
Multiple sclerosis (MS)

Definition

- MS is an autoimmune inflammatory disease of the CNS white matter characterized by a relapsing or progressive course.

Introduction

- One of the most common central nervous disease (CNS) diseases.
- Characterized by appearance of patches of demyelination in the white matter of the CNS, generally starting in the optic nerve, spinal cord or cerebellum.
- The myelin sheaths degenerate and the myelin is removed by the microglial cells. Astrocytes proliferate leading to formation of the gliotic scar.
- As demyelination occurs the conduction of the nerve impulses in the axons is impeded.

MULTIPLE SCLEROSIS (MS)

is an autoimmune disease that affects the

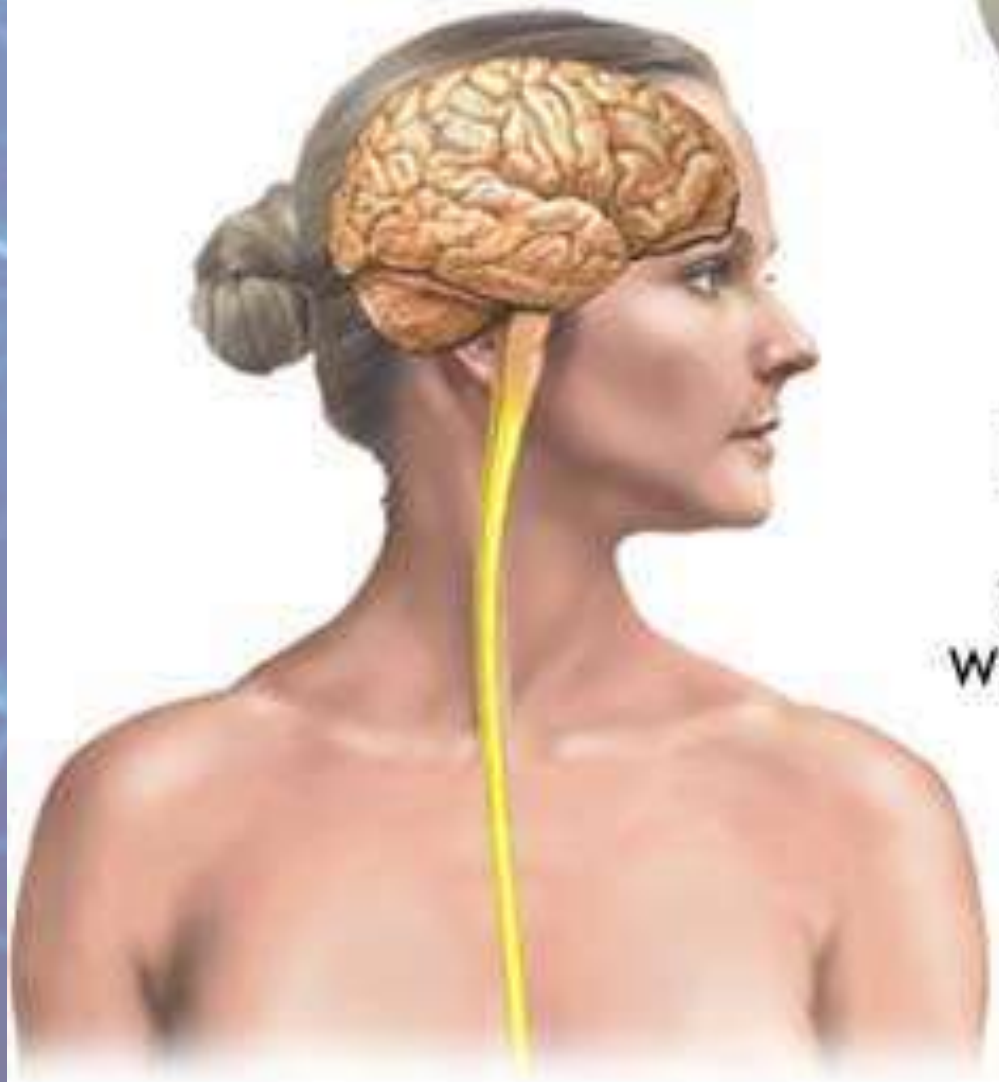
CENTRAL NERVOUS SYSTEM

Researchers believe that MS causes the body's immune system to attack **MYELIN**, an insulating coating around nerve cells.

Pathophysiology

- MS is confined to the CNS, causing demyelination of ascending and descending tracts.
- Blood brain barrier breach results in invasion of brain and spinal cord by some infection allowing leukocytes to enter normally immunologically protected CNS.
- The inflammation and demyelination with loss of myelin sheath results in breakdown of the insulation around the axons and the velocity of AP is reduced and ultimately becomes blocked.

Central nervous system
(brain and spinal cord)



In multiple sclerosis the myelin sheath, which is a single cell whose membrane wraps around the axon, is destroyed with inflammation and scarring

- Myelin is relatively rich in lipid (70-80%), it also contains proteins that play a role in it's compaction.

- Many of the proteins found in CNS differ from those in peripheral nervous system (PNS).

- It is possible that mutations in the structure of the myelin protein can occur and be responsible for some inherited forms of demyelination. It is also possible that autoantigens develop in MS.

- The course of MS is chronic with exacerbations and remissions. Due to the widespread involvement of the different tracts at different levels of neuroaxis, the signs and symptoms are multiple.

- Remissions in MS is by the remodeling of the demyelinated axonal plasma membrane so that it acquires a higher than normal number of sodium channels which permit AP conduction despite myelin loss.

- In progressive form of disease without remissions patients have substantial damage to the axons as well as myelin suggesting MS has axonal pathology.

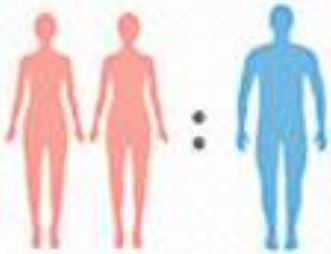
Etiology

- It is a disease of young adults. Most cases occur between the age of 20 and 40 years.
- Females are affected more than males.
- The cause of disease is unknown; may interplay between a viral infection, host immune response and hereditary alone or in combination may play a role.
- Breach in blood brain barrier in genetically predisposing individual would be responsible for MS.

YOU CAN GET MS AT **ANY AGE,**

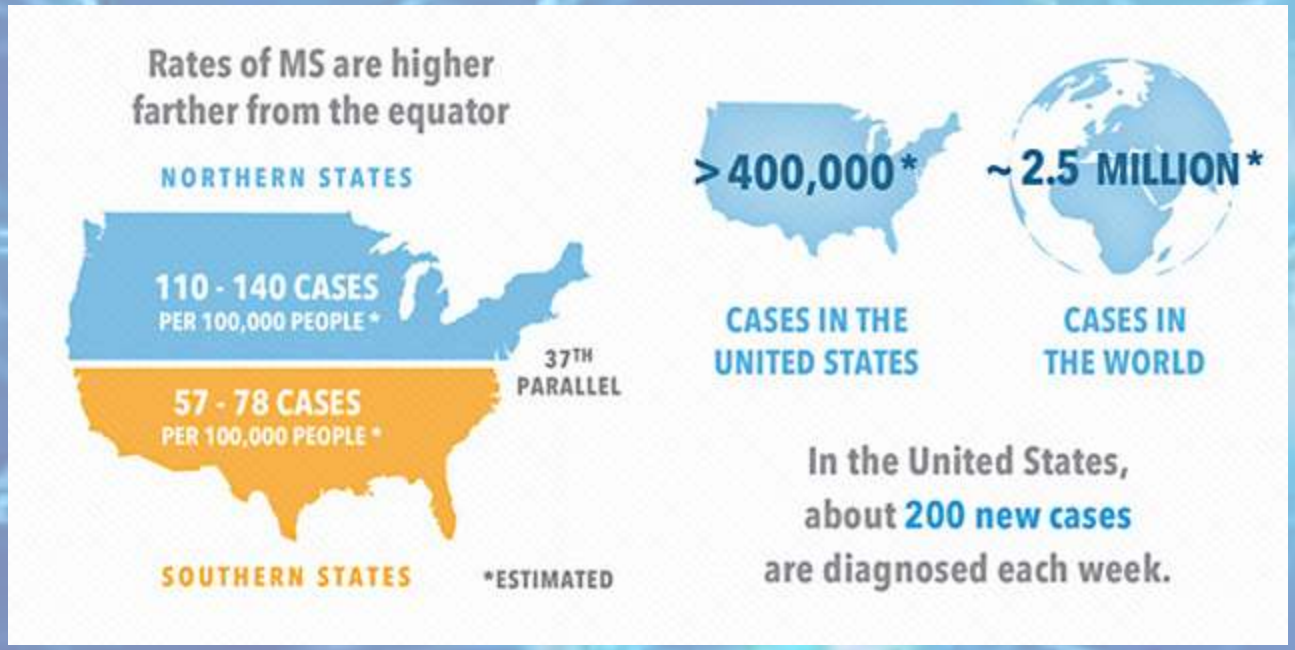
BUT MOST PEOPLE ARE DIAGNOSED BETWEEN THE AGES OF

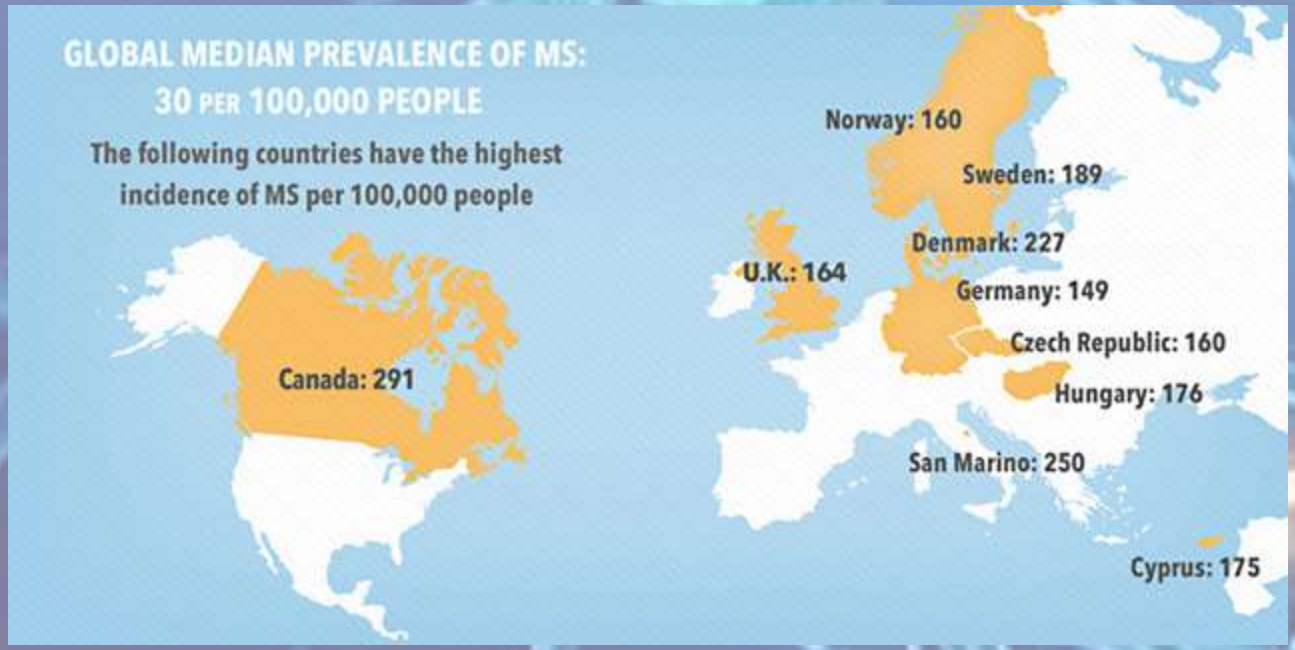
The ratio of **women** with MS to **men** with MS is 2 : 1.



If you have a **parent or sibling** with MS, you have a **1 - 3% chance** of developing it.

An **identical twin** with MS raises your risk to **30%.**


Rates of MS are higher farther from the equator
NORTHERN STATES
110 - 140 CASES
PER 100,000 PEOPLE *
37TH PARALLEL
57 - 78 CASES
PER 100,000 PEOPLE *
SOUTHERN STATES
*ESTIMATED
>400,000*
CASES IN THE UNITED STATES
~2.5 MILLION*
CASES IN THE WORLD
In the United States, about 200 new cases are diagnosed each week.


GLOBAL MEDIAN PREVALENCE OF MS:
30 PER 100,000 PEOPLE
The following countries have the highest incidence of MS per 100,000 people
Canada: 291
Norway: 160
Sweden: 189
Denmark: 227
U.K.: 164
Germany: 149
Czech Republic: 160
Hungary: 176
San Marino: 250
Cyprus: 175

Clinical presentation

- Weakness, numbness, tingling or unsteadiness of the limbs is the most common sign.
- Ataxia due to involvement of the tracts of cerebellum may occur, spastic paralysis may also be present.
- Urinary urgency or retention, blurry vision and double vision are all common initial manifestations of the disease.
- Symptoms may persist for several weeks or may resolve spontaneously over a few days.

The most common early symptoms of MS are:

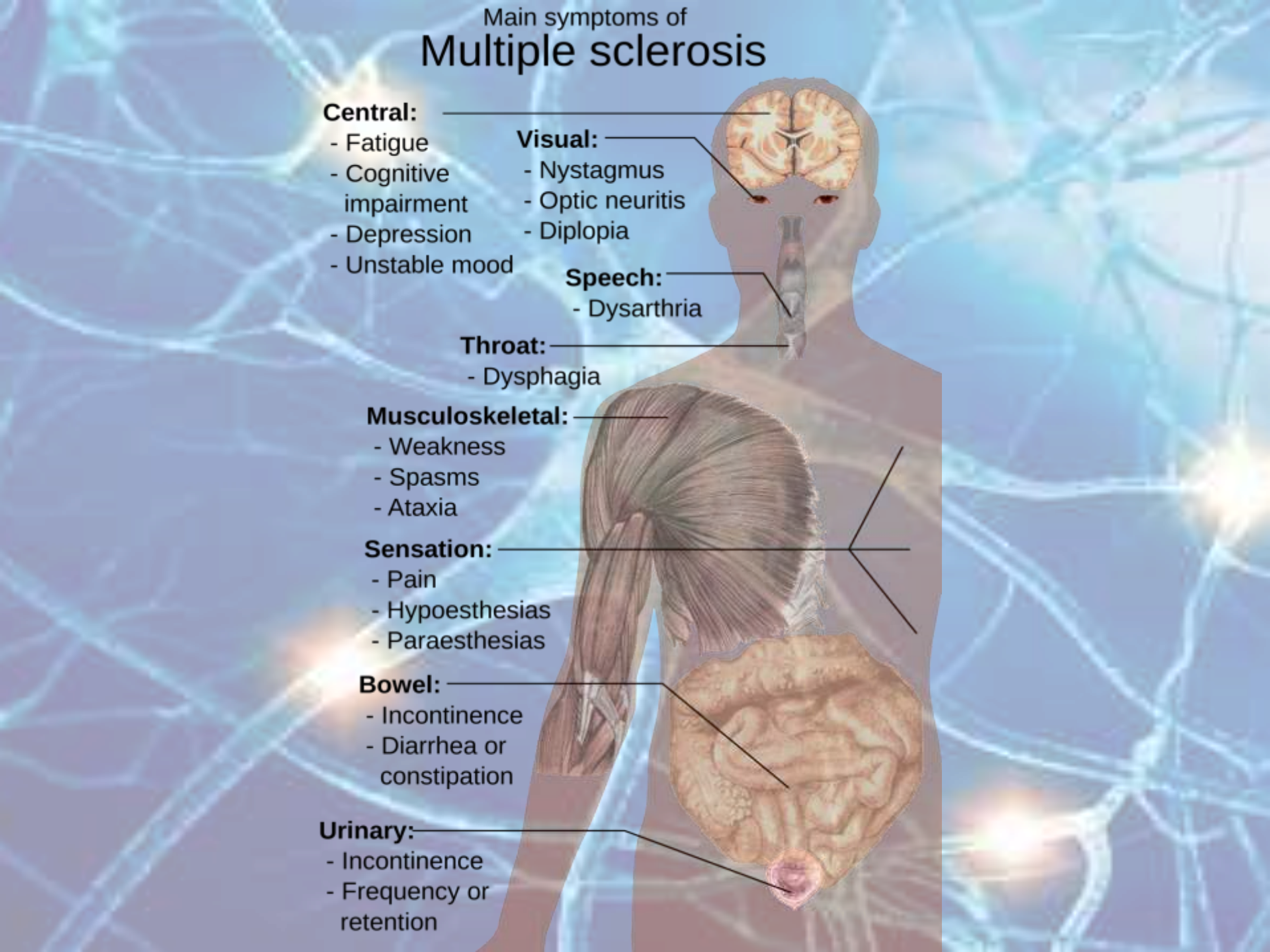
- Fatigue
- Vision problems
- Tingling and numbness
- Vertigo and dizziness
- Muscle weakness and spasms
- Problems with balance and coordination

Other, less common, symptoms include:

- Speech and swallowing problems
- Cognitive dysfunction
- Difficulty with walking
- Bladder and bowel dysfunction
- Sexual dysfunction
- Mood swings, depression

Main symptoms of

Multiple sclerosis



Types of MS

- The disease has several forms which change the course of the management and are therefore important to recognize. Most patients will have a months-long to year-long disease free after their first exacerbation.
- ***Relapsing remitting disease:*** progression is characterized by relapses of active disease with incomplete recovery during periods of remission.
- ***Secondary progressive disease:*** progression becomes more aggressive so that a consistent worsening of function occurs.
- ***Primary progressive disease:*** symptoms are progressive from the onset of disease with the early onset of disability.

Percentage of patients diagnosed with **relapsing-remitting MS (RRMS)** at onset

Percentage of people with **RRMS** who transition to **secondary-progressive MS (SPMS)** within a decade of initial diagnosis

Percentage of people diagnosed with **primary-progressive MS (PPMS)** at onset

Percentage of people with **progressive-relapsing MS (PRMS)**, the rarest form of MS

Triggers that exacerbate MS

- Since raising the temperature shortens the duration of action potential(AP) one of the early signs is improvement on cooling and worsening by hot bath.
- Infections or trauma may acutely worsen the disease.
- Pregnancy especially the 2 to 3 months following birth.

People with

1 TYPE 1 DIABETES

THYROID DISEASE

INFLAMMATORY BOWEL DISEASE

are at a slightly increased risk of developing MS.

Women with MS often experience relief from symptoms during pregnancy, however...

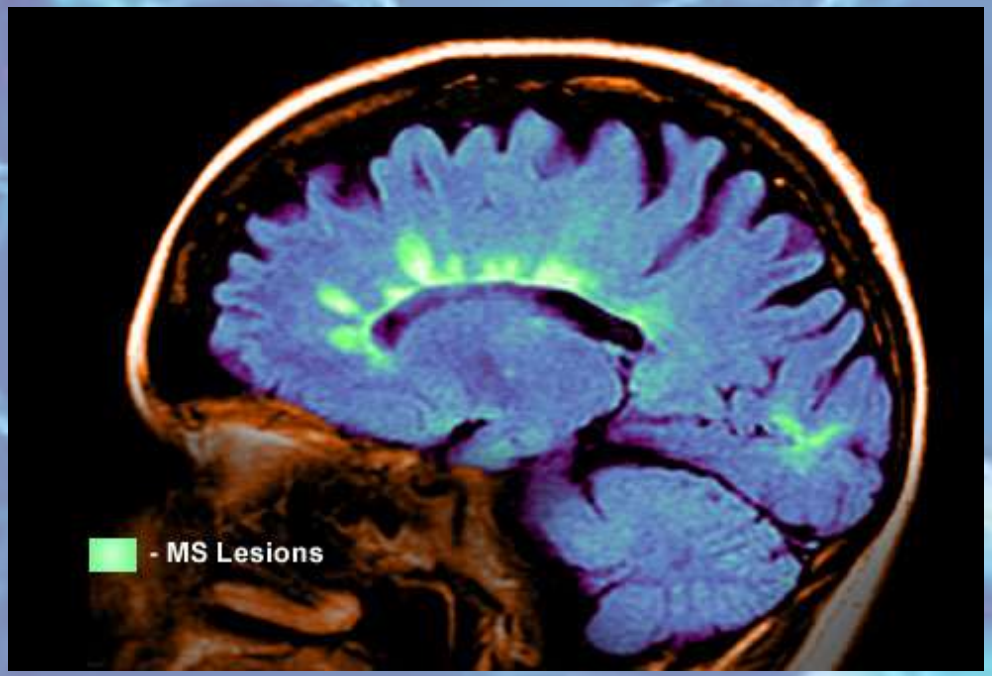
about 20 – 40% of pregnant women with MS have a relapse within a few months of giving birth.

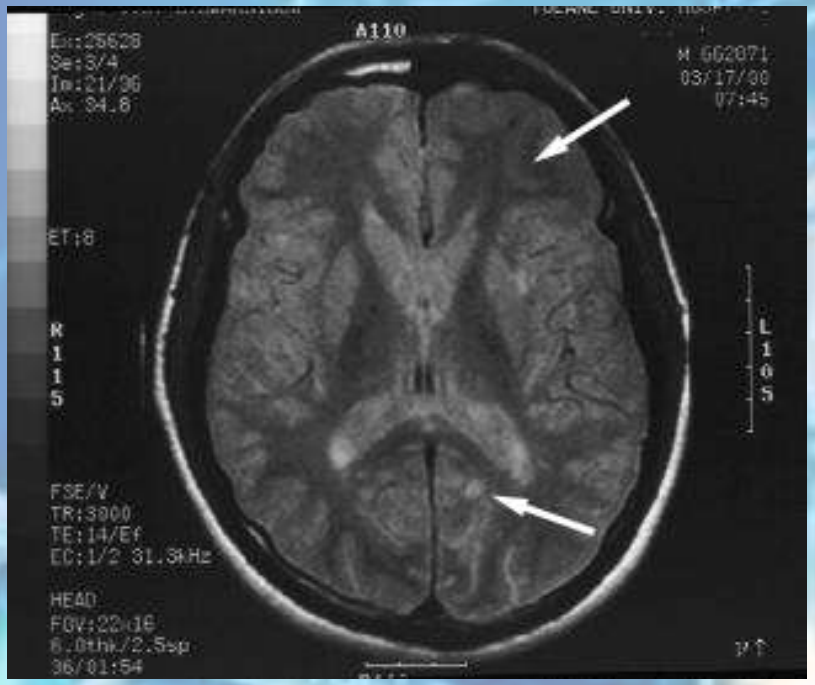
Investigations

- MRI of the brain is the most accurate test to diagnose MS, reaching a sensitivity of 85 to 95% in symptomatic persons.

- Increased T2 and decreased T1 intensity represent the increased water content of demyelinated plaques in the cerebrum and spine.

- Enhancement of lesions with gadolinuim indicates active MS lesions that may enhance for up to 2 to 6 weeks after an exacerbation.


- MS Lesions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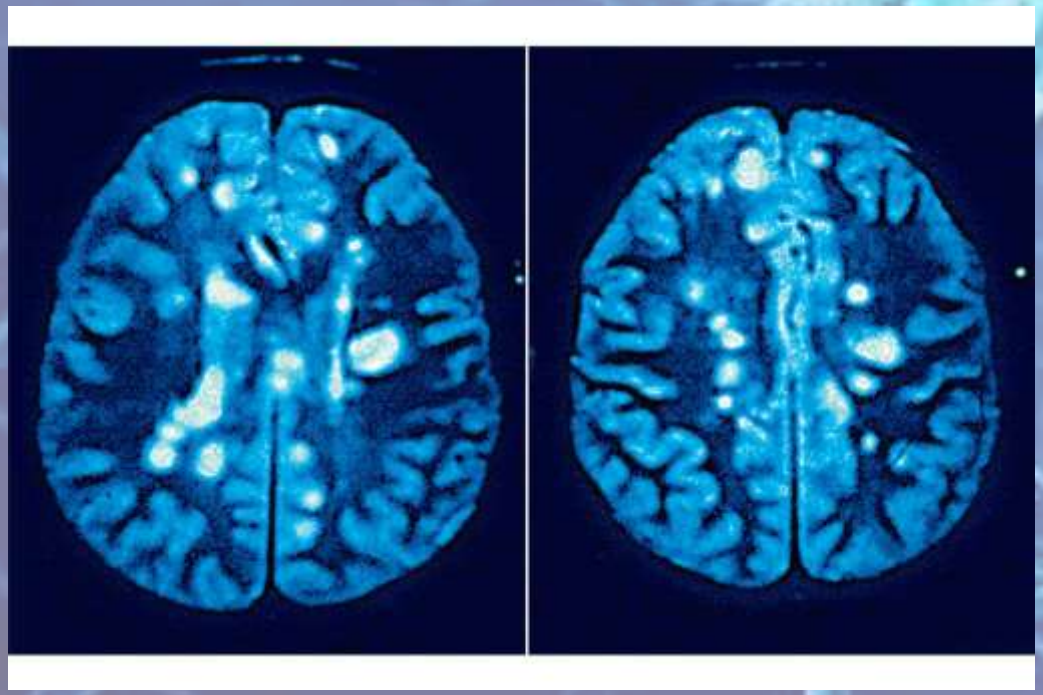

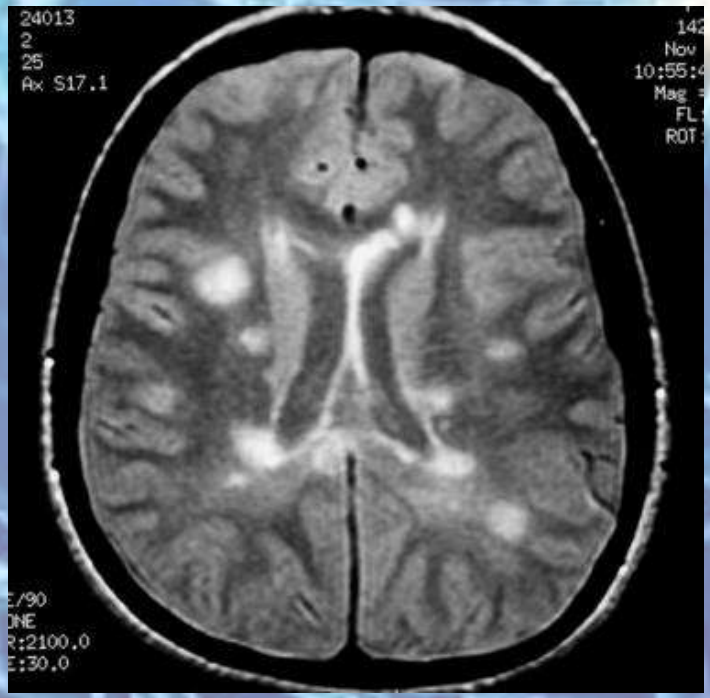
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Characteristic differences between small-vessel disease (SVD) and multiple sclerosis (MS)

Involvement	SVD	MS
Corpus callosum	Rare	Common
U-fibers	Rare	Often
Infratentorial	Late in the course of the disease	Common
	Brainstem: involvement of central transverse fibers	Brainstem: involvement of pial and ventricular surface and intra-axial trigeminal segment
Temporal lobe	Never*	Often
Gadolinium enhancement	Exceptional (subacute infarction)	Common
Black holes	Rare	Typical
Lacunae	Typical	Never
Spinal cord	Never	Common

*With the exception of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

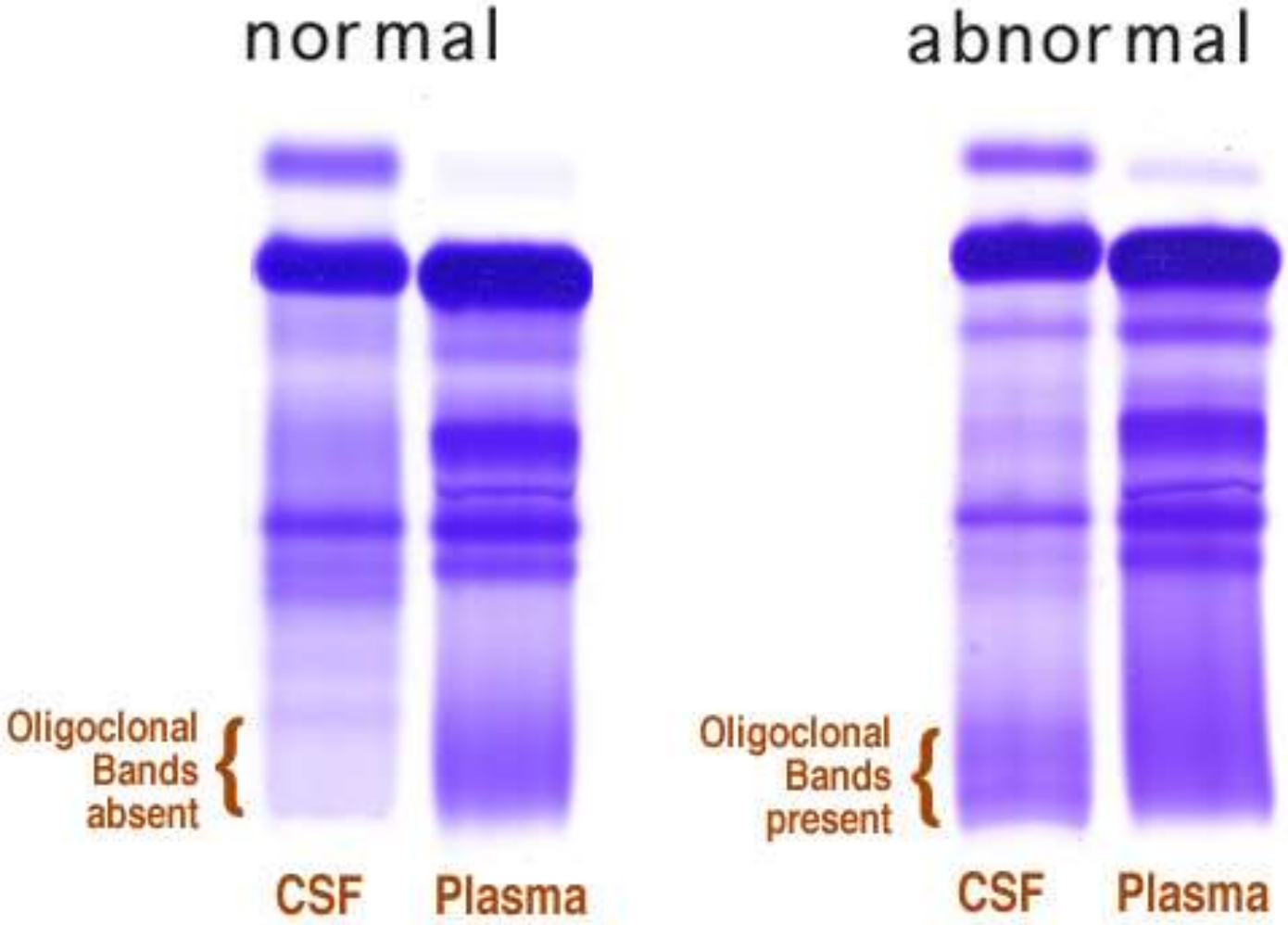
- Evoked response potentials detect slow or abnormal conduction in response to visual, auditory or somatosensory stimuli.

- The limitations of this test for the diagnosis of MS is that many other neurologic diseases can give an abnormal result.

- CSF analysis usually reveals a mild pleocytosis and a total protein that is mildly elevated. A protein level exceeding 100mg/dl is unusual and should be considered as evidence against the diagnosis of MS.

- An elevated IgG index is found in 70 to 90% of patients with MS. The finding is non specific.

Oligoclonal Bands in CSF



Treatment

- The treatment of MS can be divided into disease modifying therapy, treatment of symptomatic relief during an acute exacerbation.

- In relapsing remitting disease, there are three disease modifying agents(IFN-β1a, IFN-β1b and glatiramer acetate) that have been shown to reduce the number of clinical exacerbations and the number of MRI lesions.

- These medications delay disability onset. Glatiramer is also a known copolymer I.

- In secondary progressive disease, IFN-β1b and mitoxantrone have been shown to reduce the number of exacerbations, MRI activity, and delay onset of disability.

- In patients who receive mitoxantrone, dose-related cardiotoxicity is a concern; mitoxantrone should only be given to patients with normal EF. Mitoxantrone is not first line agent due to cardiotoxicity.

- In patients with relapsing remitting disease or secondary progressive disease who can not tolerate treatment with IFN-β1b, IFN-β1a or glatiramer acetate treatment can be considered with methotrexate, mitoxantrone, cyclophosphamide, IV immunoglobulin or azathioprine. ACTH is no longer used.

- No approved disease modifying therapy exists at this time of progressive disease.

- Mitoxantrone, cyclophosphamide and natalizumab are not used for a first episode of disease. Natalizumab is associated with progressive multifocal leukoencephalopathy(PML).

- The length and intensity of an acute exacerbation is shortened by the administration of gluco-corticoids. An exacerbation is treated with 3 days of intense IV steroids followed by a course of oral medication tapered over 4 weeks.

- In patients with severe disease who are unresponsive to steroid therapy, plasma exchange can be used as an alternative treatment.

- For patients with spasticity, baclofen is the most effective medication. Tizanidine and diazipam are useful for nocturnal spasticity but are limited in their use for daytime symptoms because they cause intense somnolence.

- Pain secondary to trigerminal neuralgia and dysthesias responds well to carbamazepine, gabapentin, phenytoin, pregabalin or tricyclic antidepressants.

- Bladder hyperactivity is treated with oxybutynin, whereas urinary retention is treated with bethanecol. Fatigue may be treated with amantadine or fluoxetine.

- Erectile dysfunction can be treated with sildenafil acetate.

- Disease modifying therapies are contraindicated in pregnancy.

References

- Snell's clinical neuroanatomy 7th edition
- Kaplan lecture notes USMLE step 2 CK internal medicine


Thank you