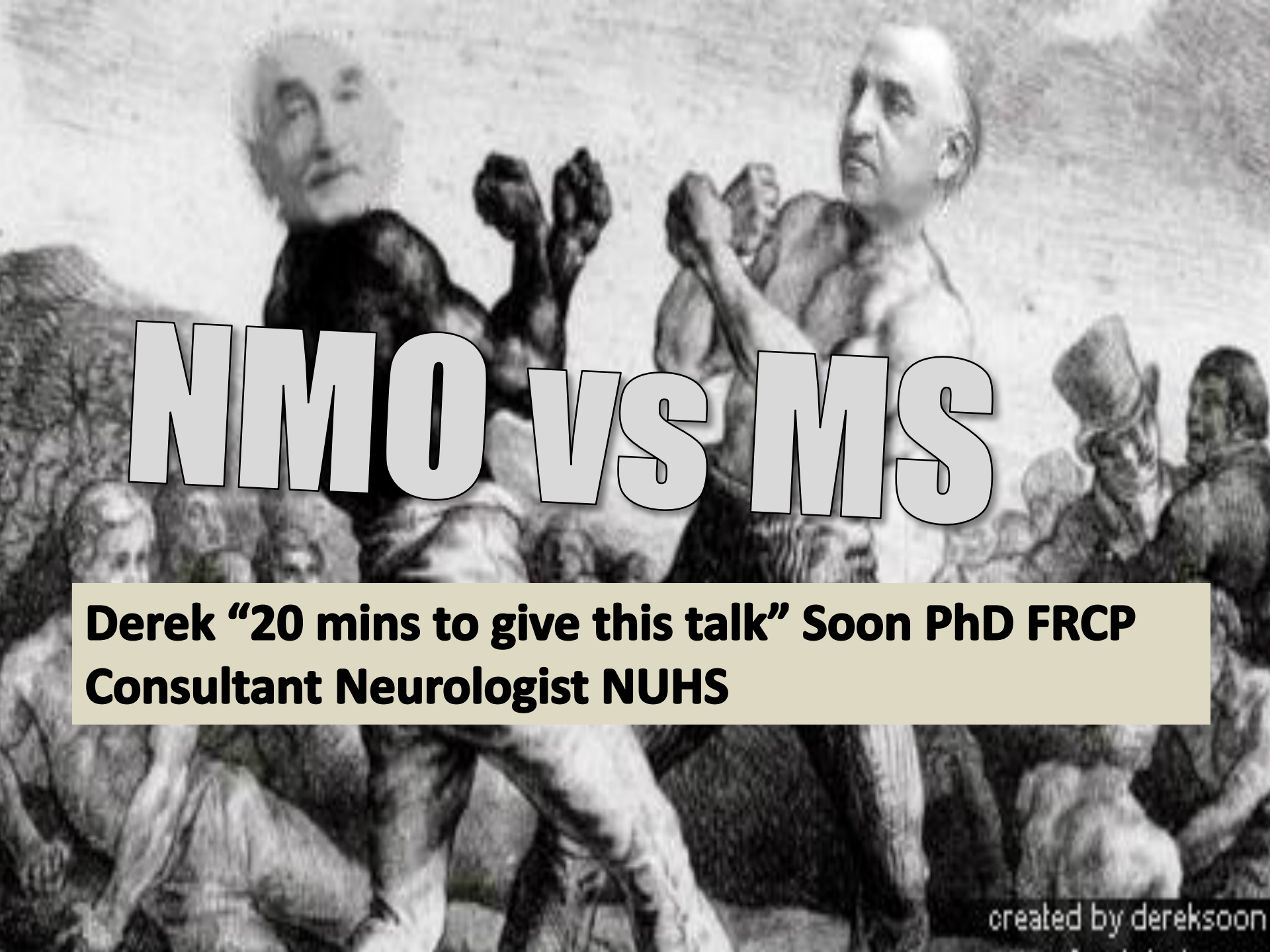


Derek "20 mins to give this talk" Soon PhD FRCP
Consultant Neurologist NUHS

Assumptions

- That you already know the conditions
  - Multiple sclerosis
  - Neuromyelitis Optica
- If not
  - Meet me later at the back and I explain to you
  - Bring beer please

Take Home Messages

MS is NOT NMO

Although they can look similar

NMO

MS

They just aren’t

if you treat an NMO patient with MS DMT

BAD THINGS HAPPEN

Shimizu *et al.*, 2010
Kim *et al.*, 2012

Prognosis markedly different

Relapsing course in 90%

In 1st 5 years

Blindness in 60%

Wingerchuk *et al.,* 1999

25 to 30% mortality

Cabre *et al.,* 2009

50% mobility difficulties

Cabre *et al.,* 2009

NMO

Whereas

RRMS 85%

MS

90% still alive at 40 years

Weinshenker *et al.,* 1989

Blindness is rare

Significant mobility impairment in 23 years

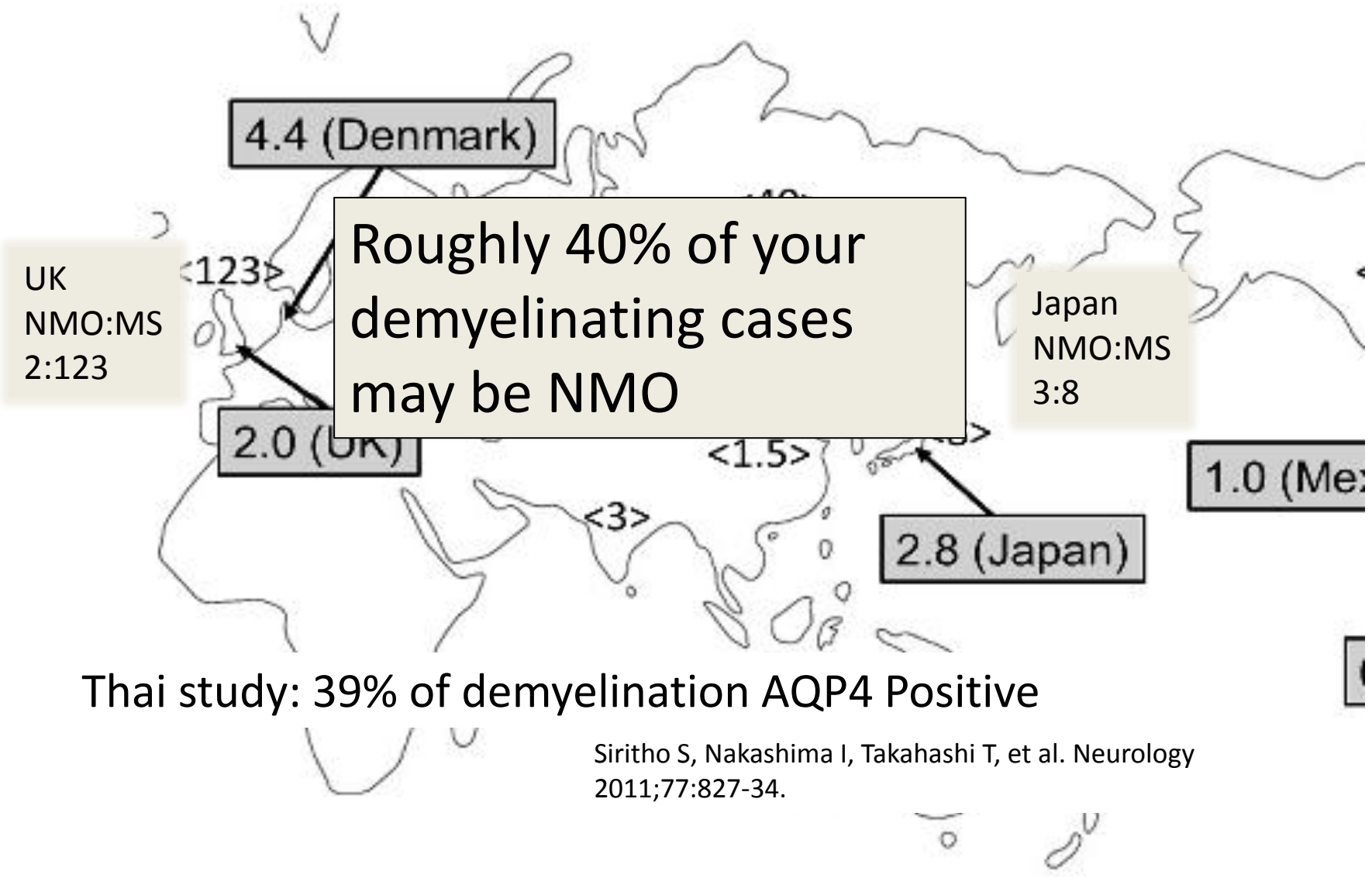
Confavreux *et al.,* 2006

So, it's important to tell the 2 apart

Implications on

1. Prognosis
2. Treatment

Especially in Asia



Thai study: 39% of demyelination AQP4 Positive

Siritho S, Nakashima I, Takahashi T, et al. Neurology 2011;77:827-34.

Uzawa *et al.,* J Clin Neurosci, 2013

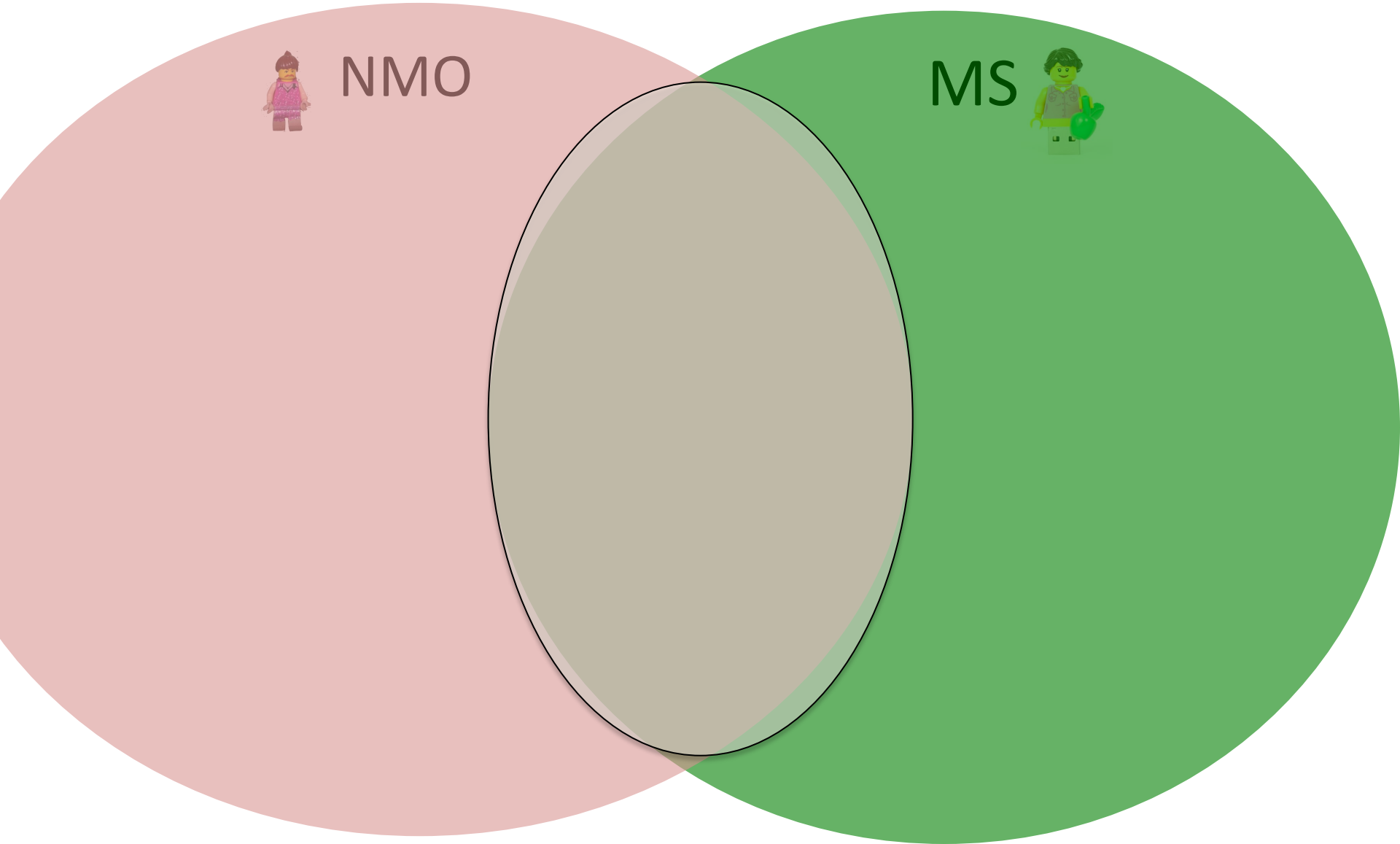
Sometimes, discernment not so easy

MS?
NMO?

Especially early in disease course

Similarities vs differences

Similarities



Similarities in clinical presentation

NMO

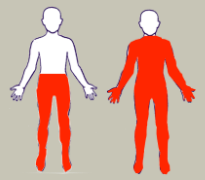
MS

Subacute onset (hours)

Inflammatory Aetiology

CNS location

Optic Nerve 

Spinal Cord 

Brainstem

Therefore consider MS/NMO if

- You have a neurological deficit that is
  - Central Nervous System in nature
  - Subacute (hours) in onset

- But other things can present this way too!
  - Infection
  - Other Autoimmunities (Sjoegren, Sarcoid)
  - (Unlikely stroke)

Differences in clinical presentation

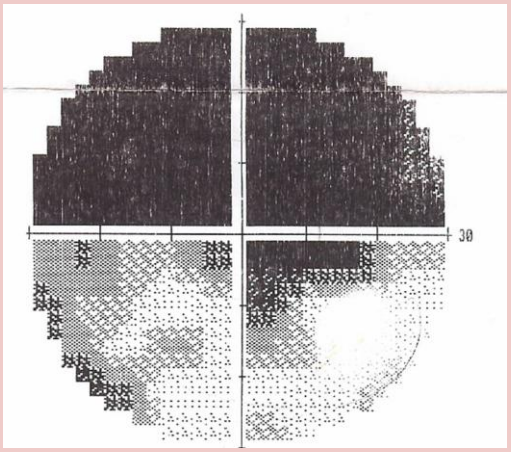
NMO

Subacute onset (hours)

MS

severe
Bilateral/recurrent unilateral

Non central scotomata
Altitudinal defect



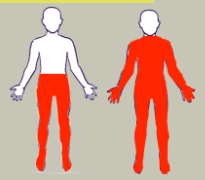
Inflammatory Aetiology

CNS location

Optic Nerve

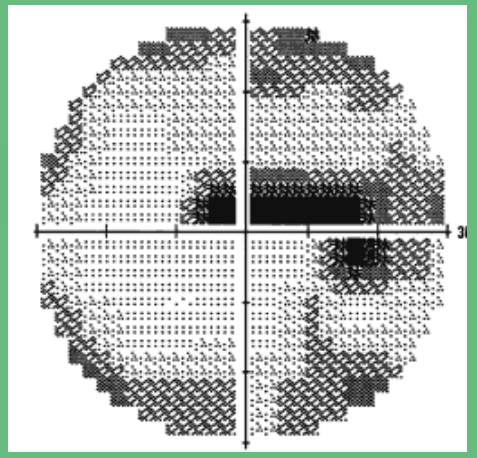
Spinal Cord

Brainstem



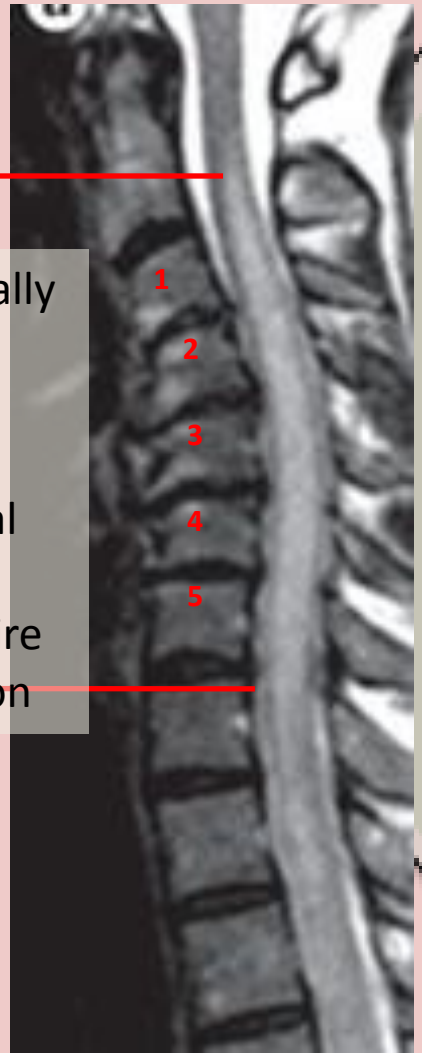
Less severe
rarely bilateral

Central scotomata/
desaturation



Differences in clinical presentation

NMO



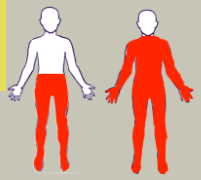
Longitudinally extensive transverse myelitis
>3 vertebral segments
Affects entire cross section

Subacute onset (hours)

Inflammatory Aetiology

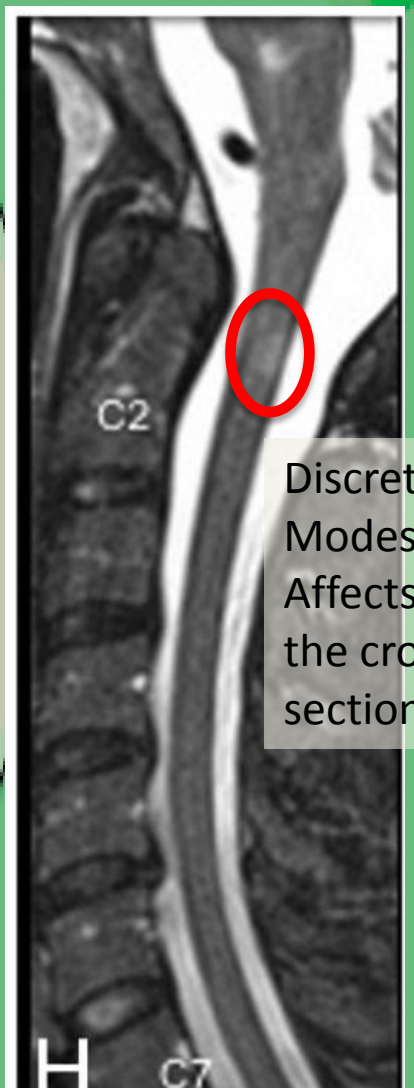
CNS location

Optic Nerve 

Spinal Cord 

Brainstem

MS



Discrete
Modest in size
Affects part of the cross section

Differences in clinical presentation

NMO

Frequently extension of cord lesion- lower brainstem

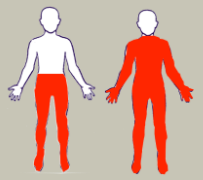
Hiccups and Vomiting

Subacute onset (hours)

Inflammatory Aetiology

CNS location

Optic Nerve 

Spinal Cord 

Brainstem

MS 

Ataxia

Vertigo

Diagnosis (diagnostic criteria)

MS

- CNS
- Dissemination in time
- Dissemination in space
- Exclusion of other pathologies/mimics
- (but more of that later)

~~Neuromyelitis optica~~
~~ADEM~~
~~SLE~~
~~Antiphospholipid syndrome~~
~~Sjoegren syndrome~~
~~Stroke~~

MS diagnosis through the years

Criteria	Dissemination in time and space		Paraclinical/CSF	Exclusion of other conditions	Comments
	Clinical	MRI			
Schumacher 1956	✓			✓	
Poser 1983	✓		✓	✓	CSF CT scan VEP
McDonald 2001 2010	✓	✓	✓	✓	Heavy use of MRI CSF still for PPMS

The beauty of McDonald Criteria is it is now possible to diagnose MS at 1st clinical episode

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Brenda Banwell, MD,[3]

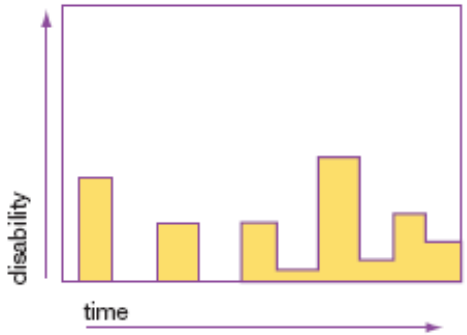
Sensitive and specific when applied to 1st episode

TABLE 4: The 2010 McDonald Criteria for Diagnosis of MS

Clinical P	
≥2 attack evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

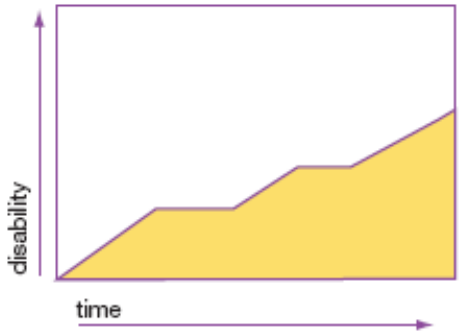
MADE SIMPLE

MacDonald Criteria Applied To Diagnose



Relapsing Disease

1. Clinical or MRI demonstration of
    1. Dissemination in space
    2. Dissemination in time
2. Exclusion of other pathologies



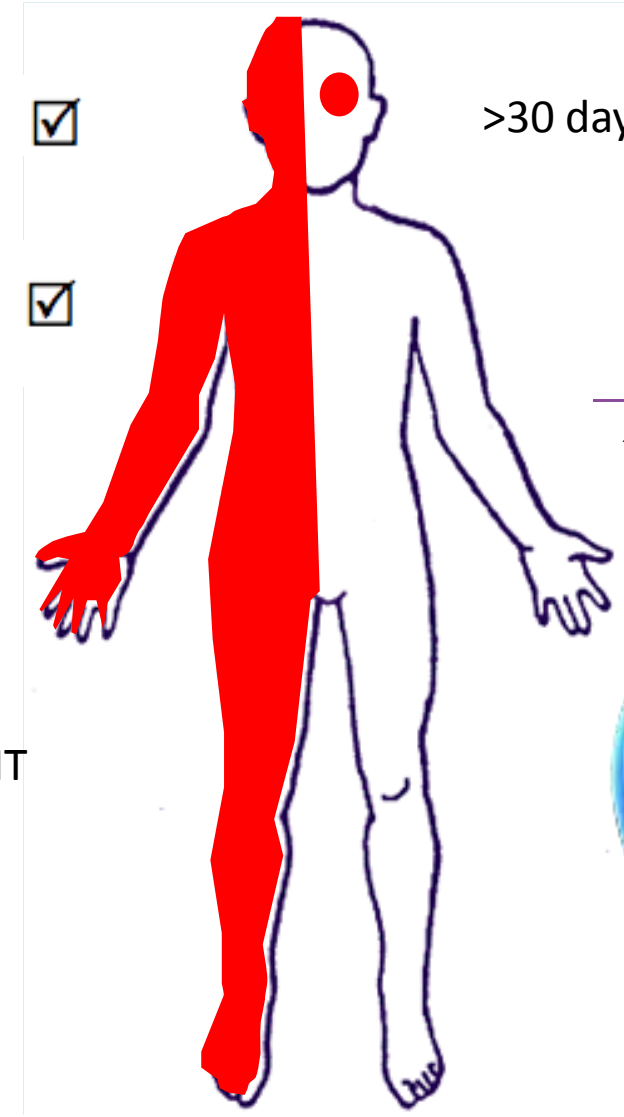
PPMS

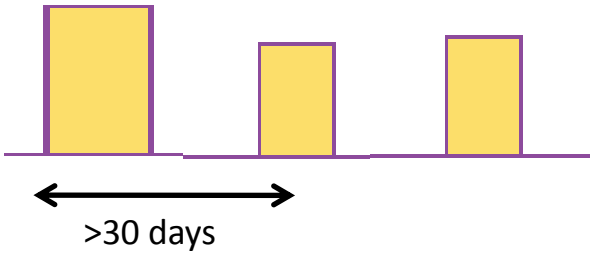
1. Clinical demonstration of progression in the last year
2. 2 of the 3 following
    1. Typical brain lesion (JC/PV/PF)
    2. 2 cord lesions
    3. CSF oligoclonal bands

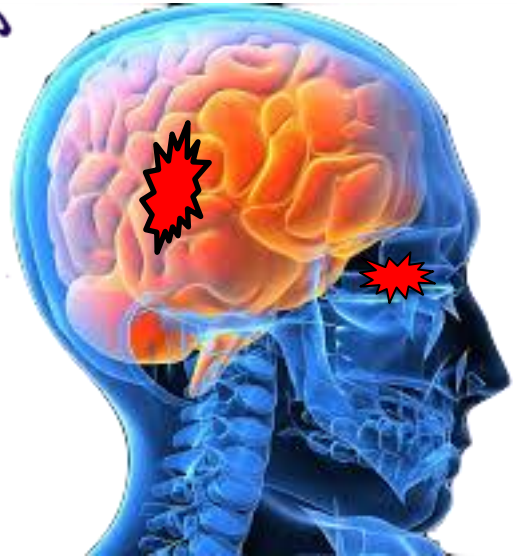
Clinical Criteria for dissemination in time and space: RRMS

Dissemination in time ☑ >30 days later

Dissemination in space ☑







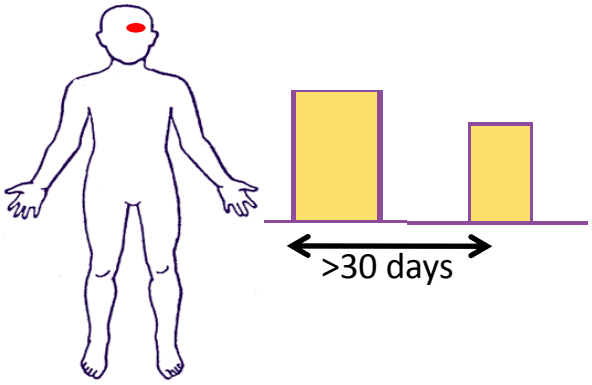
In order to diagnose MS

1. Solid clinical evidence of DIS/DIT
2. Exclusion of other pathologies

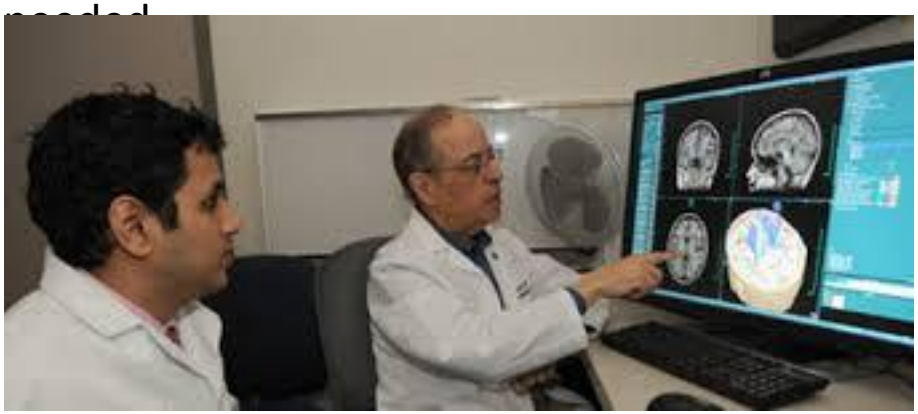
Is sufficient

But often not all clinical criteria are met

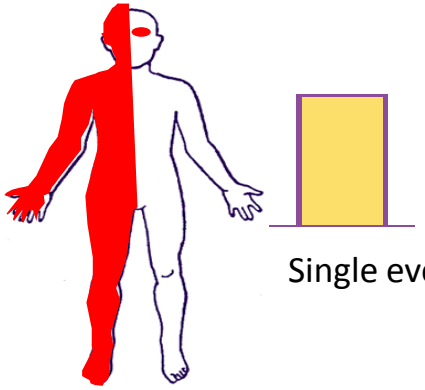
Dissemination in time ☑
Dissemination in space ☐



In such instances, MRI evidence, **<u>in consultation with a good neuroradiologist</u>** is needed



Dissemination in time ☐
Dissemination in space ☑



Sequences
MR Brain (T2, T1 pre and post Gad)
MR Spine

MRI criteria in RRMS

TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:
Periventricular
Juxtacortical
Infratentorial
Spinal cord[b]

Based on Swanton et al 2006, 2007.[22,27]
[a]Gadolinium enhancement of lesions is not required for DIS.
[b]If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.
MRI = magnetic resonance imaging; DIS = lesion dissemination in space; CNS = central nervous system.

TABLE 2: 2010 McDonald MRI Criteria for Demonstration of DIT

DIT Can Be Demonstrated by:
1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Based on Montalban et al 2010.[24]
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

Any 2, Any new

MRI Dissemination in Space

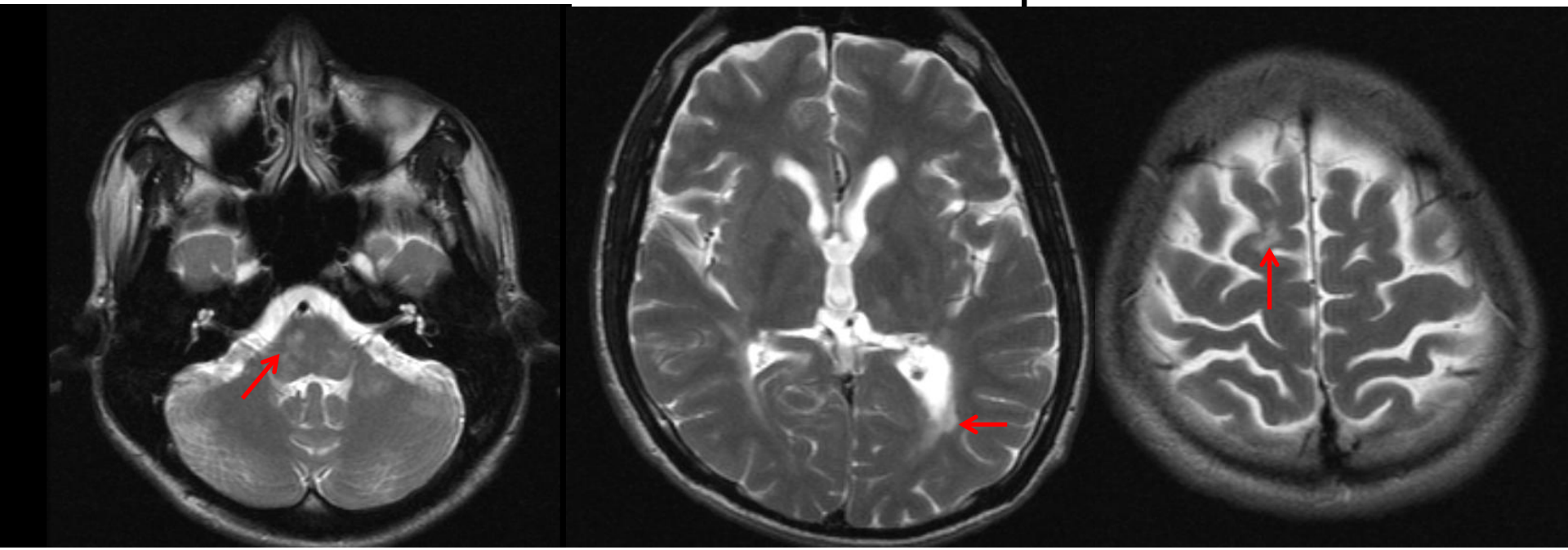


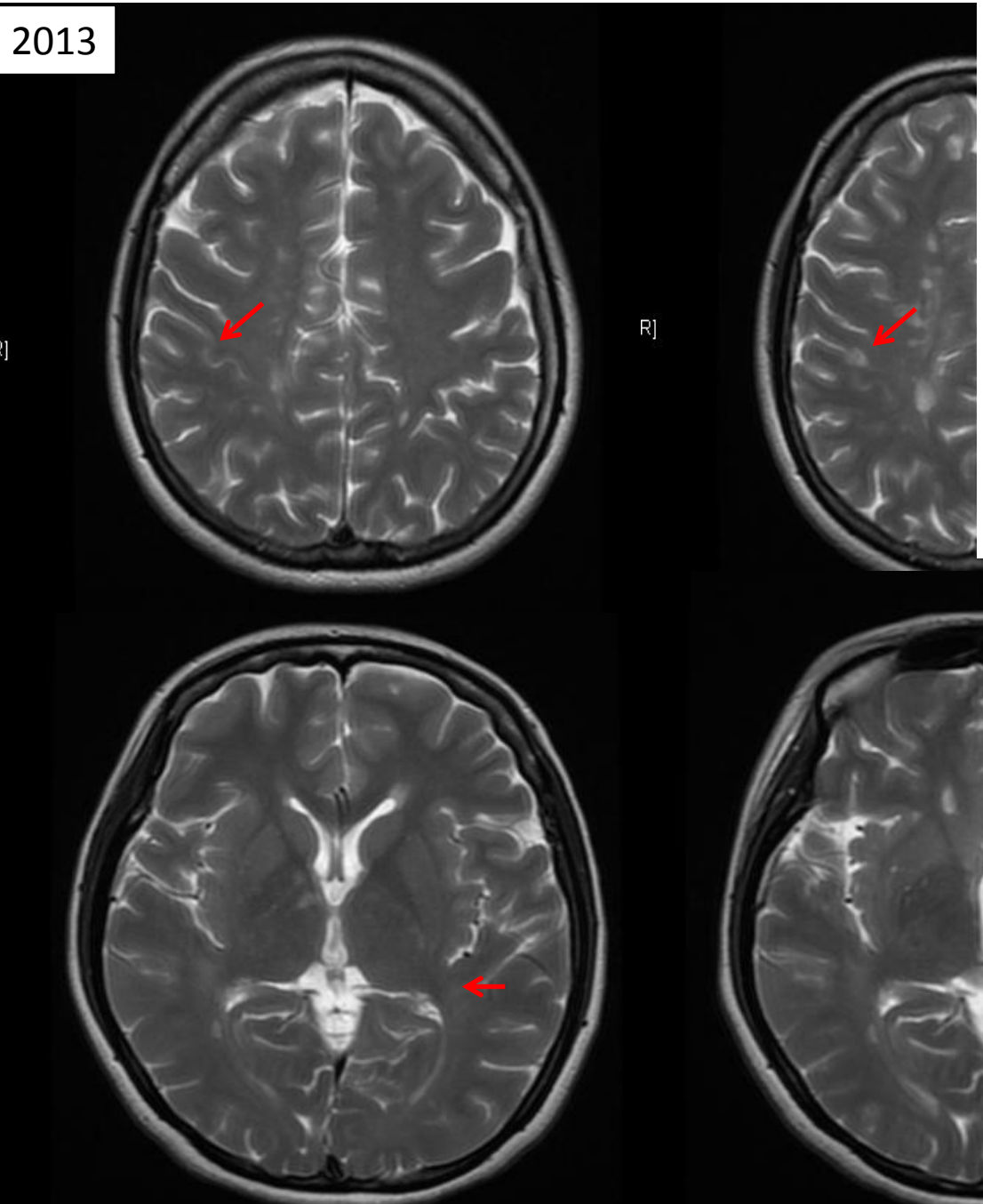
TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:
Periventricular
Juxtacortical
Infratentorial
Spinal cord[b]

Any 2

MRI dissemination in time

2013



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DIT Can Be Demonstrated by:

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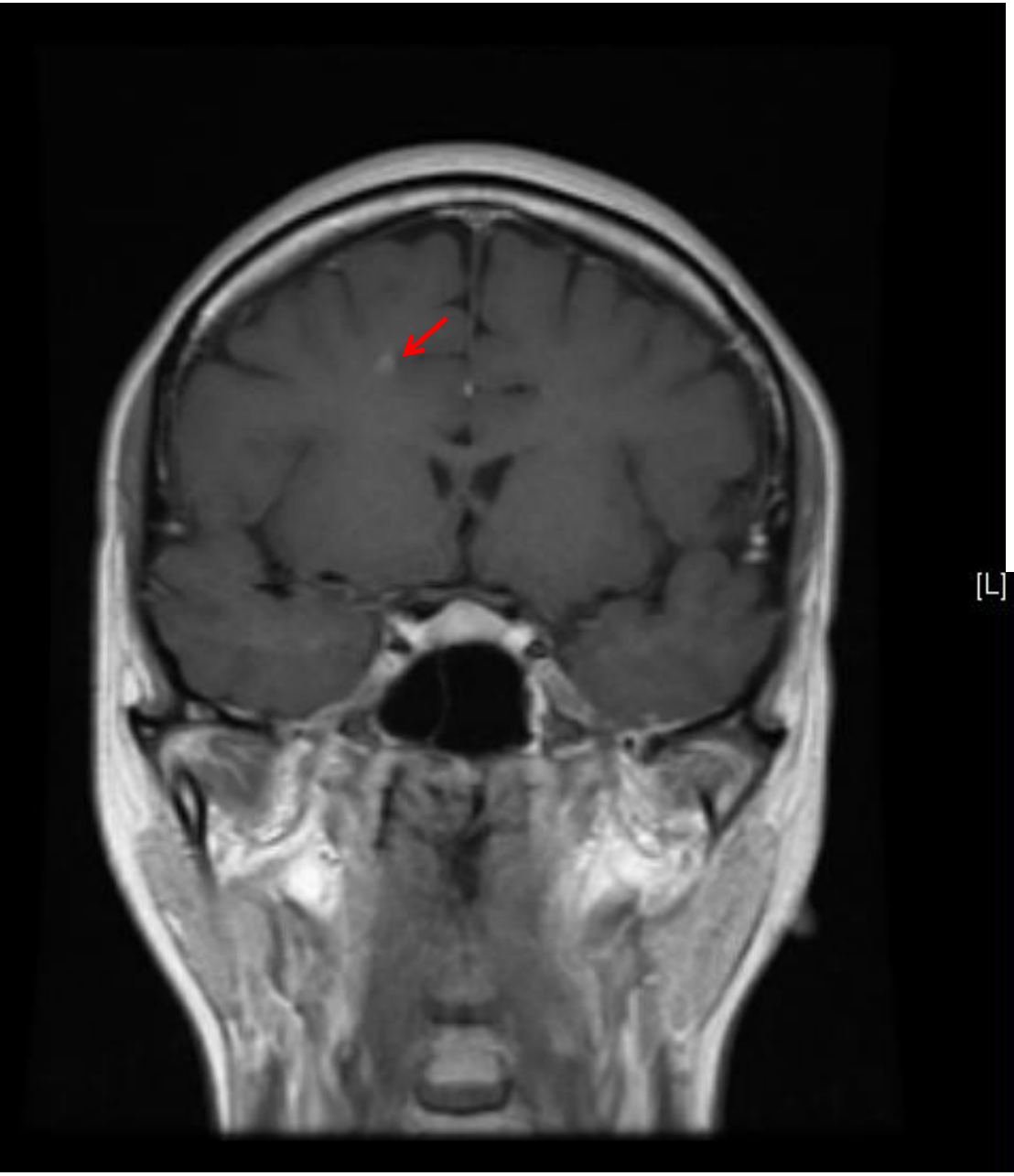
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Based on Montalban et al 2010.[24]
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

Any new

MRI dissemination in time



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2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Based on Montalban et al 2010.[24]
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

In a patient with cerebellar symptoms and no hemiparesis

Diagnosis of NMO

Table 3 *Proposed diagnostic criteria for neuromyelitis optica (NMO)*

Definite NMO

Optic neuritis

Acute myelitis

At least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

Wingerchuk 2006

About Wingerchuk Criteria

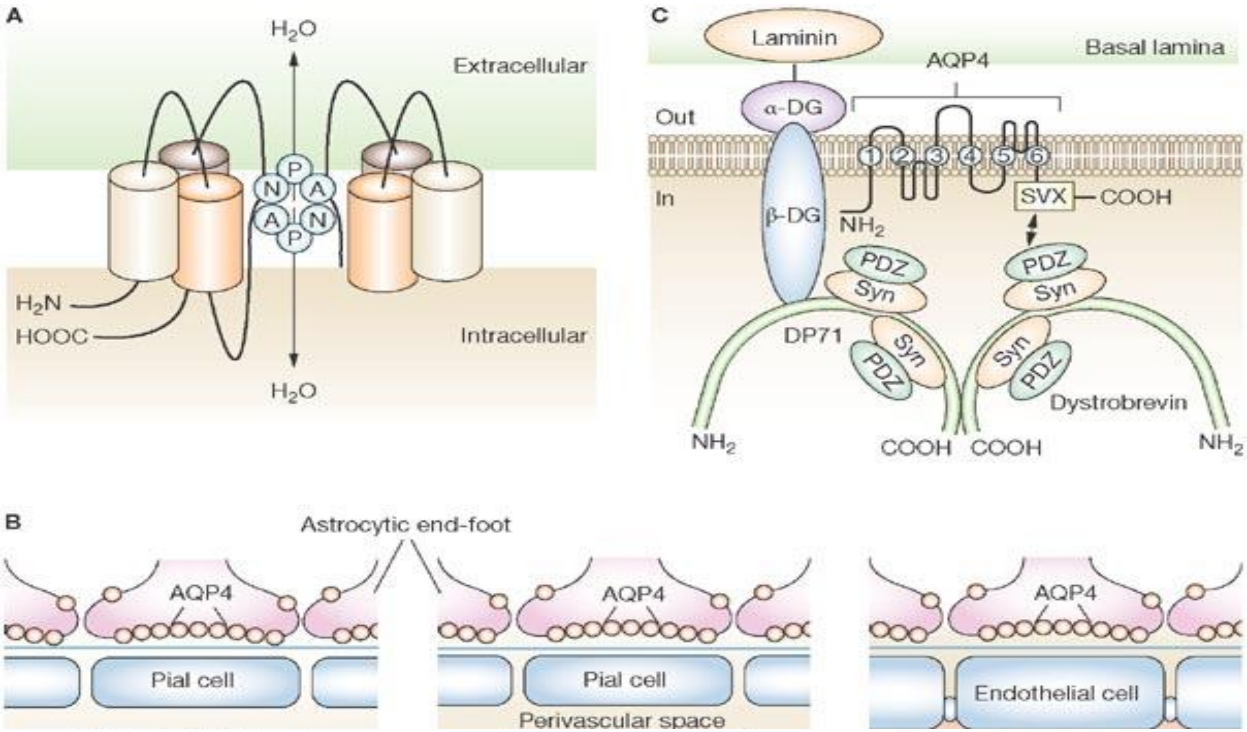
- Leverage on the following
  - LETM is very rarely seen in MS
  - NMO has relatively few brain lesions- if early in the disease
  - Specificity of NMO IgG

NMO IgG

Antibody binds to Aquaporin 4 water channel

Aquaporin 4 found in high concentrations in ON, subependymal tissues, area postrema

Antibody binding leads to complement mediated destruction of astrocytic foot processes



Jarius S *et al*. (2008) *Nat Clin Pract Neurol*

Different ways of detecting NMO IgG, more sensitive measures- include cell based assays
80% sensitivity, close to 100% specificity

If you have NMO IgG

1. You have NMO/NMOSD
2. You will have a worse form of the disease with heightened severity and disabilty

Diagnosis of NMO

Table 3 *Proposed diagnostic criteria for neuromyelitis optica (NMO)*

Definite NMO

Optic neuritis

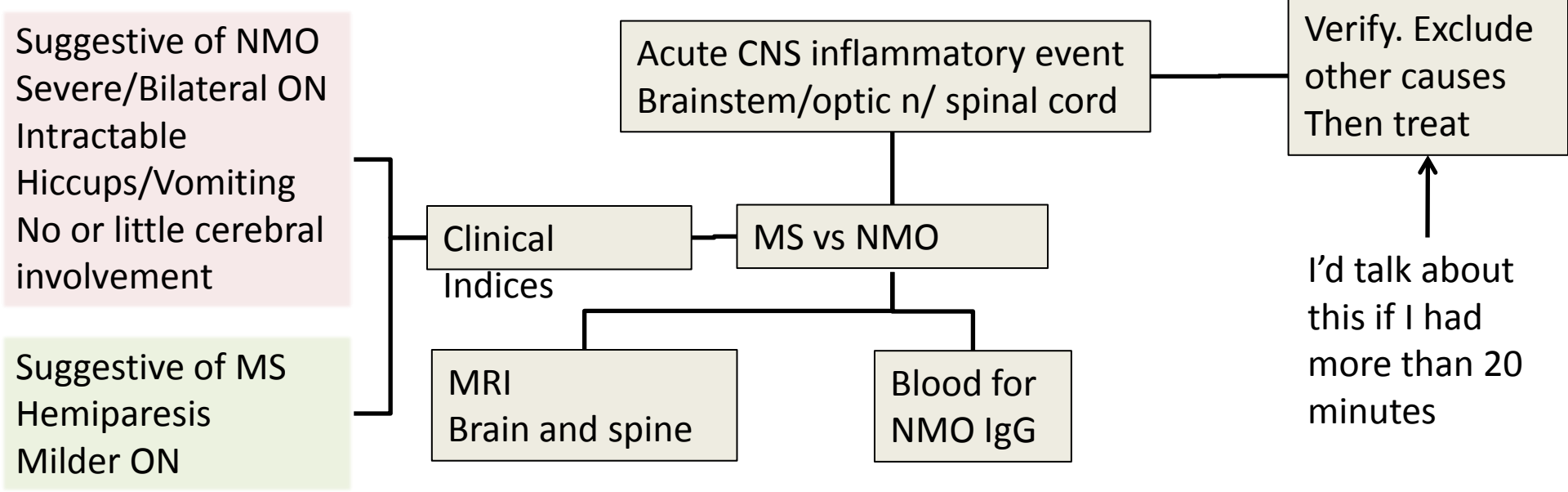
Acute myelitis

At least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

Wingerchuk 2006

Putting it all together



MS diagnosed if:

1. Dissemination in Time
2. Dissemination in space
3. Other entities excluded

NMO diagnosed if:

1. Optic Neuritis AND Transverse myelitis

And 2 out of 3

1. LETM
2. NMO IgG
3. Early MRI not in keeping with MS

Let’s play: MS vs NMO vs others

You can refer to the diagnostic criteria in your handouts to help you

Ready your ARS

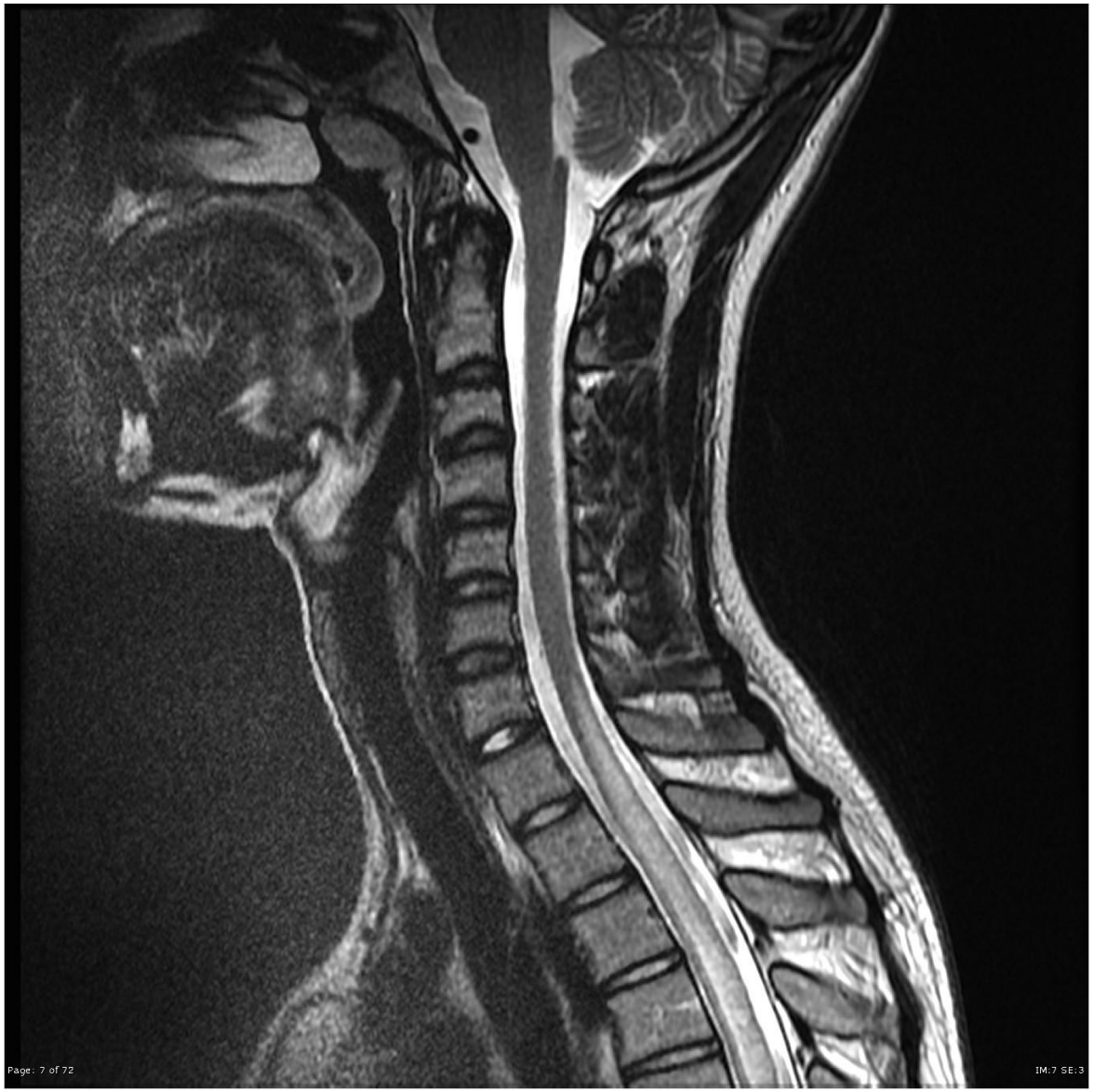
Case 1

- 20 year old girl
- Half a day onset of sensation alteration
- From umbilicus down, everything feels cold
- “my legs feel frozen”
- Brisk lower limb reflexes, upgoing plantars
- She has difficulty peeing: “I just can’t let it go”

Where is the lesion?

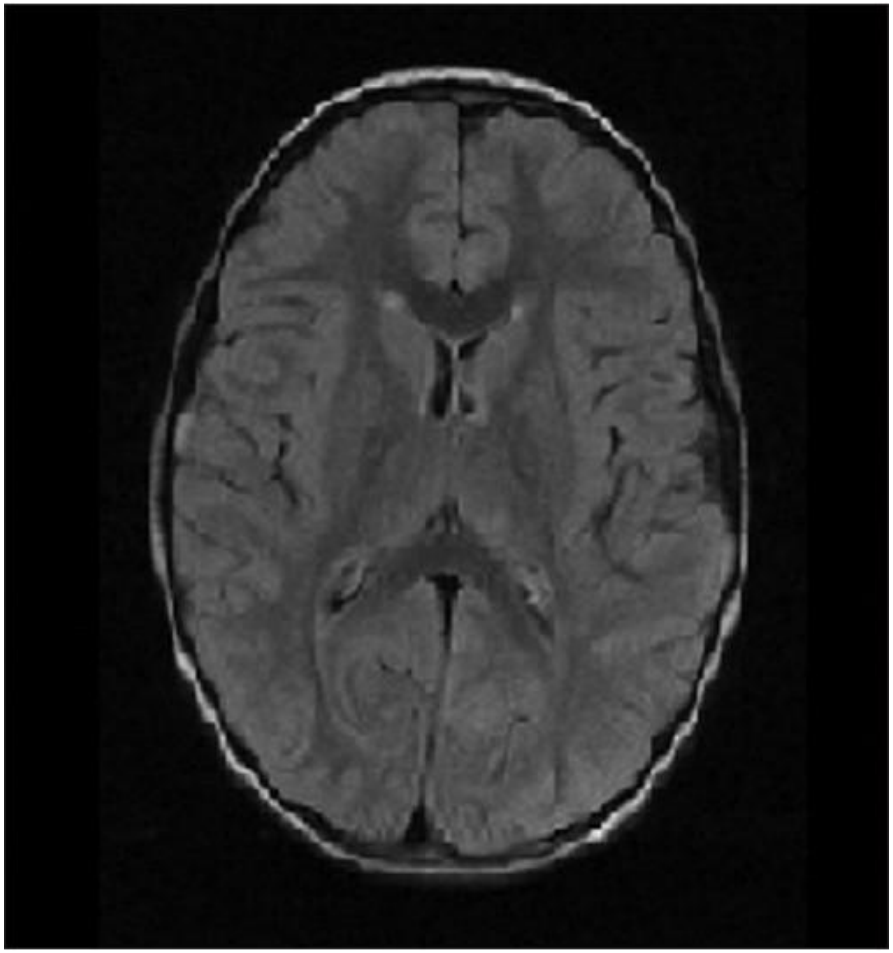
1. Brainstem
2. Spinal cord
3. Peripheral nerves
4. Disneyland
5. In her mind (psychogenic)

She has an MRI of her cord



Spot the abnormality

And of her brain



No lesions on T2 or FLAIR

What do you think it’s gonna be?

1. MS
2. NMO
3. Something else

What would be the highest value investigation?

1. Visual evoked response
2. Repeat MRI in 1 month's time
3. Aquaporin 4 antibodies
4. CSF oligoclonal bands

then

- Repeat MRI in 1 month's time- no change
- VEPs negative
- CSF result- negative for oligoclonal bands
- **NMO antibody positive**
- 3 months later she presents with visual loss in right eye

Diagnosis of NMO

Table 3 *Proposed diagnostic criteria for neuromyelitis optica (NMO)*

Definite NMO

Optic neuritis

Acute myelitis

At least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

Wingerchuk 2006

Scenario 2

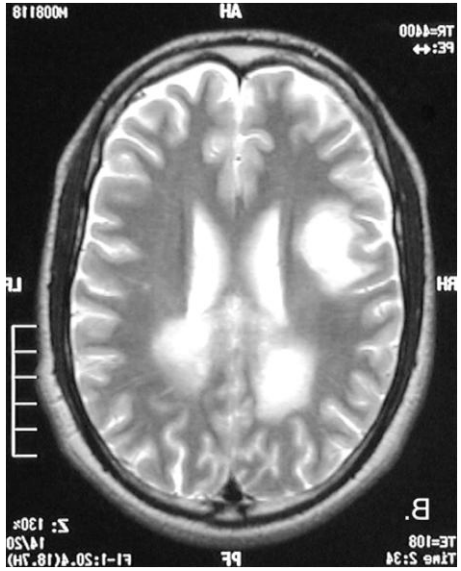
20 year old girl

4 weeks ago had a corhyzal illness

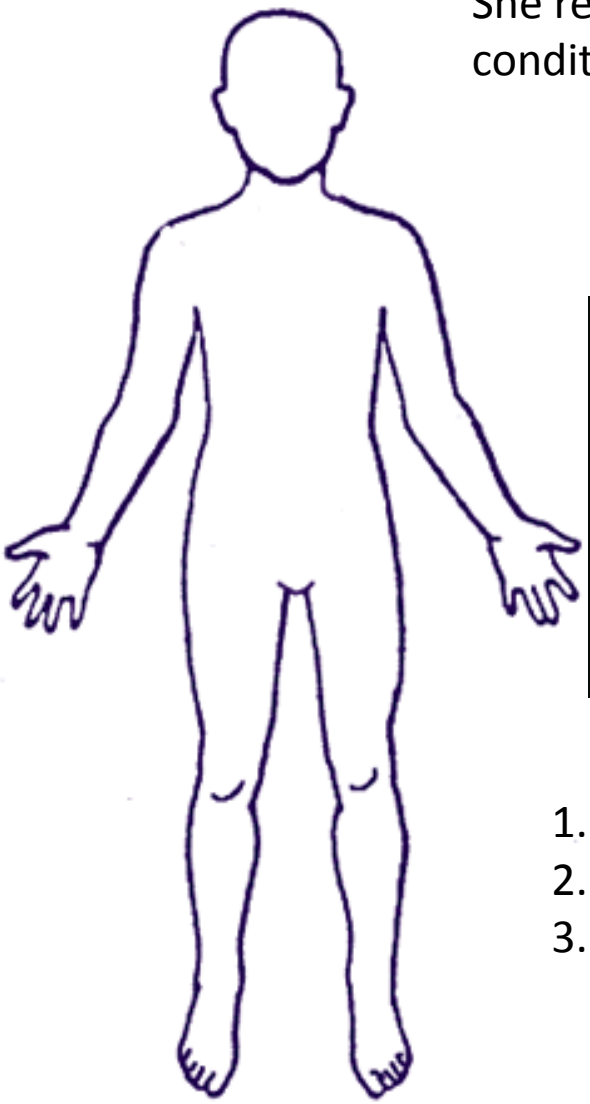
Now presents with gradual onset

Right hemiparesis (UMN)

Confusion

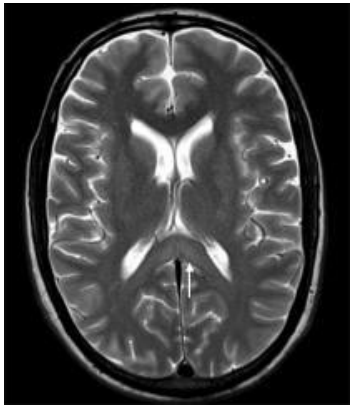


MRI shows scattered <u>fluffy</u> enhancing WM lesions of same age



She receives steroids and her condition improves

Repeat MRI shows resolution of lesions



1. MS?
2. NMO?
3. Something else?

ADEM

- Acute disseminated encephalomyelitis
- Post-infectious encephalomyelitis
- Often a CSF pleocytosis and elevated CSF protein observed
- MRI shows lesions all of the same age
- Monophasic illness

Scenario 3

30 year old man

2010 Subacute onset vertigo, diplopia

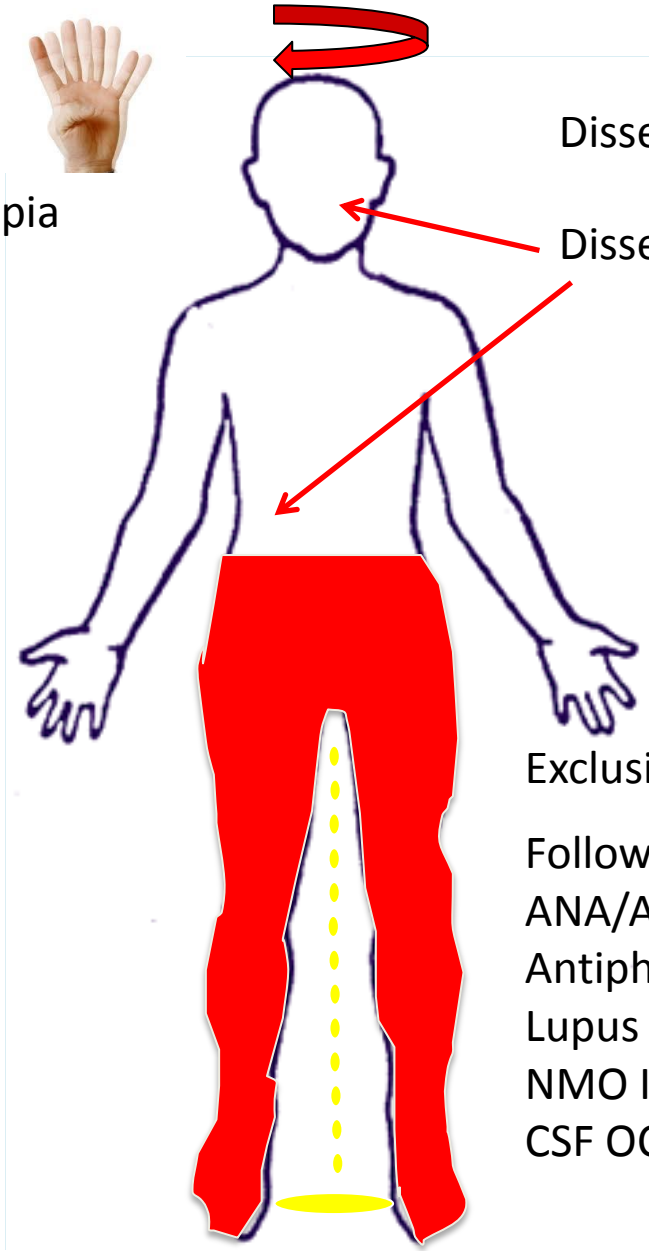
Resolution with IVMP

2012 spastic paraparesis

MRI findings
"in keeping with demyelination"

12 months later, new lesions

a. MS
b. NMO
c. Something else



Dissemination in Time? ☑

Dissemination in Space? ☑

Exclusion of other pathology ☑

Following screens done
ANA/ANCA/ENA
Antiphospholipid Ab
Lupus anticoagulant
NMO IgG
CSF OCB positive

Scenario 4

35 year old lady

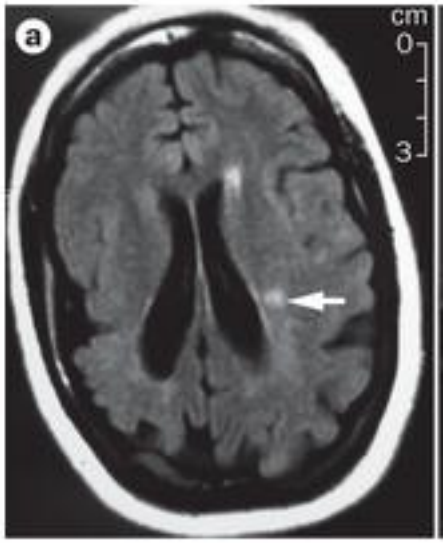
2010 right hemiparesis

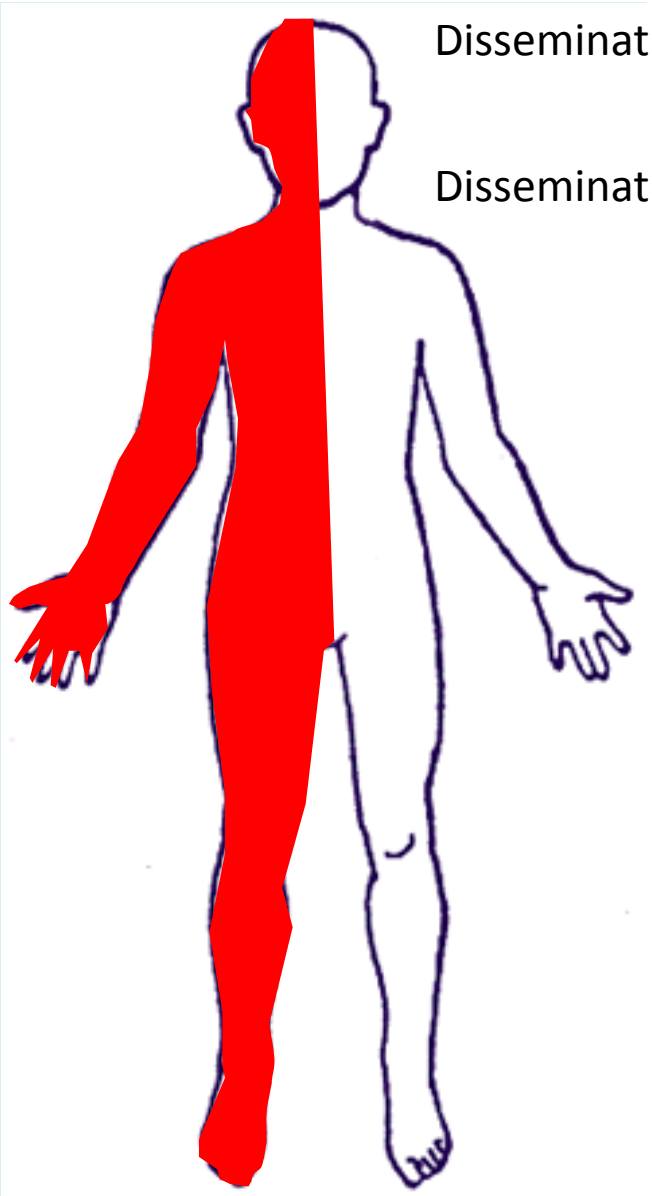
2012 Left cerebellar features

2013 Seizures

2014 joint pain, violaceous rash

On examination- Absent reflexes





Dissemination in Space?

Dissemination in Time?

1.MS?
2.NMO?
3. Something else?

Then

- ANA and ds DNA positive

Lupus

- Multi-systemic (skin, joint)
- Can manifest with CNS and PNS
- Seizures (rare in MS)
- Psychiatric manifestations

Take home points

- Both MS and NMO are CNS disorders
- There are ways of differentiating the 2
- Also beware of mimics

Handout (crib sheet) for Dr Derek Soon's talk

2010 MacDonald Criteria for diagnosis of MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Criteria also specify that all potential differentials are excluded

Wingerchuk (2006) Criteria for NMO

Table 3 *Proposed diagnostic criteria for neuromyelitis optica (NMO)*

Definite NMO

Optic neuritis

Acute myelitis

At least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status