Inserm
Institut national
de la santé et de la recherche médicale

Hospices Civils de Lyon

Diplôme interuniversitaire
Diagnostic et prise en charge maladies d'Alzheimer et apparentées
Lille
29 Mars 2019

Encéphalites autoimmunes à révélation cognitives

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AGENCE NATIONALE DE LA RECHERCHE
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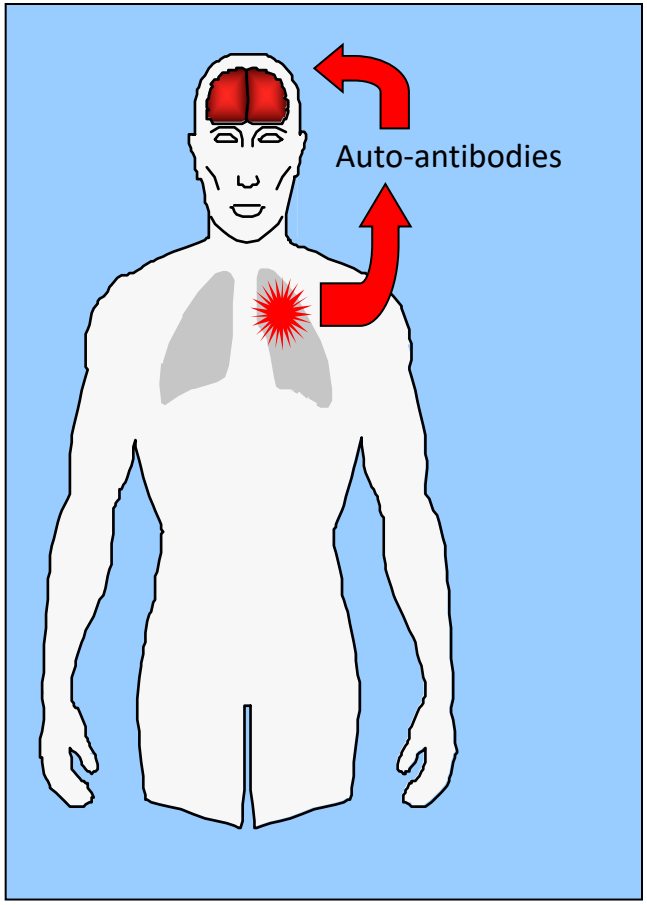
FONDATION RECHERCHE MÉDICALE

ORIGIN OF AUTOIMMUNE ENCEPHALITIS CONCEPT: THE PARANEOPLASTIC NEUROLOGICAL SYNDROMES

A REMOTE EFFECT OF CANCER



Clinical diagnosis : No metastasis, No metabolic, carential or infectious disease

CSF : pleocytosis
elevated protein levels
increased IgG concentration
oligoclonal bands

Brain : T lymphocytes infiltration

Onco-neuronal autoantibodies (first described in 1983) :

- specificity 99 %
- sensitivity 50 %
- determine tumor types
  neurological signs

Syndromes neurologiques paranéoplasiques

Début subaigue, évolution rapide, tumeurs de petit volume

Neuronopathie sensitive et anti-Hu

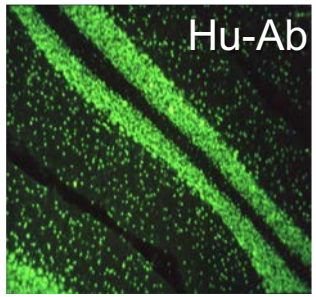
Ataxie cérébelleuse et anti-Yo

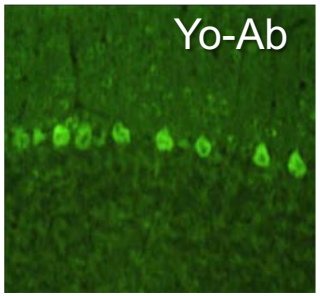
Main onco-neural antibodies associated with PNS

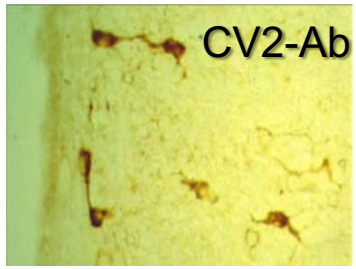
(Graus et al, JNNP 2004;75:1135-1140)

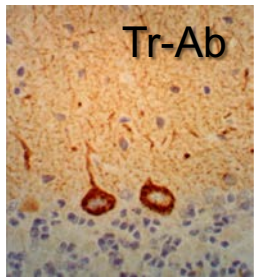
Antibodies	Main associated neurological syndromes	Cancer	frequence cancer
Hu-Ab	Sensory neuronopathy Encephalomyelitis Chronic gastrointestinal pseudoobstruction Cerebellar ataxia Limbic encephalitis	SCLC	98%
Yo-Ab	Subacute cerebellar ataxia	Ovary, breast, uterus	98%
CV2-Ab	cerebellar ataxia Sensory-motor neuropathy Uveitis, retinopathy Encephalomyelitis	SCLC, thymoma	96%
Ri-Ab	Opsomyoclonus Cerebellar ataxia	Breast, SCLC	97%
amphiphysin-Ab	Stiff-person syndrome Sensory neuronopathy Encephalomyelitis	Breast, SCLC	95%
Tr/DNER-Ab	Cerebellar ataxia	Hodgkin	ND
Ma2-Ab	Limbic encephalitis	Testicular	96%

specificity 99 % ; sensitivity 50 % ; **intra-cellular antigens**









PNS with onconeural antibodies are rare

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)

In the French reference center: - 30 to 40 anti-Hu per year
- 7 to 12 anti-Yo per year

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

Cerebellar ataxia and sensory neuronopathy were the most frequent PNS

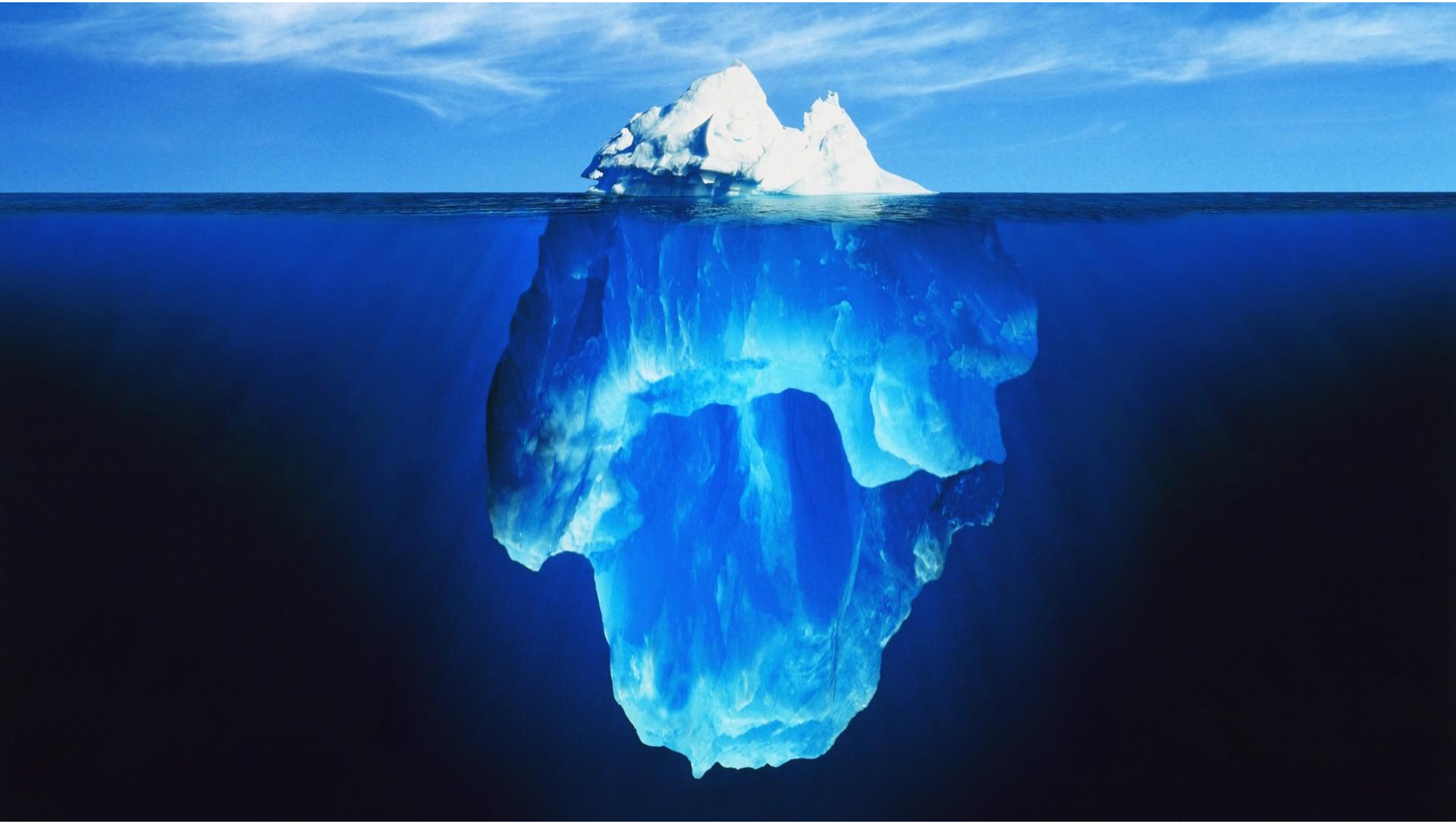
Table 1. Paraneoplastic Neurologic Syndrome (PNS) in the PNS Euronetwork Database

Type of PNS	Patients, No. (%)[a] (N=979)
Central nervous system	
Cerebellar degeneration	238 (24.3)
Limbic encephalitis	98 (10.0)
Paraneoplastic encephalomyelitis	55 (5.6)
Brainstem encephalitis	55 (5.6)
Opsoclonus or myoclonus	23 (2.3)
Motor neuron disease	20 (2.0)
Necrotic myelopathy	3 (0.3)
Stiff person syndrome	6 (0.6)
Peripheral nervous system	
Sensory neuronopathy	238 (24.3)
Acute inflammatory polyradiculopathy	16 (1.6)
Chronic inflammatory polyradiculopathy	13 (1.3)
Dysautonomia	51 (5.2)
Mononeuritis neuropathy	6 (0.6)
Lambert-Eaton myasthenic syndrome	43 (4.4)
Neuromyotonia	10 (1.0)
Muscle	
Dermatomyositis or polymyositis	14 (1.4)
Necrotic myopathy	2 (0.2)
Other	
Central nervous system	60 (6.1)
Peripheral nervous system included	117 (12.0)
End-plate disorder	23 (2.3)
Cancer-associated retinopathy	4 (0.4)

979 patients with definite PNS collected
By the PNS Euronetwork consortium between 2000 and 2008

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

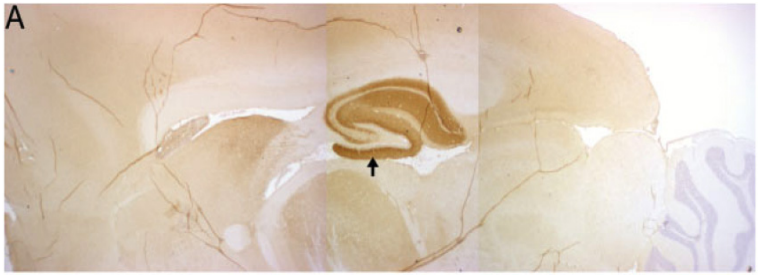
Syndromes neurologiques paranéoplasiques et encéphalites autoimmunes



Les patients avec cancer ne représentent qu'une petite partie

The studies of diseases mechanisms changed with the description of NMDA-R-Abs encephalitis

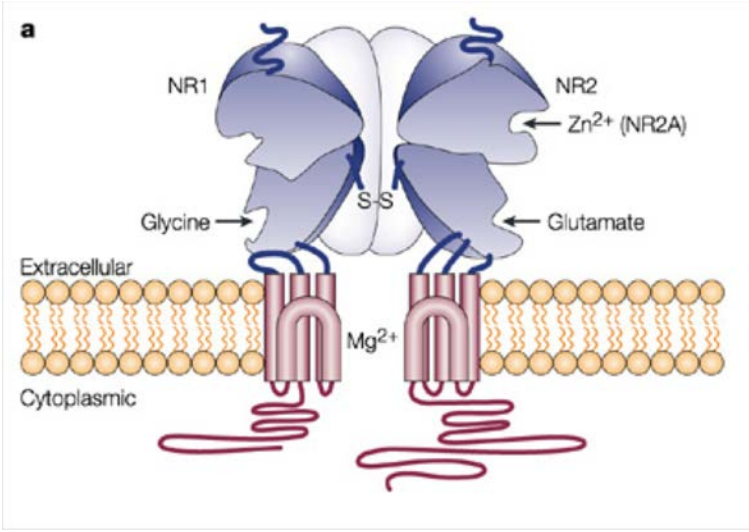
Dalmau et al, Ann Neurol 2007



Indirect immunohistochemistry on rat brain
With CSF of a patient with NMDAR encephalitis.
IgG recognizing NMDAR in rat hippocampus

Bayreuther et al, Epileptic Disord 2009

Ovarian teratoma



NMDA receptor

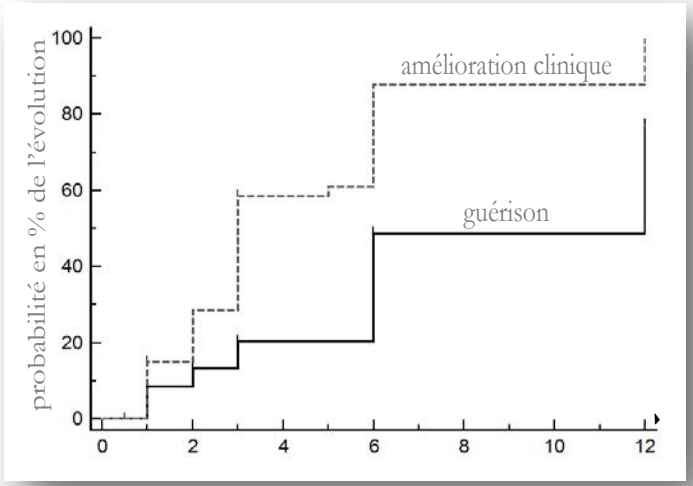
Encephalitis with anti-NMDA-R antibodies
40% of cases are Children without tumor

Trousseau, France

3 years old boy
Acute agitation

Bordeaux, France. Dr Villega

Girl 6 years old
First seizure in july 2009
Aphasia, mutism, abnormal mouvements
Many seizures, beddriden, gastrostomy
No tumour



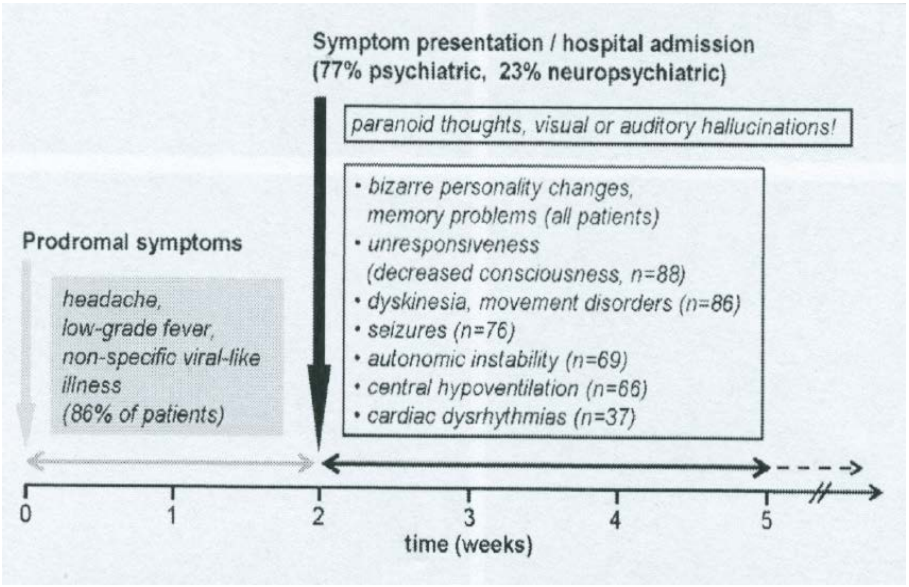
Animal model do not reflect human NMDAR-Abs encephalitis

Complete improvement occurs in 90% of cases
But is very long
Treatments: No guideline
Corticosteroids, Ivlg
Rituximab, Cyclophosphamide
Azathioprine, Mycophenolate Mofétil

March 2013 October 2013 March 2014

What we learnt from NMDAR-Ab encephalitis ?

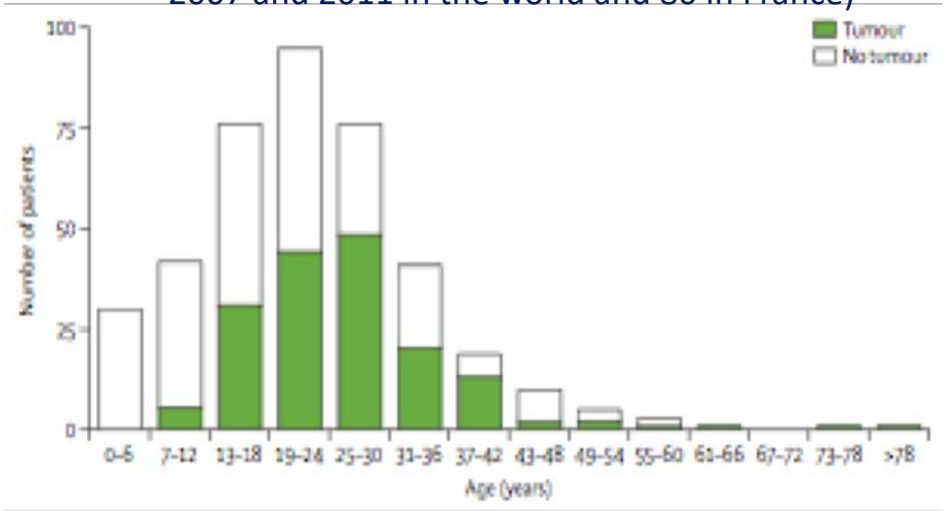
Typical clinical presentation



More than 50% of patients have no tumor

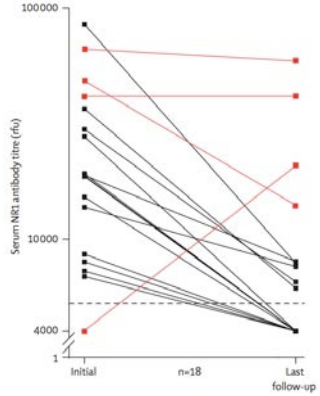
Frequence > all onconeural antibodies

(> 700 patients with NMDAr identified between 2007 and 2011 in the world and 80 in France)



Dalmau et al, Lancet Neurol. 2011

Autoantibodies level decrease with clinical improvement



Dalmau et al, Lancet Neurol. 2010;10:63-74

Tumor frequency in 400 patients

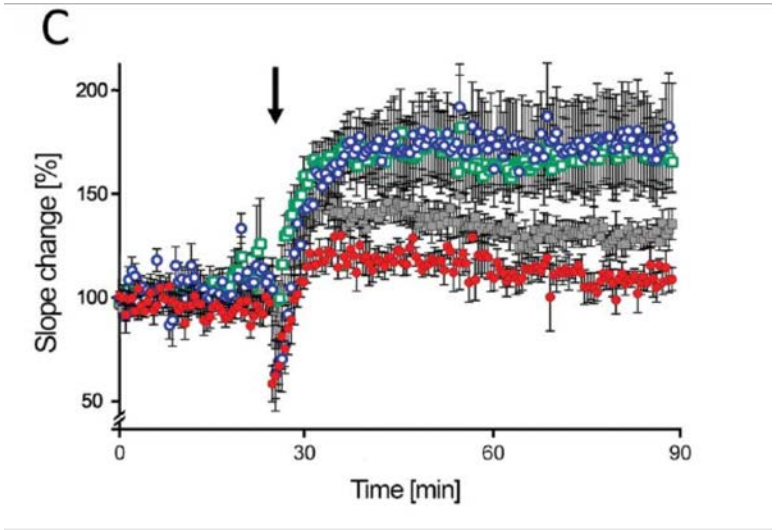
Women (335 pts) : > 18 ans : 58% of tumors (98% ovary teratoma)
< 18 ans : 35% of tumors
< 14 ans : 15% of tumors

Hommes (65 pts) : > 18 ans : 5% of tumors (testicular seminoma, SCLC)
< 18 ans : 0%
< 14 ans : 1% Neuroblastoma

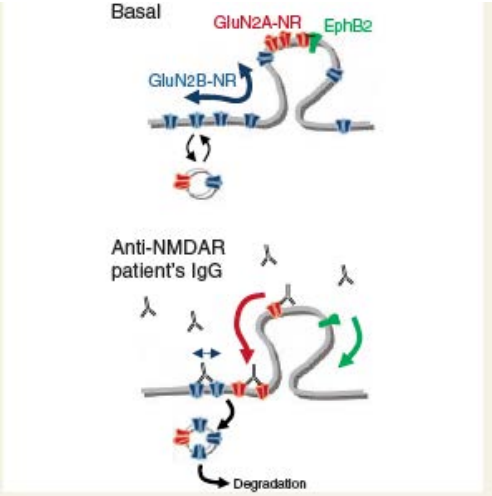
Encephalitis with NMDAR autoantibodies
More questions than answers

Clinical and experimental arguments suggest a direct role of NMDAR-Abs but:

- No animal model with all the patients' signs
- No explanation of the long time to improve
- Which trigger in the absence of cancer ?
- Why only few cancer can trigger NMDAR-Abs encephalitis ?



Planaguna et al, Ann Neurol 2016



Mikasova et al, Brain 2012;135:1606-1621
Dupuis et al, EMBO J 2014

Encephalitis with autoantibodies directed against cell surface antigens Are observed with or without cancer According the autoantibodies

	NMDAr	AMPAr	$GABA_{BR}$	Lgi1	CASPR2	Glycine R	mGluR1	mGluR5	GAD
Number of published cases	>1000	>80	>80	>150	>60	>50	5	3	>100
Clinical signs	encephalitis	LE	LE	LE	LE myotonia	LE myoclonus	ataxia	LE	Ataxia Stiff LE
Role	antagonist	antagonist	?	?	?	antagonist	agonist	?	?
Paraneoplastic cases	50%	70%	70%	15%	15%	0%	25%	100%	15%
Associated tumors	Ovary teratoma	Thymoma breast, SCLC	SCLC	SCLC, thymoma	SCLC, thymoma	-	Hodgkin	Hodgkin	lung

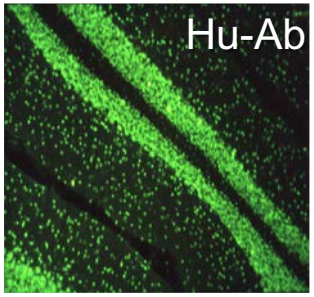
Anti-VGKC = anti-Lgi1 and anti-CASPR 2 +++
LE = limbic encephalitis

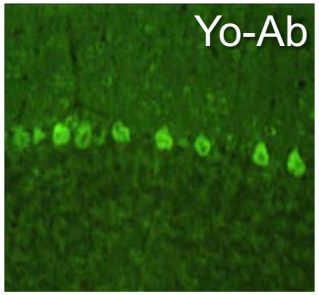
Lai et al, Lancet Neurol 2010;9:776-785
Irani et al, Brain 2010;133:2734-2748

New concept in paraneoplastic neurological syndrome

Classification according antibodies and the targeted antigens

Group1: Intra-cellular





Hu

Yo

CV2

Ma2….

Biomarkers of cancer and immune reaction, but no direct role ? Neuronal death+++

Group2: Membrane or synaptic proteins

NMDA-R

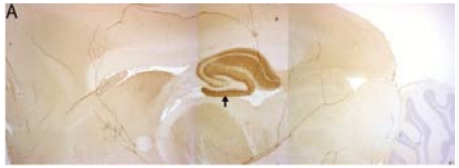
AMPA-R

GABAB-R

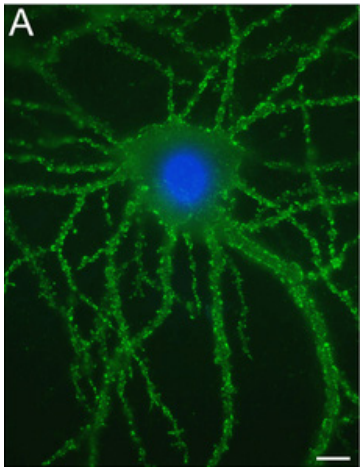
DNER/Tr

Lgi1

CASPR2…



Dalmau et al, Ann Neurol 2007



Not always associated with cancer, direct role of antibodies,

No or limited neuronal death ?

Group3: Two are particular

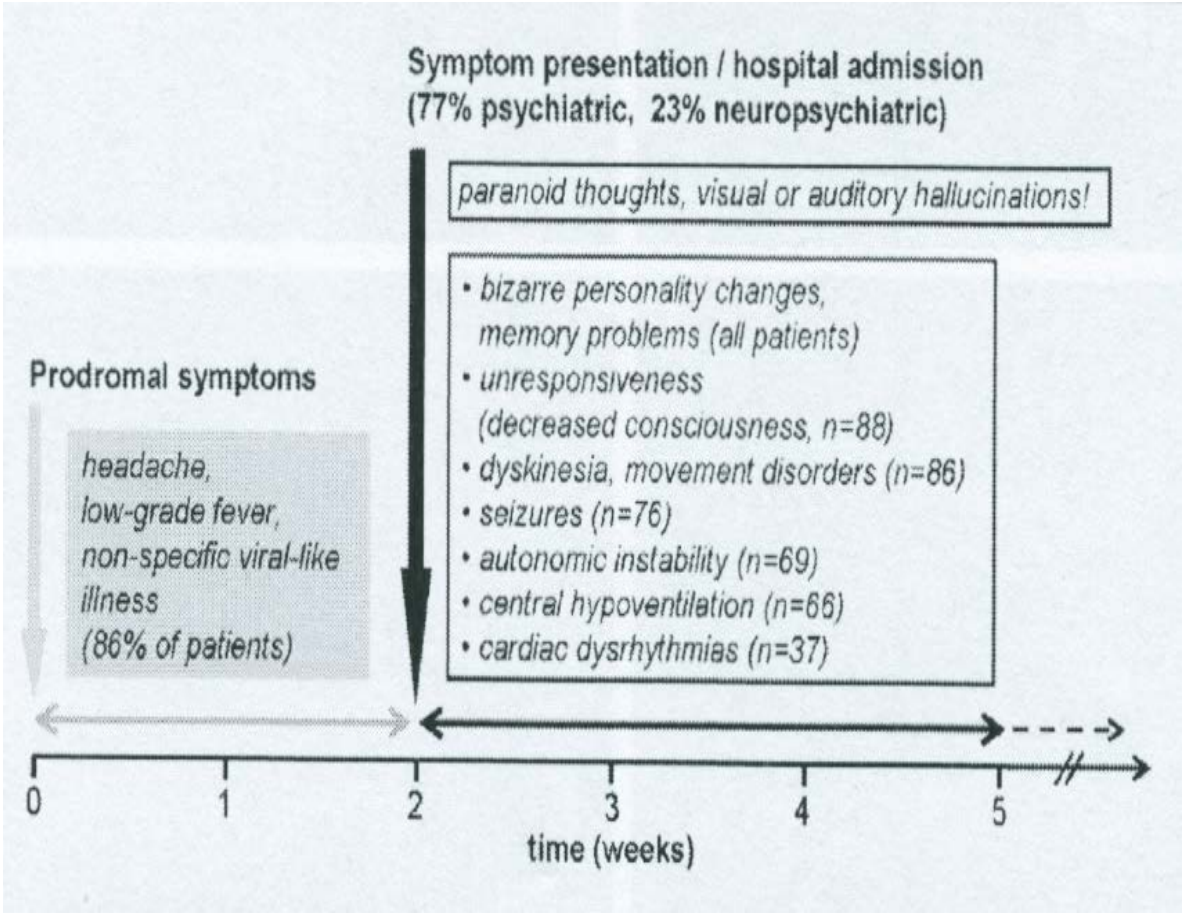
GAD

Amphiphysine

Intra-cellular antigen but possible direct role of antibodies

La symptomatologie clinique est caractéristique en fonction de l'âge, du sexe et de l'autoanticorps associé

Exemple anti-NMDAR

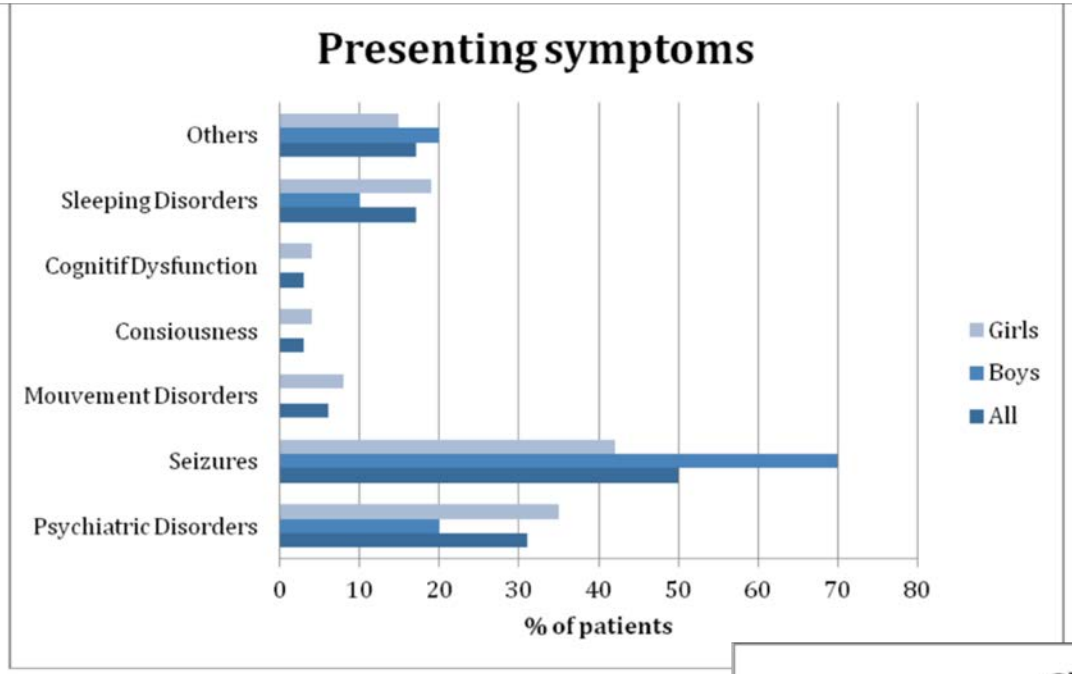


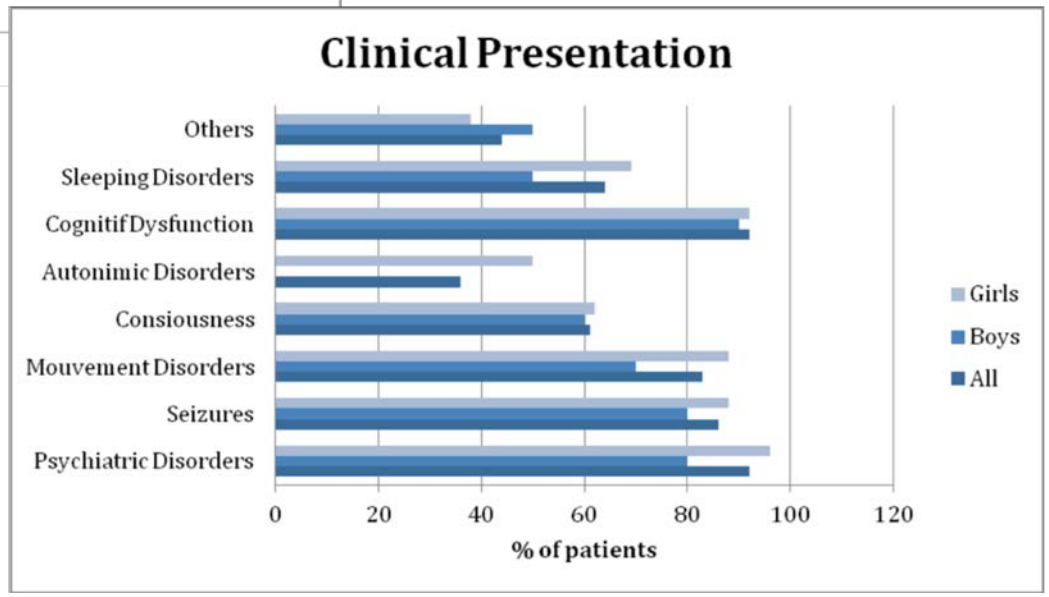
Frequence : 35 à 40 par an en France
Intolérance aux neuroleptiques +++
Formes frustres possibles (4% purement psychiatriques)

Dalmau et al, Lancet Neurol. 2008;7:1091-8

Présentation différente chez les enfants

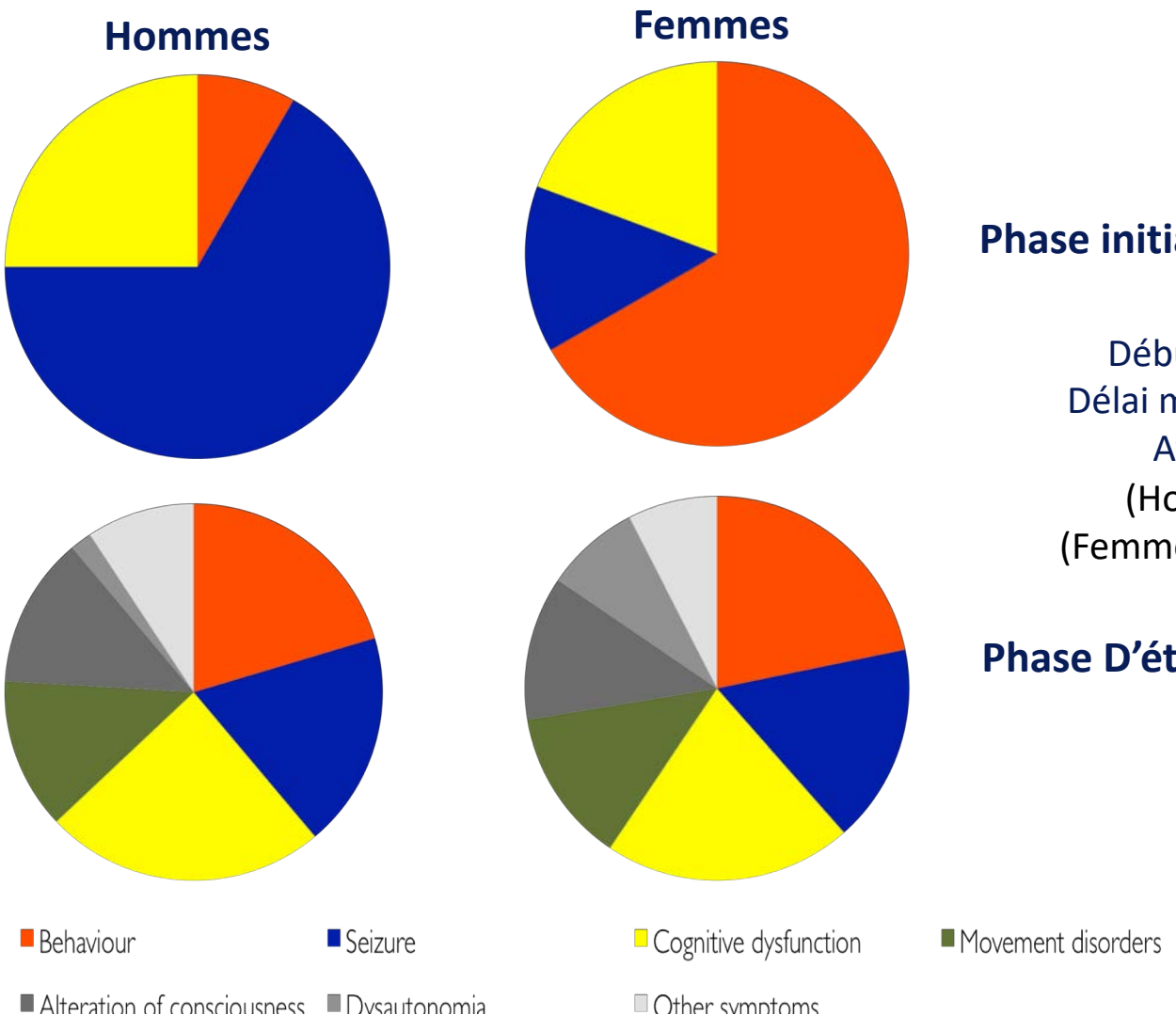
Série française de 36 enfants





Zekeridou et al, soumis

Encéphalites à auto-antonticorps anti-NMDAr
Différences Hommes/femmes adultes
(13 hommes versus 58 femmes)



Phase initiale

Début épilepsies partielles
Délai médian de 12 jours (2-17)
Avant la phase d'état
(Hommes : 8/13, 61.5%)
(Femmes : 8/58, 14%, p<0.001)

Phase D'état

Viaccoz et al, Neurology 2014

ATTENTION AUX FORMES FRUSTRES

Jeune femme née en 1992
BEP Hôtellerie et restauration, Tabac 4PA, Pas de toxique
Un frère ainé en BS

2010 (18 ans): Troubles schizo-affectifs, dépression
15 jours d'hospitalisation en psychiatrie
Anti-dépresseurs pendant 6 mois et suivi 1 an

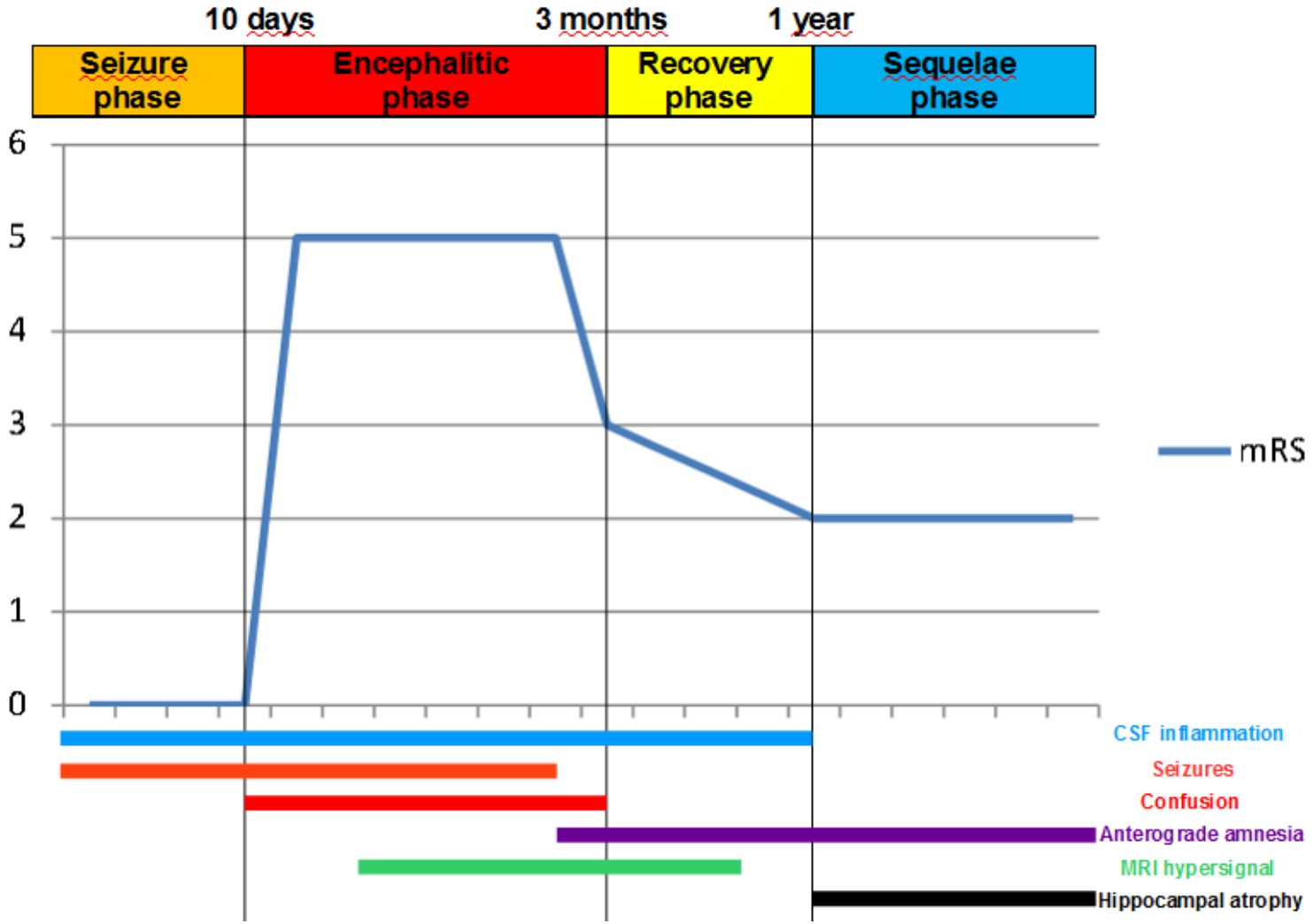
2012 (20 ans): progressivement sur 3 mois
agressivité
troubles du jugement
propos incohérents
idées délirantes
Hospitalisation quelques semaines sur demande d'un tiers
Abilify 15 mg/Jr
Normalisation comportementale

Mais : Ralentissement idéo-moteur, troubles de mémoire anciens (depuis âge 17 ans)
Rappel évènements récents
Orientation
Gène dans le travail
Langage, mémoire ancienne, comportement, praxies, examen NORMAUX
MMS: 20/30 ; BREF 18/18 ; mots 3/5 rappel immédiat, 0/5 différé
Contact étrange avec regard fixe

PL : Prot 0,37g/l ; 20 Lymphocytes ; Anti-NMDAR positifs ; IRM Normale

Les encéphalites à anti-GABABR commencent par une phase de crises généralisées de plus en plus fréquentes

Après 45 ans, systématiquement paranéoplasiques avec CPPC

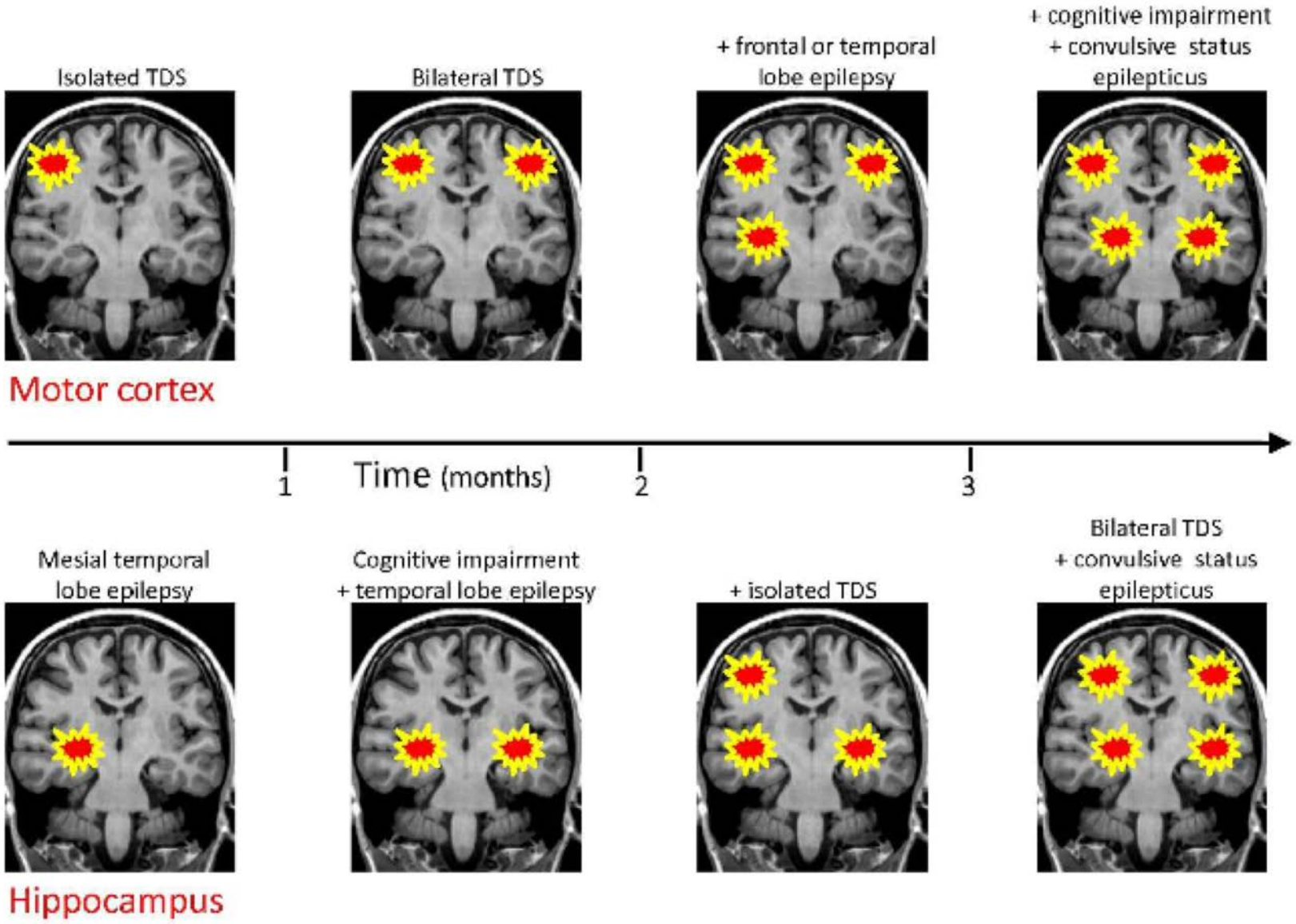


Les patients avec anti-Lgi1 ont deux types de présentations cliniques
Dystonie bracchio-faciale ou dysfonction hippocampique

Les dystonies répondent aux corticoides mais sont aggravées par les anti-epileptiques

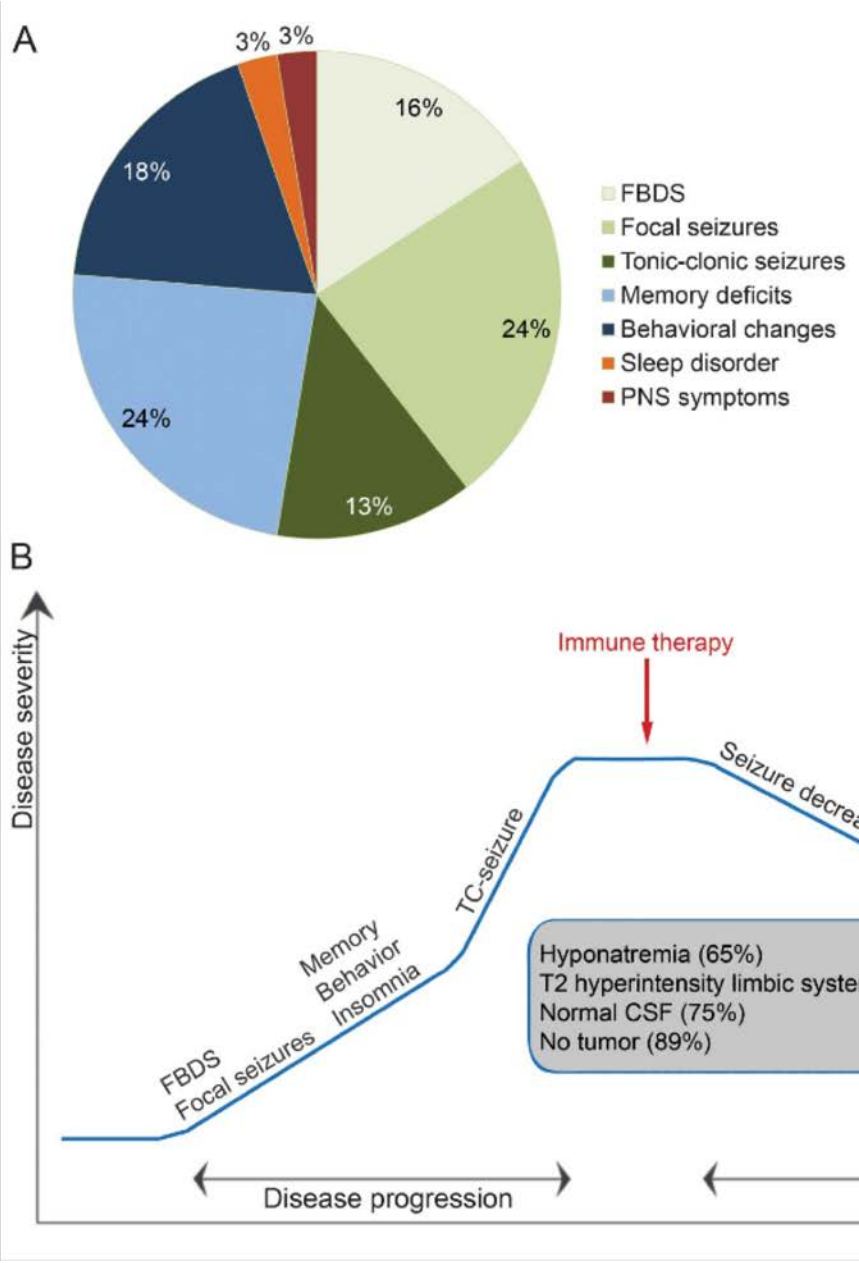
Movies from V. Navarro, Pitié-Salpétrière

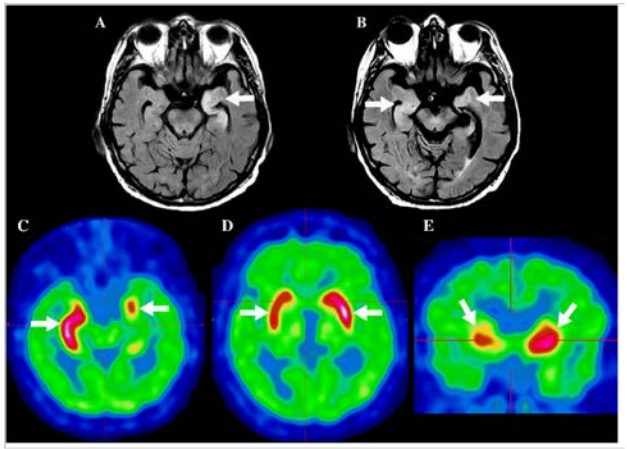
Evolution des encéphalites à anti-Lgi1



Navarro et al, Brain 2016

Présentation clinique et évolution des encéphalites à anti-Lgi1



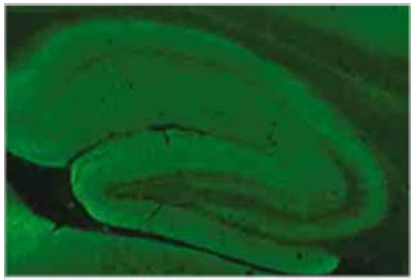


Renard et al, Acta Neurol Bel 2015

HLA-DRB1*07:01-DQA1*02:01-DQB1*02:02

Binks et al, Brain 2018

Agnes van Sonderen et al, Neurology 2016;87:1–8



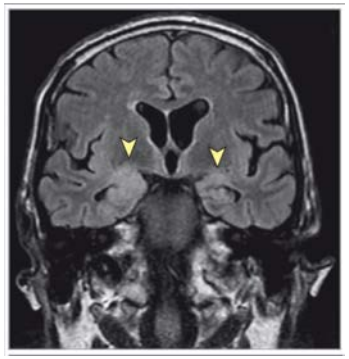
CASPR2, 2 tableaux cliniques : Morvan et EL

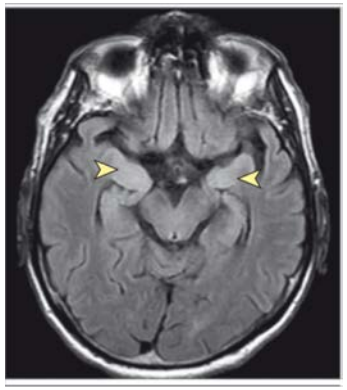
Encéphalites auto-immunes avec anticorps anti-CASPR2

Atteinte hippocampique peu invalidante (qqs crises, tbs mémoire modérés)
Très sensible au Tt immunomodulateurs

Table 2. Baseline Characteristics and Immunological Findings of Patients With Anti-CASPR2 Antibodies in the CSF Compared With Patients With NMT or MoS

Characteristic	No./Total No. (%)		
	Patients With Anti-CASPR2 Antibodies in the CSF	Patients With NMT or MoS	*P* Value
No. of patients	18	15	
Male	17/18 (94.4)	9/15 (60.0)	.03
Age, y, median (range)	64.5 (53-75)	51 (1 mo-75 y)	.002
Serum titers, median (range)	1/15 360 (1/10 240-1/81 920)	1/800 (1/20-1/5120)	<.001
CSF titers, median (range)	1/1280 (1/80-1/10 240)	0	<.001
Detected IgG4 anti-CASPR2 antibodies			
Serum	11/12 (91.7)	512 (41.7)	.03
CSF	17/17 (100)	0	<.001
Detected IgG1 anti-CASPR2 antibodies			
Serum	12/12 (100)	10/12 (83.3)	.48
CSF	10/17 (58.8)	0	<.005
Recognition of discoidin and laminin G1	18/18 (100)	11/11 (100)	>.99
Additional epitopes	10/18 (55.6)	8/11 (72.7)	.45
Malignant thymoma	0	9/15 (60.0)	.001
Other cancers	3/18 (16.7)	0	.23
Other autoimmune disturbances	1/18 (5.6)	8/15 (53.3)	.004



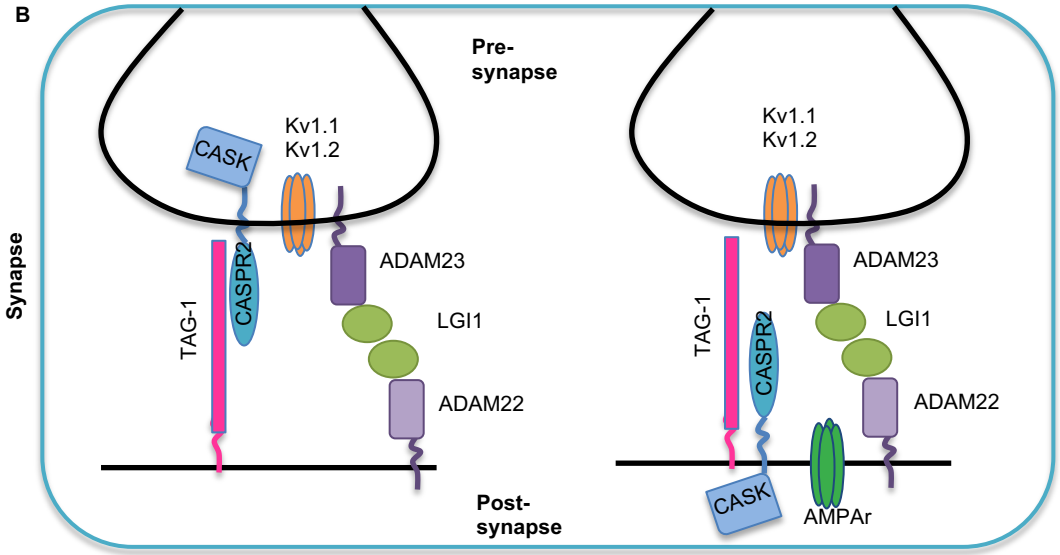


In LE, 74% : HLA : DRB1*11:01-DQB1*03:01

Joubert et al, JAMA Neurol 2016

EL avec anti-CASPR2
>30% d'ataxies cérébelleuses paroxystiques

- Patient de 61 ans
- Crise d'épilepsie partielle, secondairement généralisée
-Troubles de mémoire discrets
- Accès paroxystiques de dysarthrie et d'instabilité
- PL inflammatoire
- Anti-CASPR2 dans le LCR



Joubert et al, 2017 Neurology, neuroimmunol neuroinflammation

Characteristics in limbic encephalitis with anti–adenylate kinase 5 autoantibodies

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ABSTRACT

Objective: To report 10 patients with limbic encephalitis (LE) and adenylate kinase 5 autoantibodies (AK5-Abs).

Methods: We conducted a retrospective study in a cohort of 50 patients with LE with uncharacterized autoantibodies and identified a specific target using immunohistochemistry, Western blotting, immunoprecipitation, mass spectrometry, and cell-based assay.

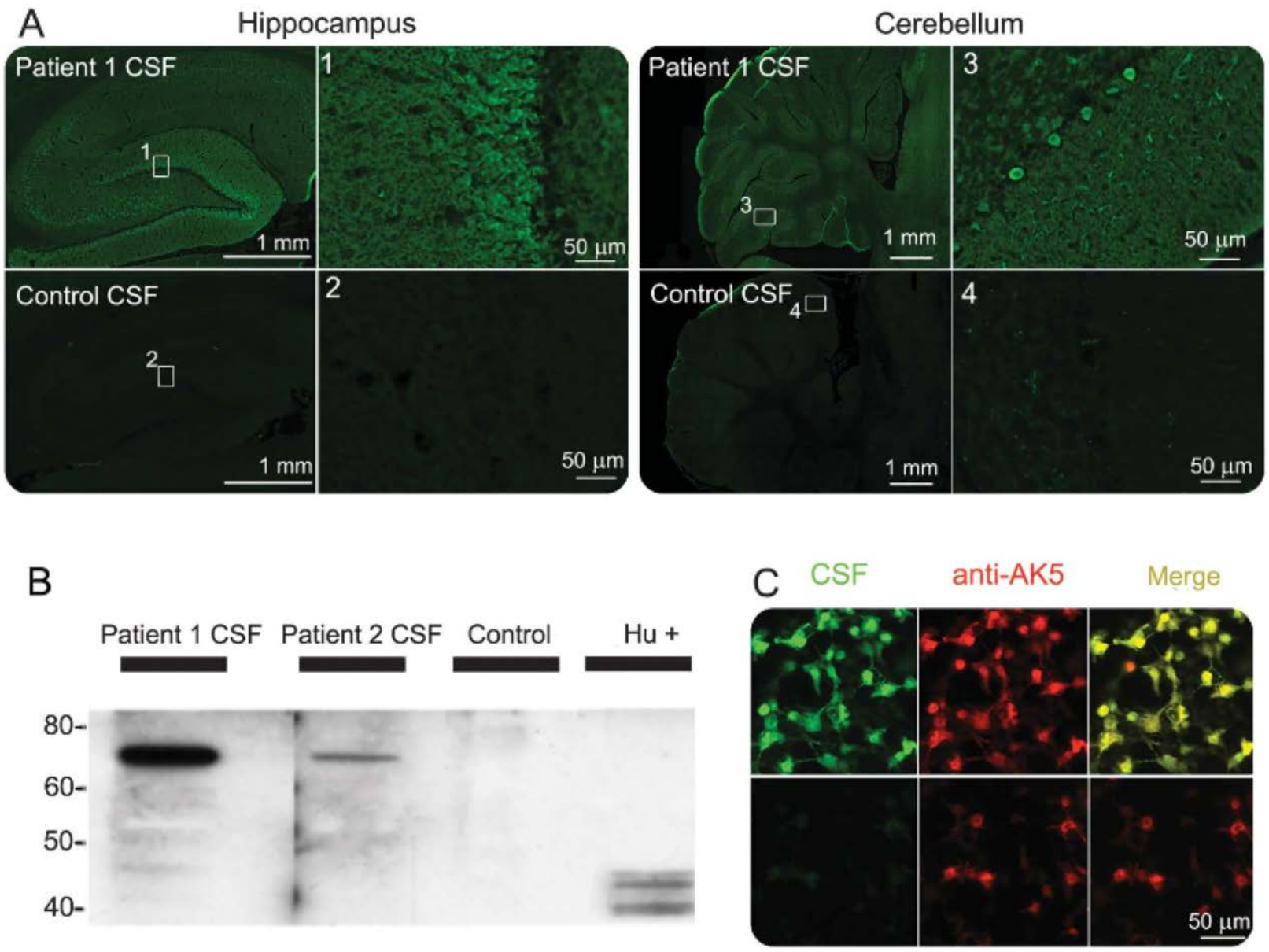
Results: AK5 (a known autoantigen of LE) was identified as the target of antibodies in the CSFs and sera of 10 patients with LE (median age 64 years; range 57–80), which was characterized by subacute anterograde amnesia without seizure and sometimes preceded by a prodromal phase of asthenia or mood disturbances. Anterograde amnesia can be isolated, but some patients also complained of prosopagnosia, paroxysmal anxiety, or abnormal behavior. No associated cancer was observed. All 10 patients had bilateral hippocampal hypersignal on a brain MRI. CSF analysis generally showed a mild pleiocytosis with elevated immunoglobulin G index and oligoclonal bands, as well as high levels of tau protein with normal concentration of Aβ42 and phospho-tau, suggesting a process of neuronal death. Except for one patient, clinical response to immunotherapy was unfavorable, with persistence of severe anterograde amnesia. Two patients evolved to severe cognitive decline. Hippocampal atrophy was observed on control brain MRI. Using in vitro tests on hippocampal neurons, we did not identify clues suggesting a direct pathogenic role of AK5-Abs.

Conclusions: AK5-Abs should be systematically considered in aged patients with subacute anterograde amnesia. Recognition of this disorder is important to develop new treatment strategies to prevent irreversible limbic damage. *Neurology*® 2017;88:1–11

GLOSSARY

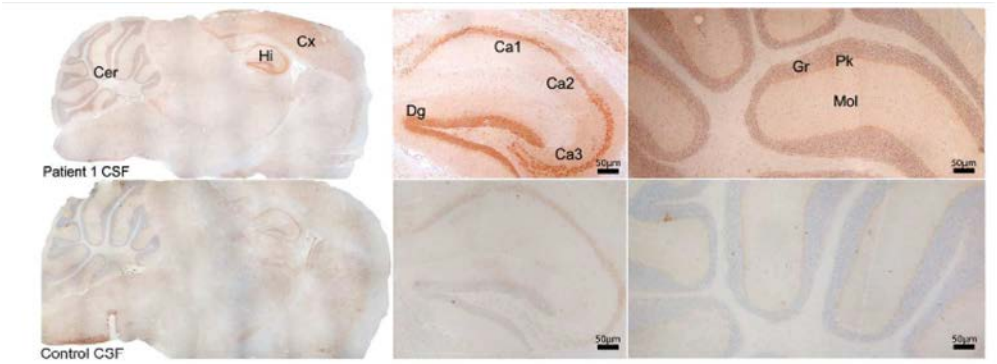
AK5-Abs = adenylate kinase 5 autoantibodies; **FLAIR** = fluid-attenuated inversion recovery; **IgG** = immunoglobulin G; **IVIg** = IV immunoglobulin; **LE** = limbic encephalitis.

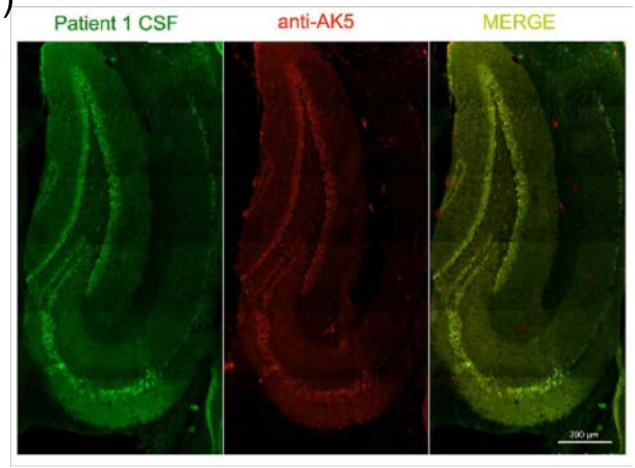
Figure 1 **Identification of 2 new patients with limbic encephalitis with unknown autoantibody**

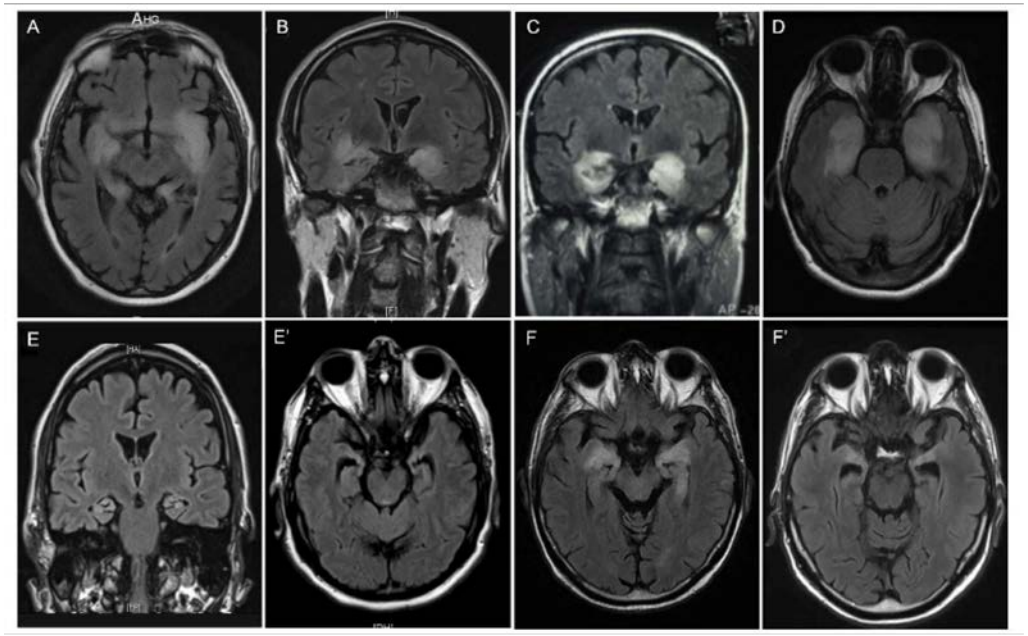


Encéphalites à anticorps anti-AK5

(série de 10 patients)





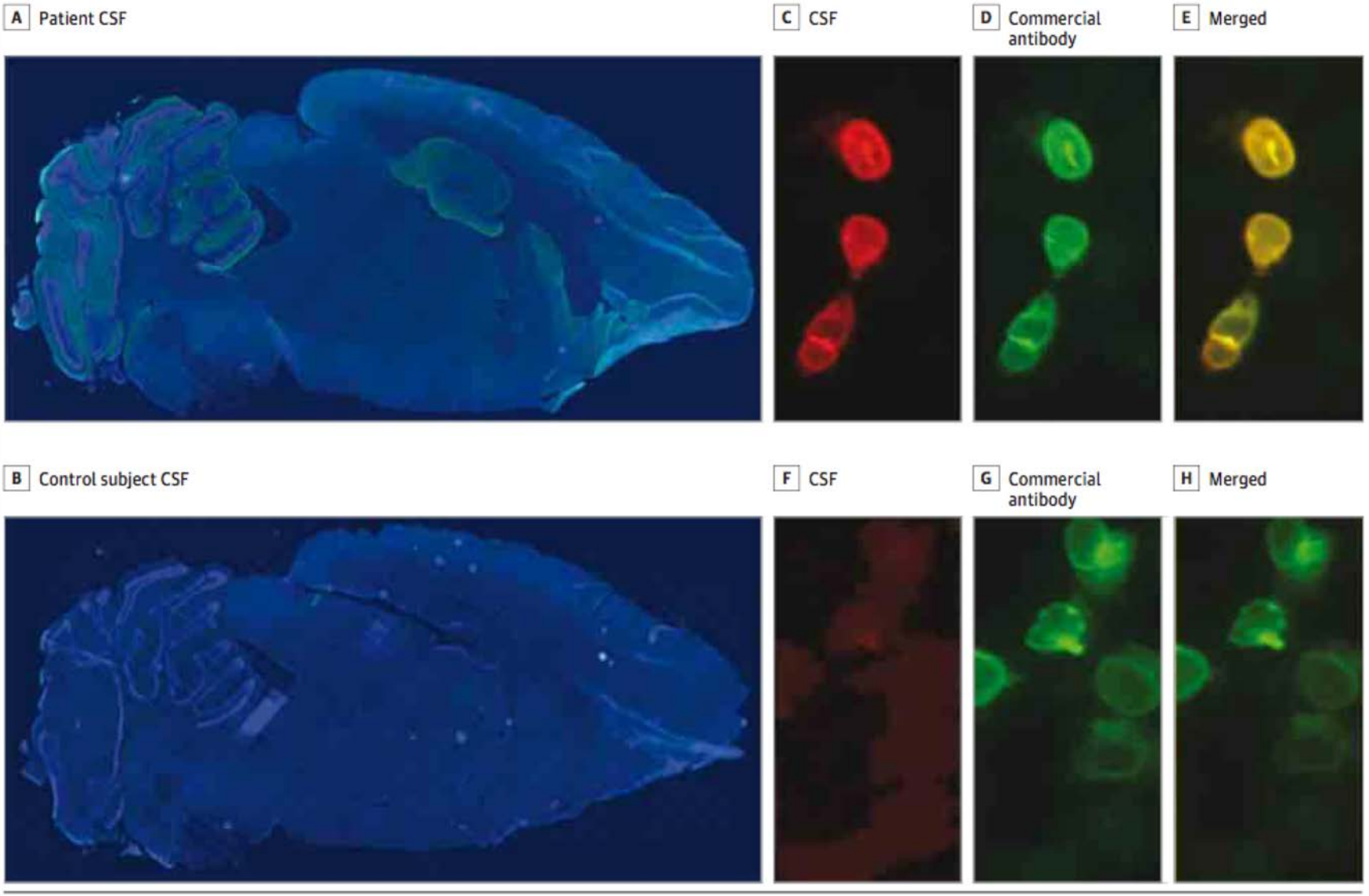


Age médian 64 ans (57-80)
Amnésie antérograde sur 6 semaines
Pas de crise d'épilepsie
Anxiété, prosopagnosie
Hypersignaux FLAIR
LCR inflammatoires ++
Tau augmentée, Phospho tau Nle
Évolution vers stabilité et atrophie Hippo

Do et al, Neurology 2017

Encéphalites et anticorps anti-AMPAR

Figure 1. Characterization of Antibodies Against the α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) Receptor



Joubert et al, JAMA Neurology 2015;72:1163-1169

Encéphalites et anticorps anti-AMPAR

Table 1. Clinical Features and Outcomes in 7 Patients With Encephalitis Associated With Antibodies Against the α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor

Variable	Mode of Onset			
	Confusion (n = 3)	Epileptic (n = 1)	Amnestic (n = 1)	Fulminant Encephalitis (n = 2)
Age, y	56, 58, 75	43	92	21, 22
Main clinical features	Confusion, psychiatric, behavioral, cognitive (memory, executive)	Temporal seizures	Subacute anterograde amnesia	Stereotypical presentation: (1) confusion, headache, memory problems; (2) hypertonic coma, fever, eye deviation; (3) resolution of behavioral, psychiatric, cognitive disorders
Additional clinical features	Cognitive (aphasia, apraxia), sensory and motor deficits, sleep disorder (insomnia), headache, cerebellar symptoms	Slight memory impairment, dysexecutive features, mild cerebellar symptoms, sleep disorder (insomnia)	Slight ataxia	Motor deficits, downbeat nystagmus, oculogyric crisis, abdominal pain, sleep disorder (insomnia), sphincter dysfunction
Brain magnetic resonance imaging	Temporomesial T2-weighted hyperintensities, complete resolution or slight bilateral HA at 6 mo	Bilateral temporomesial T2-weighted hyperintensities, lateralized HA at 6 mo	Normal	Diffuse T2-weighted hyperintensities, resolution or severe cortical atrophy
Electroencephalogram	Normal	Right temporal seizures	Normal	Bifrontal sharp and slow waves (1 patient)
Cerebrospinal fluid	Inflammation (pleiocytosis, oligoclonal bands) or normal	Normal	Oligoclonal bands	Pleiocytosis
Oncological status	Lung cancer (1 patient)	Thymus hyperplasia	None	Thymus carcinoma (1 patient)
Central nervous system antibodies	Anti-Hu (1 patient)	Anti-Lgi1, anti-GAD65	None	None
Systemic antibodies	Antinuclear, anti-intrinsic factor (1 patient)	Anti-IA2	None	Antinuclear (1 patient)
Follow-up period, mo	2, 9, 15	31	6	18, 12
Outcome	Progressive improvement, persistence of significant cognitive impairment	Seizure control, slight residual memory impairment	Stabilization	Marked improvement (1 patient), death (1 patient)
Modified Rankin Scale score at the last visit	2, 3, 3	1	1	1, 6

Abbreviation: HA, hippocampal atrophy.

Joubert et al, JAMA Neurology 2015;72:1163-1169

Un nouveau syndrome: une tauopathie auto-immune ….

A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study

Lidia Sabater, Carles Gaig*, Ellen Gelpi*, Luis Bataller, Jan Lewerenz, Estefanía Torres-Vega, Angeles Contreras, Bruno Giometto, Yaroslau Compta, Cristina Embid, Isabel Vilaseca, Alex Iranzo, Joan Santamaría, Josep Dalmau, Francesc Graus*

Summary

Background Autoimmunity might be associated with or implicated in sleep and neurodegenerative disorders. We aimed to describe the features of a novel neurological syndrome associated with prominent sleep dysfunction and antibodies to a neuronal antigen.

Lancet Neurol 2014
Published Online
April 3, 2014

5F/3H
Age moyen 59 ans
Maladie d'aspect neuro-dégénérative
Tbs du sommeil, tronc cérébral, dysautonomie
LCR, IRM, EEG normaux
HLA DQB1*501

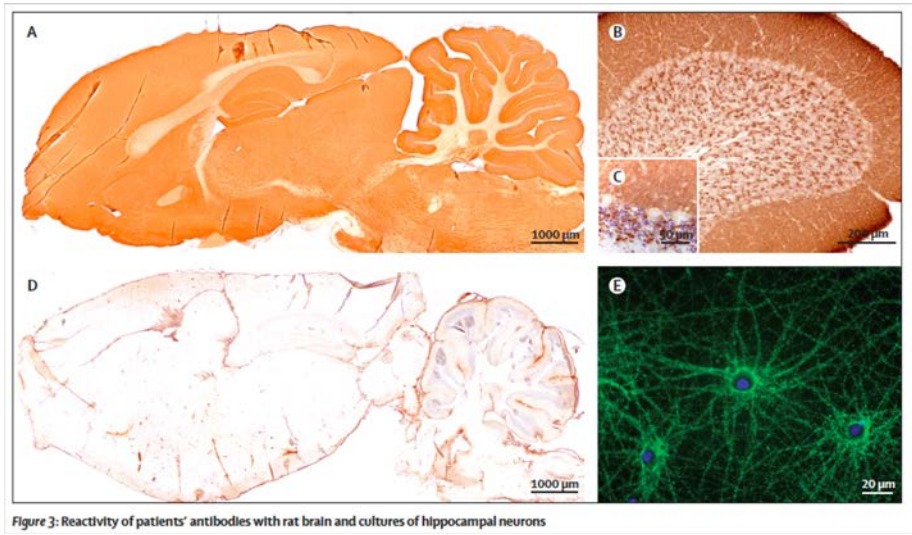


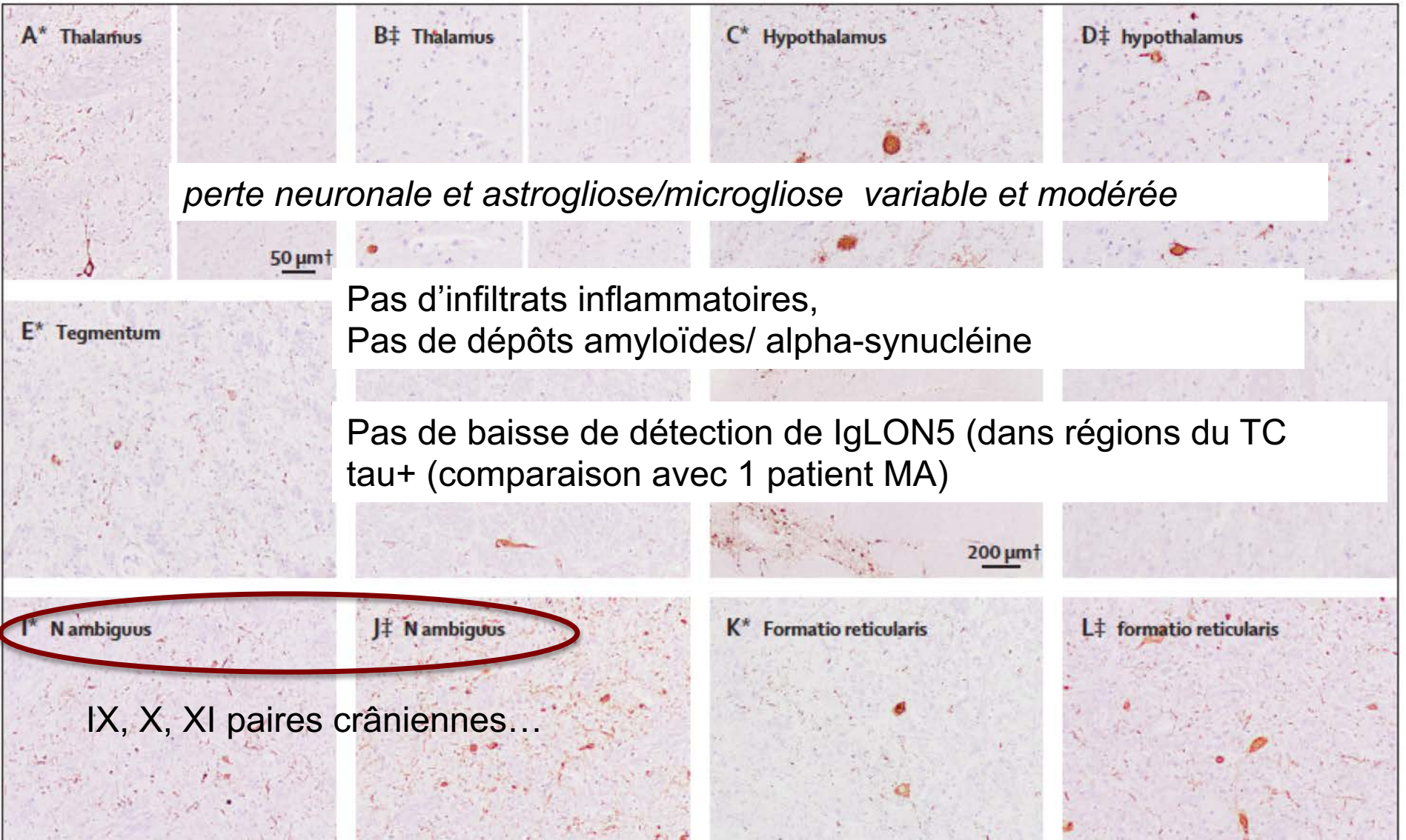
Figure 3: Reactivity of patients' antibodies with rat brain and cultures of hippocampal neurons

***Caractéristiques neuropathologiques:* une taupathie**

Accumulation anormale intra-neuronale de tau (anormalement phosphorylée)

Pretangles/tangles et neuropil threads.

Pas de taupathie gliale



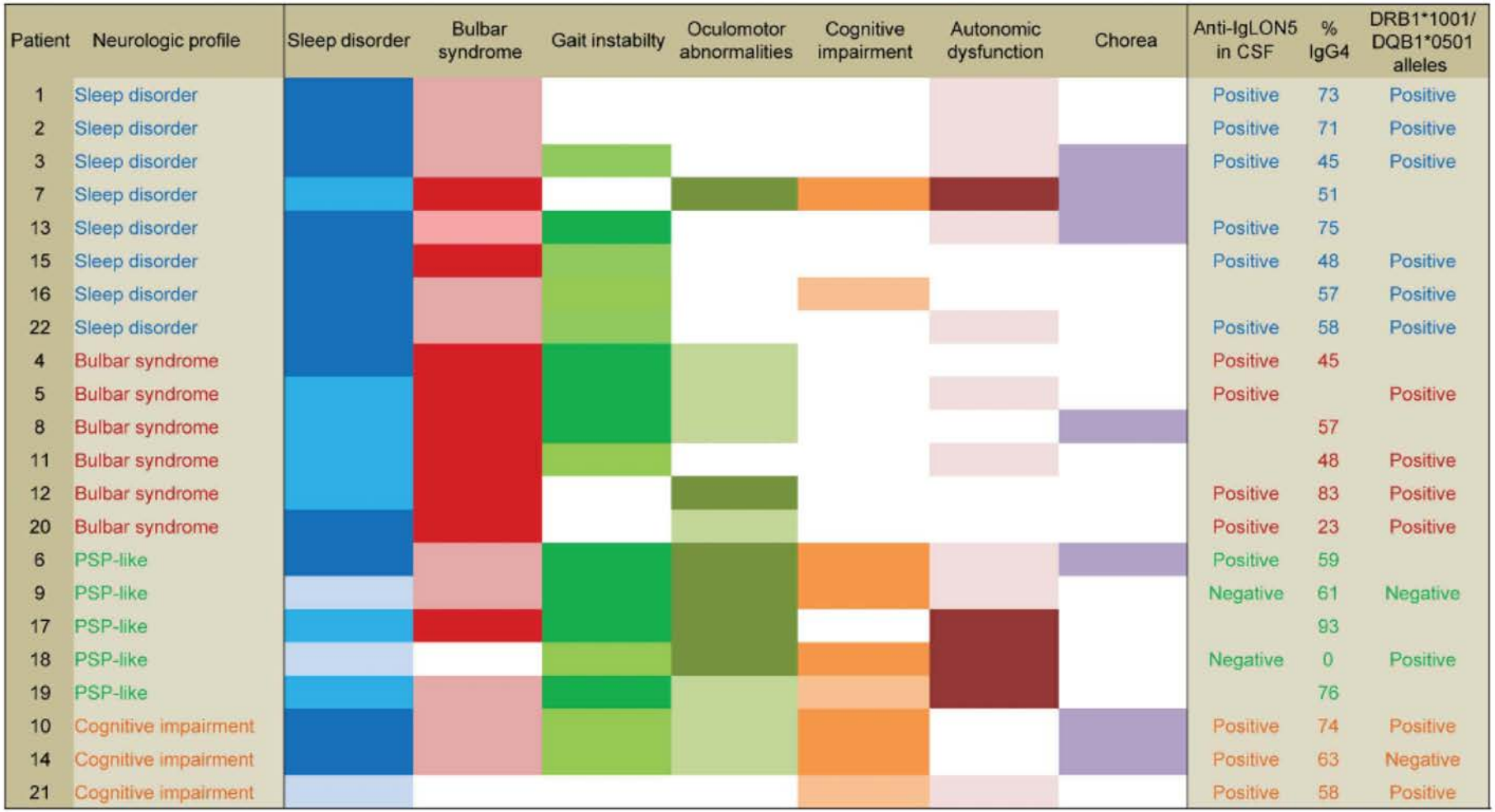
perte neuronale et astrogliose/microgliose variable et modérée

Pas d'infiltrats inflammatoires,
Pas de dépôts amyloïdes/ alpha-synucléine

Pas de baisse de détection de IgLON5 (dans régions du TC tau+ (comparaison avec 1 patient MA)

IX, X, XI paires crâniennes…

Figure 1 **Neurologic profile at diagnosis**

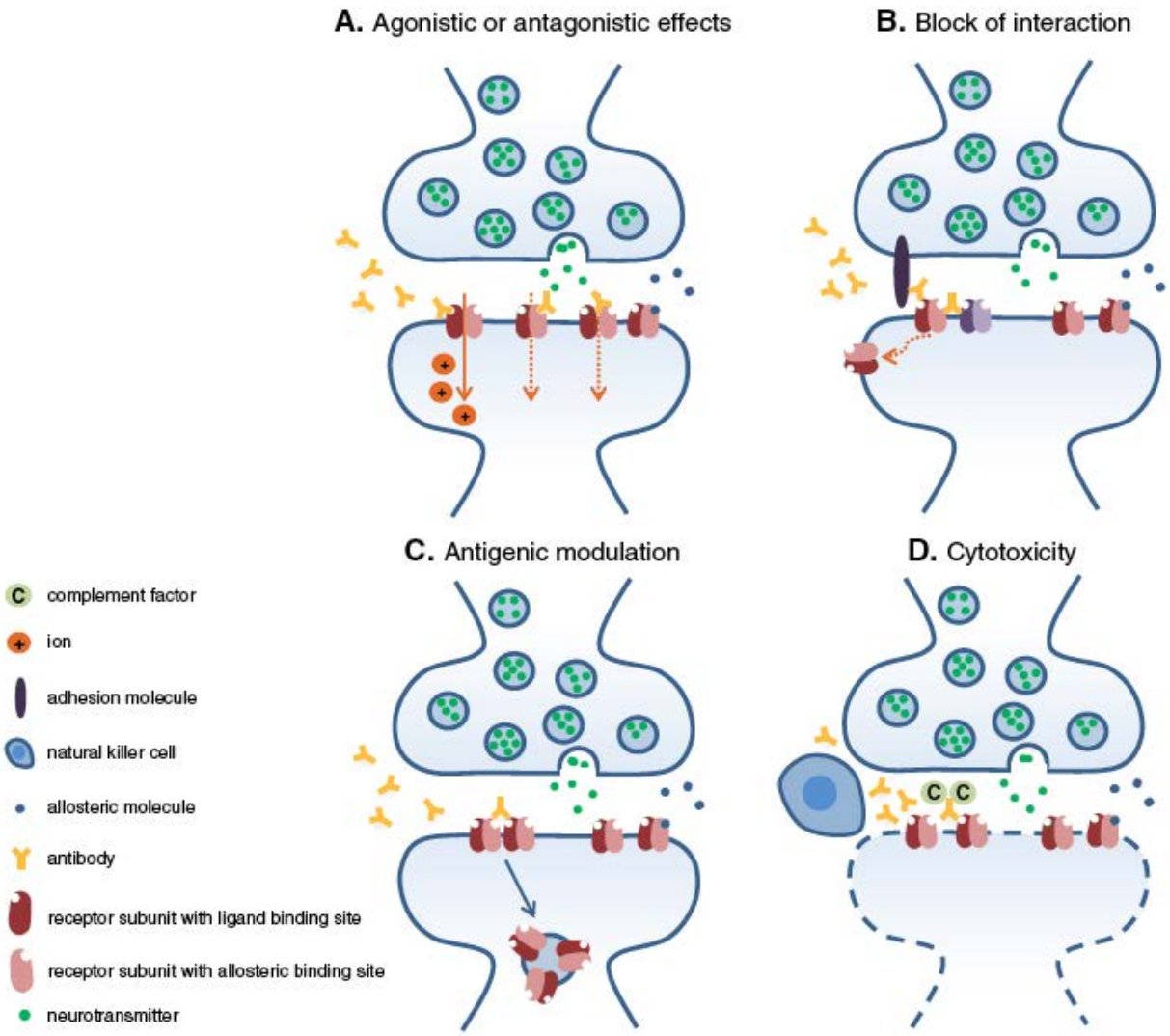


Gaig et al, Neurology 2017;88:1736-1743

Main autoantibodies associated with autoimmune encephalitis

Hu	Old subjects with history of smoking or SCLC; rarely associated with pure LE; frequently accompanied by encephalomyelitis or sensory neuronopathy Children with pharmacoresistant epilepsy
Ma2	Men younger than 45 years, with germ-cell tumor of the testis.. The syndrome develops as LE, upper brainstem or diencephalic encephalitis.
LGI1	Patients older than 50 years, with mild male predominance. In most cases the clinical picture is a typical LE; 60% of the patients develop hyponatremia. Fascio-brachial dystonic seizures.
GABAbR	Usually affect adults; 50% have an underlying SCLC or neuroendocrine tumor. The syndrome presents as typical LE with early and prominent seizures..
AMPAR	Mildly predominates in women. About 50% of the patients present with LE; the rest develop LE combined with other symptoms. Some cases present with pure psychosis. About 65% of the patients have an underlying tumor (mainly SCLC, thymoma).
GAD	May occur as pure or predominant LE. In these cases the syndrome is often paraneoplastic and screening for an underlying tumor is recommended. Possible co-existence of GAD antibodies and cell surface neuronal antibodies (e.g., AMPA or GABAbR)
NMDAR	Predominantly young women with psychiatric symptoms, seizures, abnormal movements and dysautonomia
CASPR2	Pure LE without cancer. Only few described patients. Also described in Morvan's syndrome and Neuromyotonia
CRMP5	Rarely associated with pure LE. Accompanying features may include uveitis, retinopathy, optic neuropathy, chorea, and peripheral neuropathy
DPPX	Patients often have gastrointestinal dysfunction, diarrhea, and loss of weight preceding the neurological syndrome (psychiatric manifestations, confusion, seizures, tremor, myoclonus, nystagmus).
GABAaR	Patients present with multifocal (cortical-subcortical FLAIR MRI changes) or diffuse encephalitis, with prominent seizures and status epilepticus, often requiring induced coma. Presentation as classical LE is unusual. Most patients do not have a tumor; some have thymoma.
mGluR5	Patients present with non-focal encephalitis, and a clinical picture suggesting involvement beyond the limbic system. Most patients have Hodgkin's lymphoma.
AK5	Patients with subacute anterograde amnesia, no epilepsy, bilateral FLAIR hypersignal, CSF inflammation and high tau protein level. No cancer

Différents modes d'action des autoanticorps à déterminer

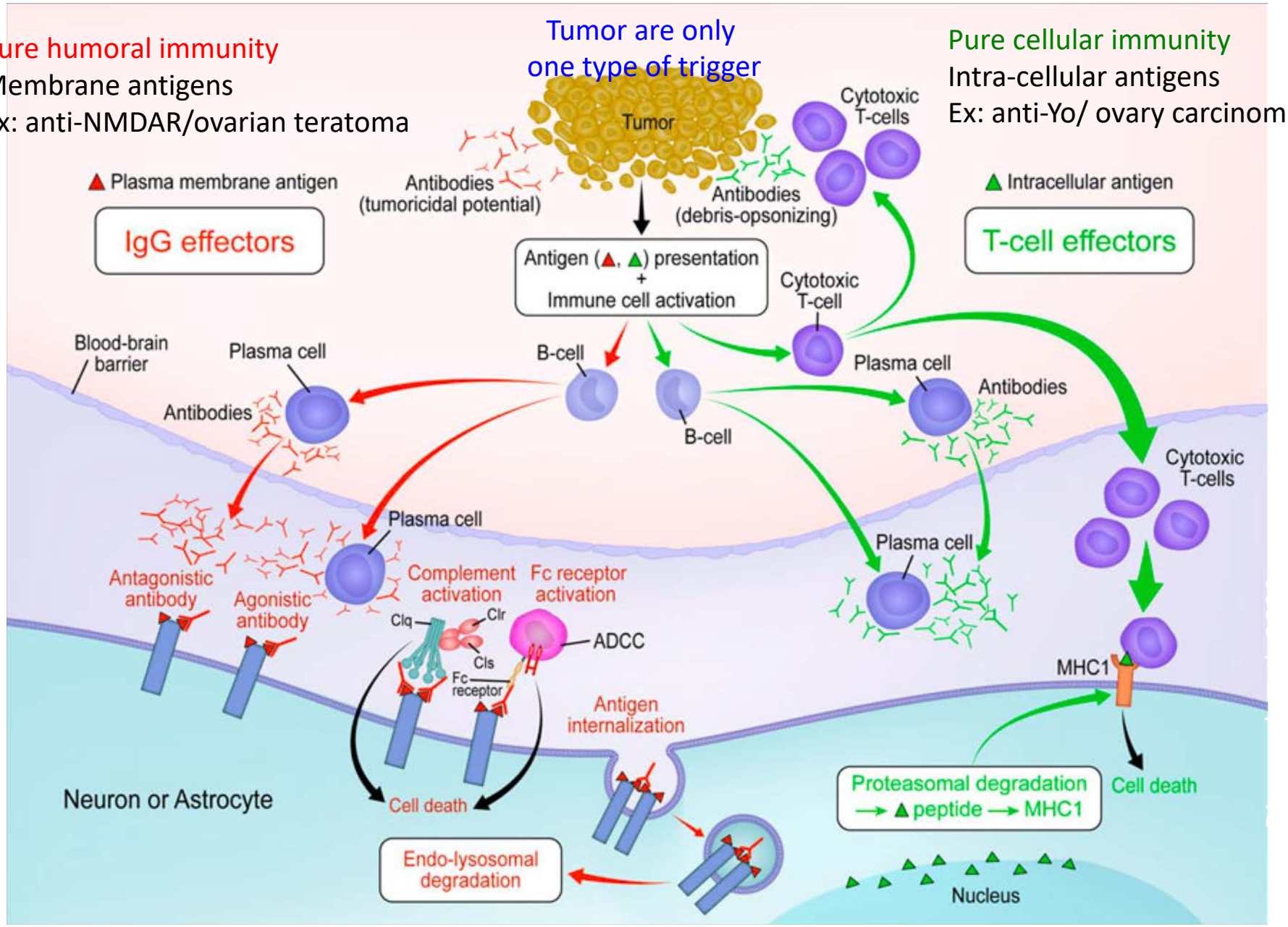


Probablement en lien avec des présentations cliniques différentes

Pure humoral immunity
Membrane antigens
Ex: anti-NMDAR/ovarian teratoma

Tumor are only
one type of trigger

Pure cellular immunity
Intra-cellular antigens
Ex: anti-Yo/ ovary carcinoma



In some patients both cellular and humoral immunity may be involved

Antibody-associated CNS syndromes without signs of inflammation in the elderly

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Helena Ariño, MD, PhD
Carles Gaig, MD, PhD
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ABSTRACT

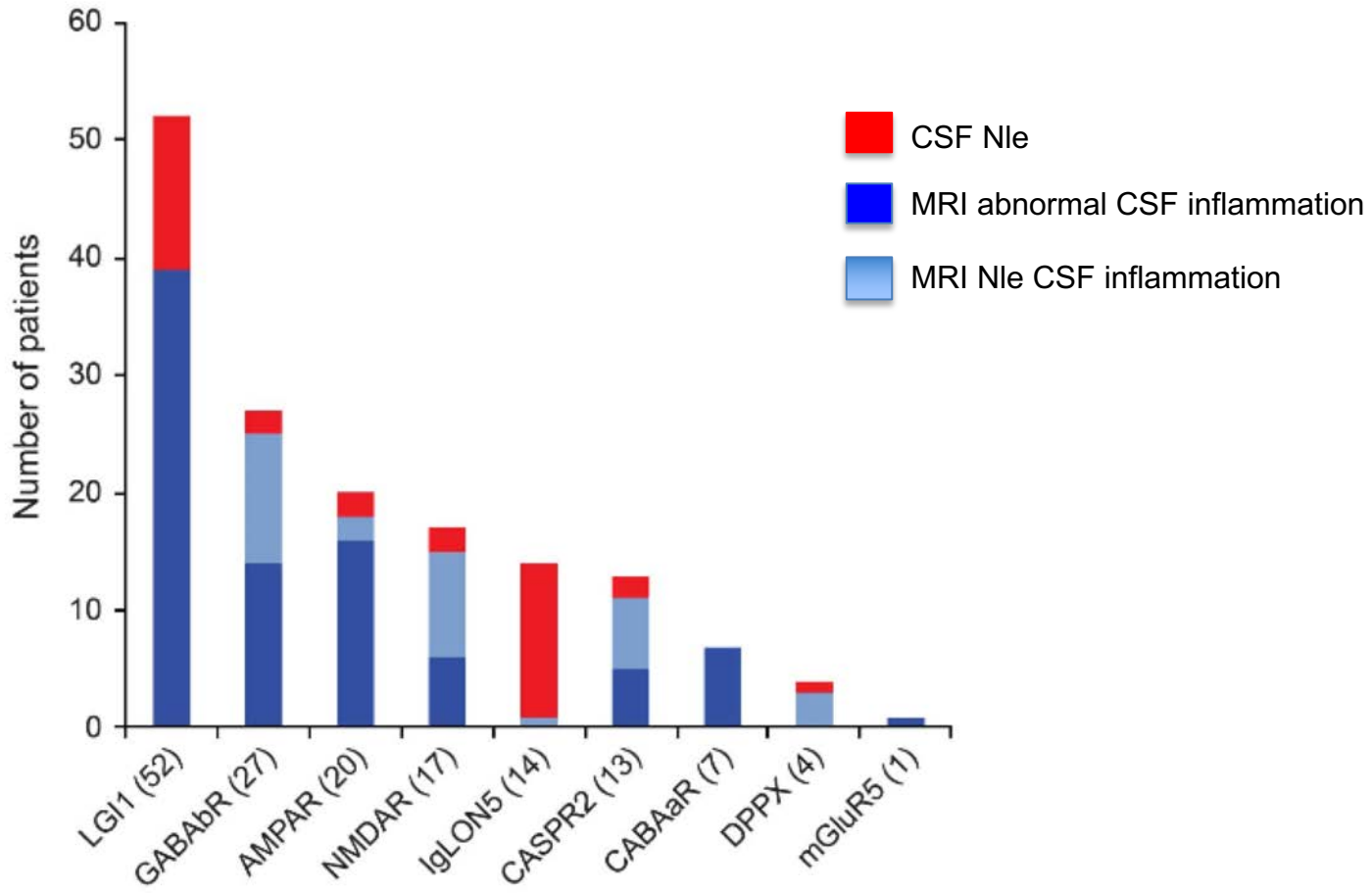
Objective: To report the CNS syndromes of patients ≥60 years of age with antibodies against neuronal surface antigens but no evidence of brain MRI and CSF inflammatory changes.

Methods: This was a retrospective clinical analysis of patients with antibodies against neuronal surface antigens who fulfilled 3 criteria: age ≥60 years, no inflammatory abnormalities in brain MRI, and no CSF pleocytosis. Antibodies were determined with reported techniques.

Results: Among 155 patients ≥60 years of age with neurologic syndromes related to antibodies against neuronal surface antigens, 35 (22.6%) fulfilled the indicated criteria. The median age of these 35 patients was 68 years (range 60–88 years). Clinical manifestations included faciobrachial dystonic seizures (FBDS) in 11 of 35 (31.4%) patients, all with LGI1 antibodies; a combination of gait instability, brainstem dysfunction, and sleep disorder associated with IgLON5 antibodies in 10 (28.6%); acute confusion, memory loss, and behavioral changes suggesting autoimmune encephalitis (AE) in 9 (25.7%; 2 patients with AMPAR, 2 with NMDAR, 2 with GABAbR, 2 with LGI1, and 1 with CASPR2 antibodies); and rapidly progressive cognitive deterioration in 5 (14.3%; 3 patients with IgLON5 antibodies, 1 with chorea; 1 with DPPX antibody–associated cerebellar ataxia and arm rigidity; and 1 with CASPR2 antibodies).

Conclusions: In patients ≥60 years of age, the correct identification of characteristic CNS syndromes (FBDS, anti-IgLON5 syndrome, AE) should prompt antibody testing even without evidence of inflammation in MRI and CSF studies. Up to 15% of the patients developed rapidly progressive cognitive deterioration, which further complicated the differential diagnosis with a neurodegenerative disorder. *Neurology*® 2017;89:1471–1475

Figure 1 Distribution of patients according to antibody type



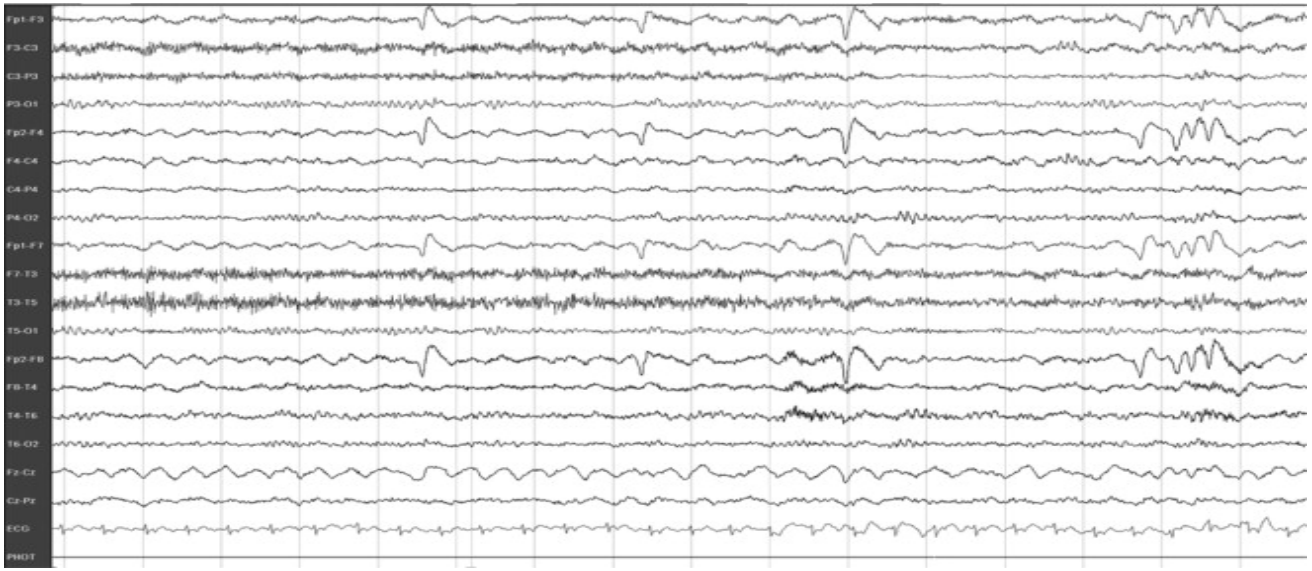
Frequency of patients ≥60 years of age with (blue) or without (red) CSF pleocytosis or inflammatory changes in the brain MRI. Number of cases for each antibody is shown in parentheses. Dark blue in the column indicates number of patients with brain MRI findings compatible with encephalitis; light blue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

Escudero et al, Neurology 2017;89:1471–1475

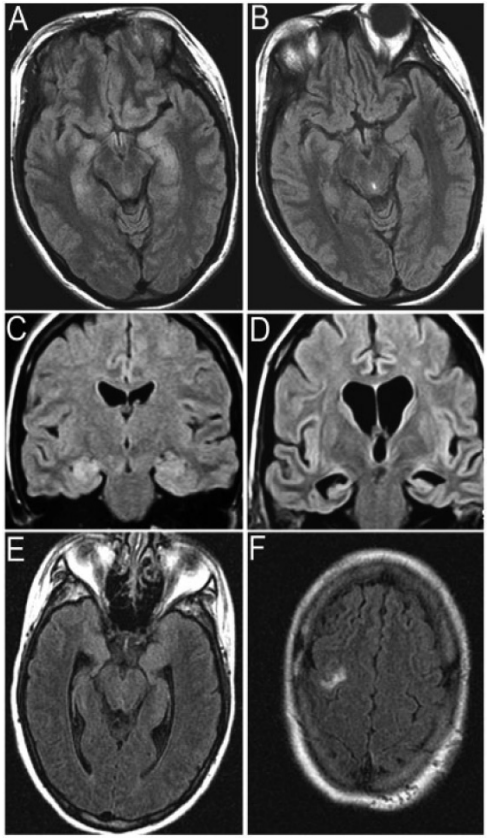
Diagnostic des encéphalites autoimmunes :

1) CSF : inflammation in 95% of cases (oligoclonal bands+++)

2) EEG unspecific (slow waves, delta brush (NMDAR), focal temporal seizures…)



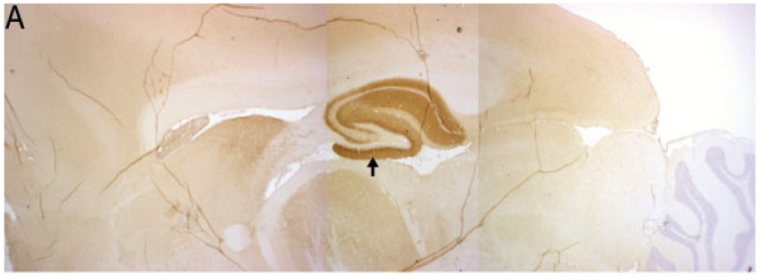
Greiner et al, Seizure 2011;20:266 - 270



3) Brain MRI abnormal according the autoantibodies

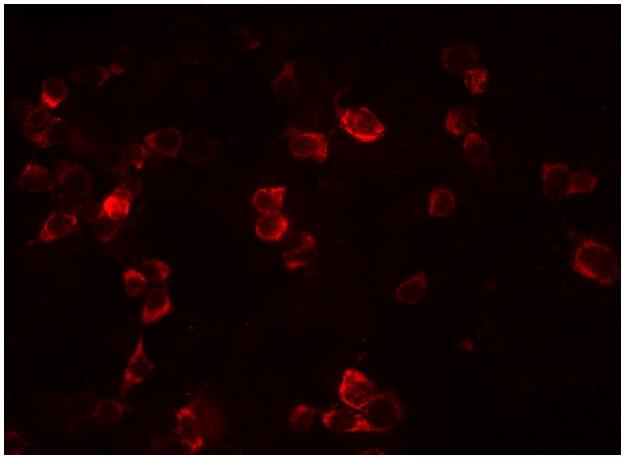
- Lgi1, GABABR, AK5 : Bitemporal hypersignal
- NMDAR, Iglon5 : frequently normal

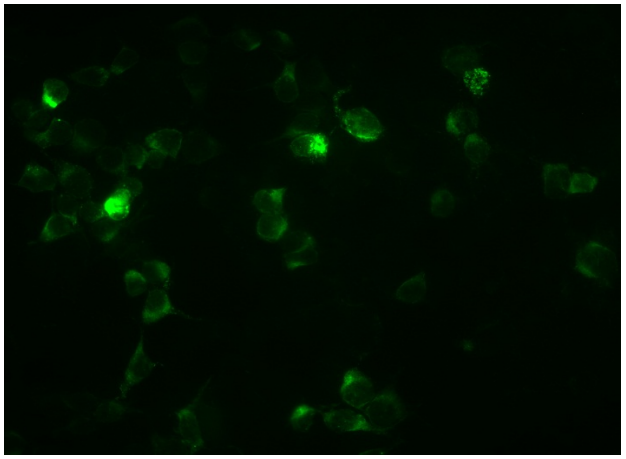
Example anti-NMDAR

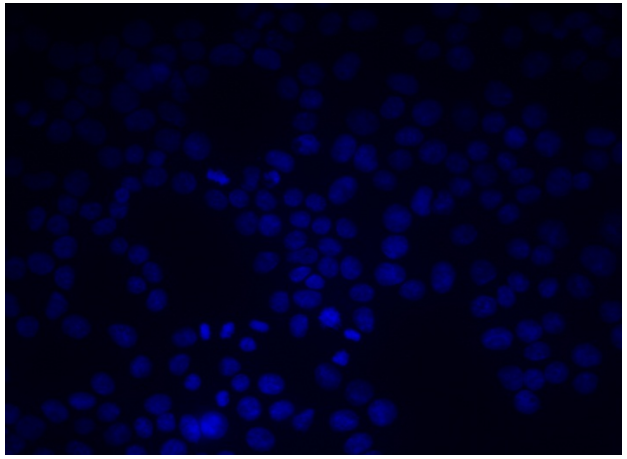


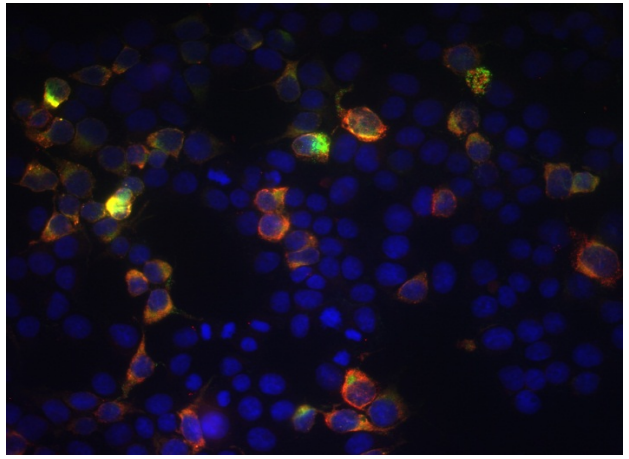
Detection of anti-autoantibodies : CSF +++
Serum according the Abs (Lgi1 +++)

- Indirect immunohistochemistry on rat brain slices
- Indirect immunohistochemistry on HEK 293 cells transfected with NR1/NR2B plasmids









CONCLUSIONS

- Les syndromes neurologiques paranéoplasiques et les encéphalites sont des maladies rares

- Ces syndromes sont en cours de description et leur incidence est inconnue

- Ils sont classées en fonction du type d'autoanticorps associé

- Il existe des caractéristiques cliniques particulières en fonction du sous type d'autoanticorps

- Le liquide céphalo-rachidien n'est pas systématiquement inflammatoire et l'IRM encéphalique est souvent normale

- Les autoanticorps doivent être recherchés ou vérifiés dans un centre expert avant d'envisager des traitements immunosuppresseurs lourds

- Les mécanismes physiopathologiques impliquent l'immunité cellulaire et humorale de façon variable en fonction des autoanticorps associés

- La recherche d'un cancer associé est fonction du type d'autoanticorps, de l'âge et du sexe des patients

- Les traitements ne sont pas encore codifiés

auto-immunes encephalitis and paraneoplastic neurological syndromes
Multiple actors (medical and basic research) in close relationship

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Inserm
Institut national
de la santé et de la recherche médicale

Hospices Civils de Lyon

Institut NeuroMyoGène

Université Claude Bernard Lyon 1

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