

Multiple Sclerosis

Immune-mediated CNS demyelination

Pathogenesis · morphology · clinical correlations

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Learning objectives

- Explain the immune mechanisms and genetic–environmental predisposition of MS.
- Recognize macroscopic, microscopic and spatial patterns of demyelinating plaques.
- Relate lesion location and disease course to clinical findings and investigations.
- Distinguish MS from selected other demyelinating syndromes.

Multiple sclerosis: Defining pathology

- Acquired immune-mediated demyelination primarily within the CNS.
- Patchy lesions often affect widely separated white matter sites.
- Secondary axonal injury and gray matter pathology contribute to long-term disability.

Demyelination is not failed myelin synthesis

- Demyelination: Destruction of previously formed myelin.
- Axons are relatively preserved early, but can become damaged with time.
- Inherited leukodystrophies involve abnormal myelin synthesis or turnover.

Myelin loss disrupts axonal signaling

Preserved conduction insulation



Continuous myelin segments support efficient impulse propagation.

Inflammatory demyelination



Loss of insulation causes impaired signal transmission; Axons initially persist.

Schematic — segment count and lesion size are illustrative, not quantitative.

Why the symptoms can initially improve

- Early neurologic deficits arise partly from impaired conduction in demyelinated tracts.
- Inflammation may decline following an attack, permitting partial functional recovery.
- Remyelination is limited; Cumulative axonal damage restricts later recovery.

Dissemination in time and space

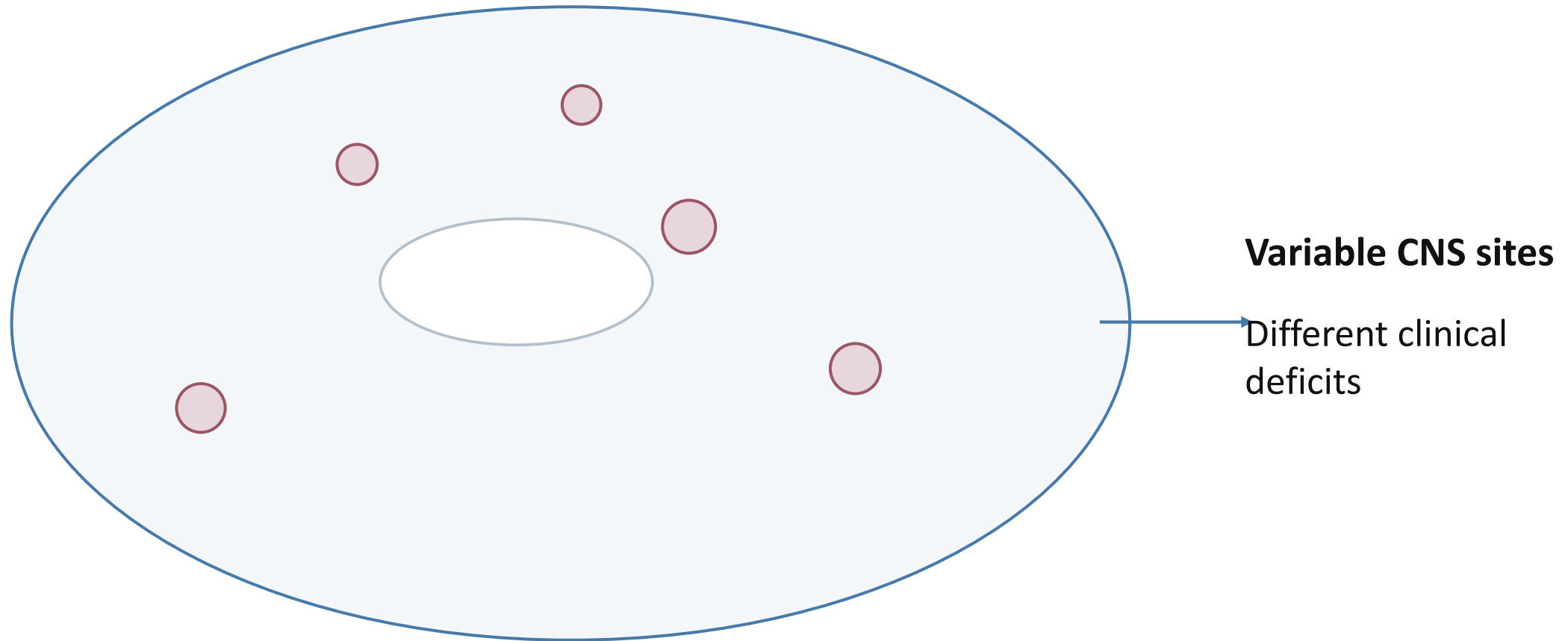
Time

- Distinct episodes of neurologic dysfunction
- Clinical remissions may be incomplete
- New manifestations can emerge later

Space

- Separate CNS lesions at different locations
- Different tracts explain different deficits
- A single symptom does not define the full lesion burden

Multifocal anatomy explains variable findings



Conceptual map — not an MRI, anatomical section, or lesion prevalence map.

MS has a characteristic epidemiologic pattern

- Textbook estimate: Approximately 1 per 1,000 persons in much of the United States and Europe.
- Clinical onset can occur at many ages; Childhood and onset after age 50 are uncommon.
- Females are affected more than twice as often as males.

Most patients initially have a relapsing course

- Neurologic attacks and remissions are separated by variable intervals.
- Deficits may last weeks to months; Intervals between attacks may be long.
- Recovery after attacks is often gradual and incomplete.

Secondary progressive MS

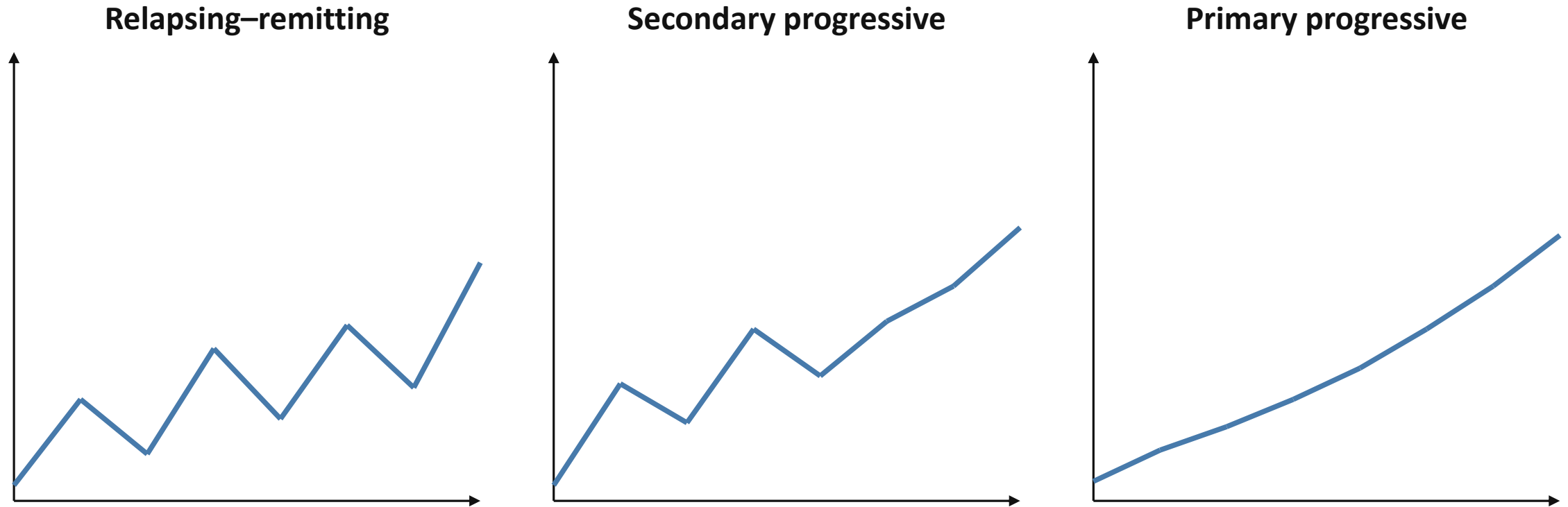
- A proportion of relapsing–remitting patients later accumulate disability steadily.
- Relapses may become less prominent while progression continues.
- Progressive decline can occur despite suppression of acute relapses.

Primary progressive MS

- Disability progresses from clinical onset.
- Sustained neurologic deterioration occurs without a preceding relapsing–remitting phase.
- Intermittent improvement, if present, is limited.

Three clinical trajectories are not equivalent

The distinction concerns the temporal pattern of neurologic disability.



Horizontal axis: Time · Vertical axis: Neurologic disability (qualitative)

Illustrative clinical trajectories — qualitative axes, not patient data or estimated probabilities.

Relapses and progression are distinct dimensions

- Acute inflammatory activity contributes to clinical attacks.
- Steady disability accumulation reflects additional neurodegenerative pathology.
- Effective relapse prevention does not completely prevent late deterioration.

MS has both genetic and environmental components

- No single causative variant explains the disease.
- Familial aggregation supports inherited susceptibility.
- Environmental exposure is important and interacts with susceptibility.

Family and twin studies indicate susceptibility

- ~15-fold greater incidence with an affected first-degree relative.
- The reported increase is ~150-fold with an affected monozygotic twin.
- These comparisons indicate strong susceptibility, not deterministic inheritance.

Relative incidence reported by Robbins

First-degree relative

~15-fold

Monozygotic co-twin

~150-fold

Associations, not individual probabilities

Conceptual schematic — not a specimen or patient image.

MHC region is a major genetic association

- A strong relationship exists with a major histocompatibility complex DR haplotype.
- Antigen presentation biology fits the proposed autoimmune mechanism.
- MHC association alone cannot account for the variability of clinical course.

Immune regulatory genes contribute

- Genome-wide associations include genes for IL-2 and IL-7 receptors.
- Additional associations involve B-cell functions and cytokine signaling.
- Other associated loci regulate costimulation and intracellular immune signaling.

Genetics does not explain clinical variability

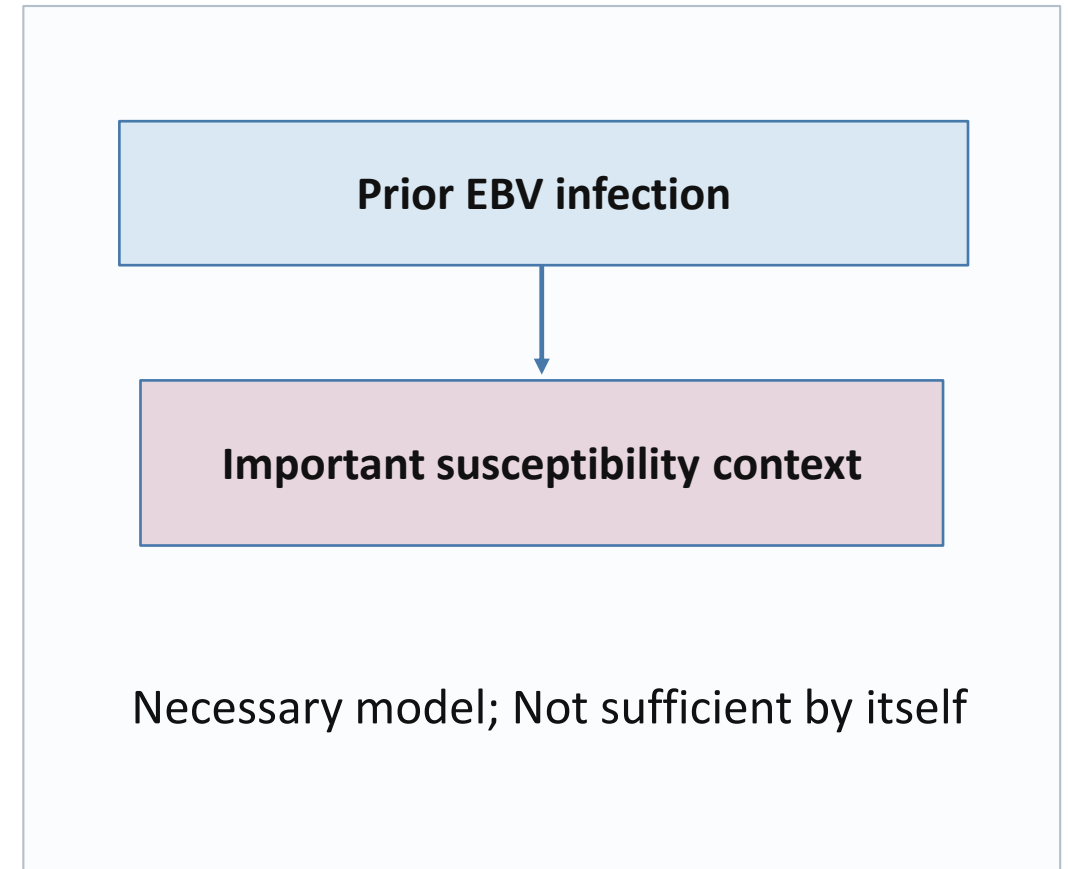
- Only part of the inherited predisposition is currently accounted for.
- Many associated immune loci are shared with other autoimmune disorders.
- Genetic studies have not explained why outcomes differ substantially between patients.

Geographic variation implicates environment

- MS is diagnosed more frequently in populations farther from the equator.
- The mechanism of this geographic association remains uncertain.
- Association should not be interpreted as proof of a single environmental cause.

EBV exposure is closely associated with MS

- Large epidemiologic studies strongly link prior Epstein–Barr virus infection to MS.
- EBV infection as likely necessary, but insufficient alone.
- Most EBV-exposed people do not develop MS.



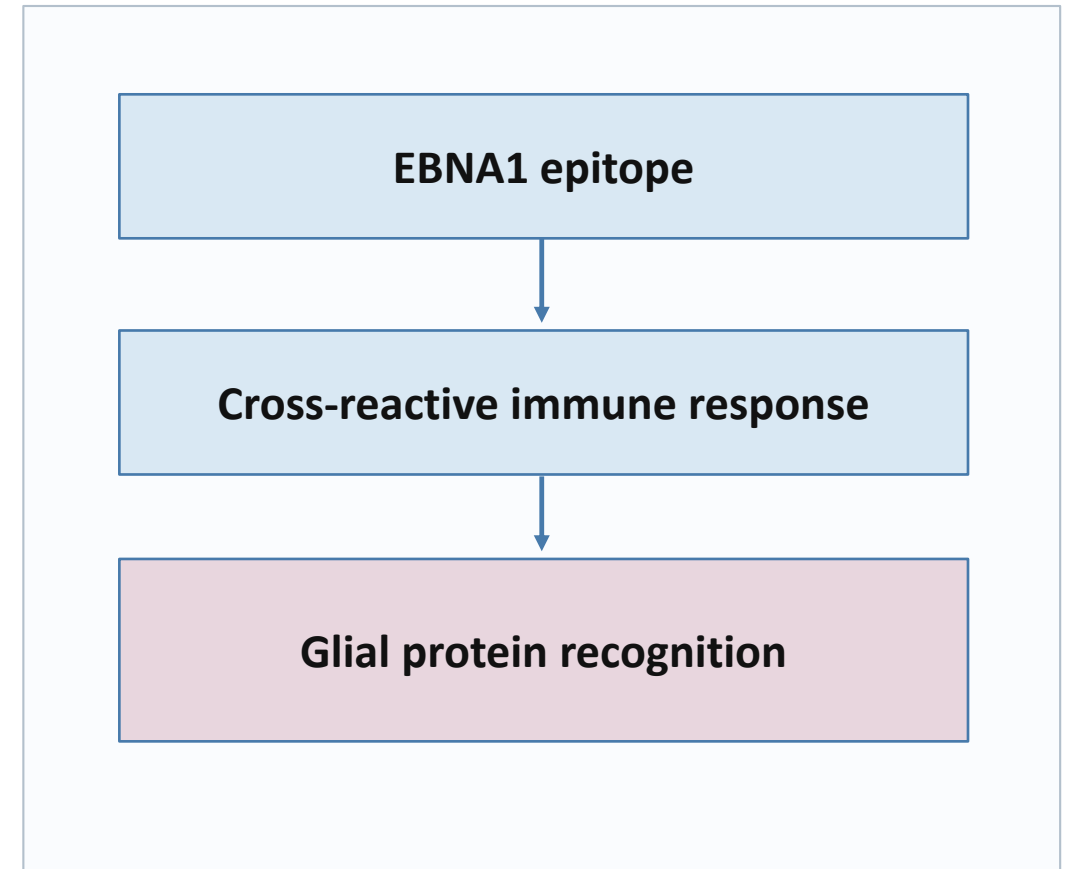
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Timing of EBV infection appears important

- A pronounced increase in risk with later EBV infection.
- The reported ~40-fold association pertains to infection during adolescence rather than early childhood.
- An epidemiologic association does not itself establish a complete causal mechanism.

Molecular mimicry offers a mechanistic link

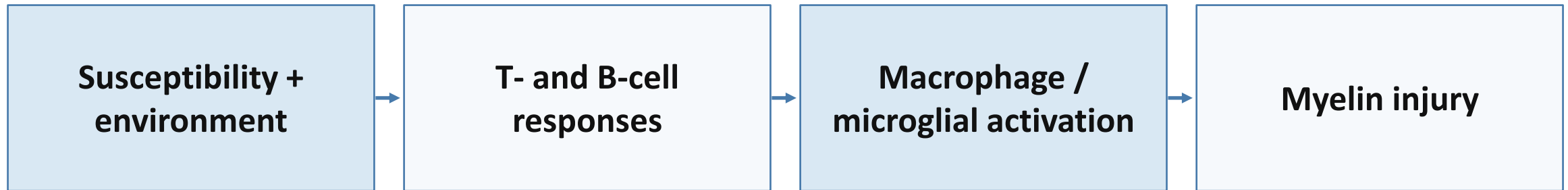
- EBV nuclear antigen 1 (EBNA1) can show immunologic cross-reactivity with glial proteins.
- Cross-reactive antibodies and T cells are both plausible participants.
- Mimicry is a proposed contributing mechanism—not a defined universal autoantigen.



Conceptual schematic — not a specimen or patient image.

Autoimmune pathways converge on myelin injury

Multiple immune processes act together; The relevant antigenic targets remain incompletely defined.



Biologic sequence is a teaching abstraction: Exact autoantigen and causal weighting remain uncertain.

Schematic: Cellular interactions are bidirectional in vivo.

The classic T-cell model is incomplete

- Experimental autoimmune encephalomyelitis historically emphasized myelin-reactive CD4 and CD8 T cells.
- Th1/Th17 responses and activated macrophages can participate in myelin destruction.
- Human MS is not fully explained by these animal models.

Animal models have limitations

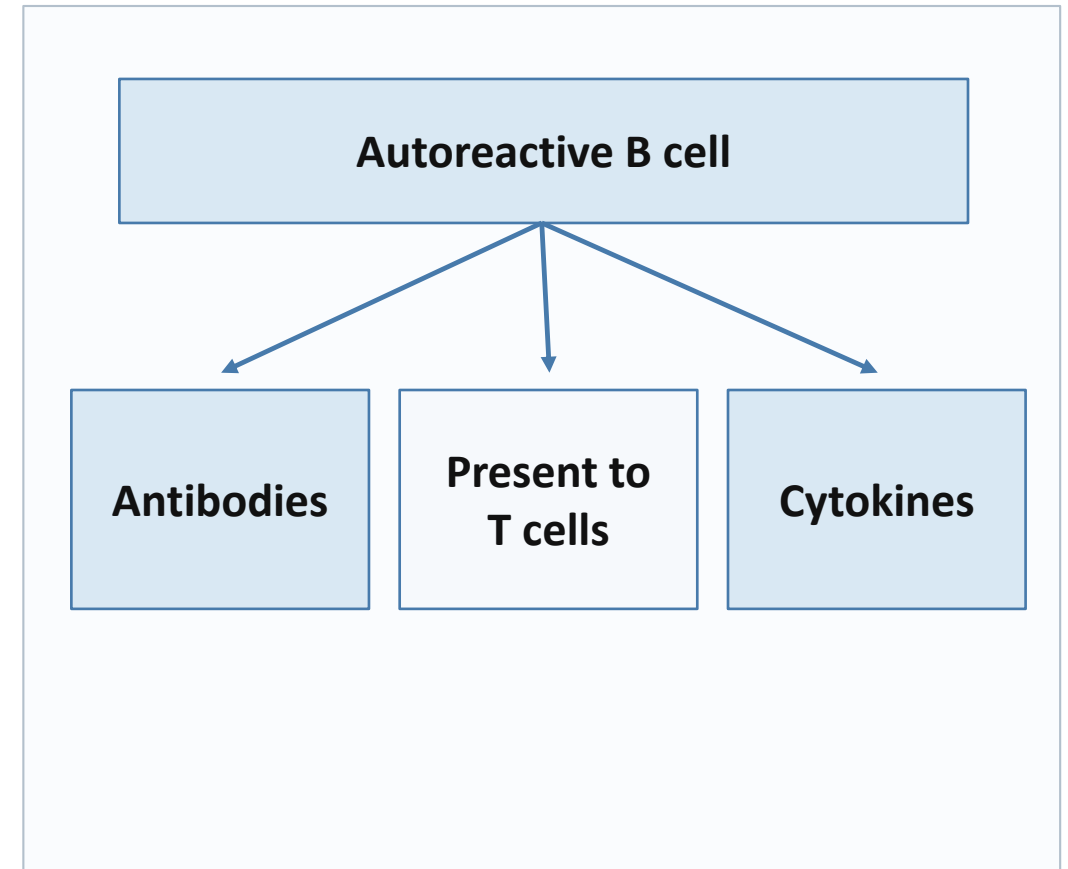
- Immunization with myelin proteins and strong adjuvants induces inflammatory demyelination experimentally.
- Such models may exaggerate the role of T cells relative to human disease.
- Mechanistic extrapolation should not be confused with direct evidence in patients.

B cells are central to contemporary models

- Benefit from B-cell depletion supports an important pathogenic role.
- Clonally expanded B cells occur in CSF.
- B-cell function is more complex than simply producing antibody.

Three potential pathogenic roles of B cells

- Production of antibodies reactive with glial proteins, including GlialCAM.
- Presentation of self antigens that may activate T cells.
- Secretion of inflammatory cytokines that amplify immune injury.



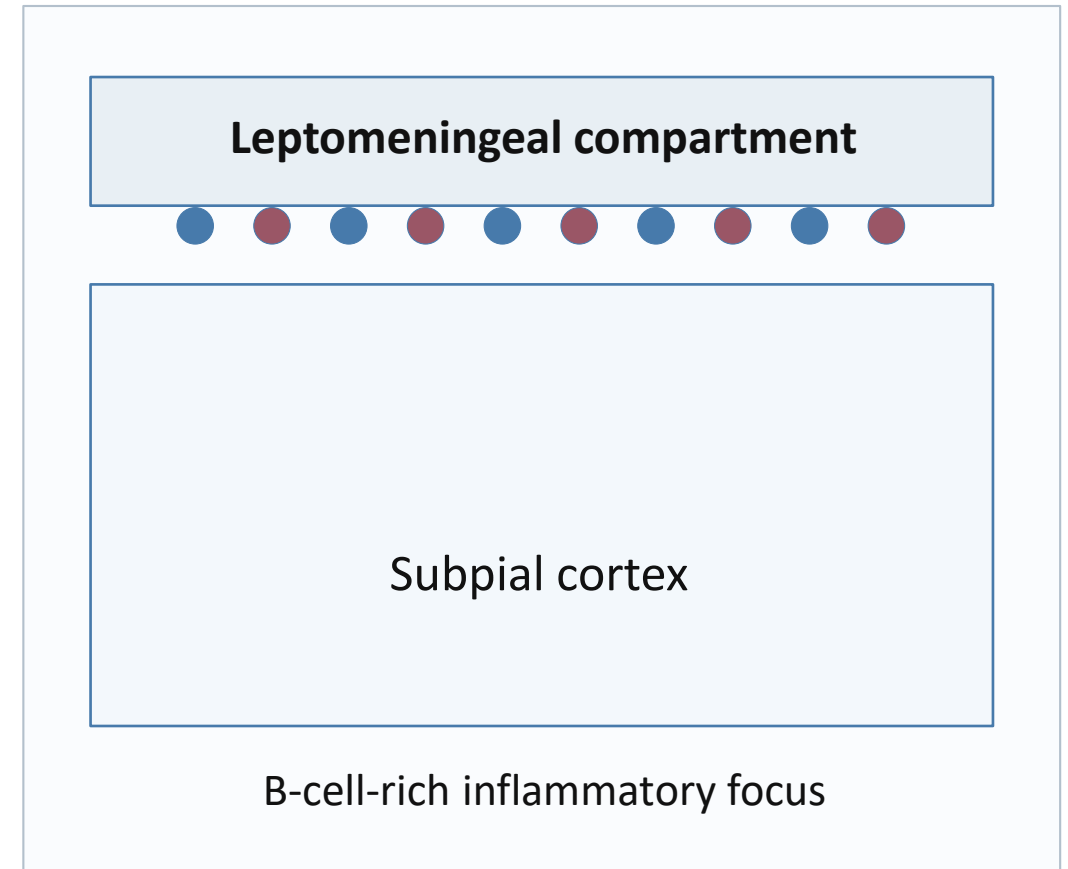
Conceptual schematic — not a specimen or patient image.

Intrathecal B-cell responses are expanded

- Somatically mutated, clonally expanded B cells have been detected in CSF.
- Increased CSF IgG and oligoclonal bands reflect compartmentalized antibody production.
- These findings support an intrathecal humoral immune response.

Meningeal lymphoid structures link immunity to severity

- B-cell-rich inflammatory foci may organize into lymphoid follicles in the meninges.
- An association between follicle burden and disease severity.
- Meningeal immune activity is associated with cortical pathology.



Conceptual schematic — not a specimen or patient image.

EBV biology may intersect with B-cell disease

- EBV activates B cells, potentially increasing autoreactive antibody production.
- Immune cross-reactivity may connect viral epitopes and glial targets.
- Neither hypothesis establishes EBV as the sole explanation for MS.

Inflammation and degeneration coexist

- Active attacks are linked to immune-mediated myelin injury.
- Progression includes slowly enlarging plaques and diffuse low-grade inflammation.
- Cortical damage and secondary axonal loss contribute to persistent deficits.

Progressive pathology extends beyond acute plaques

- Slowly enlarging white matter lesions may persist in progressive disease.
- Diffuse white matter inflammation continues at low grade.
- Subpial cortical injury is important to neurodegenerative progression.

Gross plaques are demarcated and firm

- On fresh sections, plaques are firmer than adjacent white matter.
- Lesions appear glassy, gray-tan, somewhat depressed and irregular.
- Their firmness is the basis of the term “sclerosis.”

Lesions vary in size and may coalesce

- Small microscopic foci can be found alongside large confluent plaques.
- Myelin stains reveal sharper borders than some routine preparations.
- Lesion size alone does not define clinical severity.

Characteristic anatomic distribution

- Common sites include periventricular white matter and corpus callosum.
- Optic nerves and chiasm, brainstem and cerebellum are also affected.
- Spinal cord and long ascending or descending tracts may contain plaques.

Periventricular lesions are a classic site

- Plaques frequently occur adjacent to lateral ventricles.
- Corpus callosum involvement illustrates the white matter predilection.
- Distribution provides an anatomic framework for MRI interpretation.

Cortical demyelination is also important

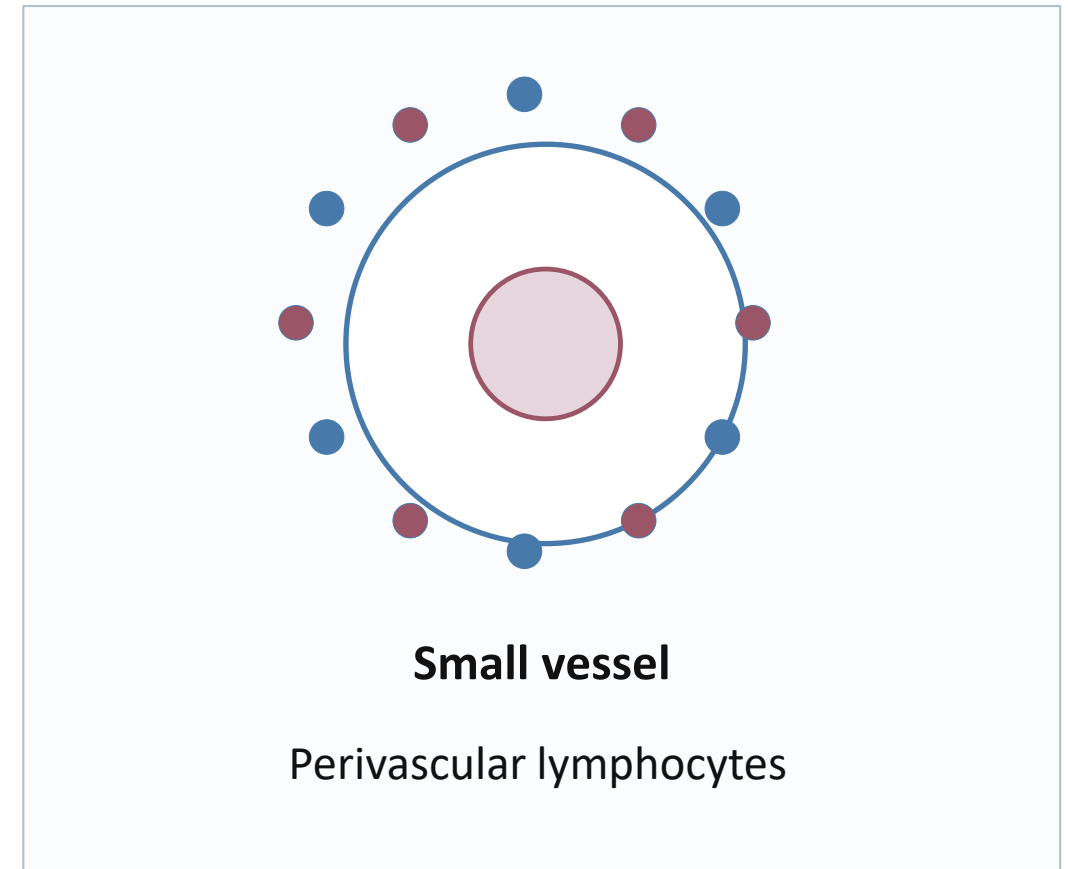
- Extensive subpial demyelination can affect thin myelinated cortical fibers.
- Subpial lesions as a hallmark of MS pathology.
- These lesions are often associated with B-cell-rich leptomeningeal foci.

Active plaques show ongoing myelin destruction

- Abundant lipid-laden or foamy macrophages contain ingested myelin debris.
- Lymphocytes cluster around vessels, particularly near the lesion edge.
- Small-vein-centered inflammation is characteristic of active lesions.

Perivascular cuffs identify local inflammation

- Lymphocytes may form concentric cuffs around small vessels.
- Inflammatory infiltrates are typically prominent around the active border.
- This must be interpreted with demyelination and other morphological features.



Conceptual schematic — not a specimen or patient image.

Macrophages are a direct clue to active breakdown

- Foamy macrophages indicate phagocytosis of myelin lipids.
- Active plaques are more cellular than inactive gliotic plaques.
- Macrophage abundance reflects activity, not specific proof of the initiating autoantigen.

Myelin loss exceeds early axonal loss

- Stains for myelin often show extensive or complete local loss.
- Axonal markers can show relative preservation in the same active lesion.
- With progression and chronicity, axon numbers can markedly decline.

Same lesion: Different tissue compartments

Myelin: Markedly depleted

Axons: Relatively retained

Relative preservation is not permanent

Conceptual schematic — not a specimen or patient image.

Astrocytic gliosis evolves as plaques age

- Reactive astrocytes become conspicuous during the tissue response.
- Inflammatory cells wane as active lesions become quiescent.
- Sustained gliosis is a defining feature of old sclerotic plaques.

Inactive plaques lack macrophage-rich infiltrates

- Inflammatory infiltrates are sparse or absent.
- Myelin remains severely depleted, and oligodendrocyte nuclei are reduced.
- Reactive gliosis and chronic axonal loss are prominent.

Smoldering plaques have an active border

- Progressive MS can contain lesions with a hypocellular inactive-like center.
- Activated microglia or macrophages occupy a rim at the lesion periphery.
- This pattern differs from a uniformly active acute plaque.

Shadow plaques represent limited remyelination

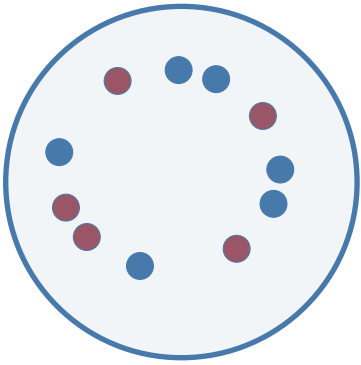
- The affected white matter is less pale than a fully demyelinated plaque.
- Thinner-than-normal myelin sheaths can be demonstrated.
- Remyelination is partial and often most apparent toward the plaque edge.

Remyelination does not fully restore structure

- Surviving oligodendrocytes may remyelinate some axons.
- Many remaining axons within established lesions stay unmyelinated.
- Secondary axonal depletion limits the opportunity for later functional recovery.

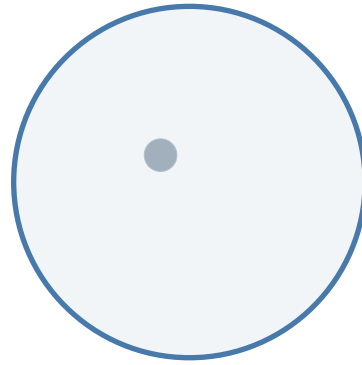
Plaque histology changes with activity

Active plaque



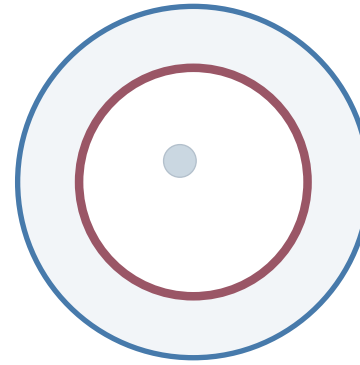
Macrophages +
inflammation

Inactive plaque



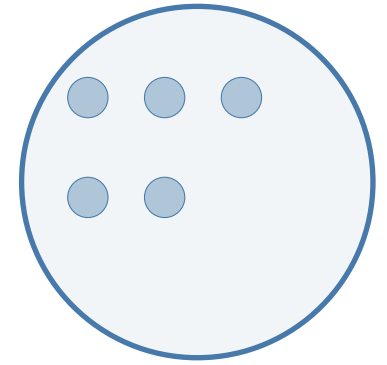
Hypocellular + gliosis

Smoldering plaque



Quiet center; Active rim

Shadow plaque



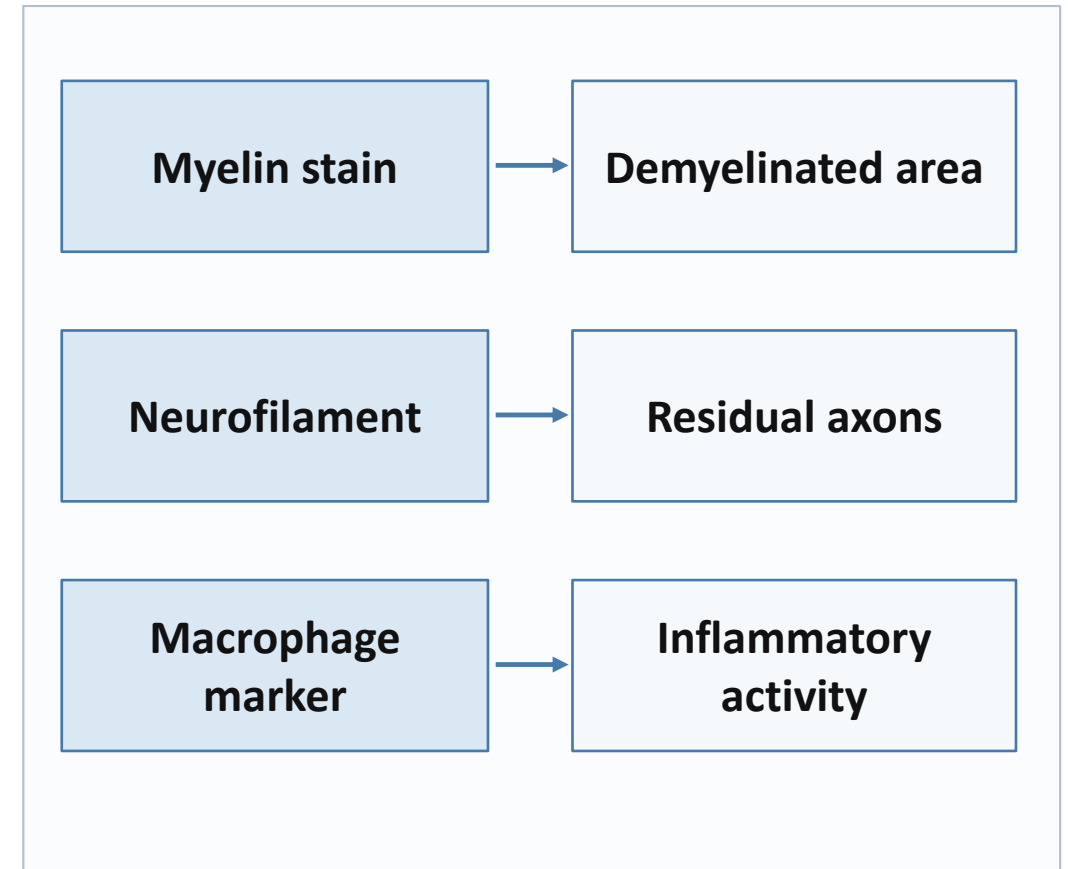
Thin residual myelin

Compare major plaque morphologies

Plaque pattern	Predominant finding	Structural implication
Active	Foamy macrophages; Perivascular lymphocytes	Ongoing demyelination
Inactive	Gliosis; Sparse inflammation	Chronic demyelinated scar
Smoldering	Quiet center; Activated rim	Persistent edge activity
Shadow	Thin myelin sheaths	Partial remyelination

Histologic methods answer different questions

- Myelin stains delineate the extent of demyelination.
- Neurofilament immunostaining assesses residual axons.
- Macrophage markers emphasize phagocytic inflammatory burden.



Conceptual schematic — not a specimen or patient image.

Optic neuritis may be the first presentation

- Inflammation of the optic nerve can cause unilateral visual impairment.
- It is a frequent presenting event but is not specific to MS.
- Population-dependent subsequent MS occurrence after optic neuritis.

Optic neuritis is not equivalent to MS

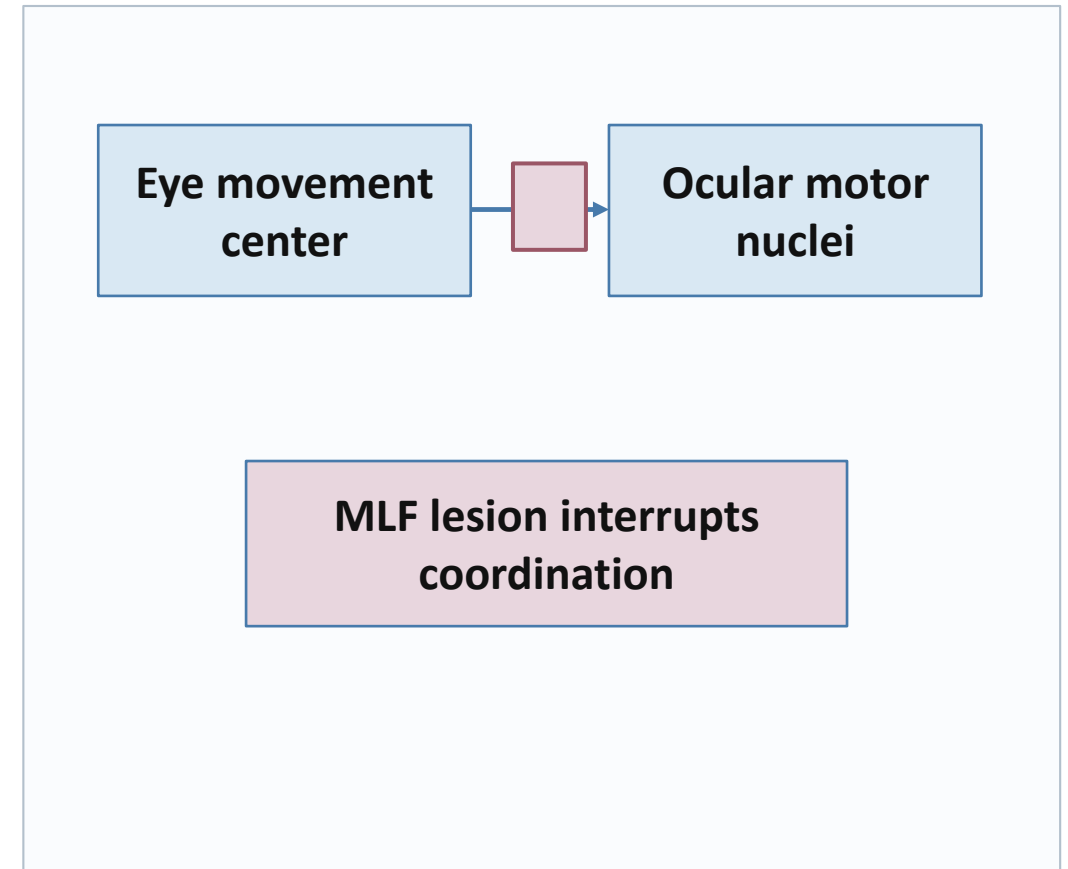
- An approximate 10–50% subsequent MS range after isolated optic neuritis.
- Population selection strongly affects that estimate.
- An isolated event does not establish the historical relapsing–disseminated phenotype.

Brainstem plaques affect cranial pathways

- Brainstem involvement may cause nystagmus and cranial nerve deficits.
- Ataxia can reflect interruption of brainstem and connected cerebellar pathways.
- Distinct localizations explain the broad variety of clinical syndromes.

Internuclear ophthalmoplegia localizes to the MLF

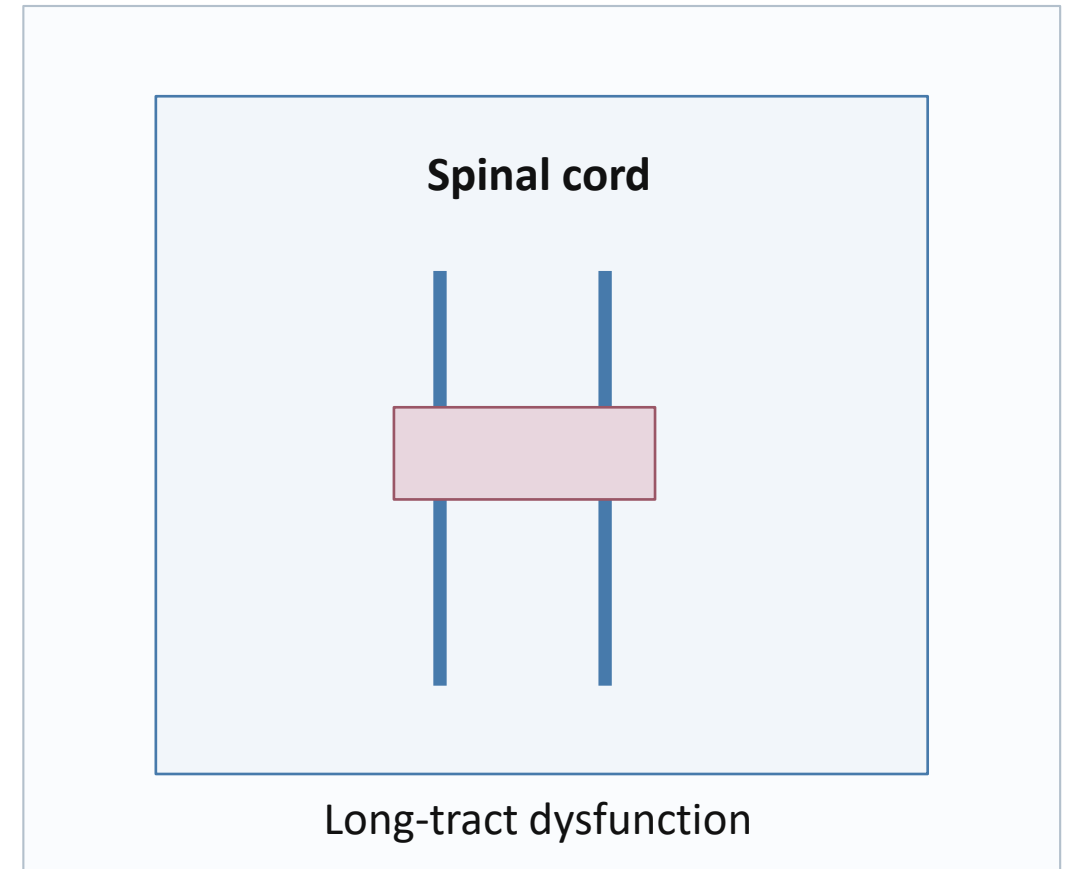
- The medial longitudinal fasciculus links pathways coordinating horizontal eye movement.
- An MS plaque can interrupt this connection and cause internuclear ophthalmoplegia.
- Recognizing the tract explains the ocular motor findings.



Conceptual schematic — not a specimen or patient image.

Spinal cord plaques impair long-tract function

- Motor and sensory deficits may involve limbs and trunk.
- Descending pathway disruption may produce spasticity.
- Autonomic pathway dysfunction can impair bladder and bowel control.



Conceptual schematic — not a specimen or patient image.

Localize symptoms to the affected system

Predominant symptom	Likely affected region	Clinicopathologic principle
Unilateral visual impairment	Optic nerve	Optic neuritis
Internuclear ophthalmoplegia	Medial longitudinal fasciculus	Brainstem tract interruption
Ataxia or nystagmus	Brainstem / cerebellar pathways	Coordination and eye-movement networks
Spasticity, sensory changes	Spinal cord tracts	Long-tract dysfunction

CSF provides evidence of intrathecal immunity

- Total CSF protein is usually normal or only mildly elevated.
- Moderate pleocytosis occurs in a subset of patients.
- CSF IgG may be increased, with oligoclonal IgG bands usually detectable.

Oligoclonal IgG bands have a mechanistic meaning

- Bands suggest expanded antibody-producing B-cell clones within the CNS compartment.
- They support intrathecal immune activity but do not uniquely identify MS.
- Interpret laboratory findings with compatible clinical and anatomic evidence.

MRI is central to assessment

- Magnetic resonance imaging is prominent in monitoring MS lesions and progression.
- Anatomic distribution can be related to neurologic symptoms.
- Morphologic and temporal assessment complement the clinical examination.

Clinical, CSF and imaging findings are complementary

CSF

- Increased intrathecal IgG
- Oligoclonal IgG bands
- Normal or mildly elevated total protein
- Moderate pleocytosis in some cases

MRI

- Prominent tool for assessing disease
- Visualizes distribution of CNS lesions
- Important for monitoring course
- Interpret alongside clinical findings

Neuromyelitis optica differs from MS

Multiple sclerosis

- Multifocal CNS plaque distribution
- Prominent immune-mediated myelin destruction
- Often relapsing–remitting onset

AQP4-associated NMO

- Often severe optic and spinal attacks
- Aquaporin-4 autoantibody-associated astrocyte injury
- Necrosis and complement-associated pathology may occur

ADEM and MOG-associated disease are distinct

Multiple sclerosis

- Often recurrent attacks or progression
- Plaques of differing ages and activity
- Meningeal B-cell and cortical pathology

ADEM / MOGAD

- ADEM often acute and monophasic
- Commonly follows antecedent infection
- Encephalopathy may dominate clinical presentation

Other demyelinating processes require separation

- Progressive multifocal leukoencephalopathy causes infectious myelin destruction.
- Leukodystrophies affect myelin synthesis or turnover by inherited mechanisms.
- Osmotic demyelination follows major osmotic disturbance; It is not typical MS.

Immunomodulatory therapy primarily targets inflammation

- Broad use of immunomodulatory and immunosuppressive treatments.
- These treatments substantially suppress acute relapses.
- The later neurodegenerative stage is only partially controlled by immune treatment.

Anti-CD20 therapy supports B-cell importance

- B-cell-depleting anti-CD20 therapies are emphasized treatment discussion.
- Their clinical efficacy reinforces an important causal role for B cells.
- Treatment response does not specify which B-cell function is dominant in every patient.

Early effective treatment may reduce later disability

- Accumulating evidence supporting prompt effective immunomodulation.
- Suppression of inflammatory activity is an important preventive opportunity.
- Residual progression highlights a continuing need to address neurodegeneration.

Case 1: An optic pathway presentation

- A young adult develops a unilateral episode of visual impairment.
- A subsequent neurologic episode affects a different CNS pathway.
- Question: Which pathologic feature unifies spatially distinct events?

Case 1: Clinicopathologic reasoning

- The recurrent, multifocal pattern is compatible with a CNS demyelinating process.
- Inflammatory plaques at different sites account for different deficits.
- Confirmation requires appropriate clinical evaluation and exclusion of mimics.

Case 2: Progression despite fewer relapses

- A patient initially has attacks with partial recovery.
- Later, disability slowly accumulates while overt attacks become infrequent.
- Question: What pathological processes can sustain the decline?

Case 2: Explain disability accumulation

- Secondary progressive disease is suggested by steady deterioration after a relapsing phase.
- Chronic active plaques, cortical injury and axonal loss contribute to decline.
- Anti-inflammatory control of relapses does not fully block neurodegeneration.

Integrated pathology of multiple sclerosis

- Immune dysregulation causes multifocal destruction of previously normal CNS myelin.
- Active plaques contain inflammatory cells; inactive lesions show gliosis; chronic lesions lose axons.
- Anatomic distribution determines deficits, while tissue injury and repair failure shape progression.