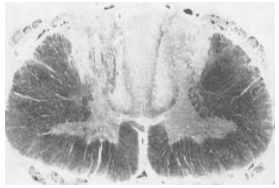
Syndromes Neurologiques Paranéoplasiques

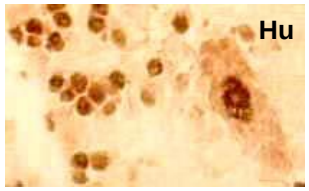
l'approche clinique

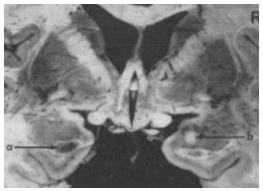
Dimitri Psimaras
Pitié Salpêtrière

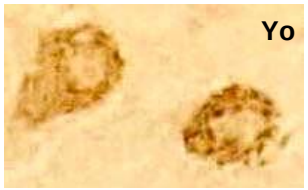
Histoire

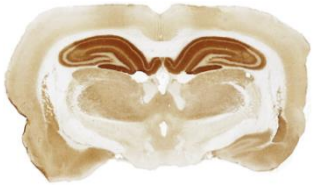
< 1970 | **1985** | **2007** | **2018** | **Future**

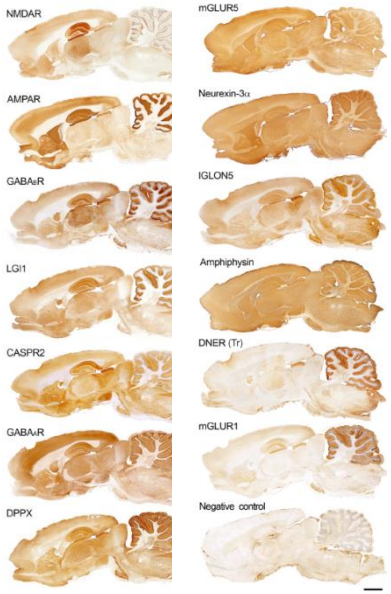












-Rare (<1% de cancer)
-Precede le cancer (2/3)
-Pleomorphique

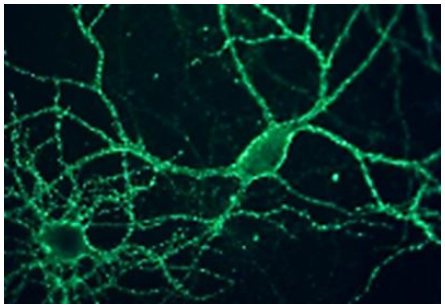
encéphalites autoimmunes

Neurodegeneration?

Syndrome cérébelleux?

Psychiatry?

Denny-Brown D 1948; Corsellis JAN 1968; Henson RA, Urich H 1982; Posner JB, Graus F, Dalmau J- 1985-2018



	ENCEPHALITE AUTO-IMMUNE Antigène de surface	SYNDROME PARANEOPLASIQUE Antigène intracellulaire
Cancer	Variable	Constant
Infection	Oui	Non
Age du patient	Tout âge	Age avancé
Début	Aigue	Subaiguë, progressif
Rôle de l'antigène	Oui	Non
Réponse à l'immunotherapie	≈ 75-80%	≈ 10%
Evolution de la maladie	Rémission avec rechute dans 5-8 %	Monophasique, irreversible
Mécanisme physiopathologique	Anticorps	Cellules T cytotoxiques

Présentations cliniques suggestives

Syndrome subaiguë et sévère

SNP
Neuronopathie sensitive
SNC
-Encéphalite
-Syndrome cérébelleux
-Stiff person syndrome
-Opsoclonus-myoclonus
-Epilepsie ou sd psy récent inexpliqué

+

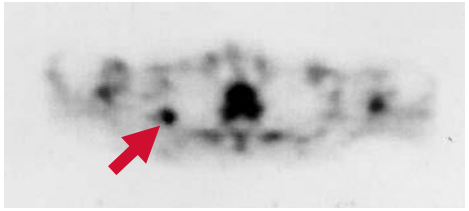
Inflammation du LCR (90%)

Suspicion

-Chercher pour des Ac IC et membrannaire
-Chercher pour une tumeur (petites, inconnue)
-Eliminer autres causes

Syndrome cérébelleux

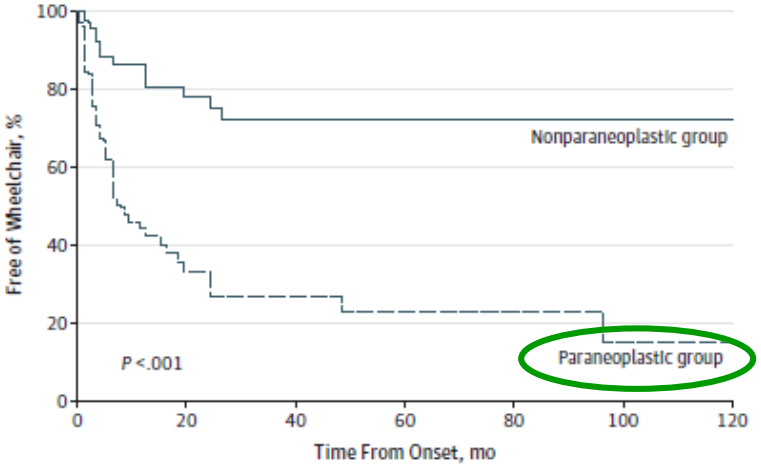
Anticorps anti-Yo
Cancer de l'ovaire



Responses to and Outcomes of Treatment of Autoimmune Cerebellar Ataxia in Adults

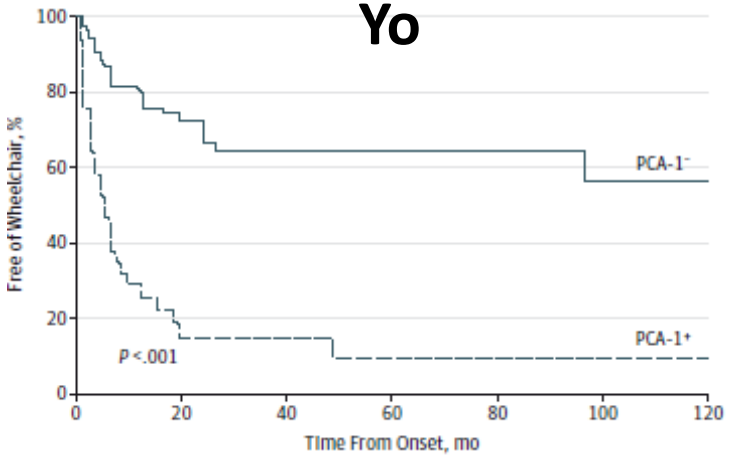
JAMA Neurol. doi:10.1001/jamaneurol.2015.2378
Published online September 28, 2015.

Amy L. Jones, MD; Eoin P. Flanagan, MD; Sean J. Pittock, MD; Jay N. Mandrekar, PhD; Scott D. Eggers, MD; J. Eric Ahlskog, PhD, MD; Andrew McKeon, MD

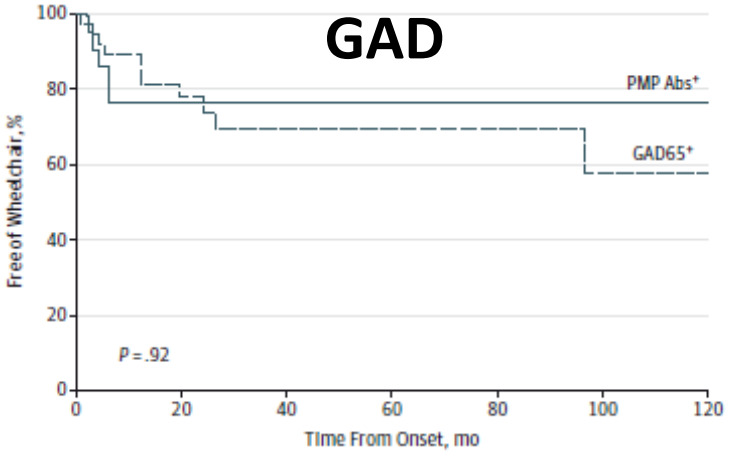


PARANEOPLASTIC CEREBELLAR DEGENERATION: POOR PROGNOSIS

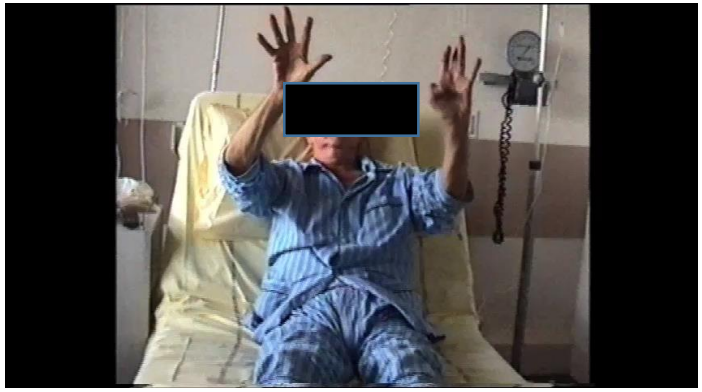
Yo



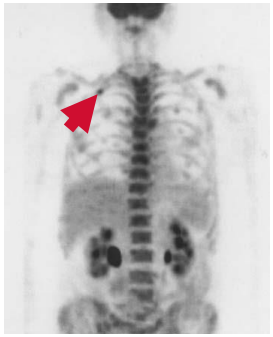
GAD



Neuronopathie sensitive

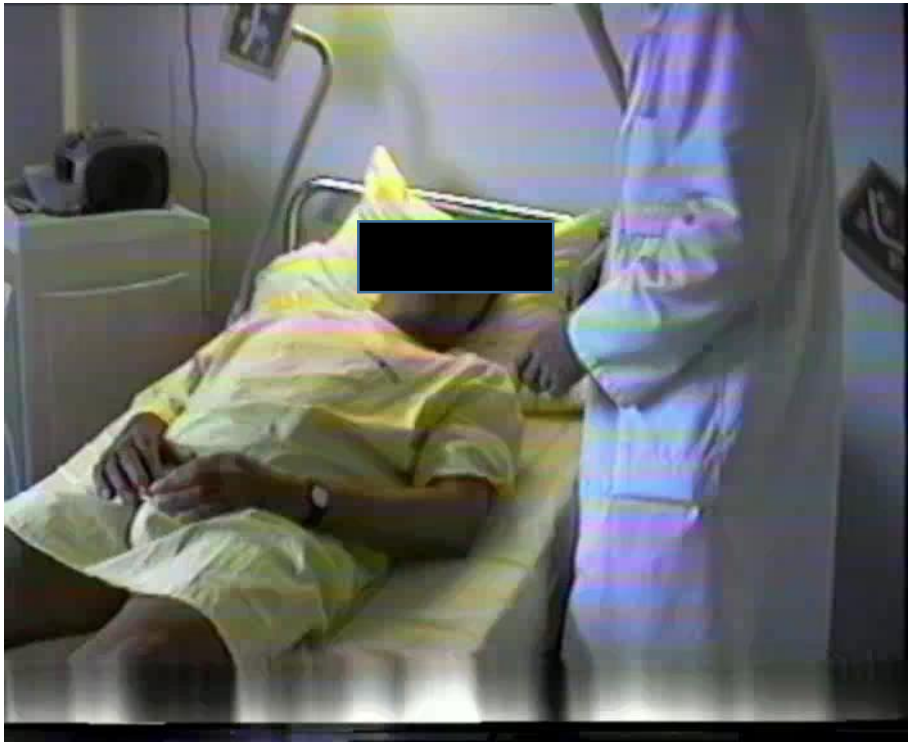


Mr I…, 65 ans, <u>neuronopathie sensitive</u> installée en 2 mois,
Anticorps anti-Hu,
CPPC (découvert 2 mois après début neuro)



Mr I…, 63 ans, <u>neuronopathie sensitive</u> installée en 1 mois,
Anticorps anti-Hu,
CPPC (découvert 4mois après début neuro)

Syndrome de Lambert Eaton



DELTA P score

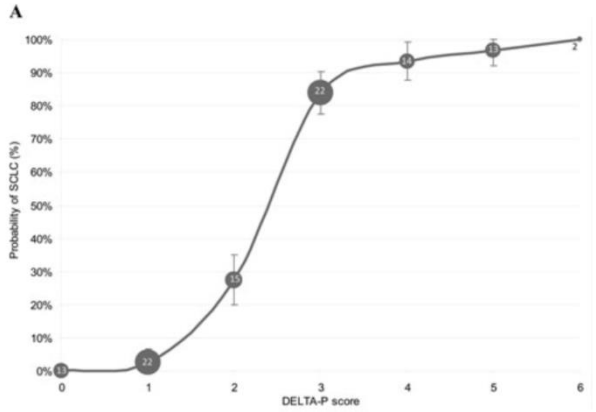
Étude 219 patients

Score diagnostic

-Age ≥ 50 ans
-Tabac
-Amaigrissement ≥ 5%
-IK < 70%
-S. bulbaires
-Tb érectiles

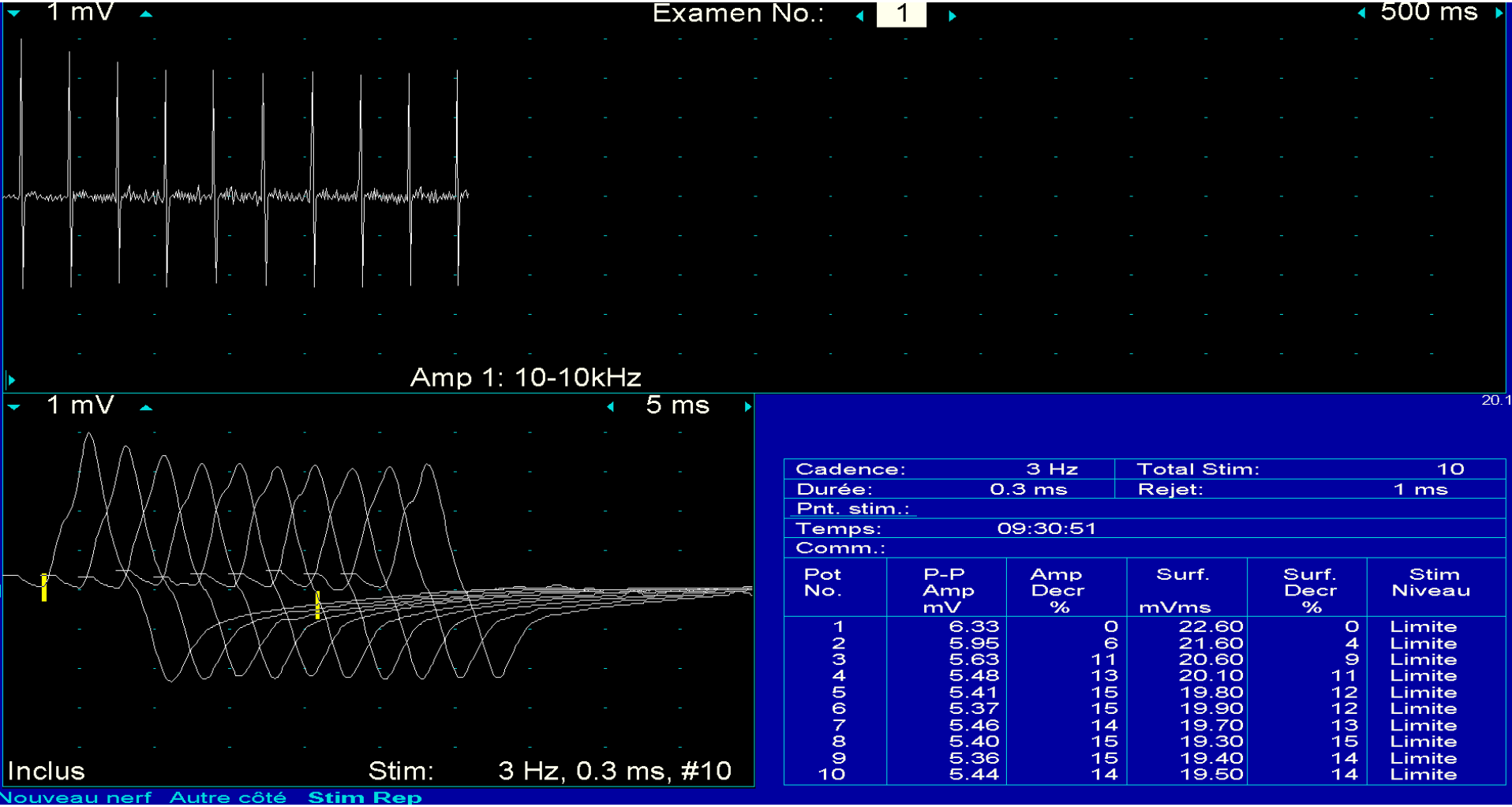
Risque SCLC

≥ 3 : 90%
2 : 30%
0-1 : 2%



Titulaer et al,J Clin Oncol, 2011

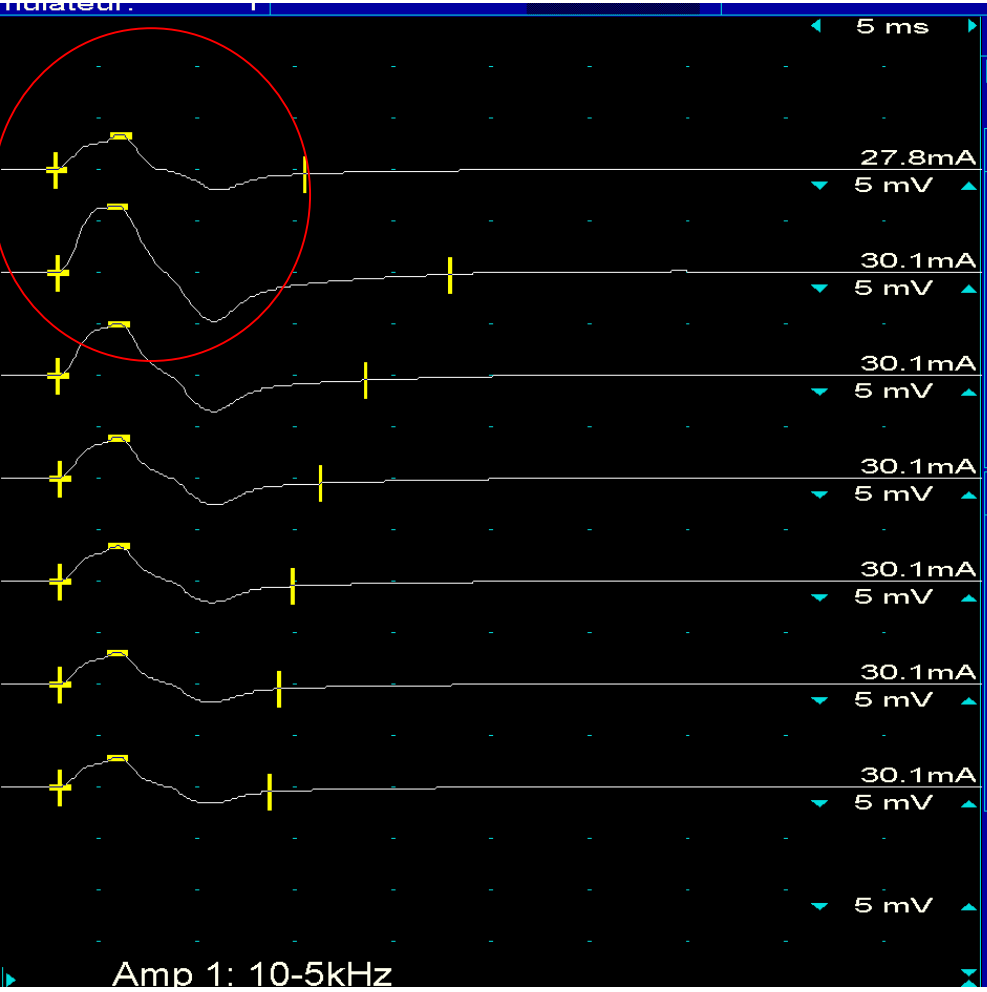
Adducteur du V gauche: Stimulation répétitive 3Hz



Cadence:	3 Hz	Total Stim:	10
Durée:	0.3 ms	Rejet:	1 ms
Pnt. stim.:			
Temps:	09:30:51		
Comm.:			

Pot No.	P-P Amp mV	Amp Decr %	Surf. mVms	Surf. Decr %	Stim Niveau
1	6.33	0	22.60	0	Limite
2	5.95	6	21.60	4	Limite
3	5.63	11	20.60	9	Limite
4	5.48	13	20.10	11	Limite
5	5.41	15	19.80	12	Limite
6	5.37	15	19.90	12	Limite
7	5.46	14	19.70	13	Limite
8	5.40	15	19.30	15	Limite
9	5.36	15	19.40	14	Limite
10	5.44	14	19.50	14	Limite

Test effort bref Adducteur V gauche



Examen: 8 | Moy.: Non | Corr. Signal: Non

A1 A2 A3 A4 A5 A6 A7 A8

Point de Rec.: add du V-effort bref 1

Point de Stim.	Lat1 ms	Dur ms	Amp mV	Surf mVms
A1: avant effort	S 4.2 (2.8)	12.7	14.00 (3.5)	18.
A2: 2 s après effort	S 8.8 (2.9)	20.0	14.30 (6.5)	46.
A3: 10 s après effort	S11.6 (2.9)	15.7	14.30 (5.1)	32.
A4: 20 s après effort	3.0	13.3	4.0	23.
A5: 30 s après effort	3.0	11.9	3.5	18.
A6: 40 s après effort	3.0	11.2	3.2	15.
A7: 50 s après effort	3.0	10.7	3.0	14.
A8: 60 s après effort				

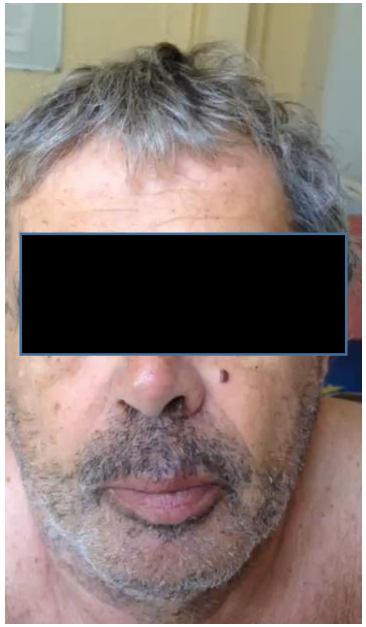
Segment	Diff ms	rAmp %	rSurf %
avant effort-2 s après effort	0.1	188.1	248.
avant effort-10 s après effort	0.1	146.5	172.
avant effort-20 s après effort	0.2	114.8	124.
avant effort-30 s après effort	0.2	101.6	97.
avant effort-40 s après effort	0.2	91.3	84.
avant effort-50 s après effort	0.2	87.1	76.
avant effort-60 s après effort			

Chorée paranéoplasique

Mr Mi…, 56 y
CPPC 2000
Neuronopathie sensitive, anti-CV2+

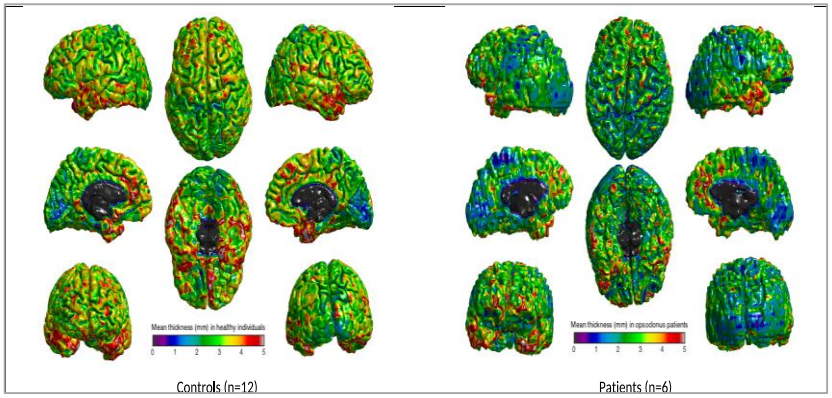
Decemebre 2003 : Chorée et metastases ganglionaires

Flutter / Opsoclonus



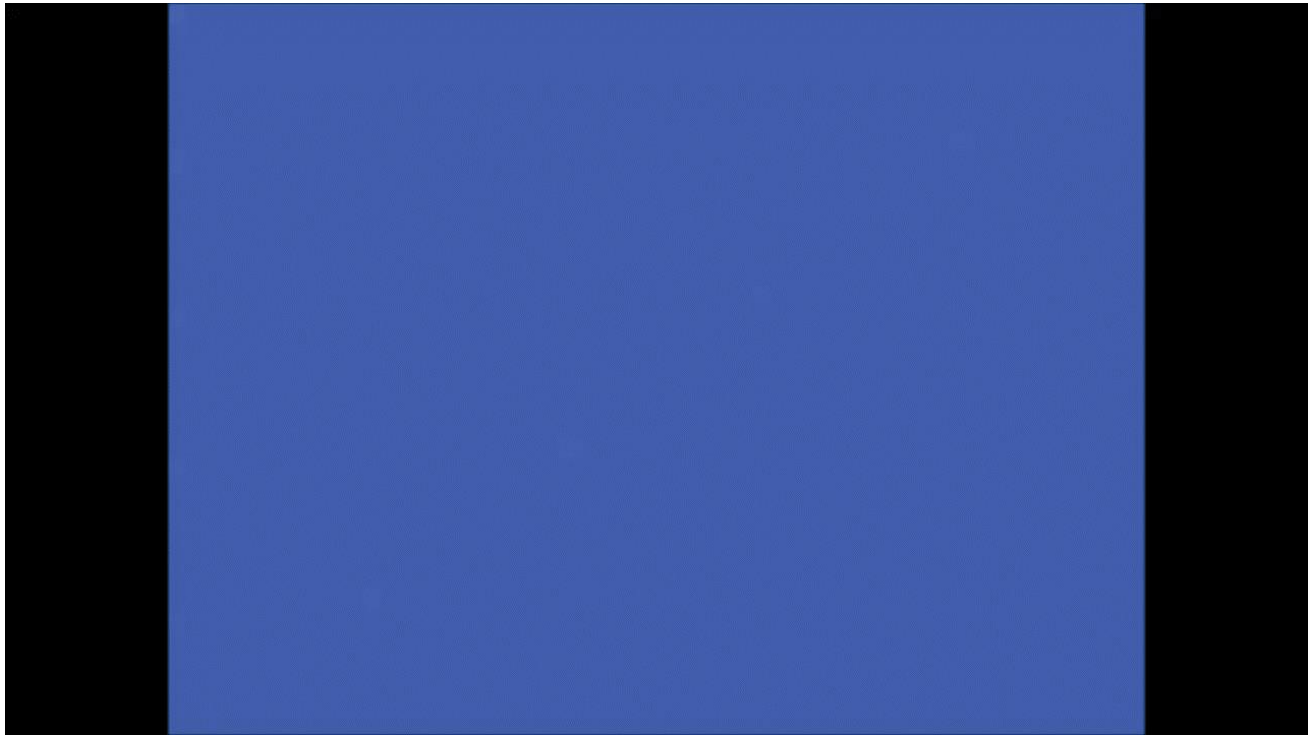
Opsoclonus
Anti-Ma2+
CPPC

Brain volumetric analysis and cortical thickness in adults with saccadic intrusions

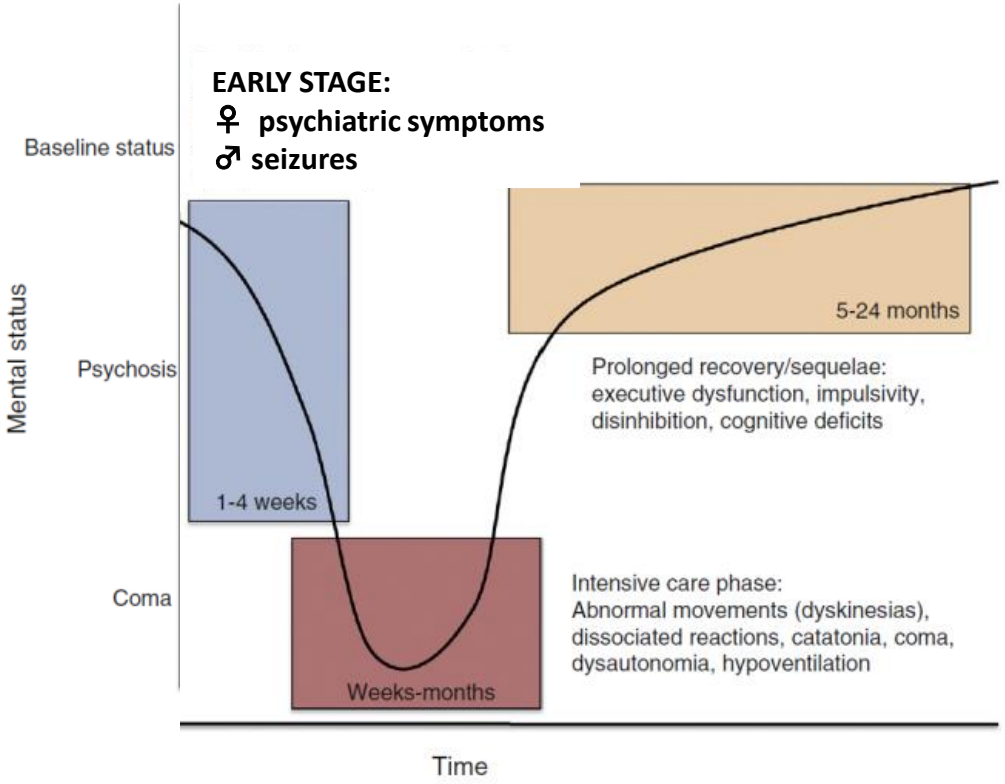


Ibanez et al, 2017

Encéphalite anti-NMDAr

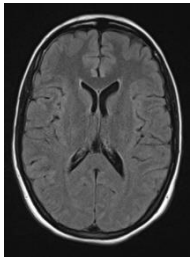


Young (♀>> ♂)

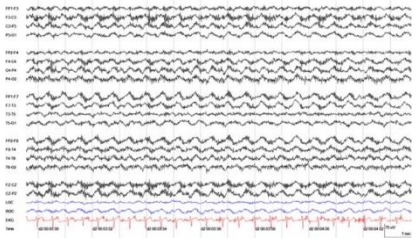


Red flags

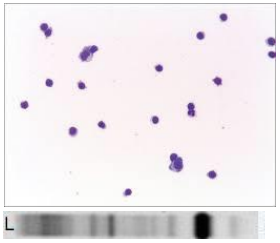
Hallucinations visuels
Catatonie
Non réponse au ttt
Traitement mal supporté
Syndrome confusionnel



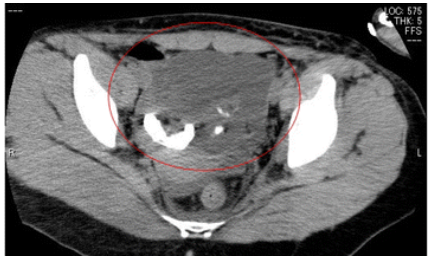
IRM souvent normale



Extreme delta brush (30%)



Pleiocytosis < 100, OCB

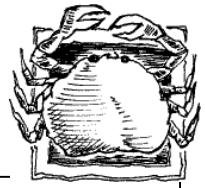


Teratoma, 60% 18-45 y

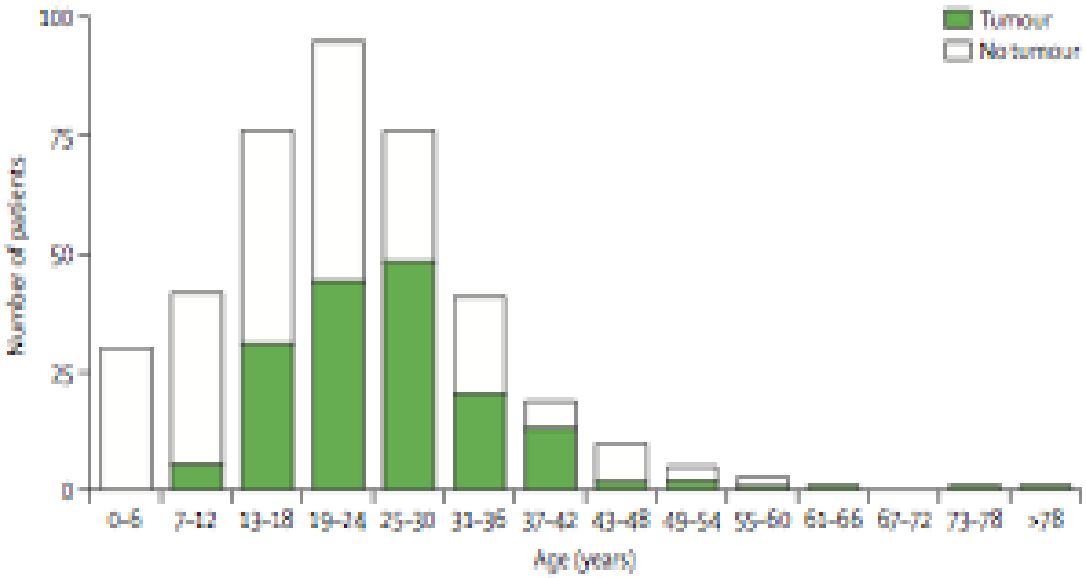
triggers …

Limbic encephalitis and paraneoplastic antibodies (GABAbR, AMPAR)

Cancer **10-60%**



Antigen	Tumor
NMDAR	Ovarian teratoma (58% in patients >18 years)
LGI1	Thymoma (<10%)
CASPR2	Thymoma (38%)
AMPAR	SCLC, breast, thymoma (60%)
$GABA_BR$	SCLC (50%)



Femme (335 pts) : > 18 ans : 58% de K (98% teratome de l'ovaire)
< 18 ans : 35% de K
< 14 ans : 15% de K

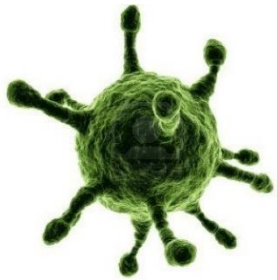
Homme (65 pts) : > 18 ans : 5% de K (séminome testiculaire, CPPC)
< 18 ans : 0%
< 14 ans : 1% Neuroblastome

Dalmau et al, Lancet Neurol. 2011

triggers …

Choreoathetosis post-herpes simplex encephalitis (= anti-NMDAR encephalitis)

Viral Infection

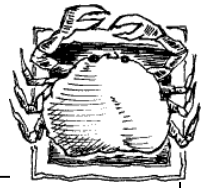


Herpes Simplex Virus Encephalitis Is a Trigger of Brain Autoimmunity

ANN NEUROL 2014;75:317–323

Limbic encephalitis and paraneoplastic antibodies (GABAbR, AMPAR)

Cancer **10-60%**



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AMPAR	SCLC, breast, thymoma (60%)
$GABA_BR$	SCLC (50%)

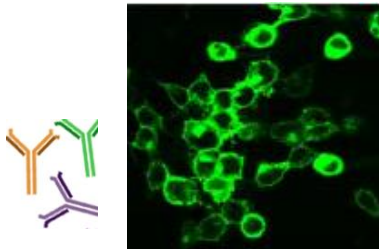
Encéphalites auto-immunes

Antigen	Clinical symptoms
NMDAR	Encephalitis
LGI1	LE, myoclonia, hyponatremia
CASPR2	Encephalitis and/or Morvan syndrome
AMPAR	LE, psychosis
$GABA_BR$	LE, ataxia
$GABA_AR$	Status epilepticus, seizures, encephalitis
mGluR1	Cerebellar ataxia
mGluR5	Ophelia syndrome
DPPX (Kv4.1)	Hallucinations, agitation, myoclonus, tremor, seizures, diarrhea
IgLON5	Non-REM and REM-sleep disorder, brainstem, and limbic dysfunction
GlyR	SPS, PERM
Dopamine 2R	Basal ganglia encephalitis, Sydenham's Chorea

[•••]

2007

2020



Caspr-2

Ag de surface

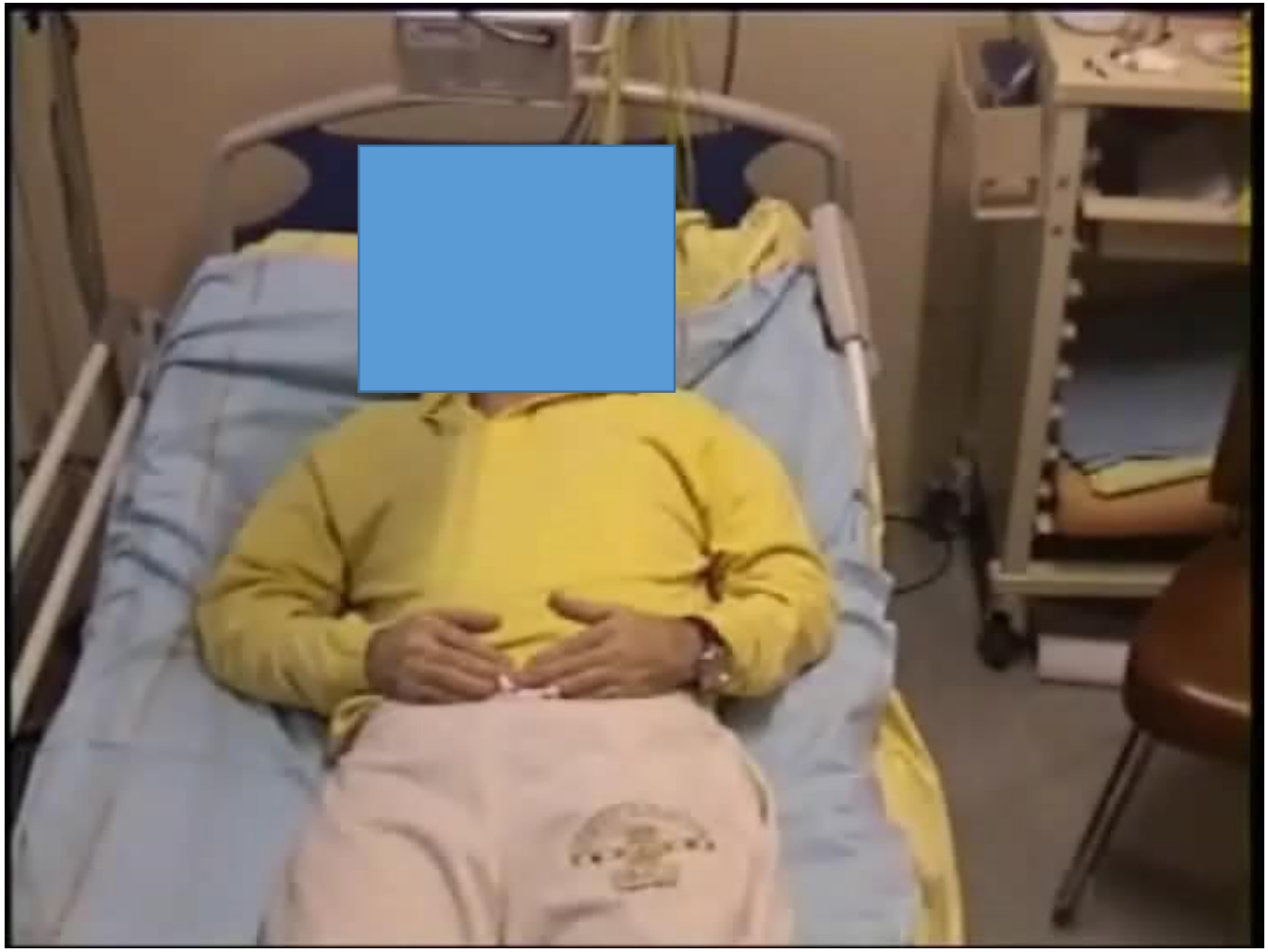
Rôle pathogène

Déclenché par un cancer ou une infection

Irani, Ann Neurol, 2014

Hoftberger, Frontiers in Immunology, 2015

Encéphalite anti-LGi1



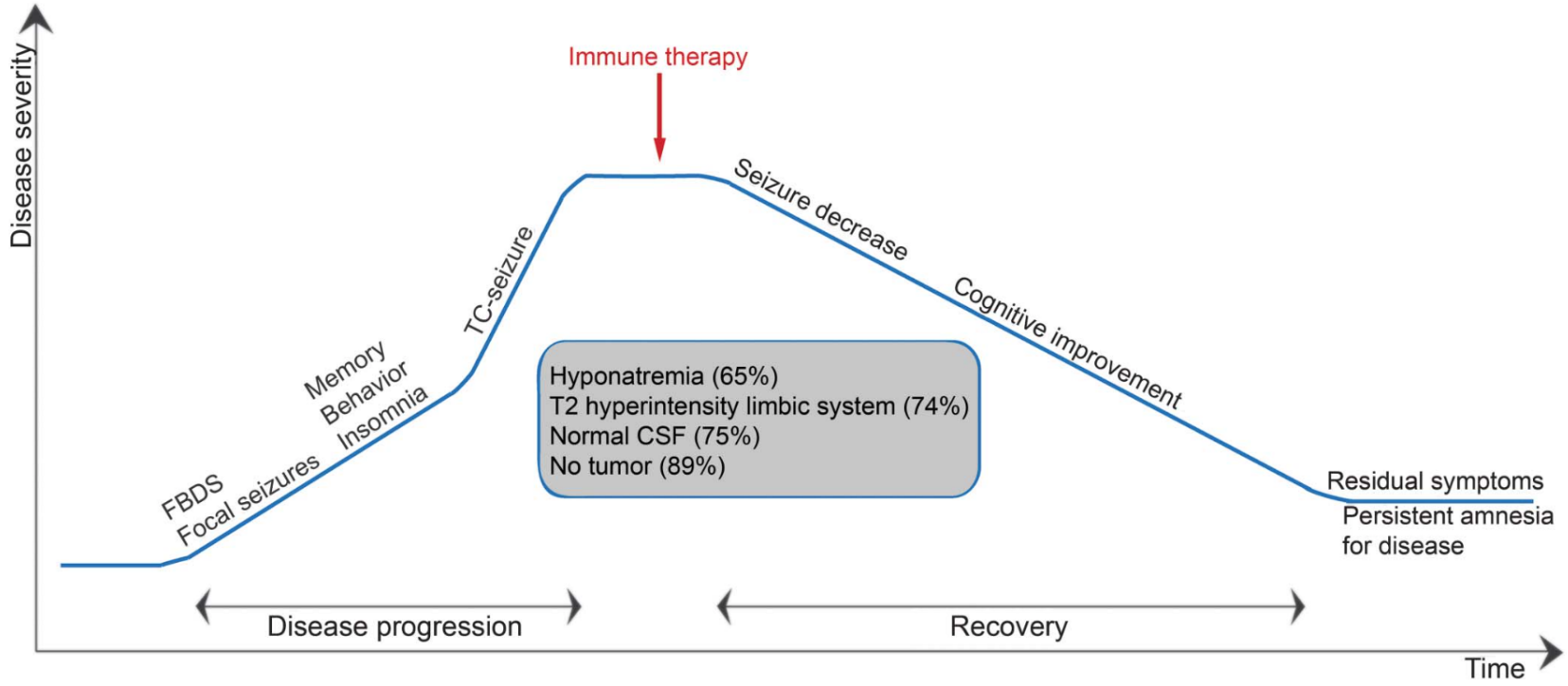
Navarro et al

Anticorps anti-LGi1

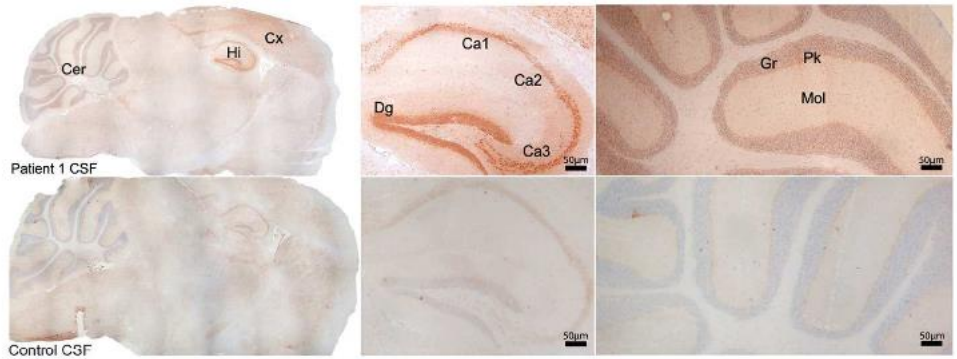
Anti-LGI1 encephalitis

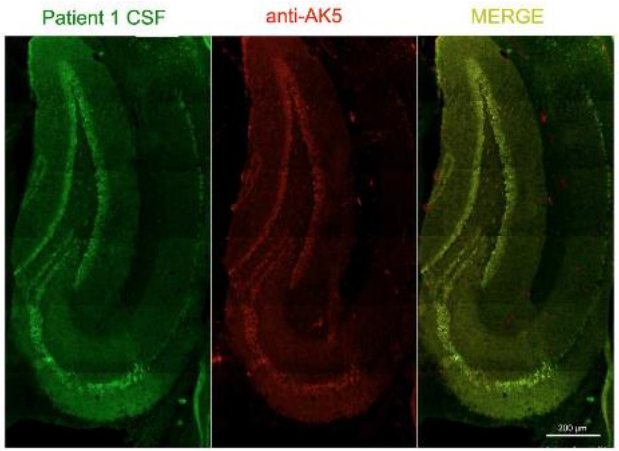
Clinical syndrome and long-term follow-up

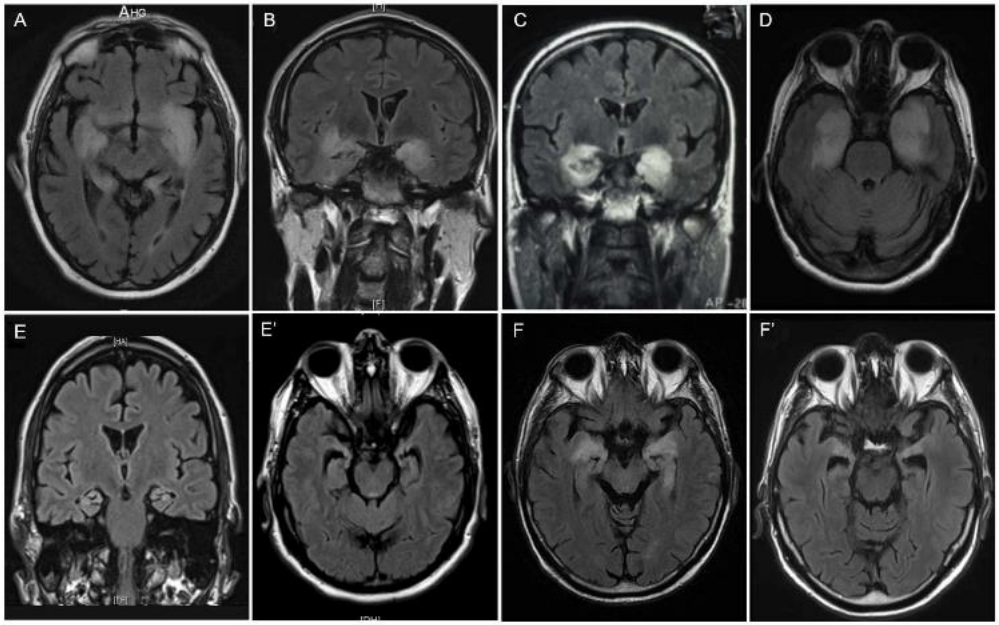
Agnes van Sonderen, *Neurology*® 2016;



Trouble mnésique isolé: EAI anti-AK5







Age médian 64 ans (57-80)
Amnésie antérograde sur 6 semaines
Pas de crise d'épilepsie
Anxiété, prosopagnosie
Hypersignaux FLAIR
LCR inflammatoires ++
Tau augmentée, Phospho tau Nle
Évolution vers stabilité et atrophie Hippo

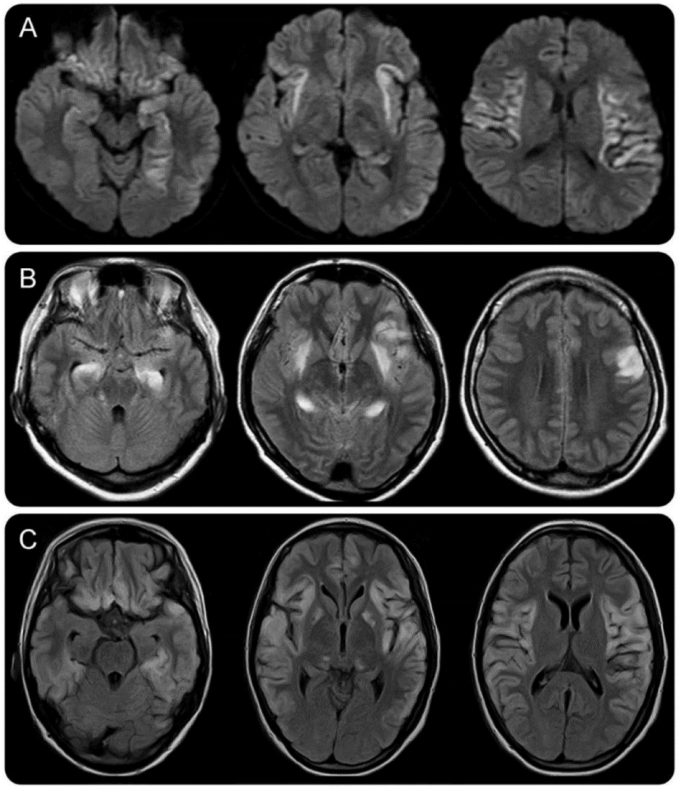
Do et al, Neurology 2017

Trouble épileptique isolé:

Cryptogenic NORSE

Neurol Neuroimmunol Neuroinflamm 2017;

Its distinctive clinical features and response to immunotherapy



Epilepsie et auto-immunité

et encéphalite auto-immune

	Epilepsie	Symptômes associés	Tumeur
LGi1	FBDS	Troubles mnésiques Hyponatrémie	5% (thymome)
GABAa	E. réfractaire	Troubles du comportement	25% (thymome)
GAD	E. résistante	Troubles mnésiques et ataxie	< 5%
GABAb	E. précoce	Troubles mnésiques	70% (CPPC)

Trouble psychiatrique isolé?

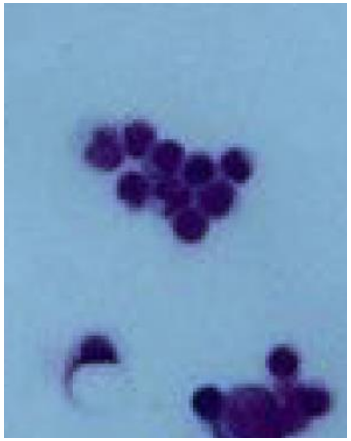
Drapeaux rouges

- Episode infectieux récent
- Symptômes neurologiques (Syndrome confusionnel/Régression cognitive
- Hallucinations visuelles / Syndrome catatonique
- Fluctuation des symptômes
- Résistance au traitement antipsychotique
- Effets secondaires nombreux et inhabituels
- Anomalies examens paracliniques: LCR, EEG, IRM

Bonnot et al., 2014

Bilan étiologique

Ponction Lombaire

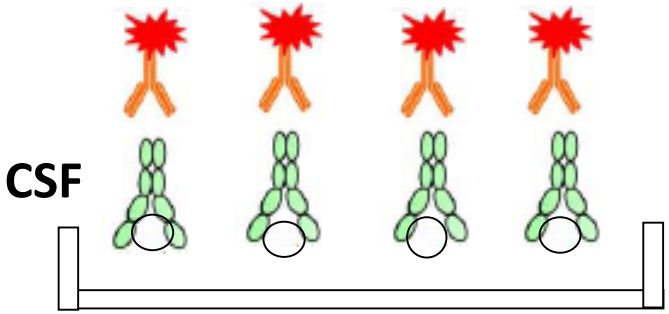


Pléocytose LCR

Diagnostique biologique

Indirect immunofluorescence

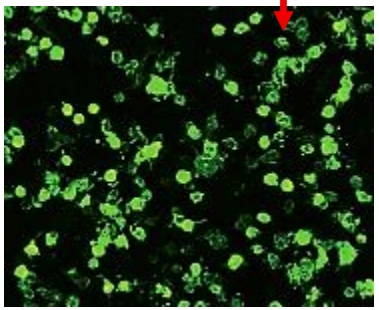
cell-based assays



GABA	AMPA2
LGI-1	AMPA1
Caspr-2	NMDAr

CELL-BASED ASSAYS

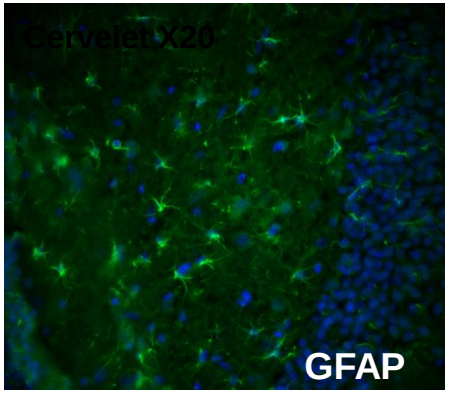
HEK293 cells transfected with the Ag of interest

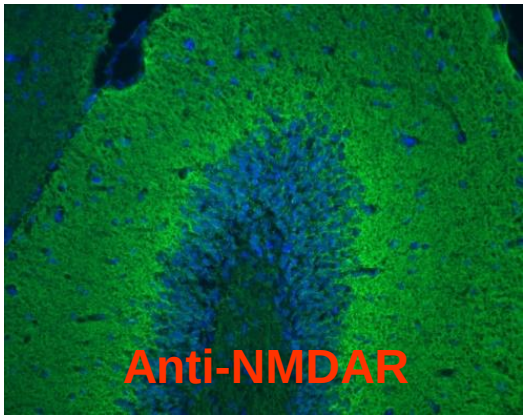


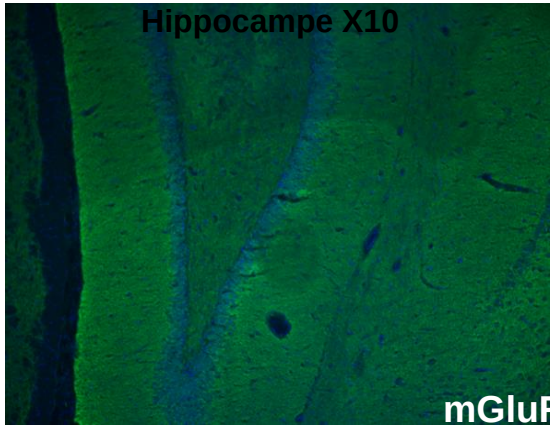
NMDAr

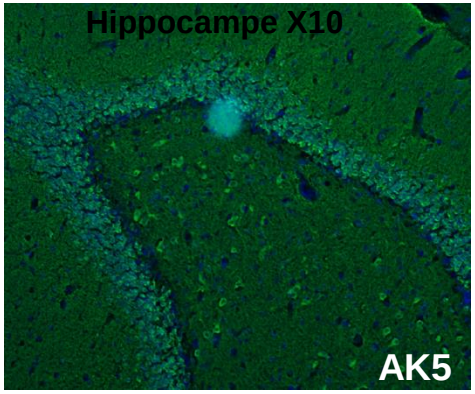
Hoftberger, Frontiers in Immunology, 2015

Exemples…

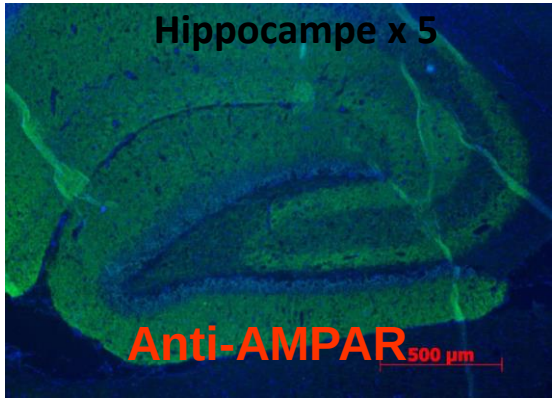

Cervelet X20
GFAP

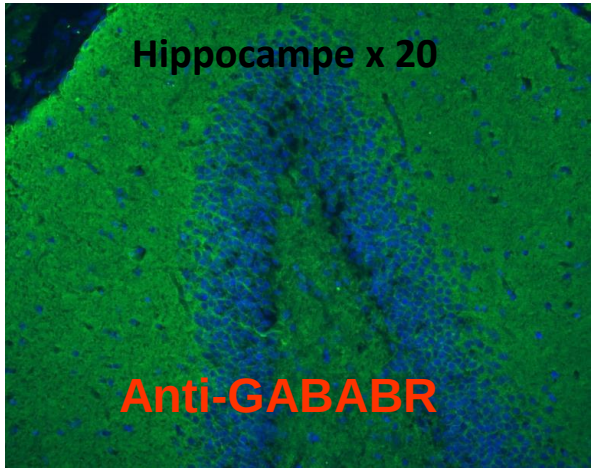

Anti-NMDAR

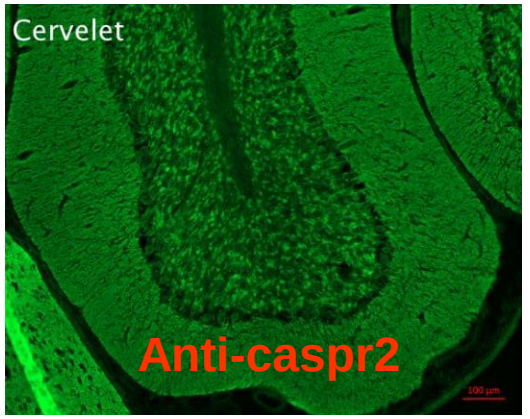

Hippocampe X10
mGluR


Hippocampe X10
AK5


Cervelet
Anti-LGI1

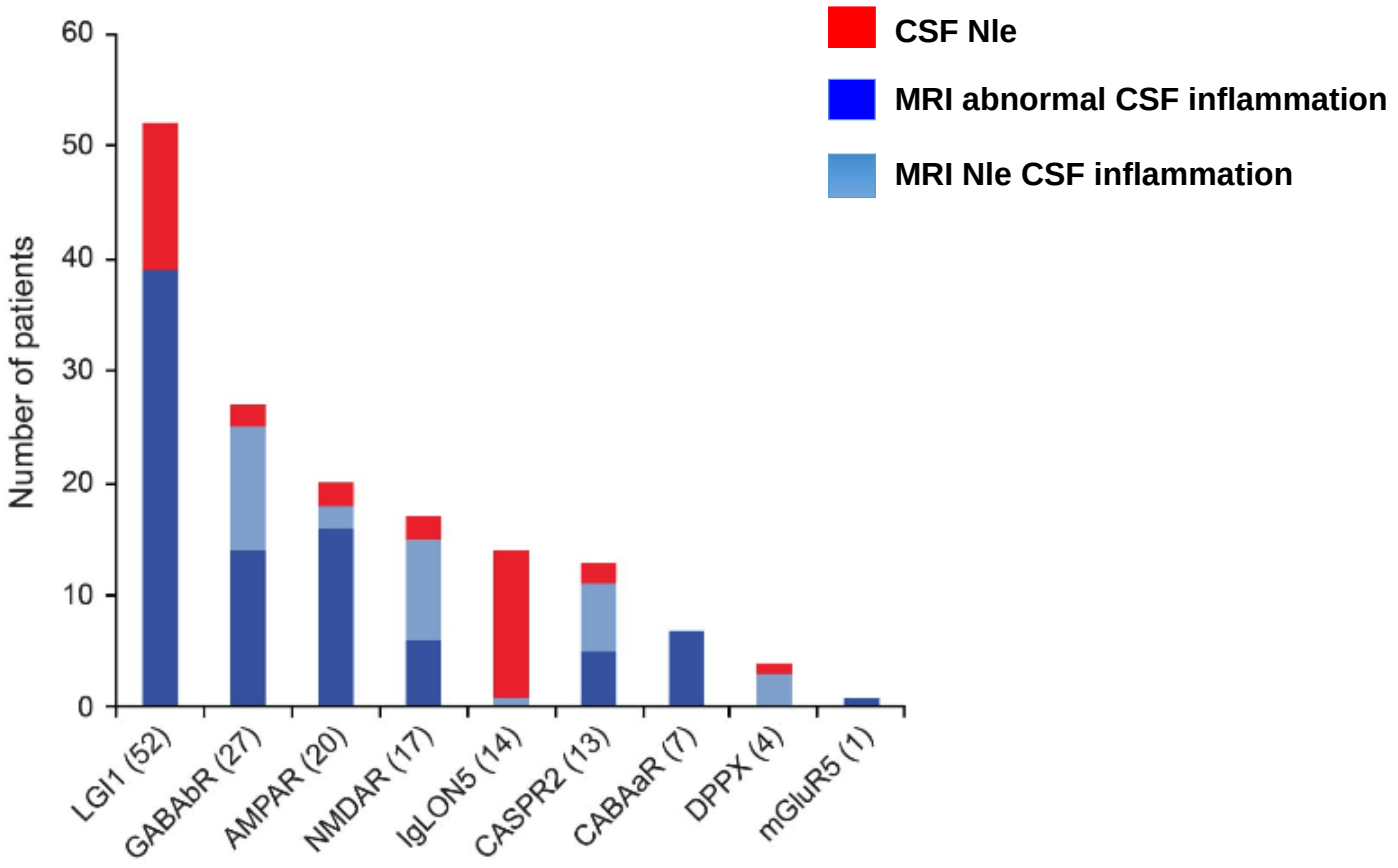

Hippocampe x 5
Anti-AMPAR
500 µm


Hippocampe x 20
Anti-GABABR


Cervelet
Anti-caspr2

Inflammation et LCR

Figure 1 **Distribution of patients according to antibody type**

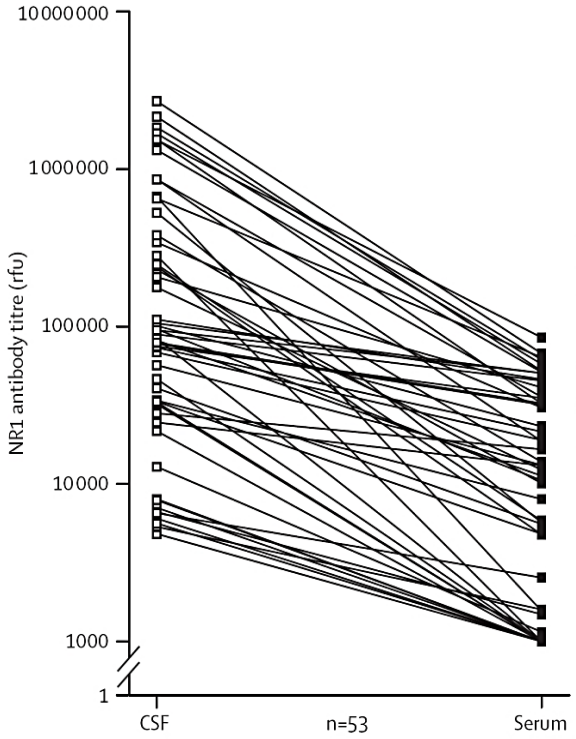


Frequency of patients ≥60 years of age with (blue) or without (red) CSF pleocytosis or inflammatory changes in the brain MRI. Number of cases for each antibody is shown in parentheses. Dark blue in the column indicates number of patients with brain MRI findings compatible with encephalitis; light blue indicates number of cases with normal MRI and CSF pleocytosis.

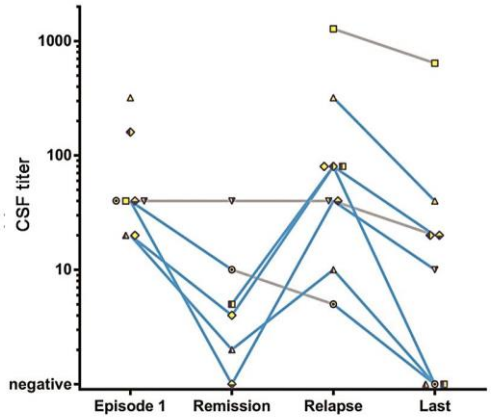
Escudero et al, Neurology 2017

Evolution des titres d'anticorps: ex. NMDA

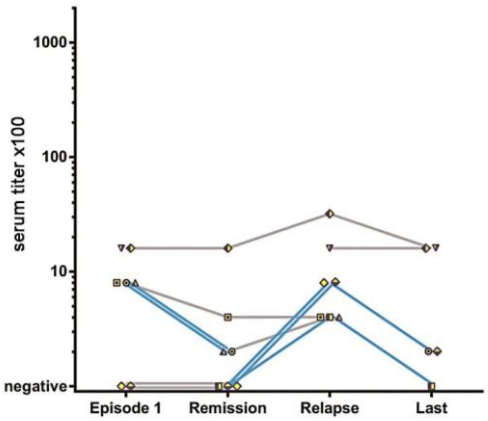
Intrathecal synthesis of antibodies



Relapses



LCR

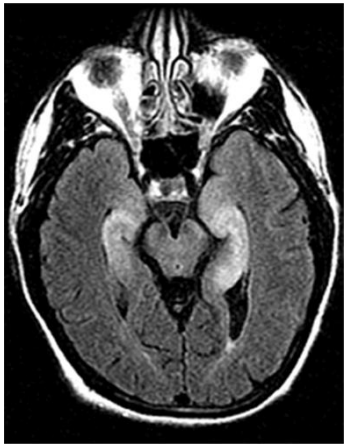


Serum

Gresa, Titulaer et al. Lancet Neurol 2014

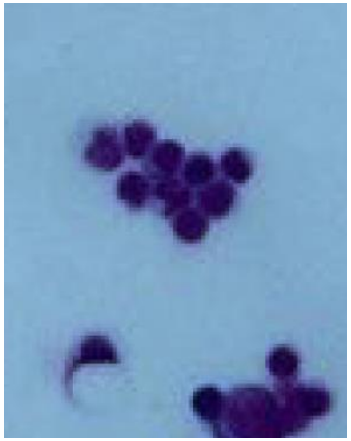
Bilan étiologique

IRM cérébrale



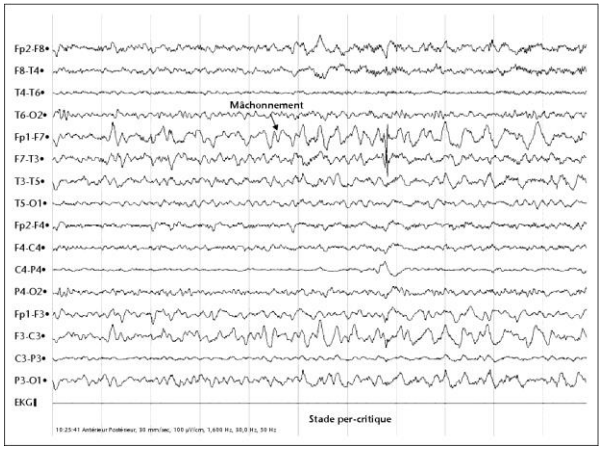
hypersignal temporal interne

Ponction Lombaire



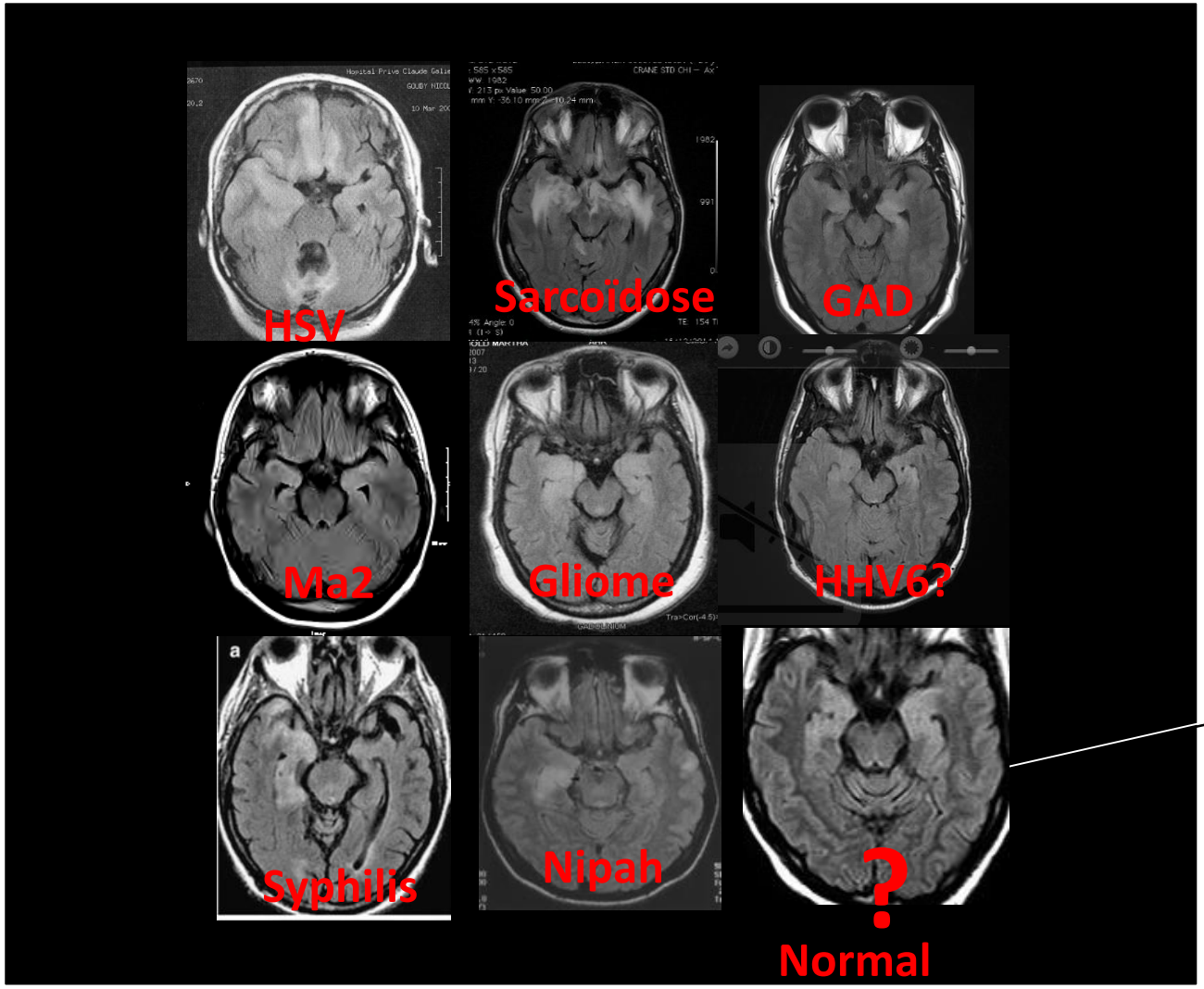
Pléocytose LCR

Electroencéphalogramme



Epilepsie/ondes lentes

extreme delta brush (6-8%) dans NMDA


HSV
Sarcoïdose
GAD
Ma2
Gliome
HHV6?
Syphilis
Nipah
?
Normal

Approche diagnostique

A clinical approach to diagnosis of autoimmune encephalitis

Francesc Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Iizuka, Sarosh R Irani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Reindl, Myrna R Rosenfeld, Kevin Rostásy, Albert Saiz, Arun Venkatesan, Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau

Panel 2: Diagnostic criteria for definite autoimmune limbic encephalitis

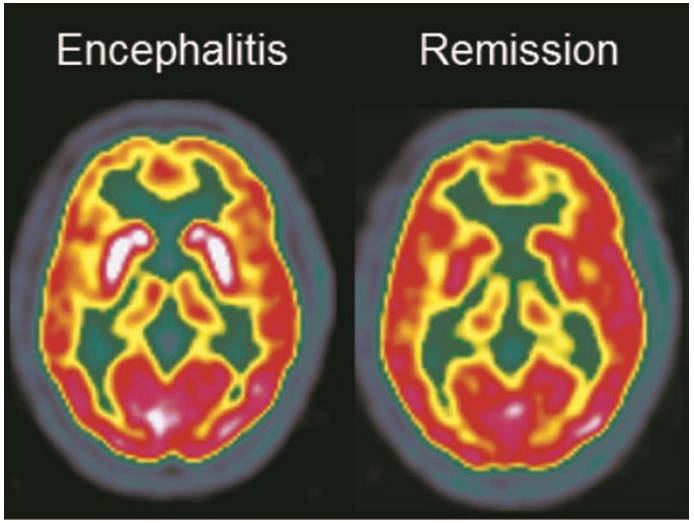
Diagnosis can be made when all four* of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
3. At least one of the following:
   - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes (appendix)

Lancet Neurol 2016

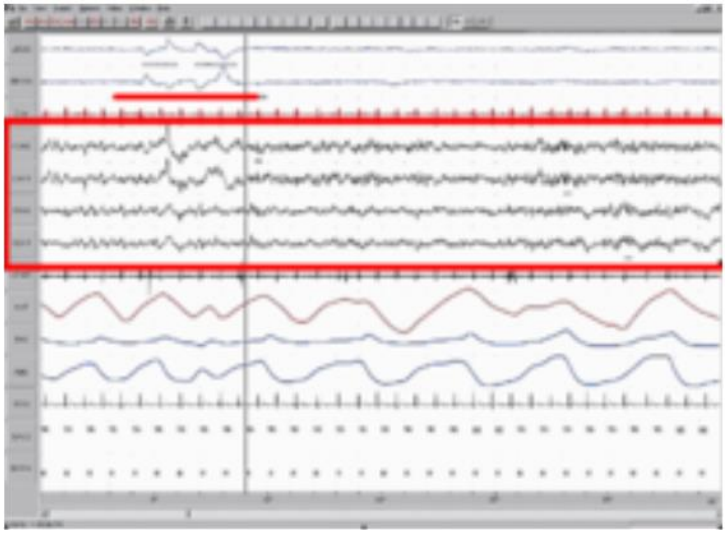
Bilan étiologique de 2eme intention

PET scanner



Navarro et al

Polysomnographie



A. Gales

Stratégie thérapeutique

TRAITEMENT TUMORAL ± **IMMUNOTHERAPIE** ± **ATTENTION TRAITEMENTS ASSOCIEES**

↓

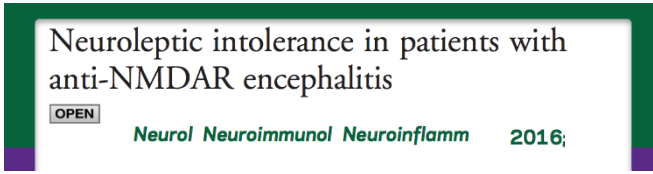
<u>1ère ligne</u>:
high-dose steroids, IVIg, plasma exchange

↓

<u>2ème ligne</u>:
cyclophosphamide et/ou rituximab

↓

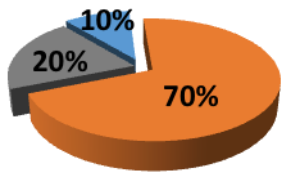
Agonistes glutamatergiques
(Ketamine, sévoflurane, Propofol, Phencyclidine)
Neuroleptiques 1ème génération


Neuroleptic intolerance in patients with anti-NMDAR encephalitis
OPEN
Neurol Neuroimmunol Neuroinflamm 2016;

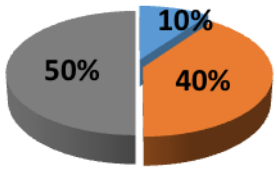
Evolution

Antigène intracellulaire

Hu, Yo, Ri, Ma2..



3 months



24 months

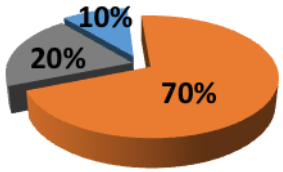
- **Improvement**
- **Stable/deteriorate**
- **Death**

Berzero G and Psimaras D 2018 literature review

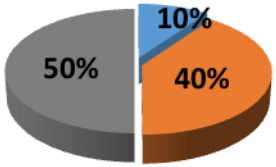
Evolution

Antigène intracellulaire

Hu, Yo, Ri, Ma2..



3 months

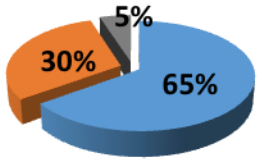


24 months

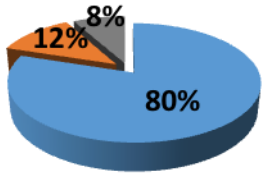
- **Improvement**
- **Stable/deteriorate**
- **Death**

Antigènes membranaires

NMDAR, LGI1, AMPAR, GABAR..



3 months



24 months

Berzero G and Psimaras D 2018 literature review

Conclusion

le passé et le futur

PNS et Ac intracellulaires

Description années 1950

Rares

Associés au **cancer**

Sujets âgés

Subaiguë, multifocal

Mauvaise réponse au traitement

Encephalite Autoimmune

Description récente

Relativement fréquents

Associés au cancer ou **infection**

Sujets jeunes

Aigüe, Subaiguë

Bonne réponse au traitement

Efforts pour trouver des nouveaux traitements

Efforts pour caractériser des nouveaux anticorps