BIOLOGIE CLINIQUE & *PATHOLOGIES NEURO-INFLAMMATOIRES DU SNC*

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PLAN

- **Sclérose en plaques**
- **Spectre NMO**
- **Encéphalites auto-immunes & paranéoplasiques**

PLAN

- **Sclérose en plaques**
- **Spectre NMO**
- **Encéphalites auto-immunes & paranéoplasiques**

Sclérose en plaques

Maladie du **système nerveux CENTRAL**

✓Cerveau

✓Moelle

✓Nerfs optique

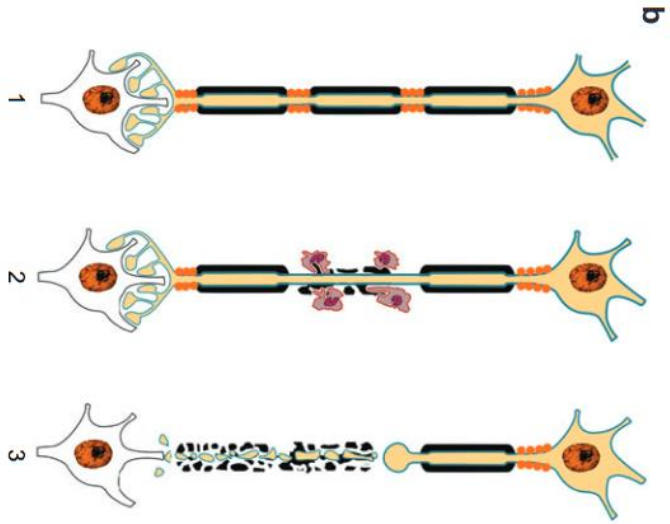
PHYSIOPATHOLOGIE : **dysimmune**

> Inflammation

> Démyélinisation

> Perte axonale et synaptique

- Fréquence!
  - 14000 pers/Belgique → +- 1/1000
- 1ère cause non traumatique de handicap du jeune adulte
- Patients JEUNES
- Pathologie TRAITABLE

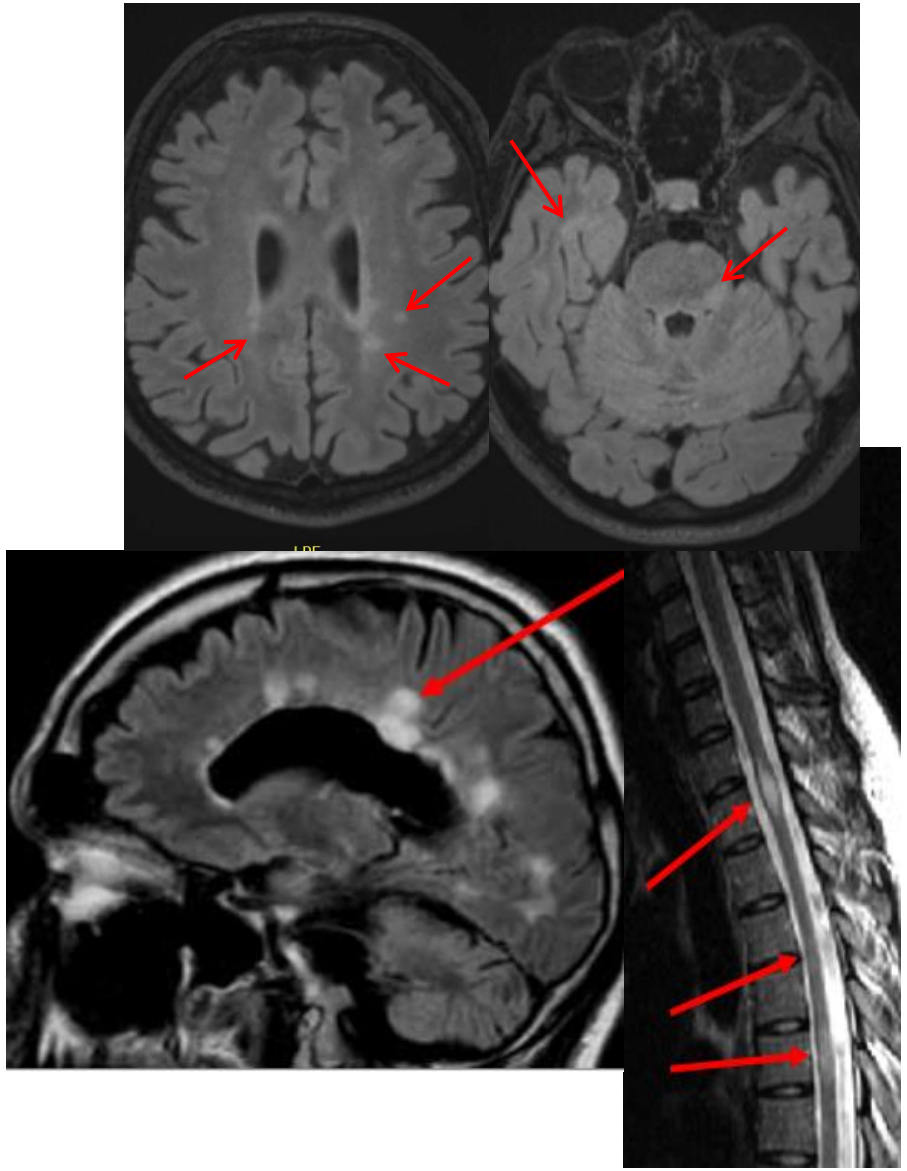


Trapp et al. 2008

Sclérose en plaques

- **CLINIQUE : « poussées et progression »**
  - Déficits neurologiques sensitivo-moteurs
  - Déficits visuels
  - Troubles cognitifs

- **PRONOSTIC FONCTIONNEL** ?
  - ≠ d'il y a 30 ans…
  - Dépendant d'une prise en charge précoce et efficace



SEP & Biologie clinique

- **Bandes oligo-clonales spécifiques dans le LCR**
  - Témoin de la synthèse intrathécale d'IgG
  - Comparaison SERUM >< LCR
    => prélèvement le même jour
  - **ISOFOCALISATION**

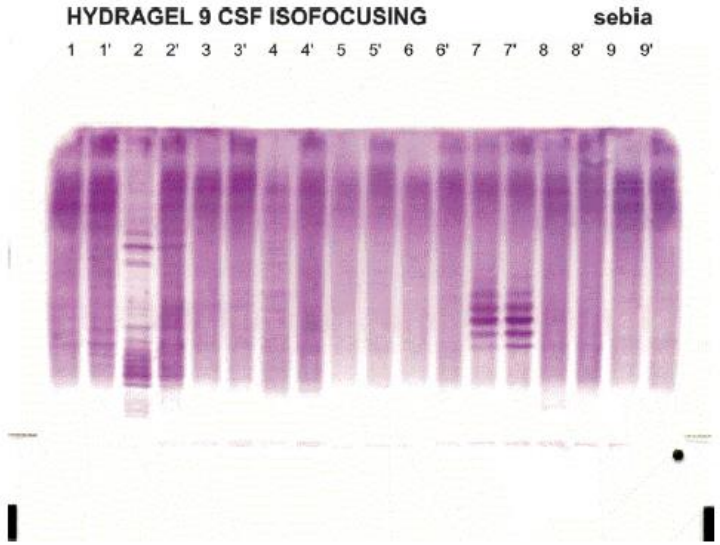


Fig. 1. La recherche des bandes oligoclonales.
1/1′ : bandes en miroir dans le LCR et le sérum (négatif).
2/2′ : plus de bandes dans le LCR que dans le sérum (positif).
3/3′ : bandes en miroir dans le LCR et le sérum (négatif).
4/4′ : bandes dans le LCR, pas dans le sérum (positif).
5/5′ : bandes en miroir dans le LCR et le sérum (négatif).
6/6′ : pas de bandes (négatif).
7/7′ : bandes dans le LCR et le sérum : paraprotéine (négatif).
8/8′ : pas de bandes (négatif).
9/9′ : pas de bandes (négatif).
Nous présentons un Hydragel dont la reproduction est plus facile ; dans cette étude, c'est la technique Helena qui a servi de référence.

Remerciements à Mme Lutteri

SEP & Biologie clinique

- **Bandes oligo-clonales spécifiques dans le LCR**
  - **ISOFOCALISATION**

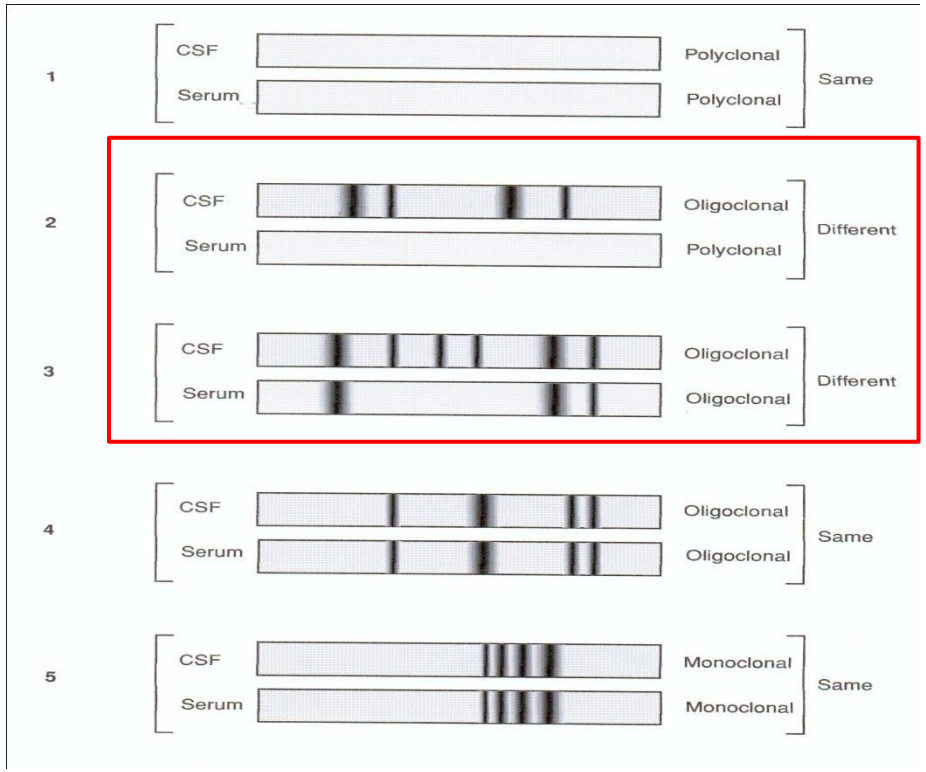
Normal

IgG local synthesis

IgG local synthesis

No local synthesis

No local synthesis
Monoclonal band splitted in several bands by IEF



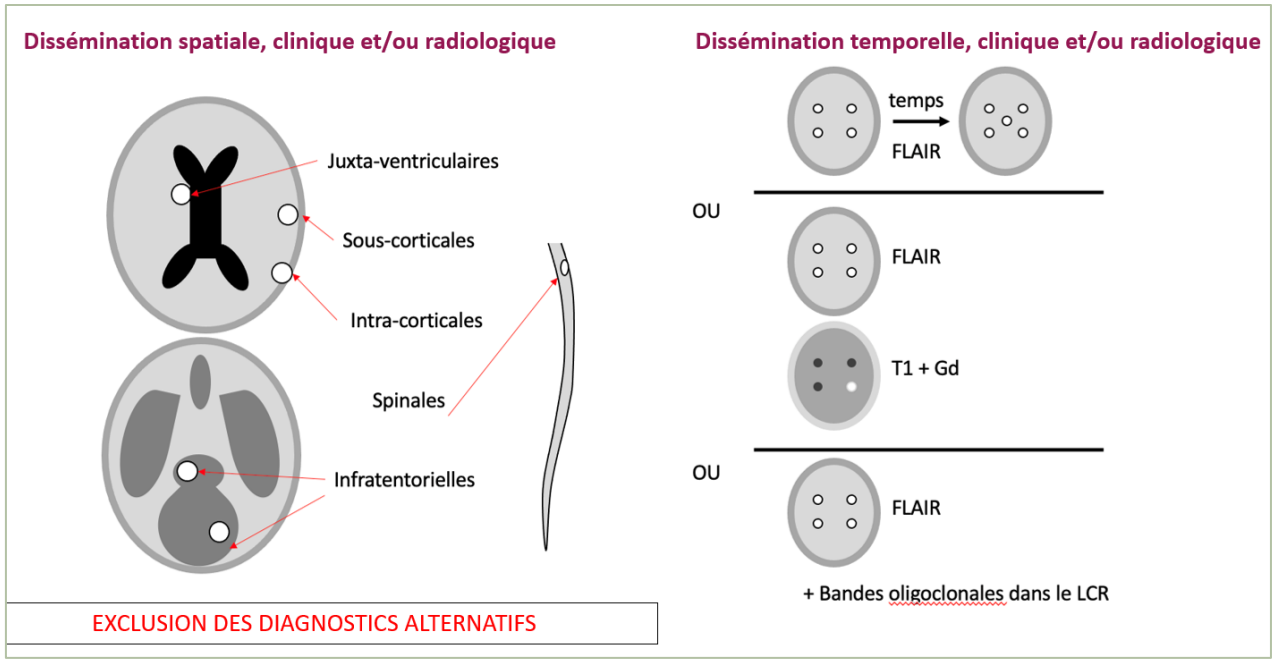
Remerciements à Mme Lutteri

SEP & Biologie clinique

- **Bandes oligo-clonales** < LCR
  - Présentes chez 90% des SEP
  - Non spécifiques
  - Mais… **valeur diagnostique** ++

DIAGNOSTIC

CRITERES DIAGNOSTIQUES DE SEP



Remerciements à E. Lommers

SEP & Biologie clinique

- **Bandes oligo-clonales**

➔ Reprises dans les critères diagnostiques de McDonald de 2017

DIAGNOSTIC

PRECOCE !

2017 revisions to the McDonald criteria

CSF oligoclonal bands

Numerous studies[65–73] have provided evidence that, in adult patients with a clinically isolated syndrome, CSF oligoclonal bands are an independent predictor of the risk of a second attack when controlling for demographic, clinical, treatment, and MRI variables. After considering these data, the Panel recommended that with a typical clinically isolated syndrome, fulfilment of clinical or MRI criteria for DIS, and no better explanation for the clinical presentation, demonstration of CSF oligoclonal bands in the absence of atypical CSF findings allows a diagnosis of multiple sclerosis to be made, even if the MRI findings on the baseline scan do not meet the criteria for DIT and in the absence of either a second attack or MRI evidence of a new or active lesion on serial imaging (table; panel 4).[73] This consensus recommendation allows the presence of CSF oligoclonal bands to substitute for the requirement of fulfilling DIT in this situation. This criterion is similar to the laboratory-supported definite multiple sclerosis category in the earlier Poser criteria.[2]

Thompson et al. 2018

SEP & Biologie clinique

- **Chaines légères libres kappa ?**
  - Comparaison SERUM >< LCR

  => KFLC index = (CLL Kappa LCR / CLL Kappa sérum) / (Albumine LCR / Albumine sérum)

  - **Meilleure sensibilité mais moins bonne spécificité que les BOC**

Intérêt = récupérer qqs patients SEP qui auraient des BOC négatives

→ DIAGNOSTIC

SEP & Biologie clinique

- Bandes oligo-clonales LCR
- Chaines légères K
- **« Bilan immuno-inflammatoire »**

DIAGNOSTIC DIFFERENTIEL

PLAN

- Sclérose en plaques
- **Spectre NMO**
- Encéphalites auto-immunes & paranéoplasiques

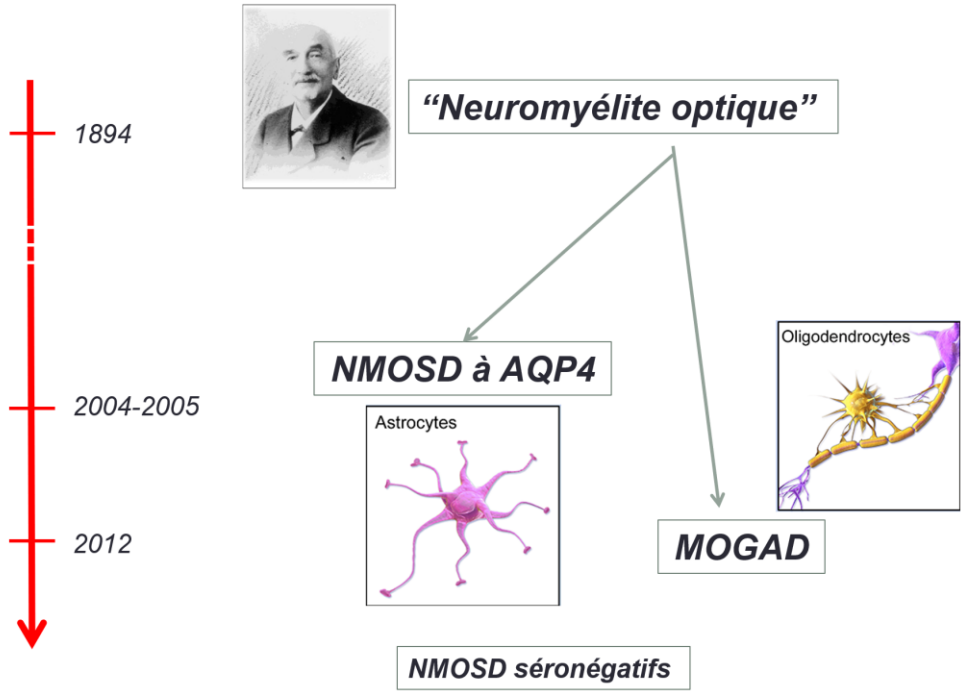
Spectre NMO

Au départ, groupe de maladies caractérisées par une atteinte dysimmune démyélinisante des **nerfs optiques** et de la **moelle épinière**

« Neuro-Myélite Optique »

Anciennement « Maladie de Devic »

- Nettement plus rare
- GRAVITE !
- DD avec SEP



Spectre NMO

Maladie du **système nerveux CENTRAL**

PHYSIOPATHOLOGIE :

dysimmune/auto-immune

⇒Pathogénicité de l'Ac : OUI pour AQP4 - ?? pour MOG…

⇒***Astrocytopathie >< Oligodendrocytopathie***

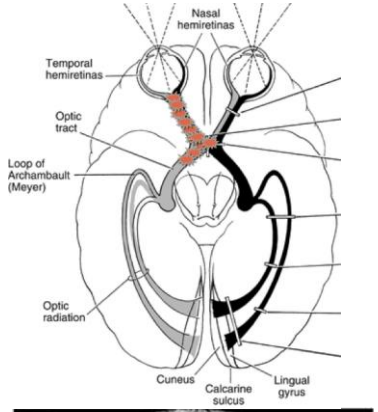
⇒Dans les 2 cas : recrutement C immunitaires, inflammation, démyélinisation (perte axonale AQP4++)

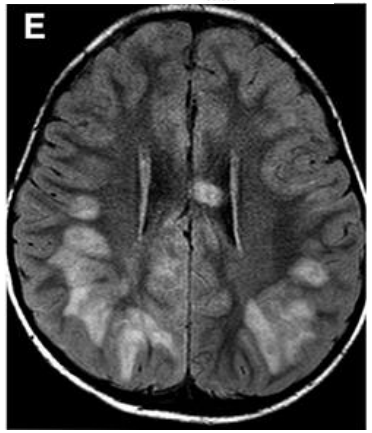
- Connaissance récente !
- Rare
  - ≈ 1/100 000
- Age de survenue + variable
  - MOG + jeunes
  - AQP4 + âgés

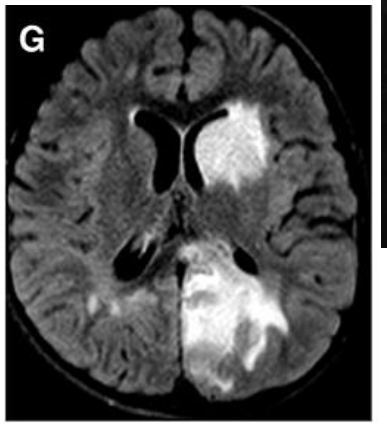
Spectre NMO

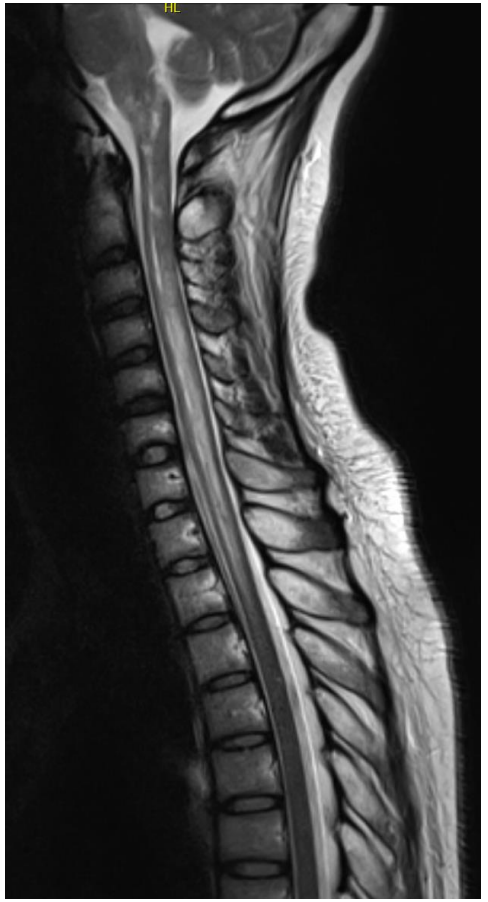
CLINIQUE

- **Névrites optiques** : sévères, étendues, volontiers bilatérales
- **Myélite** : sévères, étendues (long/transv)
- Aréa postrema, ADEM, atteinte parenchymateuse pseudo-tumorale, encéphalite, rhombencéphalite,..









Parrotta et al. 2020

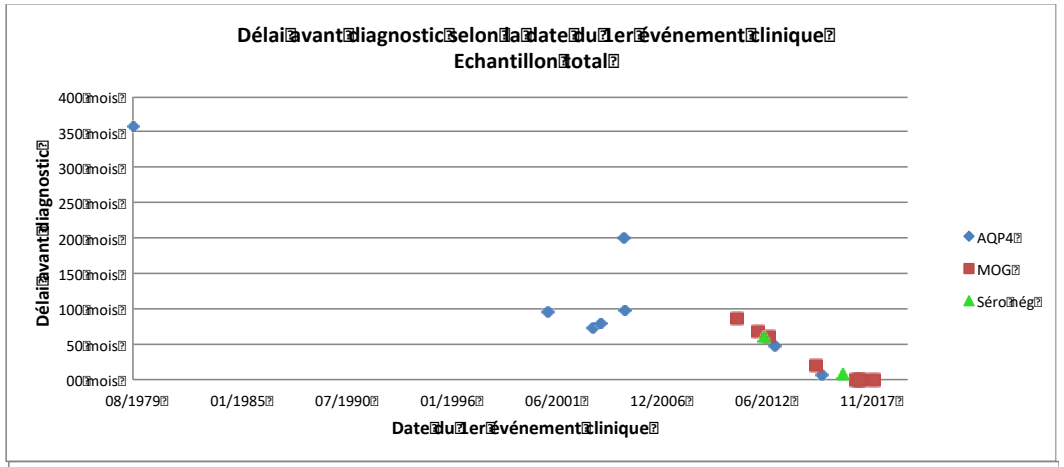
Spectre NMO

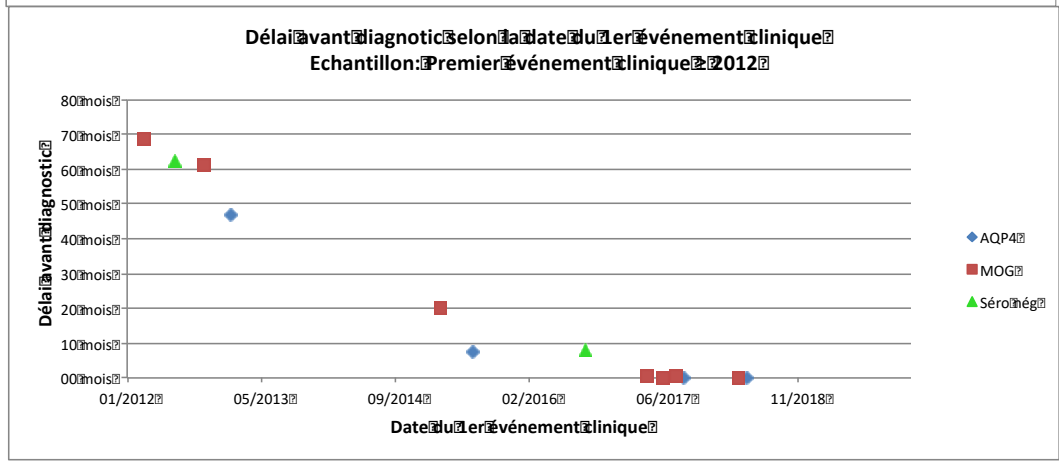
NMOSD-AQP4	MOGAD
Ac anti-AQP4 Cible = astrocyte	**Ac anti-MOG** Cible = oligodendrocyte
9 F : 1H	1,5 F : 1 H
Rechutes ++	Monophasique ou rechutes
Attaques sévères ++	Attaques sévères ++
BOC 15-30%	BOC < 10%
B cortico-sensibilité ; PLEX souvent nécessaires	TB cortico-sensibilité/dépendance ; PLEX/IVIG parfois nécessaires
Récupération incomplète	Bonne récupération

+ NMOSD séronég

NMO & Biologie clinique

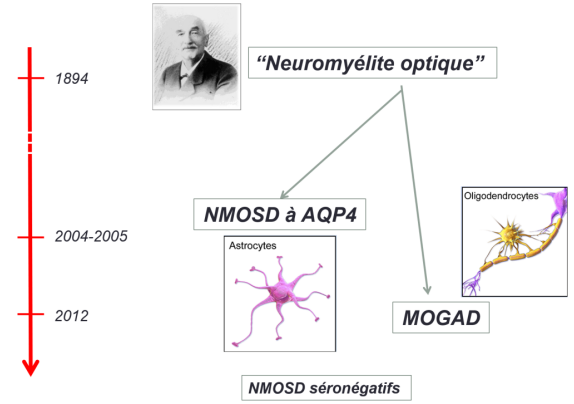
- **Diagnostic et diagnostic différentiel !**





Délai médian

4,5 ans



Si premier événement > 2012 :

7,4 mois

DD : SEP, NO inflammatoire isolée ou vasculaire, HTIC, MY lupique, syringomélie, Harding, lymphome, post-anti TNF, neuroBK

NMO & Biologie clinique

- **Diagnostic et diagnostic différentiel !**

DIAGNOSTIC

DIAGNOSTIC DIFFERENTIEL

⇒**Détections des Ac (CBA euroimmun)**
- Sérum
- (LCR si sérum - pour MOG)

⇒**BOC : plutôt DD avec SEP**

⇒**Bilan « immuno-inflammatoire »**

DD **&** co-pathologies (AQP4>MOG)

Multiple sclerosis	
Serum anti-AQP4 Ab **negative** Anti-MOG Ab **negative** **CSF** Moderate pleiocytosis (lympho) OCB ~ 80% MRZ reaction ~ 78%	
Neuromyelitis optica	**MOGAD**
Serum anti-AQP4 Ab **positive** Anti-MOG Ab **negative** **CSF** Frequent pleiocytosis (lympho/neutro) OCB ~ 28% MRZ reaction ~ 1-2 %	**Serum** anti-AQP4 Ab **negative** Anti-MOG Ab **positive** **CSF** Frequent pleiocytosis (lympho/neutro) OCB ~ 6-13% MRZ reaction ~ 1-2%

DD SEP !! Car aggravation sous certains traitements de la SEP !

NMO & Biologie clinique

- **Diagnostic et diagnostic différentiel !**

DIAGNOSTIC

DIAGNOSTIC DIFFERENTIEL

- **SUIVI & stratégie thérapeutique**
  - Pour les **anti-MOG**

ADAPTATIONS THERAPEUTIQUES

PLAN

- Sclérose en plaques
- Spectre NMO
- Encéphalites auto-immunes & paranéoplasiques

Encéphalites auto-immunes / paranéoplasiques

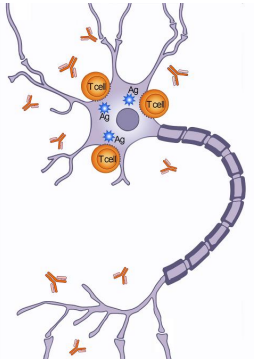
- GRAVITE !
- DD difficile
- Sentinelle T+

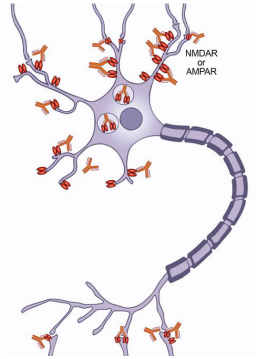
Encéphalite = « inflammation de l'encéphale »

CAUSES : INFECTIEUSES >> **AUTO-IMMUNES**

"Encéphalites"

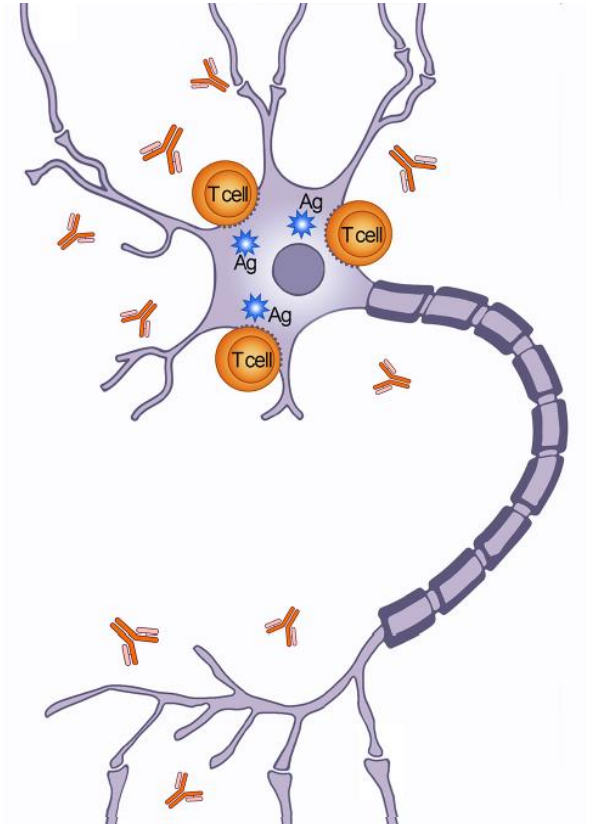
- Infectieuses
- **Auto-immunes**
  - Ac onconeuronaux (cible INTRA)
  - Ac membranaires (cible EXTRA)



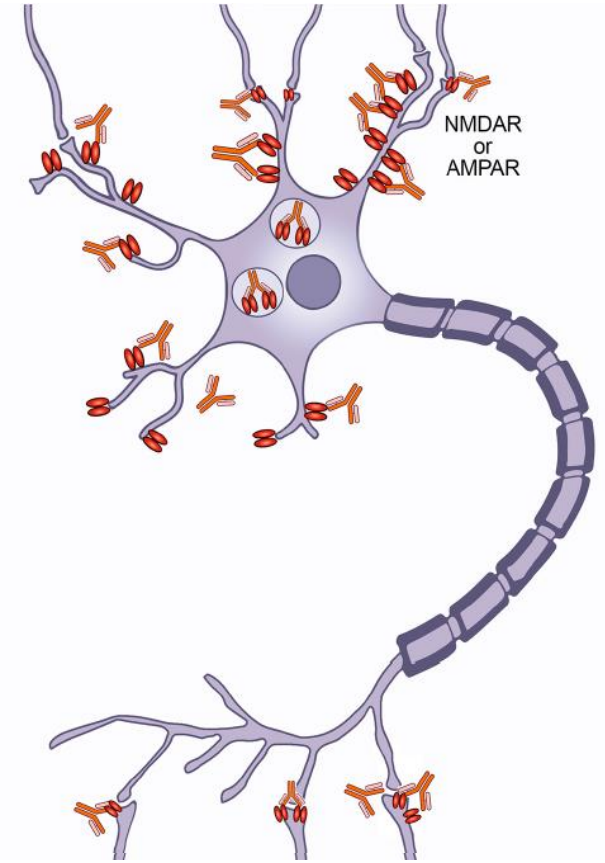


Ac onconeuronaux (cible INTRA)

Anti-Hu
Anti-Yo
Anti-GAD
Anti-CRMP5
Anti-Ma1
Anti-Ma2
Anti-Ri
…



Ac membranaires (cible EXTRA)



Anti-NMDAR
Anti-LGI1
Anti-CASPR2
Anti-AMPAR
Anti-GABAE
Anti-mGLUR1
Anti-mGLUR2
…

Dalmau et al. 2017

Ac à cible INTRA-cellulaire

Table 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

Abbreviations: ANNA = antineuronal nuclear antibody; CRMP5 = collapsin response-mediator protein 5; DNER = delta/notch-like epidermal growth factor–related receptor; EM = encephalomyelitis; KLHL11 = Kelch-like protein 11; LE = limbic encephalitis; LEMS = Lambert-Eaton myasthenic syndrome; MAP1B = microtubule-associated protein 1B; MG = myasthenia gravis; NMDAR = NMDA receptor; NSCLC = non–small-cell lung cancer; OMS = opsoclonus-myoclonus syndrome; PCA = Purkinje cell antibody; SCLC = small-cell lung cancer; SNN = sensory neuronopathy; SPS = stiff-person syndrome.

Graus et al. 2021

Ac à cible EXTRA-cellulaire

Table 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.

Abbreviations: AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; $GABA_BR$ = gamma-aminobutyric acid-b receptor; KCTD16 = potassium channel tetramerization domain containing; LEMS = Lambert-Eaton myasthenic syndrome; mGluR5 = metabotropic glutamate receptor type 5; NMDAR = NMDA receptor; SCLC = small-cell lung cancer; VGCC = voltage-gated calcium channel.

Graus et al. 2021

Ac à cible EXTRA-cellulaire

Table 3 Lower-Risk Antibodies (<30% Associated With Cancer)

Antibody	Neurologic phenotypes	Frequency of cancer (%)	Usual tumors	Sex, age-related, and other specificities
mGluR1[e55]	Cerebellar ataxia	30	Mostly hematologic	
$GABA_AR$[39,e56]	Encephalitis	<30	Malignant thymoma	Paraneoplastic origin is less frequent (10%) in children than in adults (60%)
CASPR2[51,52,e57,e58]	LE, acquired neuromyotonia (Isaac syndrome), and Morvan syndrome	<30	Malignant thymoma	Morvan syndrome is more associated (≈50%) with malignant thymoma, whereas LE is almost always nonparaneoplastic
GFAP[e59,e60]	Meningoencephalitis	≈20	Ovarian teratomas and adenocarcinomas	May occur as an immunologic accompaniment in anti-NMDAR encephalitis with ovarian teratomas
GAD65[e61,e62]	LE, SPS, and cerebellar ataxia	<15	SCLC, other neuroendocrine tumors, and malignant thymoma	Paraneoplastic patients are older, more frequently male, with associated neuronal antibodies, and atypical clinical presentations
LGI1[e63-e67]	LE	<10	Malignant thymoma and neuroendocrine	Paraneoplastic cases are mainly observed in patients with Morvan syndrome and both serum LGI1 and CASPR2 antibodies
DPPX[e68,e69]	Encephalitis with CNS hyperexcitability and PERM	<10	B-cell neoplasms	
GlyR[55,56]	LE and PERM	<10	Malignant thymoma and Hodgkin lymphoma	
AQP4[e70]	Neuromyelitis optica spectrum disorder	<5	Adenocarcinomas	Older age, male, and severe nausea/vomiting at onset
MOG[e71-e73]	MOG antibody–associated disease	5 cases reported	Mostly ovarian teratomas	

Abbreviations: AQP4 = aquaporin 4; CASPR2 = contactin-associated protein-like 2; DPPX = dipeptidyl peptidase-like protein; $GABA_AR$ = gamma-aminobutyric-acid-A receptor; GAD = glutamic acid decarboxylase; GFAP = glial fibrillary acidic protein; GlyR = glycine receptor; LE = limbic encephalitis; LGI1 = leucine-rich glioma-inactivated protein 1; mGluR1 = metabotropic glutamate receptor type 1; MOG = myelin oligodendrocyte glycoprotein; NMDAR = NMDA receptor; PERM = progressive encephalomyelitis with rigidity and myoclonus; SCLC = small-cell lung cancer; SPS = stiff-person syndrome.

Graus et al. 2021

Encéphalites auto-immunes / paranéoplasiques

- **Difficile !**
- Pas de signe /symptôme spécifique

- **À ne pas rater !**
- Grave / mortel /… curable

- **Différentiel**
- Avec pathologies psychiatriques

Ψ

Encéphalites auto-immunes / paranéoplasiques

- **CLINIQUE : variable selon Ac ! → « Syndromes neurologiques »**

Mais ++

- Troubles psychiatriques : agitation, comportement, hallucinations…
- Mouvements anormaux
- Epilepsie
- Ataxie / Sd cérébelleux

Le plus souvent : **décours (SUB)-AIGU**

- **PRONOSITC** : parfois risque VITAL
  - Lié au syndrome neurologique AI/paraN
  - Lié à la tumeur associé → onconeuronaux +++

Encéphalites auto-immunes / paranéoplasiques

- **CLINIQUE → « Syndromes neurologiques »**

« Sd neurologiques »	Signes / symptômes
Ataxie cérébelleuse rapidement progressive	Sd cérébelleux axial, segmentaire + nystagmus
Encéphalite limbique	Epilepsie, mémoire, psy++
Encéphalite du tronc cérébral	Ataxie cérébelleuse, dysarthrie, Sd vestibulaire, ophtalmoparésie…
Opsomyoclonus	Mvts oculomoteurs
Neuronopathie sensitive	Ataxie proprioceptive
Pseudo-obstructions gastro-intestinales	Obstruction intestinale
Syndrome de Lambert-Eaton	« Myasthénie-like » + dysautonomie
Syndrome de la personne raide/MA	Mouvements anormaux/raideurs
…	…

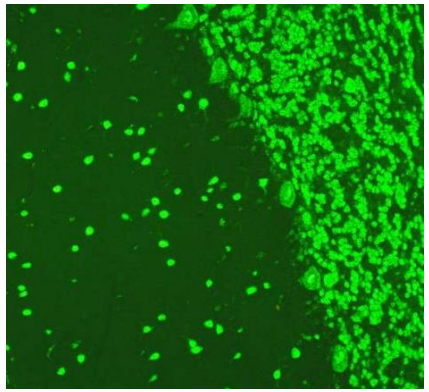
Encéphalites auto-immunes / paranéoplasiques

	Cible INTRA-cellulaire	Cible MEMBRANAIRE
Physiopathogénie	~~Ac pathogène~~ → « marqueur » Mécanisme de destruction neuronale IRREVERSIBLE	Ac pathogène > altère structure/fonction de l'Ag cible → REVERSIBLE
Association aux TUMEURS	Fréquente +++	Moins fréquente
Réponse à IMMUNO-THERAPIE	MAUVAISE	BONNE ++
Pronostic neurologique	Dépend du pronostic ONCO	Dépend de la réponse à l'immunothérapie

EAI/paraN & Biologie clinique

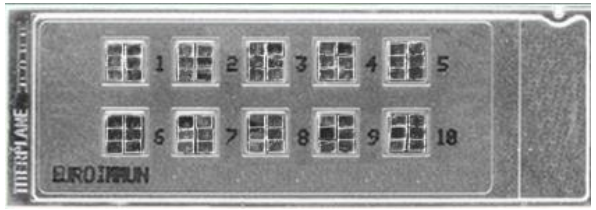
- ETIOLOGIE de l'encéphalite !
- CARACTERISER L'ANTICORPS

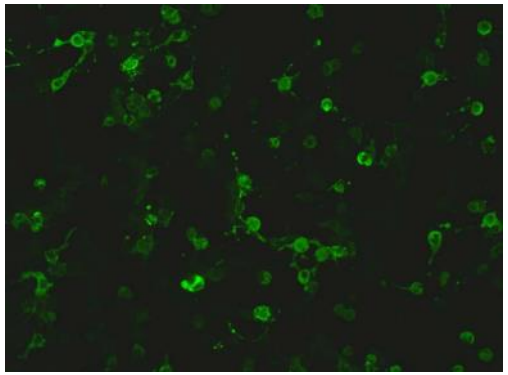
IF coupe cervelet



DOT

Ac onconeuronaux (cible INTRA)





Cellules transfectées

Ac membranaires (cible EXTRA)

EAI/paraN & Biologie clinique

- ETIOLOGIE de l'encéphalite !
- CARACTERISER L'ANTICORPS

Où CHERCHER L'ANTICORPS ?

➔ **SANG** suffisant pour les Ag intracellulaires : Hu, CRMP5, Yo, Ma2, Amphy, DNER

➔ **SANG et LCR** pour les Ag de surface : AMPAR, GABAR, LGI1, CASPR2 etc

➔ **LCR** pour le NMDAR

➔ En gros, dans le doute, faire les 2 !

Sclérose en plaques	Fréquence PEC précoce	BOC Ch. Légères K
Spectre NMO	DD SEP Gravité	Anticorps spécifiques MOG et AQP4
Encéphalites AI et Sd N paraN	DD psy Gravité	Anticorps spécifiques Intra/extra

Merci pour votre attention