AMPA, Amphiphysine
- Couche moléculaire → VGKC, GABA, amphiphysine

ANA	*POSITIF
ANA	POSITIF
titrage Fluor Ana	1:2560
CENP-A/B	NEGATIF
A_DSDNA	*102.8 U/mL
A_MDNA	*2.3 U
A_NUCL	*21.8 U/mL
A_ENA	Positif
A_ENA	*Positif
A_NUCLDOT	NEGATIF
A_HISTONE	NEGATIF
A_SM	++
A_PL7	NEGATIF
A_PL12	NEGATIF
A_EJ	NEGATIF
A_OJ	NEGATIF
A_SRP	NEGATIF
A_PM75	NEGATIF
A_PM100	NEGATIF
RNP68kD/A/C	+++
A_SSA	(+)
A_SSA52	NEGATIF
A_SSB	NEGATIF
A_JO1	NEGATIF
A_MI2	NEGATIF

Anti-Hu



ANA+



AC_CERV	*POSITIF
Ac_Yo	NEGATIF
Ac_Hu	NEGATIF
Ac_Ri	NEGATIF
Ac_Amphi	NEGATIF
Ac_PNMA2	NEGATIF
Ac_CV2.1	NEGATIF

Stratégie recherche Ac anti-Neurones

Immunofluorescence indirecte
(cervelet primate +/- syst limbique)

Négatif

Discussion avec clinicien

Faible suspicion clinique

STOP

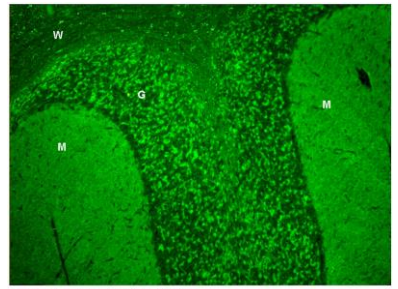
Forte suspicion clinique

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

selon présentation

Cell based assays
(cellules transfectées)

Positif



Marquage du Neuropile
(couche moléculaire)

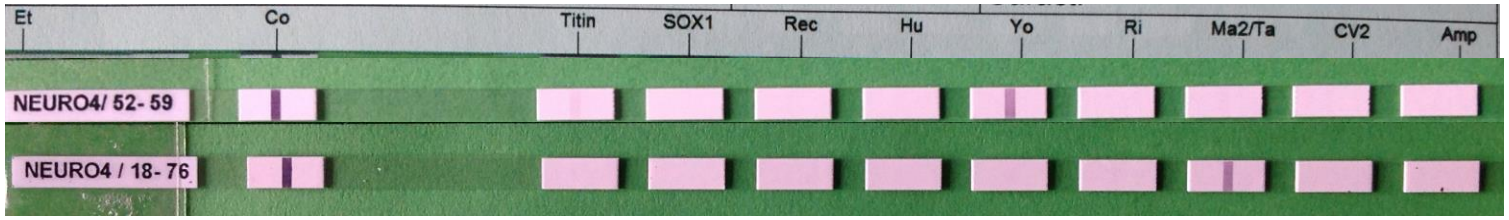
selon pattern

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

Immunoblot

Immunodot/blot

Antigènes sont fixés en bandes sur du papier nitrocellulose



Risque de faux positifs pour certains antigènes (amphiphysin, Ma1, Yo) *Déchelotte et al 2020*
Risque de faux négatifs pour d'autres (CRMP5/CV2) *Sabater et al 2016*

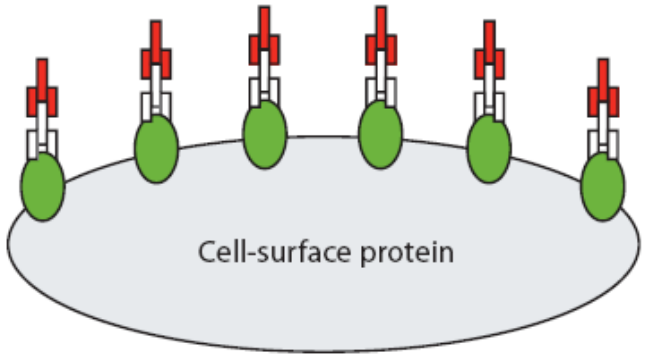
↓

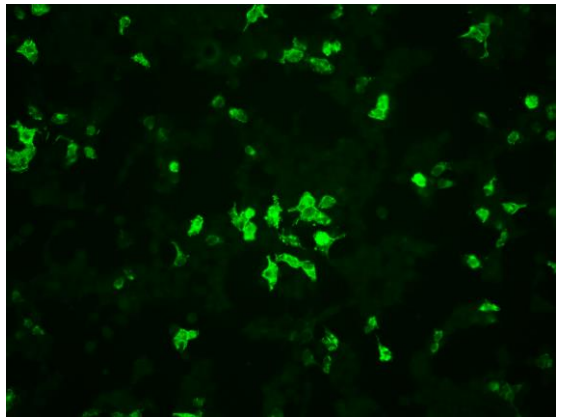
Un résultat positif doit toujours etre confirmé par l'IIF
Les résultats (positifs ou négatifs) doivent être interprétés en fonction du contexte clinique

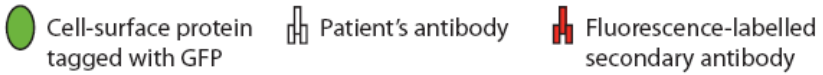
Cell based assays

Human Embryonic Kidney cells

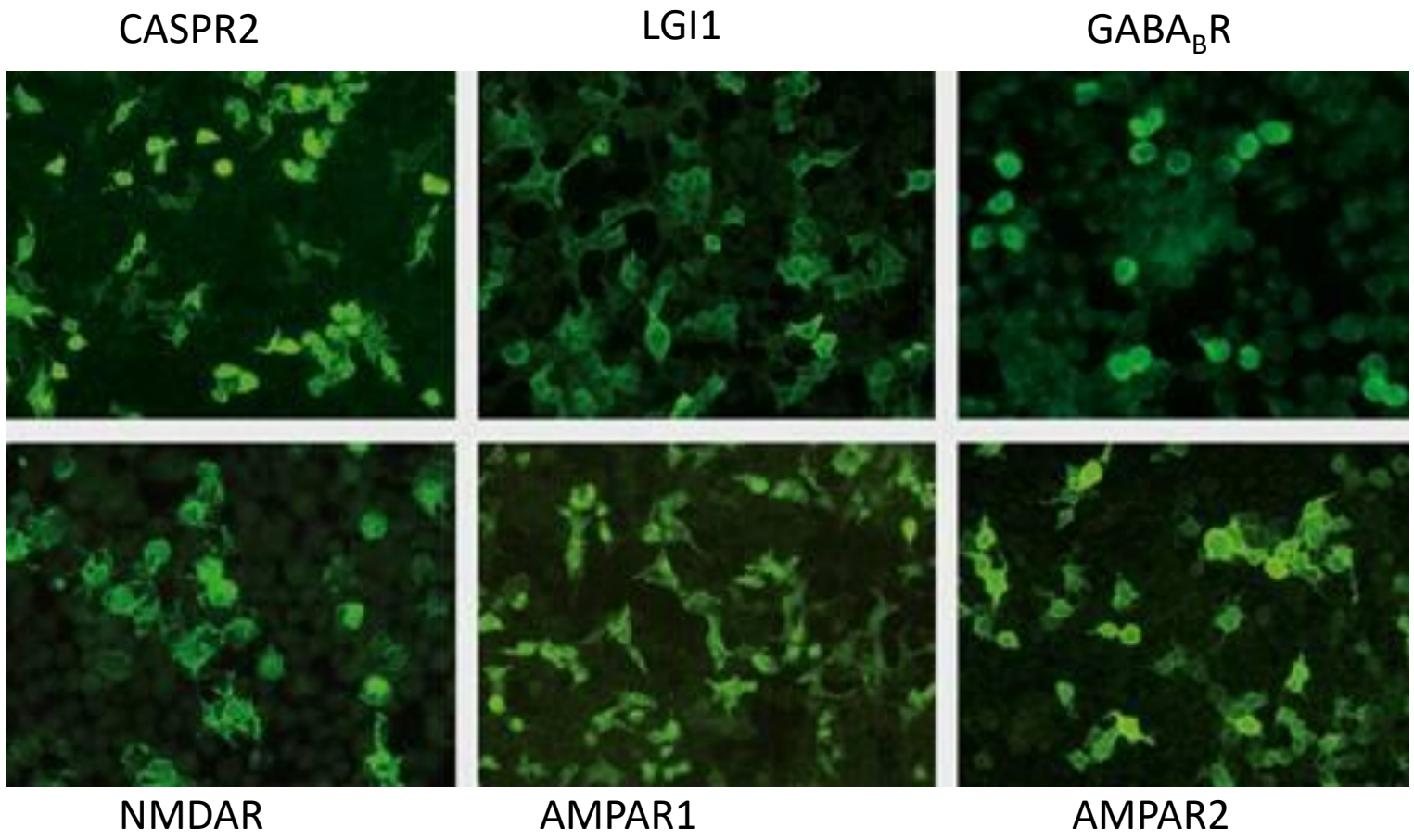
Cellule transfectée avec gène de la protéine spécifique → Exprimée en surface





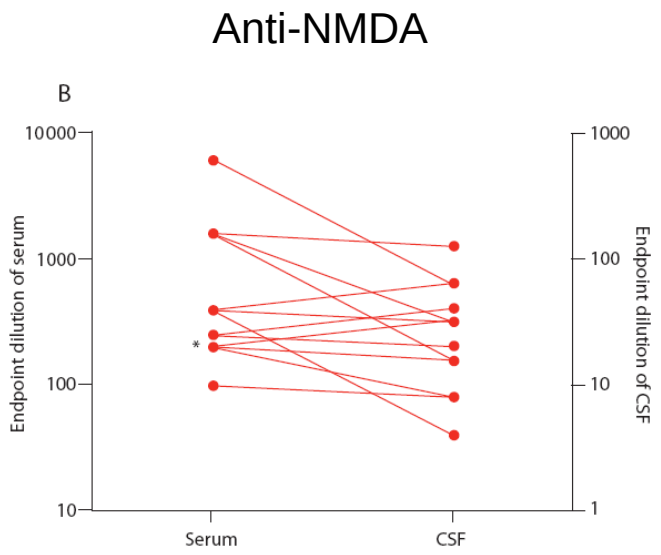


Cell Based Assays
Transfected HEK 293 cells
Anti-Neuropil antibodies



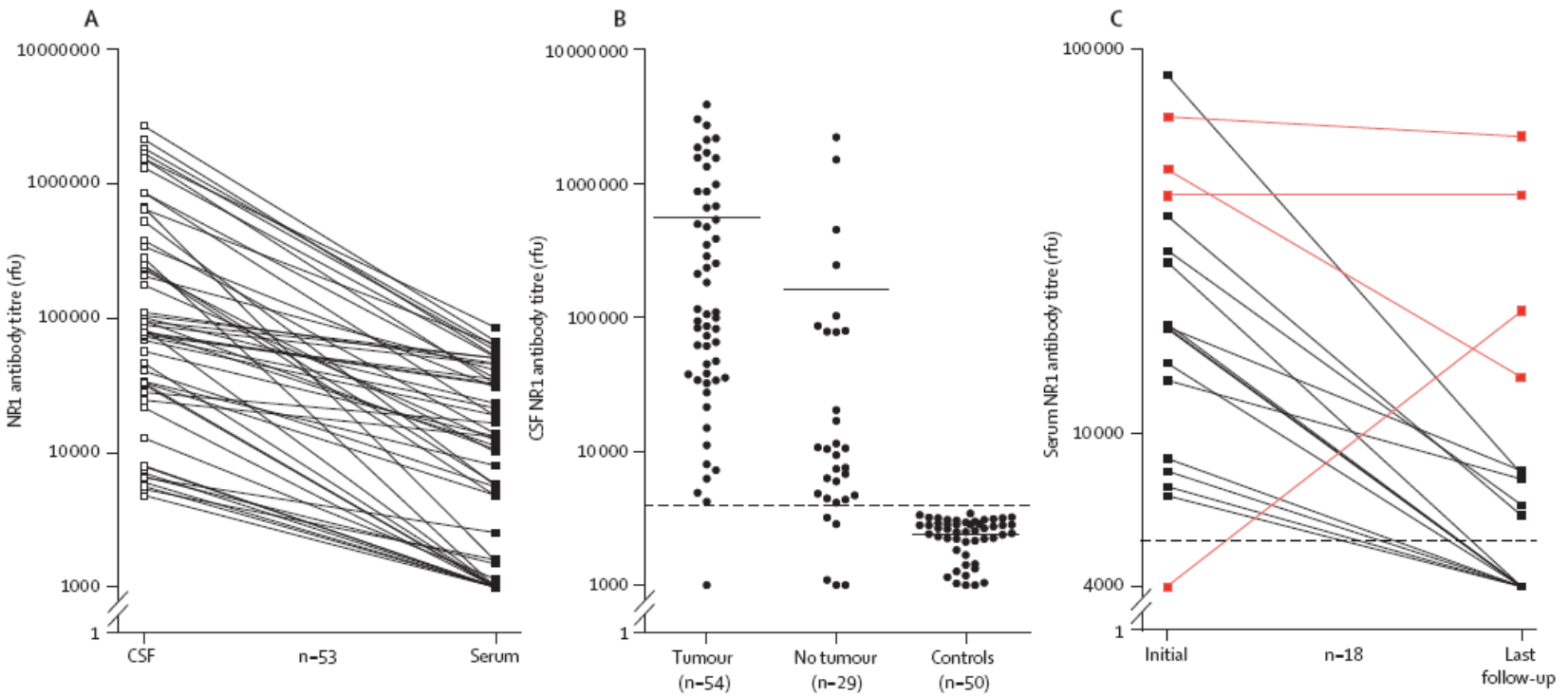
Serum ou LCR ?

- 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<0·0001) and controls (p<0·0001). 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.

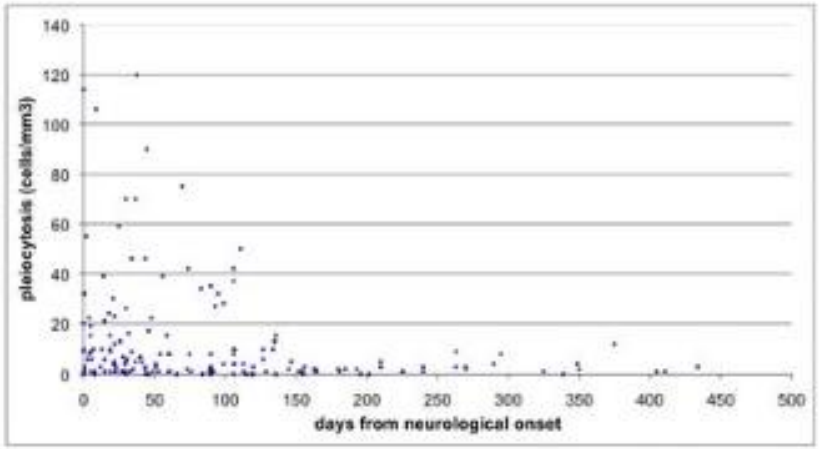
Recommandations 2021

- Tester sérum et LCR pour augmenter la sensibilité et spécificité, en particulier pour les antigènes de surface
- Ac contre des ag de surface positifs dans le sérum mais négatif dans les LCR -> contrôlé/labo de référence
- S'assurer que les résultats positifs en dot sont cohérents avec l'IIF: surtout si seul le sérum est testé, le titre bas et/ou le résultat est discordant par rapport à la clinique
- Se méfier des résultats aberrants pour le syndrome neurologique et/ou le cancer (ex anti-Yo chez un homme avec épilepsie)
- Si haute suspicion de PNS mais recherche d'Ac dans le sérum et LCR négative: répéter

Ponction Lombaire

I: Ac dirigé contre antigène intracellulaire

Liquide inflammatoire dans 93% cas



Psimaras et al, 2010

II: Ac dirigé contre un antigène de surface membranaire

Inflammation variable

Anticorps onconeuronaux :anti-NMDAr, anti-Tr, anti-antigènes neuropile hippocampe

Suivi évolutif: anti-NMDAr

+ Absence de cellule anormale: élimine méningite carcinomateuse

Urgence diagnostique et thérapeutique

1

Faire un diagnostic rapide

2

Identifier le cancer sous jacent

3

Traiter le plus vite possible

2 identifier le cancer sous-jacent

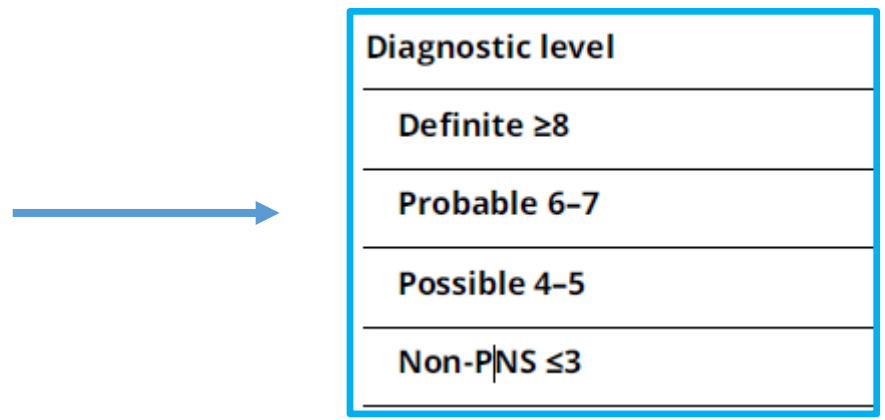
- Recherche guidée par le phénotype clinique et/ou l'anticorps identifié : CT-scan, échographie, mammo, FDG-PET/CT, IRM

- Patients peuvent avoir >1 tumeur (!si T+ trouvée atypique pour le phénotype et/ou l'ac)

- En cas de screening initial négatif, répéter tous les 4-6 mois pendant 2 ans :
  - si phénotype de haut risque + Ac de haut risque
  - si phénotype de haut risque + Ac derisque intermédiaire avec risque démographique particulier (age, tabac)
  - Sinon screening initial est suffisant

Table 5 PNS-Care Score

	Points
Clinical level	
High-risk phenotypes	3
Intermediate-risk phenotypes	2
Defined phenotype epidemiologically not associated with cancer	0
Laboratory level[a]	
High-risk antibody (>70% cancer association)	3
Intermediate risk antibody (30%–70%)	2
Lower risk antibody (<30%) or negative	0
Cancer	
Found, consistent with phenotype and (if present) antibody, or not consistent but antigen expression demonstrated	4
Not found (or not consistent) but follow-up <2 y	1
Not found and follow-up ≥2 y	0



Peut changer au cours du temps (cancer trouvé pendant le FU)

3 Traitement

A initier dès que possible pour minimiser la perte neuronale irréversible

- Traitement du cancer sous-jacent
- Immunothérapie:
  - Ag intracellulaires: mort neuronale: mauvais pronostic : réponse limitée à l'immunothérapie (sauf certains syndromes -> importants à diagnostiquer et traiter)
  - Ag surface neuronale: pronostic plus favorable

Conclusions

- Le diagnostic précoce des syndromes paranéoplasiques est cruciales pour l'identification et le traitement de la tumeur sous-jacente
- Les résultats dans le sérum doivent etre considérés avec précaution, surtout ceux des immunodots
- Les syndromes liés à des ac contre des Ag de surface répondent généralement bien à l'immunothérapie
- Certains syndromes avec des AC contre des Ag intracellulaire, mais il y a des exceptions importantes à connaitre

Méchanimes d’atteinte neuronale auto-immune