Differential Diagnosis of Multiple Sclerosis

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2nd MENACTRIMS CONGRESS 2016

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- It is hardly unusual to hear stories of people who have been misdiagnosed several times before finally being diagnosed with MS.

- Others remain in limbo for years, wondering if they will ever get a definite MS diagnosis

- **Two difficult situations :** a systemic disease with only neurological involvement miming MS or MS diagnosed long times before appearance of extra neurological signs

Difficulties about MS diagnosis

1. • No single specific test
2. • No two cases of MS are alike
3. • MS is unpredictable

WHY MIMICS MATTER

- Despite recent refinements in diagnostic criteria and the availability of ancillary studies, MS remains a clinical diagnosis.

- But sometimes, the process of elimination **is the only way** to a MS diagnosis.

- **Therefore,** the more you know about MS mimics, the quicker you can eliminate them as possibilities.

Diagnosis of MS includes

Wait -Follow- Treat ?

To prove it is M.S

To exclude other diagnoses

Dawson : 1916
Schumacher: 1965
Poser : 1983
McDonald: 2001
McDonald: 2005
McDonald: 2010

Paty : 1988
Fazekas : 1988
Barkhof : 1997
Tintore : 2000
Magnims 2016

All criteria require dissemination in time & space

Typical for MS
Fulfills Criteria → **MS Diagnosis**

Typical for MS
not Fulfilling Criteria → **Clinical/Imaging Follow Up**

Atypical for MS
Red Flags Present → **Work Up for Alternative Diagnosis**
Clinical/Imaging Follow Up

Alternative Diagnosis

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CHU

CONSENSUS

REVIEW

Multiple Sclerosis 2008; **14**: 1157–1174

Differential diagnosis of suspected multiple sclerosis: a consensus approach

DH Miller[1], BG Weinshenker[2], M Filippi[3], BL Banwell[4], JA Cohen[5], MS Freedman[6], SL Galetta[7], M Hutchinson[8], RT Johnson[9], L Kappos[10], J Kira[11], FD Lublin[12], HF McFarland[13], X Montalban[14], H Panitch[15], JR Richert[16], SC Reingold[16,17] and CH Polman[18]

Nat Clin Pract Neurol. 2009 Mar;5(3):134-5. doi: 10.1038/ncpneuro1047.

Guidelines for differential diagnosis of suspected multiple sclerosis.

Palace J[1].

Curr Neurol Neurosci Rep (2015) 15: 57
DOI 10.1007/s11910-015-0576-7

DEMYELINATING DISORDERS (DN BOURDETTE AND M CAMERON, SECTION EDITORS)

A Clinical Approach to the Differential Diagnosis of Multiple Sclerosis

Michel Toledano[1] · Brian G. Weinshenker[1] · Andrew J. Solomon[2]

The Differential Diagnosis of Multiple Sclerosis

Loren A. Rolak, MD, and John O. Fleming, MD†*

The Neurologist • Volume 13, Number 2, March 2007

CMRO Current Medical Research & Opinion Vol. 31, No. 7, 2015, 1349–1361

0300-7995
doi:10.1185/03007995.2015.1047750

Article ST-0109/1047750

Commentary

Consensus recommendations for the diagnosis and treatment of multiple sclerosis: the Middle East North Africa Committee for Treatment and Research In Multiple Sclerosis (MENACTRIMS)

CONSENSUS

REVIEW

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❖ **The possibility of an alternative diagnosis should always be considered, particularly when :**

a) Symptoms are localized exclusively to the posterior fossa, or spinal cord.
b) The patient is aged <15 or >60 years;
c) The clinical course is progressive from onset;
d) The patient has never experienced visual, sensory, or bladder symptoms ;
e) Laboratory findings (e.g., MRI, CSF, or EPs) are atypical.

DH Miller, BG Weinshenker, M Filippi & all. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler. 2008 Nov; 14(9): 1157–1174.

RED FLAGS

Outline

The Red Flags

- Clinical

Intermediate red flags definitively MS.

- Lab

Minor red flags may be consistent with MS or an alternative diagnosis.

- Imaging

DH Miller, BG Weinshenker, M Filippi & all˙ Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler. 2008 Nov; 14(9): 1157–1174.

Clinical Red Flags (Major)

- Bone lesions
- Lung involvement
- Multiple cranial neuropathies or polyradiculopathy
- Peripheral neuropathy
- Tendon xanthomas
- Cardiac disease
- Myopathy
- Renal involvement
- Extrapyramidal features
- Livedo reticularis
- Retinopathy
- Diabetes insipidus
- Persistently monofocal manifestations
- Hematological manifestations
- Mucosal ulcers

- Myorhythmia
- Hypothalamic disturbance
- Recurrent spontaneous abortion or thrombotic events
- Rash
- Arthritis, polyarthalgias, myalgias
- Amyotrophy
- Headache or meningismus

DH Miller, BG Weinshenker, M Filippi & all˙ Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler. 2008 Nov; 14(9): 1157–1174.

Clinical Red Flags

(Intermediate)

- Sicca syndrome
- Gastrointestinal symptoms
- Loss of hearing
- Fulminant course
- Prominent family history
- Constitutional symptoms

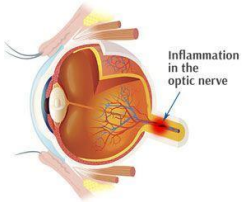
- Progressive ataxia alone
- Neuropsychiatric syndrome
- Seizure
- Uveitis
- Pyramidal motor involvement alone

(Minor)

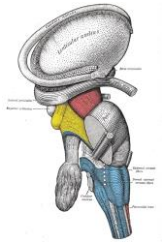
- Brainstem syndrome
- Myelopathy alone
- Onset before age 20
- Abrupt onset
- Onset after age 50

DH Miller, BG Weinshenker, M Filippi & all˙ Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler. 2008 Nov; 14(9): 1157–1174.

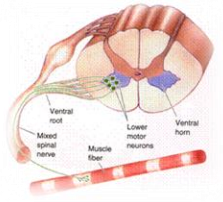
Topographic clinical Red Flags



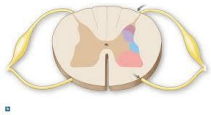
Optic neuritis: Absence of pain, retinal exudates or hemorrhages, severe disc swelling, bilateral involvement, no visual recovery after 1 month, uveitis.



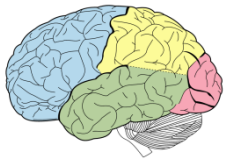
Brainstem syndrome: Hyperacute onset, vascular territory distribution, isolated trigeminal neuralgia, fluctuating ocular/bulbar weakness, non-remitting symptoms, fever, meningismus, complete external ophthalmoplegia, focal dystonia or torticollis.



Marked LMN signs: Areflexia, proximal weakness, bilateral LMN facial palsy, cauda equina lesion.



Spinal cord syndrome: Hyperacute onset or insidiously progressive, **complete transverse myelitis**, sharp sensory level, Radicular pain, failure to remit, anterior spinal artery distribution (sparing posterior columns only), complete Brown-Sequard syndrome.



Cerebral hemisphere: obtundation, confusion, cortical blindness, aphasia, dementia.

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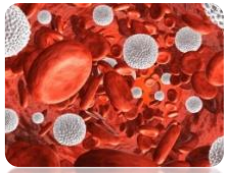
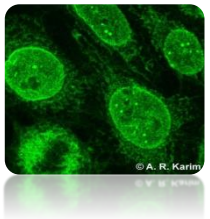
Laboratory Red Flags
BLOOD

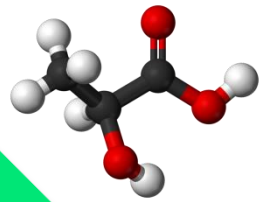


CBC: Marked cell count abnormality

High ESR, Low B12 vit



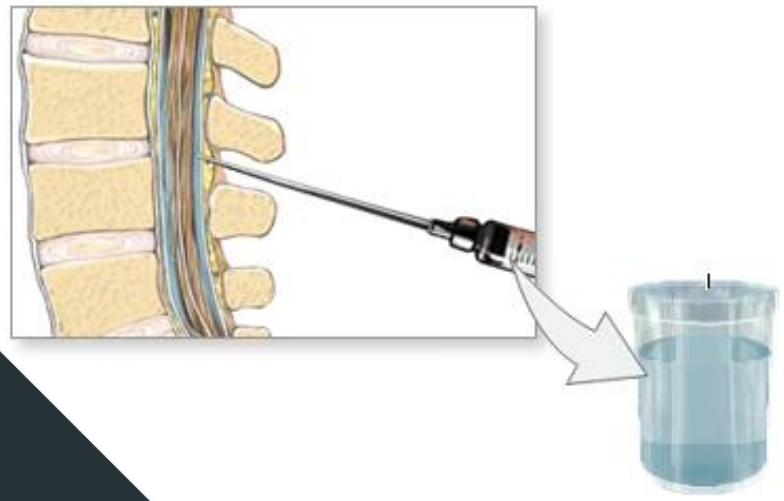
+ve ANA



Elevated lactate

Laboratory Red Flags

CSF



Cell count : >50 White blood cells: CNS Lymphoma , CNS vasculitis

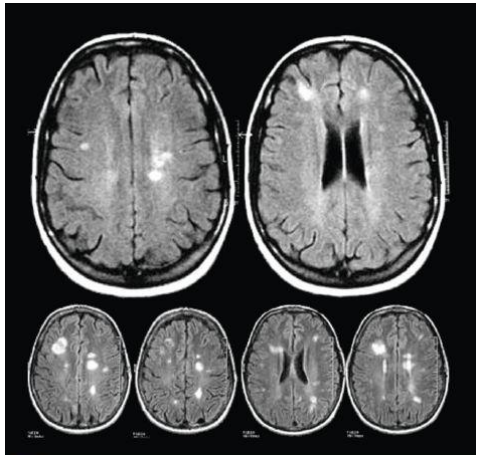
Cell differential : Lymph: BK,NB ++, Neutrophilic pred : CNS Whipple, CNS Lupus

Protein : Significant elevation >1G/L: Neurosarcoid, Spinal stenosis

Glucose : Low glucose <2/3 serum: Neurosarcoid, CNS Lymphoma

Persistance of OB : ADEM, NB

MS IMAGING Red Flags



- Context
- Number
- Size
- Topography

- Gad enhanc activity > 3 months
- Mass effect
- Leptomeningeal enhanc ?

Jan-Mendelt Tillema , Istvan Pirko˙ Neuroradiological evaluation of demyelinating disease. Ther Adv Neurol Disord. 2013 Jul; 6(4): 249–268.

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The Differential Diagnosis of Multiple Sclerosis

Loren A. Rolak, MD, and John O. Fleming, MD†*

The Neurologist • Volume 13, Number 2, March 2007

The "Abnormal" MRI

It has often been said that MS is a clinical diagnosis. This is not entirely true. It is unlikely a patient would be diagnosed with MS today (at least in Europe or North America) without undergoing MRI scanning. The introduction and refinement of MRI has changed the diagnostic process in MS, and most diagnostic criteria for MS rely heavily on interpretation of MRI.[1]

The most common reason for falsely attributing a patient's symptoms to multiple sclerosis is faulty interpretation of the magnetic resonance imaging.

Rolak LA[1], Fleming JO.The differential diagnosis of multiple sclerosis. Neurologist. 2007 Mar;13(2):57-72

MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines

*Massimo Filippi, Maria A Rocca, Olga Ciccarelli, Nicola De Stefano, Nikos Evangelou, Ludwig Kappos, Alex Rovira, Jaume Sastre-Garriga, Mar Tintorè, Jette L Frederiksen, Claudio Gasperini, Jacqueline Palace, Daniel S Reich, Brenda Banwell, Xavier Montalban, Frederik Barkhof, on behalf of the MAGNIMS Study Group**

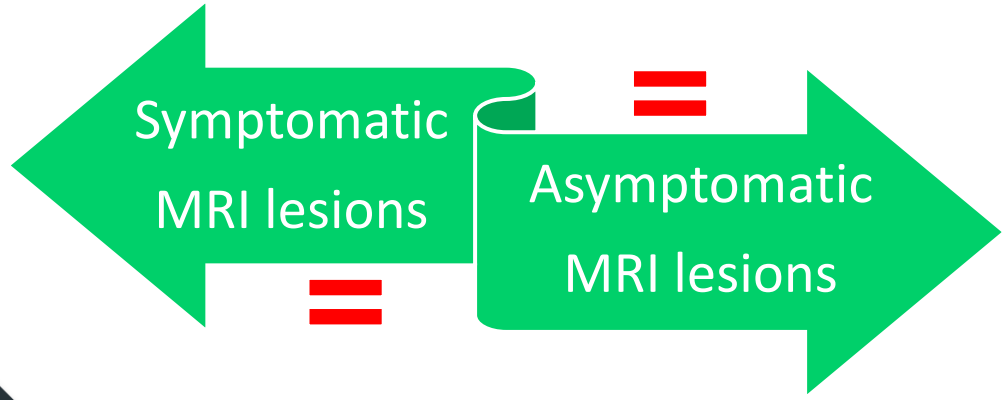
Dissemination in space: at least two of the following area

- Three or more periventricular lesions
- One or more infratentorial lesion
- One or more spinal cord lesion
- One or more optic nerve lesion
- One or more cortical or juxtacortical

Filippi M[1], Rocca MA[2], Ciccarelli O[3] & MAGNIMS Study Group. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 2016 Mar;15(3):292-303

MAGNIMS 2016

No distinction needs to be made for dissemination in T/S



primary progressive MS	• criteria for dissemination in space should be used
children > 11 years with no ADEM signs	• MRI criteria are used to establish dissemination in T/S
Asymptomatic MS **RIS**	• MRI criteria are applied to establish dissemination in Space

• MRI criteria can be applied equally well to patients in Asia or Latin America as to patients from Europe and North America, once **alternative neurological disorders** have been carefully excluded. **What about MENA !!!???**

Filippi M[1], Rocca MA[2], Ciccarelli O[3] & MAGNIMS Study Group. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 2016 Mar;15(3):292-303

DISSEMINATION

Diseases Sometimes Disseminated in Space but Not in Time

1. Shower of cerebral emboli
2. Thrombocytopenic purpura
3. CNS vasculitis
4. Mitochondrial encephalopathies
5. Drugs and toxins
6. Acute disseminated encephalom
7. PML (progressive multifocal le
8. Mycoplasma encephalopathy
9. Lyme disease
10. Vitamin B12 deficiency
11. Behçet disease
12. Sarcoidosis
13. Paraneoplastic syndromes
14. Periventricular leukomalacia
15. Psychiatric syndromes

Diseases Often Disseminated in Both Time and Space

1. Cerebrovascular disease, including emboli
2. Familial cavernous hemangiomata
3. CNS lymphoma
4. SMON (Subacute myelo-opticoneuropathy)
5. CNS vasculitis
6. Migratory sensory neuritis
7. Myasthenia gravis
8. Mitochondrial disease
9. Sjögren disease
10. HIV
11. Eale disease
12. Systemic lupus erythematosus
13. Lyme disease
14. Porphyria
15. Sarcoidosis
16. Antiphospholipid antibody syndrome
17. Spinocerebellar degeneration
18. CADASIL
19. Psychiatric syndromes
20. Devic disease

s Disseminated in Time but

n or spinal cord)

Rolak LA[1], Fleming JO.The differential diagnosis of multiple sclerosis. Neurologist. 2007 Mar;13(2):57-72

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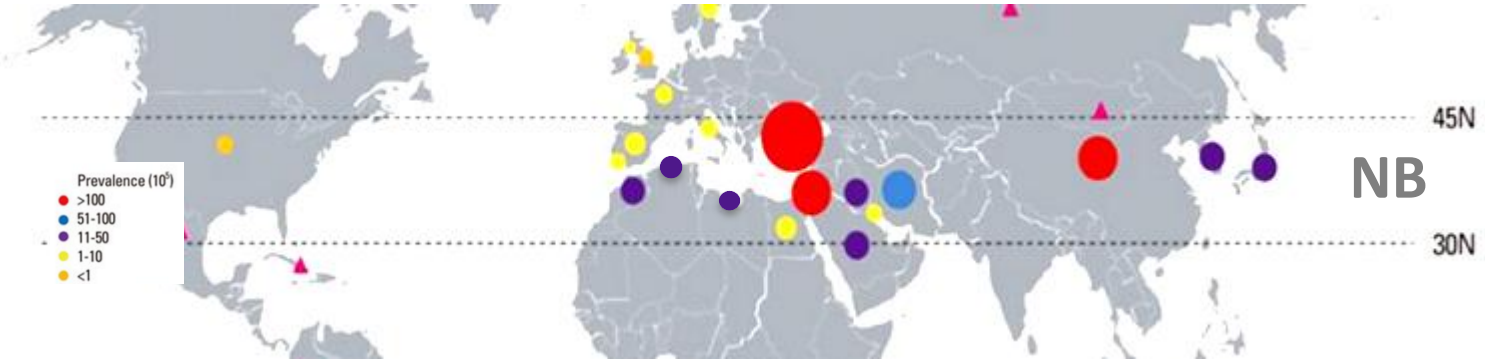
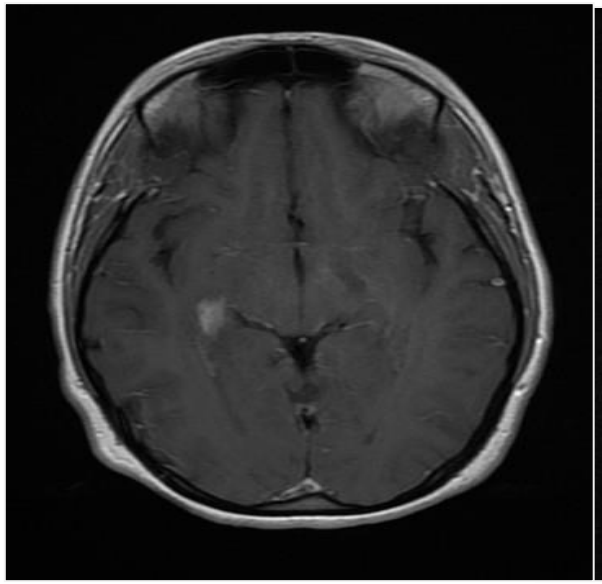


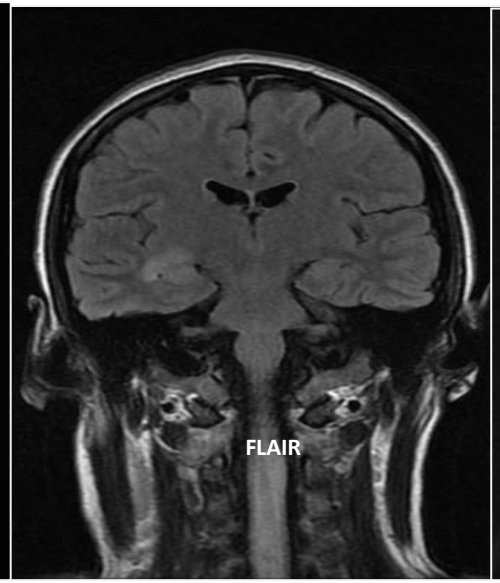
- Systemic disorders with possible involvement of the nervous system include a variety of diseases with presumed inflammatory and autoimmune pathomechanisms, among them Behçet disease, sarcoidosis, systemic lupus erythematosus, juvenile idiopathic arthritis, scleroderma, and Sjögren syndrome.

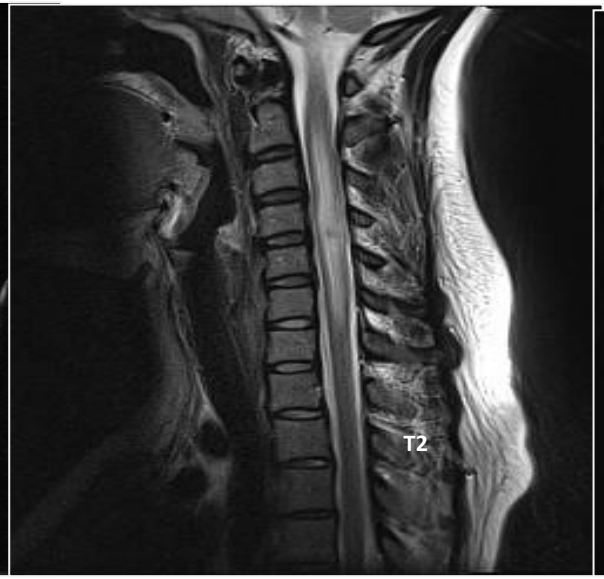
- Neurological involvement may represent the **initial** and or the **only** manifestation; with no validated diagnostic criteria, within extra-neurological manifestations, the diagnosis can be very difficult.

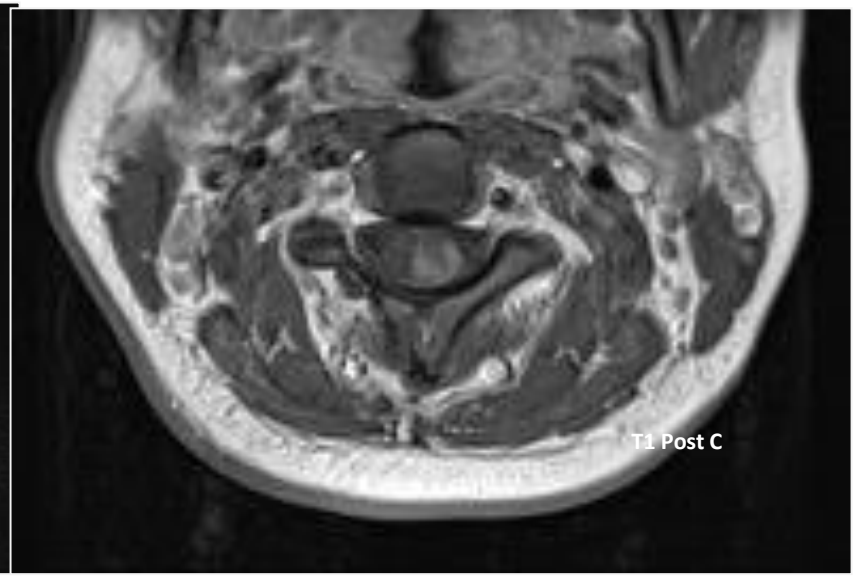
INFLAMMATORY

Behcet's









BS, WM (periventricular and superficial), internal capsule, basal ganglia, and thalamus.

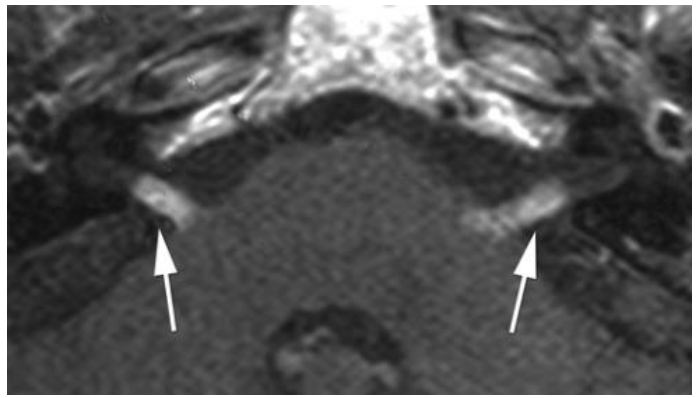
Brainstem atrophy ++++

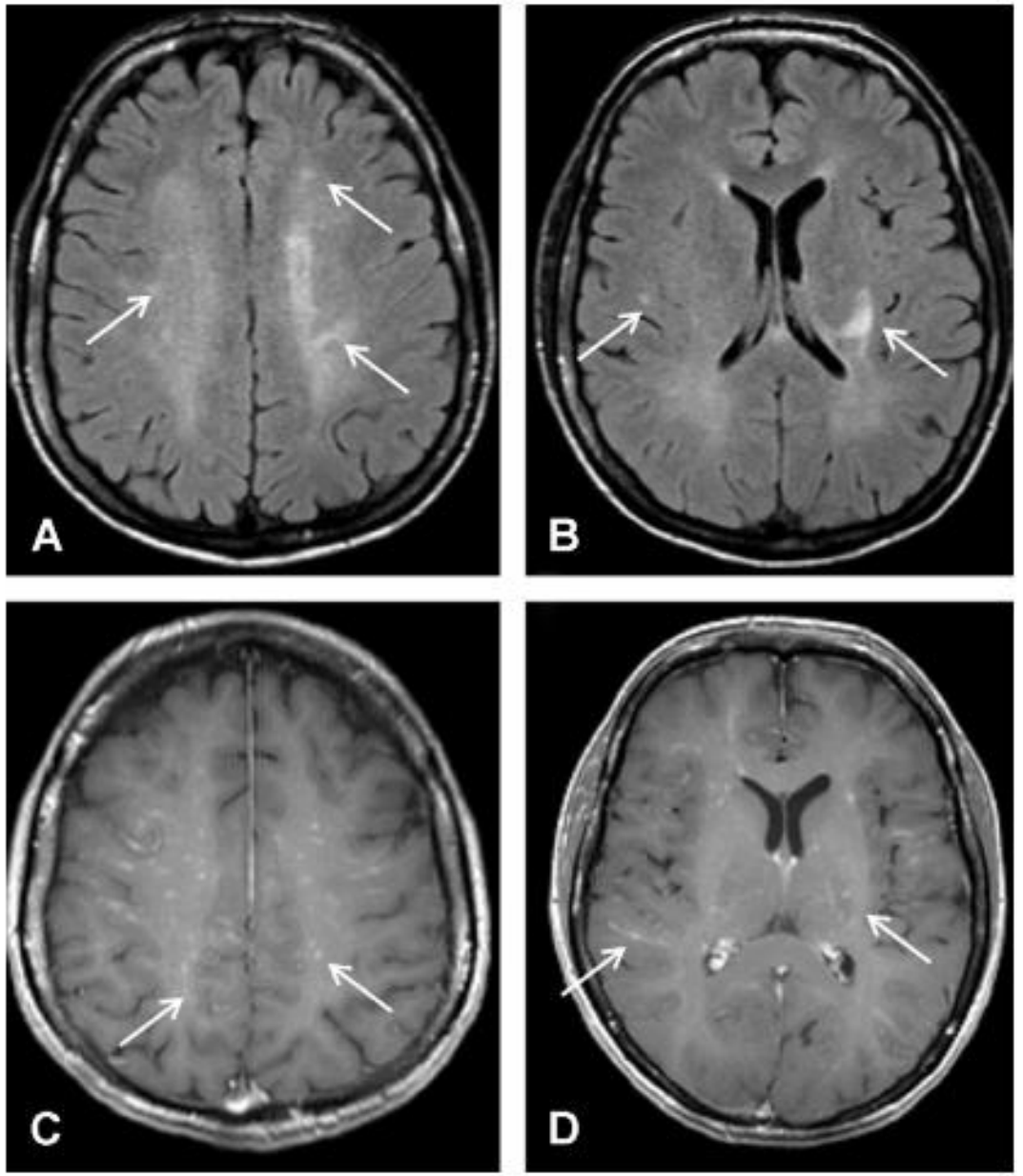
Lesions in the spinal cord spanning multiple segments in the cervical or thoracic spine are rare.

Inflammatory

SARCOIDOSIS

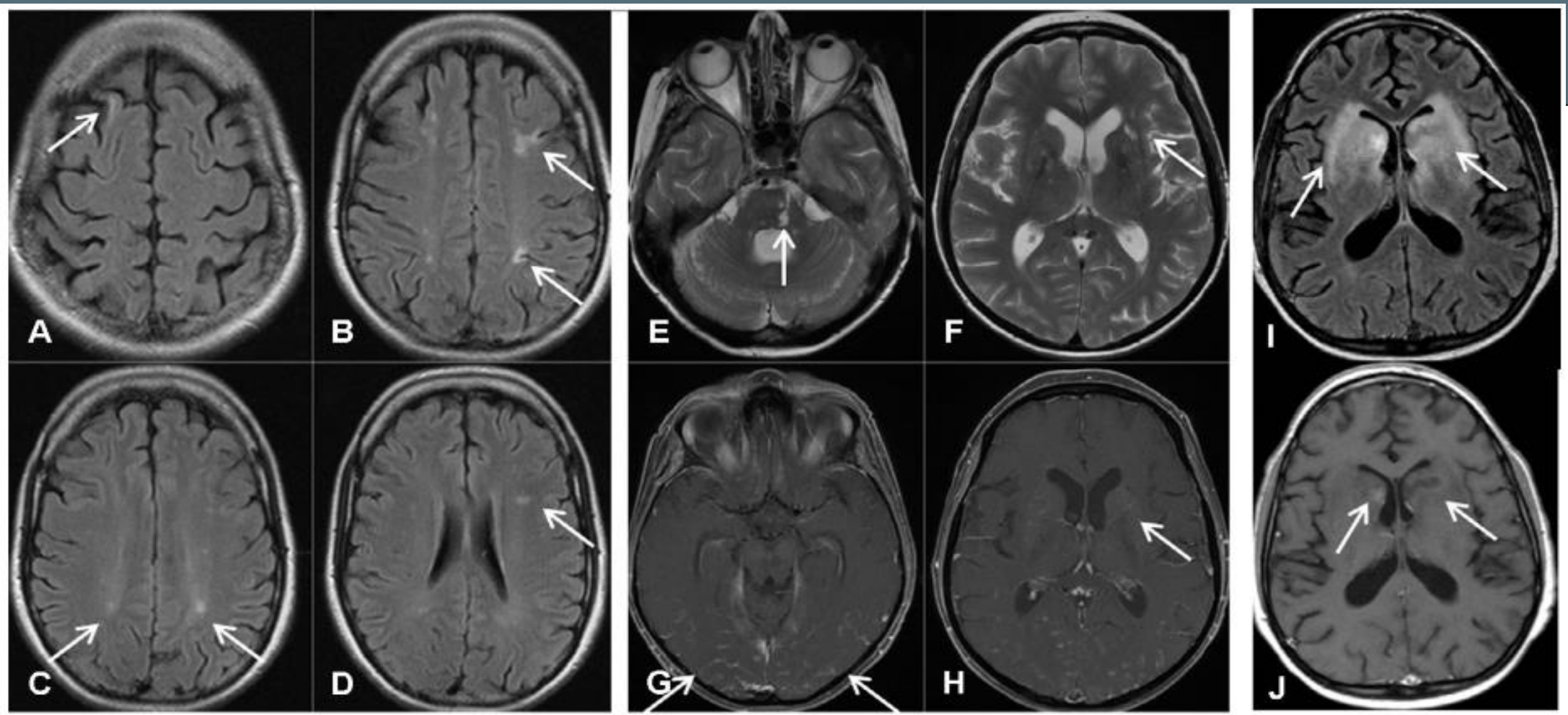
- Multiple hyper intense intraparachymal lesions.
- Chronic basilar leptomeningitis
- Enhancement along the Virchow-Robin spaces
  - Leptomeningeal enhancement along the third cranial nerve, and spinal nerve roots. Enhancement of the lacrimal gland
    - Hydrocephalus is a common finding.





Inflammatory

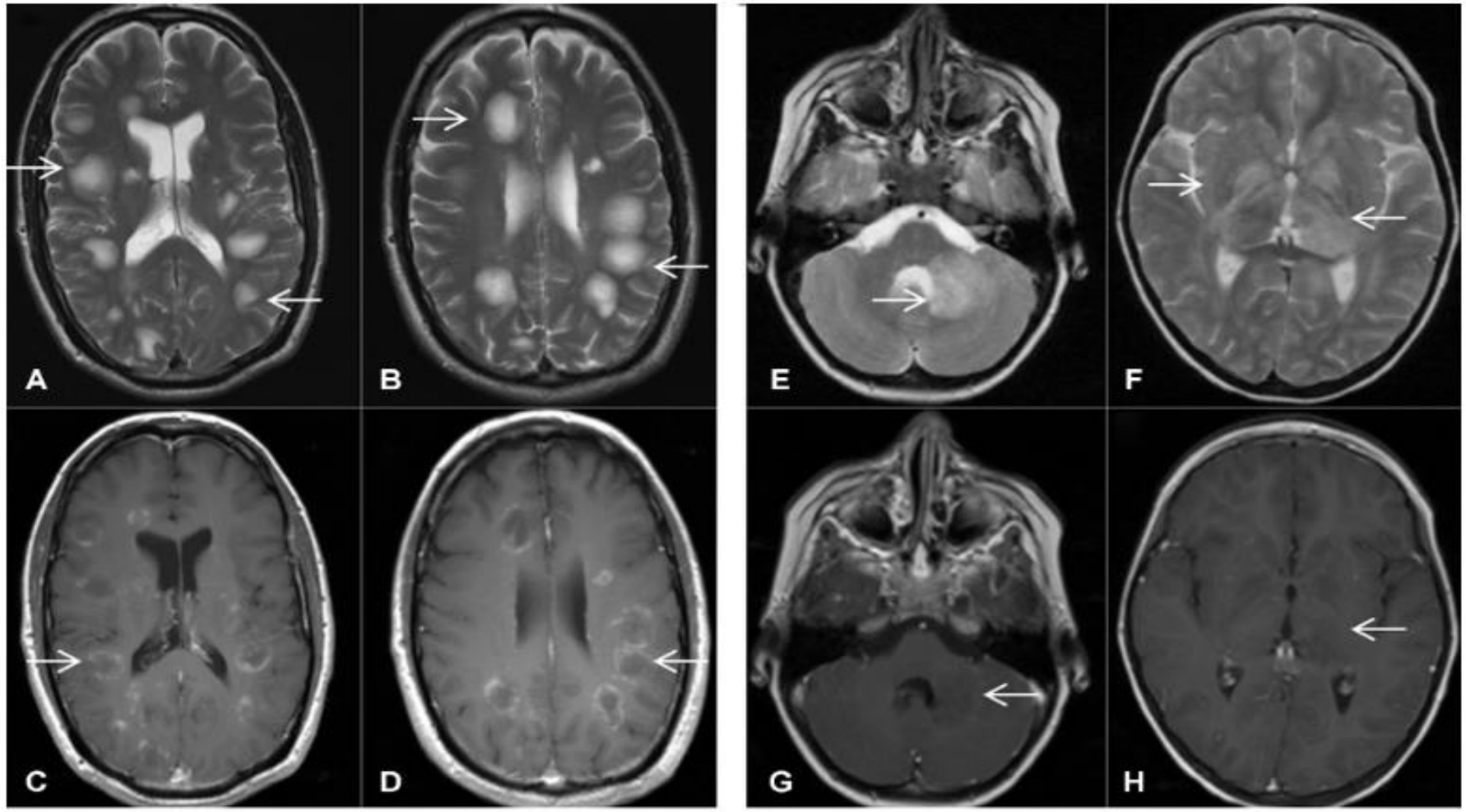
Systemic Lupus Erythematosus



- Focal & punctate hyper-intensities in W and / or G matter are indicative of vasculitis
- Unlike MS, WM lesions are less periventricular & more peripheral
- WM hyper-intensities are more common if neuropsychiatric symptoms present.

Inflammatory

ADEM



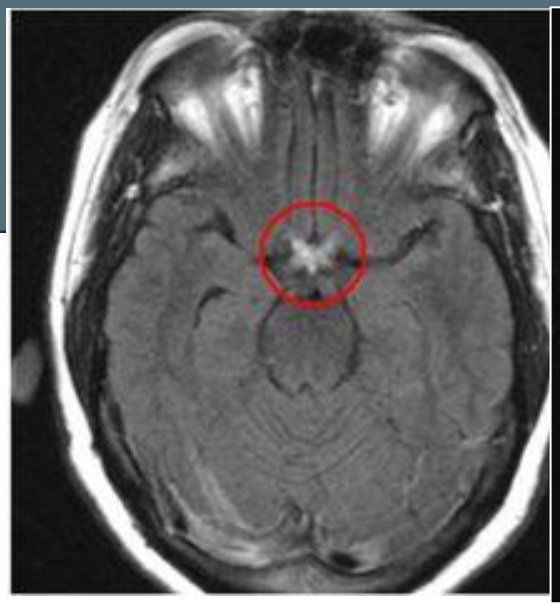
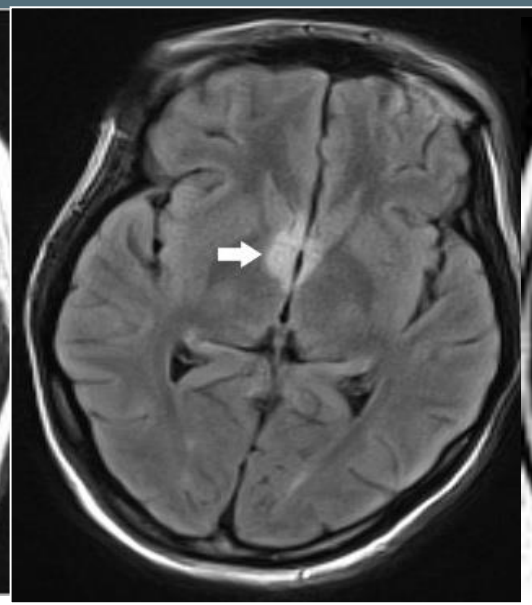
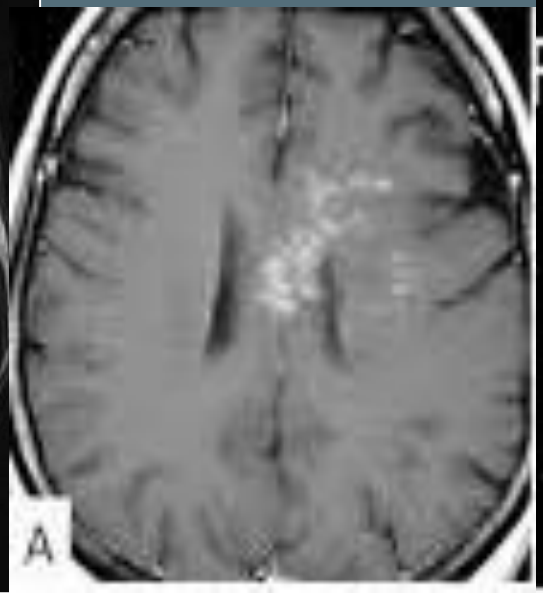
Multiple large T2 lesions predominantly located in the corticosubcortical junction, not sharply delineated

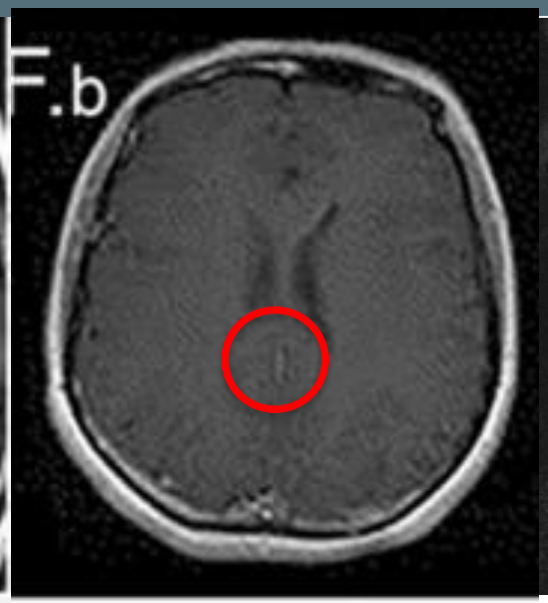
enhance simultaneously

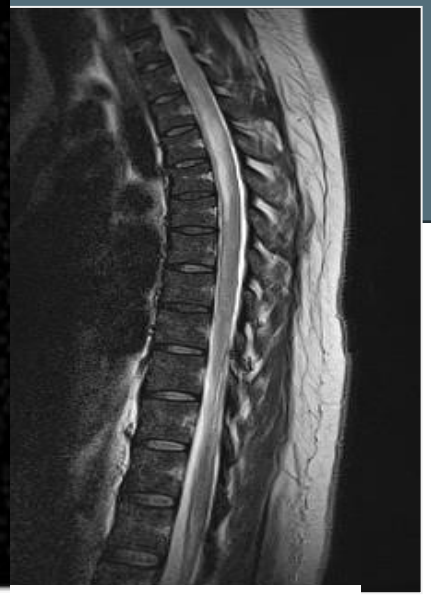
Large T2-hyperintense in basal ganglia,

No black holes

NMO syndrome

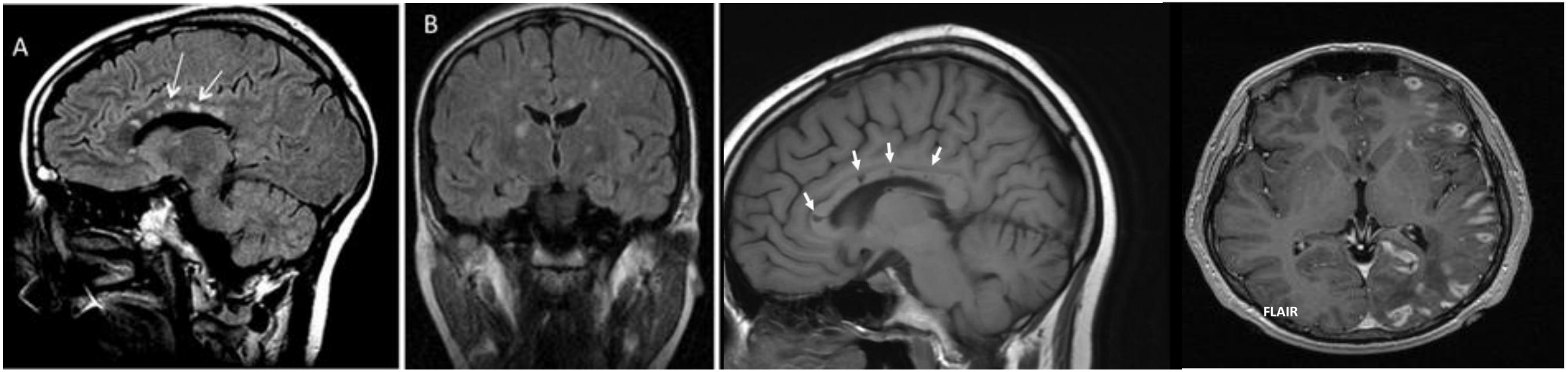




	NMOSD	MS
Spinal cord	Longitudinally extensive lesion (≥3 vertebral segments)	Short, often multiple lesions
	Central/gray matter involvement	Peripheral/asymmetrical/often posterior
	T1 hypointensity common on acute lesions	T1 hypointensity rare
Optic nerve	Long-length/posterior-chiasmal lesions	Short-length lesions
Brain	Periependymal lesions surrounding the ventricular system (wide-based along the ependymal lining)	Dawson fingers (perpendicular to ventricles)/S-shaped U-fiber lesions, inferior lateral ventricle and temporal lobe lesions
	Hemispheric tumefactive lesions	Cortical lesions
	Lesions involving corticospinal tracts	Perivenous lesions
	"Cloud-like" enhancing lesions / **pencil-thin lesion**	Ovoid or ring/open-ring enhancing lesions

Wingerchuk DM[1], Banwell B[2], Bennett JL[2] & all. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul 14;85(2):177-89

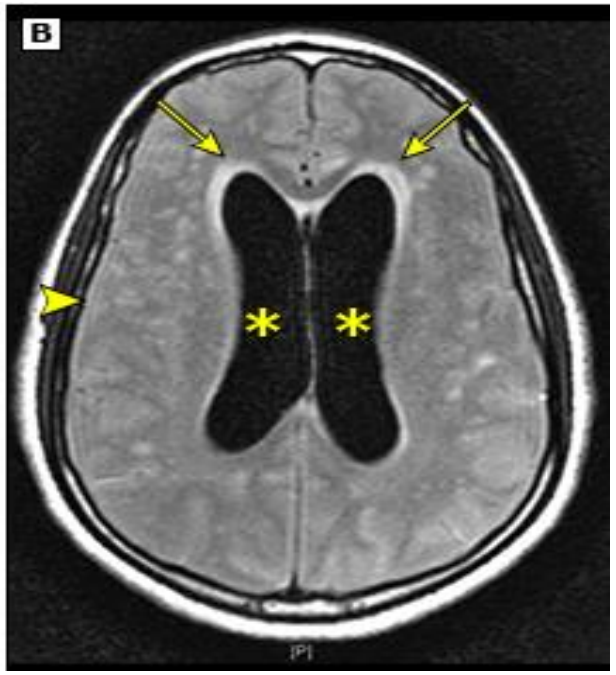
Susac's syndrome

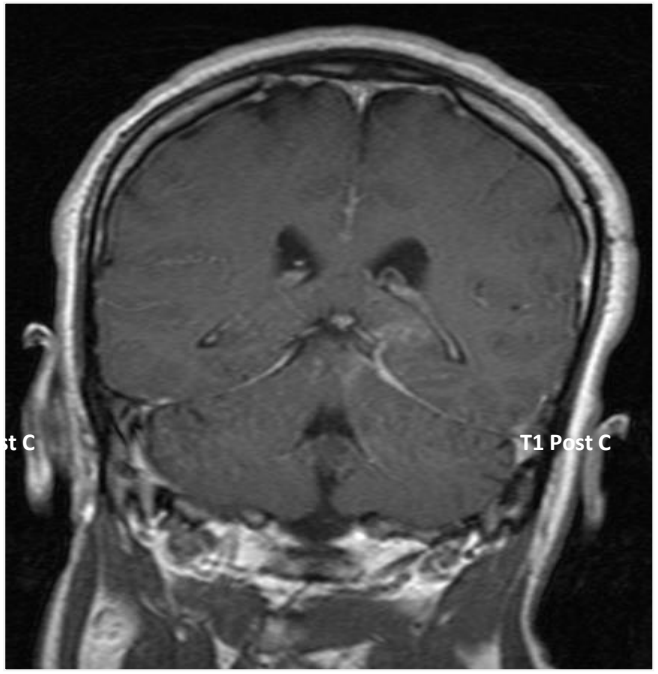


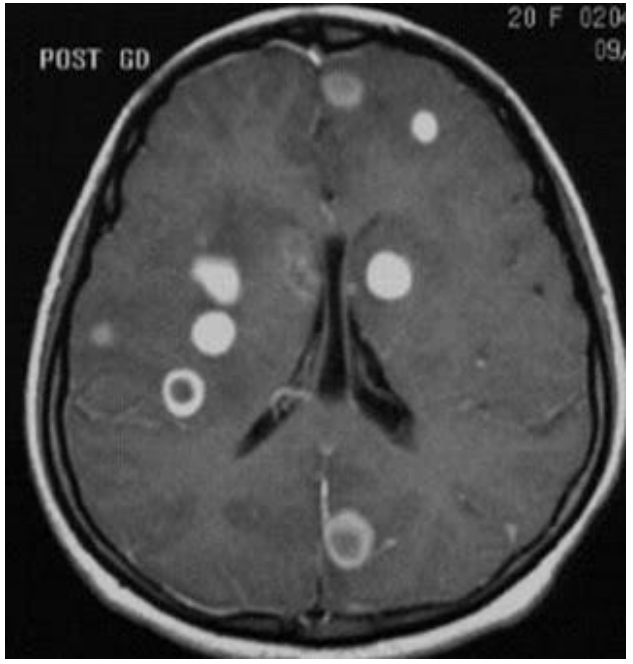
- Small WM lesions
- T1 Lesions like black holes in central callosal are due to micro-infarcts
- Flair snowball' lesions whose central location in the callosum makes them pathognomonic
- Parenchymal and leptomeningeal enhancement

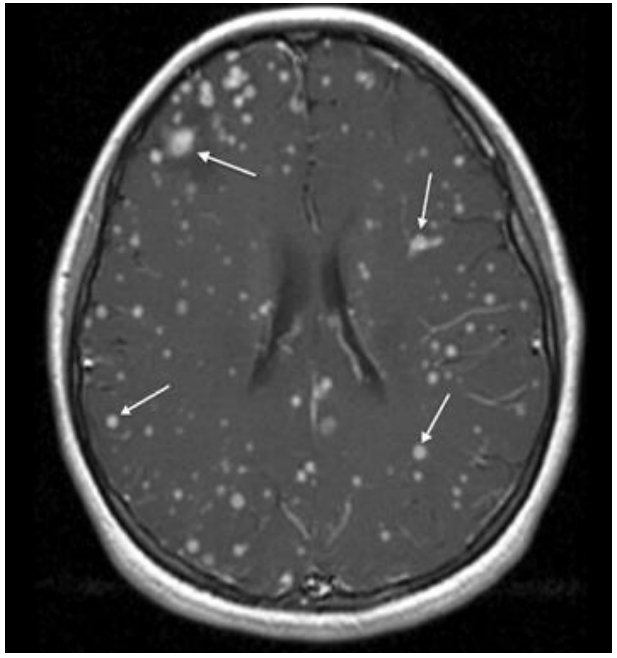
INFECTIOUS

Tuberculosis





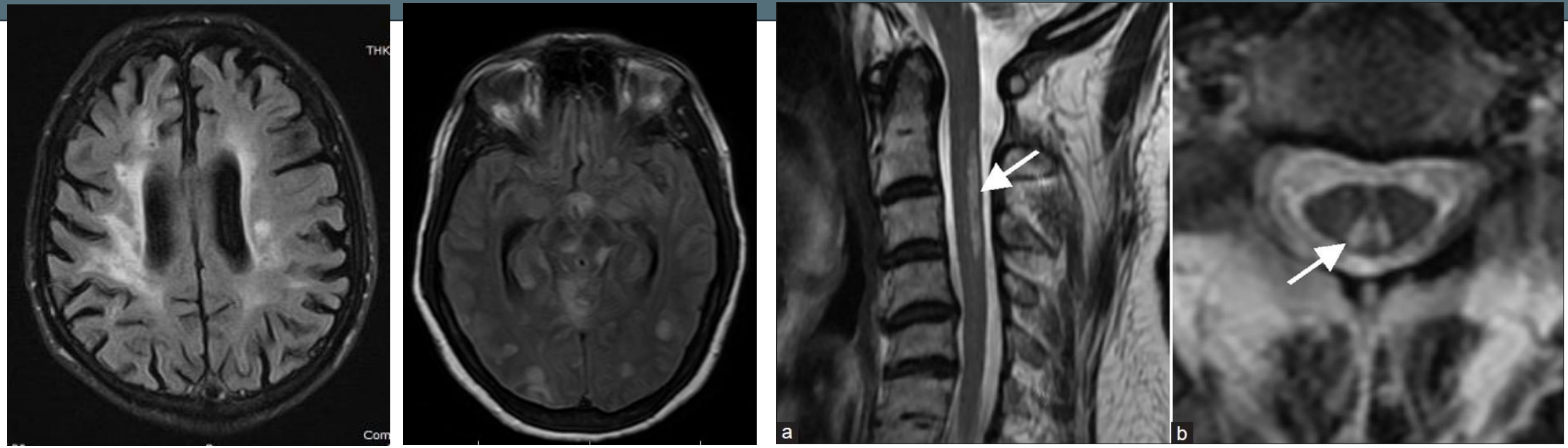




- In tuberculosis we can see multiple HST lesions MS like
- Hydrocephalus, leptomeningeal enhancement and arachnoiditis make the big difference with MS
- Tuberculoma , spectroscopy shows a lipid peak, which can be seen in MS also due to myelin breakdown

Infectious

HIV



- Diffuse WM HST2 particulary in PV
- Basal ganglia involvement is more common in HIV than MS.
- The axial spine image shows bilaterally enhancement in the corticospinal tracts
- Atrophy is a predominant finding.

Inflammatory

PML

- **Patients MS under natalizumab +++**

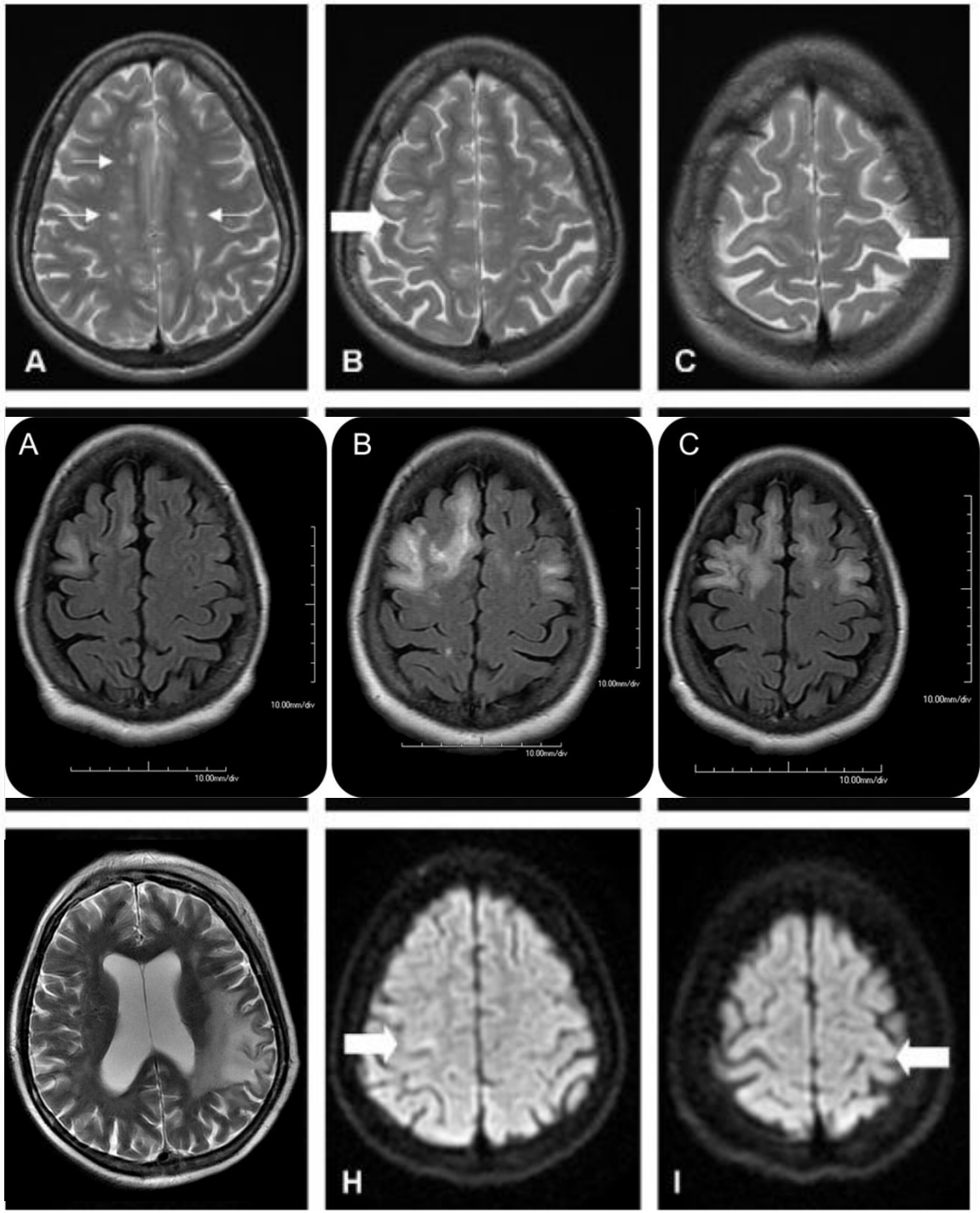
- Surveillance protocol includes FLAIR and DWI sequences.

- 50% of early PML lesions showed T1 CE

  - Subcortical lesions (occur in the frontal lobes)

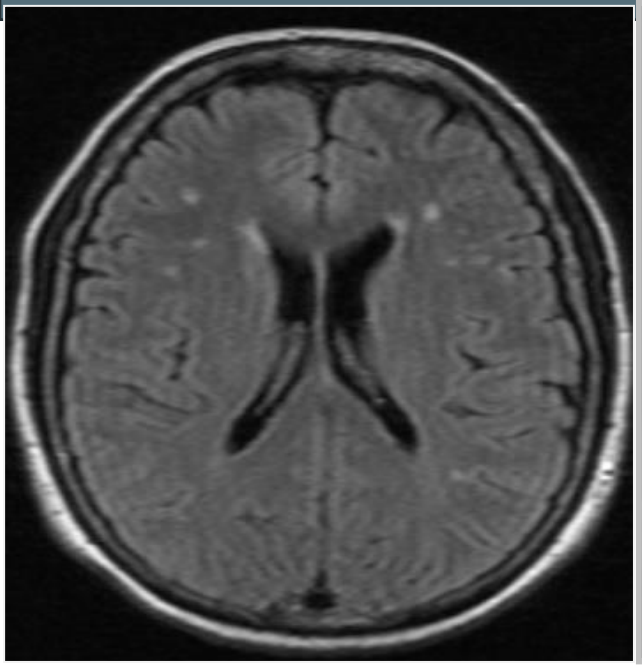
  - ill-defined borders toward the WM and sharp borders toward GM

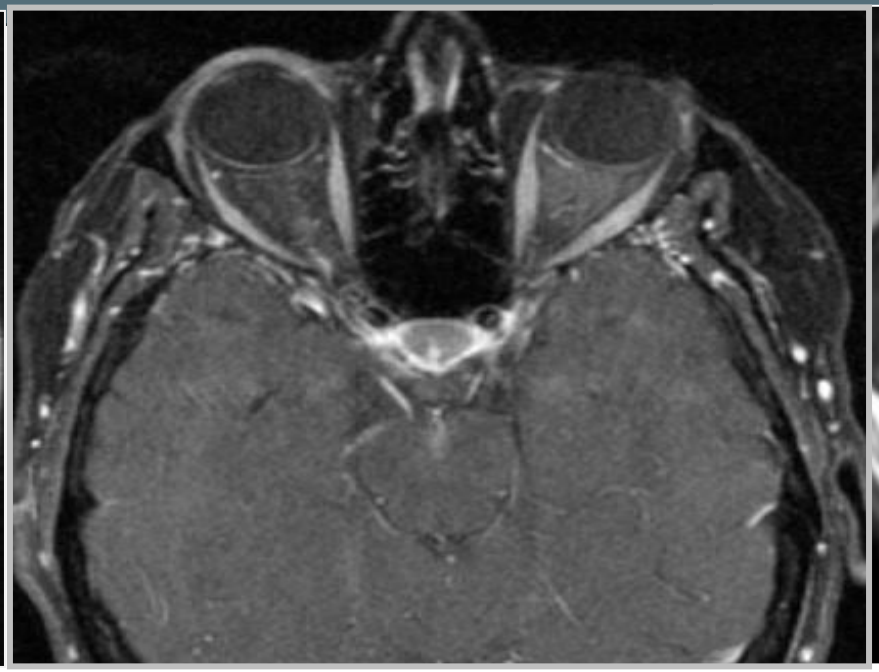
  - High signal intensity on DWI.

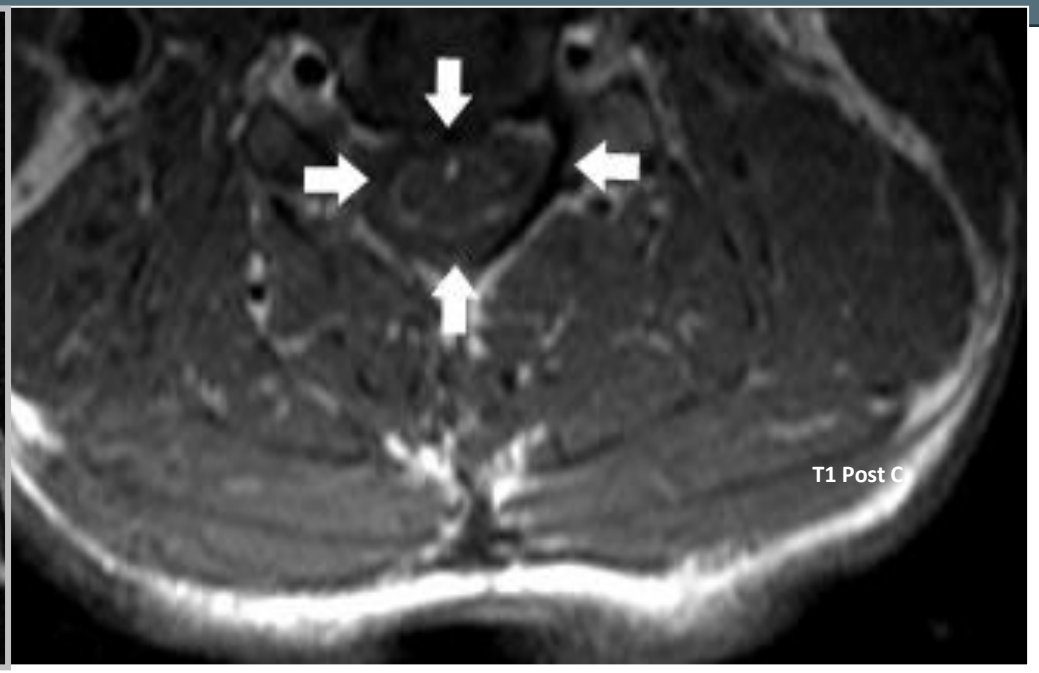


Infectious

Neuroborreliosis (Lyme disease)







Lyme disease can cause a phenotype very similar to MS.

MRI may show multifocal white matter lesions.

Meningeal and cranial nerve III enhancement are seen .

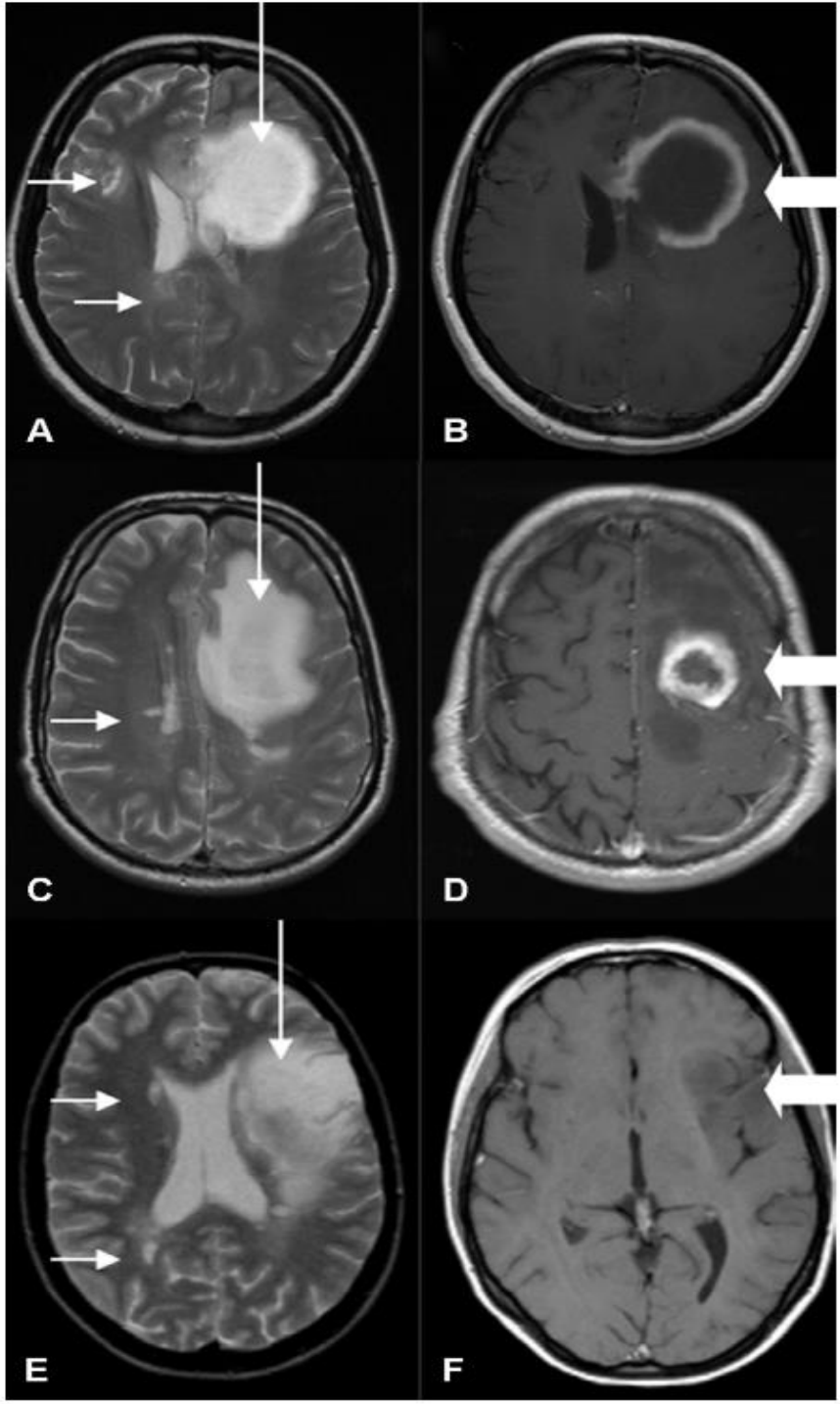
DWI and FLAIR imaging will show ischemic lesions.

Tumefactive MS (Tumor like MS)

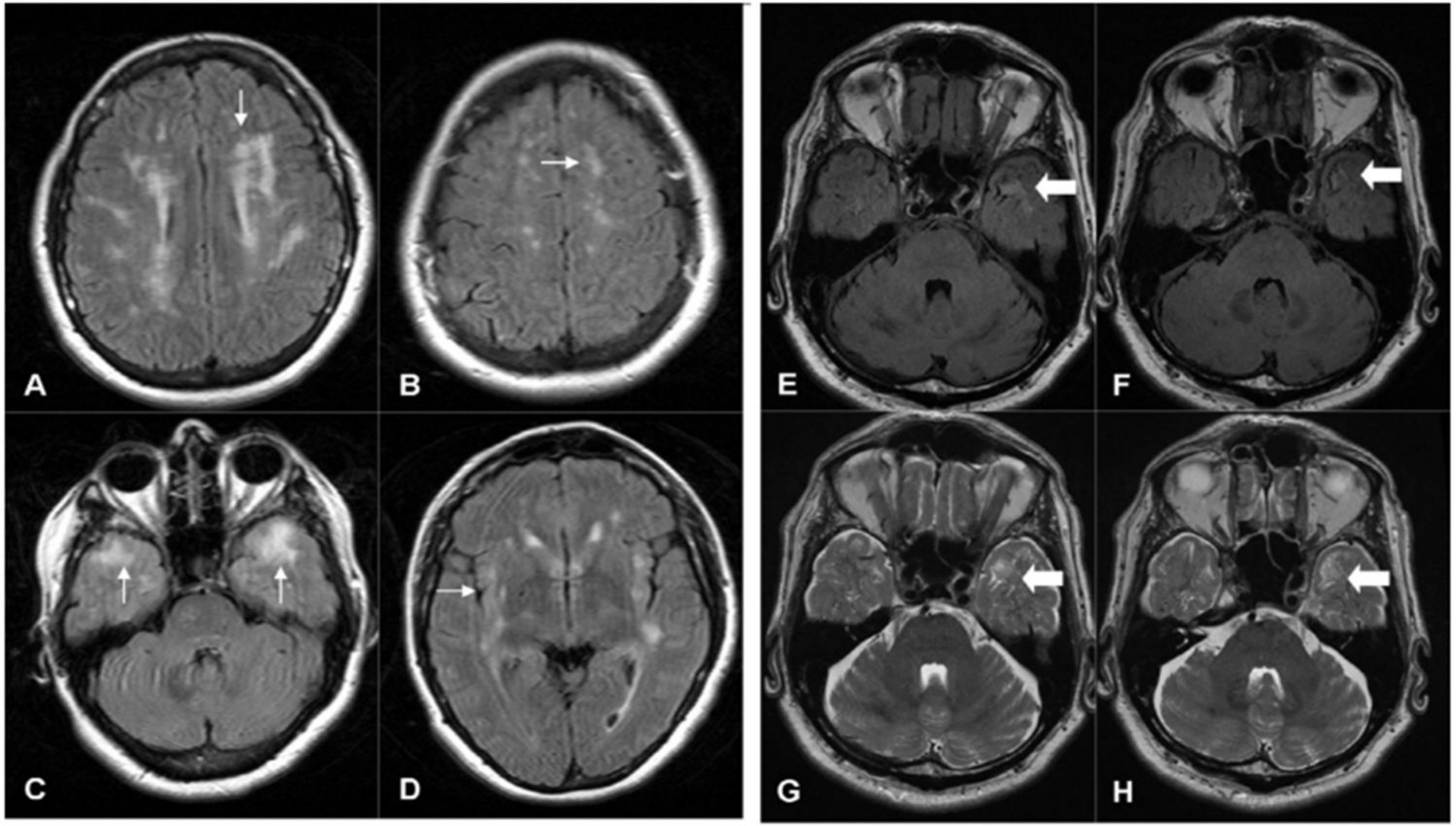
- The lesion is well-circumscribed with incomplete sharp ring enhancement, often with mass effect.
- Irregular ring of enhancement in GB
- Non-enhancing mass in low grade astrocytoma

- MR Spectroscopy may show increased glutamate/glutamine peaks. Increased choline to N-acetyl-aspartate ratios are seen in Tumefactive MS and malignancy.

- FDG-PET can be differentiating (hyper-metabolism in malignancy is > than Tumefactive MS).

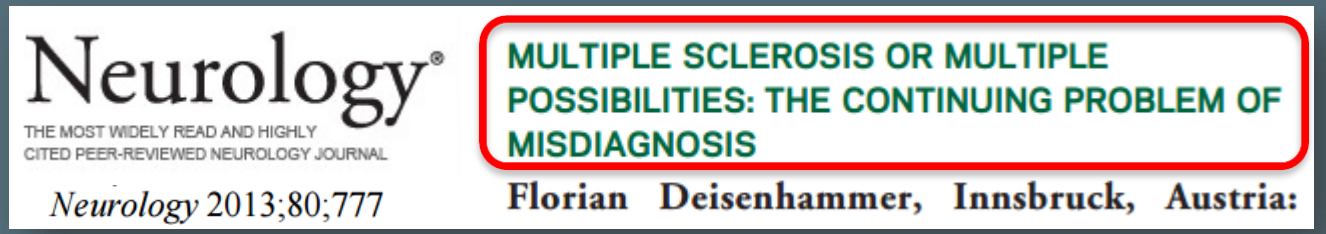


CADASIL



- focal and confluent lesions located **bilaterally symetric** in the PV region (A).
- involvement of the WM in the temporal pole, external capsules
- Association of lacunar infarcts and hemorrhages ++++
- subcortical cysts caused by distension of the perivascular space at the gray–white-matter junction

CONCLUSION



Deisenhammer F. Multiple sclerosis or multiple possibilities: the continuing problem of misdiagnosis. Neurology. 2013 Feb 19;80(8):777

- **1- Undiagnosing MS** has important clinical, psychosocial, and economic consequences for the patient, the treating neurologist, and the healthcare system at large.

- **2-** Recognizing **"red flags"** can be useful for the diagnostic evaluation of suspected cases of MS, facilitating the correct differential diagnosis by assessing the **combined** clinical, laboratory and MRI informations.

- **3-** Recognition and **rigorous interpretation of MRI** is extremely sensitive and specific for MS and is often sufficient to establish the right diagnosis.

THANK YOU

2nd MENACTRIMS CONGRESS 2016

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