Demyelinating diseases of the central nervous system

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I) Multiple Sclerosis: introduction; epidemiology;clinical manifestations;clinical course and prognosis; diagnostic evaluation: MRI, CSF, VEP; pathology; treatment: acute relapses, disease-modifying agents, symptomatic treatment

II) Acute disseminated encephalomyelitis

III) Neuromyelitis optica(Devic disease)

IV) Leukoencephalopathies: progressive multifocal leukoencephalopathy (PML), posterior reversible encephalopathy syndrome(PRES), central pontine myelinolysis

V) Inherited disorders: leucodystrophies

I) Multiple Sclerosis

1. Introduction

Demyelinating diseases of the central nervous system (CNS) are characterized pathologically by an acquired loss of myelin with relative preservation of axons

The most common is Multiple Sclerosis(MS)

MS is also one of the most feared diagnoses in Neurology：it strikes young healthy people in the prime of their lives; its course is marked by unpredictable relapses; almost any aspect of neurological function may be affected; and some patients develop lifelong motor disability requiring a wheelchair.

MS has a wide range of presentations and an equally wide range of prognoses

Effective treatments aimed both at the underlying disease process and at some specific complications are available.

For the student, the study of demyelinating diseases provides an excellent opportunity to learn about the dysfunction of different parts of the CNS and to master the wide variety of neurological examination abnormalities that accompany these disorders.

2. Epidemiology

MS is a chronic neurological disorder that begins most commonly in young adulthood

The peak incidence of MS is between 20 and 30 years of age

Women are affected twice as often as men

MS prevalence in the United States is about 90 cases per 100000 people

There are epidemiological findings to suggest both genetic and environmental influences.

Geographically, MS is more common in northern latitudes

The incidence in Scandinavian countries is higher than that in Southern Europe(? role of vitamin D deficiency) , and the incidence in the northern United States is higher than that in the South

There are racial differences as well, with a higher prevalence in white populations

Interestingly, those who move from a low-risk to a high-risk geographical region or vice-versa before the age of 15 years retain the risk associated with their new home, whereas those who migrate after age 15 years retain the risk associated with their childhood home

The implications of this finding are unclear, but one theory is that a latent viral infection acquired in childhood may play a role in the pathogenesis of the disease

There is strong evidence supporting a genetic predisposition to MS as well

For example, there is a greater incidence of MS in monozygotic, when compared with dizygotic, twins of patients with MS, as well as an increased incidence in association with particular human leukocyte antigen alleles

3. Clinical manifestations

MS is diagnosed by finding multiple white matter lesions separated in space and time.

This means that multiple distinct areas of the CNS must be involved(rather than one area recurrently), and that the disease must not be simply a monophasic illness (with multiple areas affected simultaneously but not recurring).

The clinical features are defined by the location of the lesions, thus a right occipital lesion could result in a left homonymous hemianopia, whereas a right cervical cord lesion may lead to an ipsilateral hemiparesis and loss of joint position sense, with contralateral loss of pain and temperature sensation

Almost any neurological symptom can be produced by an MS lesion

Common clinical features (table) include corticospinal tract signs such as weakness and spasticity, cerebellar problems such as intention tremor and ataxia, sensory abnormalities such as paresthesiae and loss of vibration and proprioception sensation, and bladder dysfunction.

Fatigue is a common complaint

In later stages, cognitive and behavioural abnormalities may occur

A few syndromes merit further description

TABLE 20–1. Common Clinical Features of Multiple Sclerosis

Neurologic System	Clinical Sign or Symptom
Cranial nerves	Optic nerve dysfunction
	Visual acuity loss
	Red desaturation
	Papilledema or optic disc pallor
	RAPD
	Eye movement disorders
	Internuclear ophthalmoplegia
	Nystagmus
Motor system	Weakness
	Spasticity
	Reflex abnormalities
	Increased muscle stretch reflexes
	Babinski signs
	Clonus
Sensory system	Paresthesias
	Vibratory loss
	Joint position sense loss
	Lhermitte's sign
Cerebellar function	Ataxia
	Intention tremor
	Dysarthria
Autonomic system	Bladder dysfunction
Other	Fatigue
	Depression
	Uhthoff's phenomenon

RAPD, relative afferent pupillary defect.

A) Optic neuritis (ON)

Common initial presentation of MS

This fact reminds us that the optic nerve is actually an extension of the CNS rather than a peripheral nerve

ON is characterized by a mildly painful loss of visual acuity in one eye, worse with heat (Uhthoff's phenomenon)

The visual loss may range from mild blurriness with a loss of color discrimination to a severe episode with complete blindness

Pulling or tugging pain is most prominent when the eye moves

On examination, there is loss of acuity and color vision.

Most patients have retrobulbar optic neuritis and the optic disc appears normal in the acute stage

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In severe cases, however, the optic disc may be swollen, with indistinct margins

(papilledema or papillitis)

A past history of ON is suggested by the presence of red desaturation(subtle loss of color appreciation), optic disc pallor or atrophy, and a relative afferent pupillary defect(RAPD)

B) Transverse myelitis

Inflammatory demyelination in the spinal cord

Most commonly, this affects particular tracts at the level of the lesion in a patchy way, rather than producing complete involvement of the spinal cord

There may be unilateral or bilateral weakness or sensory loss below the lesion

Bowel and bladder function may be disrupted

Reflexes may be exaggerated below the lesion, and Babinski signs may be present

Patients may report a band of tingling or pain around the torso at the level of the lesion

C) Internuclear ophthalmoplegia (INO)

Characteristic finding in MS

INO results from dysfunction of the medial longitudinal fasciculus and leads to an inability to adduct one eye when looking toward the opposite side, with associated nystagmus of the abducting eye

The adduction of both eyes when observing a near target(convergence) is preserved

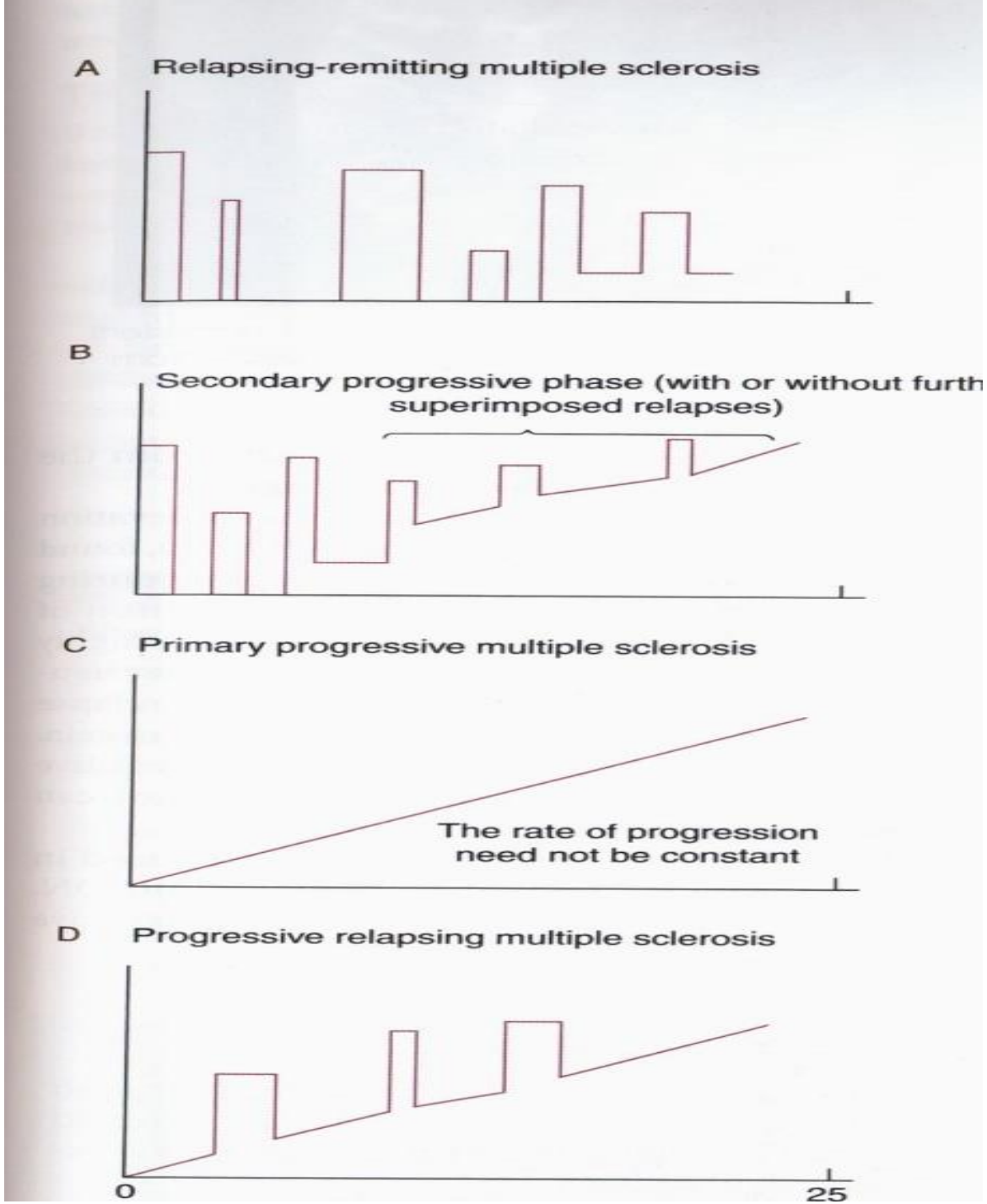
The other clinical features characteristic of MS include Lhermitte' s sign, a tingling, electric sensation down the spine when the patient flexes the neck, and Uhthoff's phenomenon, a worsening of symptoms and signs in the heat

4. Clinical course and prognosis

Most MS patients begin with a relapsing-remitting course (figure), in which there are discrete episodes of neurological dysfunction(relapses or “ flares”) that resolve after several weeks or months

Unfortunately, such a course usually evolves into one in which recovery from each relapse is incomplete and baseline function deteriorates(secondary progressive)

Rarely, patients may have a relentlessly progressive course from the onset, either with superimposed relapses(progressive-relapsing) or without (primary progressive)


A
Relapsing-remitting multiple sclerosis
B
Secondary progressive phase (with or without furth
superimposed relapses)
C
Primary progressive multiple sclerosis
The rate of progression
need not be constant
D
Progressive relapsing multiple sclerosis
0
25

To put the prognosis in broad terms, about 60% of MS patients lead lives of minimal disability, about 20 % require a walking aid but will remain ambulatory, and about 20 % have severe disability, typically becoming wheelchair-bound

There has been and will likely continue to be a trend toward better prognoses in the future because of a greater use of effective disease-modifying agents

Features predicting a good prognosis include young age at onset, female sex, rapid remission of initial symptoms, mild relapses that leave little or no residual deficits, and a presentation with sensory symptoms or ON rather than motor symptoms

5.Diagnostic evaluation

The diagnosis of MS begins with a thorough history and examination

Patients often present with what appears to be a single episode of neurological dysfunction, but upon further questioning recall earlier episodes of seemingly unrelated neurological symptoms that may in fact represent prior lesions.

It is important to inquire specifically about past neurological symptoms that suggest ON, transverse myelitis, and other typical MS features.

On examination, evidence of old optic nerve or other neurological lesions should be sought

The 2 most useful lab results are magnetic resonance imaging (MRI) and CSF analysis

On MRI, new MS lesions appear as discrete T2-hyperintense areas in the white matter of the brain or spinal cord (figures)

Fluid-attenuated inversion recovery(FLAIR) sequences also show these lesions particularly well

Acute lesions may not be evident on T1-weighted images but may enhance with gadolinium

Old chronic lesions may become T1-hypointense, with a “ black hole” appearance

MS lesions are most often ovoid in shape and have a predilection for particular areas, including the periventricular white matter, juxtacortical regions, corpus callosum, and cerebellar peduncles

Sagittal images may demonstrate foci of demyelination spreading perpendicularly from the corpus callosum, termed **Dawson's fingers**

The characteristic CSF finding in MS is an elevation in the concentration of oligoclonal bands (OCBs) , found in more than 90% of MS patients at some point during the illness

OCBs reflect intrathecal production of IgG antibodies by plasma clone cells

Although highly suggestive of MS, they can also be found in other neurological disorders

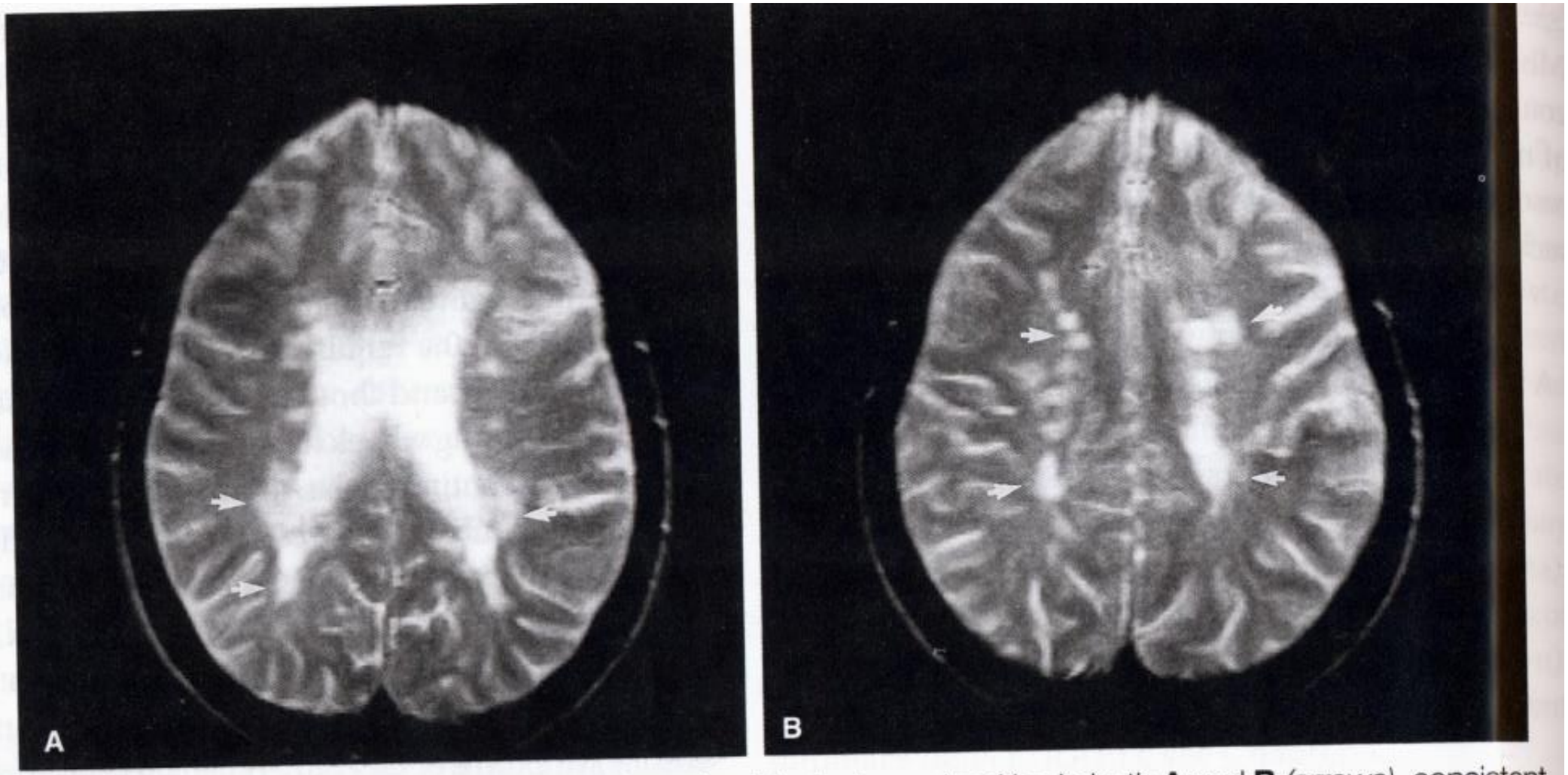
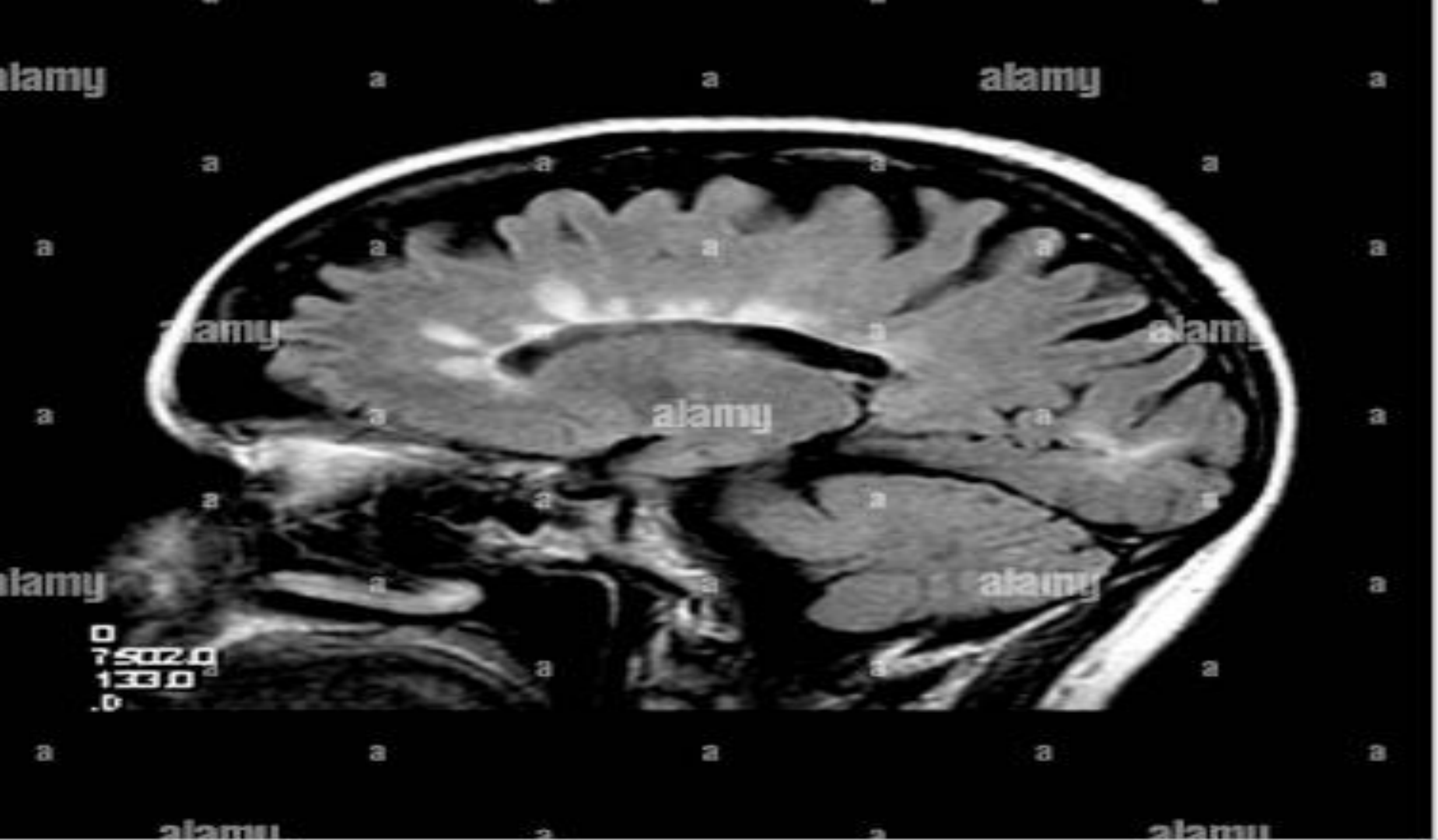


FIGURE 20-2. T2-weighted MRI demonstrating multiple periventricular hyperdensities in both **A** and **B** *(arrows)*, consistent with a diagnosis of MS. [MRI, magnetic resonance imaging; MS, multiple sclerosis.] (Reproduced with permission from Daffner RH. *Clinical Radiology*: *The Essentials*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)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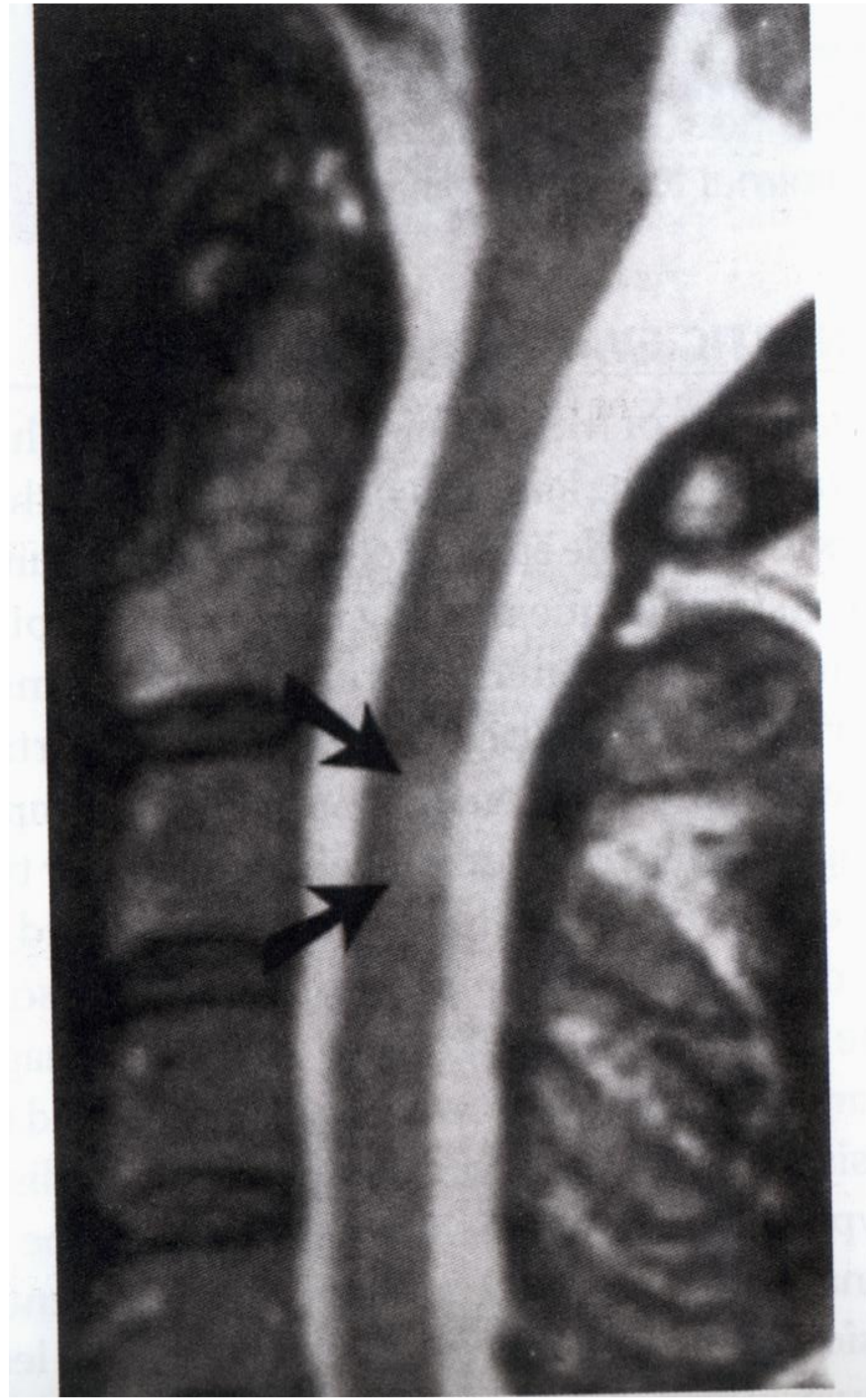


CSF studies during an acute relapse may show a moderate pleocytosis and elevated protein

Calculation of the CSF IgG index, on the basis of relative levels of IgG and albumin in the CSF and serum , can also suggest intrathecal antibody production

Finally, visual evoked potentials (VEP) can be used to document evidence of old ON

There is often an increased latency of the P100 wave on the affected side

6. Pathology

The histologic appearance of an acute MS lesion is a sharply defined area of myelin loss with relative preservation of axons, and associated signs of perivascular inflammation, including the presence of macrophages, lymphocytes, and plasma cells

Reactive astrocytes may be present

Chronic MS lesions show axon loss and extensive glial proliferation

7. Treatment

Treatment for MS falls into 3 categories: acute therapies for relapses, chronic therapies that treat the underlying disease process, and symptomatic therapies that address the various complications of the disease

A) Acute MS relapses are most commonly treated with corticosteroids

A course of intravenous methylprednisolone for 3 to 5 days, with or without an oral prednisone taper, is a common protocol

Although the effect of steroids on the long-term outcome is unclear, steroids do shorten the duration of acute relapses

The Optic Neuritis Treatment Trial demonstrated that intravenous steroids for patients with ON delayed but did not prevent the subsequent development of MS

B) Disease-modifying agents (table) are important treatments for preventing relapses and potentially for improving long-term outcomes

* These include beta-1a interferon and beta-1b interferon, which are injectable medications that have been shown to decrease the rate of relapses, the burden of lesions shown on MRI, and the rate of accumulated disability

Both are currently used in patients with relapsing-remitting MS and in some patients with secondary progressive disease

Side effects can include flu-like symptoms, depression , and injection-site reactions

It is important to check a CBC and liver function test routinely; interferons may cause leukopenia and reversible transaminitis

Patients who are doing poorly with interferons may have developed neutralizing antibodies that reduce drug effectiveness

TABLE 20-2. Immune-Modulating Agents Used in the Treatment of Multiple Sclerosis

Drug	Administration	Side Effects
Interferon beta-1a (Avonex)	30 μg IM every week	Flu-like symptoms, anemia, depression, development of neutralizing antibodies
Interferon beta-1b (Betaseron)	250 μg SC every other day	Injection-site reactions, flu-like symptoms, depression, hematologic/liver abnormalities, development of neutralizing antibodies
Interferon beta-1b (Rebif)	44 μg SC three times a week	Flu-like symptoms, anemia, depression, development of neutralizing antibodies
Glatiramer acetate (Copaxone)	20 mg SC daily	Injection-site reactions, injection-related chest pain and shortness of breath
Natalizumab (Tysabri)	300 mg IV every 4 wk	Progressive multifocal leukoencephalopathy, hepatotoxicity, hypersensitivity reaction
Fingolimod (Gilenya)	0.5 mg PO every day	Bradycardia, leukopenia, macular edema
Dimethyl fumarate (Tecfidera)	240 mg PO bid	Flushing, lymphopenia, gastrointestinal intolerance
Teriflunomide (Aubagio)	7–14 mg qD	Hair loss, transaminitis, and gastrointestinal symptoms, teratogenicity
Alemtuzumab (Lemtrada)	First course: 60 mg IV over 5 d. Second course, 12 mo later: 36 mg IV over 3 d	Infusion reactions, autoimmune disease, increased cancer risk
Ocrelizumab (Ocrevus)	600 mg IV every 6 mo	Infusion reactions, upper respiratory tract infection, cannot be administered to patients with active hepatitis B infection

* Glatiramer acetate is a polypeptide formulation injected subcutaneously , which is also used in relapsing-remitting patients

In patients who no longer respond to interferons or glatiramer acetate or who have progressive disease from onset, other immunosuppressive agents may be used

*Natalizumab is a monoclonal antibody against alpha-4-integrin that prevents lymphocytes and monocytes from crossing the blood-brain barrier

It is administered as a series of monthly infusions

Although it is likely more effective than interferons in preventing relapses and disease progression,natalizumab is associated with a small but significant risk of developing progressive multifocal leukoencephalopathy (PML), an untreatable and often fatal disorder

Patients without antibodies to John Canningham (JC) virus (the virus that produces PML) are at a lower risk for PML, and these antibodies should be measured prior to starting treatment with natalizumab

In addition,natalizumab should not be used in combination with other immunomodulatory agents used to treat MS

*Fingolimod is a mixed agonist/antagonist of the sphingosine-1P-receptor.

It was the 1st oral medication approved for use in MS

Its main activity in MS is thought to be sequestration of autoreactive T cells in lymph nodes

The most serious potential side effects of fingolimod are bradycardia and macular edema.Thus, patients must be monitored with an ECG during the first administration and undergo optical coherence tomography(OCT) to screen for macular edema

* Dimethyl fumarate is another oral medication used to treat MS

Its exact mechanism is uncertain

Potential side effects include flushing, lymphopenia, and gastrointestinal intolerance

* Teriflunomide is an oral antimetabolite that is effective in reducing relapse rate in MS

The side effects to monitor for include hair loss, transaminitis, and gastrointestinal symptoms

It is highly teratogenic and should be used cautiously in women of childbearing age

* Alemtuzumab is a CD 52 monoclonal antibody indicated for patients with relapsing forms of MS who failed 2 other MS medications

Potential side effects include infusion reactions, a precipitation of autoimmune disease, and an increased risk of malignancy

* Ocrelizumab is a CD 20 monoclonal antibody that is indicated for relapsing-remitting and primary progressive forms of MS

It is administered intravenously at a dose of 600 mg every 6 months

Side effects include infusion reactions and upper respiratory tract infections

It is contraindicated in patients with active hepatitis B infection

C) Several of the symptomatic complications that accompany MS have specific treatments

* Fatigue is often the most disabling and persistent symptom of MS

Good sleep hygiene and a gentle exercise program may be helpful

Medication treatment options include amantadine, aspirin,modafinil, and amphetamines

* Spasticity can be managed with baclofen, diazepam, tizanidine, or botulinum toxin injections

* Bladder dysfunction can be managed with anticholinergic agents (for urinary urgency) and intermittent self-catheterization

It is particularly important to address urinary problems in order to prevent recurrent infections, which can trigger MS relapses or lead to chronic renal disease

* Tremor and ataxia are disabling MS symptoms that are often difficult to treat

II) Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis(ADEM) is a monophasic illness leading to areas of demyelination within the CNS , commonly following an antecedent viral infection or vaccination

ADEM may be difficult to distinguish from the initial presentation of MS

* Clinical and radiologic manifestations

As in MS, almost any neurologic symptom or sign can occur, depending on the location of the demyelinating lesions

In ADEM, the lesions are multiple and are frequently more patchy, bilateral, and confluent than in MS, where the lesions may be more discrete

ADEM lesions have a predilection for the posterior cerebral hemisphere white matter

Clinically, behavioral and cognitive abnormalities and seizures are often seen in ADEM, whereas they are uncommon until the late stages of MS

Radiologically, all areas of demyelination in ADEM appear acute and may enhance with gadolinium

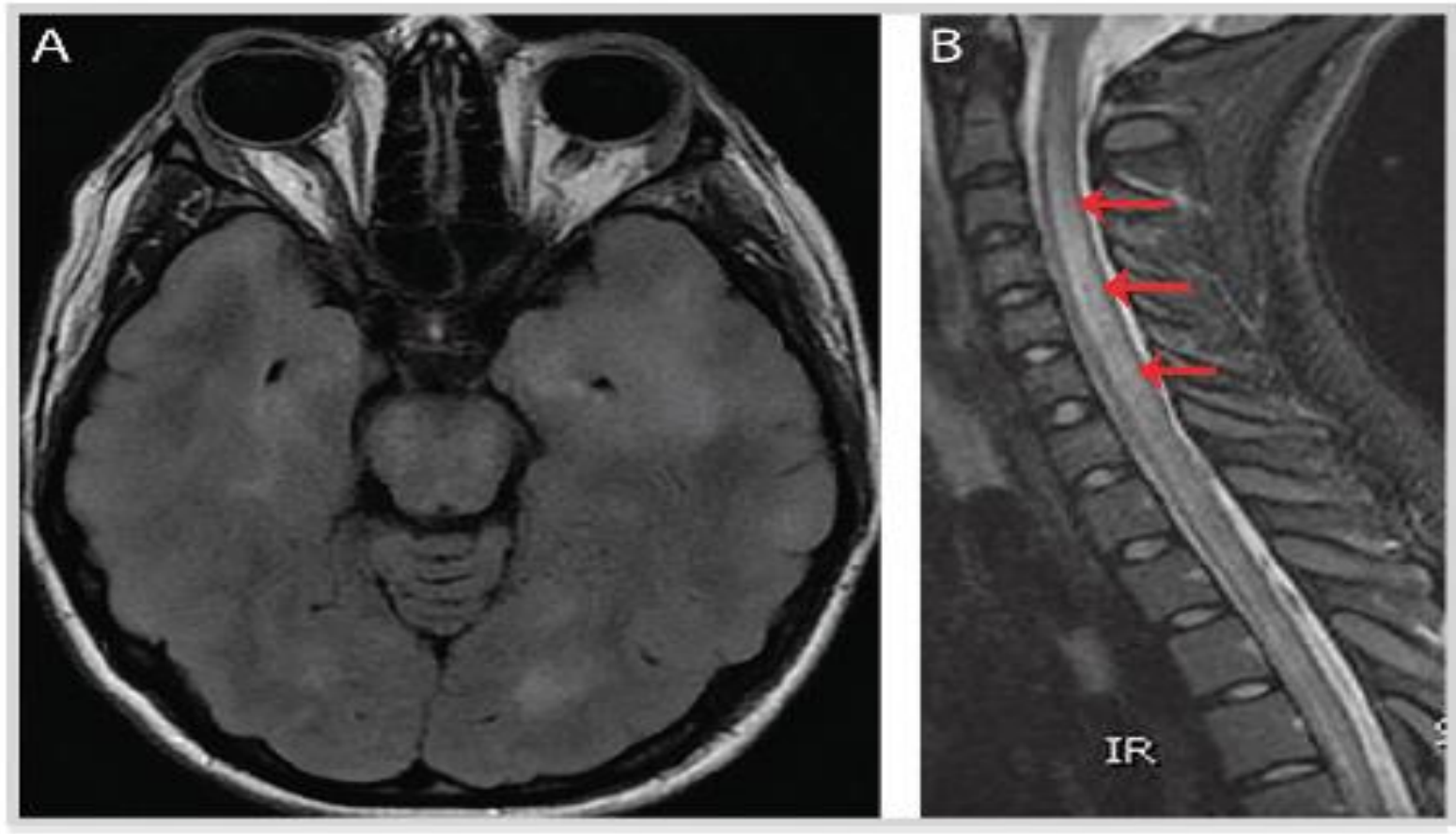


FIGURE 11-12 Imaging of the patient in **Case 11-2** with acute disseminated encephalomyelitis (ADEM). *A*, Axial fluid-attenuated inversion recovery (FLAIR) brain MRI shows poorly demarcated T2 hyperintensities in cortical, subcortical, and brainstem areas. *B*, Sagittal short tau inversion recovery (STIR) spinal cord MRI shows T2 hyperintense signal abnormality throughout the cervical cord (*arrows*).

* Diagnostic evaluation

The diagnosis of ADEM may be suspected on the basis of clinical presentation and radiologic findings

CSF typically will show a lymphocytic pleocytosis (usually with more white blood cells than seen in MS) and an elevated protein; OCB are rarely present

When the illness is distinguished clinically or radiologically from the initial episode of MS, a definitive diagnosis of MS may not be possible until a second episode of neurologic dysfunction occurs

* Prognosis and treatment

By definition, ADEM is a monophasic illness with a generally favorable outcome

A course of intravenous corticosteroids is typically administered to shorten the duration of the episode and lessen the severity of the symptoms

III) Neuromyelitis optica (Devic disease)

Neuromyelitis optica (NMO) is characterized by the development of transverse myelitis and optic neuritis

The two components of the disorder may develop simultaneously or there may be a delay of one or even two years between them

Demyelination of the brain should be absent or relatively minor

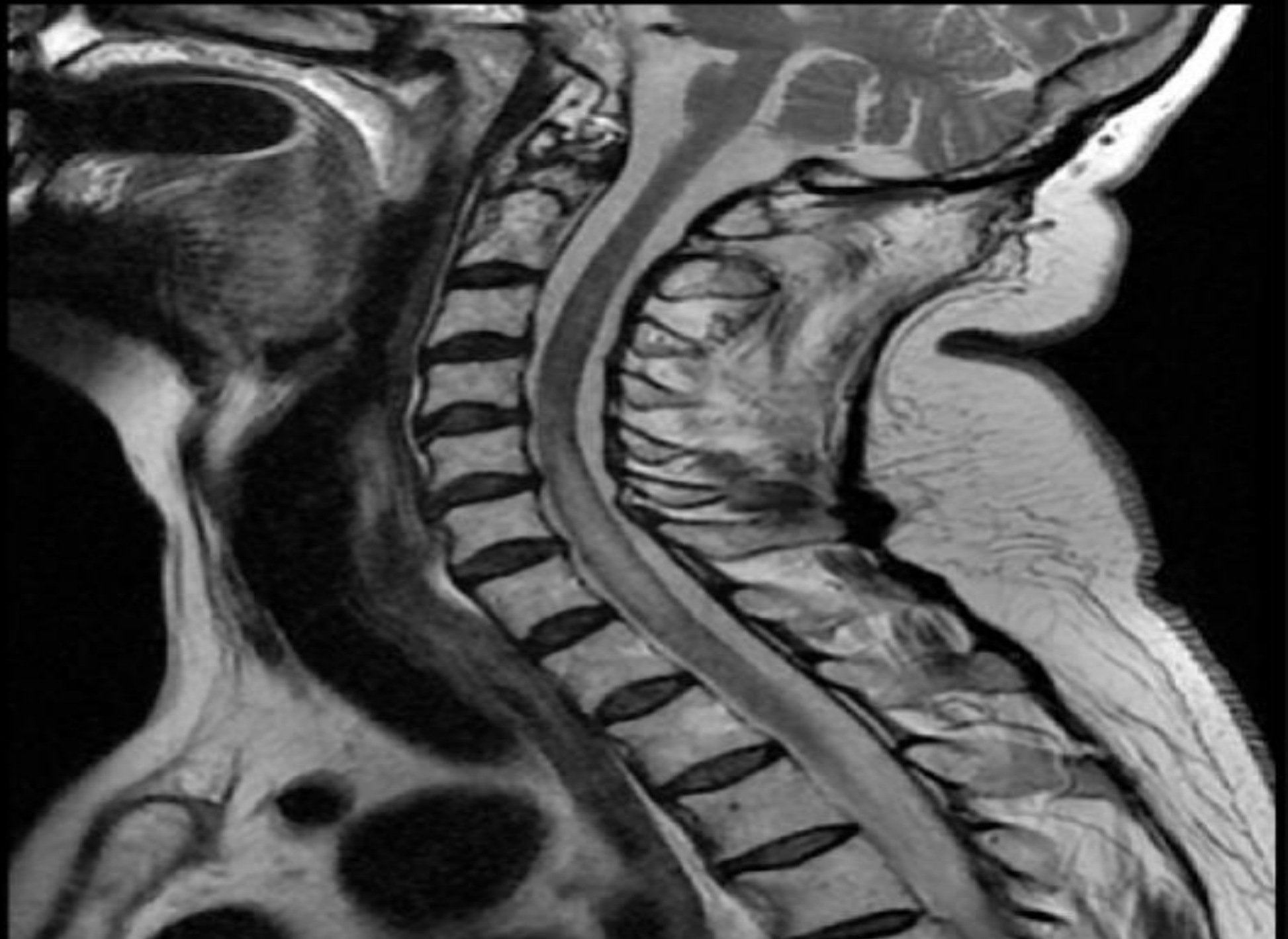
Pain is a more common and severe component of the transverse myelitis and optic neuritis than is seen in MS, and the deficits tend to be more severe in NMO than in MS

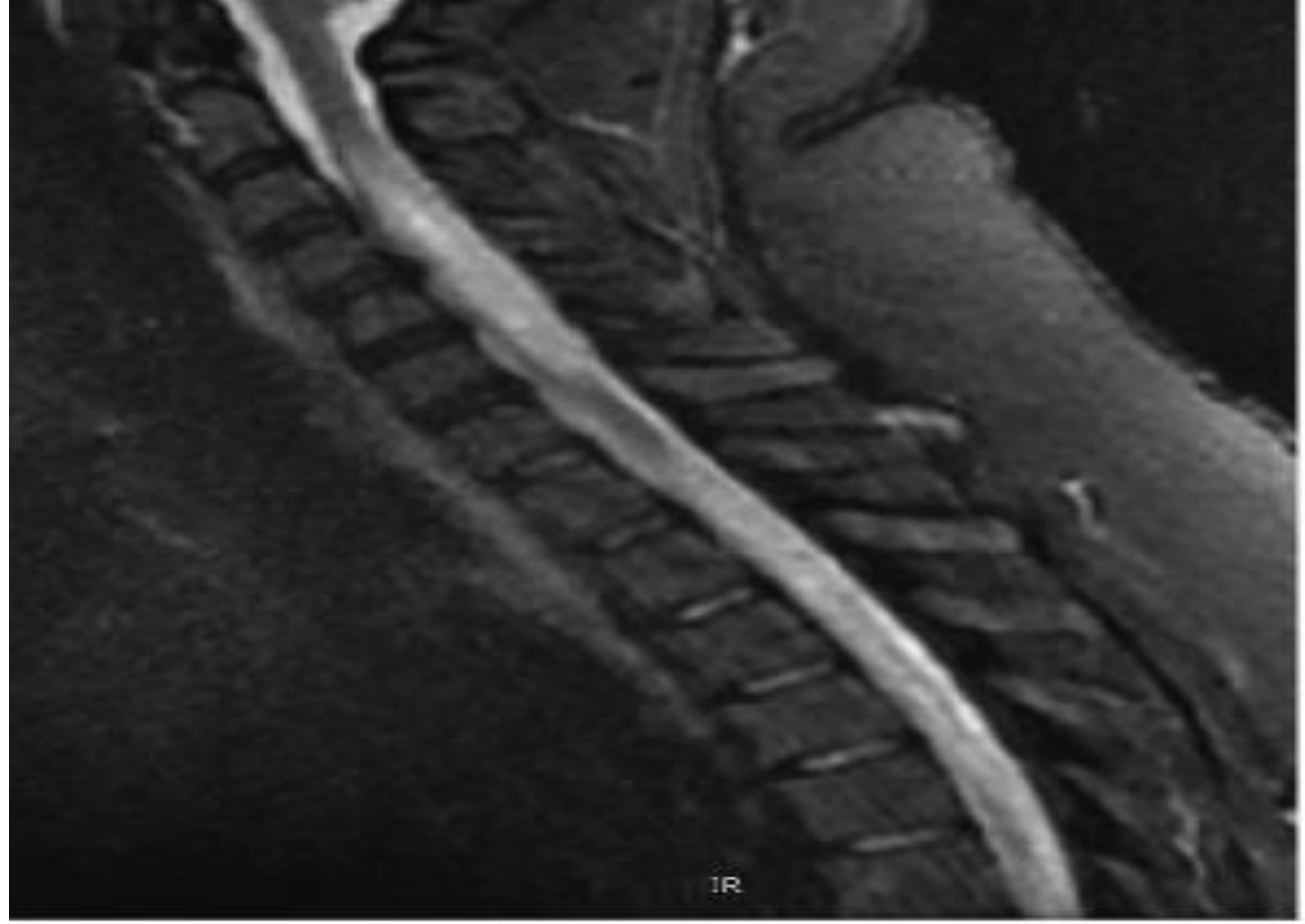
MRI of the spine in NMO is more likely to show lesions that extend over several segments of the cord and to involve an individual level of the cord in a complete rather than a patchy fashion

CSF pleocytosis, sometimes with a neutrophilic pleocytosis, is also seen with greater frequency in NMO than in MS

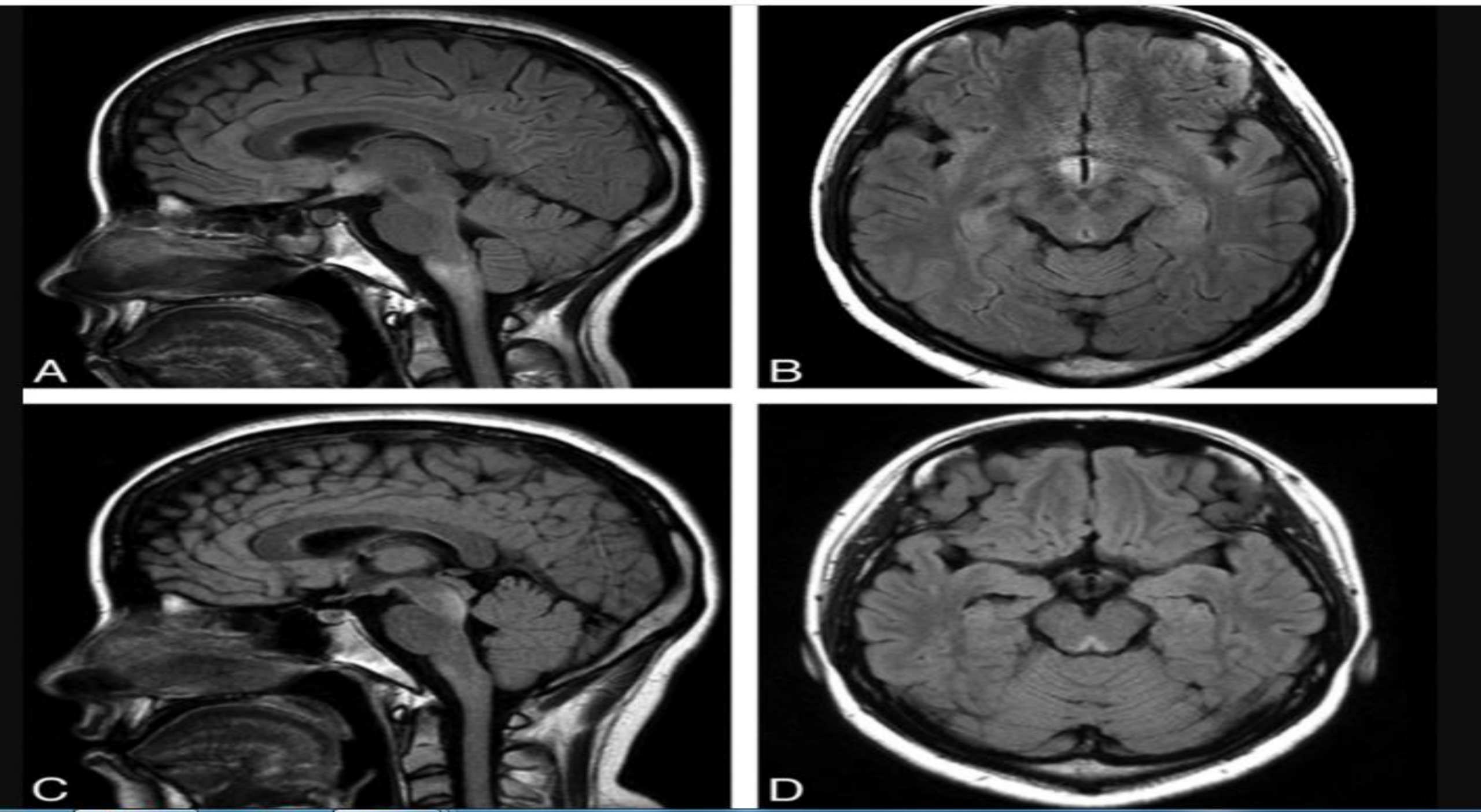
The diagnosis of NMO is confirmed with greatest certainty by finding antibodies to the aquaporin-4 channel(NMO Ab)

For patients who are NMO ab-negative, myelin oligodendrocyte glycoprotein antibodies (MOG Ab) may be present





GURE 11-11 Extensive spinal cord lesions in a 42-year-old woman with neuromyelitis optica (NMO). A sagittal spinal short tau inversion recovery (STIR) MRI shows a large area of hyperintense cord signal and cord expansion extending from the level of C3 to the level of C6-7 and from the level of T1 to the level of T5.


A
B
C
D

It is important to investigate thoroughly for NMO, because treatments that are used for MS are often harmful to patients with NMO

Acute treatment of NMO includes steroids and sometimes plasmapheresis for patients who do not improve quickly

Chemotherapeutic agents such as azathioprine, mycophenolate mofetil and rituximab are used to prevent recurrence

The prognosis is often poor, with patients developing paralysis and blindness in the long term

IV) Leukoencephalopathies

A) Progressive multifocal leukoencephalopathy (PML)

PML is characterized by dementia, focal cortical dysfunction, and cerebellar abnormalities

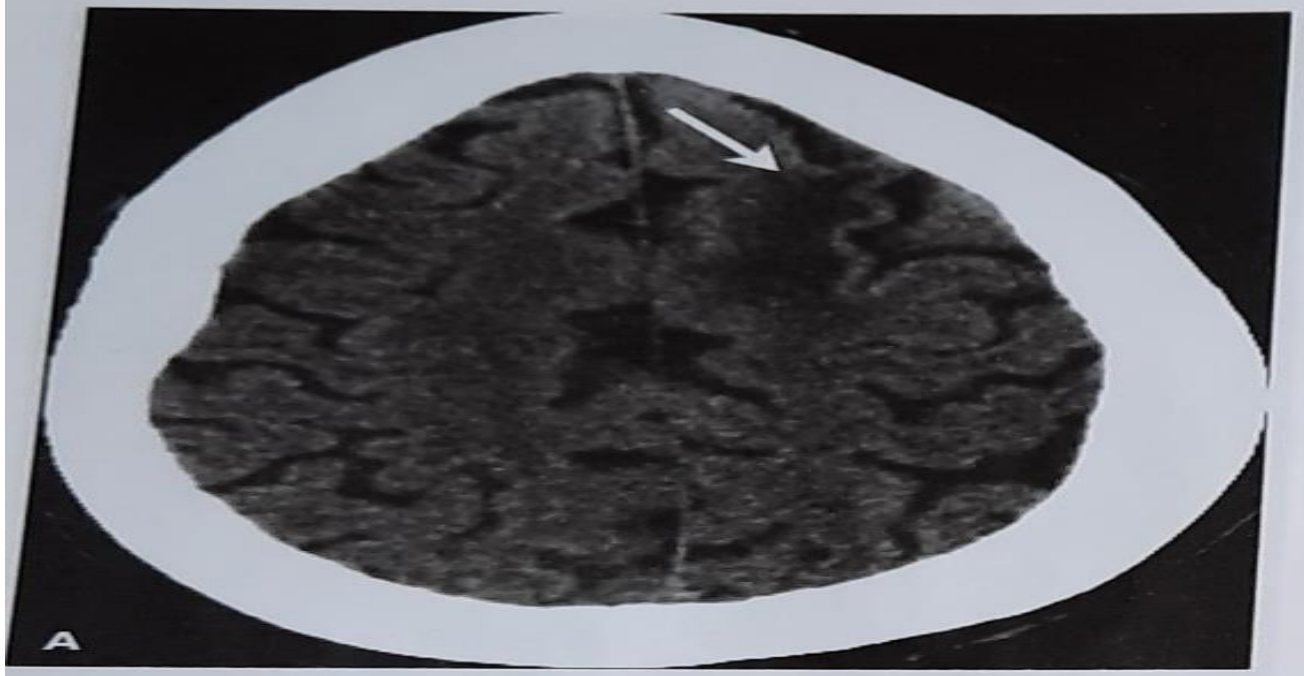
It is seen almost exclusively in patients with AIDS, leukemia, lymphoma, and other immunocompromised states(particularly in patients treated for MS with natalizumab)

The JC virus is the causative agent and leads to demyelination by infecting oligodendrocytes

MRI Brain characteristically shows multiple foci of white matter abnormalities , particularly in the posterior regions of the brain

CSF analysis is usually normal

So far, treatments for PML have not been particularly effective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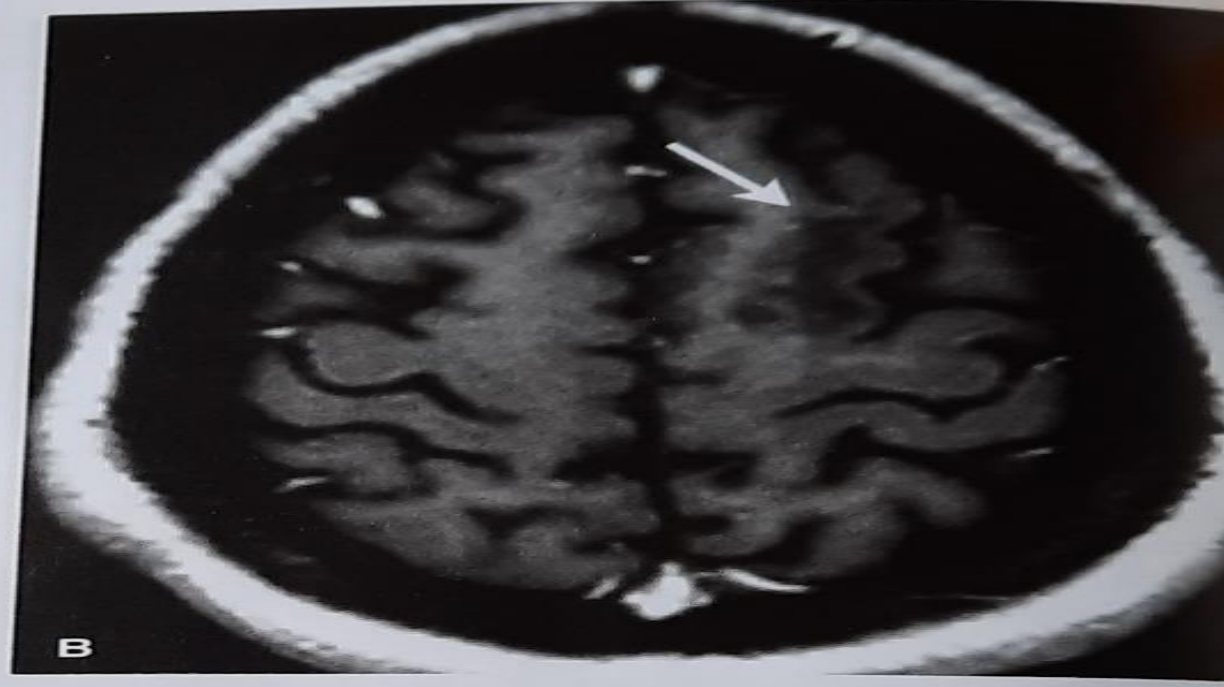
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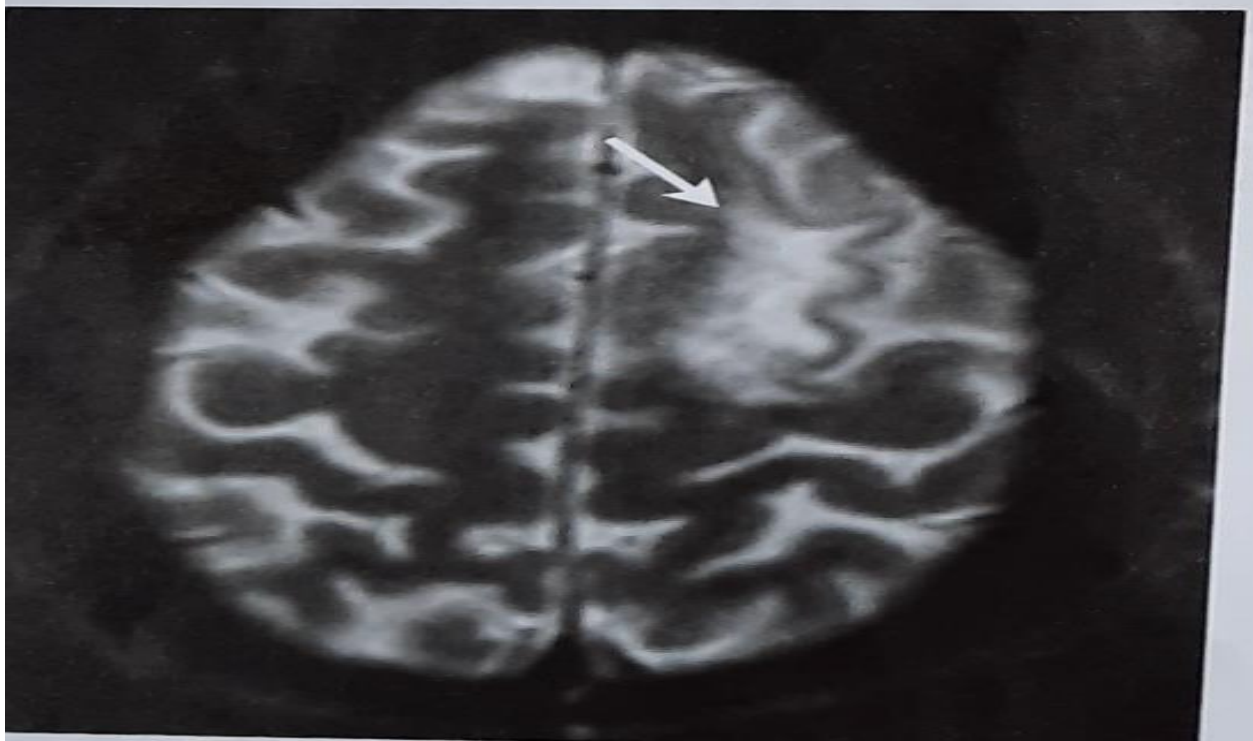

B) Posterior reversible encephalopathy syndrome (PRES)

PRES is a leukoencephalopathy that develops in the context of rapidly developing hypertension, eclampsia, or due to calcineurin-inhibiting immunosuppressants used to prevent organ transplant rejection

(tacrolimus and cyclosporine)

Most commonly, this condition is characterized by an acute confusional state and cortical visual loss(blindness with preserved pupillary reactivity)

MRI Brain shows posterior white matter hyperintensities on T2-weighted images

PRES can be treated by addressing the underlying cause: correcting hypertension, treating eclampsia, or lowering the dose of the offending immunosuppressant

Calcium channel blockers may be effective

Despite its name, PRES is not always a reversible syndrome and can result in coma or death

C) Central pontine myelinolysis

This condition, which is associated with alcoholism and with hyponatremia (and its over-rapid correction) , presents acutely(over several days) with features of a pontine and medullary lesion,i.e. bulbar palsy, tetraparesis and subsequently eye movement disorder and coma

Treatment includes gradual correction of metabolic abnormalities,and vitamin supplements, though prognosis is poor

V) Inherited disorders

Genetic disorders of myelin chemistry lead to abnormal myelin formation (**dysmyelination** rather than demyelination)

These diseases , also known as **leucodystrophies** , usually present in infancy or childhood

However, some develop in adulthood with dementia,ataxia,spasticity,

seizures,optic atrophy and sometimes peripheral nervous system involvement(polyneuropathy)

These disorders, fortunately very rare, are progressive and fatal

No specific treatment is at present available,though there is interest in enzyme replacement by bone marrow transplantation or ultimately gene therapy