
بسم الله الرحمن الرحيم
وقل رب زدنى علما
صدق الله العظيم

Demyelinating Diseases

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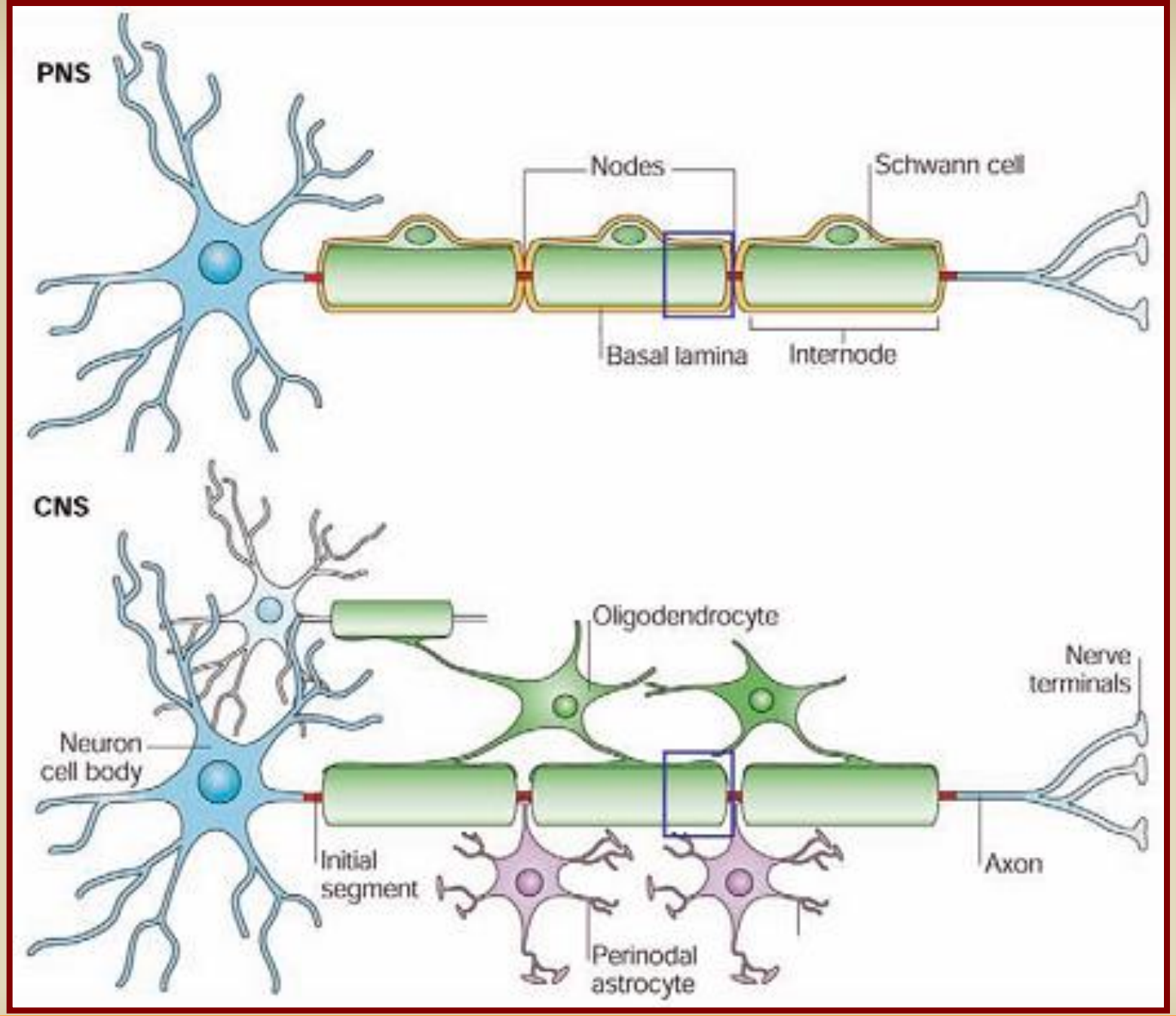
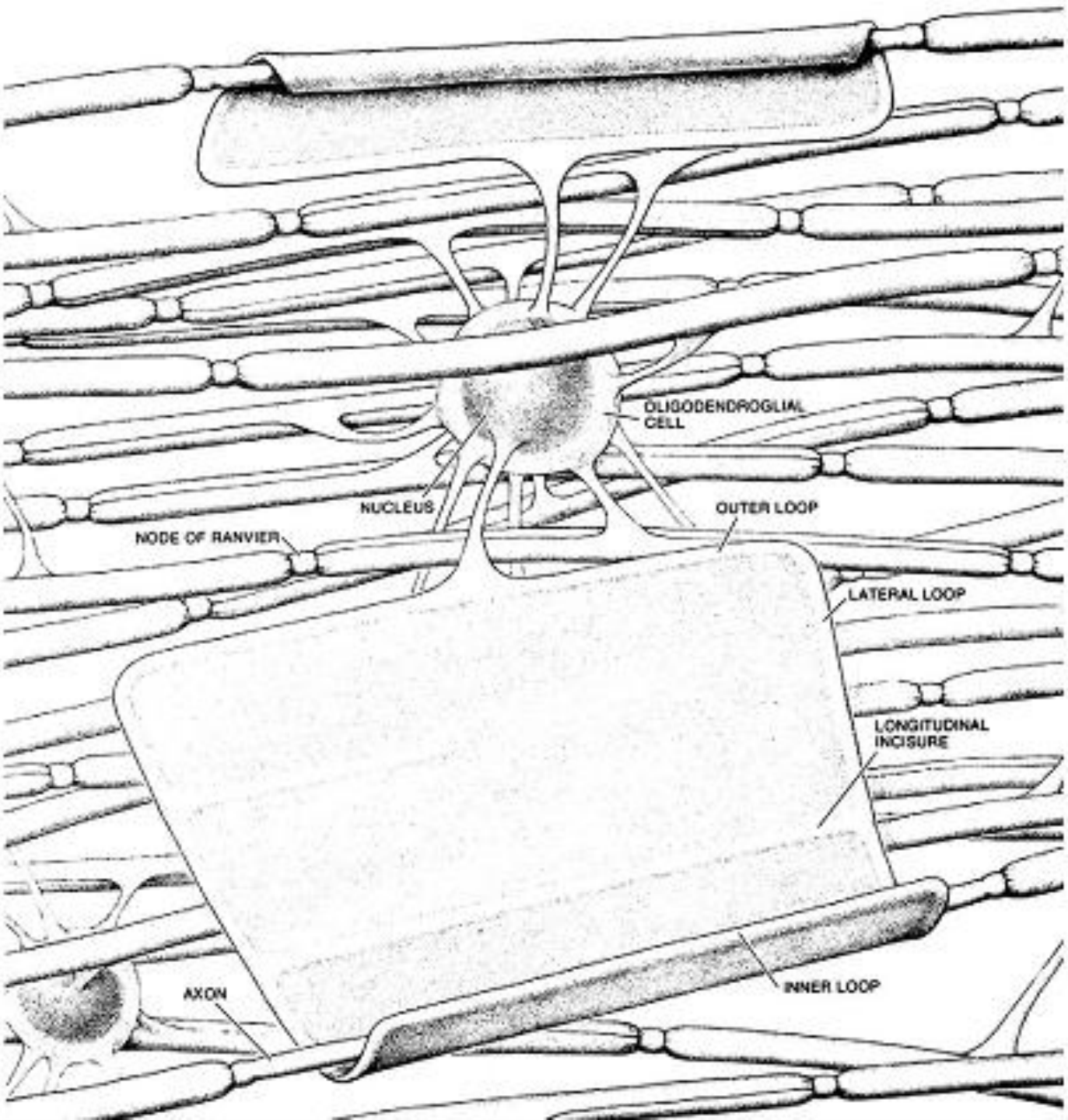
Introduction

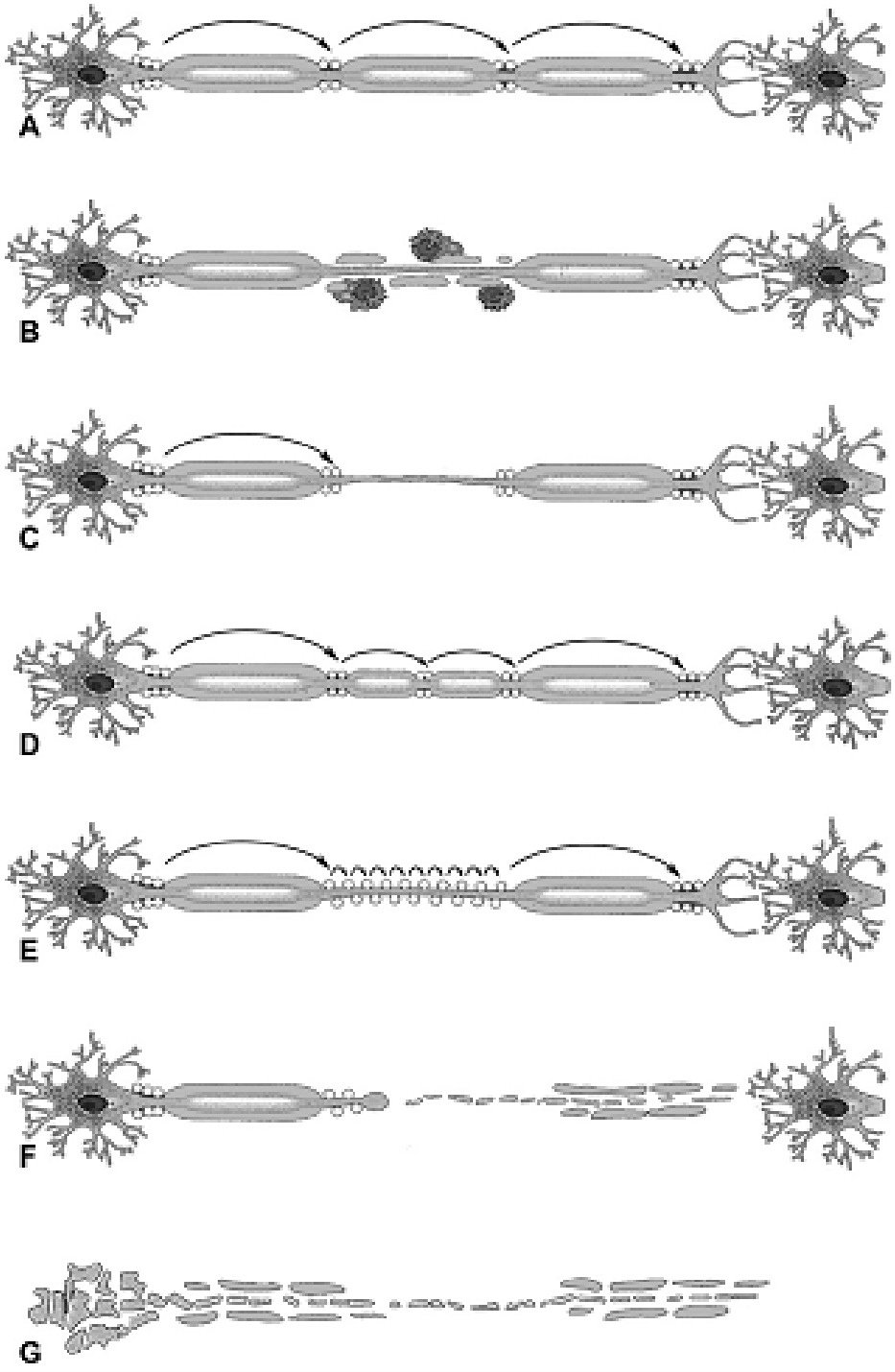
Myelination in CNS is mediated by oligodendrocytes which give multiple axons, so damage to these cells not followed by regeneration in contrast to peripheral nervous system in which each axon is covered by it's own Schwann cell so, it's liable for regeneration.



Schematic structure of myelinated axons.



Oligodendroglial cell body attached to 14 myelin sheaths, two of which have been unrolled to varying degrees to show the arrangement of the cytoplasmic strings in the sheet of myelin.



Pathogenesis of neurological disability in MS:

(A) Normal myelinated axons.

(B) Permanent disability due to immune-mediated demyelination

(C) Conduction block.

(D) Restoration of impulse conduction and neurological function may occur as a result of remyelination or

(E) Redistribution of Na+ channels.

(F) Permanent disability due to axonal transection

(G) Axonal degeneration.

Introduction

Demylinating diseases are diseases in which the structure and function of myelinated axons are distorted mostly due to inflammatory and autoimmune disorder.

In MS, demyelination is the usual explanation of this disorder with episodic neurological symptoms and signs.

Introduction

Demyelinating diseases are either inflammatory (usually episodic), or non-inflammatory (usually progressive).

Demyelination occurs throughout the CNS (especially white matter), optic nerves, brain stem, spinal cord and cerebellum

Classification of demyelinating diseases

A- Isolated demyelinating syndrome:

- *Optic neuritis.*
- *Acute dissiminated encephalomyelitis.*
- *Transverse myelitis.*
- *Chronic progressive myelopathy.*

B- Multiple sclerosis (MS):

- *Relapsing remitting.*
- *1ry Progressive.*
- *2ry Progressive.*
- *Devic's disease (variant of MS).*

C- Leucodystrophies (non inflammatory demyelination):

Genetically determined disorders of myelin formation.

- *Metachromatic leucodystrophies*
- *Adrenoleucodystrophies (Krabb's disease.)*

Multiple sclerosis

Commonest demyelinating disease.

Aetiology:

A. Genetics factors:

The most accepted theory is genetic one which explain why MS is common in some families than others.

B. Environmental factors:

Geographical distribution.

C. Viral:

EBV, HSV5

Pathology

Demyelinating diseases characterized by inflammatory cell infiltration with focal and multifocal lesions.

The hallmark in case of MS is the formation of sclerotic plaques due to:

- ***Demyelination.***
- ***Remyelination.***
- ***Oligodentrocyte depletion and astrocytosis.***
- ***Axon degeneration.***

Site

Around the lateral ventricles.

Cortical and subcortical white matter.

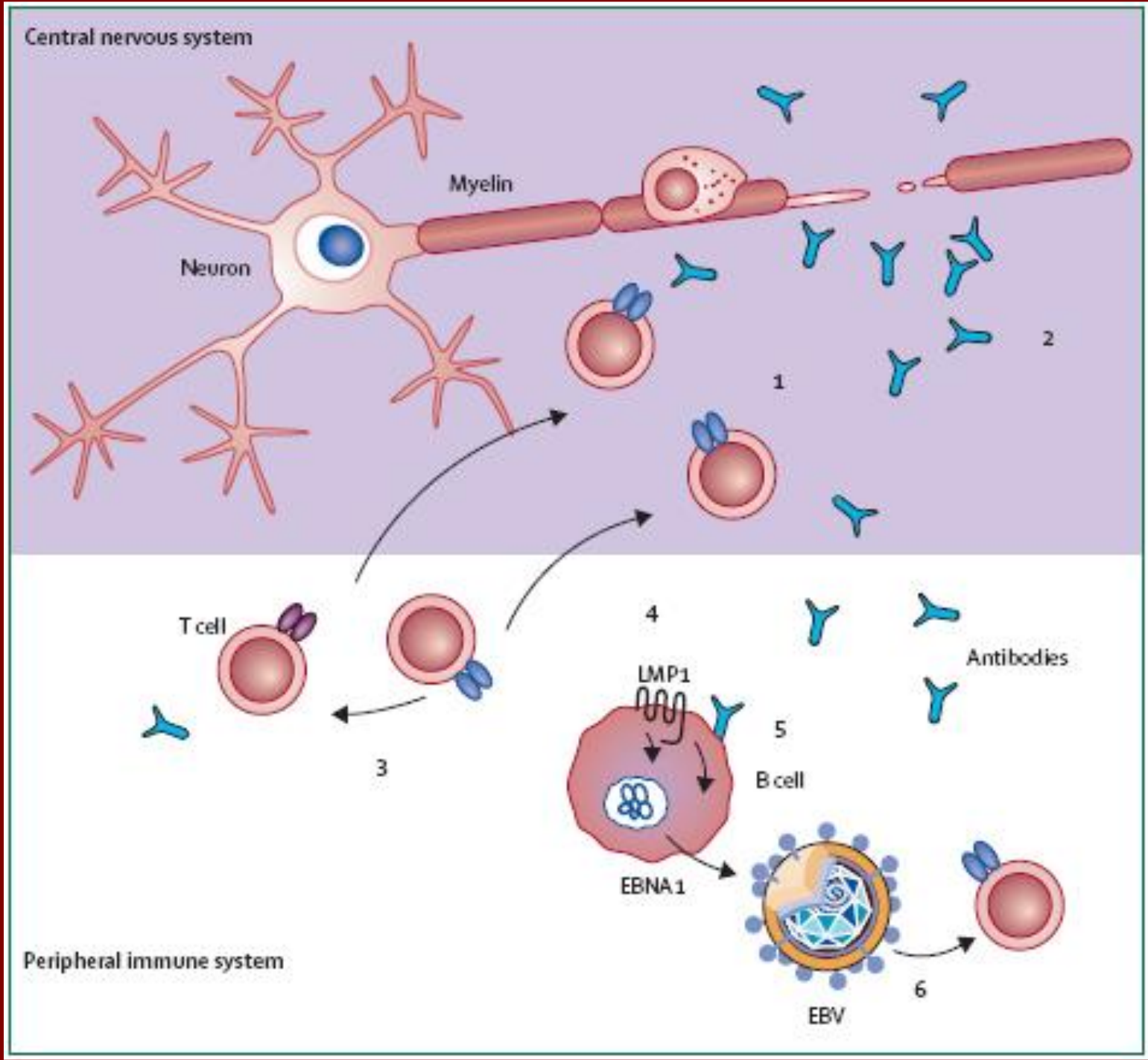
Optic nerves.

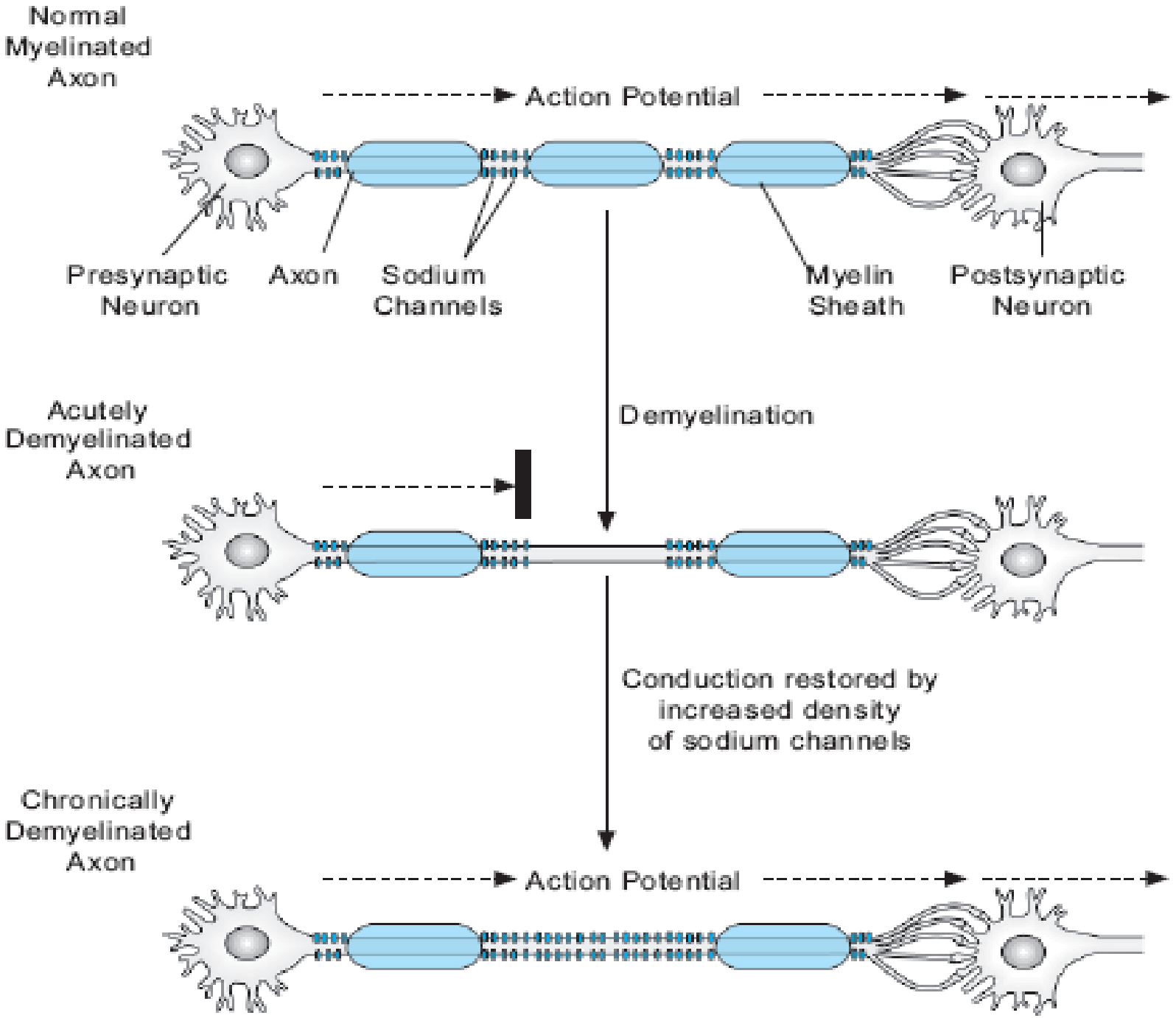
Cervical portion of spinal cord.

Corpus callosum.

4th ventricle.

Brain stem.


Central nervous system
Myelin
Neuron
1
2
T cell
3
4
Antibodies
LMP1
5
B cell
EBNA1
EBV
6
Peripheral immune system

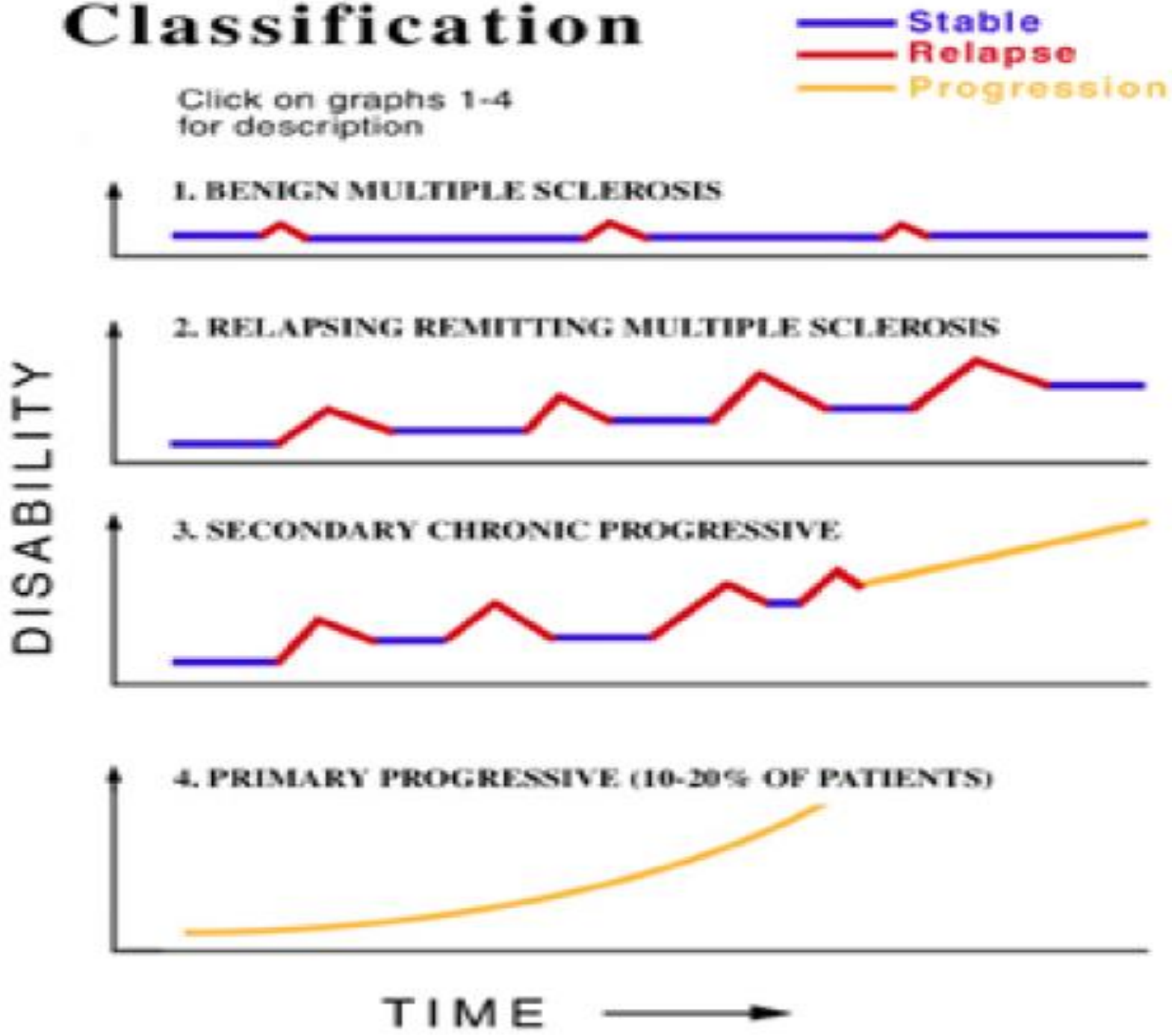

Normal Myelinated Axon
Action Potential
Presynaptic Neuron
Axon
Sodium Channels
Myelin Sheath
Postsynaptic Neuron
Demyelination
Acutely Demyelinated Axon
Conduction restored by increased density of sodium channels
Chronically Demyelinated Axon
Action Potential

Clinical features

MS or disseminated sclerosis means dissemination in time and space:

- ✓ ***Multiple lesions through the CNS e.g optic nerve spinal cord, brain stem.***
- ✓ ***Lesions differ in time (episodic) (80%).***

Classification



Clinical features

I. Motor:

- ✓ ***Weaknes, spasticity.***
- ✓ ***Seizures can occur in 3-4% of patient.***

II. Sensory:

- ✓ ***Numbness, pain.***

III. Cerebellar:

- ✓ ***Ataxia, nystagmus.***

IV. Sphincteric:

- ✓ ***Urgency, hesitancy, incontinence.***

V. Mental changes:

- ✓ ***Learning disabilities, dementia.***

Clinical features

VI. Brain stem & cranial nerves:

- ✓ *Optic nerve affection → blurring of vision, diminution of vision, monocular blindness (optic atrophy).*
- ✓ *Facial weakness.*
- ✓ *Internuclear ophthalmoplegia.*
- ✓ *Dysarrtheria, deafness, vertigo, diplopia.*
- ✓ *Trigeminal neuralgia.*

VII. Others:

- ✓ *Depression, fatigue.*

Diagnosis and differential diagnosis

Once there is evidence of multiple CNS lesions with remitting & relapsing symptoms over a period of time with exclusion of other causes (DD):

- ***Metastatic tumours***
- ***Cerebral arteritis (Behcet's disease, SLE)***
- ***CNS infection***

A single lesion causing recurrent symptoms may be due to:

- ***Vascular malformation of brain stem.***
- ***Chiari malformation.***
- ***Tumour of the foramen magnum or cerebellopontine angle.***

The Poser et al. Criteria

Clinically definite MS
- Two attacks and clinical evidence of two separate lesions
- Two attacks and clinical evidence of one, and paraclinical evidence of another, separate lesion

Laboratory-supported definite MS
- Two attacks and either clinical or paraclinical evidence of one lesion, plus CSF OCB or elevated IgG
- One attack and clinical evidence of two separate lesions, plus CSF OCB or elevated IgG
- One attack, clinical evidence of one lesion, and paraclinical evidence of another, separate lesion, plus CSF OCB or elevated IgG

Clinically probable MS
- Two attacks and clinical evidence of one lesion
- One attack and clinical evidence of two separate lesions
- One attack, clinical evidence of one, and paraclinical evidence of another separate lesion,

Laboratory-supported probable MS
- Two attacks and CSF OCB or elevated IgG

Paraclinical: evoked potentials, CT or MRI; at least two OCB, none in serum.

The 2005 Revisions to the McDonald Diagnostic Criteria for MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
Two or more attacks[a]; objective clinical evidence of two or more lesions	None[b]
Two or more attacks[a]; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: MRI[c] or Two or more MRI-detected lesions consistent with MS plus positive CSF[d] or Await further clinical attack[a] implicating a different site
One attack[a]; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: MRI[c] or Second clinical attack[a]
One attack[a]; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome [CIS])	Dissemination in space, demonstrated by: MRI[c] or Two or more MRI-detected lesions consistent with MS plus positive CSF[d] and Dissemination in time, demonstrated by: MRI[c] or Second clinical attack[a]
Insidious neurological progression suggestive of MS	1 yr of disease progression (retrospectively or prospectively determined) and two of the following: a) Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive VEP)[e] b) Positive spinal cord MRI (two focal T2 lesions) c) Positive CSF[d]

The 2005 Revisions to the McDonald Diagnostic Criteria Using MRI

Three of the following are required for demonstrating dissemination in space

1. At least one gadolinium-enhancing lesion or nine T2 hyperintense lesions if there is no gadolinium-enhancing lesion
2. At least one infratentorial lesion
3. At least one juxtacortical lesion
4. At least three periventricular lesions

There are two ways to show dissemination in time:

1. Detection of gadolinium enhancement at least three months after the onset of the initial clinical event, if not at the site corresponding to the initial event
2. Detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

The 2010 Revisions to the McDonald Diagnostic Criteria Using MRI

Relapsing Remitting MS:-

@ Dissemination in space can be demonstrated by ≥1 T2 lesion in at least 2 of 4 areas of the CNS(Periventricular, Juxtacortical, Infratentorial, Spinal cord)

@ Dissemination in time 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.

Primary progressive multiple sclerosis :

1. One year of disease progression (retrospectively or prospectively determined)
2. Plus two of the following criteriab:

A. Evidence for DIS in the brain based on Q1 T2c lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)

B. Evidence for DIS in the spinal cord based on Q2 T2c lesions in the cord

C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Conditions That Can Mimic Multiple Sclerosis

CNS infection (e.g., Lyme disease, syphilis, human immunodeficiency virus infection, human T-lymphotrophic virus type I)

CNS inflammatory condition (e.g., sarcoidosis, systemic lupus erythematosus, Sjögren's syndrome)

CNS microvascular disease (e.g., disease caused by hypertension, diabetes mellitus, vasculitis, CADASIL)

Genetic disorder (e.g., leukodystrophy, hereditary myelopathy, mitochondrial disease)

Structural or compressive condition of the brain and spinal cord (e.g., cervical spondylosis, tumor, herniated disc, Chiari's malformation)

Vitamin B_{12} deficiency

Investigations

1-CSF

- *Abnormal in 80 % of cases.*
- *Mild mononuclear pleocytosis (lymphocytosis 50%).*
- *Modest increase in total protein.*
- *More specifically the presence of oligoclonal band (IgG band) by electrophoresis (85%).*

2-Evoked potentials

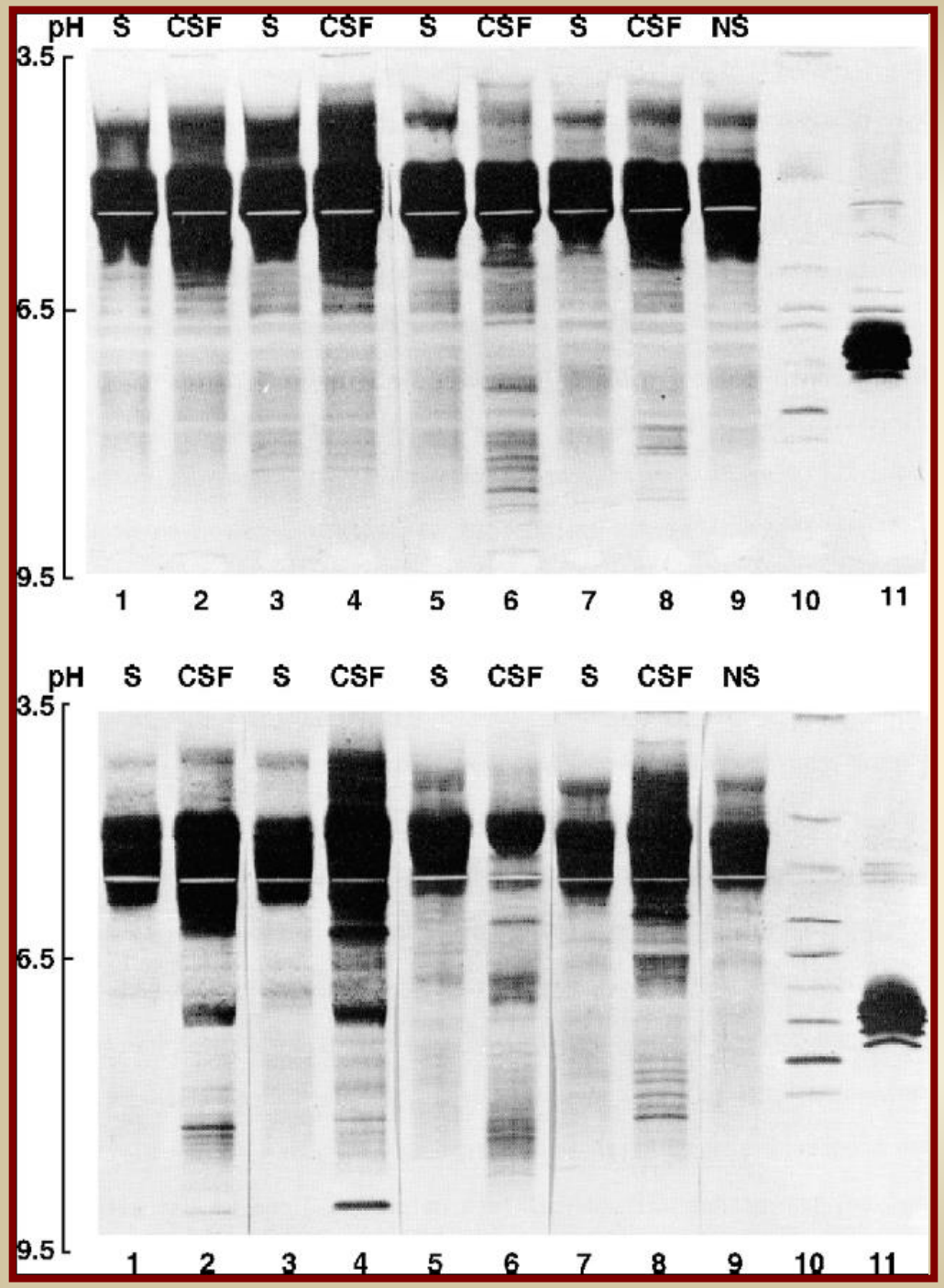
Visual, auditory and somatosensory evoked potentials for not clinically manifest lesions → delayed conduction.

3-CT

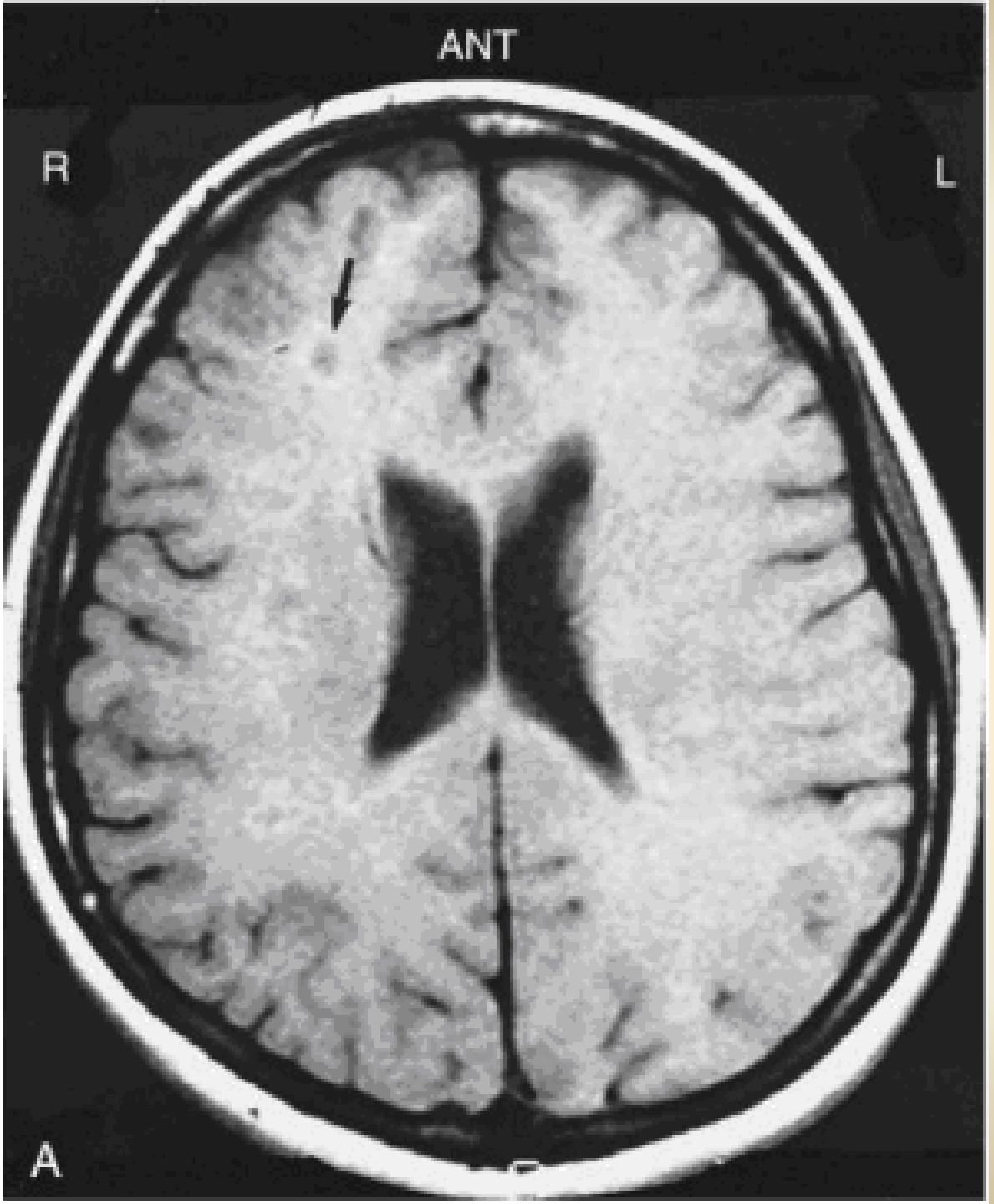
Hypodense lesions.

4-MRI (T2 weighted)

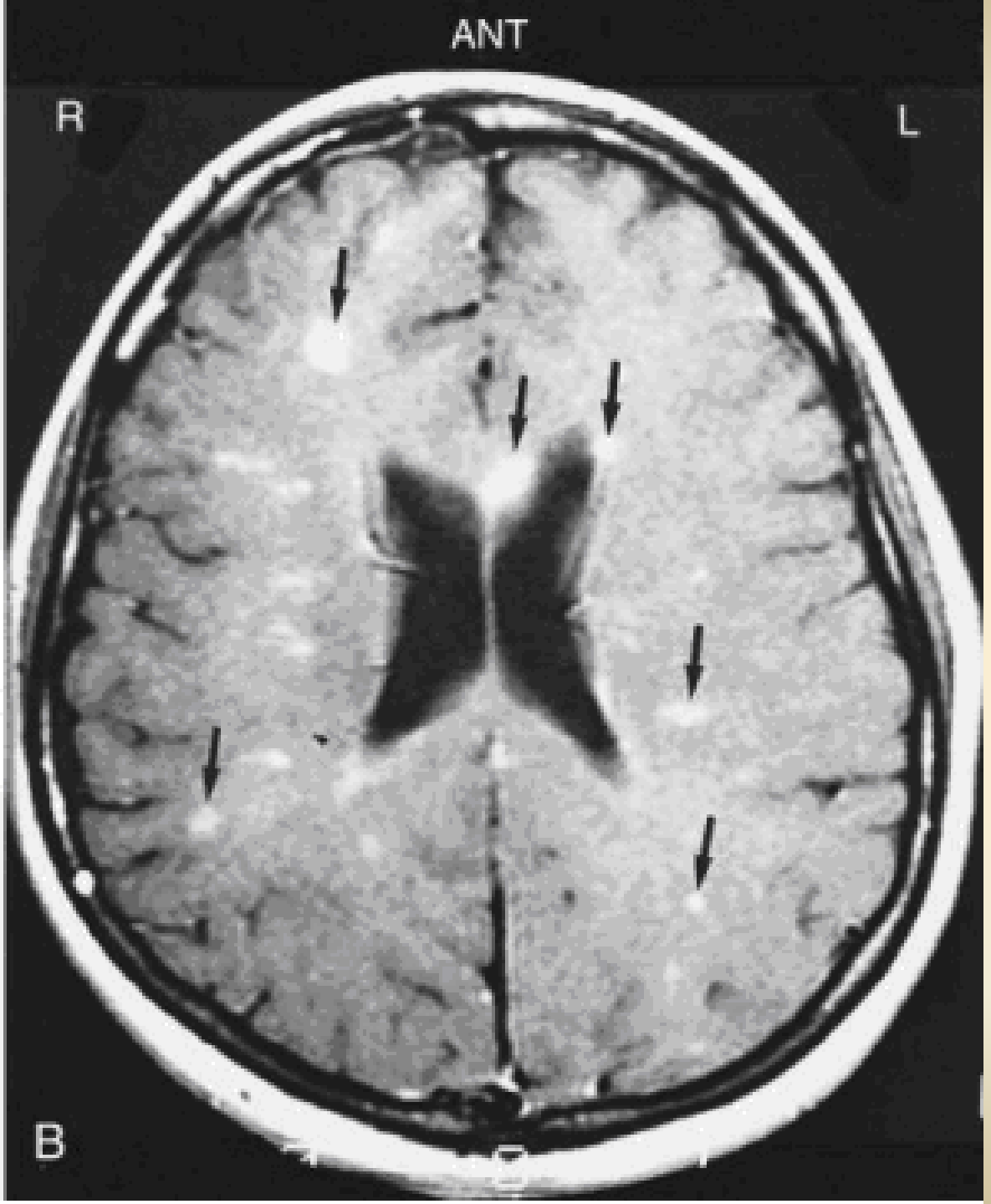
Multiple, periventricular lesions.



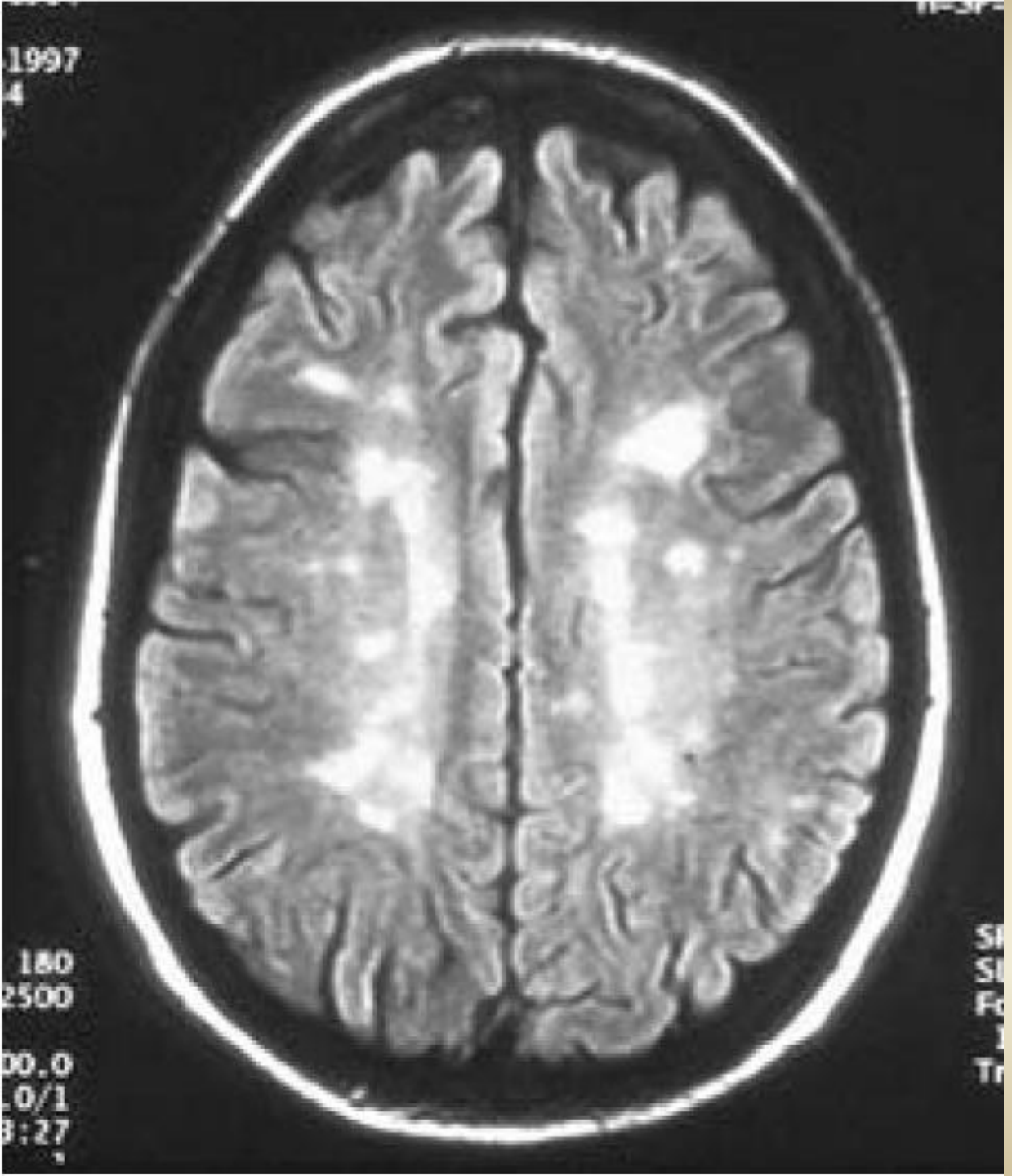
Oligoclonal band by electrophoresis



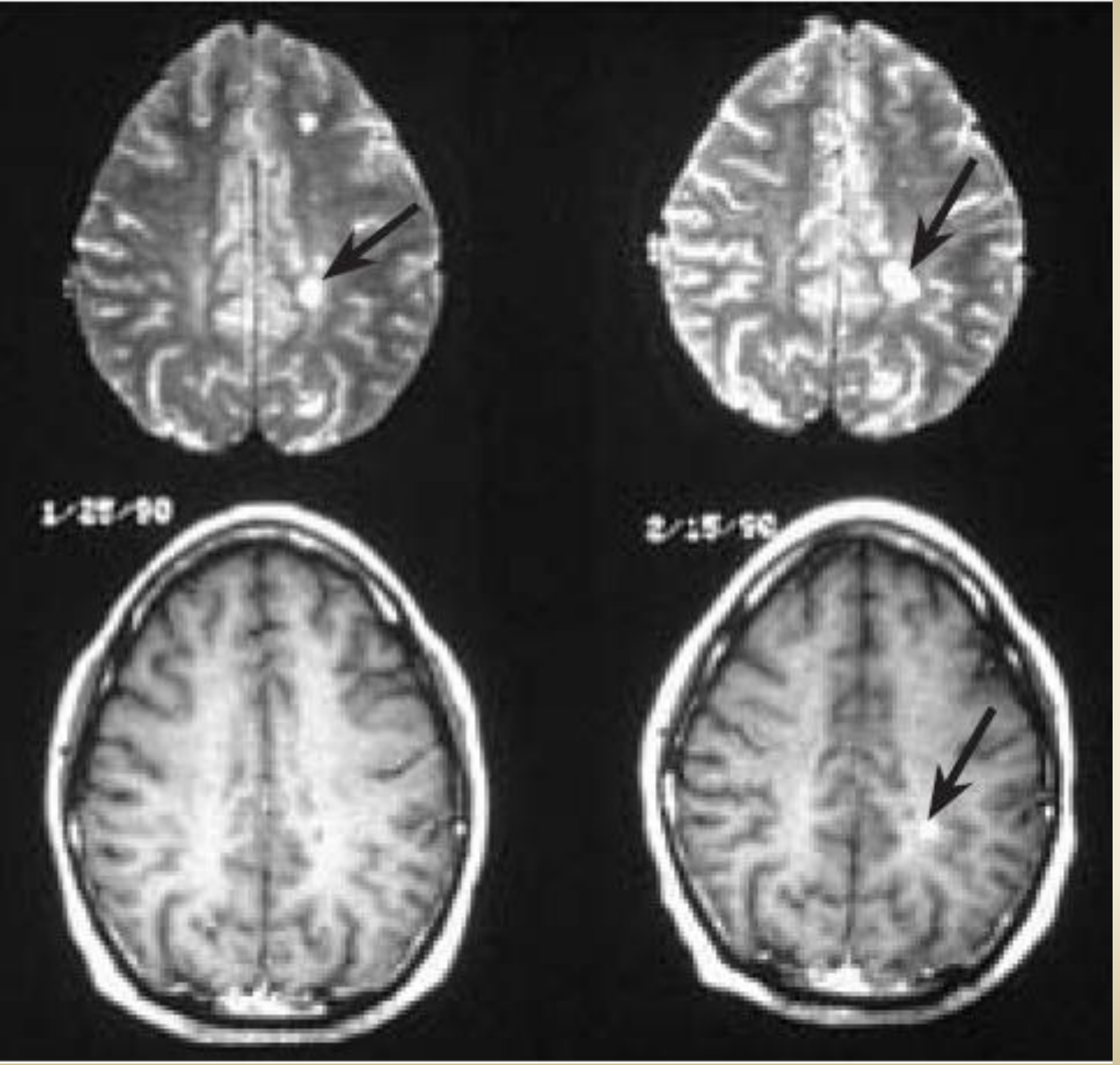
T1W show only one lesion.



T1W with gadolinium is better.

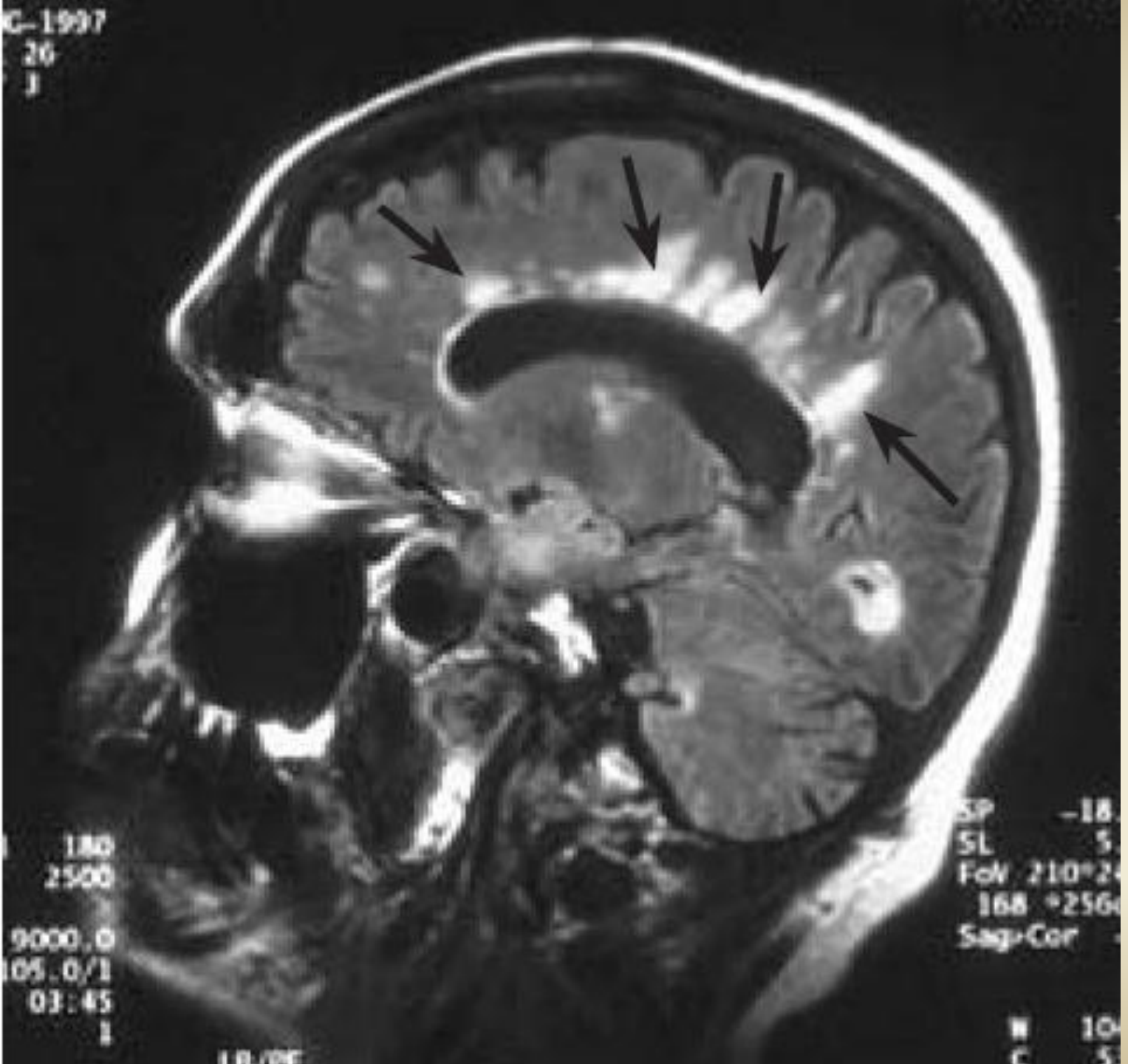


FLAIR, most sensitive for MS, not specific.

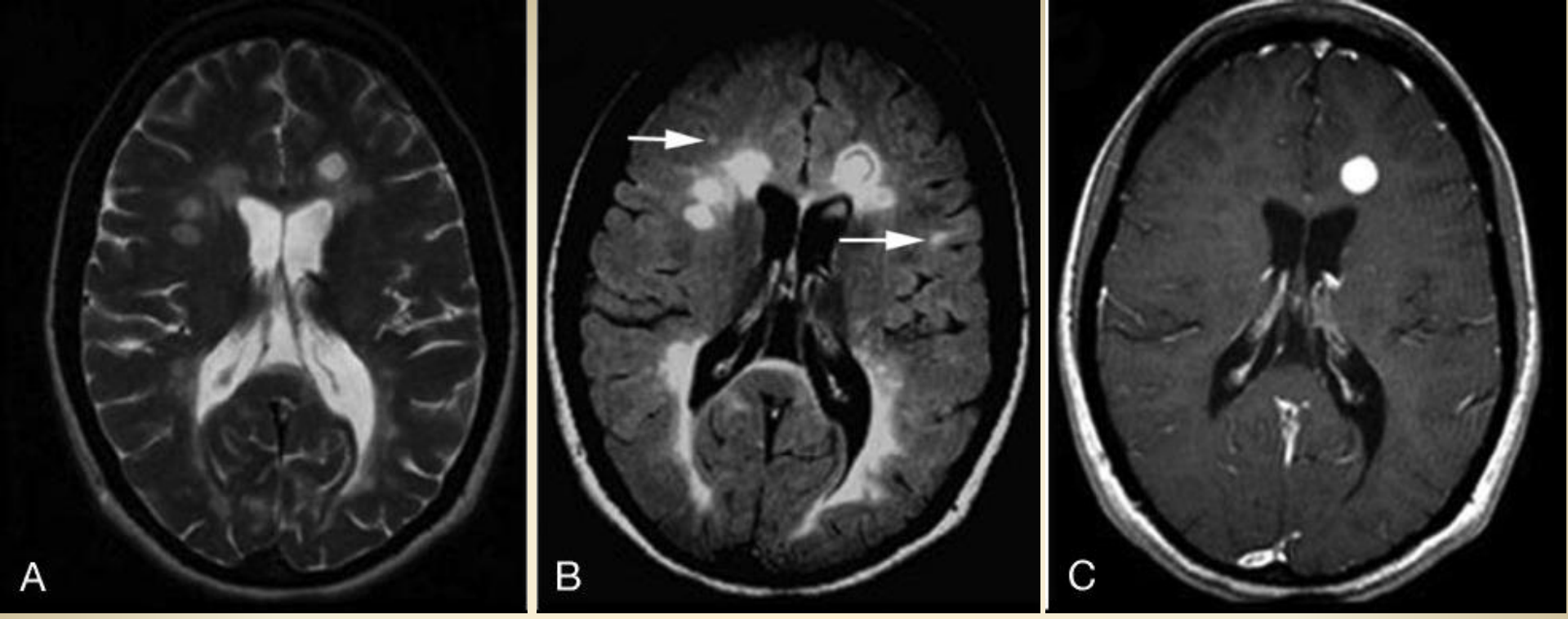


T2W

T1W with gadolinium



FLAIR

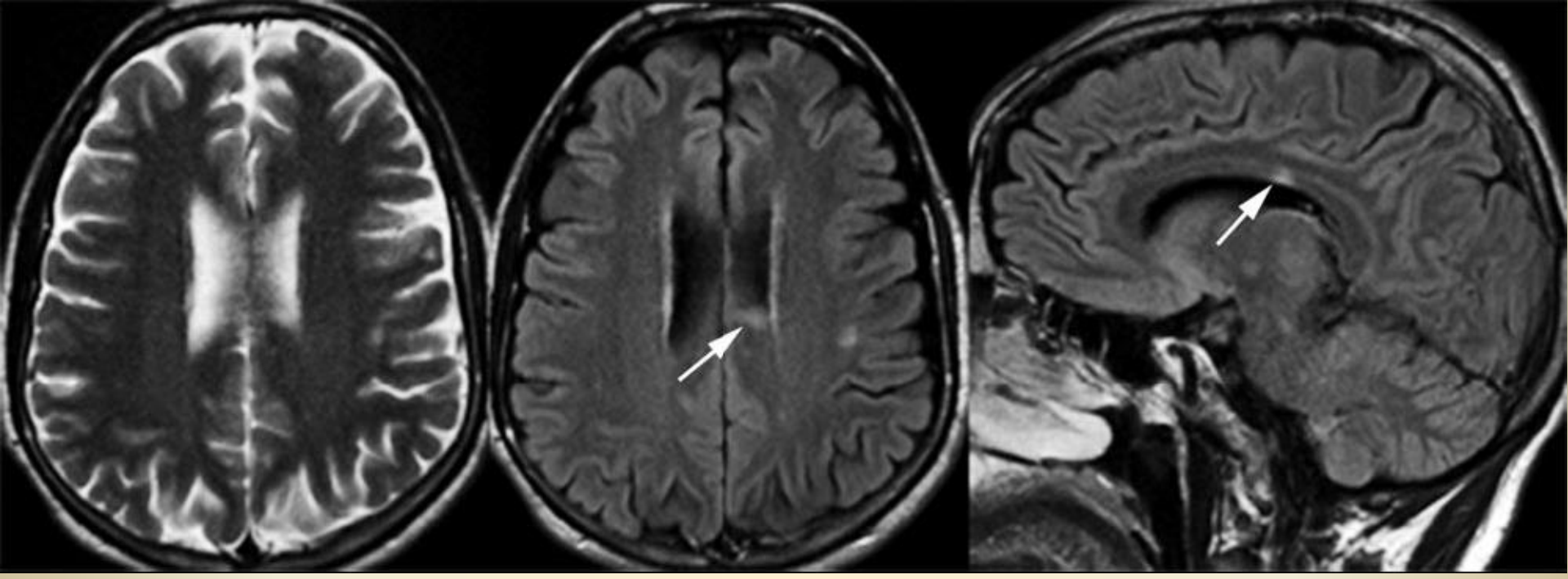


T2W

FLAIR

T1W with gadolinium

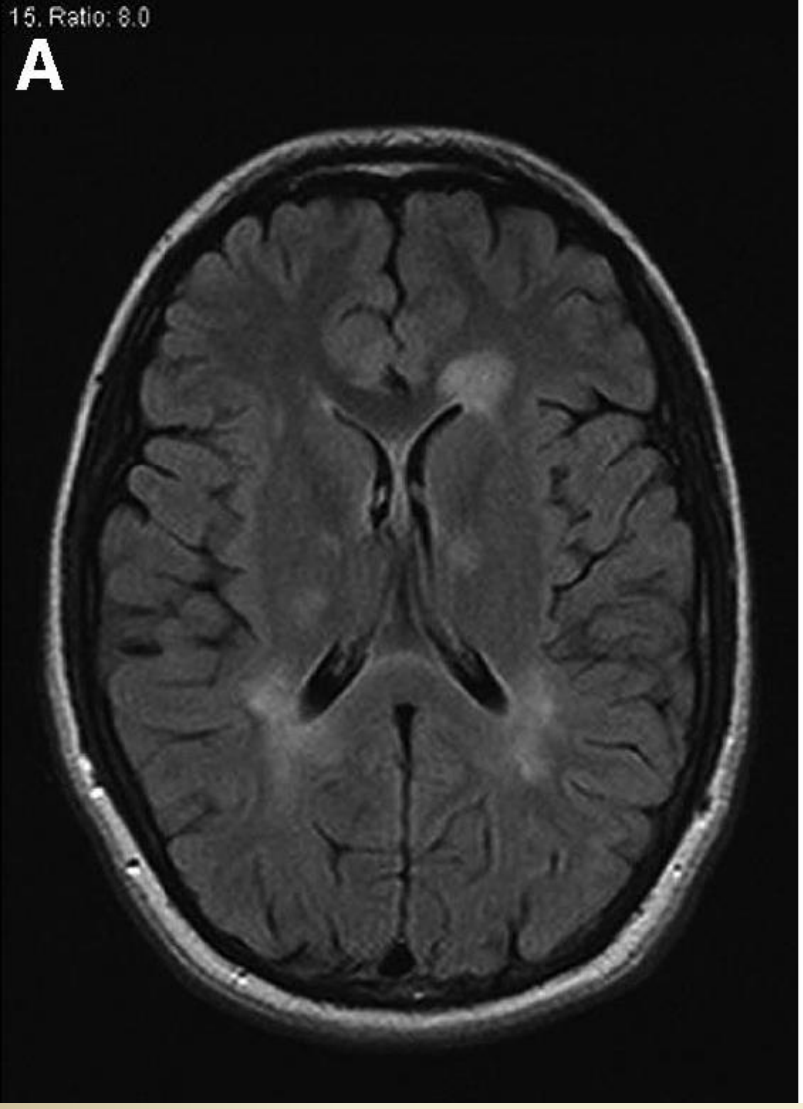
A 30-year-old female RRMS patient

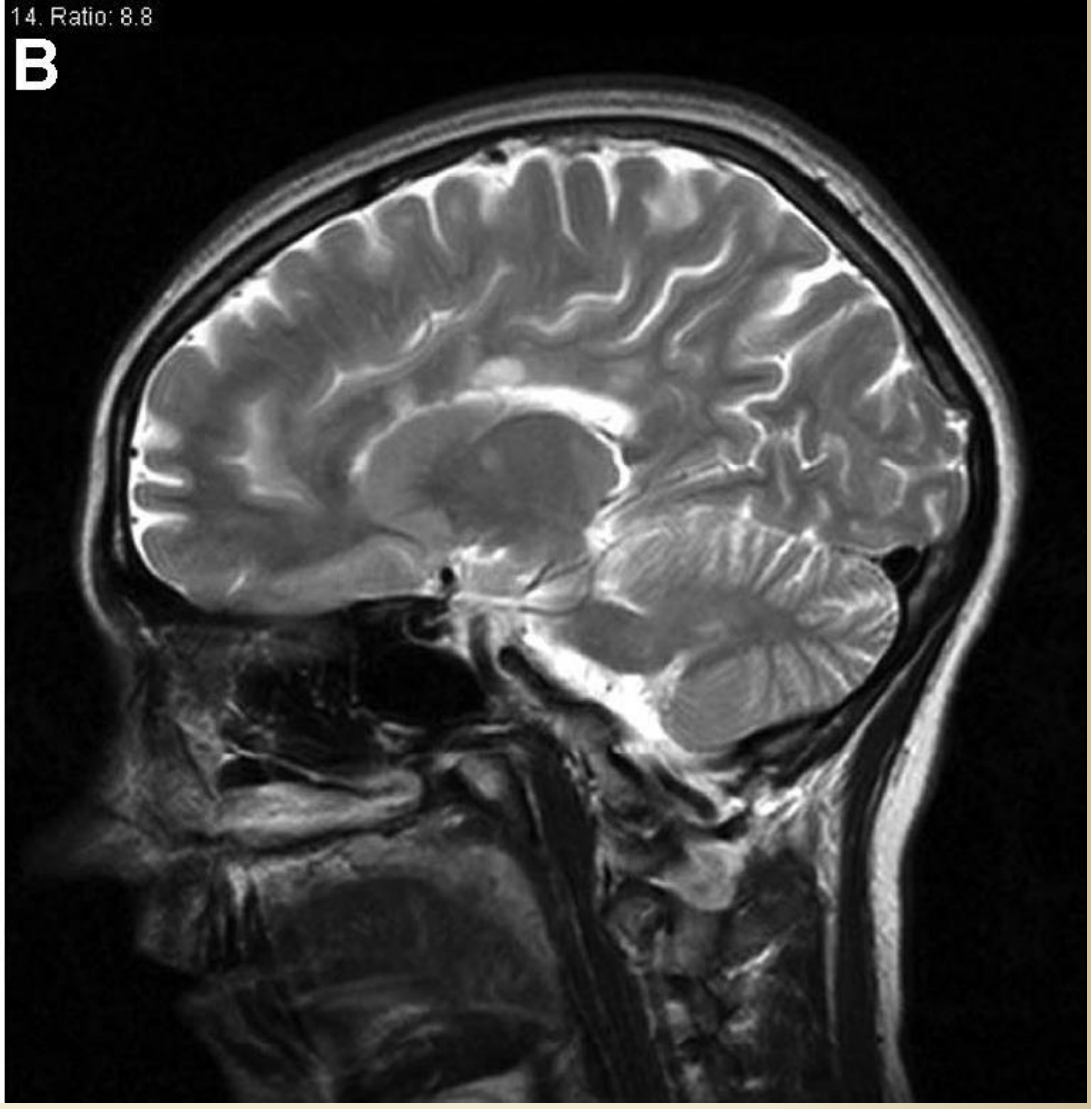


T2W

FLAIR

MS lesion (arrow) in corpus callosum.

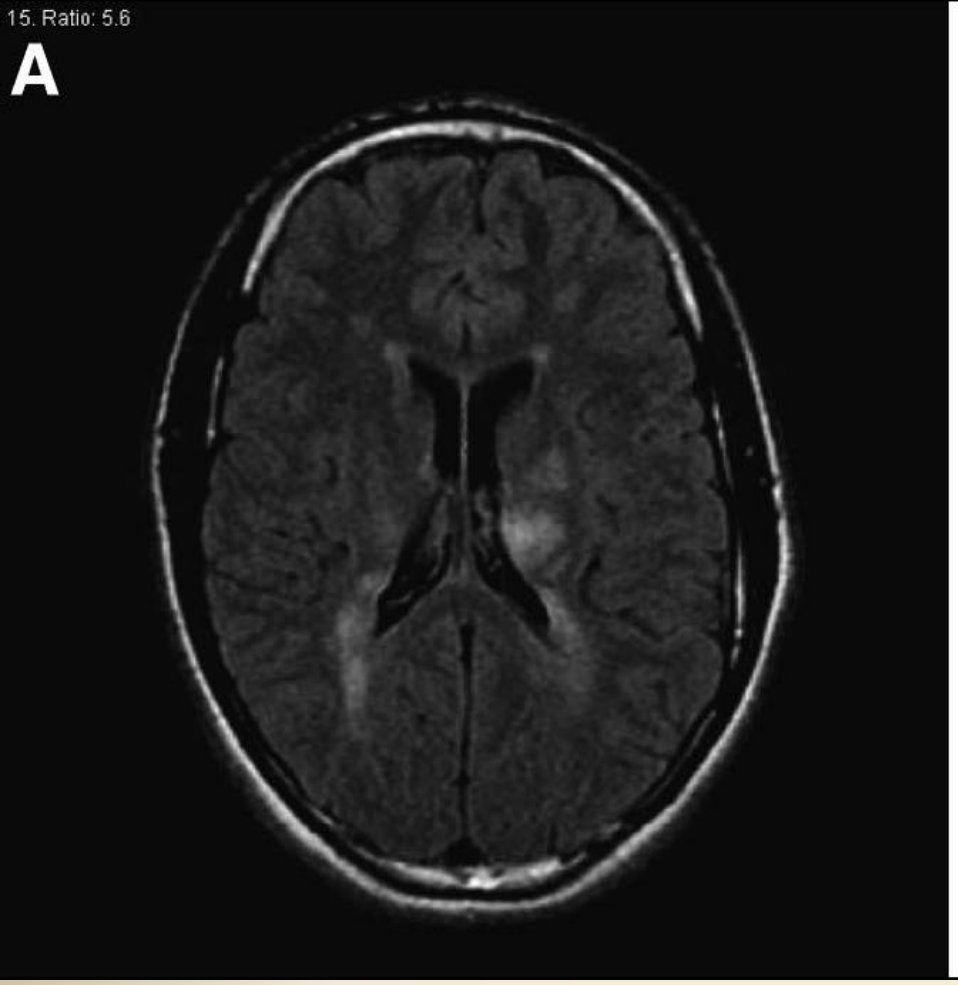


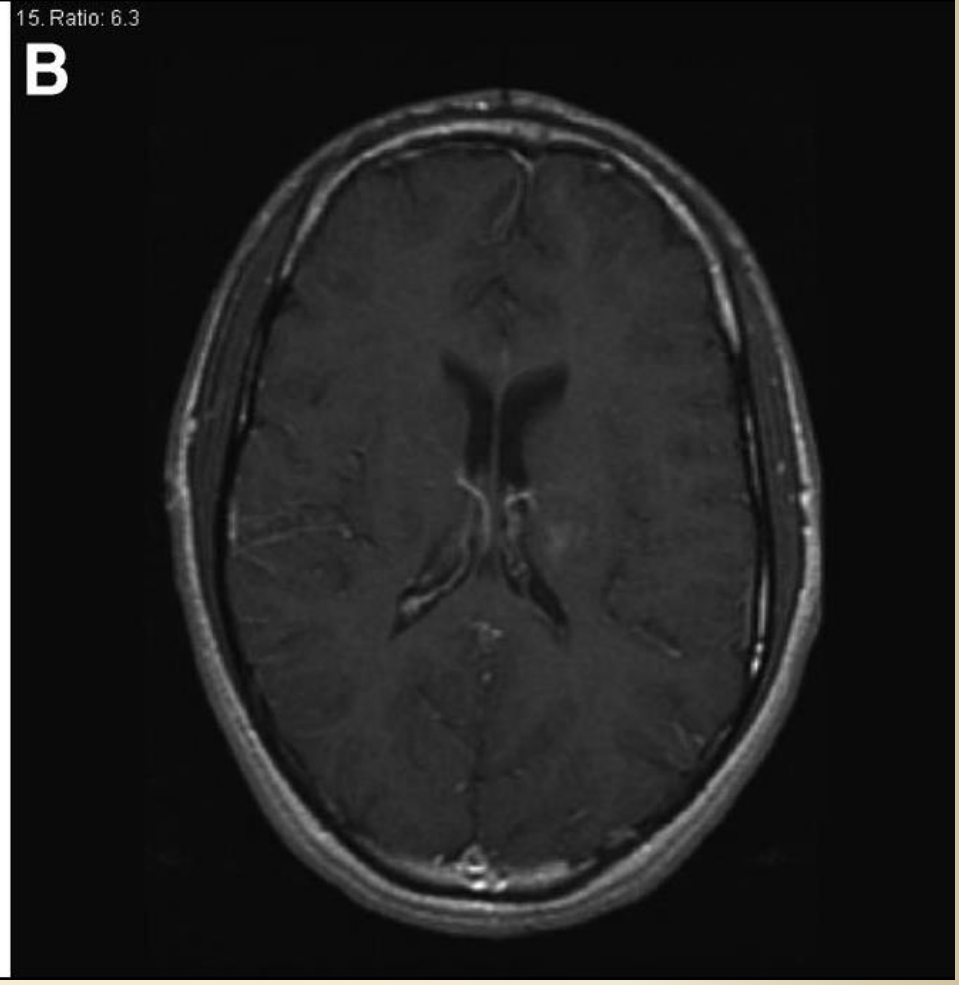


FLAIR

Sagittal T2W

A 17-year-old girl with a 2-year history of RRMS.

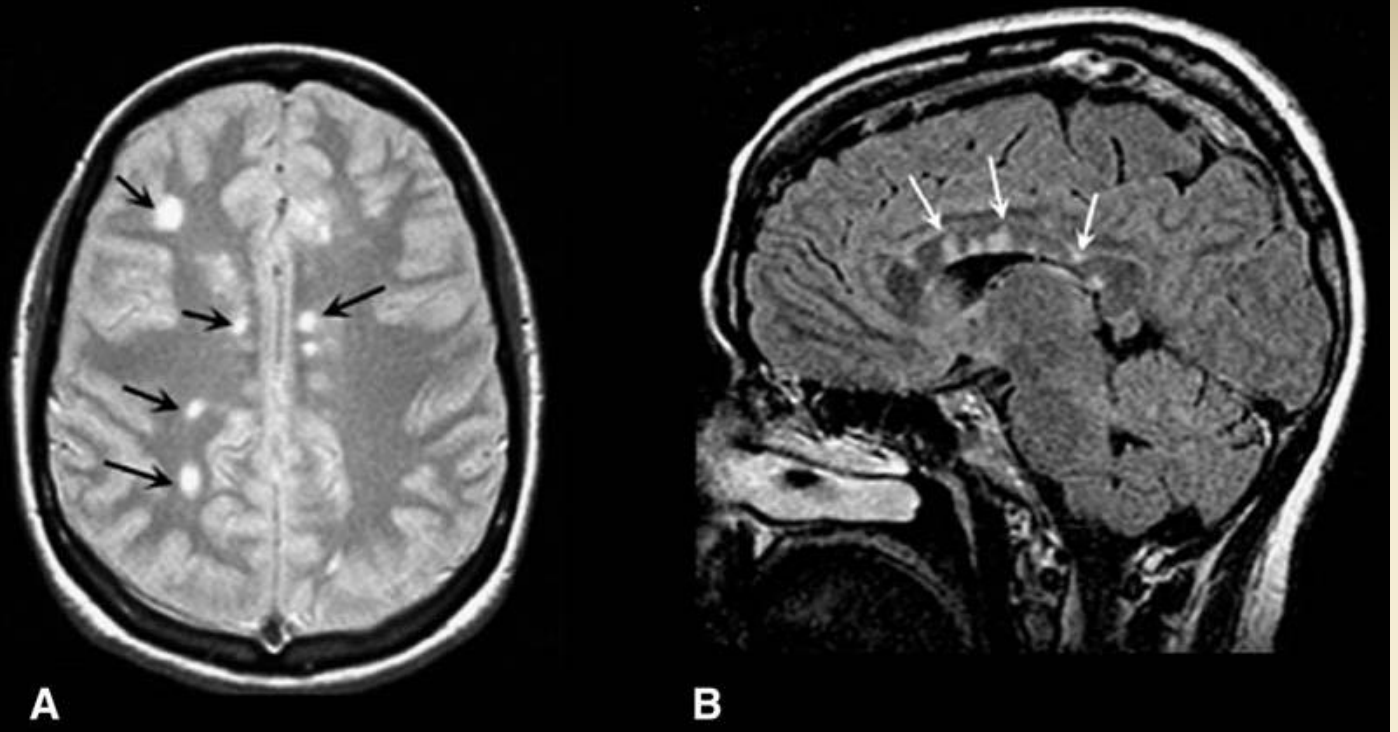


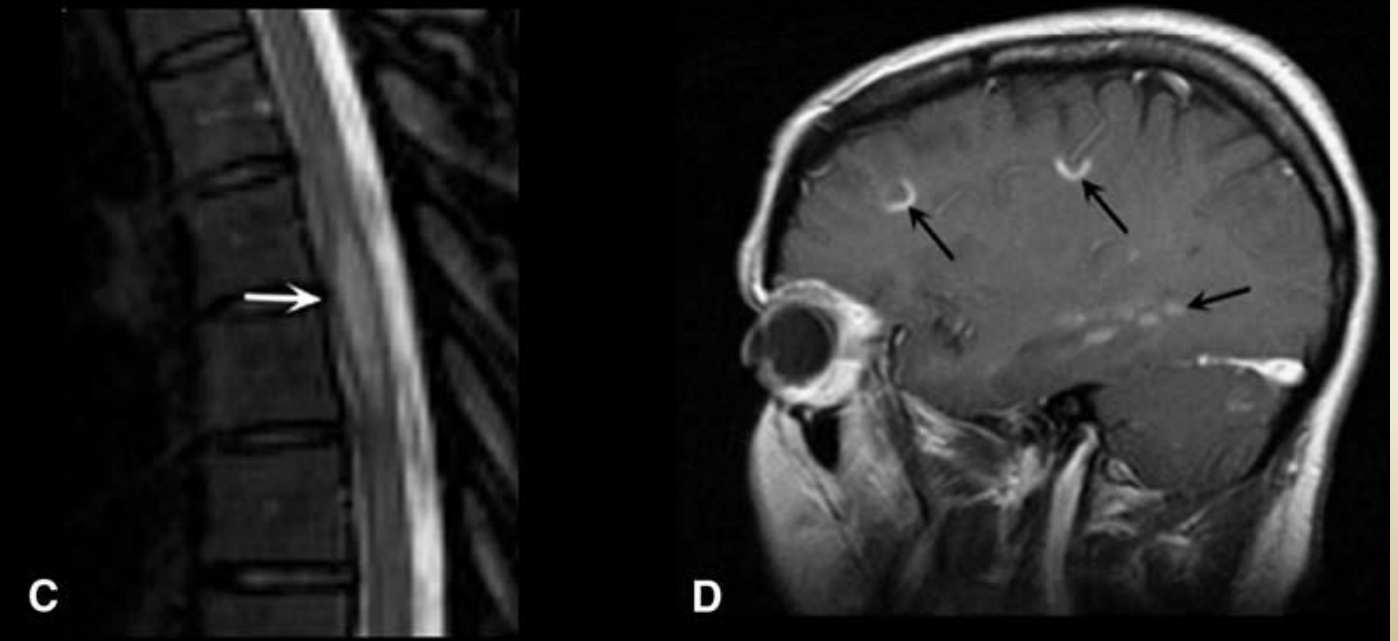


FLAIR

T1W with gadolinium

A 14-year-old boy with a 2-year history of RRMS presented with a new relapse involving weakness of his right arm and leg.



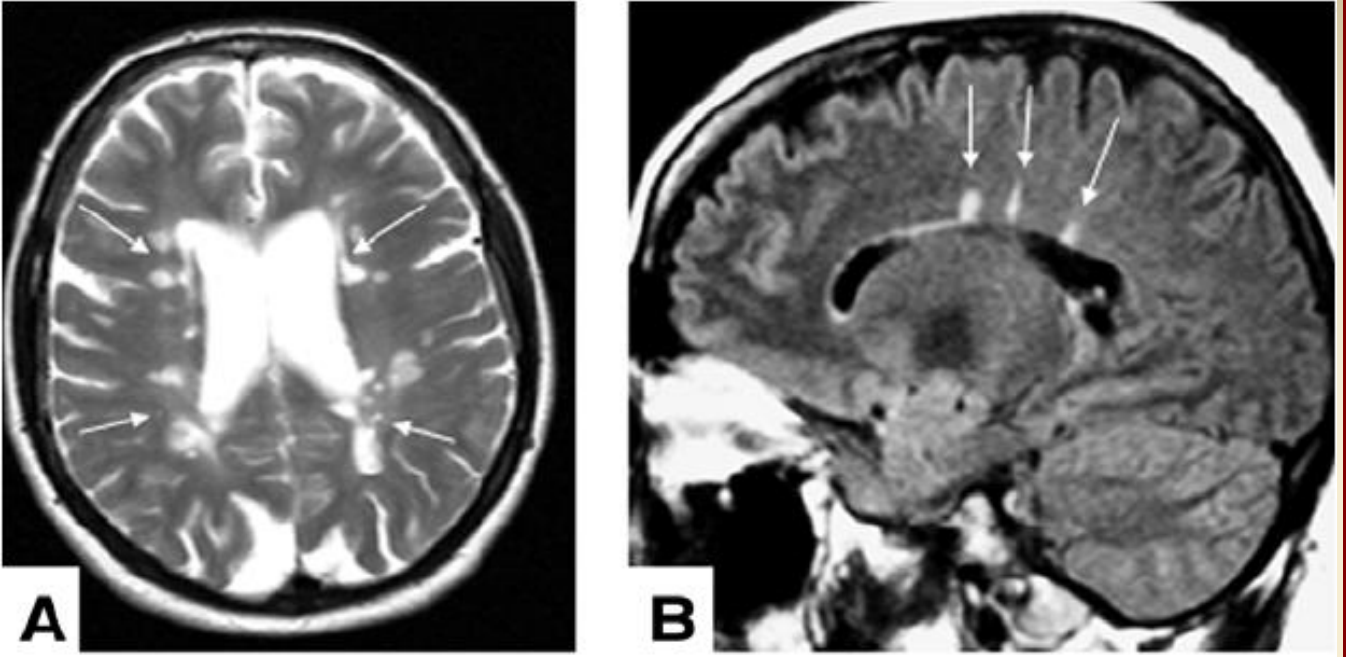


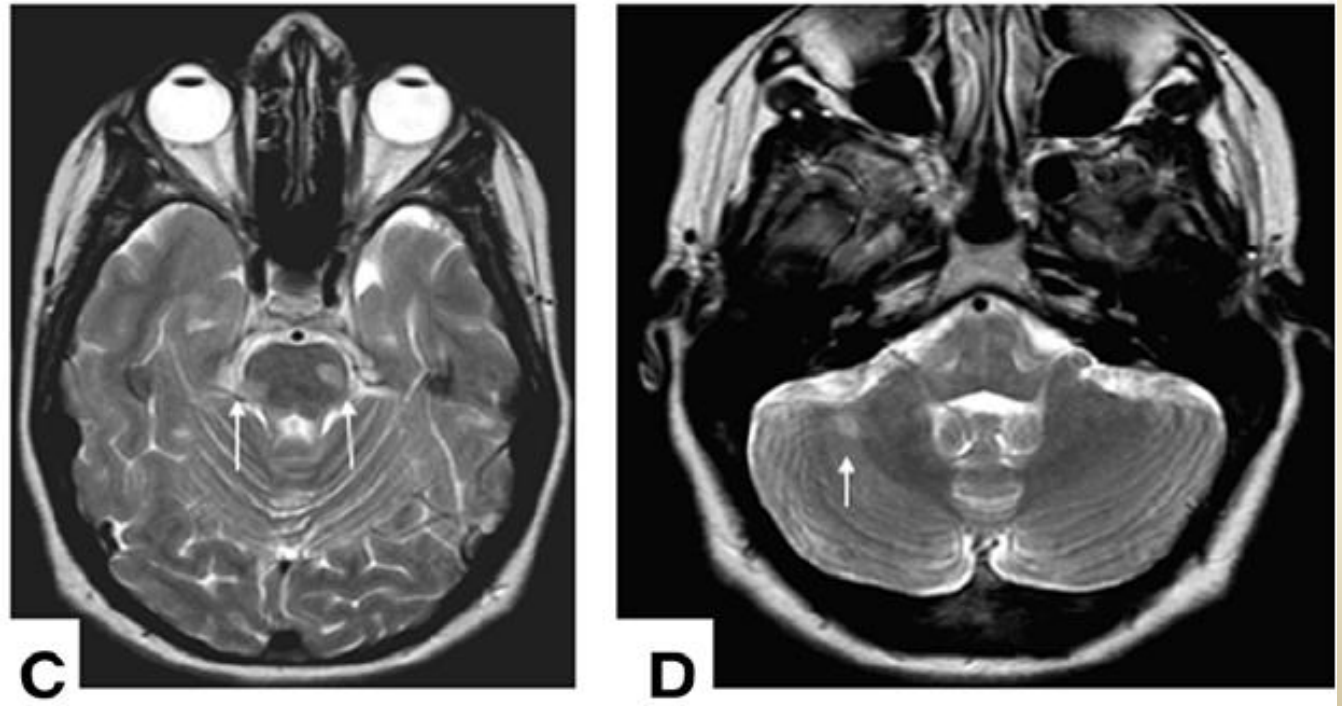
(A) T2W

B) FLAIR

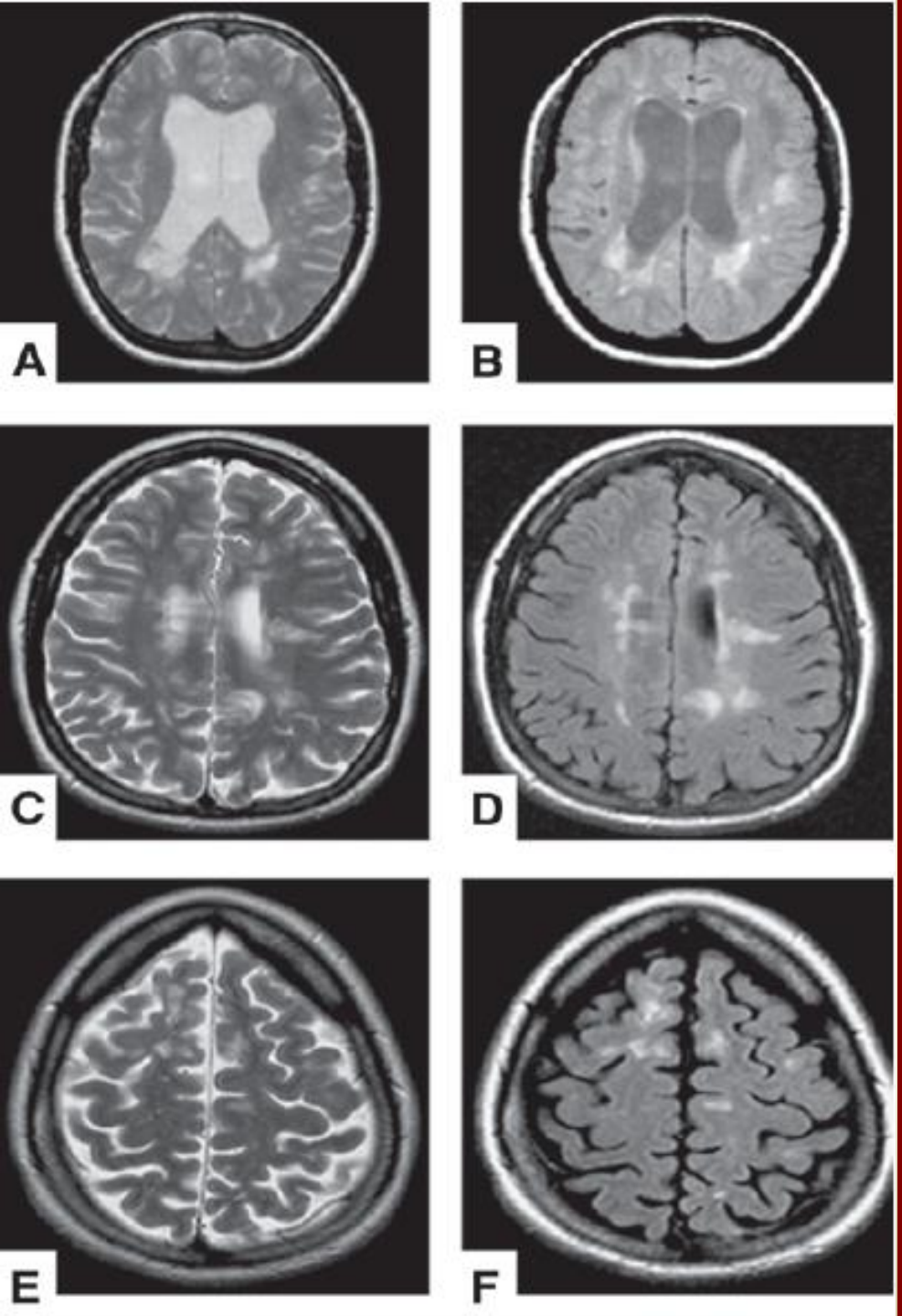
C) Sagittal T2W of the thoracic spine

(D) Sagittal T1W after gadolinium

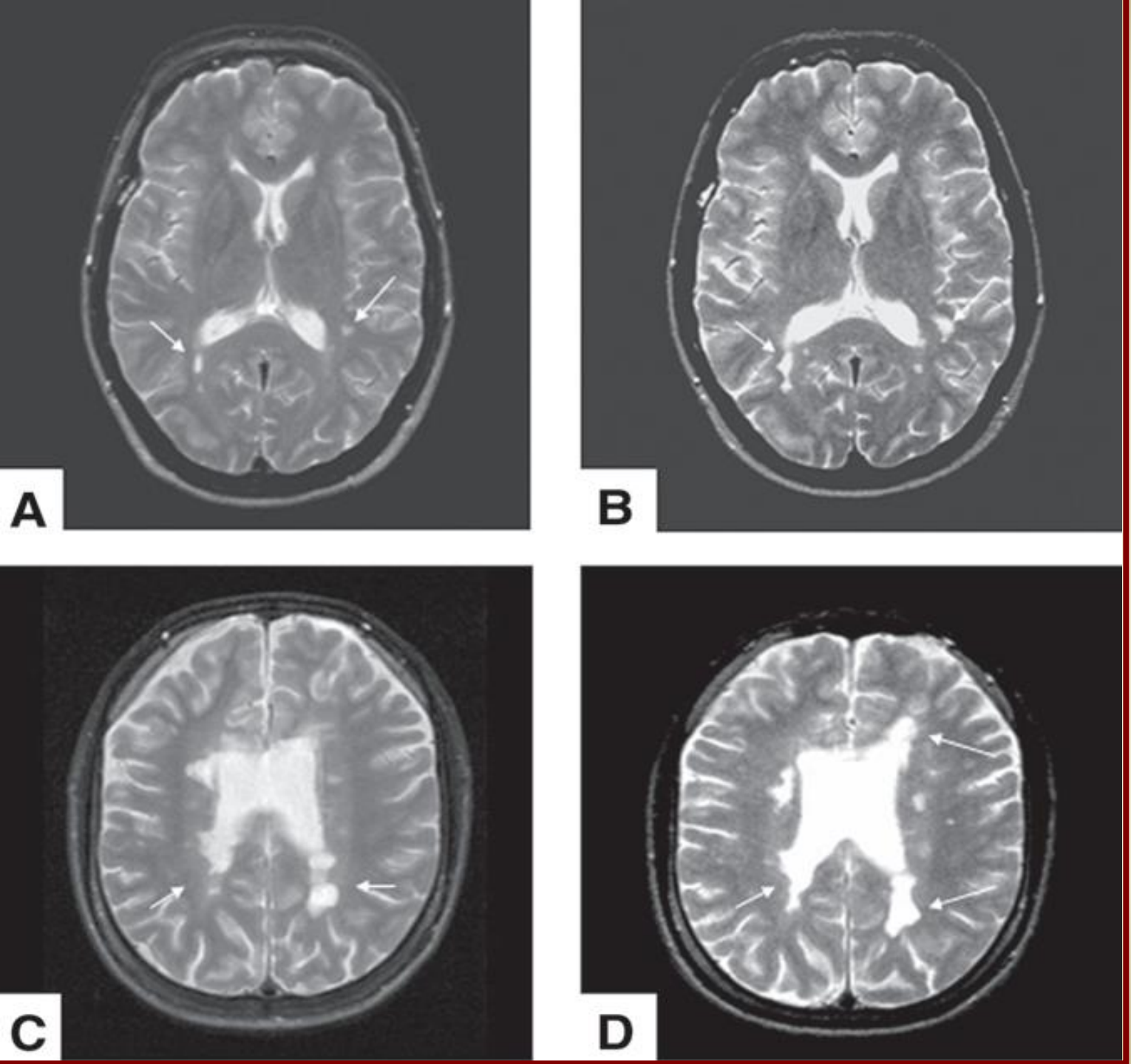




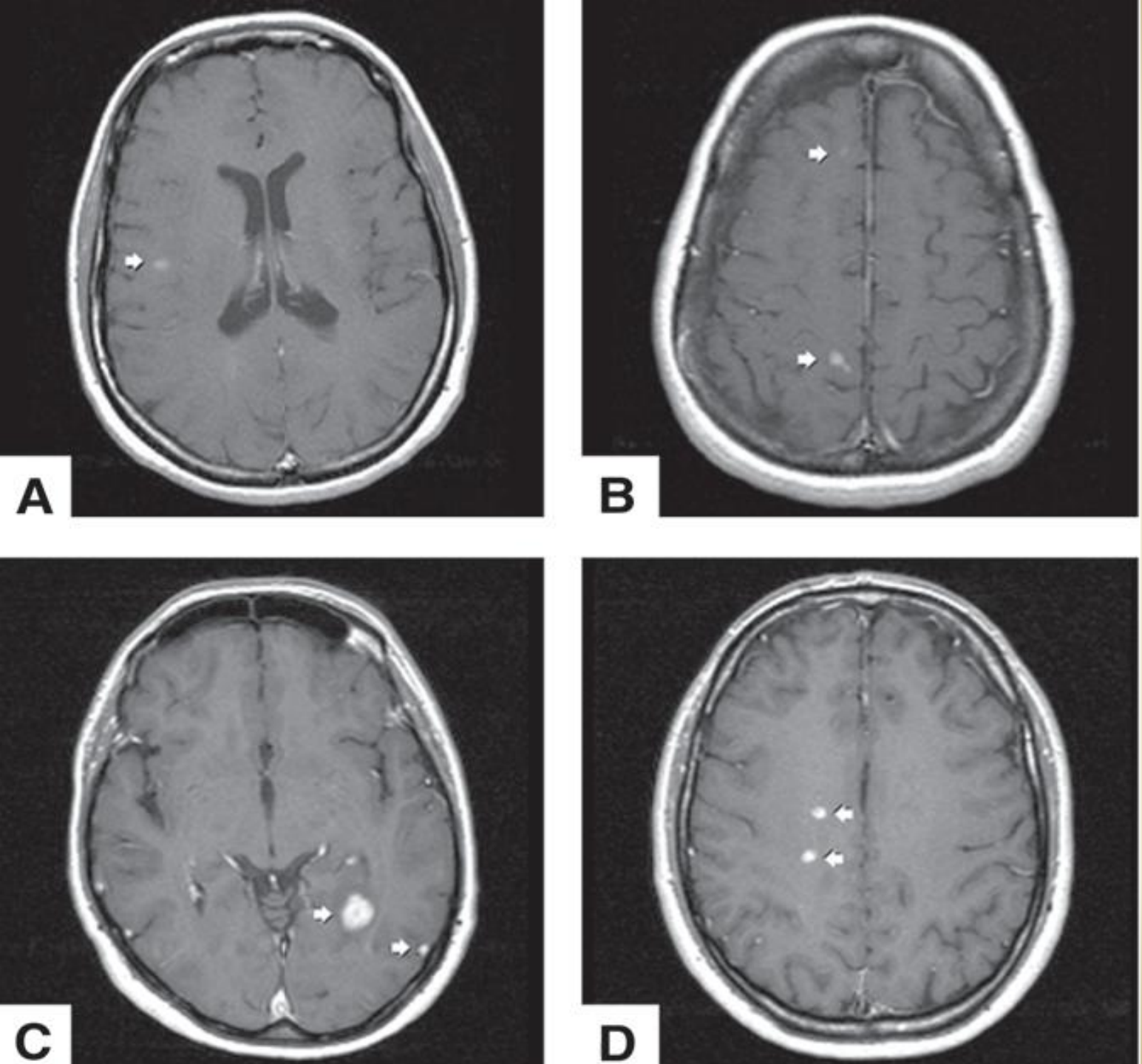
33-year-old man with RRMS



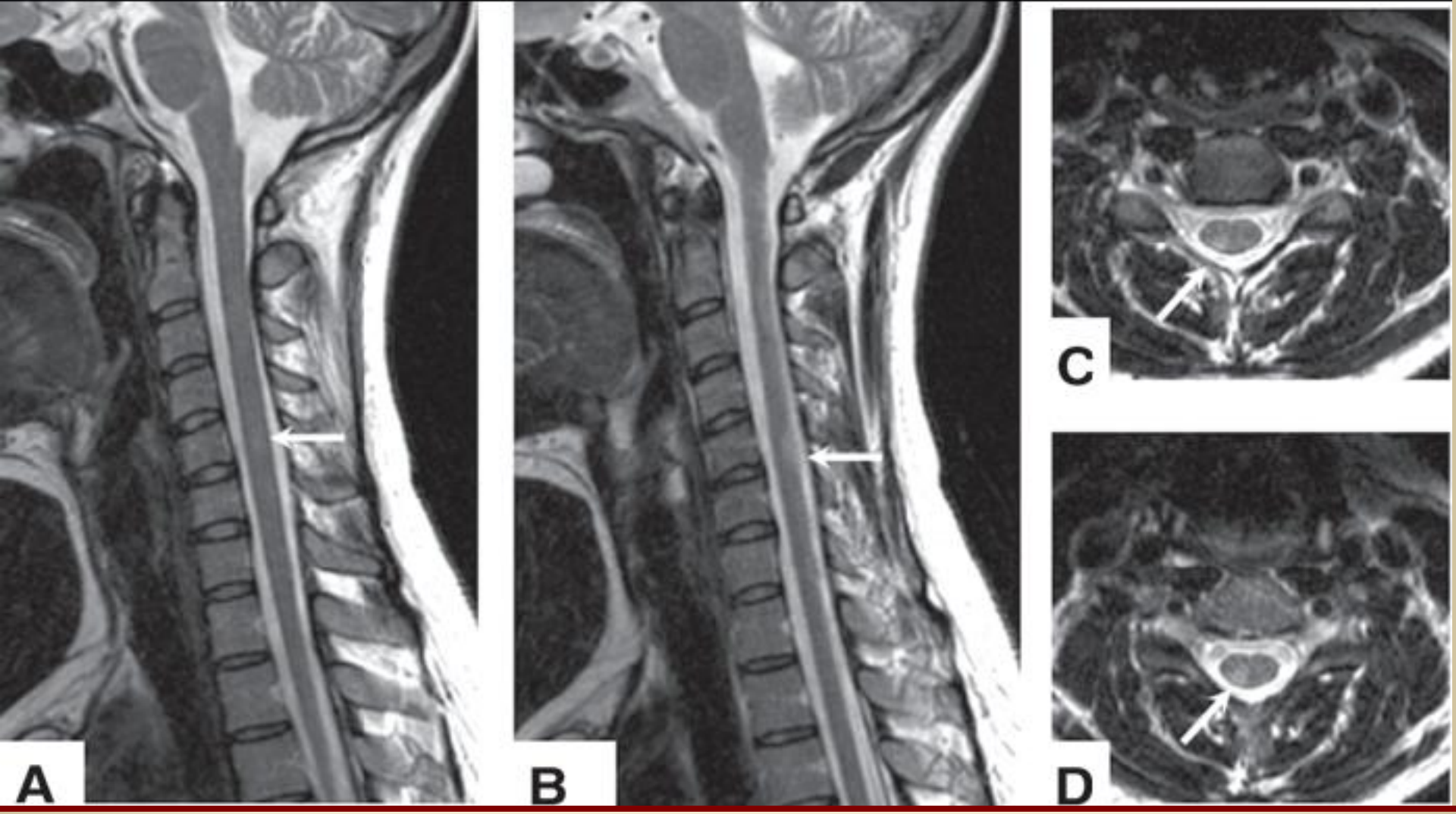
42-year-old woman with RRMS.



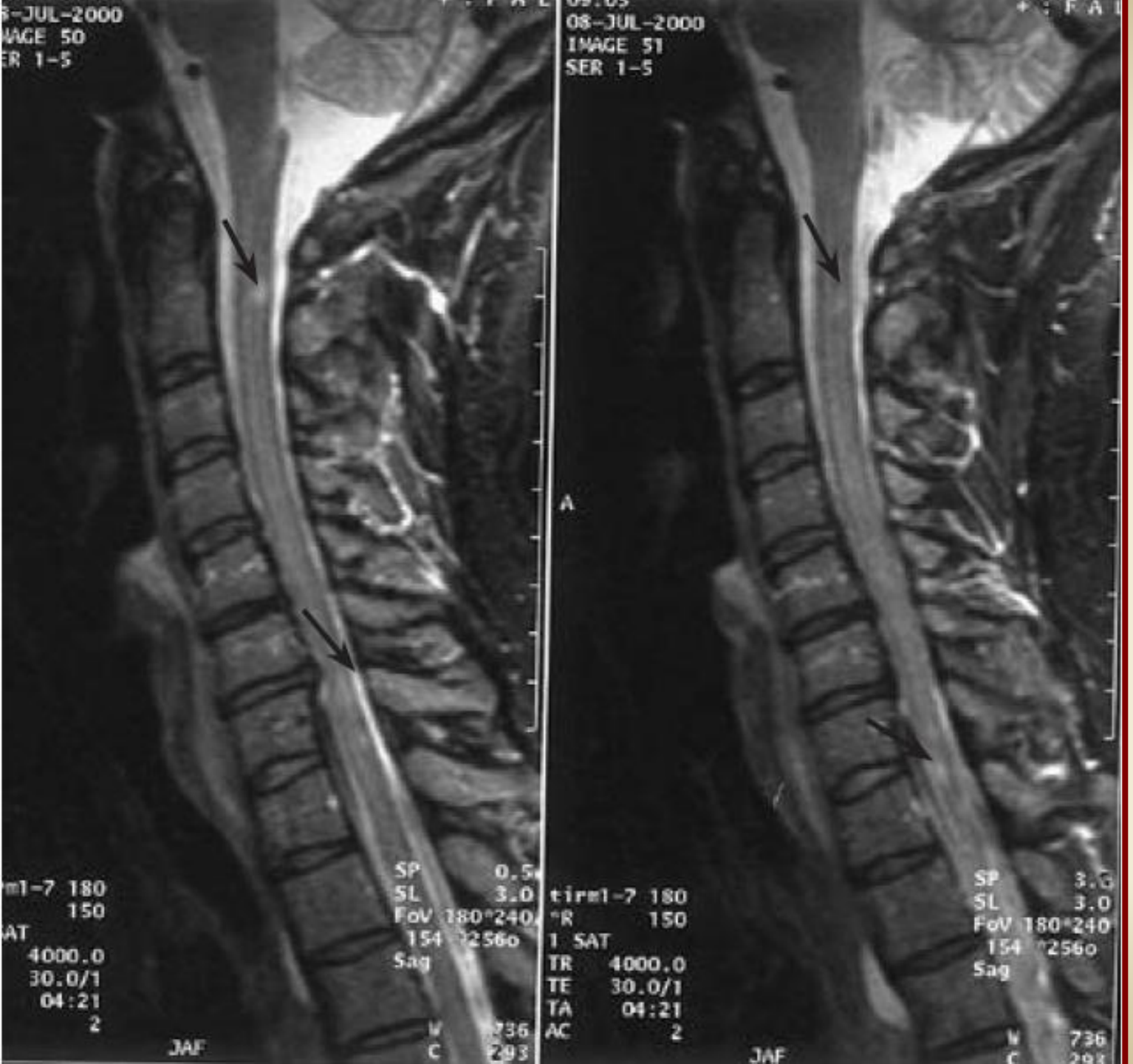
31-year-old man with RRMS.



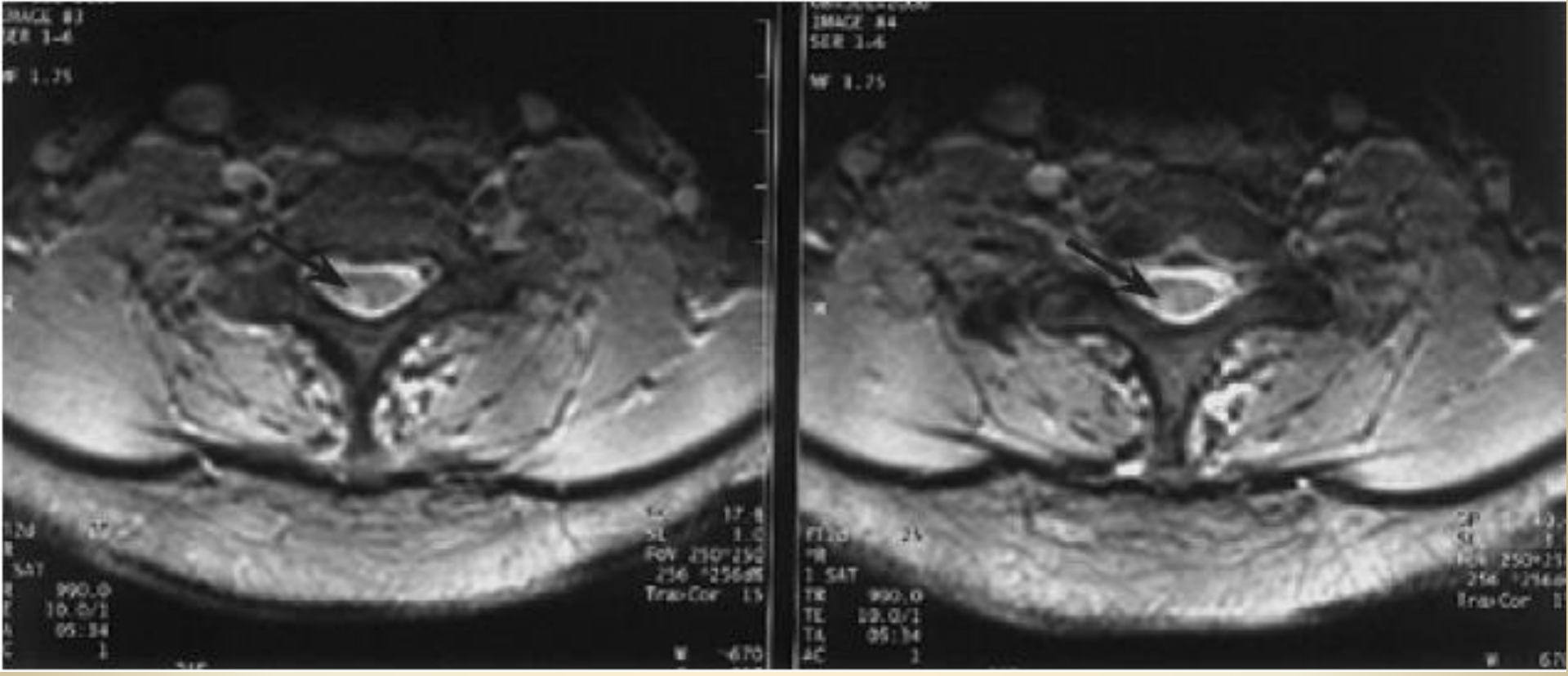
33-year-old woman with RRMS.



30-year-old man with RRMS



MRI of the spinal cord in a patient with MS



MRI of the spinal cord in a patient with MS

Treatment

I. Treatment of acute episode

Corticosteroids:

- ***Mainstay of treatment for acute attacks.***
- ***IV methylprednisolone 500 mg/d for 3-5 days.***
- ***Suppress the immune system in many ways.***
- ***The drug has no effect on recurrence.***

Plasmapheresis (plasma exchange):

Treat acute relapses, by removing harmful Abs.

55ml/kg every other day for 14 days.

IV immune globulin.

Treatment

II. Immunomodulation therapy:

1) Interferon β:

Recombinant proteins, which inhibit the adhesion and the migration of WBC across the BBB.

IFN β -1a:

Avonex, 30 g weekly IM injection.

Rebif, 22 µg or 44 µg SC injection given three times a week.

IFN β -1b:

Betaseron, 8 MIU or 250 µg SC every other day.

2) Glatiramer acetate (Copaxone).

Treatment

3)Monoclonal antibodies:

Natalizumab (Tysabri).

Alemtuzumab (Campath-1H).

Rituximab (Rituxan).

4) Cyto-toxic drugs:-

Cyclophosphamide (Cytoxan).

Methotrexate (Rheumatrex).

Azathioprine (Imuran).

mycophenolate mofetil

Mitoxanthrone (Novantrone): anticancer drug.

Treatment

III. Symptomatic treatment

Spasticity:

Baclofen, dantrolene, diazepam.

Dizziness & nystagmus:

Cinnarizine.

Fatigue:

Amantadine.

Sexual:

Yohimbine.

Pain:

Anticonvulsant.

Neuromyelitis optica (Devic's disease)

Attacks of:

- ✓ *Optic neuritis.*
- ✓ *Progressive paraparesis.*
- ✓ *Spasticity, hyperreflexia.*

Diagnostic Criteria for Neuromyelitis Optica

-Optic Neuritis

-Acute Myelitis

-At Least Two of the Three Supportive Criteria Below:

1-Contiguous spinal cord MRI lesion extending over three or more vertebral segments (reliably assessed in the context of an acute myelitis)

2-Brain MRI not meeting diagnostic criteria for multiple sclerosis

3-Neuromyelitis optica IgG seropositive status(Aquaporin -4)

NMO-spectrum

1. Intractable vomiting and/or hiccup typically associated with lesions

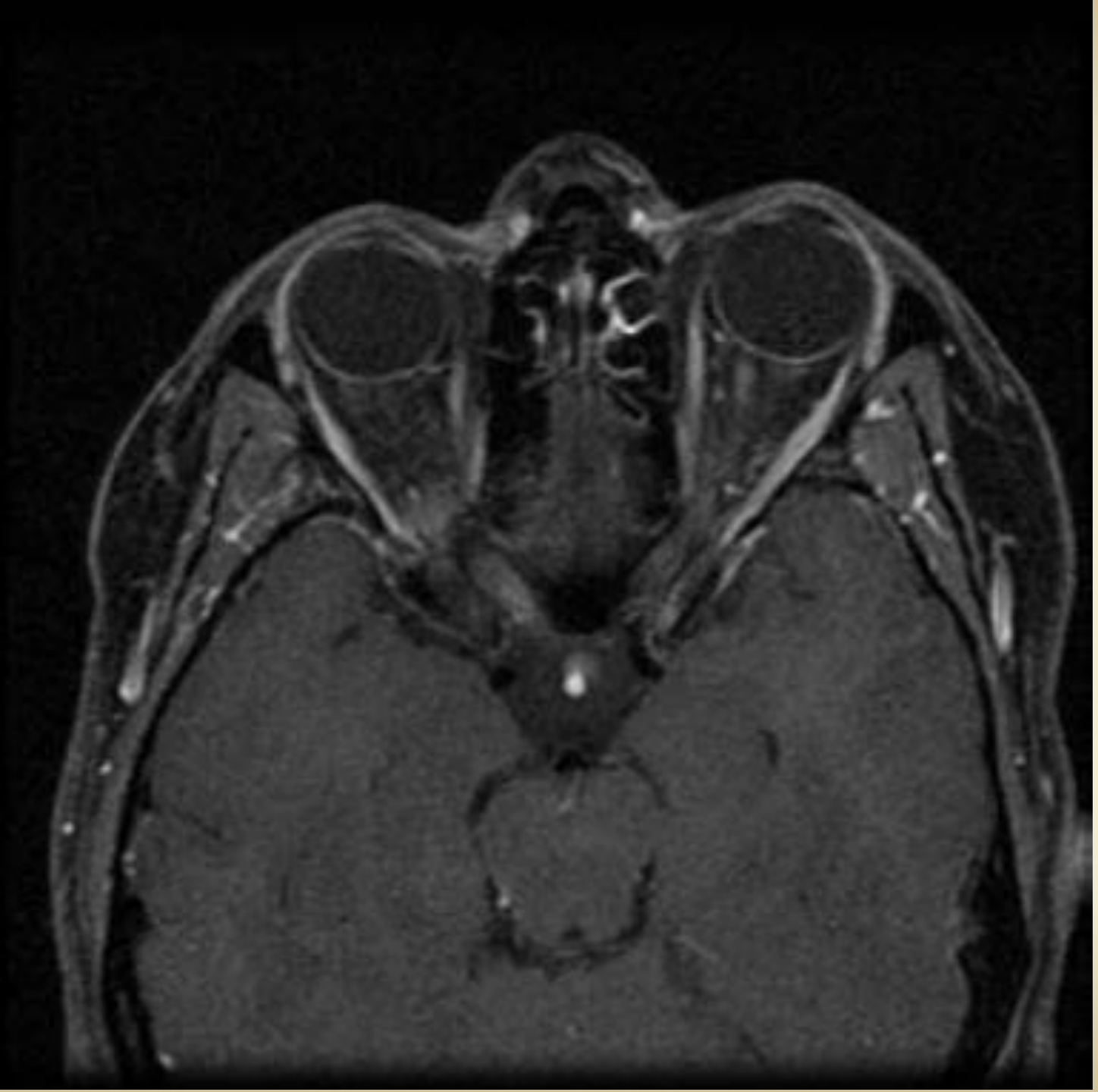
in the area postrema

2. Symptomatic forms of narcolepsy or states of altered consciousness associated with hypothalamic lesions and reduced CSF hypocretin levels

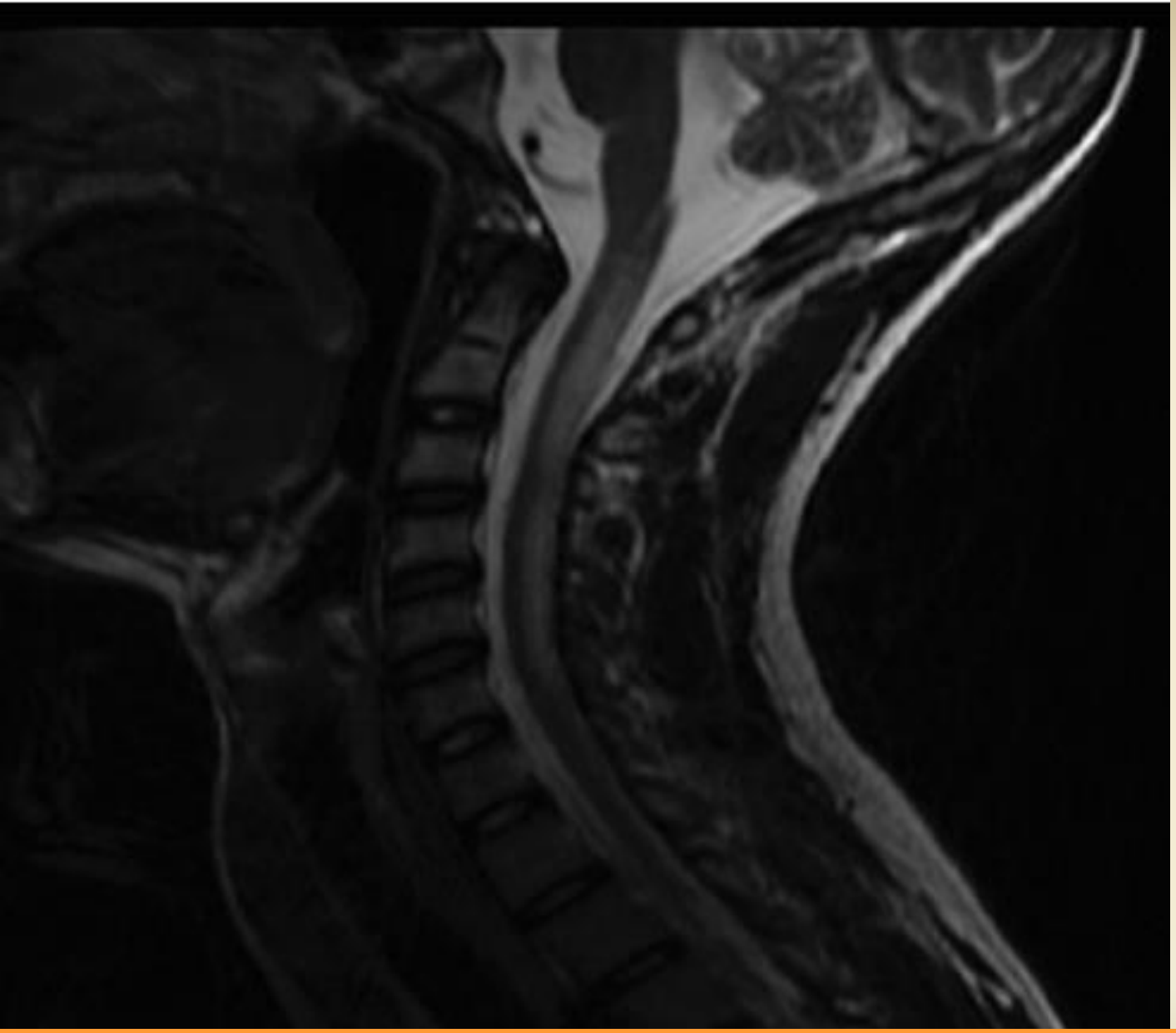
3. Encephalopathy associated with diffuse white matter CNS lesions

that may appear similar to ADEM

Monophasic	**Relapsing**
Less common	common
seronegative	seropositive
equal	Female, older age
More sever, usually full picture	Less sever

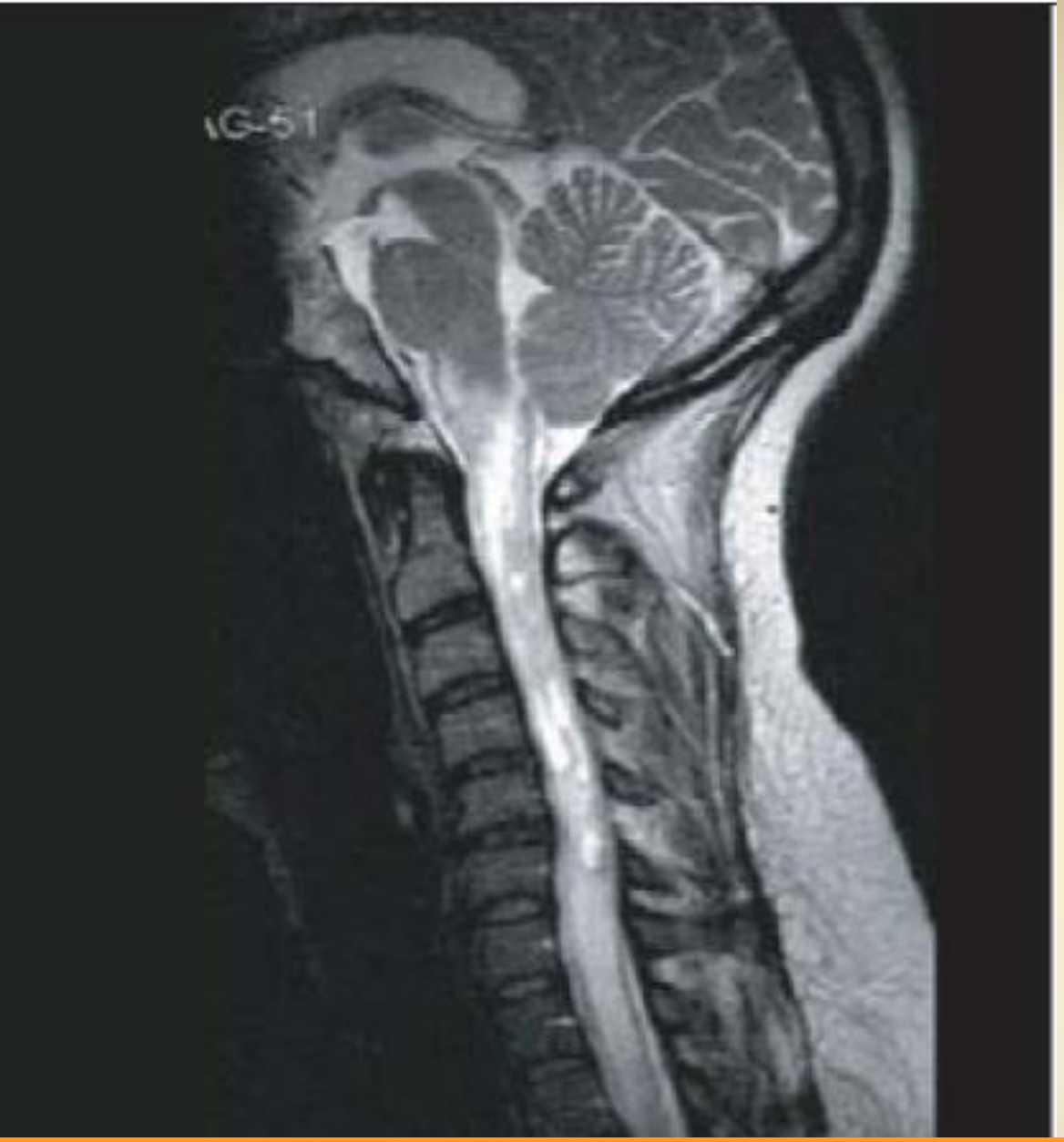


T1W demonstrating gadolinium enhancement of the left optic nerve (optic neuritis).



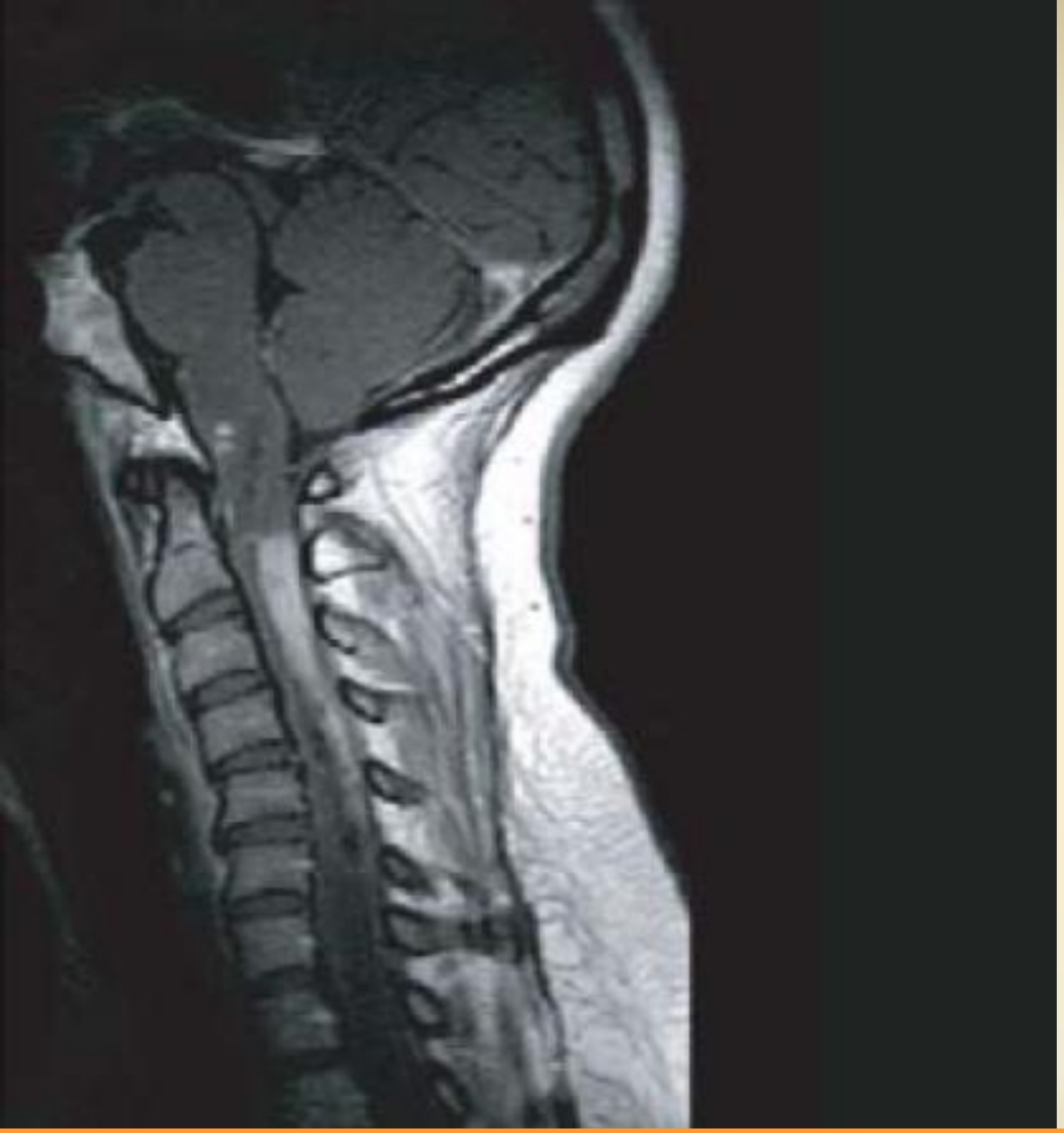
Same patient, same time

Sagittal T2W cervical spine demonstrates a longitudinally extensive lesion from the cervicomedullary junction to C6.



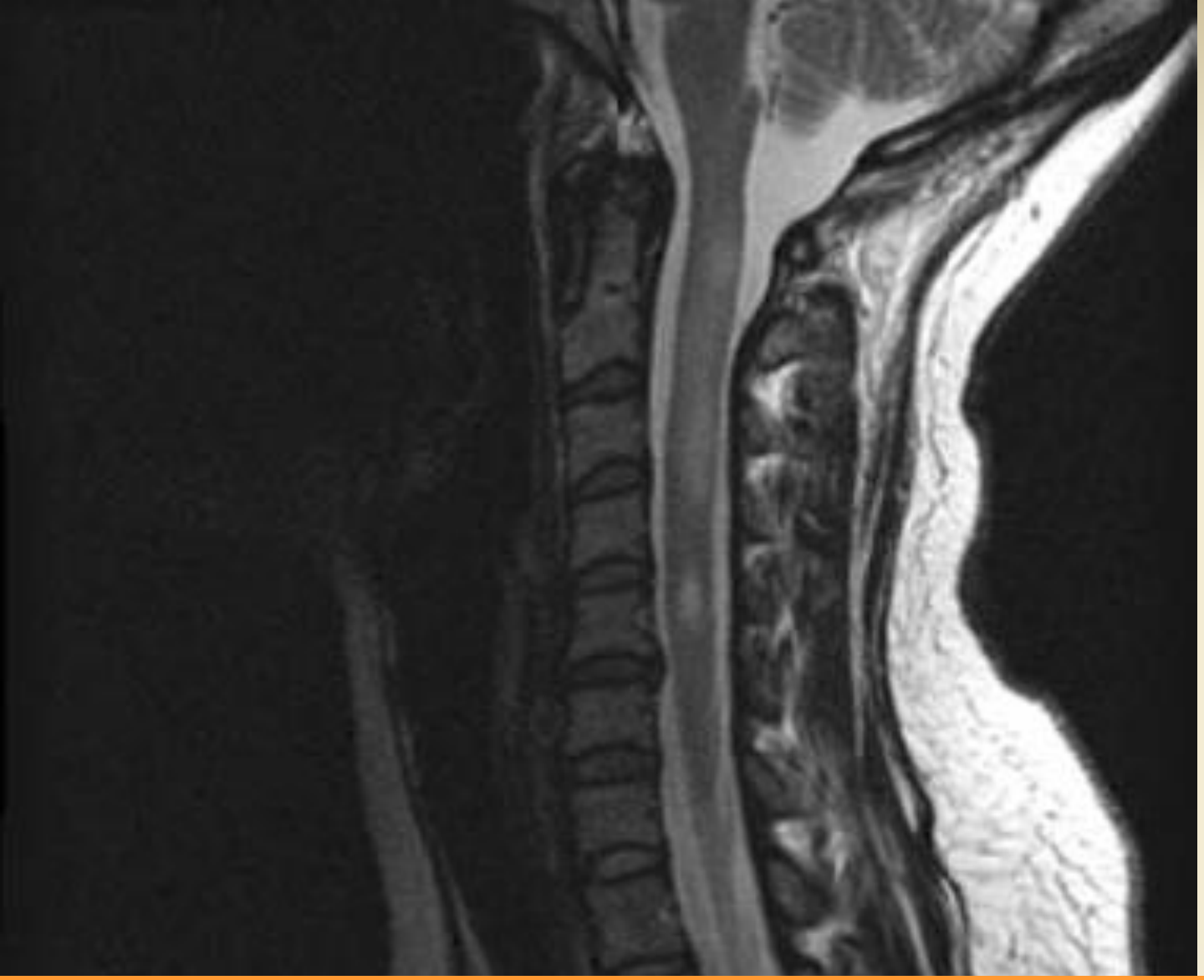
The cervical cord of a patient with neuromyelitis optica

A lesion extending from C4 to C6 is visible on T2W.



Same patient

Part of the lesion is enhancing and part is hypointense on post-contrast T1W.



Sagittal T2-weighted cervical spine demonstrates lesion extending from the cervicomedullary junction to C4. This lesion accompanied the patient's third myelitis exacerbation.

Neuromyelitis optica (Devic's disease)

Treatment:

I. Treatment of acute episode:

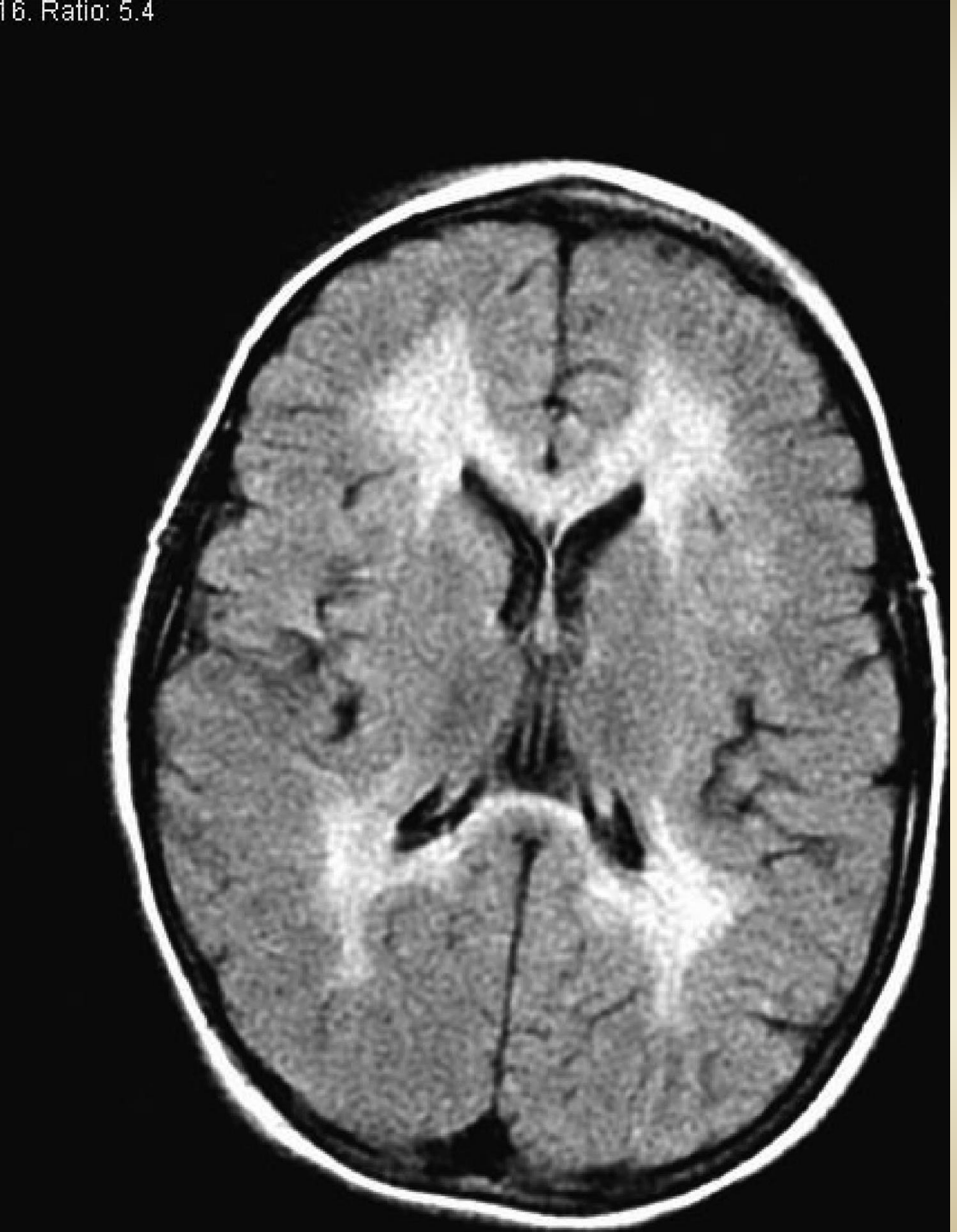
- ***IV methylprednisolone 500 mg/d for 3-5 days.***
- ***Plasmapheresis 55ml/kg/2d for 14 days.***

II. Therapy for attack prevention (if ≥ 2 attacks):

1) Azathioprine (Immuran).

3) Mitoxanthrone (Novantrone).

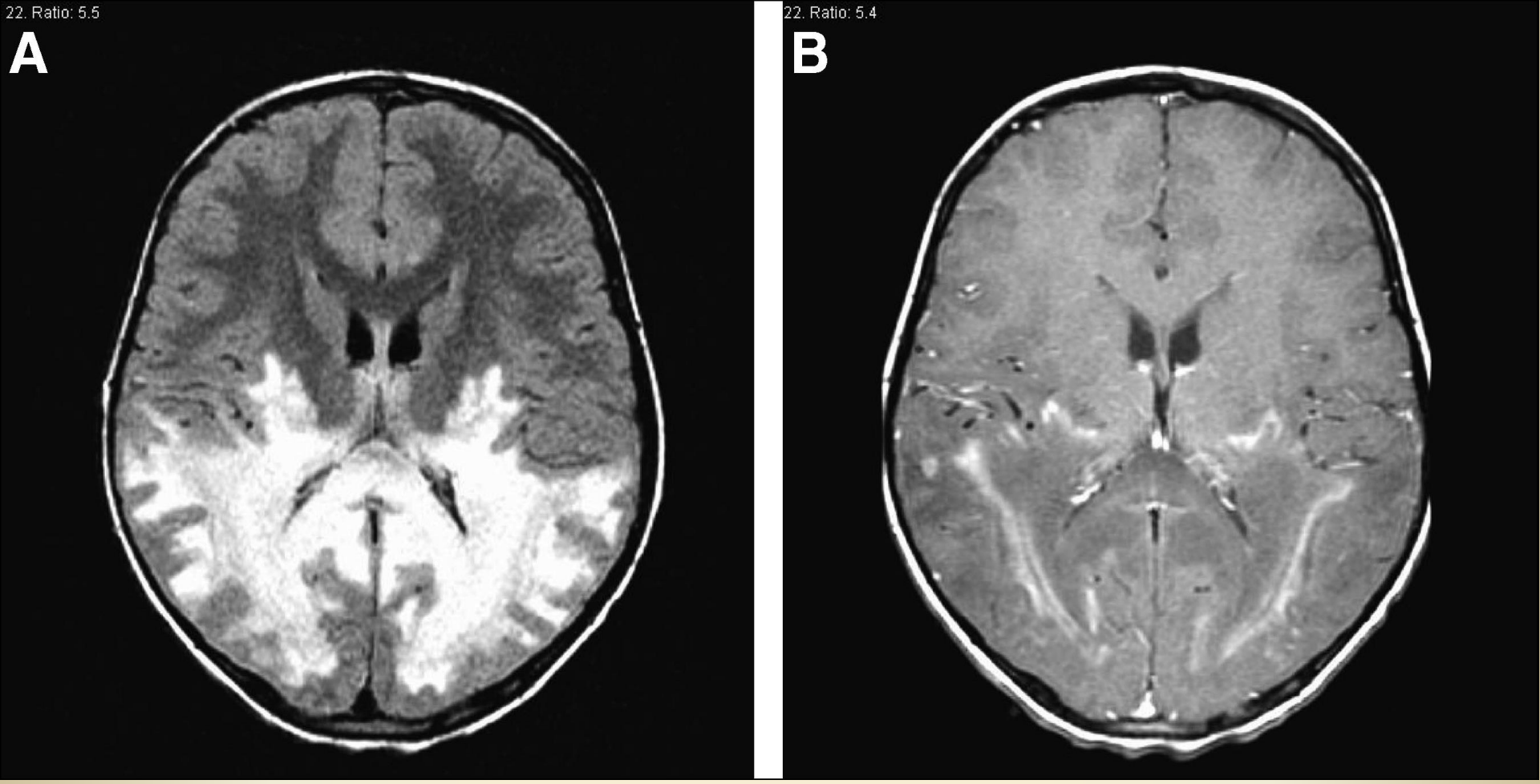
4) Monoclonal antibodies(only Rituximab).



FLAIR

A 7-year-old girl presented with difficulties in school performance and tremors. Diffuse and confluent central white matter abnormalities reaching into the subcortical U fibers.

Metachromatic leukodystrophy



FLAIR

Postgadolinium

A 6-year-old boy presented with behavioral abnormalities, followed by gait and speech difficulties and hearing loss. Posterior periventricular lesions are seen (adrenoleukodystrophy).


Thank You