

Progressive Multifocal Leukoencephalopathy

JC polyomavirus • CNS demyelination • Neuropathologic diagnosis

Clinical–pathologic teaching lecture

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Learning objectives

- Explain how JC polyomavirus produces a demyelinating CNS infection.
- Recognize lesion architecture and diagnostic cytopathology.
- Integrate the clinical course, imaging, virology, and biopsy findings.
- Distinguish PML progression from selected mimics and immune reconstitution.

Clinical entry point: Progressive focal deficits

Hypothetical teaching scenario, not a reported patient.

- An immunosuppressed patient develops steadily worsening focal neurologic deficits.
- Brain MRI reveals multifocal abnormalities predominantly involving white matter.
- The conjunction of immune risk, tempo, and lesion distribution raises PML.

Reasoning prompt: Integrate clinical tempo, lesion anatomy and diagnostic evidence

PML is viral injury to CNS myelin

JC virus → oligodendrocyte injury → demyelination

- JC polyomavirus preferentially infects oligodendrocytes.
- Damage to these myelin-forming cells causes central nervous system demyelination.
- Neurologic dysfunction reflects the distribution and evolution of white matter injury.

The disease name encodes its phenotype

PROGRESSIVE

Progressive: Neurologic deficits accumulate rather than follow a single abrupt event.

MULTIFOCAL

Multifocal: Several white matter territories may be involved.

WHITE MATTER

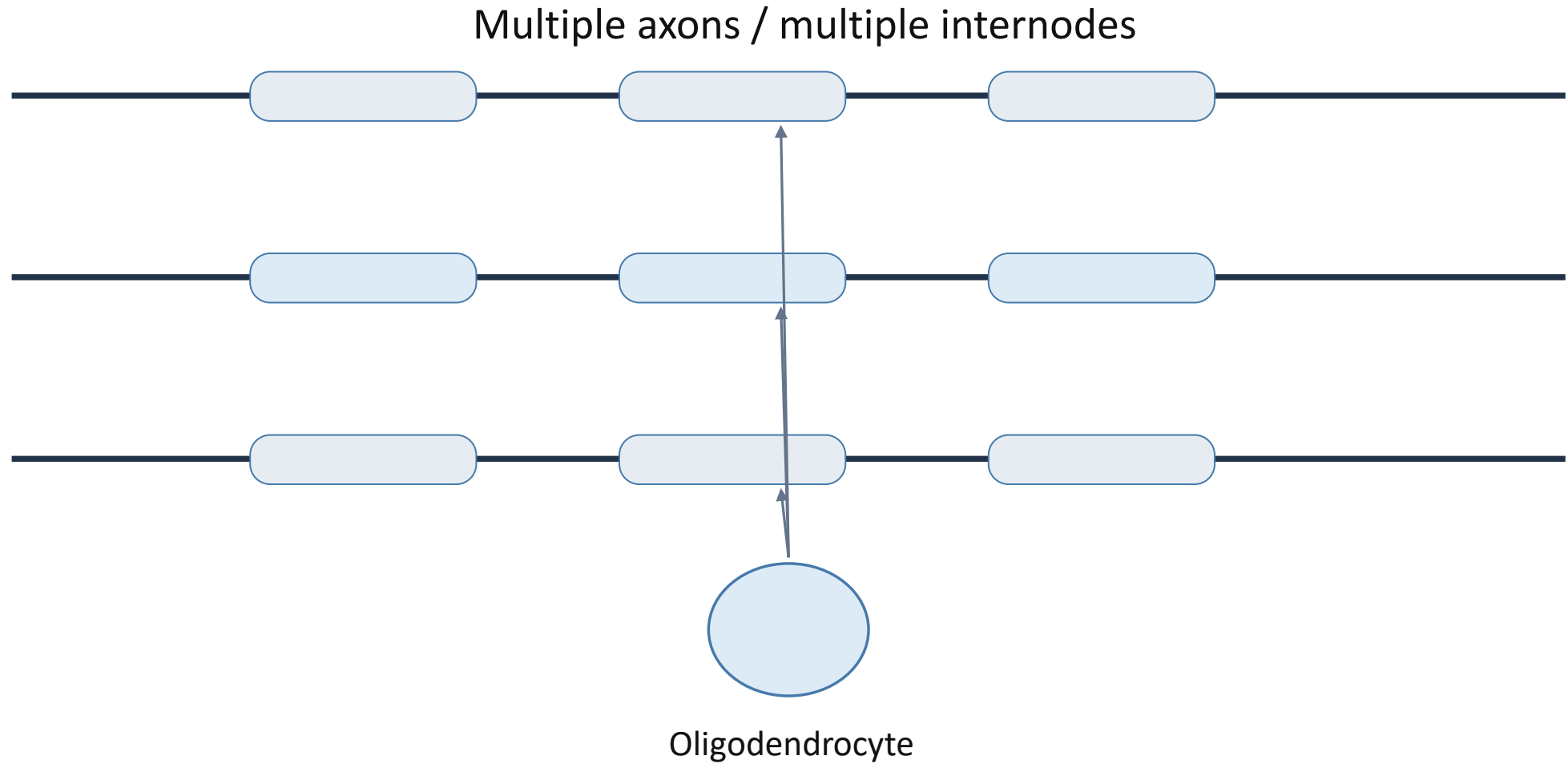
Leukoencephalopathy: The predominant lesion is in cerebral or cerebellar white matter.

PML is an infectious demyelinating disorder

PML	Autoimmune demyelination
Viral oligodendroglial injury	Immune-mediated myelin injury
Opportunistic host setting	Autoimmune disease setting
Virologic confirmation possible	Virologic confirmation absent

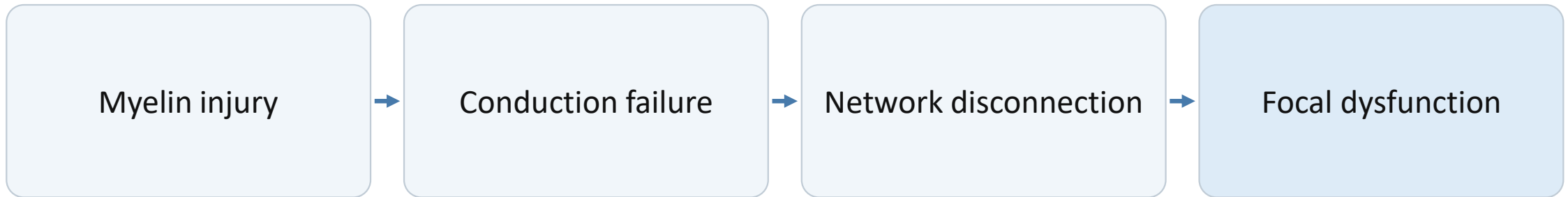
Infection, rather than primary autoimmunity, initiates tissue damage.

Oligodendrocytes maintain CNS internodes



SCHEMATIC — conceptual illustration, not a clinical or histologic specimen

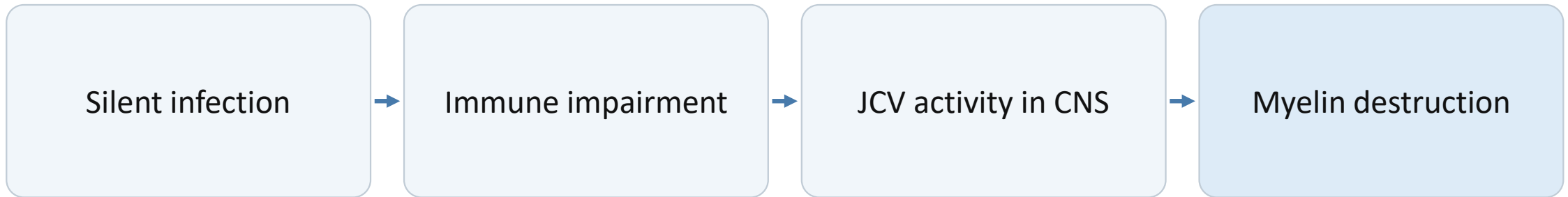
Why myelin loss produces neurologic deficits



Myelin loss reduces effective saltatory conduction along surviving fibers.

Associated axonal injury can further impair information transfer.

The core pathogenic sequence



Widespread antecedent JC virus exposure is usually clinically silent.

Immunosuppression permits clinically consequential JC virus activity.

JC virus is a human polyomavirus

Infection is common; PML is uncommon

- The etiologic agent is JC polyomavirus, also termed JCV.
- Viral replication within susceptible glial cells causes a cytopathic pattern.
- Identification of JCV in tissue or CSF links the demyelinating process to infection.

Exposure does not mean active disease

JCV exposure	PML
Often asymptomatic	Progressive CNS illness
Serologic evidence may persist	Compatible clinical and MRI syndrome
Does not prove CNS disease	Requires integrated diagnostic assessment

Most people acquire serologic evidence of JC virus exposure without neurologic symptoms.

Reactivation occurs in a permissive host

Established

Pathway remains incompletely resolved

PML follows loss of immune control

Exact viral latency/entry sequence may vary

Robbins frames PML as JC virus reactivation under immunosuppression.

The host context is diagnostically powerful

Host context + syndrome + MRI + virology

- PML occurs almost exclusively in immunosuppressed patients.
- A predisposing immune disorder increases suspicion but is not diagnostic alone.
- Atypical host history should prompt broader differential assessment.

Four risk settings named by Robbins

HIV / AIDS

Cell-mediated immune impairment

Immune-modifying drugs

Chemotherapy and biologics

Hematologic disease

Lympho- / myeloproliferative illness

Granulomatous disease

Host susceptibility context

HIV and PML: Two distinct CNS processes

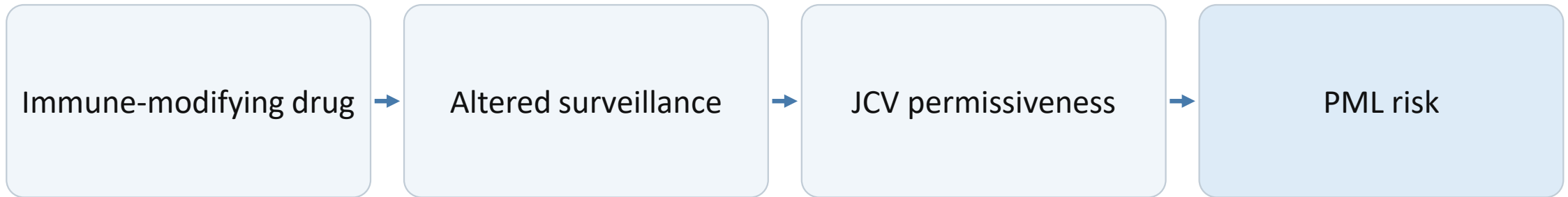
PML	HIV encephalitis
JC virus in oligodendrocytes	HIV in microglia/macrophages
Demyelinating plaques	Microglial nodules ± giant cells
Focal deficits dominate	Often diffuse neurocognitive dysfunction

HIV-associated immunodeficiency permits opportunistic JCV disease.

Hematologic illness can predispose to PML

- Chronic lymphoproliferative disease may impair cell-mediated viral control.
- Myeloproliferative disease is another context identified by Robbins.
- Risk reflects underlying disease and, in some patients, treatment-related immunosuppression.

Immunosuppressive treatments alter risk



Chemotherapy and immune-modifying therapies may permit JCV-associated disease.

Robbins specifically mentions monoclonal antibodies against selected integrins.

Natalizumab illustrates immune-surveillance disruption

Biologic action

Reduced CNS immune-cell trafficking

Diagnostic consequence

Heightened suspicion when symptoms
emerge

Natalizumab targets the α 4-integrin pathway and impairs leukocyte trafficking.

Immune control is the central protective barrier

Effective immune surveillance

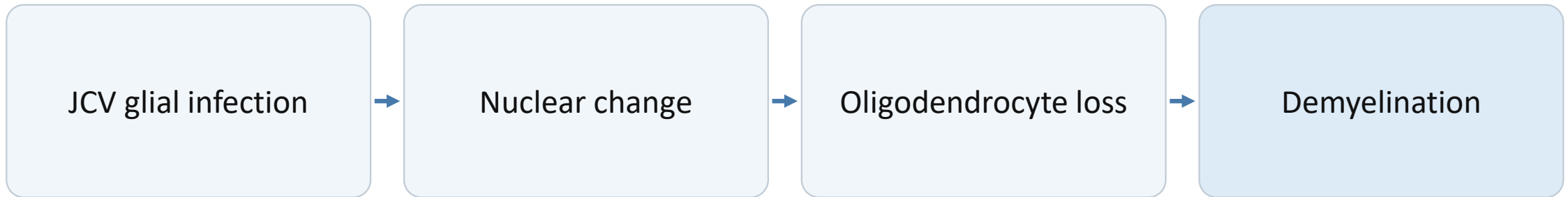


Suppressed immune surveillance

Infection generally controlled

Viral replication may cause PML

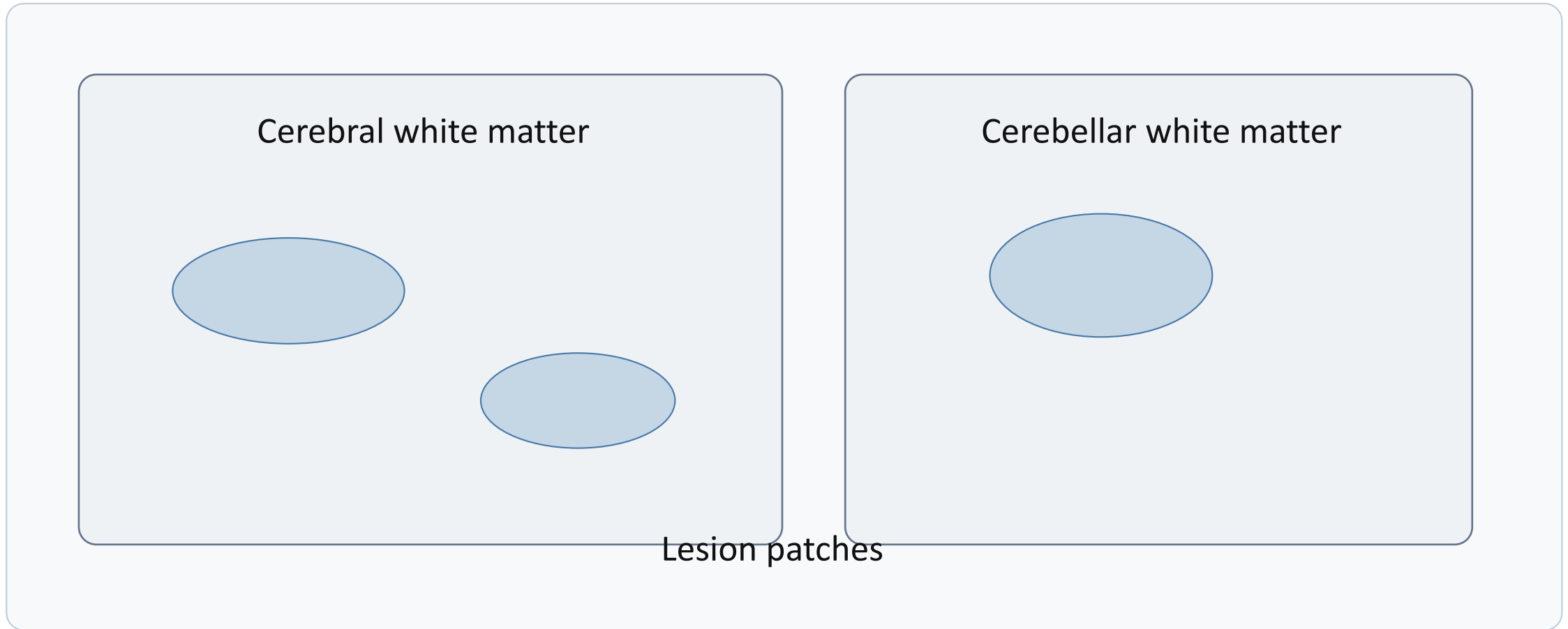
Glial tropism explains lesion identity



JC virus preferentially involves oligodendrocytes in PML.

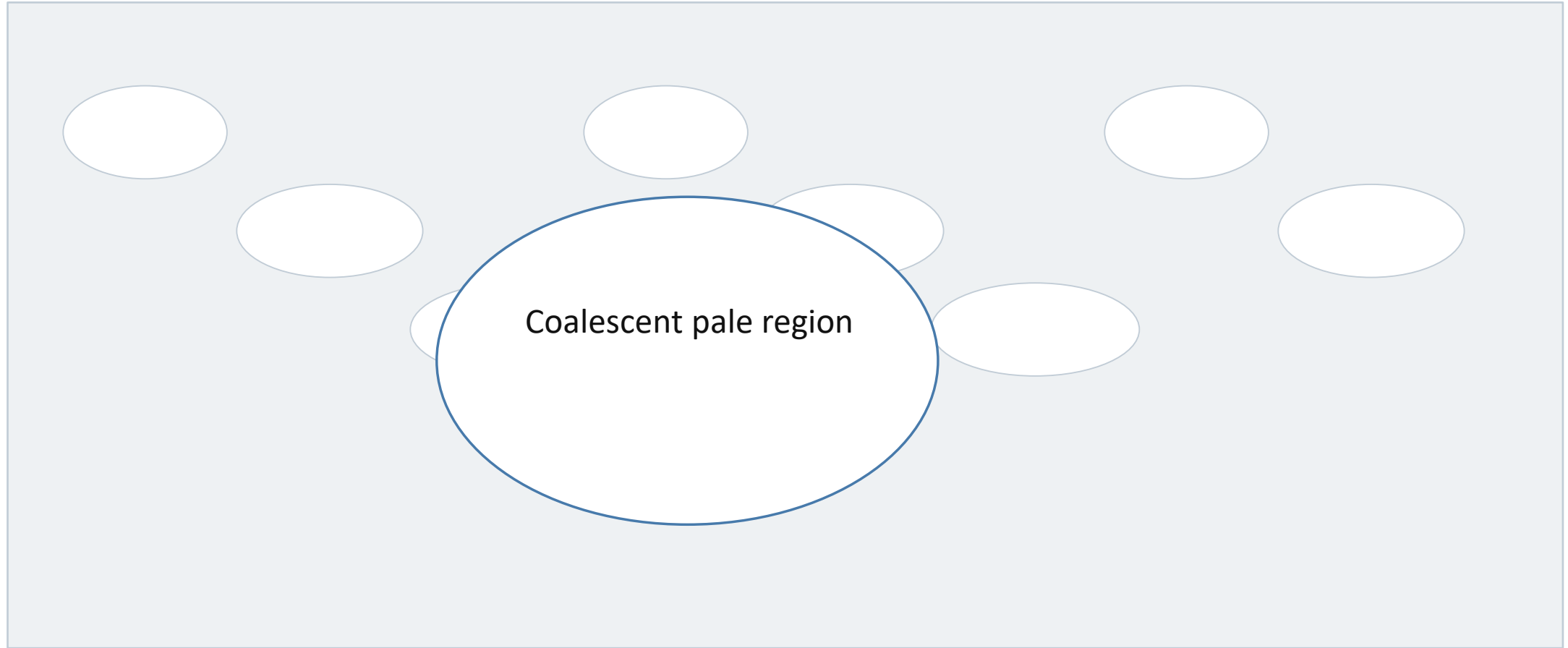
Infected oligodendrocytes show conspicuous nuclear viral cytopathic effects.

The lesion is centered in white matter



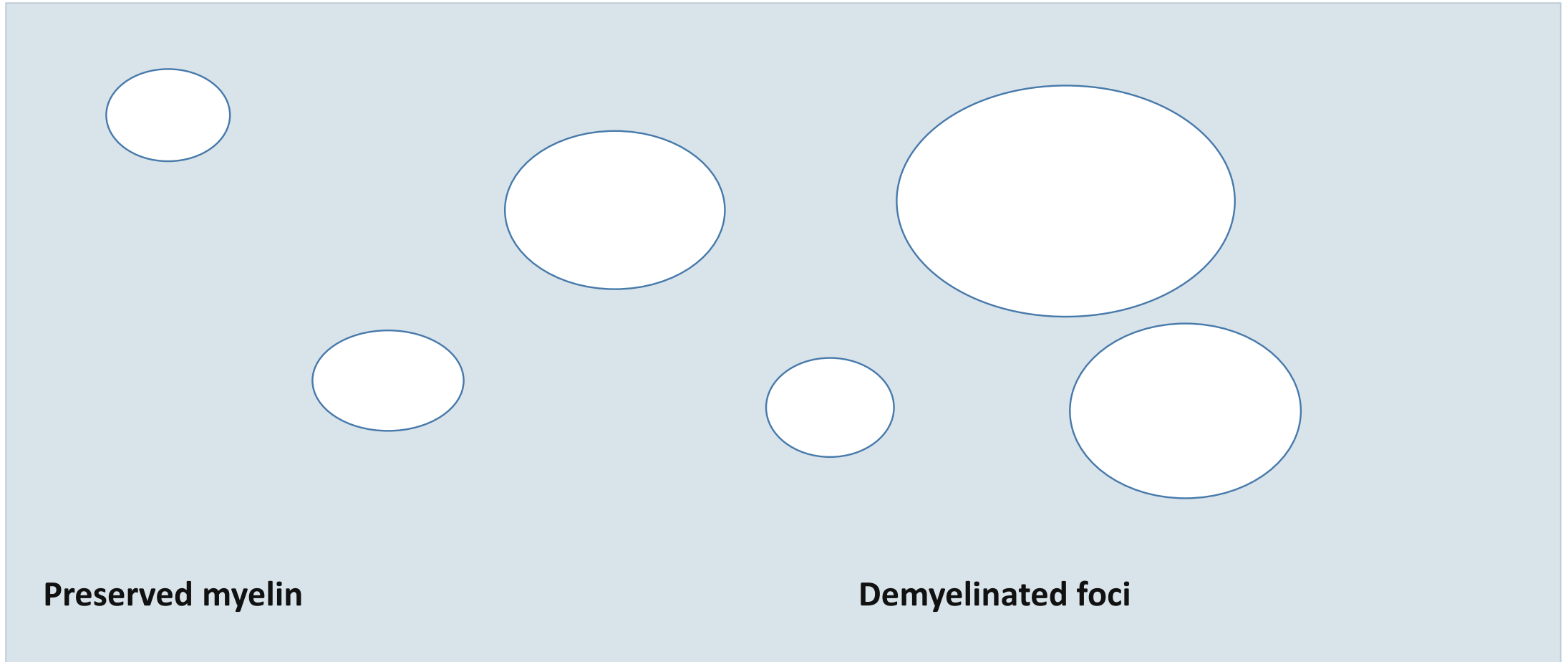
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Gross pathology: Irregular ill-defined patches



Myelin-stain appearance represented schematically; Lesion contours are not from a specimen

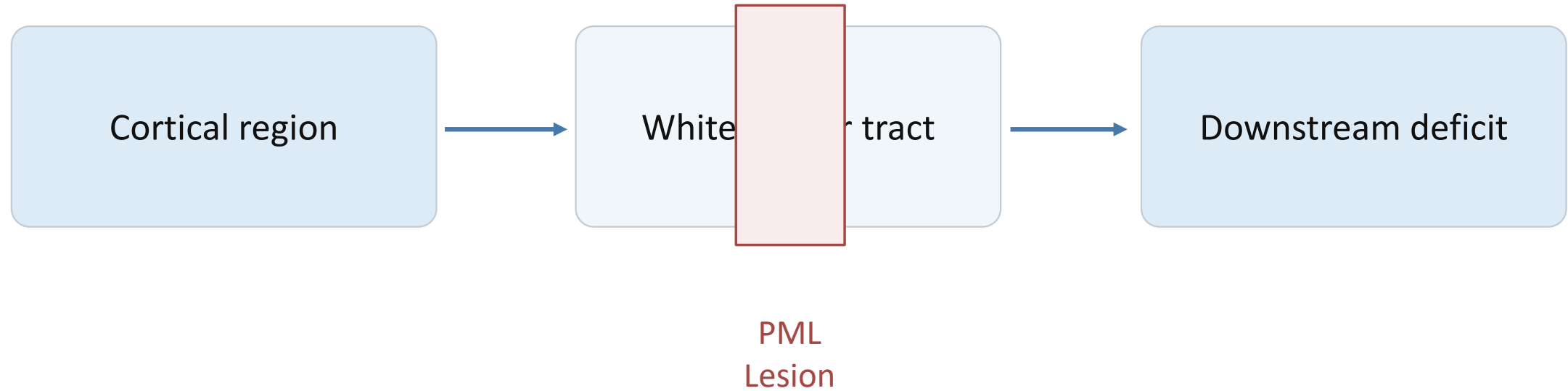
Multifocal lesions may merge



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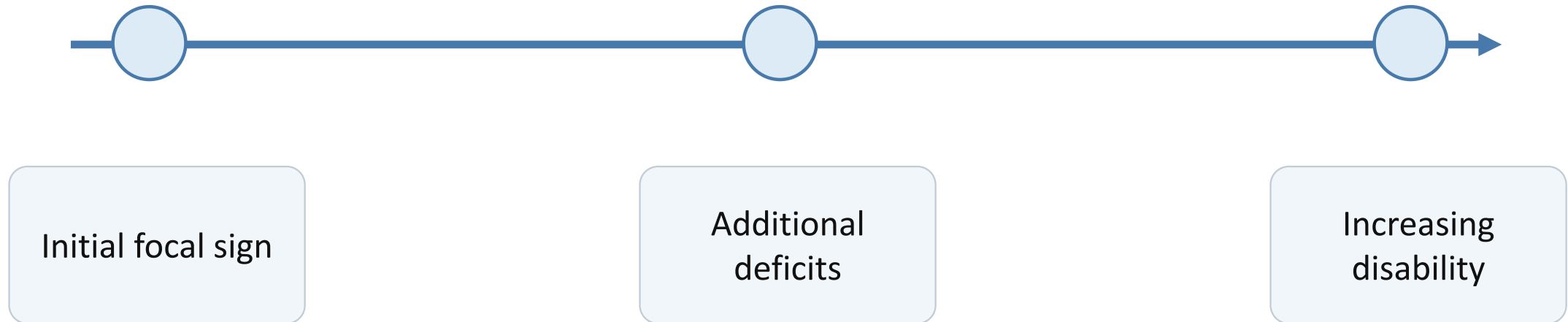
Lesion location determines the syndrome

White matter functional connection



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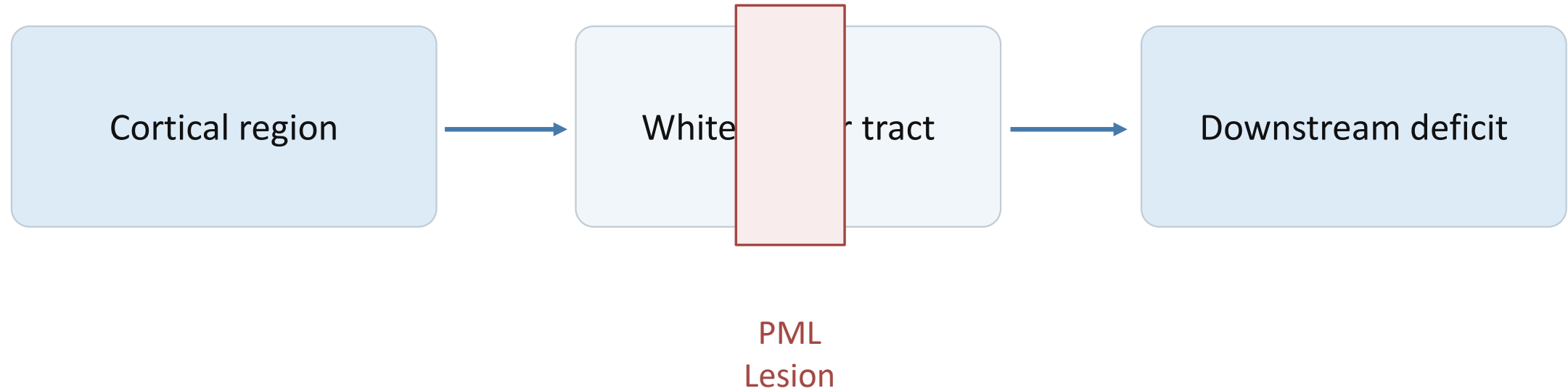
Clinical course: Subacute, cumulative deficits



Clinical evolution—not a quantitative time scale

Motor pathway involvement

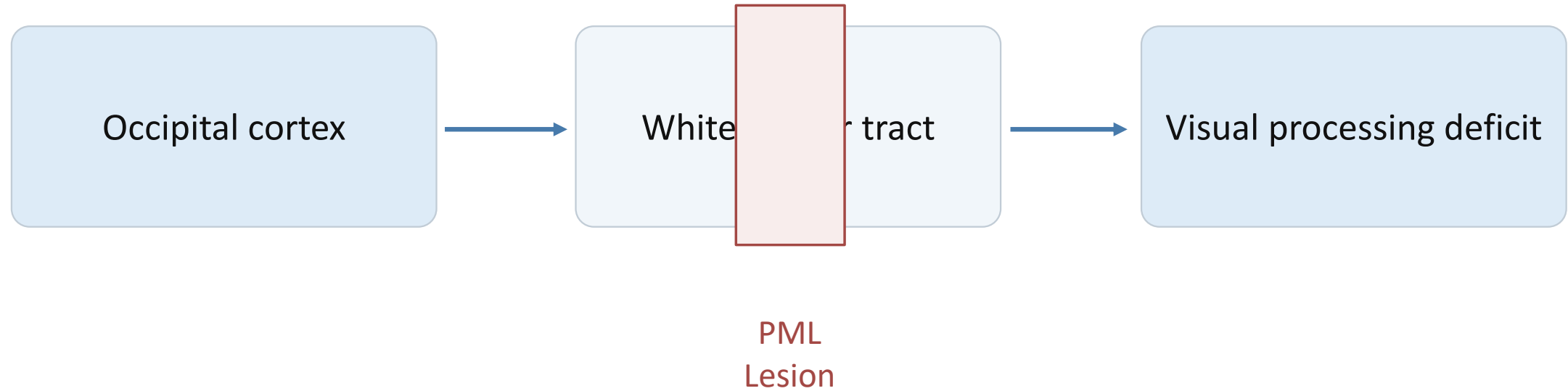
Descending motor pathway



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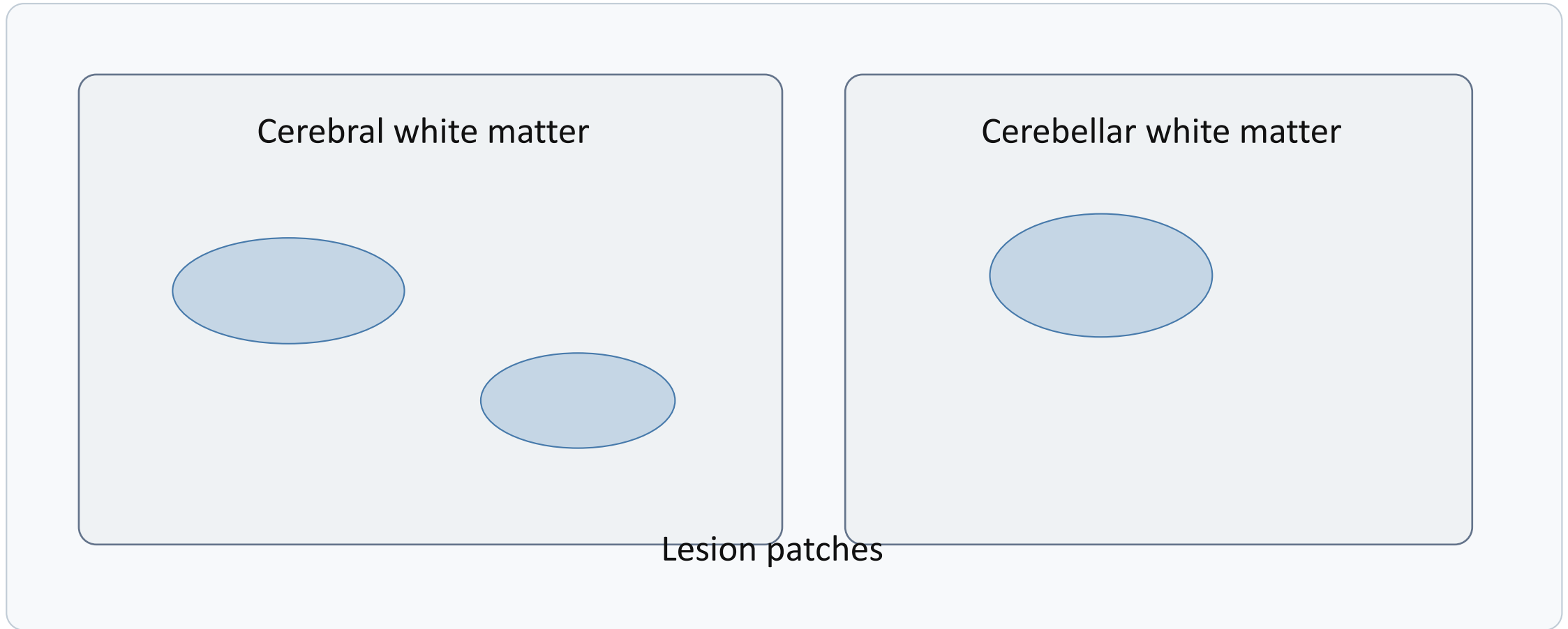
Visual and posterior pathway involvement

Visual information pathway



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Cerebellar disease can impair coordination

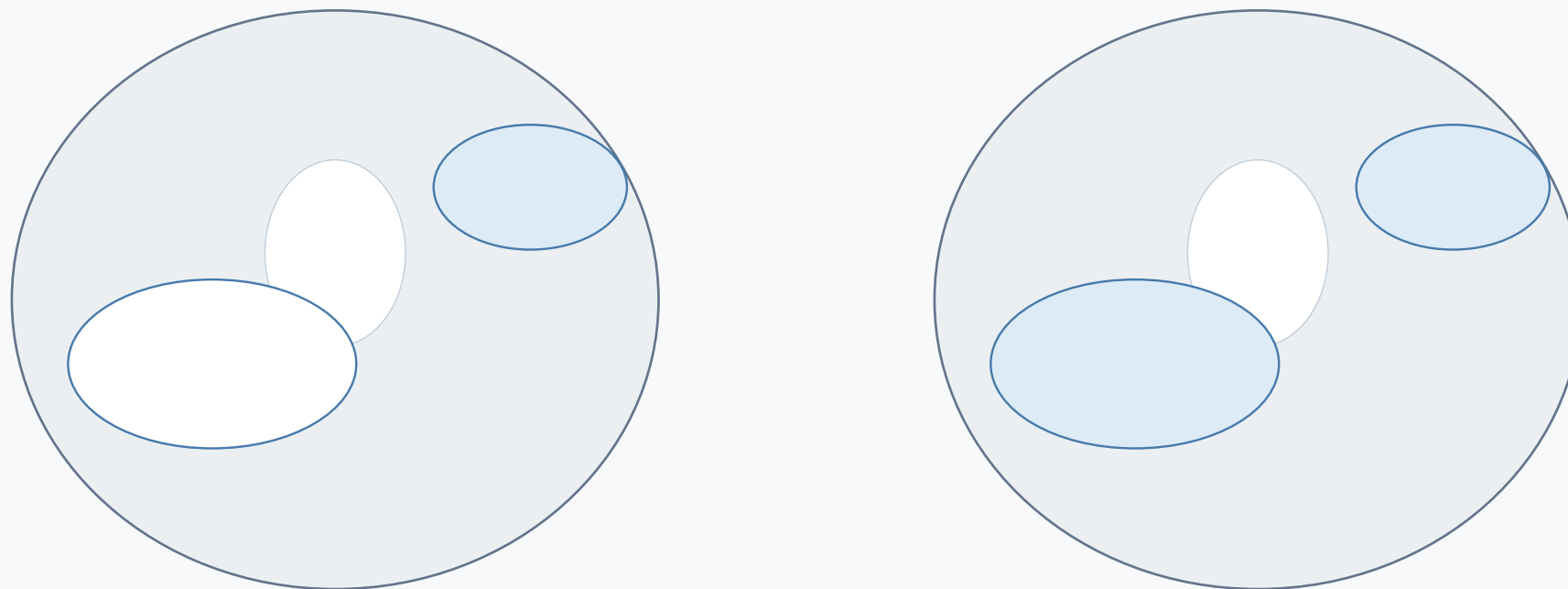


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Clinical findings are not pathognomonic

- Focal weakness, language dysfunction, and visual changes have many causes.
- Headache and fever are not characteristic in classical PML.
- The differential must integrate tempo, immune state, MRI and laboratory data.

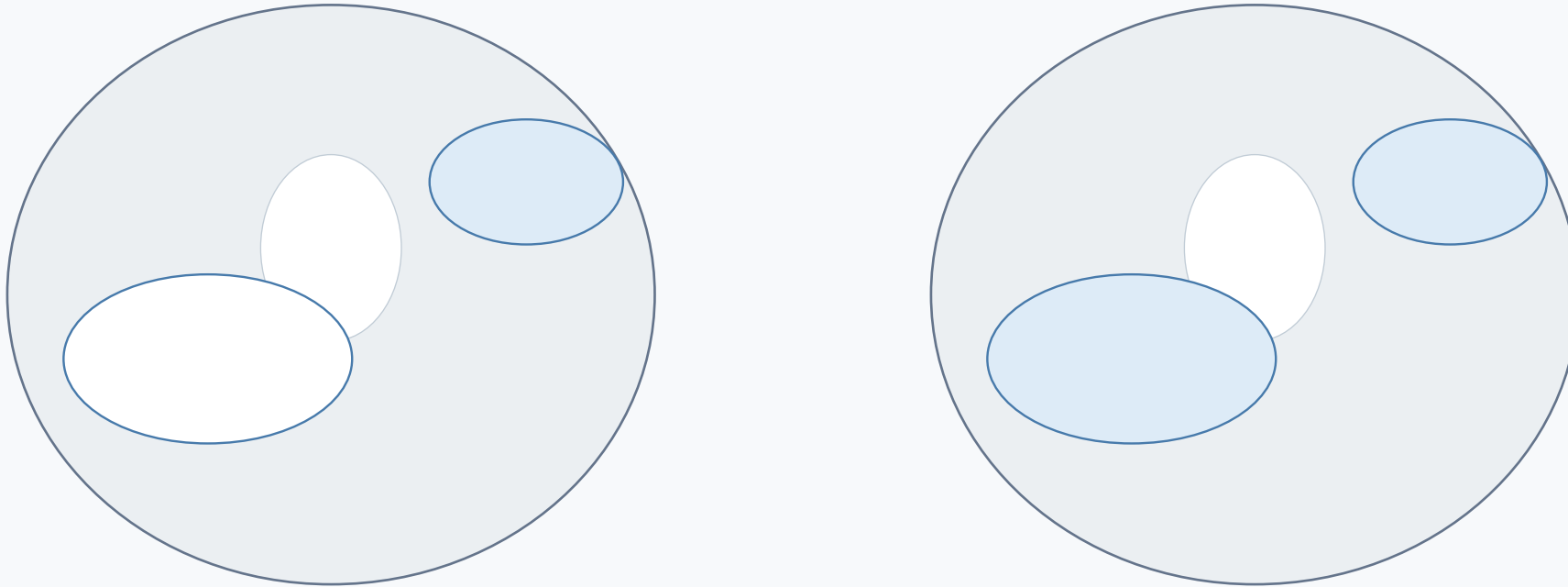
The MRI question is where myelin is lost



Illustrated abnormal regions

SCHEMATIC — not an MRI; No imaging measurement or lesion burden is implied

T2-weighted and FLAIR signal



Illustrated abnormal regions

SCHEMATIC — not an MRI; No imaging measurement or lesion burden is implied

T1 and diffusion provide complementary information

T1 weighted

Reduced signal in affected white matter

Diffusion weighted

Activity may be conspicuous at lesion borders

Affected white matter is commonly hypointense on T1-weighted sequences.

Enhancement changes the interpretation

Little enhancement

Compatible with classic PML

Marked inflammation

Raises PML-IRIS or another process

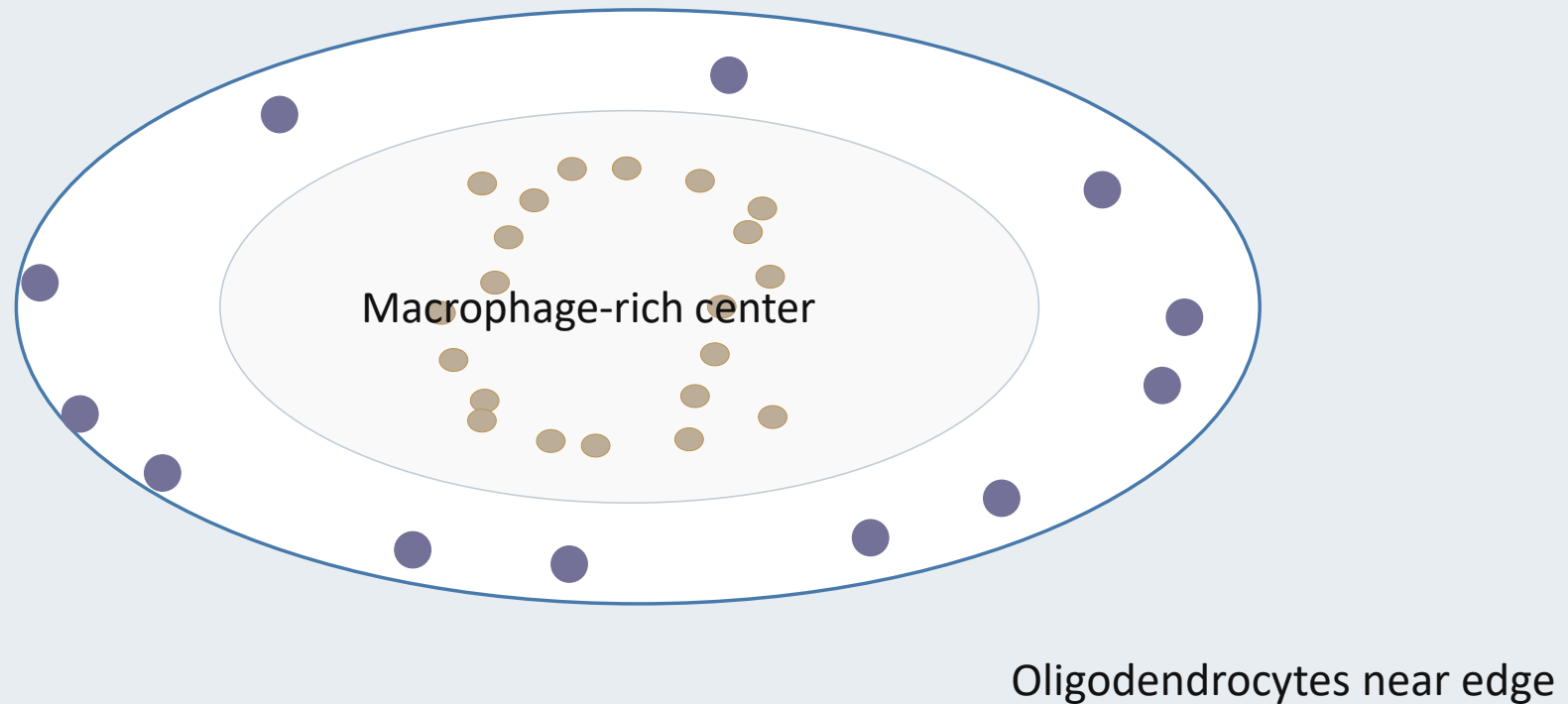
Classic PML often shows little contrast enhancement.

Imaging comparison: Pattern, not a single sign

PML	Toxoplasmosis / lymphoma
Infiltrative white matter abnormality	Often focal mass lesions
Usually limited mass effect	Mass effect may be prominent
JCV-oriented investigation	Different organism/tumor workup

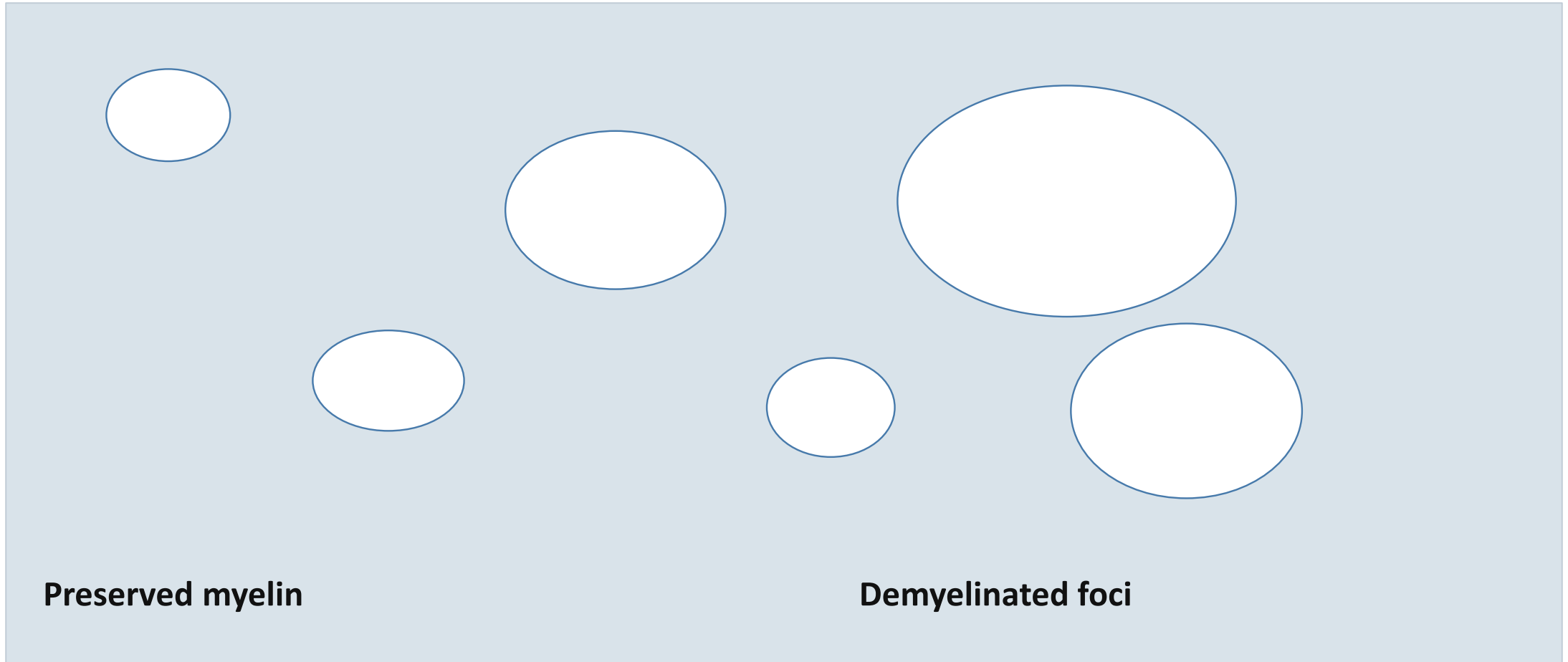
A white matter–predominant, poorly margined process supports PML in the right host.

Histologic architecture: Edge and center



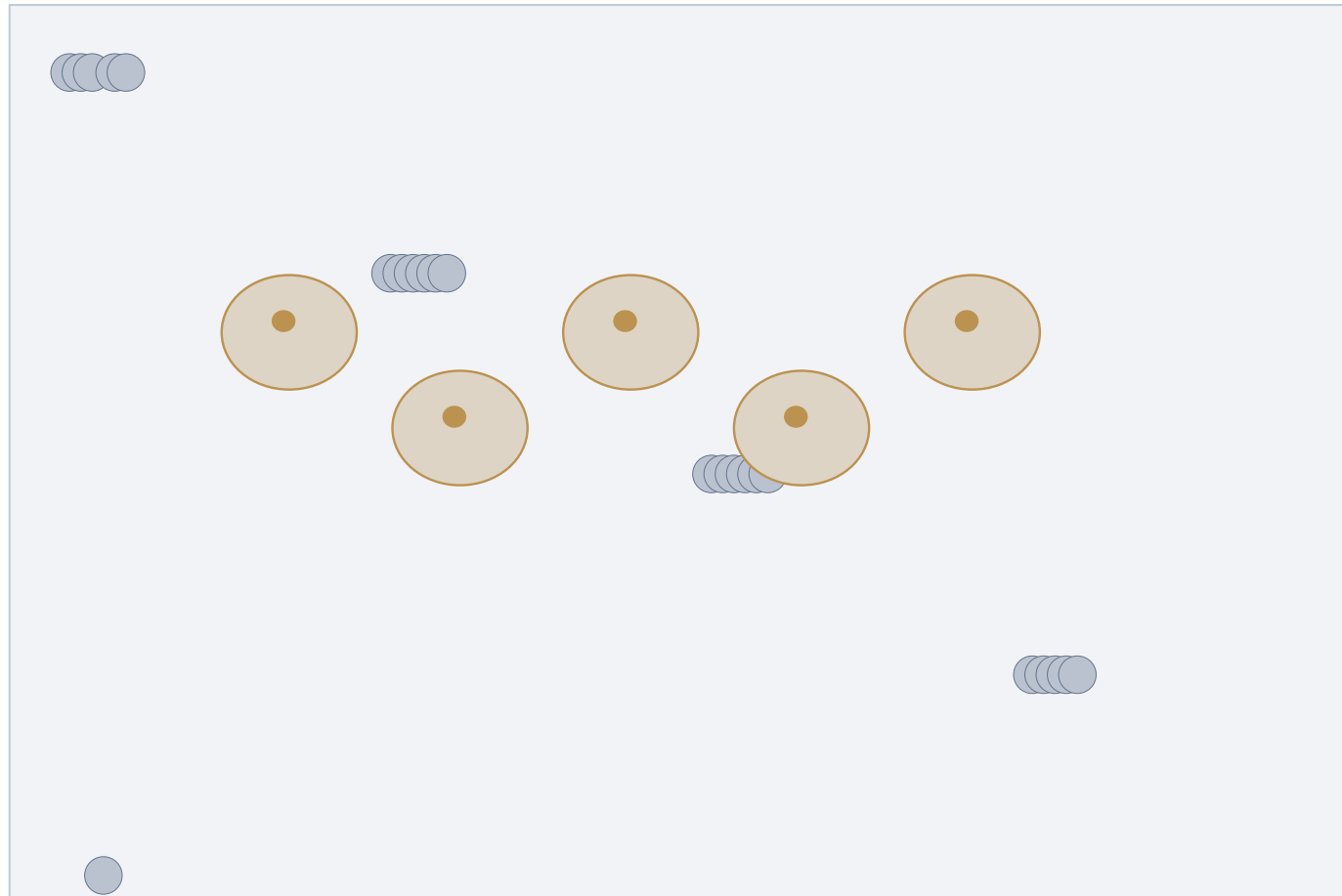
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Myelin loss is the defining tissue effect



SCHEMATIC — conceptual illustration, not a clinical or histologic specimen

Macrophages clear destroyed myelin



Foamy phagocytes

Histomorphologic concept only; Shapes
are not microscopy

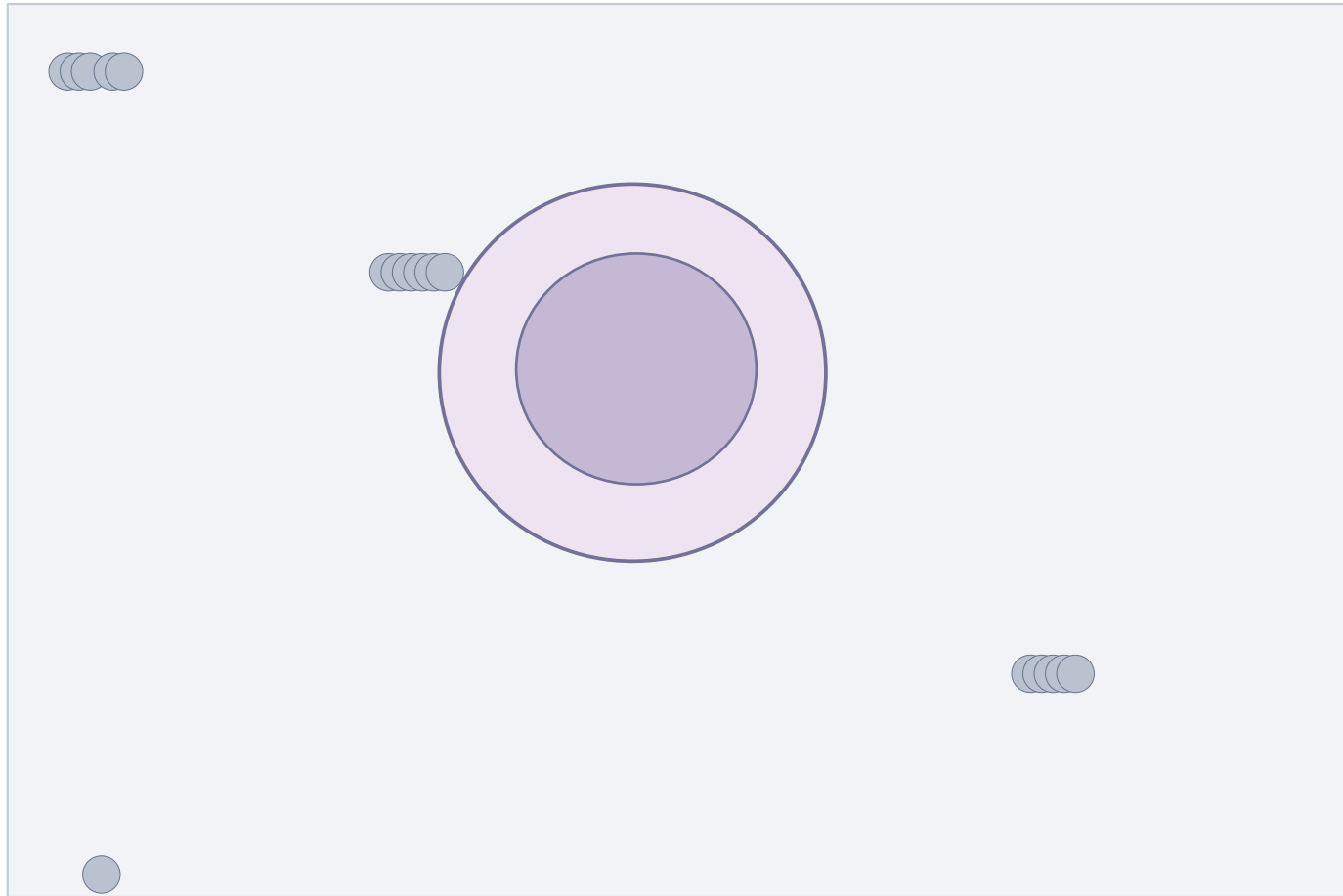
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Axonal density can also fall

Myelin loss	Axonal loss
Primary defining lesion	May accompany severe injury
Conduction impaired	Structural pathway loss
Potential remyelination if cells survive	Recovery is more constrained

Reduced numbers of axons within affected lesions.

Infected oligodendrocytes have enlarged nuclei

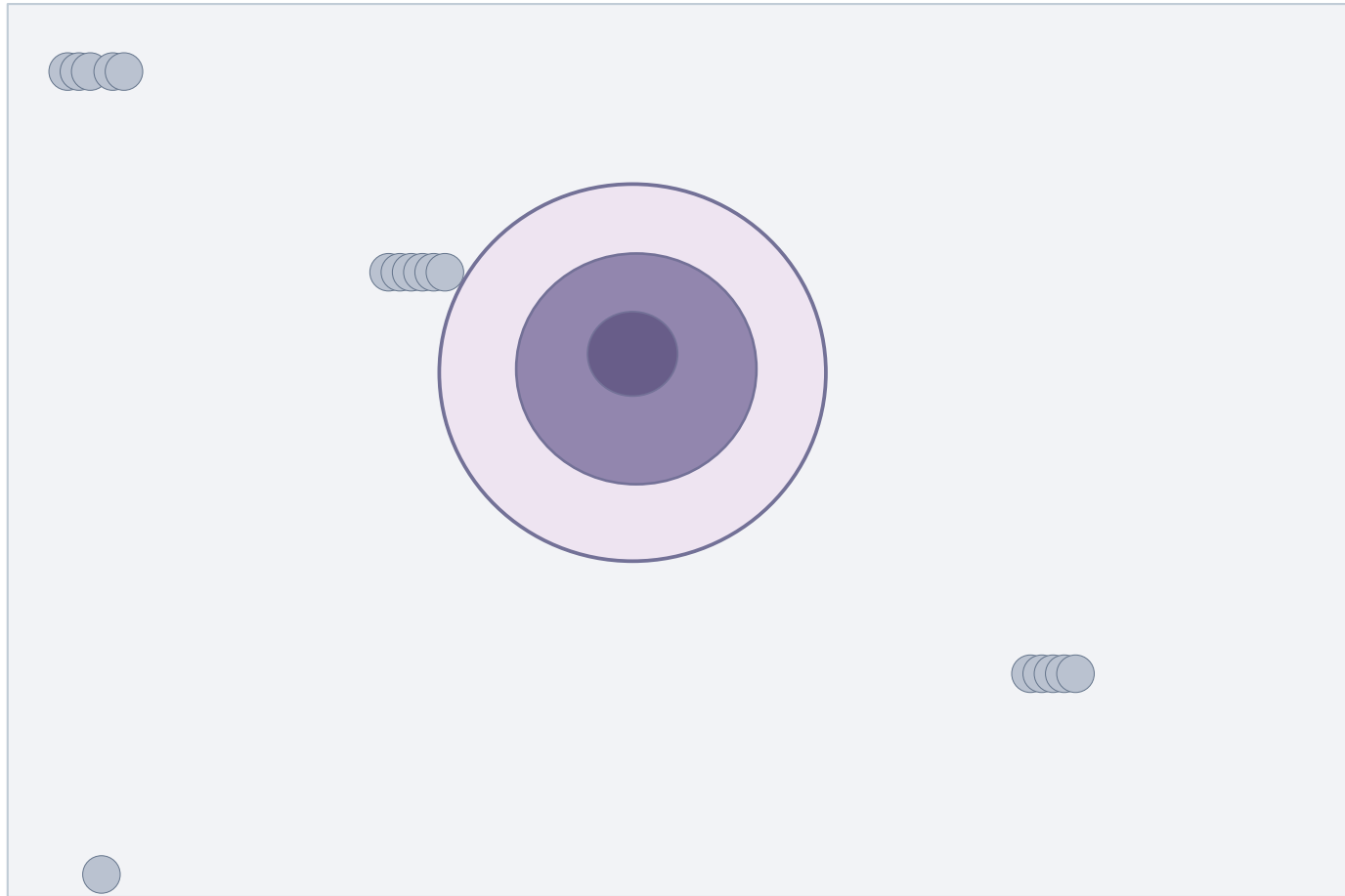


Enlarged oligodendroglial nucleus

Histomorphologic concept only; Shapes
are not microscopy

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Nuclear inclusions are an essential clue

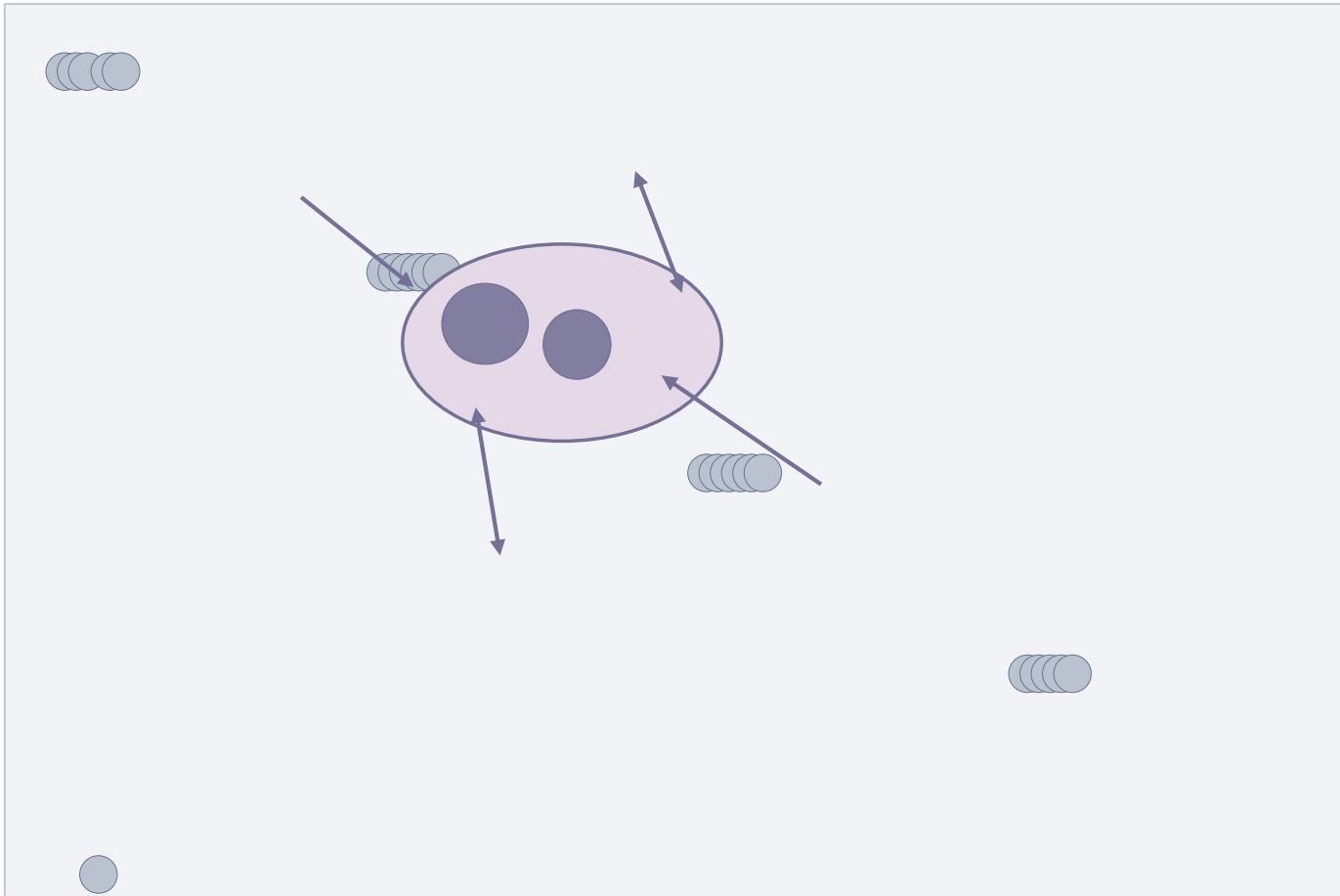


Nuclear viral inclusion

Histomorphologic concept only; Shapes
are not microscopy

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Bizarre astrocytes form the third feature



Bizarre astrocytic form

Histomorphologic concept only; Shapes
are not microscopy

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The classic histopathologic triad

Demyelination

Oligodendrocytes

Astrocytes

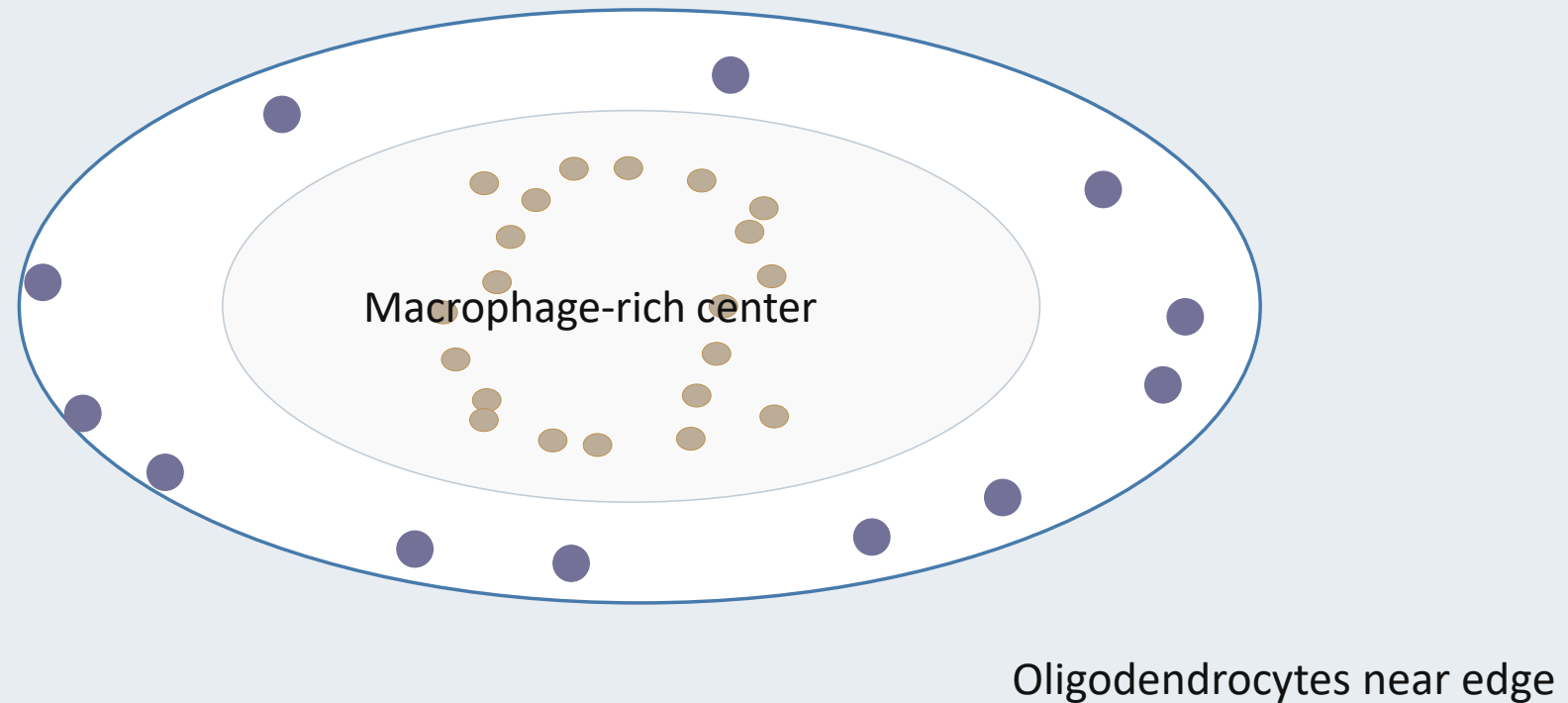
Myelin loss / foamy macrophages

Large nuclei / viral inclusions

Bizarre forms / hyperchromasia

Interpret the triad together, not as isolated findings

The advancing edge is diagnostically rich



Tissue immunohistochemistry adds specificity

Morphology

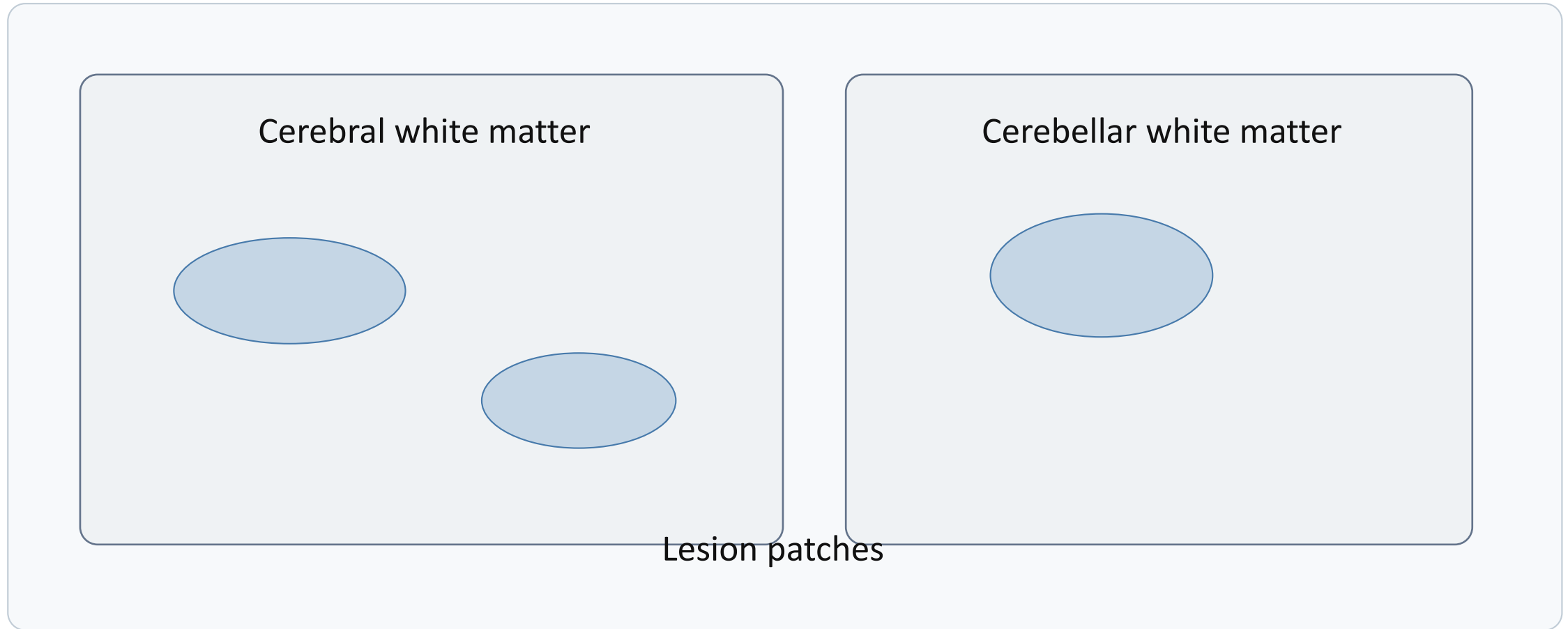
Triad suggests PML

Virologic tissue test

JCV antigen/DNA demonstrates infection

JCV-associated viral antigens can be demonstrated in infected cell nuclei.

Granule cell neuron involvement is uncommon



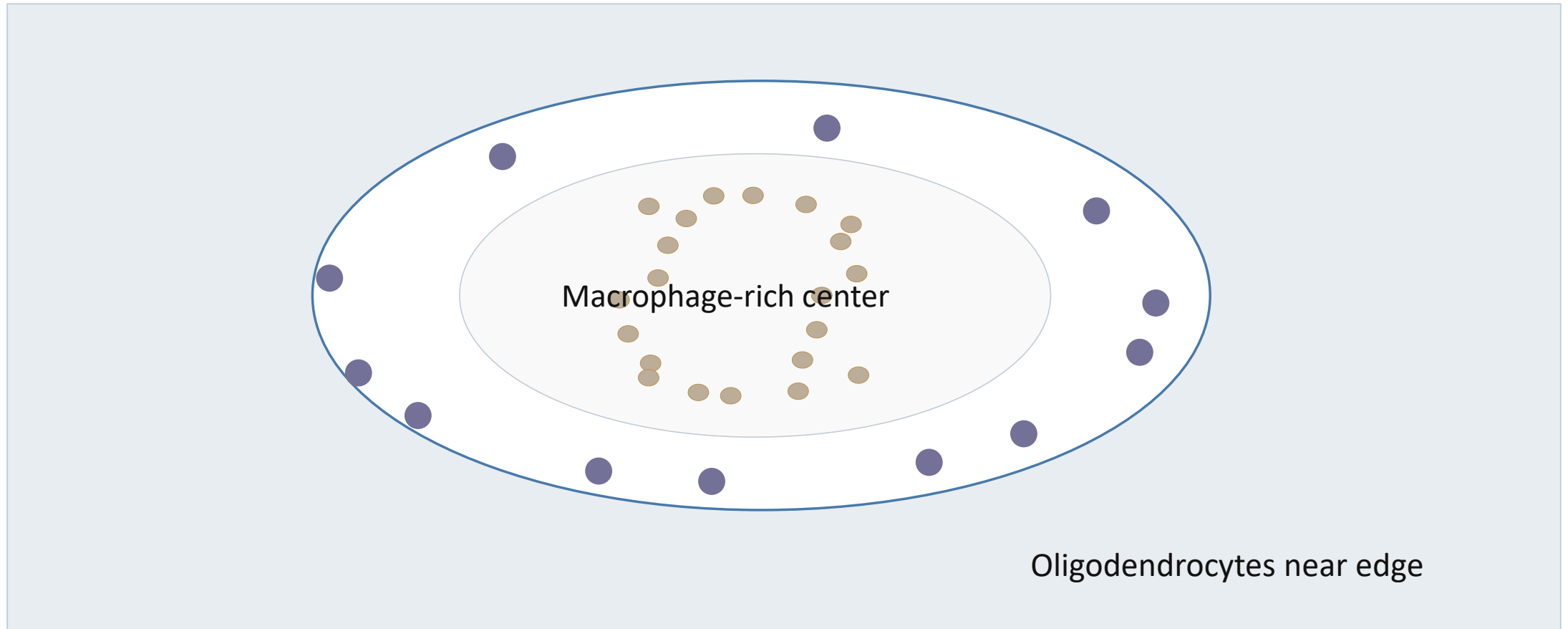
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Differentiate infection from autoimmune plaques

PML	Multiple sclerosis
JC virus–associated	Autoimmune demyelination
Viral nuclear inclusions	No JCV-specific inclusions
Immunosuppression is characteristic	Relapses and dissemination patterns are relevant

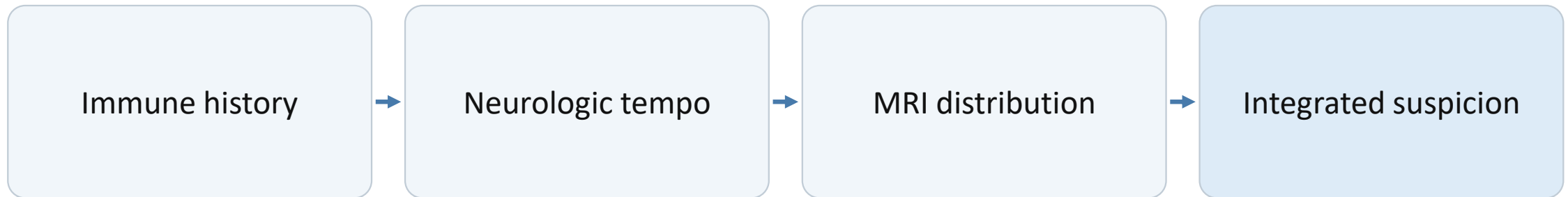
Both PML and multiple sclerosis can produce focal myelin loss.

A small biopsy has sampling limitations



SCHEMATIC — conceptual illustration, not a clinical or histologic specimen

First: Establish a coherent clinical hypothesis



Document host immune impairment and treatment exposures.

Map the evolving deficits to the anatomic distribution of MRI lesions.

CSF JC-virus PCR supports diagnosis

Compatible syndrome

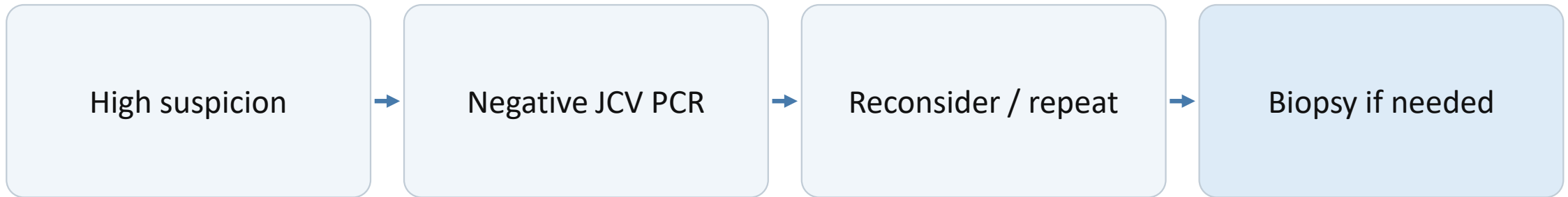
Progressive focal deficits + MRI lesions

JCV DNA detected in CSF

Supports a clinical diagnosis of PML

CSF detection of JCV DNA is a key noninvasive confirmatory investigation.

A negative CSF result does not exclude PML



Assay sensitivity varies with viral burden, treatment and laboratory methods.

Negative testing in a strongly suspicious case warrants reassessment.

Biopsy-based diagnosis follows another route

Demyelination

Myelin loss / foamy macrophages

Oligodendrocytes

Large nuclei / viral inclusions

Astrocytes

Bizarre forms / hyperchromasia

Histologic triad + JCV detection in tissue

AAN diagnostic framework uses two routes

Progressive deficit + PML-like MRI



CSF JCV PCR



Clinical diagnostic route

Demyelinating biopsy specimen



Histologic triad + JCV assay



Tissue diagnostic route

Concordance across clinical, imaging and virologic domains is essential

A practical diagnostic workflow

Progressive deficit + PML-like MRI



CSF JCV PCR



Clinical diagnostic route

Demyelinating biopsy specimen



Histologic triad + JCV assay



Tissue diagnostic route

Concordance across clinical, imaging and virologic domains is essential

PML versus HIV encephalitis

PML	HIV encephalitis
JCV-infected oligodendrocytes	HIV-associated microglia
Large focal white matter plaques	Microglial nodules / giant cells
Typically focal deficits	Often cognitive dysfunction

PML targets oligodendrocytes and produces demyelinating lesions.

PML versus focal opportunistic masses

PML	Toxoplasmosis	CNS lymphoma
Demyelination	Infection / necrosis	Neoplastic infiltrate
White matter–predominant	Often ring-enhancing	Often enhancing mass
CSF JCV / biopsy	Pathogen workup	Tissue / lymphoma workup

Toxoplasmosis can produce necrotizing abscess-like lesions.

PML versus inflammatory demyelination

Observation	Inference
Foamy macrophages	Shared, nonspecific finding
JCV-positive glial nuclei	Supports viral demyelination
Atypical astrocytes alone	Insufficient; Avoid glioma overcall

A diagnosis of multiple sclerosis cannot explain JCV-positive oligodendrocytes.

Immune reconstitution can intensify inflammation

Restoring immunity



Inflammatory lesion response

Potential paradoxical worsening after immune recovery

Recognizing PML-associated IRIS

Uncontrolled PML

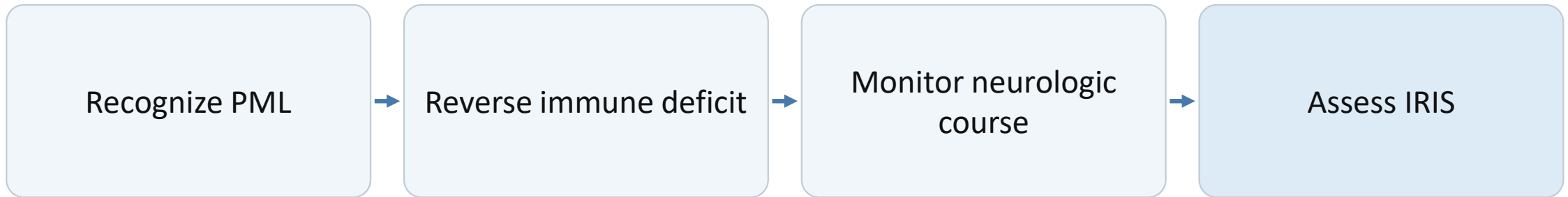
PML-associated IRIS

Ongoing virus-associated injury

Inflammation after immune recovery

Clinical deterioration may accompany new enhancement, edema or mass effect.

Therapeutic principle: Restore antiviral immunity



No reliably effective direct anti-JCV treatment is established.

The principal intervention is reversing the underlying immunosuppression when feasible.

HIV-associated PML: Effective ART is central

- Initiate antiretroviral therapy promptly when HIV-associated PML occurs without effective ART.
- Optimize virologic suppression if current ART is failing.
- Do not discontinue ART solely because PML-associated IRIS develops.

Drug-associated PML requires specialist coordination

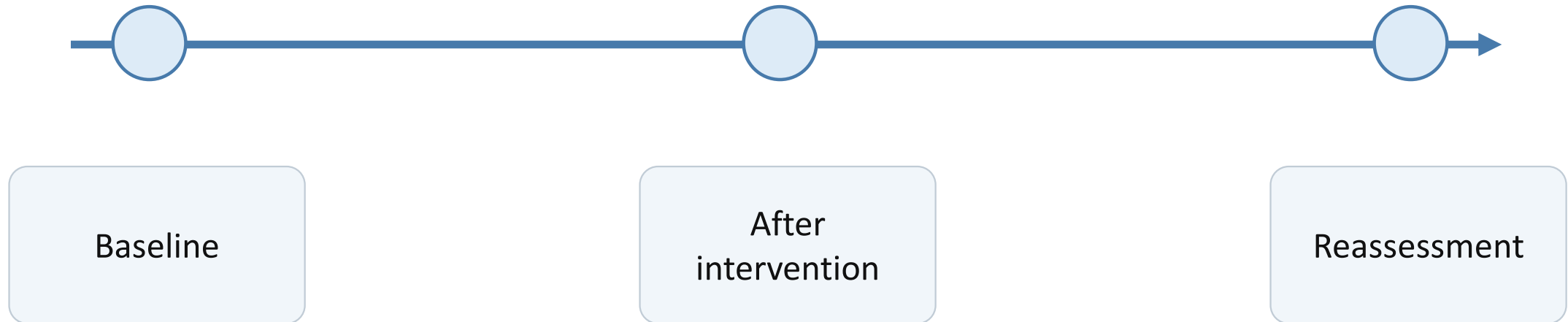
- Assess the implicated immunosuppressant and feasibility of withdrawing or modifying it.
- Management depends on the indication, persistence and pharmacology of the agent.
- Neurology, infectious disease and the treating specialty should coordinate care.

No direct antiviral has proved consistently effective

No established JCV-directed antiviral standard

- Trials of several antiviral or repurposed agents have not established routine benefit.
- Experimental immunotherapies should not be presented as accepted standards.
- Immune restoration remains the evidence-based therapeutic foundation.

Monitoring follows clinical progression



Clinical evolution—not a quantitative time scale

Prognosis is tied to immune recovery and injury

IMMUNE RECOVERY

The extent and location of damage influence functional consequences.

LESION BURDEN

The capacity to restore immune control is a major determinant of outcome.

AXONAL DAMAGE

Persistent neurologic deficits may reflect accumulated axonal and myelin injury.

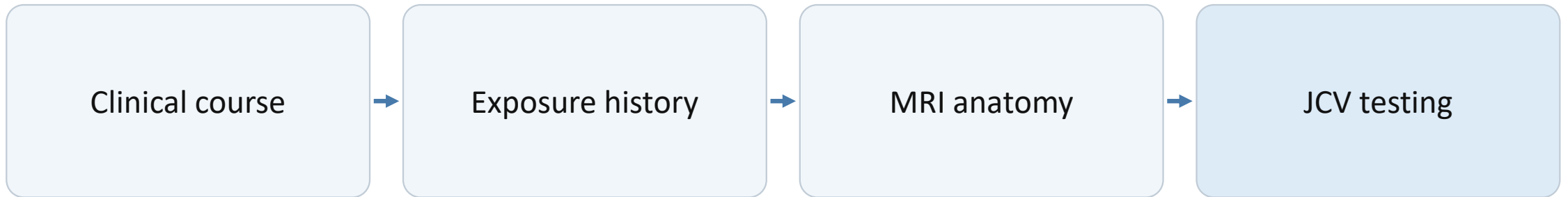
Case application: Evaluating a new deficit

Hypothetical case; No real patient image or data.

- Teaching scenario: A patient on immune-modifying therapy develops progressive aphasia.
- MRI shows an enlarging asymmetric subcortical white matter abnormality.
- What is the next diagnostic hypothesis and how should it be investigated?

Reasoning prompt: Integrate clinical tempo, lesion anatomy and diagnostic evidence

Case reasoning: Triangulate the evidence



An immunosuppressive exposure and progressive focal deficit increase PML suspicion.

MRI white matter involvement makes a demyelinating process plausible.

Case application: Reading a biopsy

- Teaching scenario: Tissue shows pallor of myelin, foamy macrophages and enlarged glial nuclei.
- At the advancing margin, inclusion-bearing oligodendrocytes and bizarre astrocytes are seen.
- Which tissue-based test most directly confirms the etiologic diagnosis?

Reasoning prompt: Integrate clinical tempo, lesion anatomy and diagnostic evidence

Case reasoning: Confirm JC virus

Demyelination

Oligodendrocytes

Astrocytes

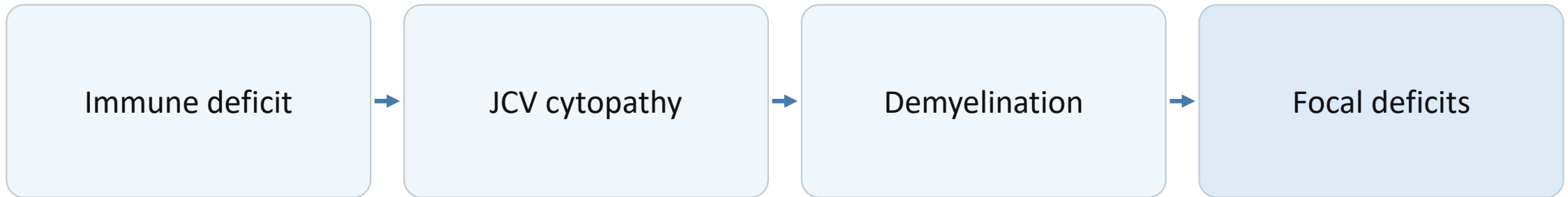
Myelin loss / foamy macrophages

Large nuclei / viral inclusions

Bizarre forms / hyperchromasia

Histologic triad + JCV detection in tissue

Integrated pathology summary



JC virus preferentially damages oligodendrocytes during severe immune impairment.

Irregular subcortical white matter lesions contain central macrophages and marginal infected glia.

Selected references

Robbins, Cotran & Kumar

Pathologic Basis of Disease, 11th ed. (2026), Chapter 28; PML pp. 1153–1154.

AAN Neuroinfectious Disease Section

PML diagnostic criteria: consensus statement. Neurology. 2013;80:1430–1438.

NIH Adult & Adolescent OI Guidelines

Progressive Multifocal Leukoencephalopathy/JC Virus; updated 2022, reviewed 2026.

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