Session « Pathologies Inflammatoires »
Cas Clinique – Mise au Point

Romain MARIGNIER

Service de Neurologie A, Hôpital Neurologique
Hospice Civils de Lyon

Centre de Recherche en Neuroscience de Lyon (CRNL)
INSERM U1028 CNRS UMR 5292- Equipe FLUID

Hospices Civils de Lyon

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Me Mon Ka 15 ans

Lycéenne

Antécédent familial ou personnel : RAS

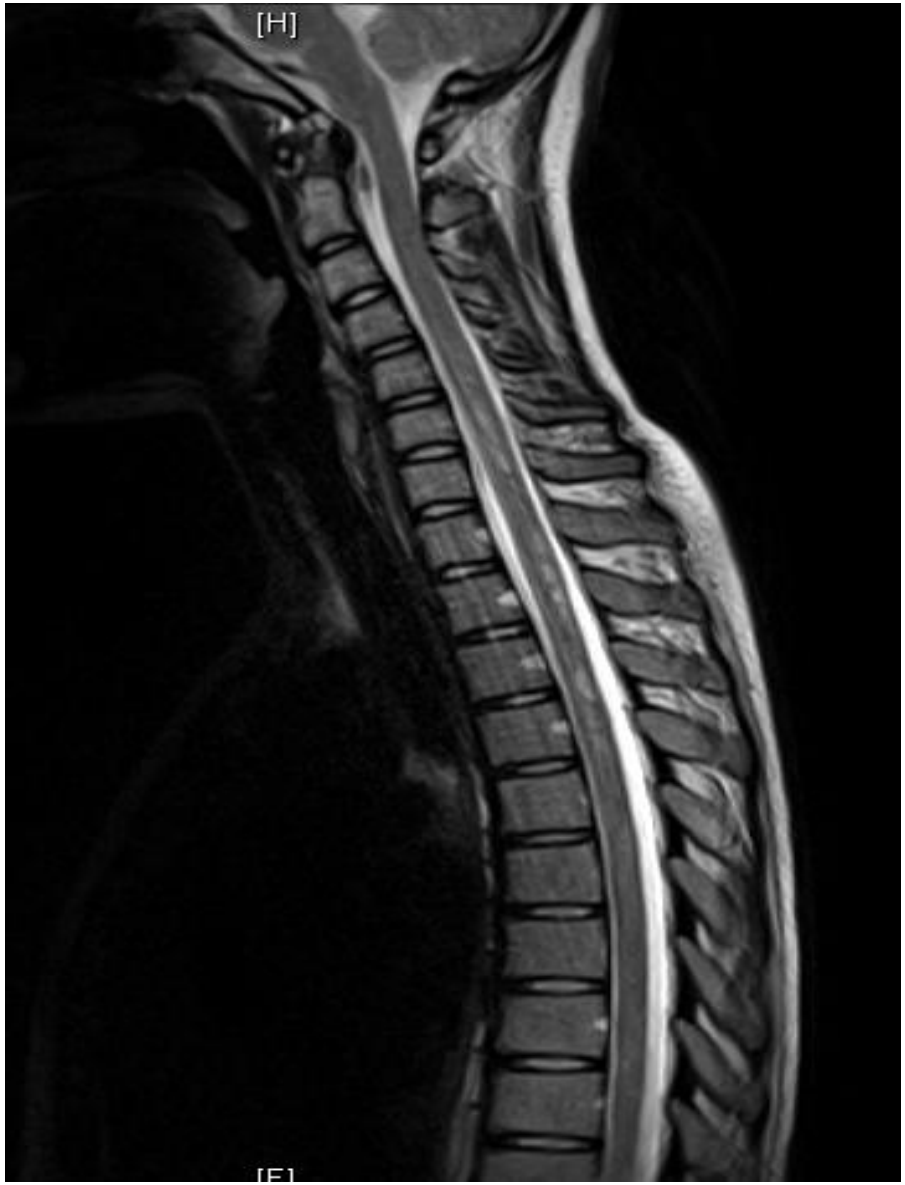
Mai 2012

Troubles sensitifs douloureux des deux membres inférieurs et du tronc

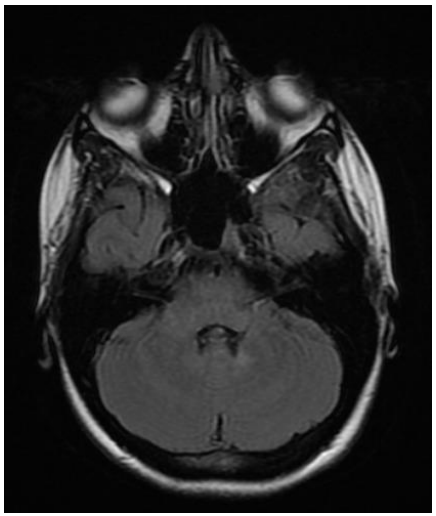
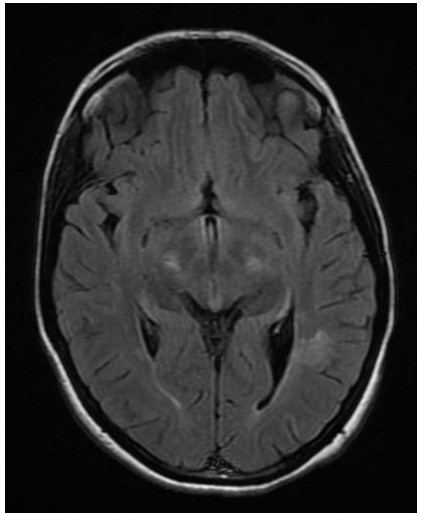
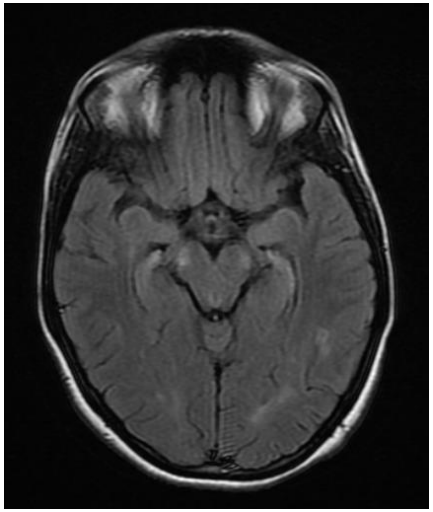
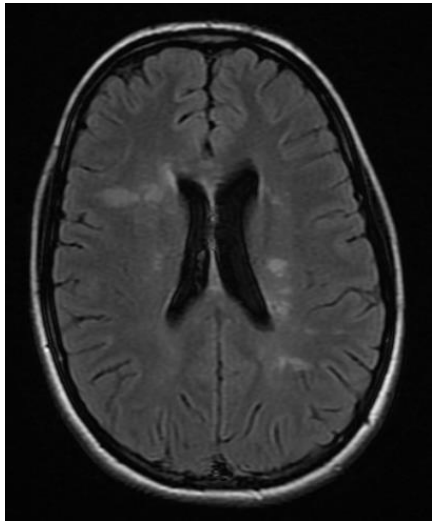
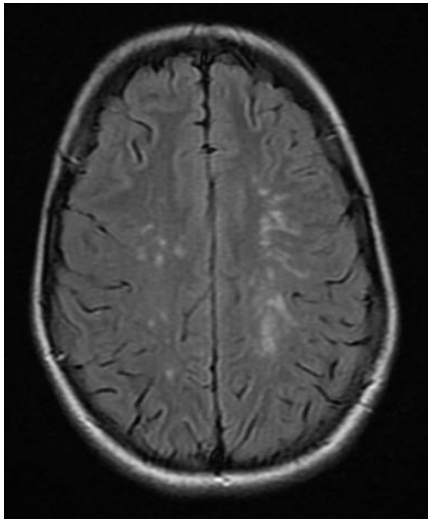
Signe de Lhermitte

Trouble de la marche

Pas de trouble vésico-sphinctérien



IRM Médullaire Séquence T2

IRM Encéphalique séquence FLAIR

Explorations Complémentaires Biologiques

Biologie sanguine standard: sans particularité

Analyse du LCS:

< 2GB

Présence de nombreuses oligoclonales surnuméraires

Index IgG 0.9

Prise en charge

Corticothérapie intra-veineuse 1gr/j pendant 3j

Evolution

Récupération clinique de l'épisode

Episodes neurologiques

Traitement de fond

Syndrome vestibulaire
céphalées

Sept. 2012

Introduction
IFN Béta1a

Dec. 2012

3 nouveaux épisodes
médullaires

Jan. 2013

Mars 2013

Switch pour
NATALIZUMAB

Déficit hémicorporel gauche

Avril 2013

Ac anti-
natalizumab -

Syndrome vestibulaire droit
déficit brachio-facial D
NORB bilatérale

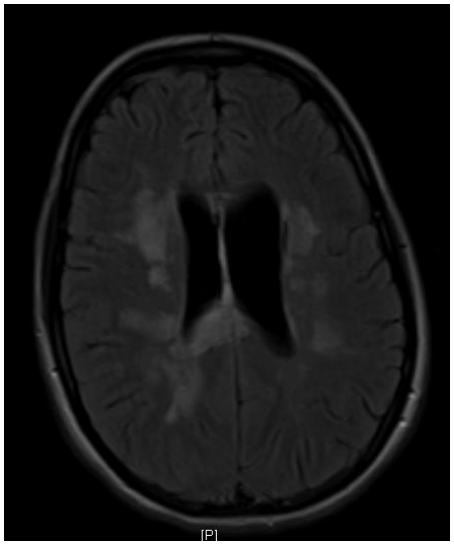
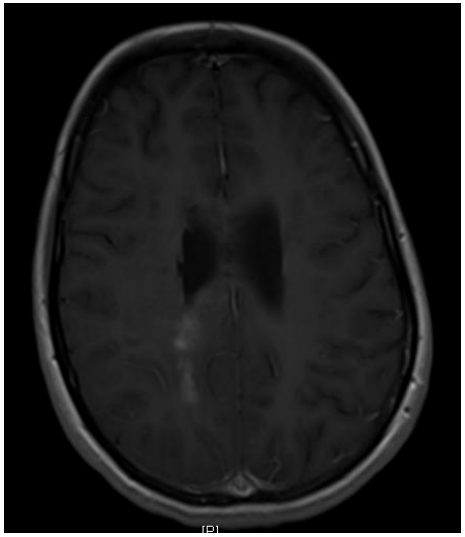
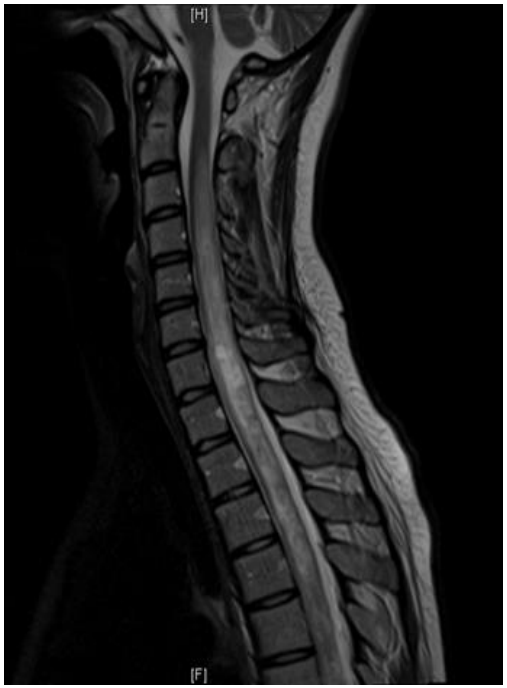
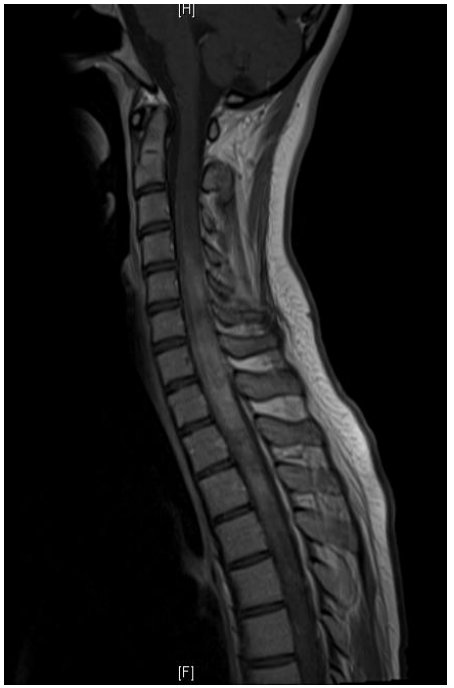
Mai 2013

Ac anti-
natalizumab -

Oct. 2014

Echec
NATALIZUMAB

Octobre 2014 : En moins de 24h, apparition d'une tétraparésie sévère + troubles vésico-sphinctériens; niveau sensitif C4

PL : < 2GB, absence de BOC, index IgG <0.7

Traitement

Corticothérapie Intraveineuse 1gr/j pendant 3j
Echec ► Echanges plasmatiques

Reprise du bilan étiologique

Bilan auto-immun négatif dont cryoglobulinémie et anticorps anti phospholipides

Fond d'œil normal; Pas d'argument pour une vascularite cérébrale

Scanner thoraco-abdomino-pelvien normal

Bilan métabolique négatif (lactate/pyruvate, AGTLC)
MAIS **anticorps anti-AQP4+** *

Révision du Diagnostic

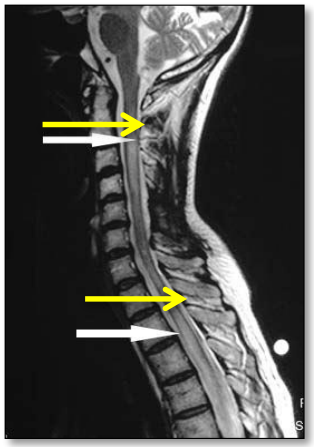
Neuromyélite Optique
► Mise sous Rituximab

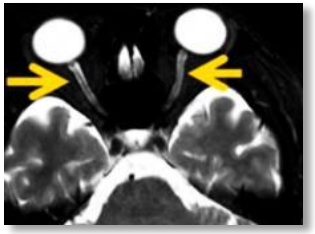
Evolution

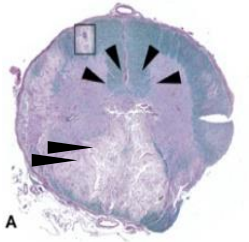
Récupération clinique
Absence de nouvelle poussée (au 01/06/2016)

Neuromyélite Optique de Devic

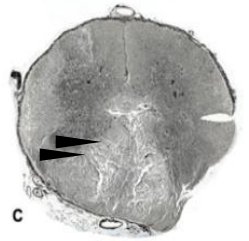
- **Neuromyelitis Optica (maladie de Devic), pathologie auto-immune du SNC**
  - Maladie grave touchant préférentiellement le nerf optique et la moelle épinière
  - Inflammatoire démyélinisante mais différente de la SEP: pronostic, traitement
  - Autoanticorps spécifique: AQP4-Ab



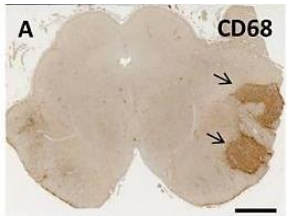




demyelinisation

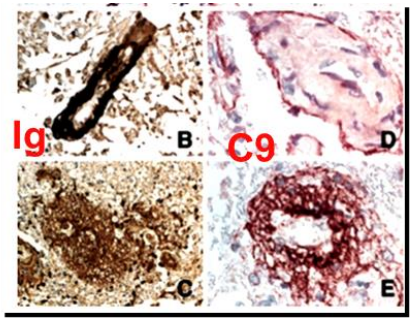


Perte axonale



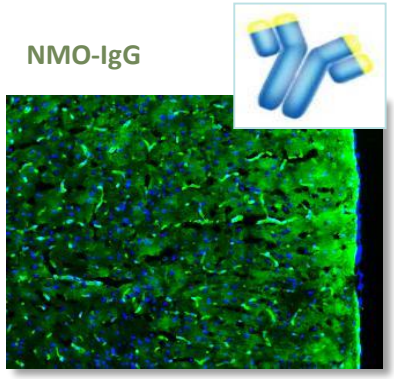
inflammation

Lucchinetti et al. Brain, 2002



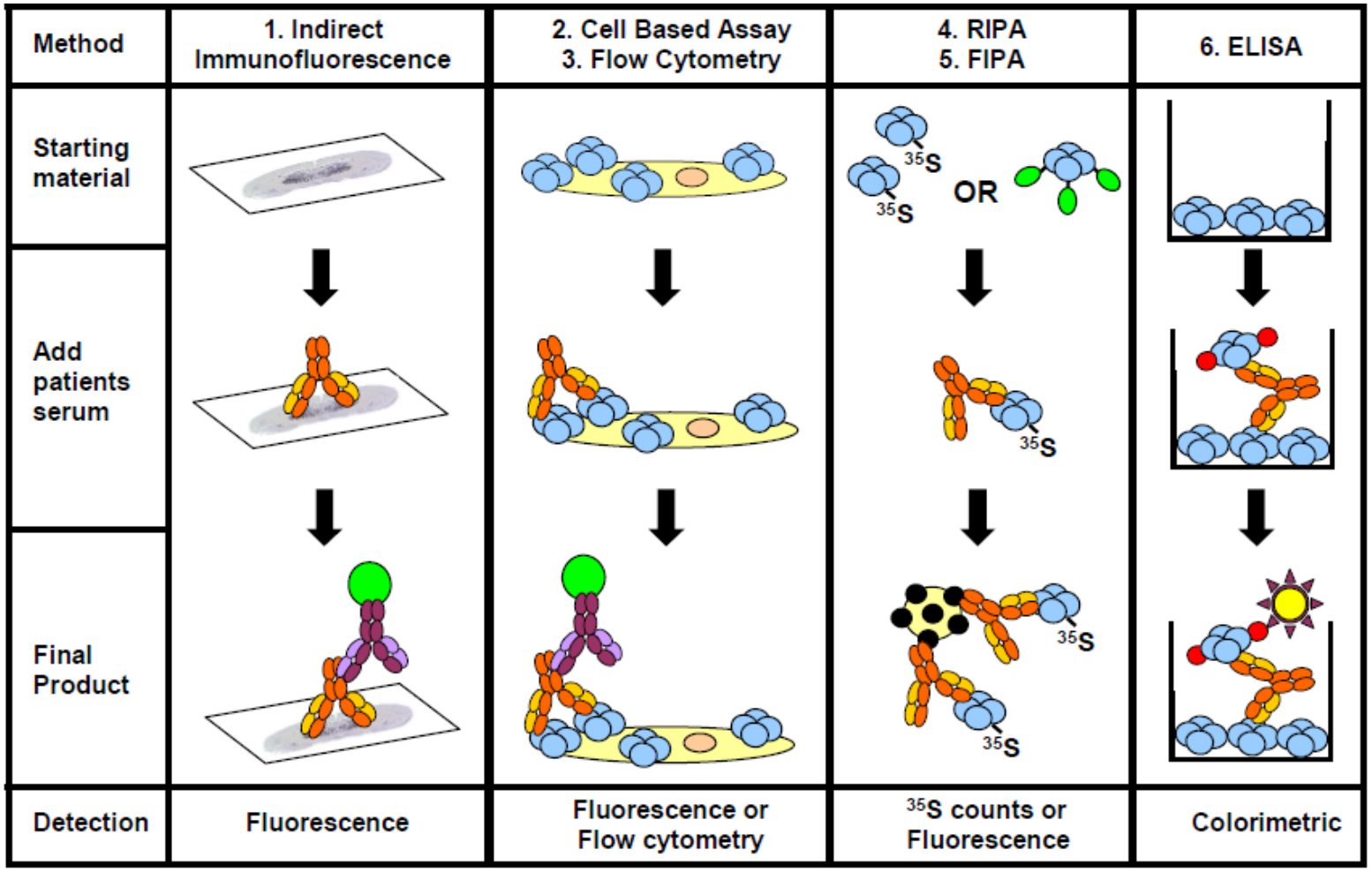
Ig et complément

NMO-IgG



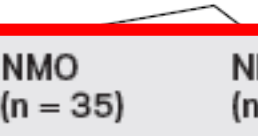
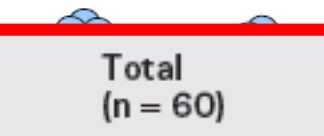
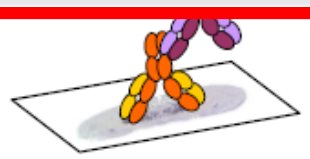
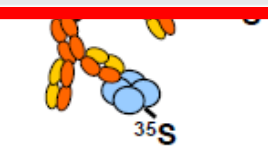
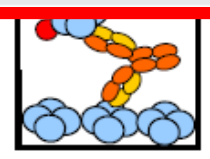
Lennon et al Lancet 2004

Méthodes de détection NMO-IgG/AQP4-IgG



From Waters et al., 2008

Méthodes de détection NMO-IgG/AQP4-IgG

Method	1. Indirect Immunofluorescence	2. Cell Based Assay 3. Flow Cytometry	4. RIPA 5. FIPA	6. ELISA
Starting				
Final Product				
Detection	Fluorescence	Fluorescence or Flow cytometry	^{35}S counts or Fluorescence	Colorimetric

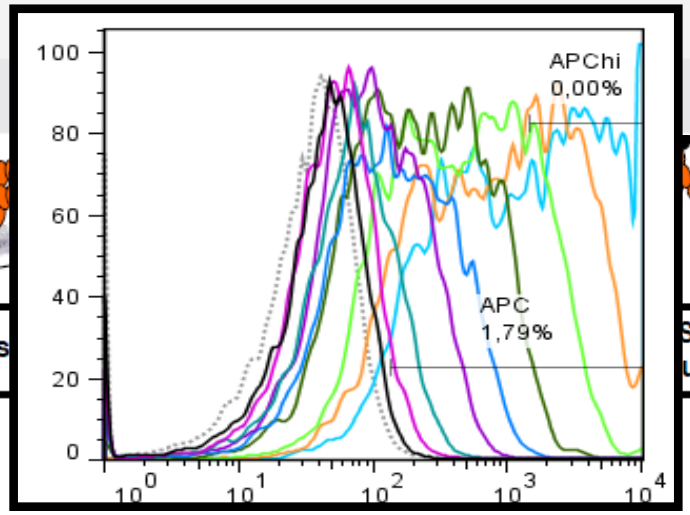
	NMO (n = 35)	NMOSD (n = 25)	Total (n = 60)	Controls (n = 86)	Sensitivity	Specificity
IIF	17	12	29	0	48.3	100.0
FACS	25	21	46	0	76.7	100.0
CBA-O	24	20	44	0	73.3	100.0
ELISA-R (5.0)	18	18	36	0	60.0	100.0
FIPA-O	16	16	32	0	53.3	100.0
FIPA-M	16	16	32	2	53.3	97.7

From Waters et al., 2008

Méthodes de détection NMO-IgG/AQP4-IgG

Method	1. Indirect Immunofluorescence	2. Cell Based Assay 3. Flow Cytometry	4. RIPA 5. FIPA	6. ELISA
Starting				
Final Product				
Detection	Fluores		S counts or uorescence	Colorimetric

	NMO (n = 35)	NMOSD (n = 25)	Total (n = 60)	Controls (n = 86)	Sensitivity	Specificity
IIF	17	12	29	0	48.3	100.0
FACS	25	21	46	0	76.7	100.0
CBA-O	24	20	44	0	73.3	100.0
ELISA-R (5.0)	18	18	36	0	60.0	100.0
FIPA-O	16				53.3	100.0
FIPA-M	16				53.3	97.7



Méthodes de détection NMO-IgG/AQP4-IgG

Method	1. Indirect Immunofluorescence	2. Cell Based Assay 3. Flow Cytometry	4. RIPA 5. FIPA	6. ELISA
Starting				

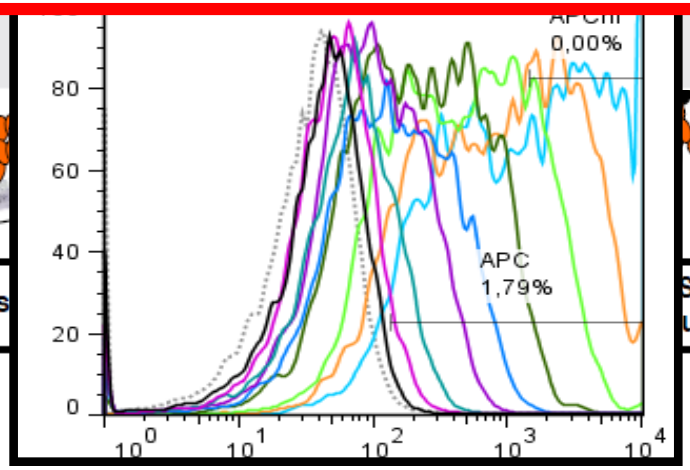
	NMO (n = 35)	NMOSD (n = 25)	Total (n = 60)	Controls (n = 86)	Sensitivity	Specificity
FIPA-M	16				53.3	97.7

Case Report

False positivity of anti aquaporin-4 antibodies in natalizumab-treated patients

Mikael Cohen, Jérome De Sèze, Romain Marignier and Christine Lebrun

Final Product				
Detection	Fluores		S counts or uorescence	Colorimetric



From Waters et al., 2008

Epidémiologie

Maladie Rare: en Europe 0.1 à 4/100.000

Plus fréquente en Asie et dans les Caraïbes

Facteur génétique : origine Africaine + grave

Touche plus la femme que homme : 5-9F /1H (surtout si présence de l'anticorps anti-AQP4)

Age de début moyen : 40 ans

Mais peut survenir à n'importe quel âge (forme pédiatrique, début possible après 80 ans)

PHYSIOPATHOLOGIE

BLOOD

T cells

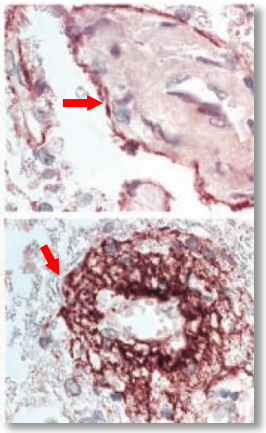
B cells

Plasma cells

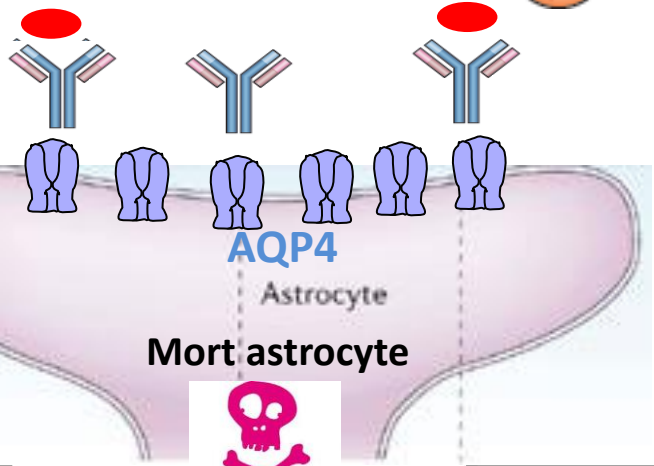
AQP4-IgG

BBB

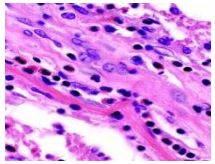
Central Nervous System

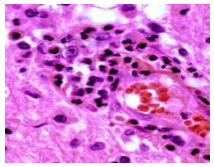


Complément

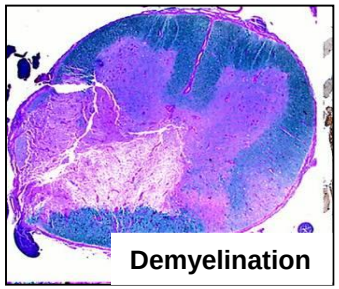


Mort astrocyte





Eosino Granulocyte

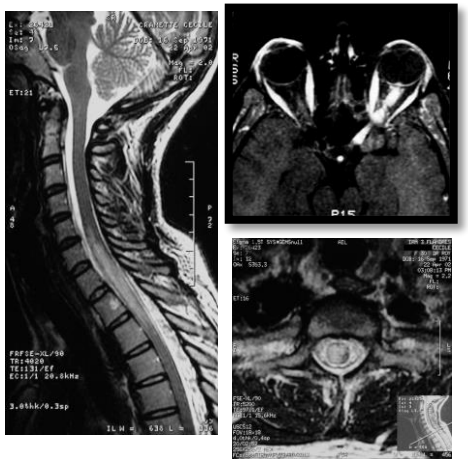


Demyelinisation

Perte axonale

Diagnostic

NMO



Critères Wingerchuk *et al, 2006*

Neuropathie optique rétrobulbaire

Myélite transverse aigue

et au moins deux des trois critères suivants:

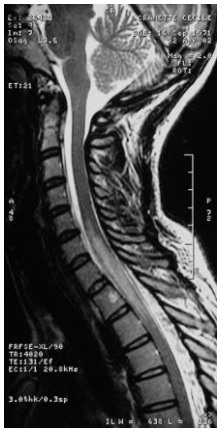
IRM encéphalique normale (ou non évocatrice de SEP)

IRM médullaire avec 1 lésion étendue sur au moins 3 segments vertébraux

NMO-IgG/AQP4Ab séropositif

Myélites de NMO

Myélite

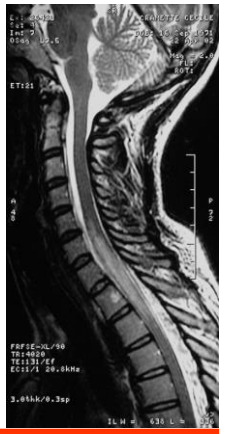


- **Clinique:**

- **Sévère** : tableau para/tetraplégie, troubles sphinctériens, détresse respiratoire
- Parfois associées à un prurit qui peut être inaugural
- À l'origine d'un handicap irréversible précoce
- **Séquelles** : phénomènes paroxystiques, douleurs+++

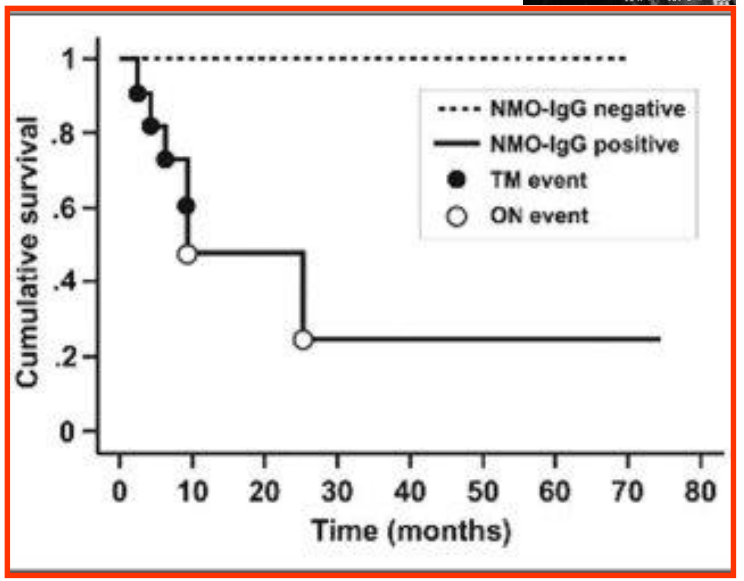
Myélite AQP4-IgG+

Myélite



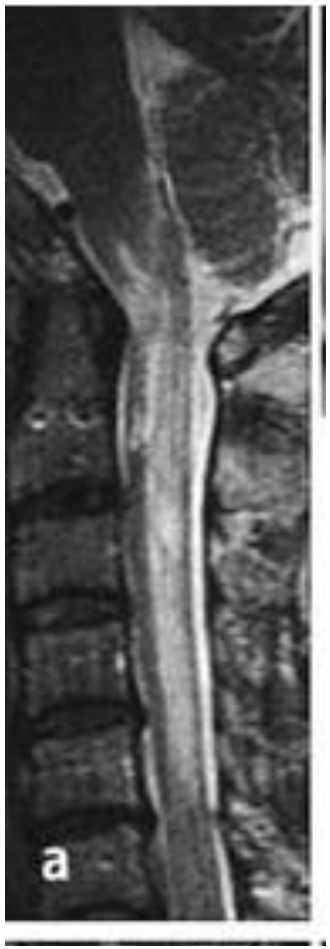
- **Clinique:**
- **Récurrente +++** *Wingerchuck et al. 2006*

- 62.5% des patients AQP4-IgG + présentèrent un deuxième épisode (MT ou NORB) dans l'année
- alors qu'aucun patient séronégatif ne présenta de poussée

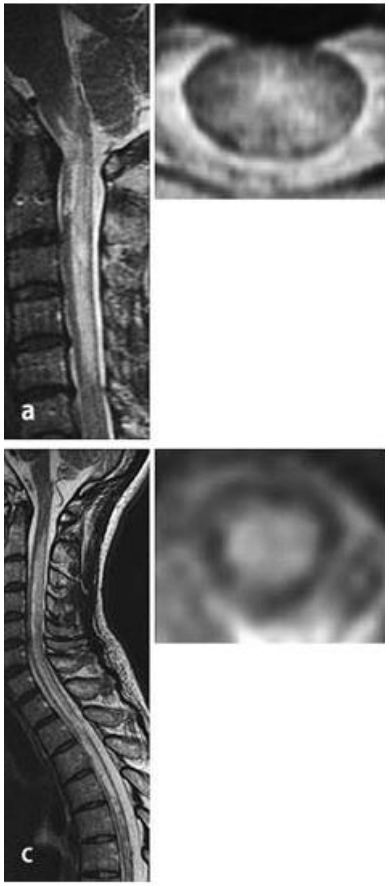


Weinshenker et al., 2006

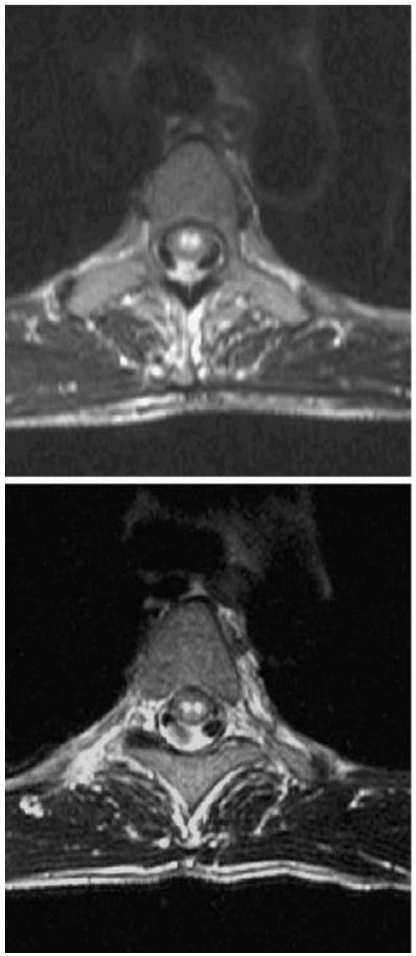
Myélite AQP4-IgG+



Longitudinale étendue

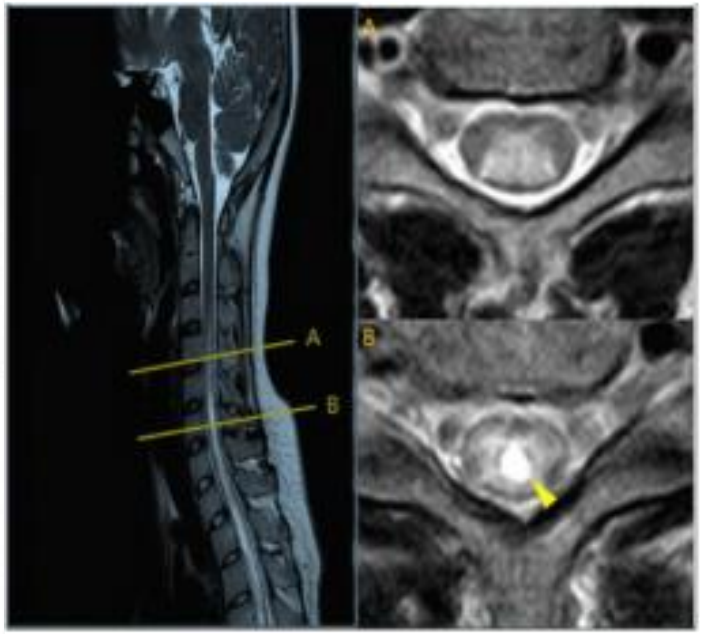


transverse



Substance grise

Nakamura et al., 2008



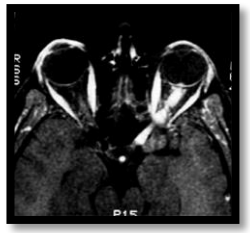
Bright Spotty Lesion

Hyun et al.,2015

NORB AQP4-IgG+

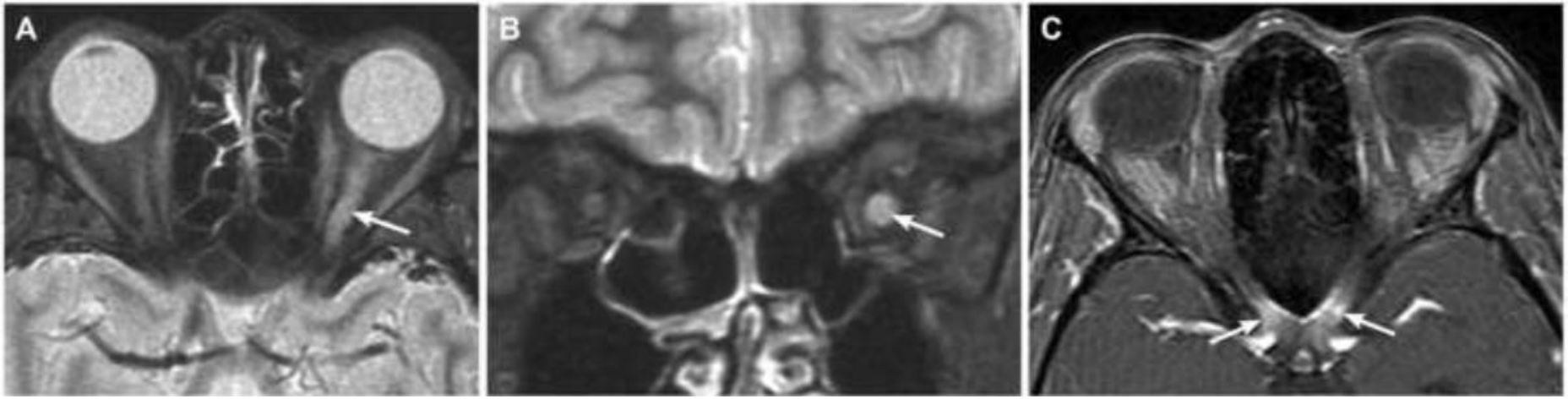
- **Clinique**

- Récidivante+++ Matiello et al., De Seze et al. 2008



- Differences avec la SEP
  - bilaterale (20%) Wingerchuck et al. 1999
  - severe (<1/10)
  - Mauvaise récupération (50% aveugle à 5 ans) Wingerchuck et al. 1999
  - Atteinte plus sévère du CV (atteinte bitemporale) Merle et al. 2013
  - Amincissement plus marqué RFNL à OCT Merle et al. 2008, Ratchord et al. 2009

NORB AQP4-IgG+



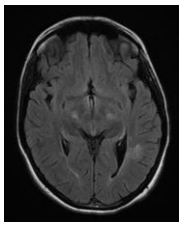
Ségment postérieure

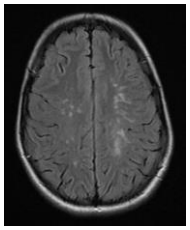
Hypersignal T2

Atteinte bilatérale
et du chiasma

Drapeaux rouges NMO???

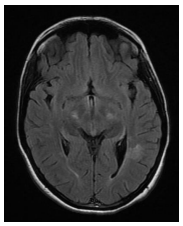
IRM encéphalique anormale?

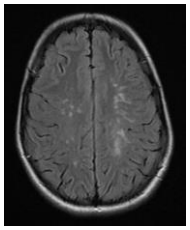


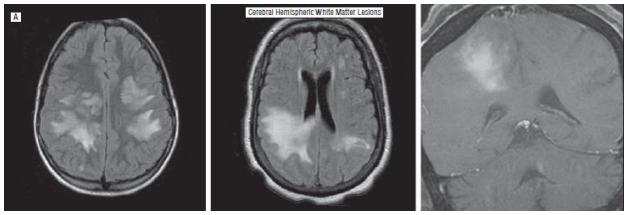


Drapeaux rouges NMO???

IRM encéphalique anormale? **NON**







ORIGINAL CONTRIBUTION

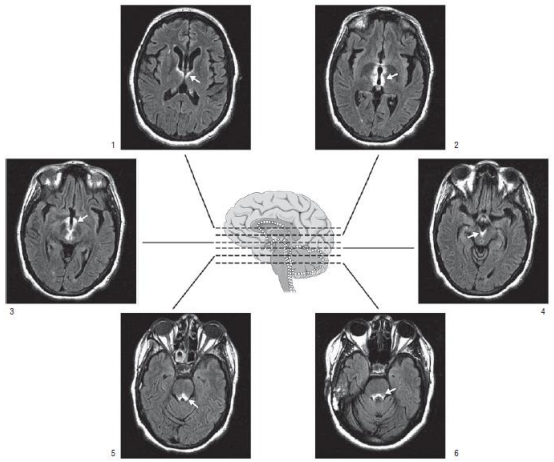
Brain Abnormalities in Neuromyelitis Optica

Sean J. Pittock, MD; Vanda A. Lennon, MD, PhD; Karl Krecke, MD; Dean M. Wingerchuk, MD;

ORIGINAL CONTRIBUTION

Neuromyelitis Optica Brain Lesions Localized at Sites of High Aquaporin 4 Expression

Sean J. Pittock, MD; Brian G. Weinshenker, MD; Claudia F. Lucchinetti, MD; Dean M. Wingerchuk, MD; John R. Corboy, MD; Vanda A. Lennon, MD, PhD

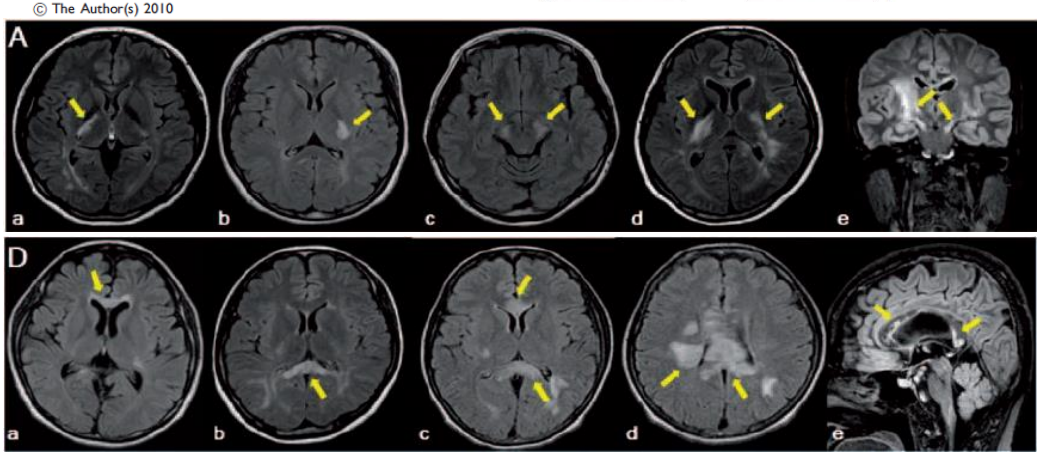


Research Paper

Multiple Sclerosis

Multiple Sclerosis
0(00) 1–8

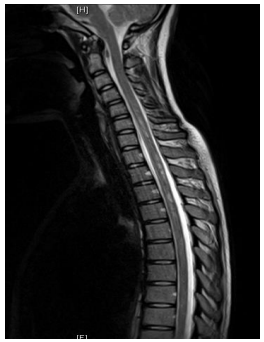
Characteristic brain magnetic resonance imaging abnormalities in central nervous system aquaporin-4 autoimmunity



Drapeaux rouges NMO???

IRM encéphalique anormale? NON

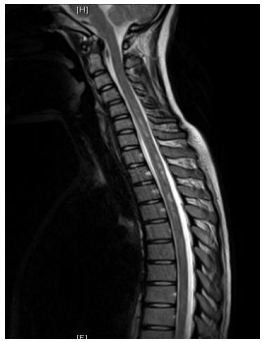
IRM médullaire non étendue?



Drapeaux rouges NMO???

IRM encéphalique anormale? NON

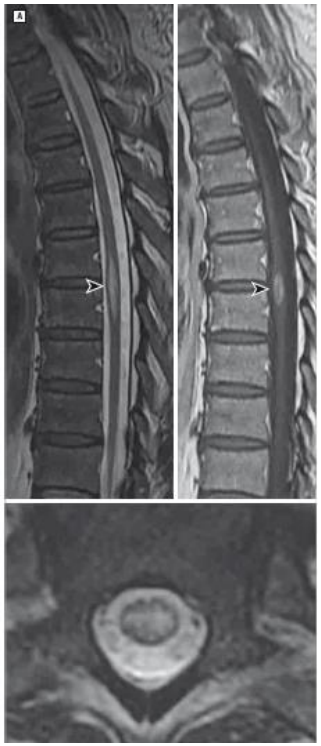
IRM médullaire non étendue? NON

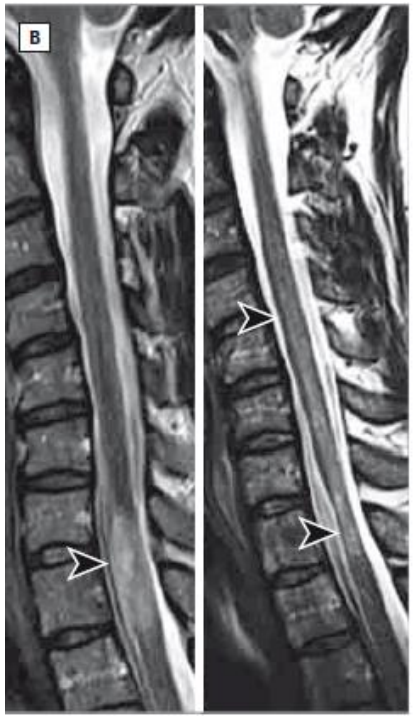


Original Investigation

Short Myelitis Lesions in Aquaporin-4-IgG–Positive Neuromyelitis Optica Spectrum Disorders

Eoin P. Flanagan, MBBCh; Brian G. Weinshenker, MD; Karl N. Krecke, MD; Vanda A. Lennon, MD, PhD; Claudia F. Lucchinetti, MD; Andrew McKeon, MBBCh; Dean M. Wingerchuk, MD; Elizabeth A. Shuster, MD; Yujuan Jiao, MD; Erika S. Horta, MD; Sean J. Pittock, MD





Asymptomatic myelitis in neuromyelitis optica and autoimmune aquaporin-4 channelopathy

Syndrome vestibulaire

Drapeaux rouges NMO???

IRM encéphalique anormale? NON

IRM médullaire non étendue? NON

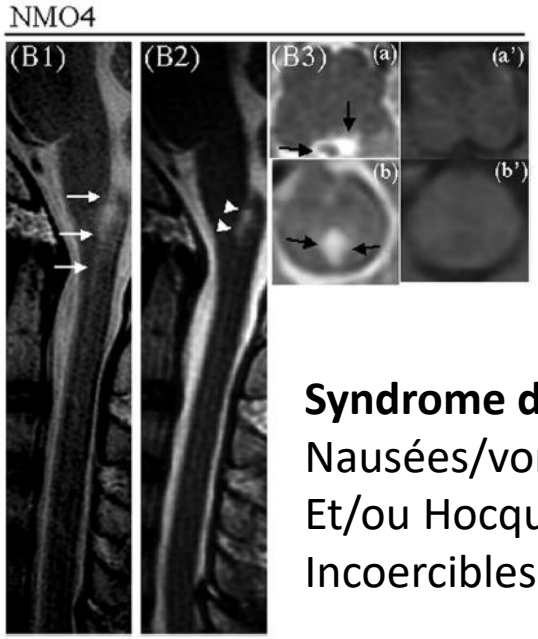
Atteinte extra optico-spinale?

Drapeaux rouges NMO???

IRM encéphalique anormale? NON

IRM médullaire non étendue? NON

Atteinte extra optico-spinale? NON



Atteinte du tronc cérébral

Vertiges, Diplopie, Nystagmus

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
2014, Vol. 20(7) 843–847

DOI: 10.1177/1352458513507822
msj.sagepub.com
SAGE

Brainstem manifestations in neuromyelitis optica: a multicenter study of 258 patients

L Kremer[1], M Mealy[2], A Jacob[3], I Nakashima[4], P Cabre[5], S Bigi[6], F Paul[7], S Jarius[8], O Aktas[9], L Elsone[3], K Mutch[3], M Levy[2], Y Takai[4], N Collongues[1], B Banwell[6], K Fujihara[4] and J de Seze[1]

Syndrome Diencéphalique

Narcolepsie/Hypersomnie

Troubles du comportement alimentaire

Syndrome de Area¨Postrema

Nausées/vomissements

Et/ou Hocquet

Incoercibles

Intractable hiccup and nausea with periaqueductal lesions in neuromyelitis optica

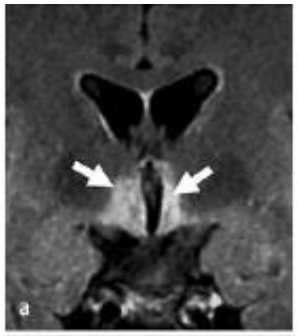
Abstract—Intractable hiccup and nausea (IHN) was found in eight of 47 cases of relapsing neuromyelitis optica (NMO) (17%) but in none of 130 cases of multiple sclerosis (MS). IHN resolved with methylprednisolone. In six cases, MRI detected linear medullary lesions involving the pericanal region, the area postrema, and the nucleus tractus solitarius. Like long and centrally located myelitis, a linear medullary lesion causing IHN may distinguish NMO from MS.

NEUROLOGY 2005;65:1479–1482

T. Misu, MD, PhD; K. Fujihara, MD, PhD; I. Nakashima, MD, PhD; S. Sato, MD, PhD; and Y. Itoyama MD, PhD

Toru Baba
Ichiro Nakashima
Takashi Kanbayashi
Masatoshi Konno
Toshiyuki Takahashi
Kazuo Fujihara
Tatsuro Misu
Atsushi Takeda
Yusei Shiga
Hiromasa Ogawa
Yasuto Itoyama

Narcolepsy as an initial manifestation of neuromyelitis optica with anti-aquaporin-4 antibody



Drapeaux rouges NMO???

IRM encéphalique anormale? NON

IRM médullaire non étendue? NON

Atteinte extra optico-spinale? NON

Atteinte optique **ET** médullaire obligatoire?

Drapeaux rouges NMO???

IRM encéphalique anormale? NON

IRM médullaire non étendue? NON

Atteinte extra optico-spinale? NON

Atteinte optique **ET** médullaire obligatoire? **NON**

***Panel 1*: Neuromyelitis optica spectrum**

Neuromyelitis optica

Limited forms of neuromyelitis optica

- Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord lesion seen on MRI)
- Optic neuritis: recurrent or simultaneous bilateral

Asian optic-spinal multiple sclerosis

Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease

Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem)

VIEWS & REVIEWS

International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

OPEN

Dean M. Wingerchuk, MD, FRCP(C)
Brenda Banwell, MD, FRCP(C)
Jeffrey L. Bennett, MD, PhD
Philippe Cabre, MD
William Carroll, MD
Tanuja Chitnis, MD
Jérôme de Seze, MD
Kazuo Fujihara, MD
Benjamin Greenberg, MD
Ana Jacob, MD
Sven Jarius, MD
Marco Lana-Peixoto, MD
Michael Levy, MD, PhD
Jack H. Simon, MD
Silvia Tenembaum, MD
Anthony L. Traboulsee, MD, FRCP(C)
Patrick Waters, PhD
Kay E. Wellik, MLS
Brian G. Weinshenker, MD, FRCP(C)

Editorial, page 118

Supplemental data at Neurology.org

ABSTRACT

Neuromyelitis optica (NMO) is an inflammatory CNS syndrome distinct from multiple sclerosis (MS) that is associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). Prior NMO diagnostic criteria required optic nerve and spinal cord involvement but more restricted or more extensive CNS involvement may occur. The International Panel for NMO Diagnosis (IPND) was convened to develop revised diagnostic criteria using systematic literature reviews and electronic surveys to facilitate consensus. The new nomenclature defines the unifying term NMO spectrum disorders (NMOSD), which is stratified further by serologic testing (NMOSD with or without AQP4-IgG). The core clinical characteristics required for patients with NMOSD with AQP4-IgG include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations. More stringent clinical criteria, with additional neuroimaging findings, are required for diagnosis of NMOSD without AQP4-IgG or when serologic testing is unavailable. The IPND also proposed validation strategies and achieved consensus on pediatric NMOSD diagnosis and the concepts of monophasic NMOSD and opticospinal MS. Neurology® 2015;85:177–189

GLOSSARY

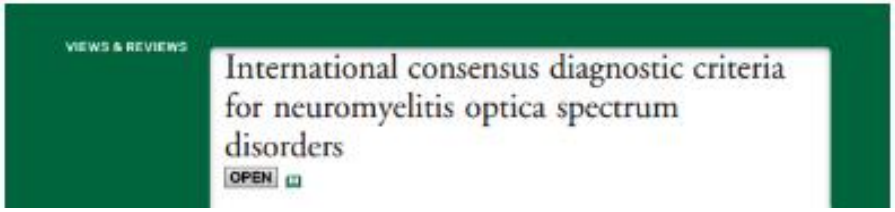
ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin-4; IgG = immunoglobulin G; IPND = International Panel for NMO Diagnosis; LETM = longitudinally extensive transverse myelitis lesions; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorders; SLE = systemic lupus erythematosus; SS = Sjögren syndrome.

Neuromyelitis optica (NMO) is an inflammatory CNS disorder distinct from multiple sclerosis (MS).[1,2] It became known as Devic disease following a seminal 1894 report.[3,4,5,6] Traditionally, NMO was considered a monophasic disorder consisting of simultaneous bilateral optic neuritis and transverse myelitis but relapsing cases were described in the 20th century.[7] MRI revealed normal brain scans and ≥3 vertebral segment longitudinally extensive transverse myelitis lesions (LETM) in NMO.[8,9] The nosology of NMO, especially whether it represented a topographically restricted form of MS, remained controversial.

A major advance was the discovery that most patients with NMO have detectable serum antibodies that target the water channel aquaporin-6 [AQP4–immunoglobulin G [IgG]).[8,9] are highly specific for clinically diagnosed NMO, and have pathogenic potential.[7,8,9,10] In 2006, AQP4-IgG serology was incorporated into revised NMO diagnostic criteria that relaxed clinical

© 2015 American Academy of Neurology 177

Critères de Wingerchuck, 2015



Anti-AQP4 positifs	Anti-AQP4 négatifs
Au moins 1 atteinte clinique caractéristique	Au moins 2 atteintes cliniques caractéristiques dont : - Au moins un épisode de NO, LETM ou Syndrome de l'area postrema - Dissémination dans l'espace (au moins 2 territoires caractéristiques) - Caractéristiques IRM remplies.
Test positif pour les anticorps anti-AQP4 par la meilleure méthode de détection (cell-based assay fortement recommandée)	Test négatif pour les anticorps anti-AQP4 par la meilleure méthode de détection ou test non disponible.
Exclusion des diagnostics différentiels	Exclusion des diagnostics différentiels.

Atteintes cliniques caractéristiques
1. **Névrite optique**
2. **Myélite aigue**
3. **Syndrome de l'area postrema**
4. Syndrome du tronc cérébral aigu.
5. Narcolepsie symptomatique ou syndrome diencéphalique clinique.
6. Syndrome encéphalitique symptomatique

NMOSD : Principes du traitement

Sévérité des poussées
Rôle direct des AQP4-IgG
Handicap lié aux poussées

Urgence+++
Hautes doses de Methylprednisolone en IV et/ou échanges plasmatiques à la phase aigue

Suivie d'une immunosuppression <u>prolongée</u>
- Azathioprine, mycophénolate mofétil, metotrexate, mitoxantrone
- Intérêt du Rituximab

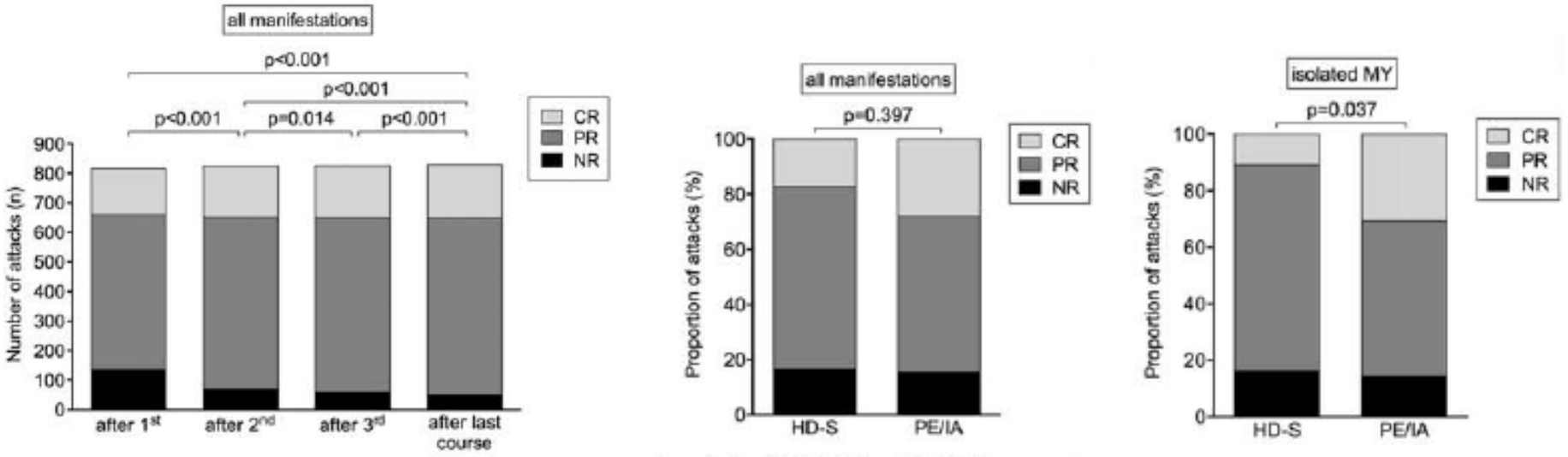
Pas d'efficacité des interferons, du Gilenya ni Tysabri (toxique?)

Futur :
- Anti-Complément : Eculizumab (Soliris®)
- Anti interleukine 6R :Tocilizumab (Roactemra ®)
- Anti CD 19

Traitement des poussées

Neuromyelitis Optica: Evaluation of 871 Attacks and 1,153 Treatment Courses

Ingo Kleiter, MD,[1] Anna Gahlen, BMed,[1] Nadja Borisow, MD,[2] Katrin Fischer, MD,[3]



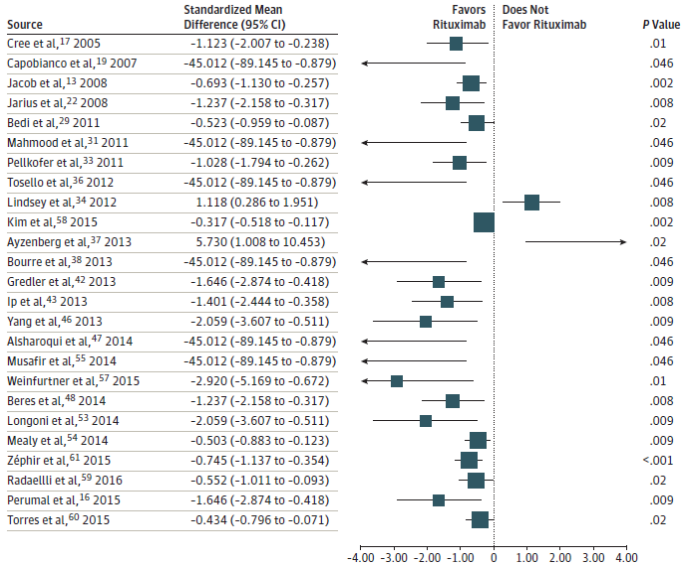
Sévérité des poussées de NMOSD
Intérêt d'un traitement de deuxième ligne
Intérêt des échanges plasmatiques: notamment en cas de Myélites +++

Intérêt du Rituximab (RTX)

+ :Rationnel physiopathologique : antiCD20 (anti-LB)

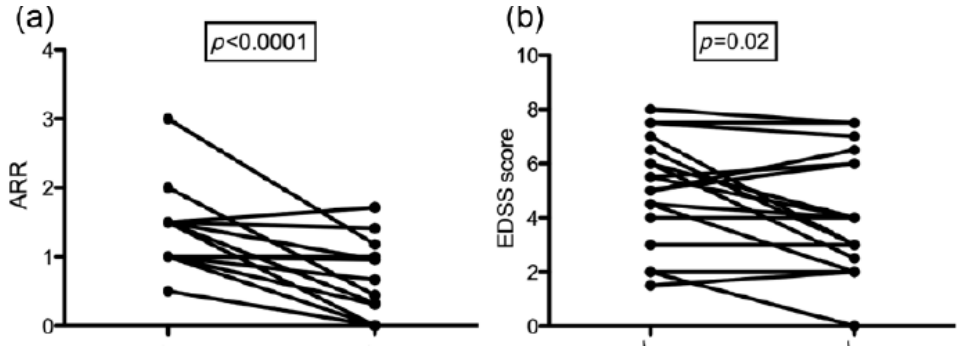
Simplicité d'utilisation ; perfusions semestrielles ou adaptés au CD19/CD27+

Efficacité en 1er intention mais aussi en « rescue therapy »



Source	Standardized Mean Difference (95% CI)	P Value
Cree et al,[17] 2005	-1.123 (-2.007 to -0.238)	.01
Capobianco et al,[19] 2007	-45.012 (-89.145 to -0.879)	.046
Jacob et al,[13] 2008	-0.693 (-1.130 to -0.257)	.002
Jarius et al,[22] 2008	-1.237 (-2.158 to -0.317)	.008
Bedi et al,[29] 2011	-0.523 (-0.959 to -0.087)	.02
Mahmood et al,[31] 2011	-45.012 (-89.145 to -0.879)	.046
Pellkofer et al,[33] 2011	-1.028 (-1.794 to -0.262)	.009
Tosello et al,[36] 2012	-45.012 (-89.145 to -0.879)	.046
Lindsey et al,[34] 2012	1.118 (0.286 to 1.951)	.008
Kim et al,[58] 2015	-0.317 (-0.518 to -0.117)	.002
Ayzenberg et al,[37] 2013	5.730 (1.008 to 10.453)	.02
Bourre et al,[38] 2013	-45.012 (-89.145 to -0.879)	.046
Gredler et al,[42] 2013	-1.646 (-2.874 to -0.418)	.009
Ip et al,[43] 2013	-1.401 (-2.444 to -0.358)	.008
Yang et al,[46] 2013	-2.059 (-3.607 to -0.511)	.009
Alsharoqui et al,[47] 2014	-45.012 (-89.145 to -0.879)	.046
Musafir et al,[55] 2014	-45.012 (-89.145 to -0.879)	.046
Weinfurtner et al,[57] 2015	-2.920 (-5.169 to -0.672)	.01
Beres et al,[48] 2014	-1.237 (-2.158 to -0.317)	.008
Longoni et al,[53] 2014	-2.059 (-3.607 to -0.511)	.009
Mealy et al,[54] 2014	-0.503 (-0.883 to -0.123)	.009
Zéphir et al,[61] 2015	-0.745 (-1.137 to -0.354)	<.001
Radaelli et al,[59] 2016	-0.552 (-1.011 to -0.093)	.02
Perumal et al,[16] 2015	-1.646 (-2.874 to -0.418)	.009
Torres et al,[60] 2015	-0.434 (-0.796 to -0.071)	.02

Ioro et al. 2016

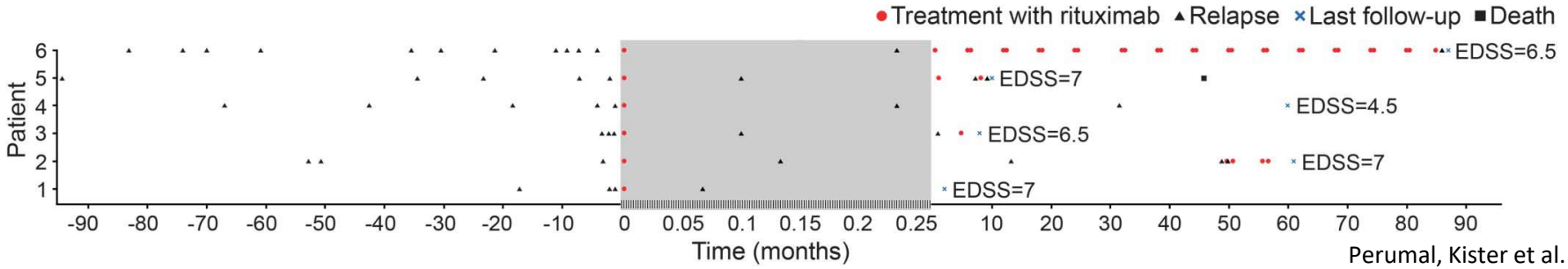


Collongues et al. 2015

-: Risque infectieux/problématique des vaccinations

Tolérance à l'infusion

Echappement ou effet paradoxal chez certains patients?



Perumal, Kister et al. 2015

NMO 2017 : Take home messages

- **Nouveaux critères diagnostiques : NMOSD**
  - Homogénéité
  - + grand nombre de patients

  Faciliter la pratique clinique, études épidemio
  - Quid des NMOSD AQP4-IgG négatifs? Des MOG-IgG?

- **Prise en charge + active des poussées**
  - PLEX en première intention?
  - Intérêt de l'immunoadsorption?

- **Intérêt du Rituximab**
  - Pas de consensus sur son utilisation
  - Echappement, effet paradoxal
  - Résultats des premiers essais de phase III

Merci!

Des questions?