CASE STUDIES IN DEMYELINATING DISEASE

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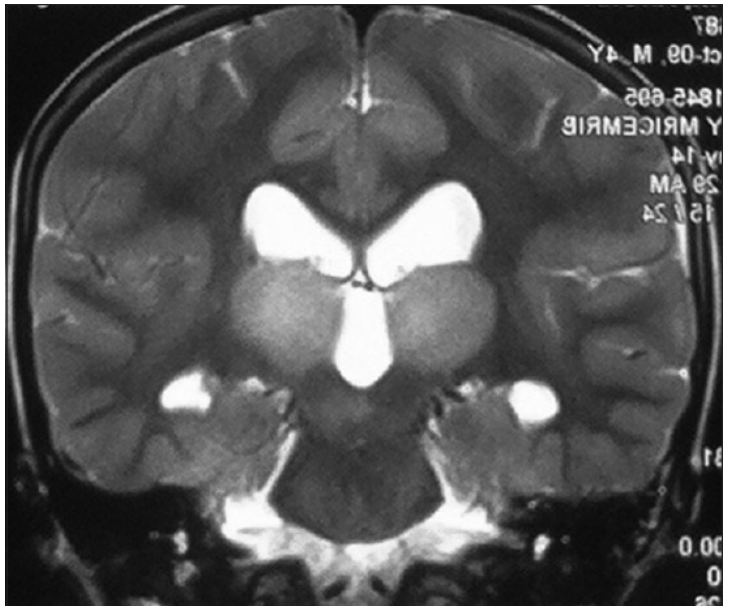
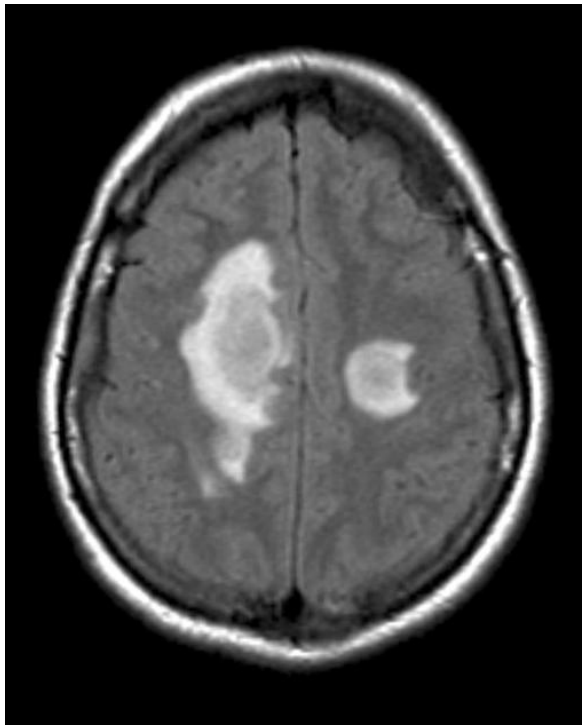
IDIOPATHIC INFLAMMATORY DEMYELINATING DISORDERS

Case 1

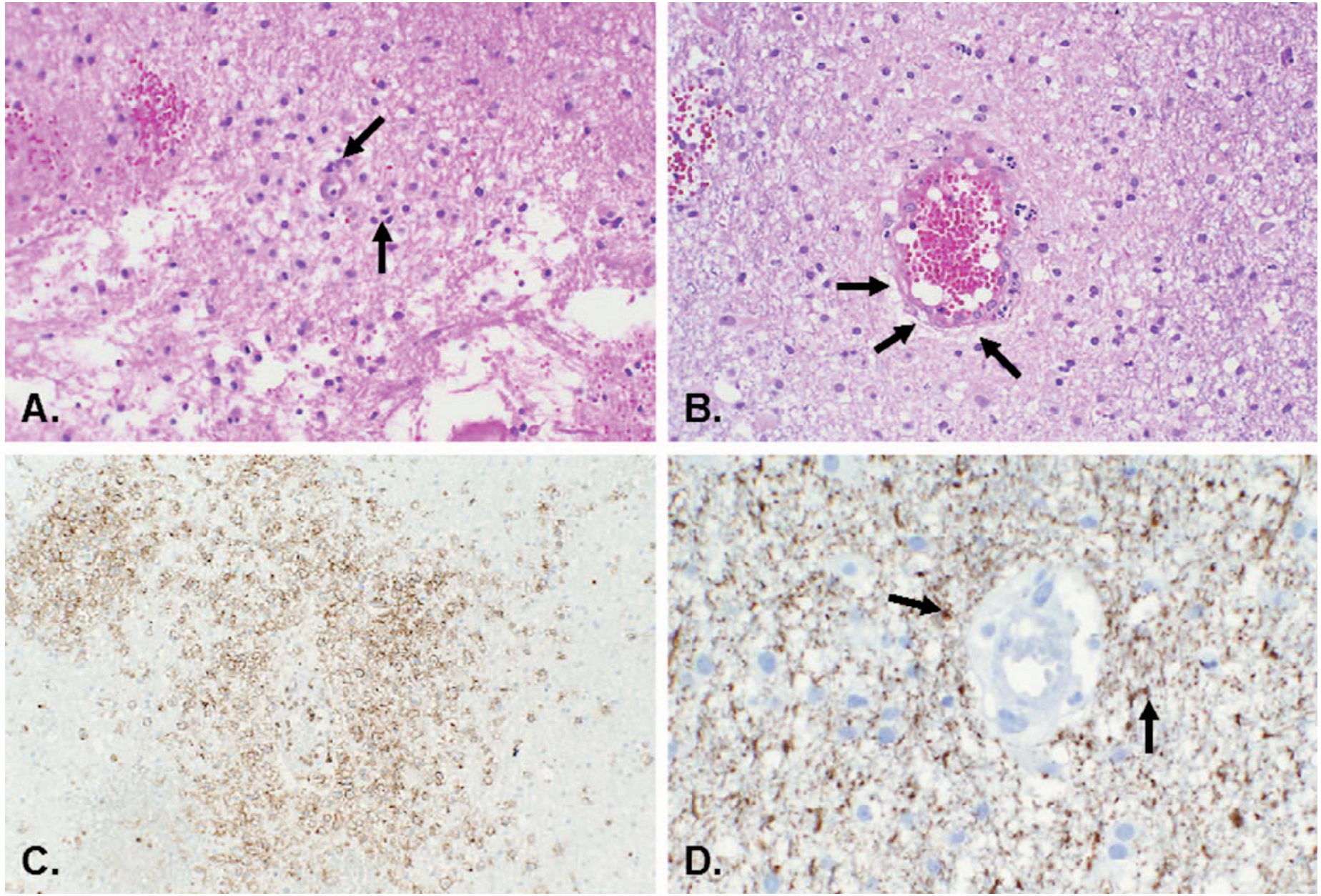
- This is a 7 year-old boy who presents with 2 days of worsening lethargy, seizure, and ataxia. The boy had a viral respiratory infection 3 weeks prior to this presentation.
- A lumbar puncture was ordered and scheduled to be performed
- MRI was performed.





Acute Disseminated encephalomyelitis (ADEM)

- Autoimmune demyelinating encephalomyelitis
- Pathogenesis is likely post-infectious through cross reactivity between antibodies developed against an infecting pathogen
  - Cross reactivity of a cell-mediated response to a pathogen
- Histopathology shows cerebral edema, perivenous infiltration of lymphocytes, and demyelination
- Myeline oligodendrocyte glycoprotein (anti-MOG) associated disorder


A.
B.
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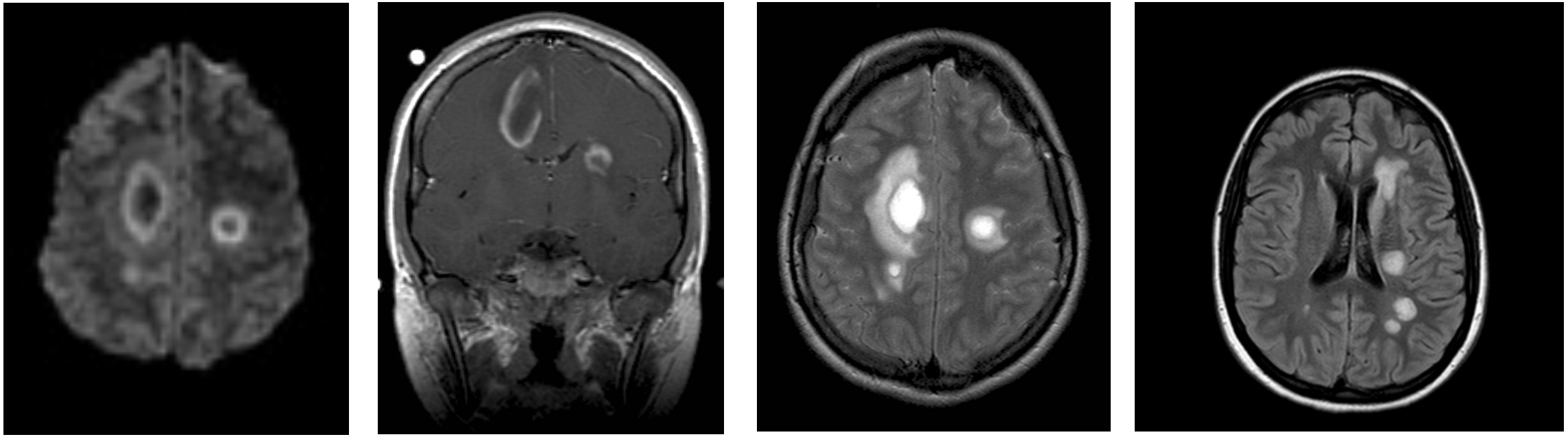
Clinical presentation ADEM

- Most cases preceded by an infection (50-70%)
  - Predominantly viral and *Mycoplasma pneumoniae*
  - Very rare cases associated with **Tdap** immunization
- Mean onset from time of infection is ~ 4 weeks but can be a few days to months
- Typical presentation
  - Infection 2-4 weeks → Encephalopathy with focal deficit
- Monophasic illness but recurrence can occur in patient with Anti-MOG Ab's

Clinical presentation ADEM

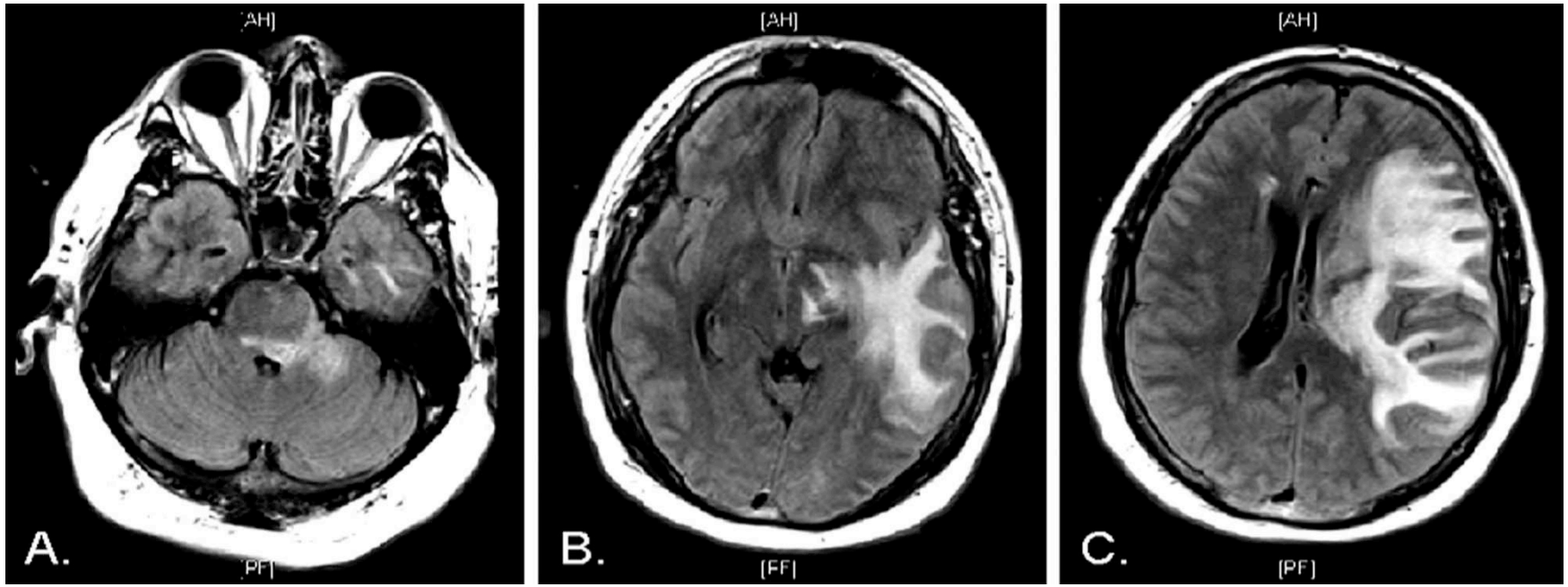
- Children
  - Diagnostic criteria for ADEM
    - A first, polyfocal clinical central nervous system event with presumed inflammatory demyelinating cause
    - Encephalopathy that cannot be explained by fever, systemic illness, or is post-ictal
    - No new clinical or MRI findings 3 months or more after initial onset
    - Brain MRI is abnormal during the 3-month acute phase
- Adult
  - Similar symptoms to children but additional symptoms may include signs of elevated intracranial pressure, ataxia, and optic neuritis

Brain findings



- Diffuse, poorly demarcated, large (>1 to 2 cm) lesions mostly involving the cerebral white matter
- Deep gray matter lesions (eg, involving the basal ganglia or thalamus) can be present
- T1 hypointense lesions in the white matter are rare

Variants



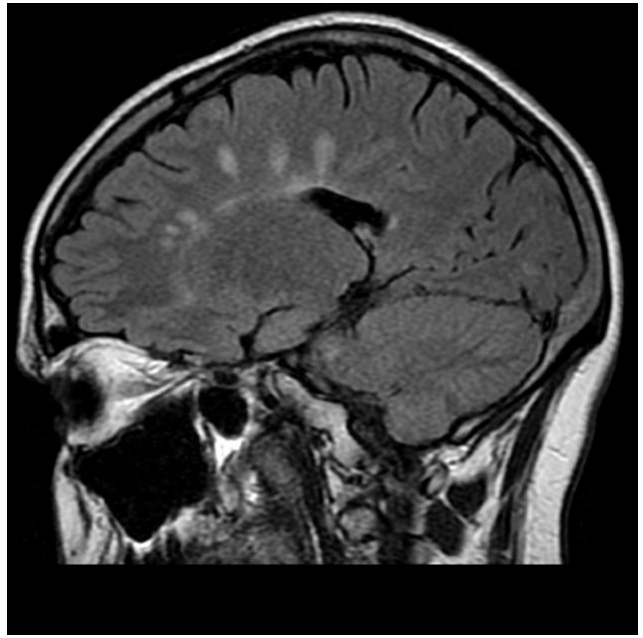
- Fulminant ADEM
- Acute hemorrhage leukoencephalitis
- ADEM with peripheral nervous involvement

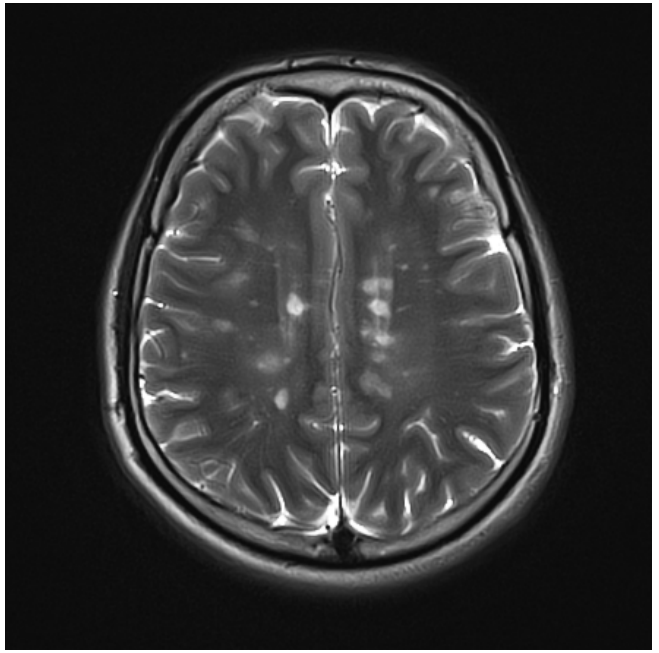
Conclusion of our case

- LP showed a mild leukocytosis, lymphocytic predominance (15 cells), and mildly elevated protein
- Given high dose methylprednisolone with significant improvement
- Adults often have a less favorable outcome
  - Could consider IVIG or plasma exchange
  - Frequent symptoms post-recovery are cognitive slowing and residual focal symptoms

Case 2

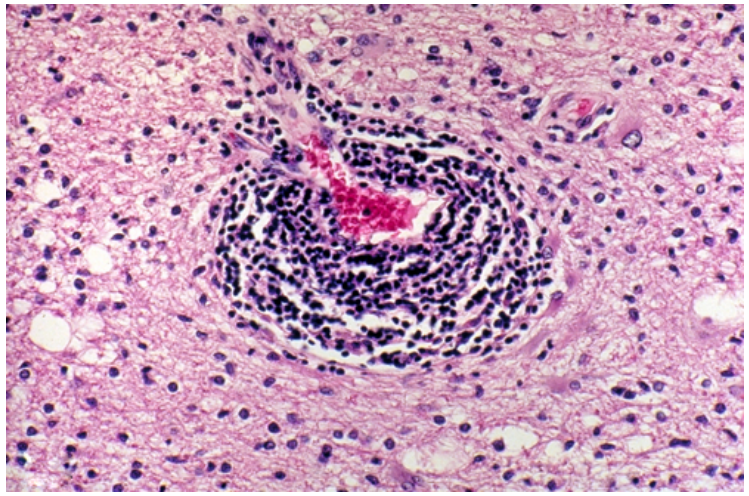
- This is a 32 year-old woman with no significant past medical history who presents with 2 days of right arm clumsiness.
- 2 months previously she experienced numbness in her left leg which had significantly but incompletely improved 1 week after onset.
- An MRI of the brain was ordered

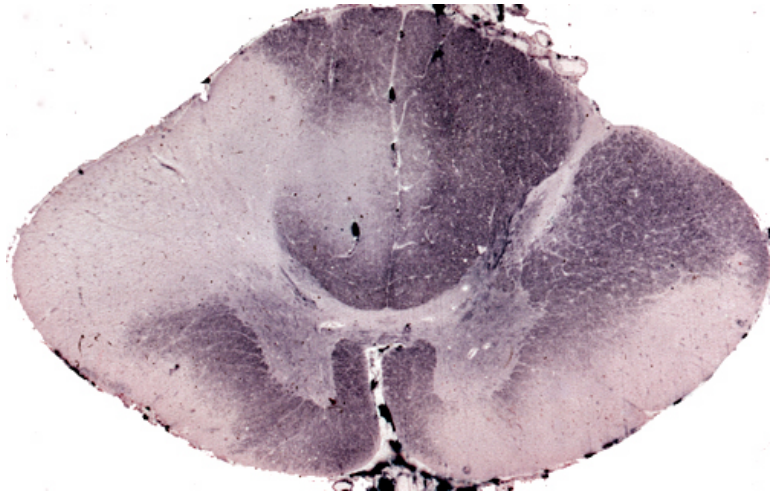




Multiple sclerosis

- The most common immune mediated inflammatory demyelinating disease of the CNS
- Multifocal areas of myelination with loss of oligodendrocytes and astroglial scarring. Axonal damage occurs but later
- Common presentation is a young adult with at least one clinically distinct episode of CNS dysfunction





Symptoms and signs	Total (percent)
Sensory in limbs	31
Visual loss	16
Motor (subacute)	9
Diplopia	7
Gait disturbance	5
Motor (acute)	4
Balance problems	3
Sensory in face	3
Lhermitte sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck)	2
Vertigo	2
Bladder problems	1
Limb ataxia	1
Acute transverse myelopathy	1
Pain	<1
Other	3
Polysymptomatic onset	

Features suggestive of multiple sclerosis
Relapses and remissions
Onset between ages 15 and 50 years
Optic neuritis
Lhermitte sign
Internuclear ophthalmoplegia
Fatigue
Heat sensitivity (Uhthoff phenomenon)
Features atypical for multiple sclerosis
Steady progression
Onset before age 10 or after age 50 years
Cortical deficits such as aphasia, apraxia, alexia, or neglect
Rigidity or sustained dystonia
Convulsions
Early dementia
Deficit developing within minutes

Types of MS

- Clinically isolated syndrome (CIS)
  - Represents the first attack of MS
  - Optic nerve – brainstem - spinal cord
- Relapsing-remitting MS (RRMS)
  - 80-85% of cases
- Secondary progressive MS (SPMS)
  - RRMS transforming into a progressive course
- Primary progressive MS (PPMS)
  - ~ 10% of cases
  - Gradual worsening with occasional plateaus
  - Resistant to therapy
- Progressive-relapsing MS (PRMS)
  - Rarest type with a progressive course but with intermittent flare-ups

Multiple sclerosis MRI diagnosis

- MS is a clinical diagnosis but MRI is crucial
  - Most commonly performed radiological modality
- MRI lesion burden and activity is incorporated in most diagnostic algorithms
- MRI of the brain and spine with contrast
  - Best sequences to visualize changes are T2 and FLAIR
  - Post-contrasted imaging can show current disease activity

	McDonald's 2010	MAGNIMS 2016	McDonald's 2017
DIS	> 1 T2 lesions in at least 2 of the 4 areas:	At least two of five areas of the CNS as follows:	At least two of five areas of the CNS as follows:
	One or more periventricular,	Three or more periventricular lesions	One or more periventricular lesions
	One or more juxta-cortical,	One or more infratentorial lesion	One or more infratentorial lesion
	One or more infra tentorial	One or more spinal cord lesion	One or more spinal cord lesion
	One or more spinal cord	One or more optic nerve lesion	One or more cortical or juxta cortical lesion
		One or more cortical or juxta cortical lesion	Includes cortical and juxta-cortical lesion for DIS
Gadolinium enhancement	Not required	Not required	Not required
Symptomatic brainstem and spinal cord lesions	Not counted	Counted	Counted except optic nerve
Optic nerve lesions	Not included	Included	Not included
Cortical lesions	Not included	Included	Included
DIT	New T2/Gd enhancing lesions on follow up MRI	New T2/Gd enhancing lesions on follow up MRI	New T2/Gd enhancing lesions on follow up MRI. Optic nerve is an exception and is not included
	Symptomatic lesions that align with an acute clinical deficit do not contribute to the dissemination in time	No distinction needs to be made between symptomatic and asymptomatic MRI lesions for dissemination in space and time	Symptomatic and asymptomatic lesions contribute to dissemination in time and space
CSF OCB as additional criteria to satisfy DIT in CIS with evidence of DIS but no evidence of DIT	No	No	Yes
Symptomatic and asymptomatic lesions included for DIS and DIT	No	Yes	Yes

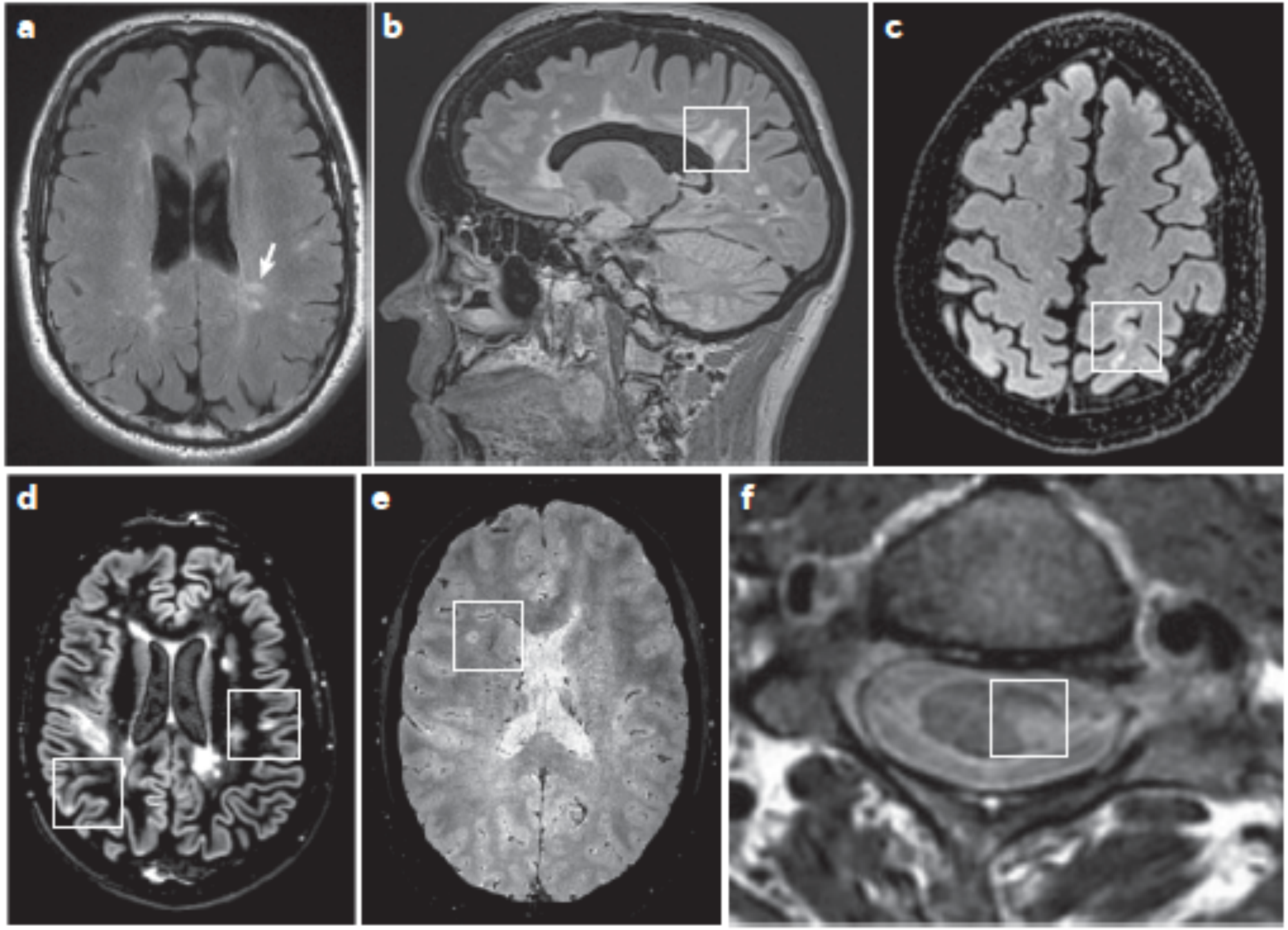
CNS: central nervous system, DIS: dissemination in space, DIT: dissemination in time OCB: oligoclonal bands, Gd: gadolinium

MS lesion characteristics on Brain MRI

- Location of MS plaques
  - Periventricular and juxtacortical
  - Corpus callosum
    - Dawson's fingers
  - Infratentorial
- Central Vein sign
- Active versus chronic
  - Active lesions
    - Enhance with gadolinium and are larger

MS lesion characteristics on Spine MRI

- Focal (well circumscribed and delineated) lesion with little or no cord swelling
- Unequivocal hyperintensity on T2-weighted sequences that is visible in two planes (eg, axial and sagittal)
- Size at least 3 mm but less than two vertebral segments in length
- Occupy only part of the spinal cord in cross-section and are typically located in the dorsolateral part of the cord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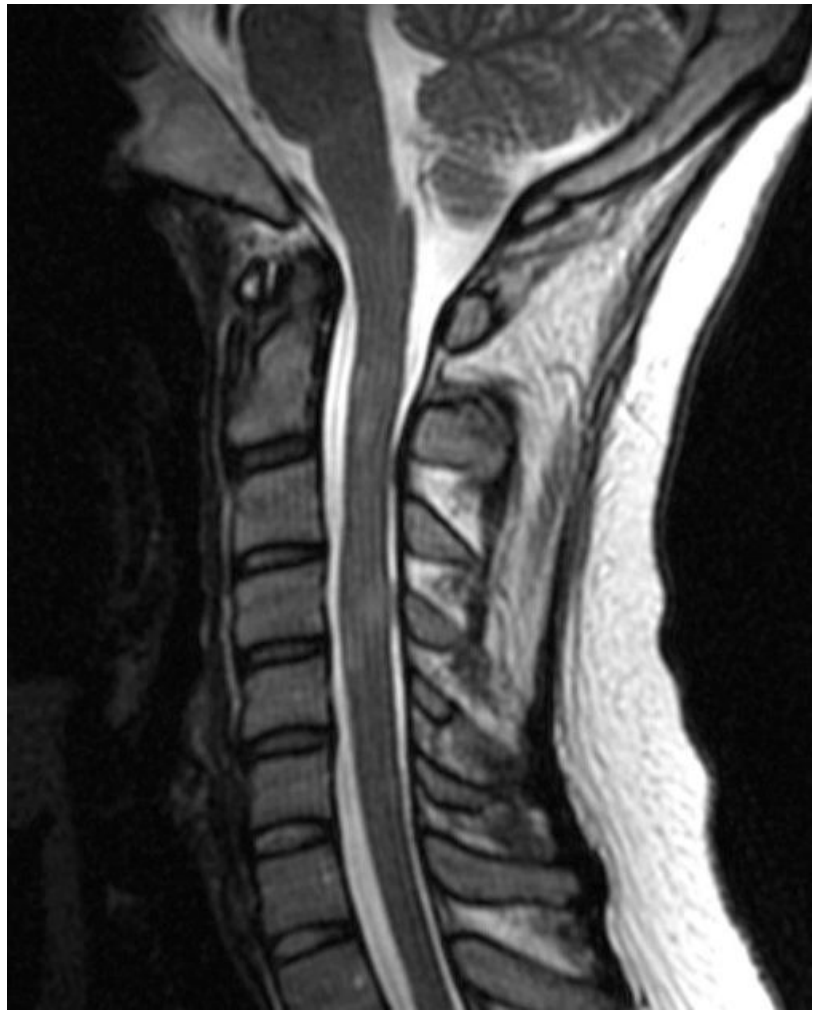
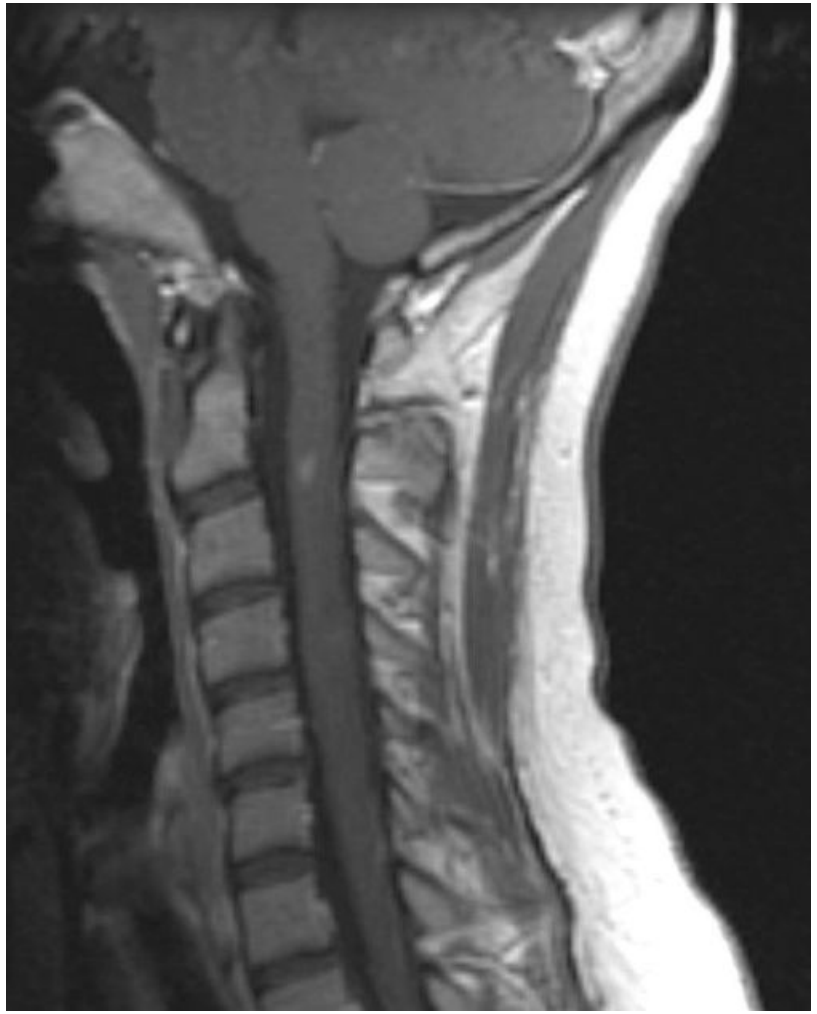




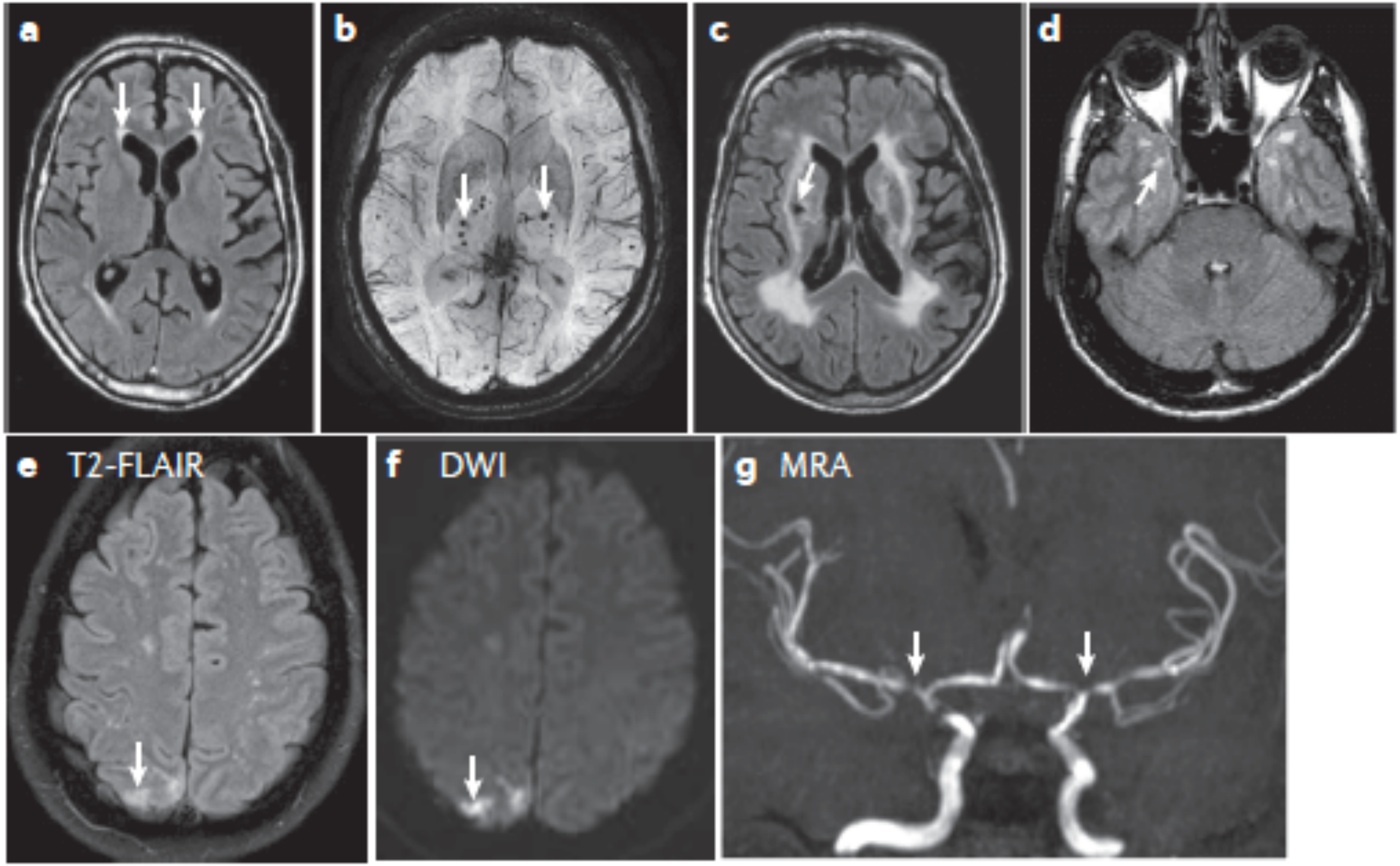
MS mimics

Characteristic differences between small-vessel disease (SVD) and MS

Involvement	SVD	MS
Corpus callosum	Rare	Common
U-fibers	Rare	Often
Brainstem	Central pons	Peripheral
Temporal lobe	Never[a]	Often
Gadolinium enhancement	Exceptional (subacute infarction)	Common
Black holes	Rare	Typical
Lacunes	Typical	Never
Spinal cord	Never	Common

[a]With the exception of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Small vessel disease type	Differentiating features
CADASIL[a]	WMLs in the external capsule and temporal poles, and lacunae in the basal ganglia and central pons
COL4A1 mutations[a]	Arterial dilatation and/or aneurysms, porencephaly and microbleeds
Fabry disease[a]	Vertebrobasilar arterial dolichoectasia, pulvinar T1 hyperintensity, and infarcts
Arteriosclerotic or related to age and vascular risk factors	• Lesions (microbleeds and lacunae) in perforating artery territory (basal ganglia, brainstem) • Symmetrical, poorly demarcated deep WMLs that spare U-fibres • Central pontine diffuse white matter changes and infarcts • Spared spinal cord
Cerebral amyloid angiopathy (sporadic and hereditary)	Lobar microbleeds and macrobleeds, convexity subarachnoid haemorrhages and/or cortical siderosis
Inflammatory or immune-mediated (for example, vasculitis associated with connective tissue disorders or primary systemic vasculitis with cerebral involvement) and infectious vasculitis	Meningeal enhancement, lacunae, microbleeds, territorial infarcts, pseudotumoural lesions in the basal ganglia and/or brainstem, and longitudinal extensive transverse myelitis
Other (for example, post-radiation angiopathy)	Diffuse WMLs, sometimes with cavitation owing to coagulative necrosis; distal artery thinning detectable with angiography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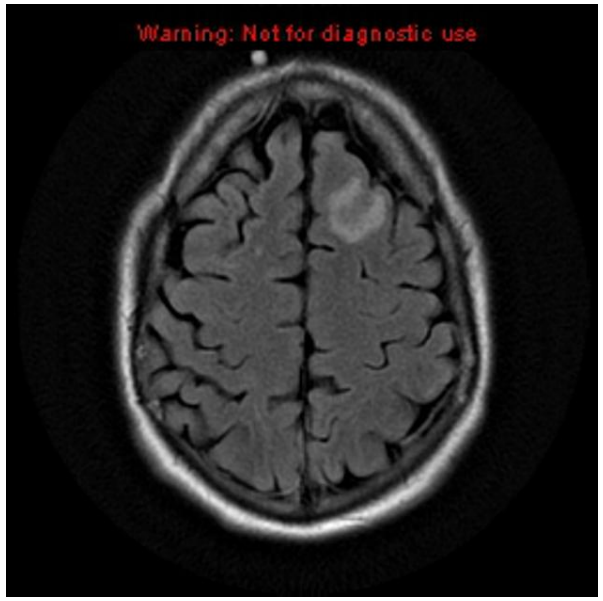
e T2-FLAIR
f DWI
g MRA

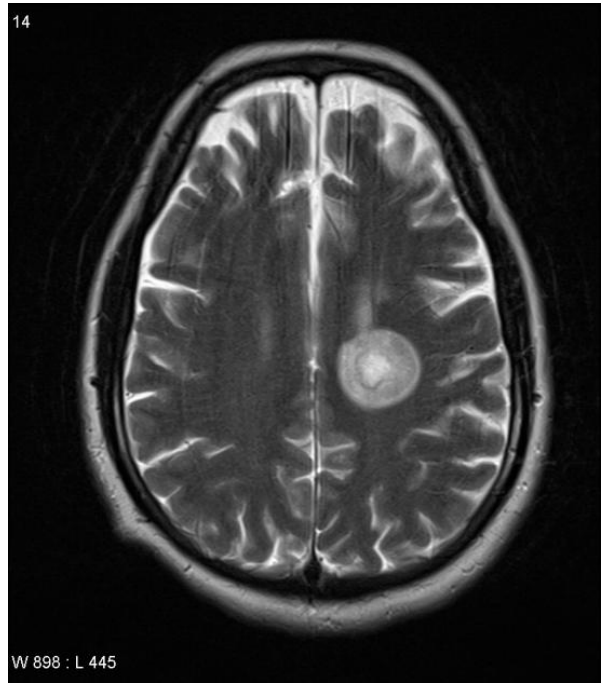
MRI differentiation of MS types

- PPMS vs RRMS
  - Less Gadolinium enhancing lesions
  - Cerebral T2 hyperintense lesions may be smaller, fewer, and develop more slowly
  - Diffuse T2 hyperintense lesions in the spinal cord
  - Atrophy of the spinal cord is more common
  - More likely to have a normal brain MRI

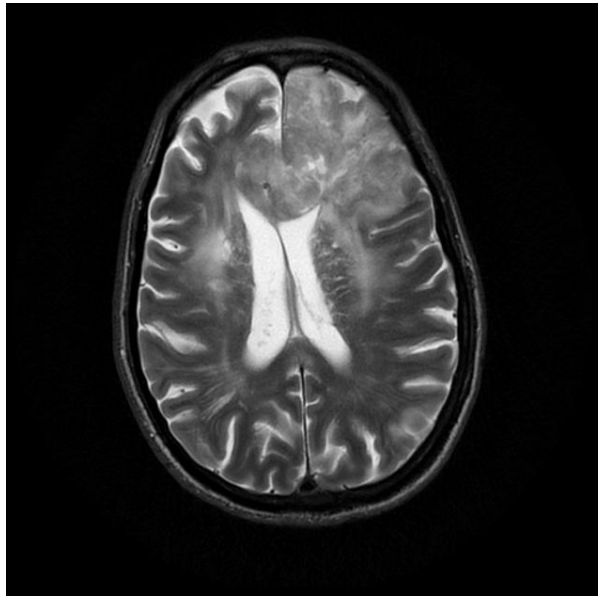
Variants

- Tumefactive MS





- Balo’s Concentric sclerosis



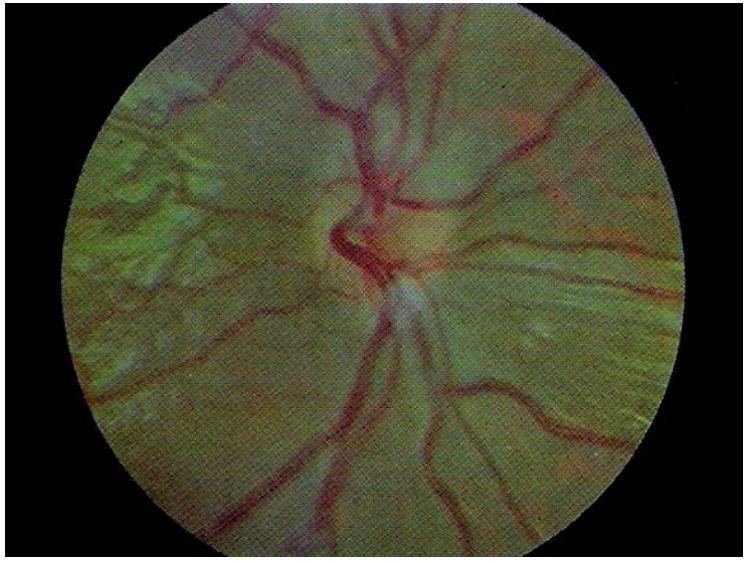
- Marburg variant

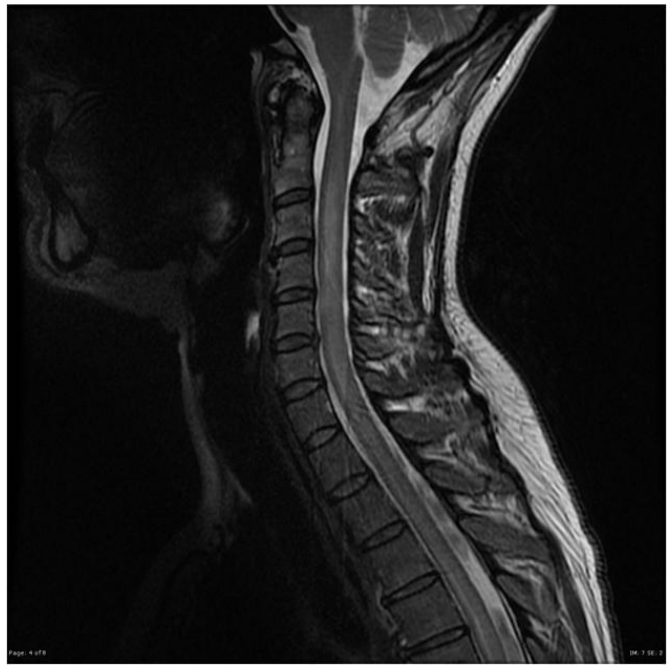
Conclusion of our case

- The patient was diagnosed with multiple sclerosis, most likely RRMS
- She was admitted, worked up and started on high dose steroids.
- In the outpatient setting, she was later prescribed glatiramer acetate

Case 3

- 28 y/o woman with a recent bout of severe optic neuritis 2 months ago who presents now with bilateral vision loss and walking difficulty that rapidly progressed to quadraparesis



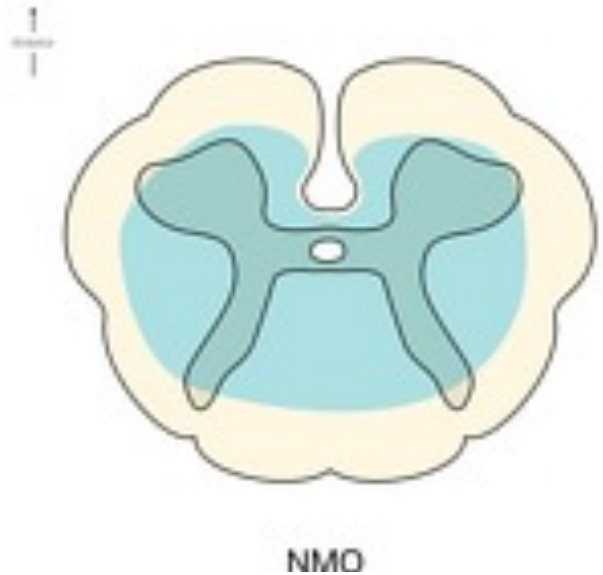


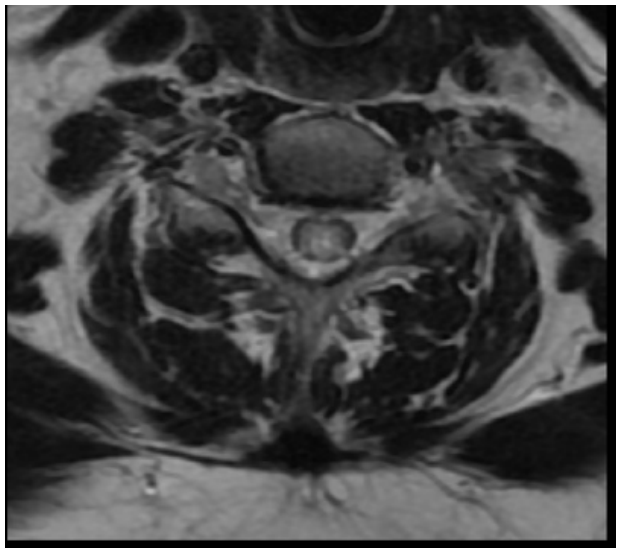
Neuromyelitis Optica (NMO)

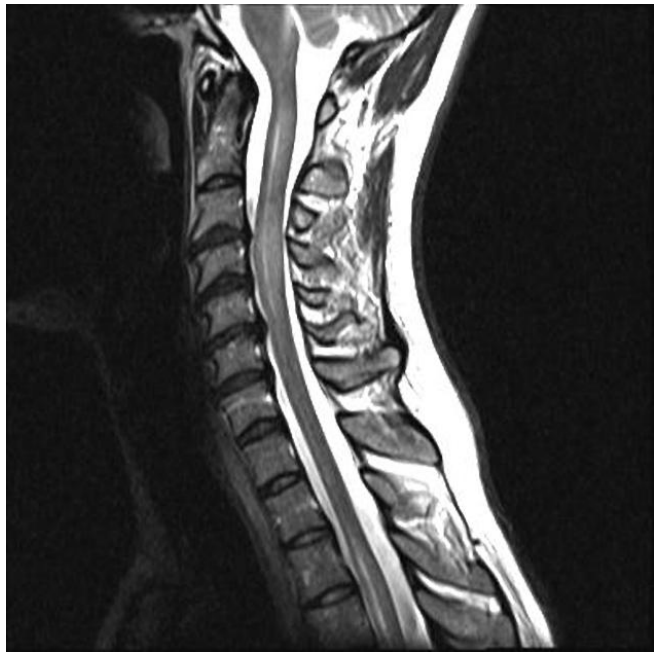
- Neuroinflammatory disorder characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord
- NMO-immunoglobulin G (IgG) antibody or aquaporin-4 (AQP4) autoantibody
  - Subset of patients who have anti-myelin oligodendrocyte glycoprotein (MOG).
- Florid demyelination and inflammation involving multiple spinal cord segments and the optic nerves with associated axonal loss, perivascular lymphocytic infiltration, and vascular proliferation
  - Necrotic demyelinating cord lesions are common

NMO

- More frequent in women than men
- Acute attacks of bilateral or rapidly sequential optic neuritis or longitudinally extensive transverse myelitis
- Lesions concentrated around areas of Aquaporin-4 channel density, especially periventricular areas







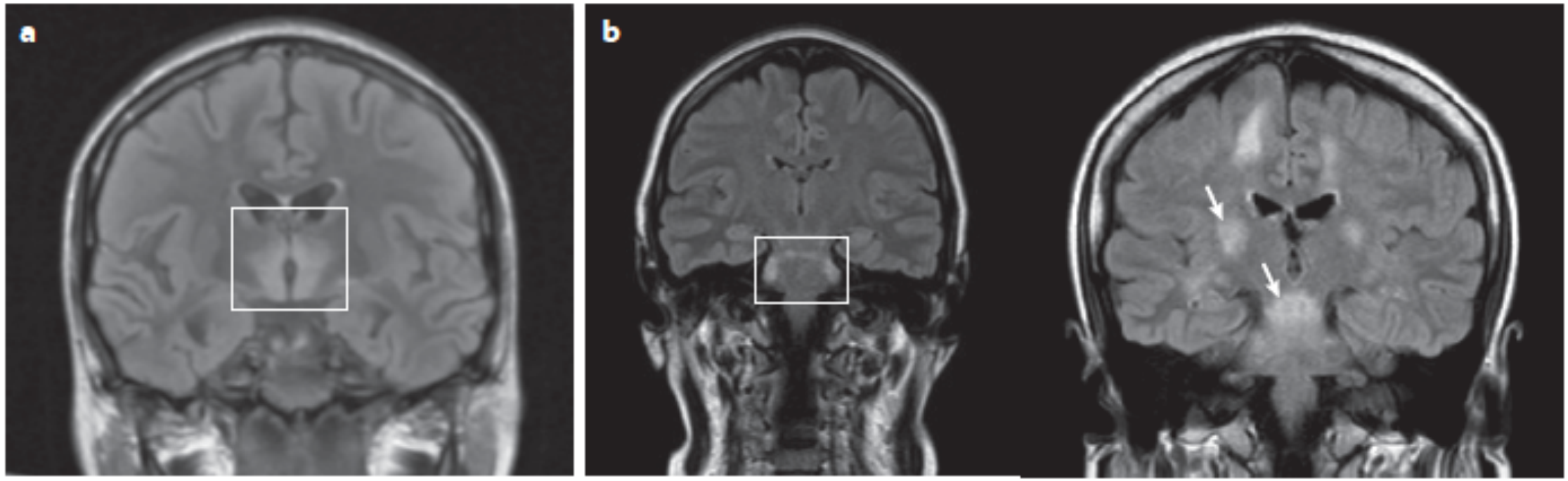
Diagnostic Criteria for NMOSD Without or Unknown AQP4-IgG Status

1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least one core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (two or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable (see below)
2. Negative tests for AQP4-IgG using best available detection method or testing unavailable
3. Exclusion of alternative diagnoses

Additional MRI Requirements

1. Acute optic neuritis: requires brain MRI showing
   a. Normal findings or only nonspecific white matter lesions
   b. Optic nerve MRI with T2w-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) or ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

NMO brain lesions



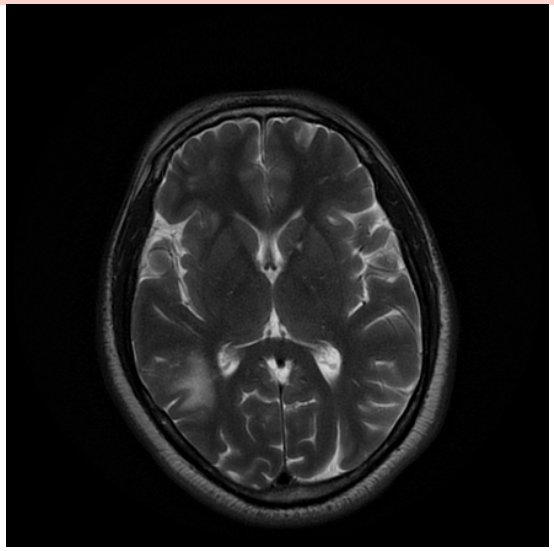
Conclusion of Case 3

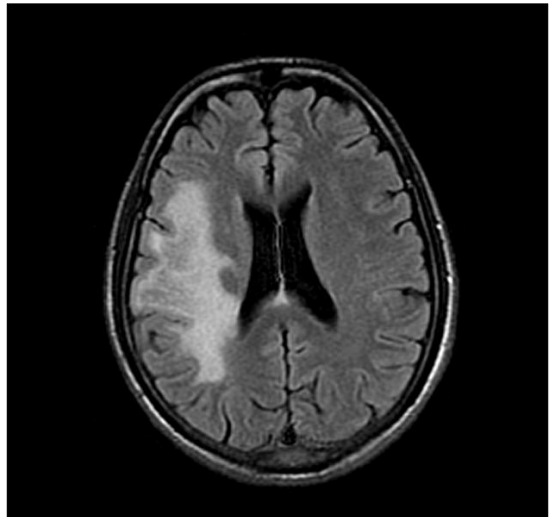
- The patient was treated with high dose methylprednisolone and plasma exchange acutely.
- She was also started on Rituximab
- She showed minimal evidence of significantly recovery initially and required a tracheostomy and feeding tube.

INFECTIOUS DEMYELINATING DISORDERS

Case 4

- A 63 y/o homeless man with HIV stopped taking his antiretroviral therapy approximately 2 years ago. He presents with left sided clumsiness and confusion over the past few weeks.
- Laboratory testing shows that he has leukopenia and CD4 count of 75.
- He required a feeding tube but passed away 2 months later from pneumonia.





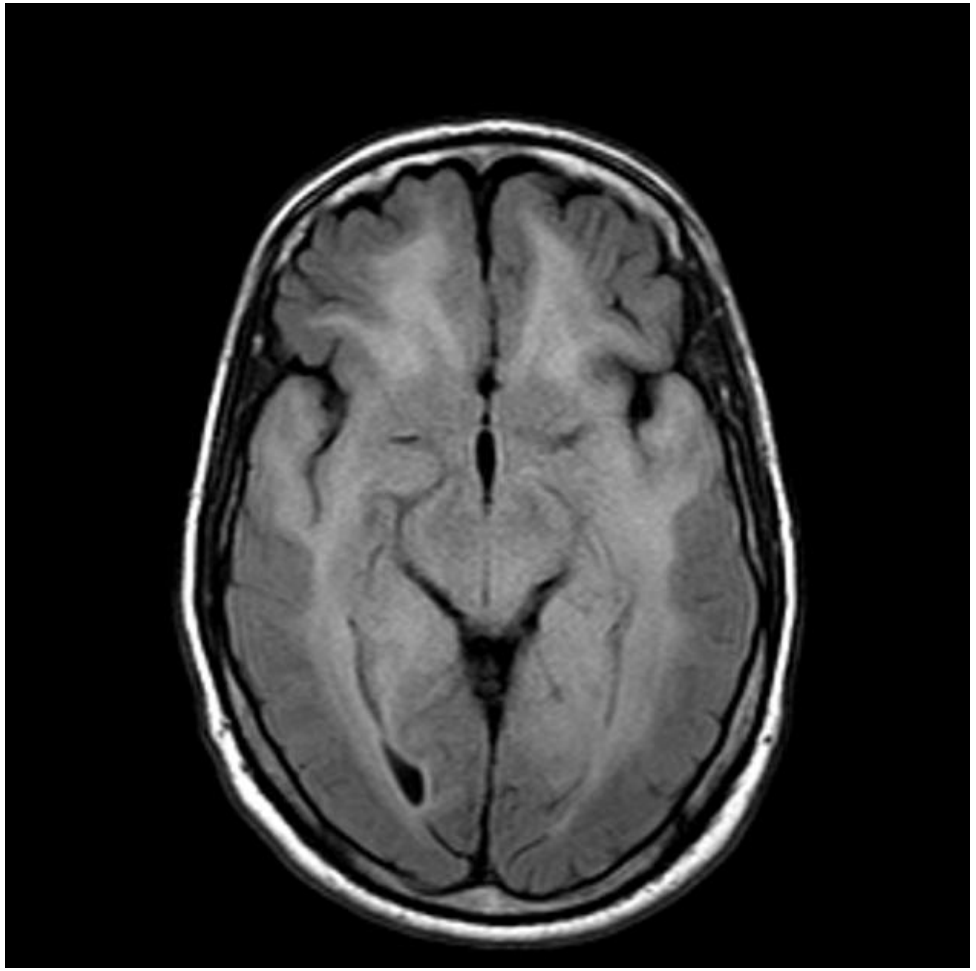
Progressive Multifocal Leukoencephalopathy (PML)

- Caused by reactivation of the papaovirus, JC, in immune-compromised patients
- Incurable condition
  - cART in HIV may improve survival
- Previously seen almost exclusively in HIV-AIDS patients but well described:
  - Transplant patients
  - Immunomodulatory drugs (Natalizumab, Rituximab, others)

Progressive Multifocal Leukoencephalopathy (PML)

MRI findings

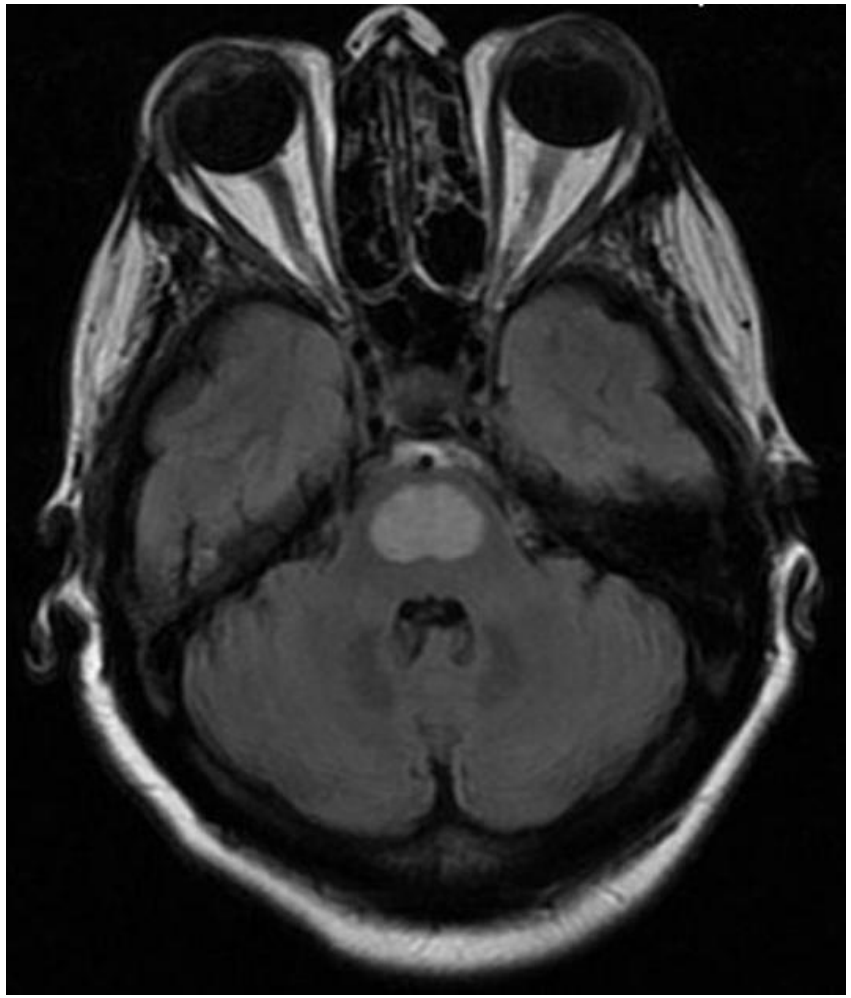
- Confluent white matter change with little mass effect or enhancement
- Predominantly supratentorial
- "Milky way" sign multiple punctate high T2 signal lesions surrounding the main area
- "Barbell" sign: parieto-occipital signal abnormality crossing the splenium



METABOLIC DEMYELINATING DISORDERS

Case 5

- A 72 alcoholic patient presented to the hospital on Monday with encephalopathy and a sodium of 115. The patient's hyponatremia was treated with hypertonic saline and was rapidly corrected to 137 in 24 hours. 2 days later, the patient becomes somnolent and diffusely weak requiring intubation.



Osmotic demyelination syndrome (ODS)

- Most frequently occurs after rapid correction of hyponatremia
  - Most frequently effected patients are patients with alcohol abuse and nutritional deficiencies, especially when accompanied by hypokalemia
- Destruction of the blood-brain barrier with hypertonic fluid accumulation in the extracellular space
- Pontine damage is most common but multiple other areas can be affected

Osmotic demyelination syndrome (ODS)