

Reactions of Other Glial Cells to Injury

Oligodendrocytes • Ependyma • Disease-associated changes

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Locate oligodendrocytes and ependymal cells within CNS tissue.
- Recognize injury patterns involving myelin, viral inclusions, and cytoplasmic protein deposits.
- Explain ependymal disruption, subependymal gliosis, and granulations.
- Distinguish these responses from astrocytic gliosis and microglial activation.

Glial injury is cell-type specific

Astrocytes
GFAP-positive gliosis

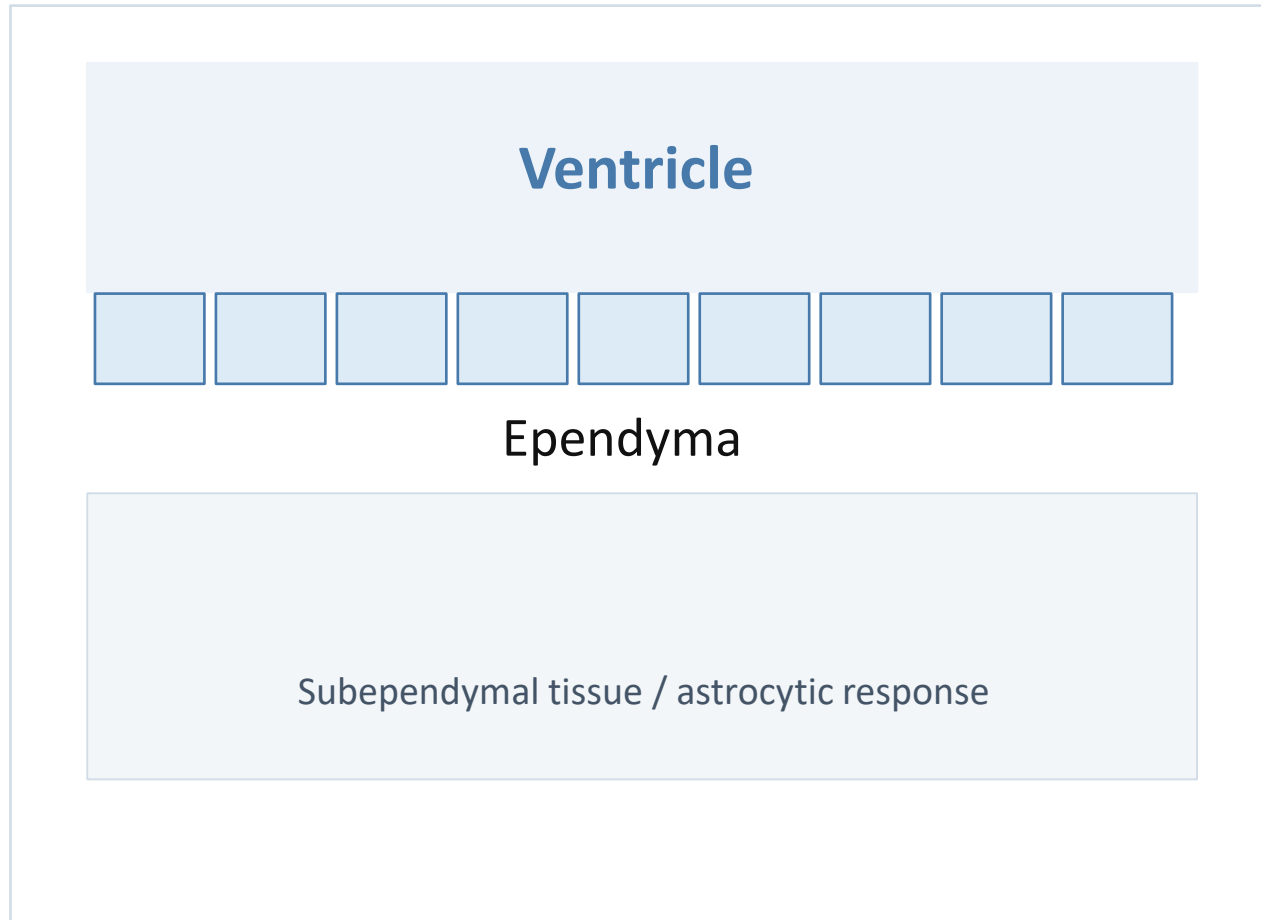
Microglia
Phagocytosis / nodules

Oligodendrocytes
Myelin / injury / inclusions

Ependymal cells
Ventricular surface
disruption

- Oligodendrocytes are specialized myelinating cells.
- Ependymal cells form the ventricular lining.
- Astrocytes and microglia mount more conspicuous reactive responses.

Anatomic map: Myelin versus ventricular lining



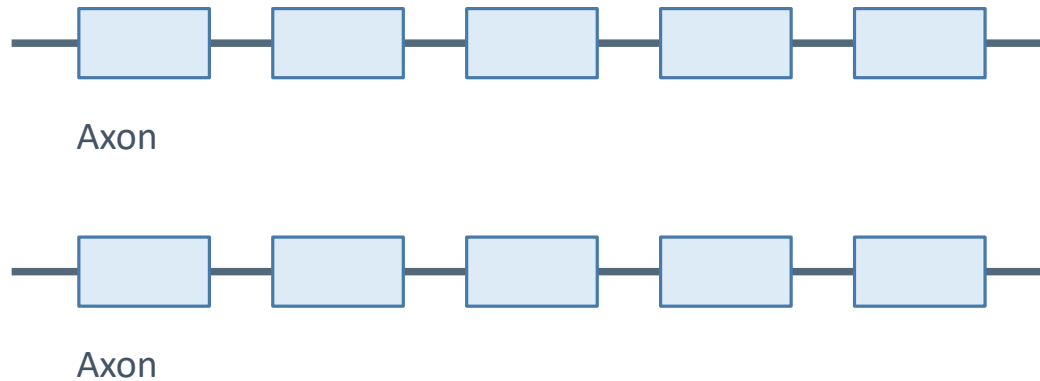
- Oligodendrocytes act on CNS axons within neural tissue.
- Ependymal cells interface with ventricular cerebrospinal fluid.
- Location helps narrow the interpretation of an injury pattern.

Schematic — not a histologic specimen

How glial injury becomes visible

Cell / site	Prominent pathology	Interpretation
Oligodendrocyte	Loss of myelin; Nuclear or cytoplasmic inclusions	Depends on disease mechanism
Ependyma	Lining disruption; Surface granulations	Damage and subependymal astrocytic response
Astrocyte	Cellular hypertrophy / hyperplasia	Gliosis: Common marker of CNS injury
Microglia	Phagocytes; Nodules; Neuronophagia	Clearance and response to injury

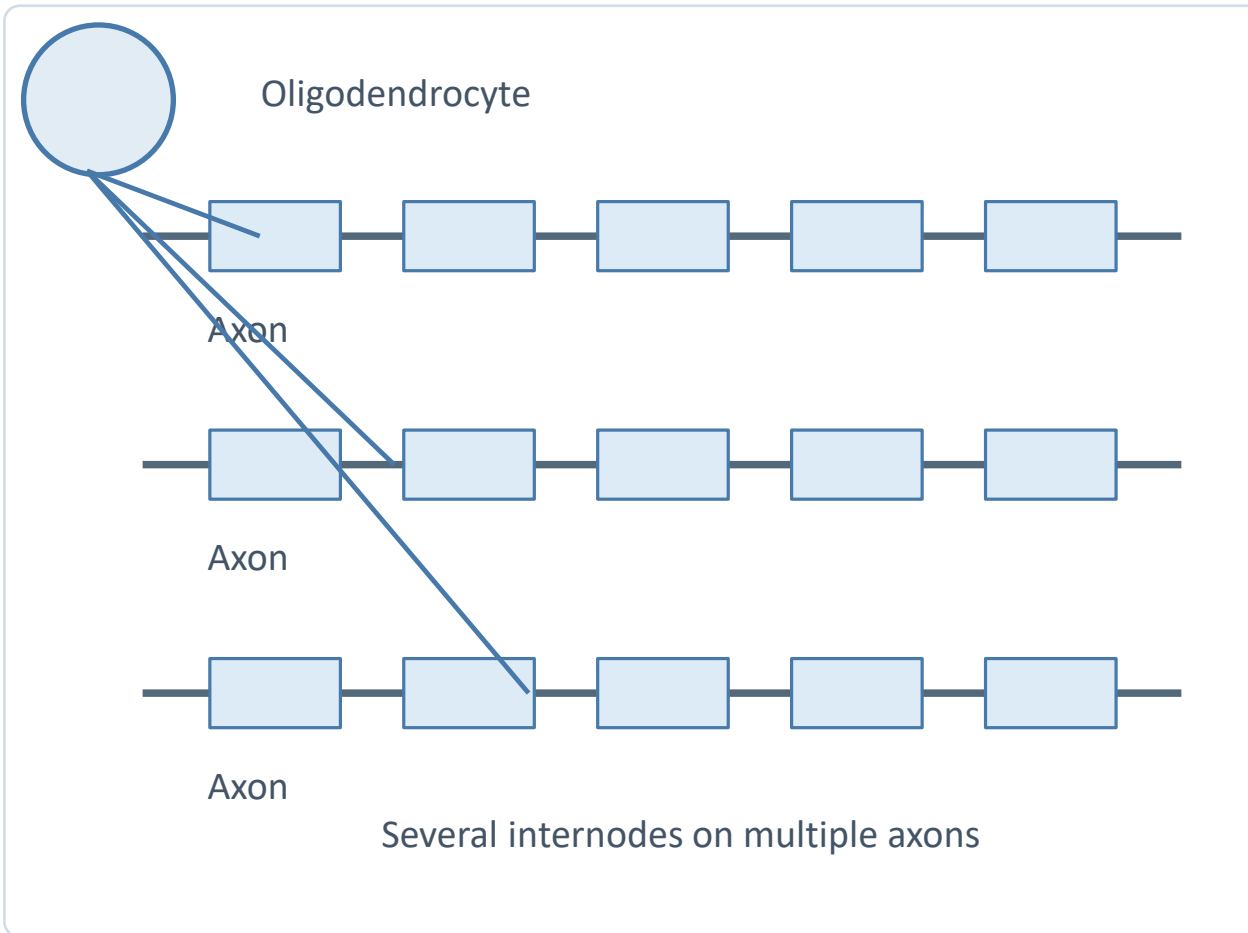
Oligodendrocytes produce CNS myelin



Myelin sheath segments are discontinuous at nodes

- Cell processes wrap axons to create myelin sheaths.
- A single oligodendrocyte can support multiple internodes.
- Its injury can disrupt conduction in several axons.

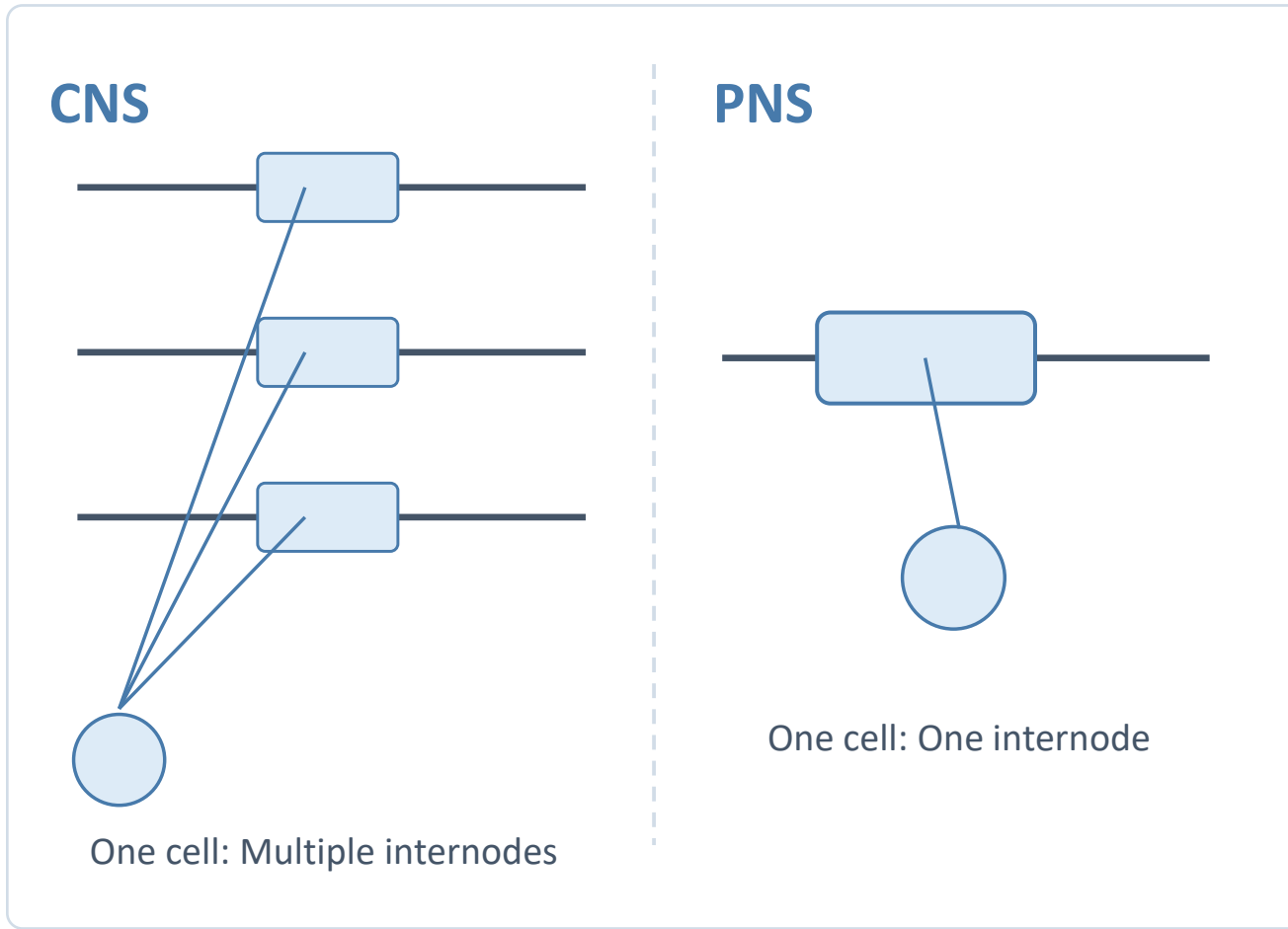
One oligodendrocyte, many internodes



- A single cell distributes processes to more than one axon.
- Each process contributes to a discrete myelin internode.
- Cell loss can therefore affect a network of myelinated segments.

Schematic — not a histologic specimen

Oligodendrocytes differ from Schwann cells



- CNS: One oligodendrocyte myelinates many internodes.
- Peripheral nerve: One Schwann cell myelinates one internode.
- Do not transfer peripheral-nerve regeneration rules directly to CNS tissue.

Schematic — not a histologic specimen

Why myelin preservation matters



When myelin is destroyed, electrical conduction becomes impaired even before the axon is lost.

Patterns of oligodendroglial injury

Immune-mediated myelin injury

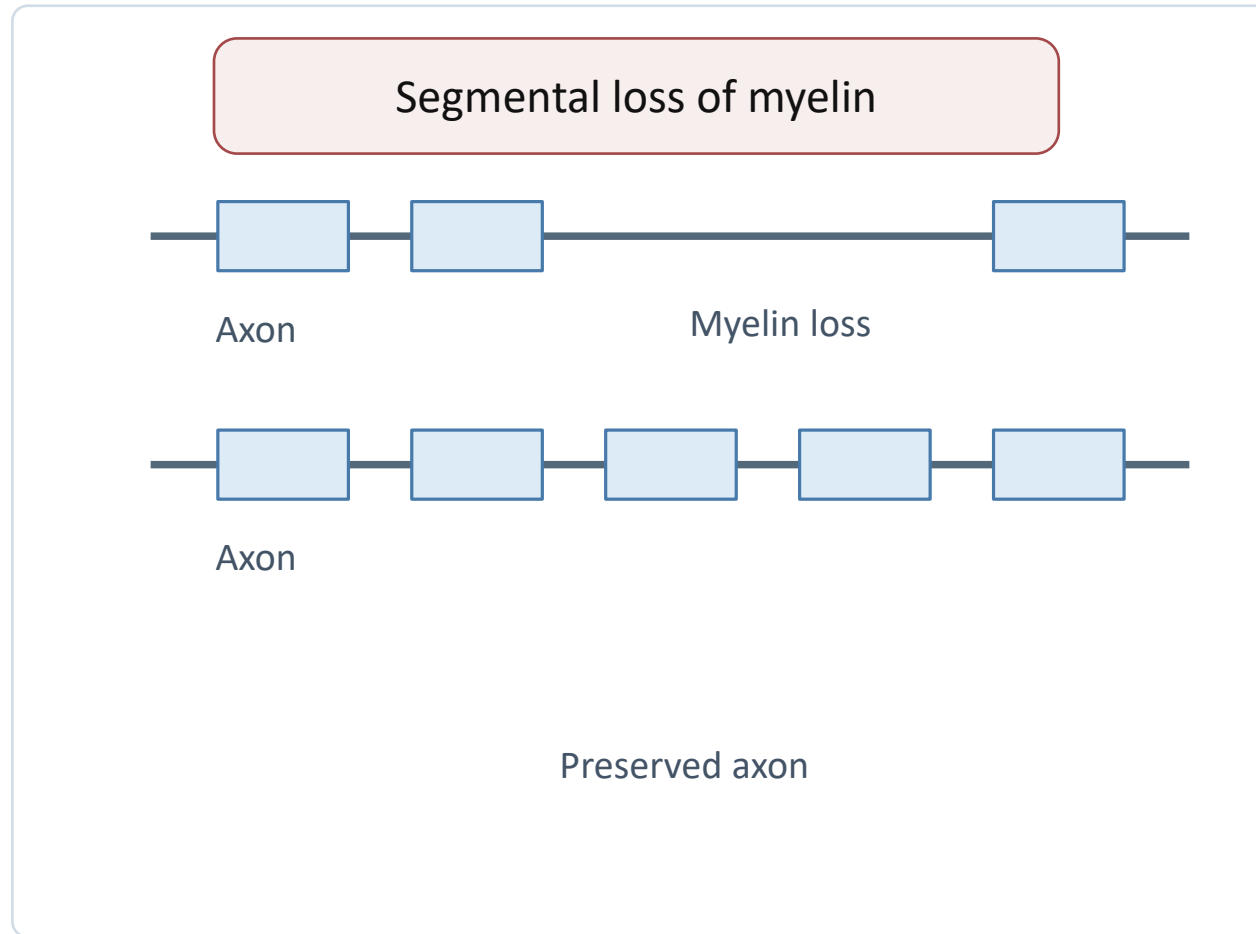
JC virus replication

Inherited myelin instability

Glial protein aggregation

- Loss of cells or myelin is common in demyelinating disease.
- Distinct inclusions identify some viral and degenerative processes.
- Inherited defects can impair the generation or maintenance of myelin.

Myelin loss does not initially require axon loss



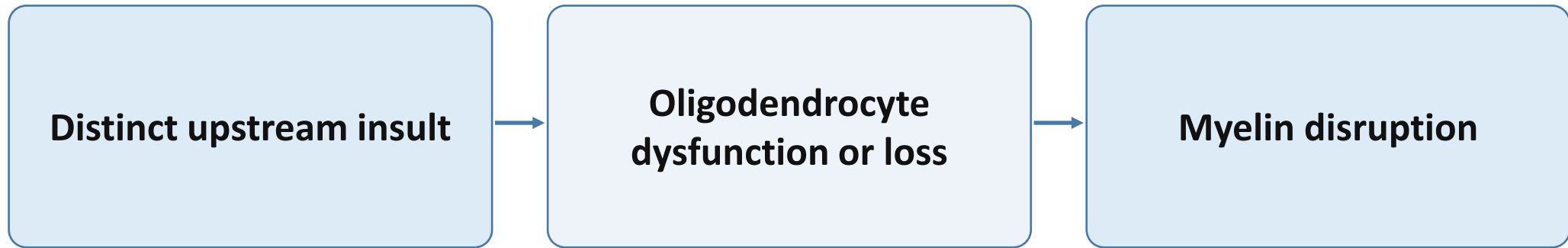
- Acquired CNS demyelination chiefly injures myelin.
- Axons may remain relatively preserved in an active lesion.
- Secondary axonal degeneration contributes to lasting deficits.

Schematic — not a histologic specimen

Acquired and inherited white-matter injury differ

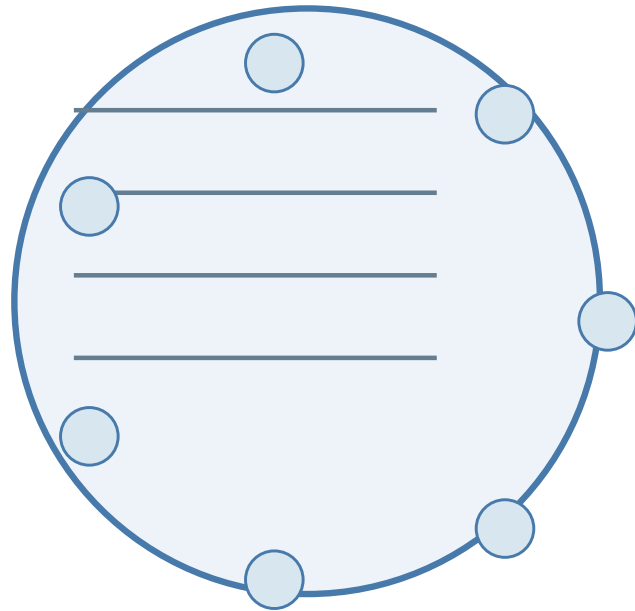
Feature	Acquired demyelination	Leukodystrophy
Principal process	Injury to existing myelin	Defective generation, turnover, or maintenance
Examples	Multiple sclerosis; PML	Krabbe; Metachromatic; Adrenoleukodystrophy
Pattern	Often multifocal / disease-specific	Frequently diffuse, symmetric and progressive

Oligodendrocyte death is not a single disease



Cell loss is a shared reaction. The causal process must be established from lesion context.

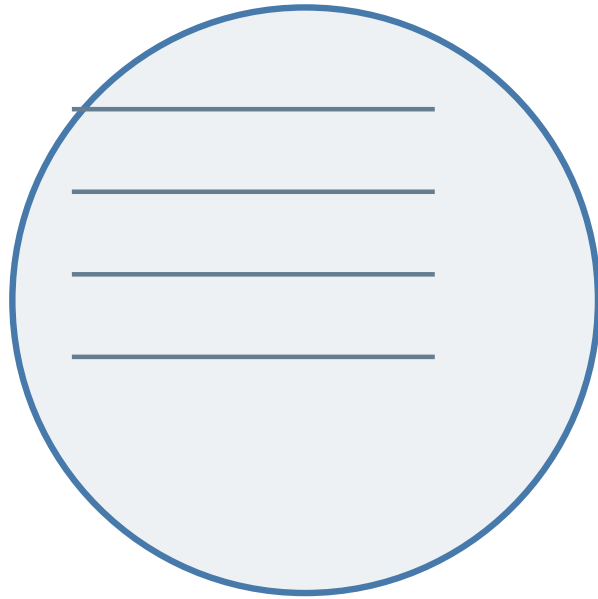
An active demyelinating lesion



Macrophage-rich active margin

- Loss of myelin can coexist with relative axonal preservation.
- Macrophages remove myelin breakdown products.
- Inflammatory cells and active lesion borders help establish activity.

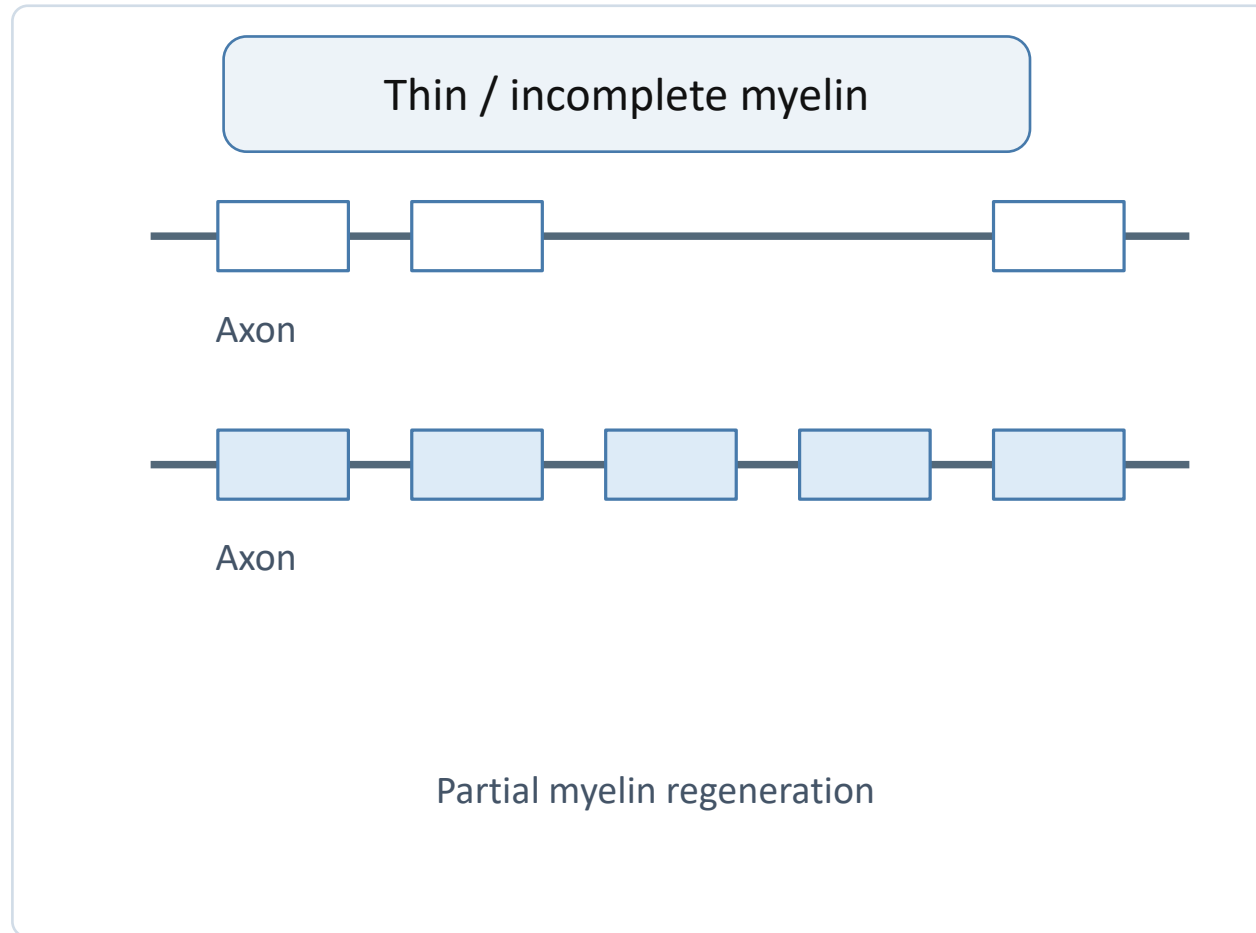
Chronic lesions may lose oligodendrocytes



Oligodendrocyte reduction and dense gliosis

- Inactive MS plaques contain fewer oligodendrocyte nuclei.
- Residual myelin is sparse or absent.
- Reactive astrocytic gliosis becomes prominent.

Remyelination is possible but limited



- Shadow plaques contain thinner-than-normal sheaths.
- This morphology suggests partial remyelination.
- Much of the axonal substrate in established plaques remains unmyelinated.

Schematic — not a histologic specimen

Why old plaques differ from active plaques

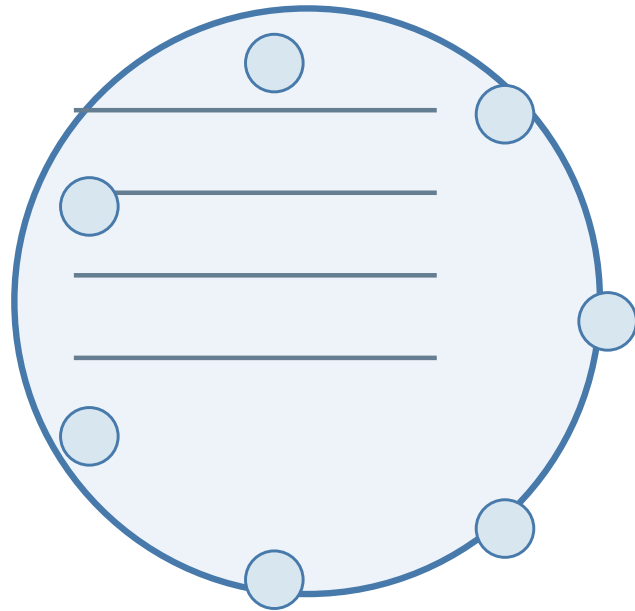


A lesion can change its cellular composition over time; Sample location and disease stage matter.

Multiple sclerosis illustrates immune injury

- Multiple sclerosis is an acquired autoimmune demyelinating disorder.
- In active plaques, macrophages and lymphocytes accompany myelin destruction.
- In inactive plaques, oligodendrocyte depletion and gliosis predominate.
- It demonstrates myelin injury with evolving secondary axonal damage.

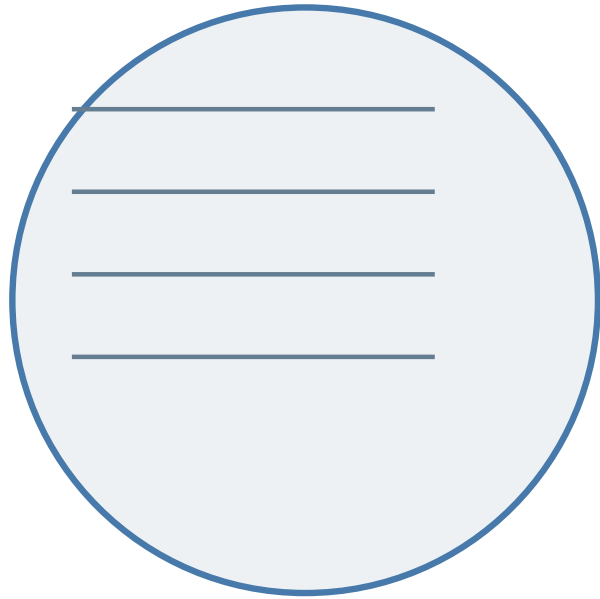
Macrophage-rich activity has a location



Macrophage-rich active margin

- Foamy macrophages characterize active myelin breakdown.
- Perivascular lymphocytes may be evident.
- The border of an active lesion may be more informative than its old center.

Chronic plaques are not simply smaller active plaques



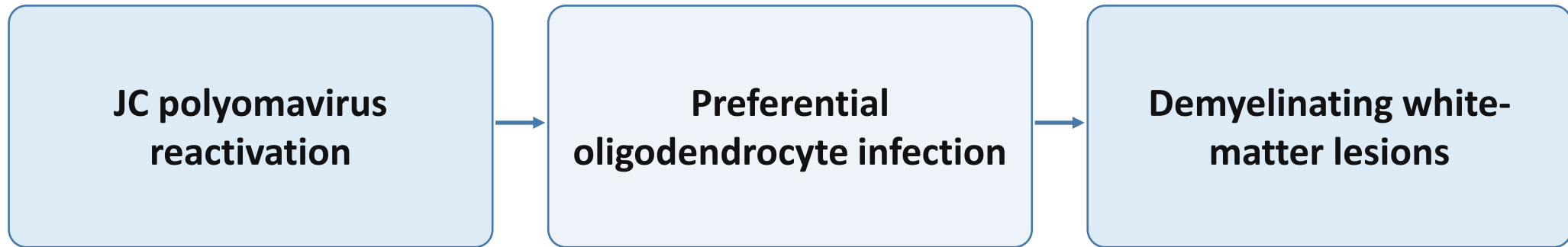
Oligodendrocyte reduction and dense gliosis

- Inflammatory cells decline in inactive lesions.
- Oligodendrocytes and axons can be reduced.
- A dense glial response remains when active inflammation fades.

Three MS plaque states

Active	Inactive	Shadow plaque
Myelin breakdown with macrophages	Little myelin; Gliosis; Fewer oligodendrocytes	Abnormally thin myelin sheaths
Inflammation can be conspicuous	Inflammatory cells mostly absent	Evidence of incomplete repair

PML is a viral oligodendroglial injury

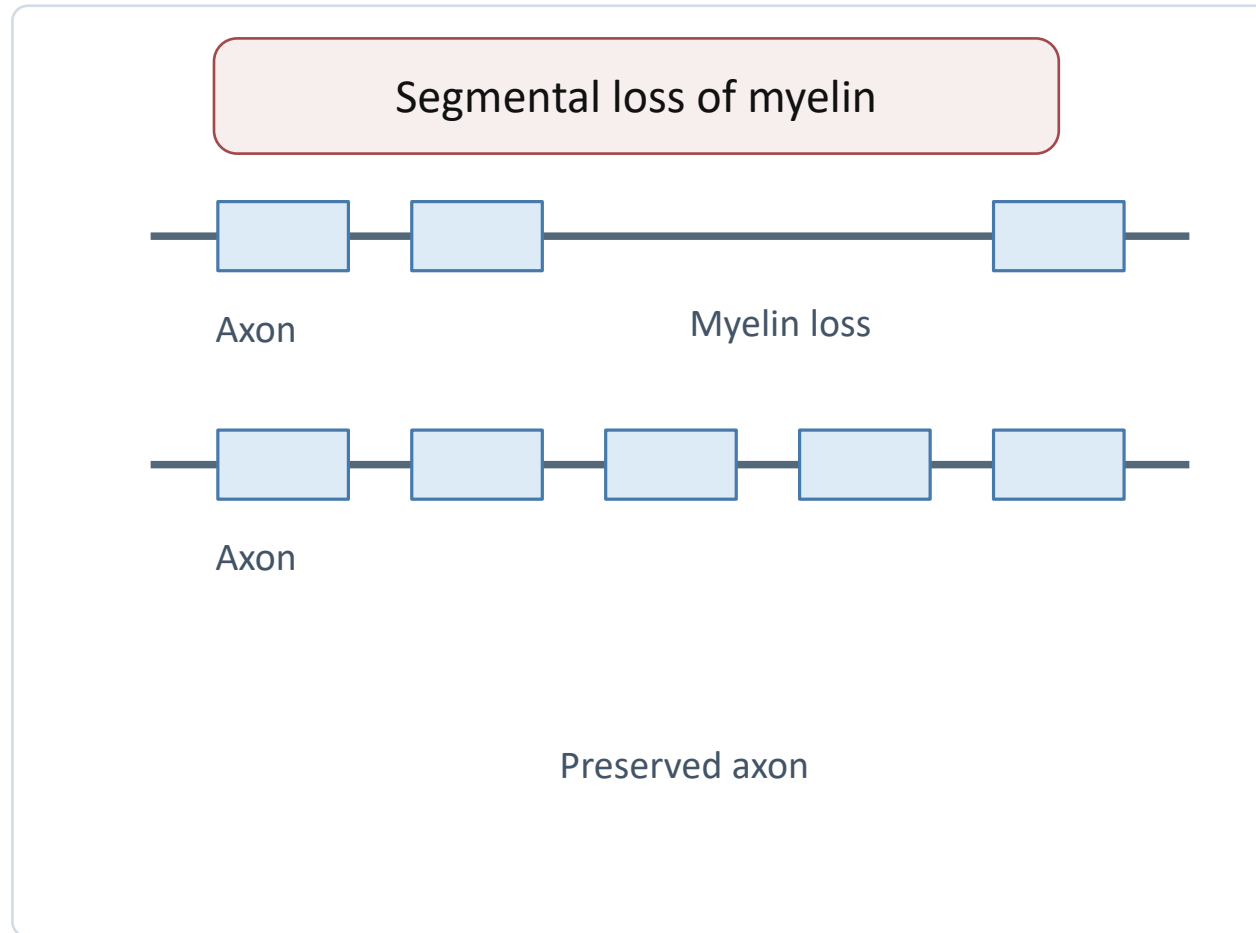


The distinctive viral cellular target explains why demyelination is a central lesion in PML.

PML usually requires impaired immunity

- Most PML develops in immunosuppressed individuals.
- Primary JC virus exposure is usually asymptomatic.
- Disease is linked to viral reactivation rather than ordinary primary infection.
- Pathologic interpretation must integrate host immune status.

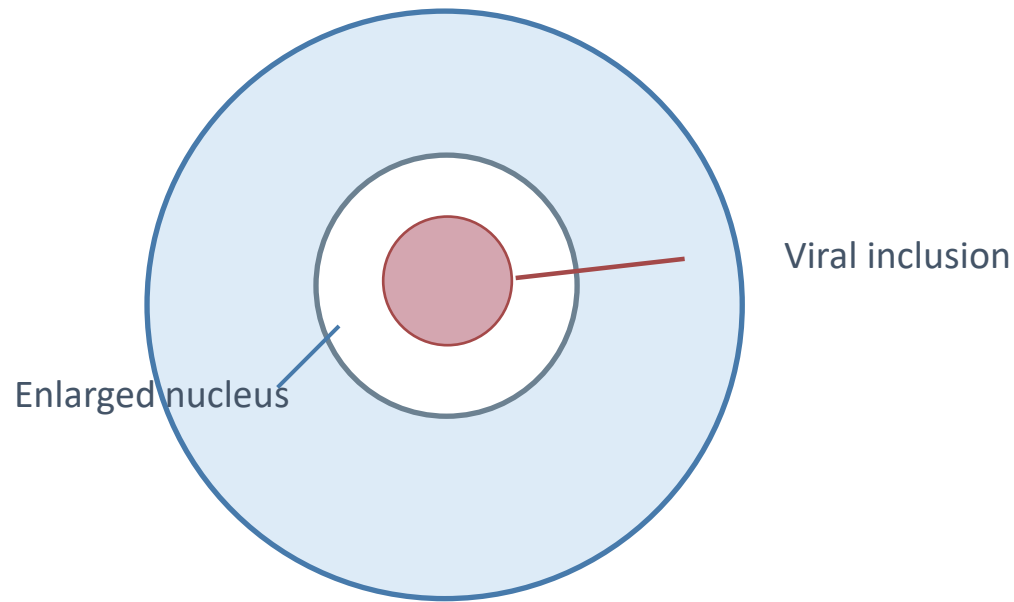
PML lesions preferentially involve white matter



- Lesions form irregular, ill-defined areas of white-matter destruction.
- Patches may merge into larger confluent regions.
- Clinical abnormalities correspond to involved neural pathways.

Schematic — not a histologic specimen

Enlarged oligodendroglial nuclei in PML



- Oligodendrocyte nuclei become enlarged.
- Glassy amphophilic viral inclusions occupy the nucleus.
- Inclusion-bearing cells are classically found near lesion edges.

Schematic — not a histologic specimen

PML has an edge-to-center gradient



Different regions of one PML lesion can display different diagnostic clues.

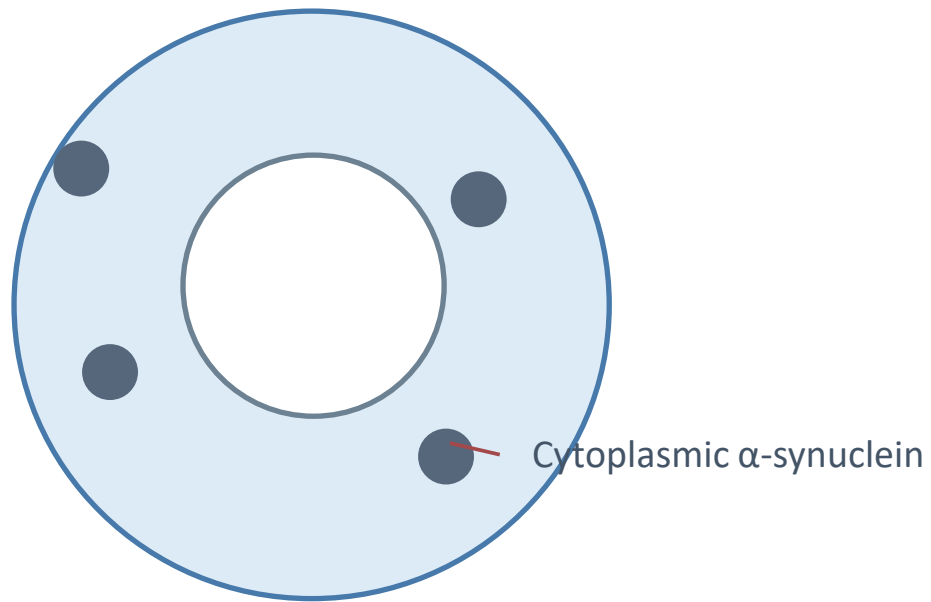
Astrocytes also change in PML

- PML can contain bizarre enlarged astrocytes.
- These may show irregular, hyperchromatic nuclei.
- They coexist with reactive astrocytes and infected oligodendrocytes.
- The distinctive oligodendroglial viral inclusion remains important for attribution.

PML versus multiple sclerosis

Feature	PML	Multiple sclerosis
Central mechanism	JC viral infection of oligodendrocytes	Immune-mediated myelin injury
Distinctive clue	Enlarged oligodendroglial nuclei with viral inclusions	Plaques with stage-specific macrophages, inflammation and gliosis
Context	Typically immunosuppression	Immune-mediated disease with characteristic clinical course

MSA demonstrates proteinopathy in glia

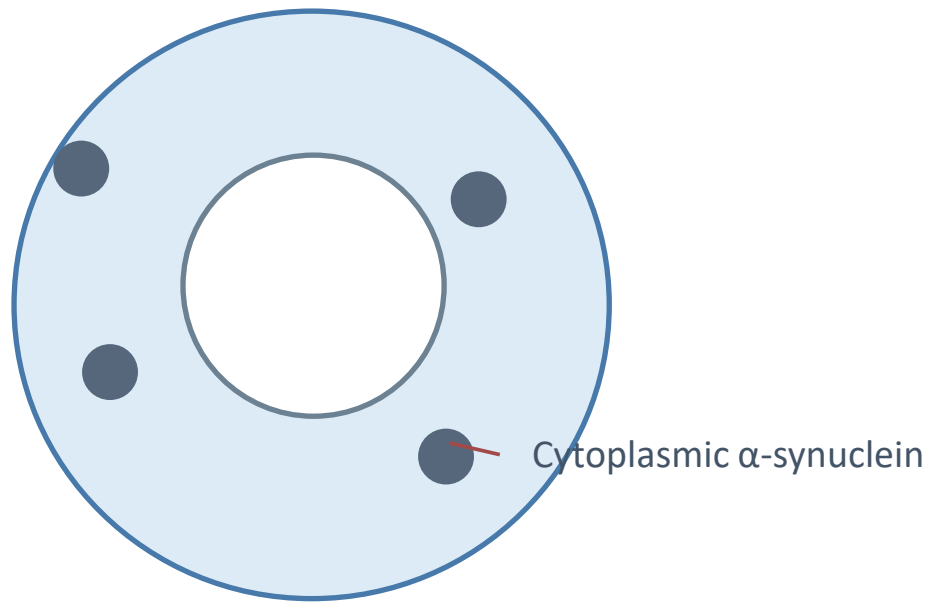


Nucleus lacks the hallmark inclusion

- Multiple system atrophy (MSA) has oligodendroglial inclusions.
- They are cytoplasmic and composed primarily of α -synuclein.
- This is different from the intranuclear viral inclusion of PML.

Schematic — not a histologic specimen

The MSA inclusion lies in the cytoplasm



Nucleus lacks the hallmark inclusion

- A glial cytoplasmic inclusion is the characteristic lesion.
- The cell is an oligodendrocyte rather than a neuron.
- Compartment and inclusion composition direct disease recognition.

Schematic — not a histologic specimen

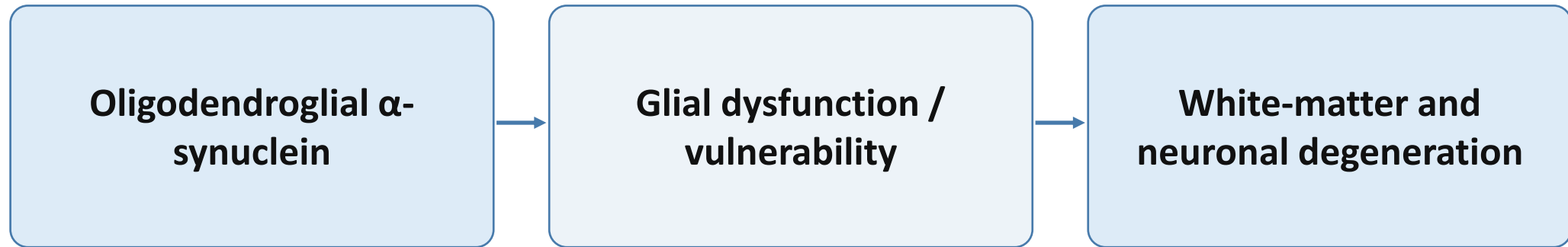
MSA affects several neural systems

System	Corresponding clinical pattern
Striatonigral circuit	Parkinsonism
Olivopontocerebellar circuit	Ataxia
Central autonomic pathways	Autonomic dysfunction, including orthostatic hypotension

Origin of α -synuclein in oligodendrocytes is uncertain

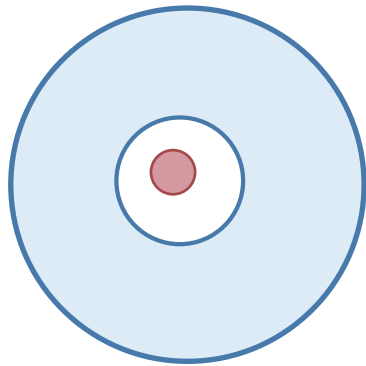
- α -Synuclein is ordinarily associated with neuronal synaptic vesicles.
- Its accumulation in MSA oligodendrocytes is puzzling.
- Acquisition of aggregates from injured neurons has been proposed.
- This proposed origin should not be presented as proven.

The glial inclusion is meaningful in MSA

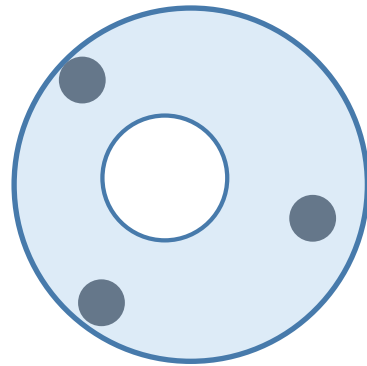


Associations; The exact initiating sequence and protein origin remain uncertain.

PML and MSA: Inclusion compartment is decisive



PML
INTRANUCLEAR viral
inclusion



MSA
CYTOPLASMIC α -synuclein

- PML: Viral material is present in enlarged nuclei.
- MSA: α -synuclein accumulates in oligodendroglial cytoplasm.
- Both affect oligodendrocytes but reflect different mechanisms.

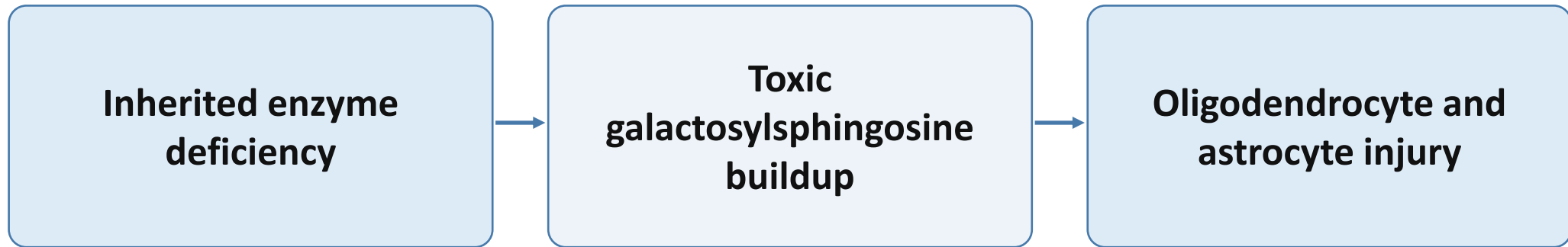
Leukodystrophies are disorders of myelin biology

- Inherited defects alter myelin formation, turnover, or maintenance.
- Presentation often involves progressive dysfunction at young ages.
- Diffuse symmetric white-matter abnormalities are a common pattern.
- Not every white-matter disorder is acquired demyelination.

Disease mechanism helps classify myelin injury

Category	Illustrative example	Primary insult
Immune-mediated	Multiple sclerosis	Autoimmune injury to myelin
Infectious	PML	JC viral oligodendroglial infection
Protein aggregation	MSA	Oligodendroglial α -synuclein inclusions
Inherited metabolic / myelin	Leukodystrophies	Defects of myelin metabolism or maintenance

Krabbe disease injures oligodendrocytes

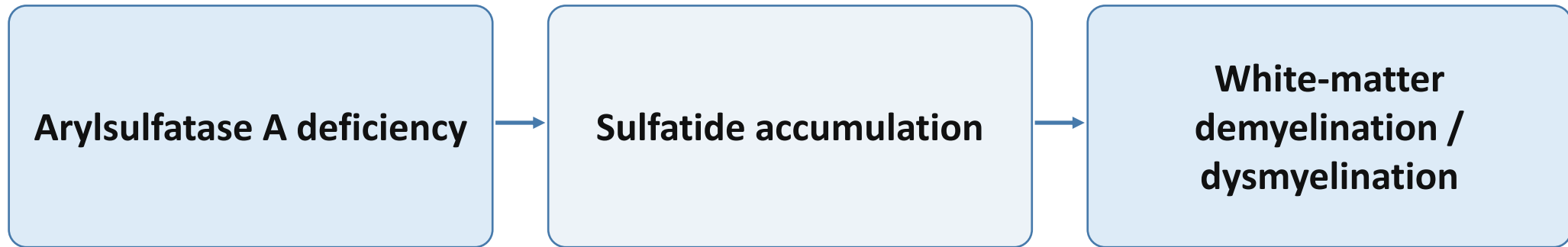


Myelin loss accompanies cell loss; The metabolic precursor lies upstream of the glial lesion.

Globoid macrophages are a clue in Krabbe disease

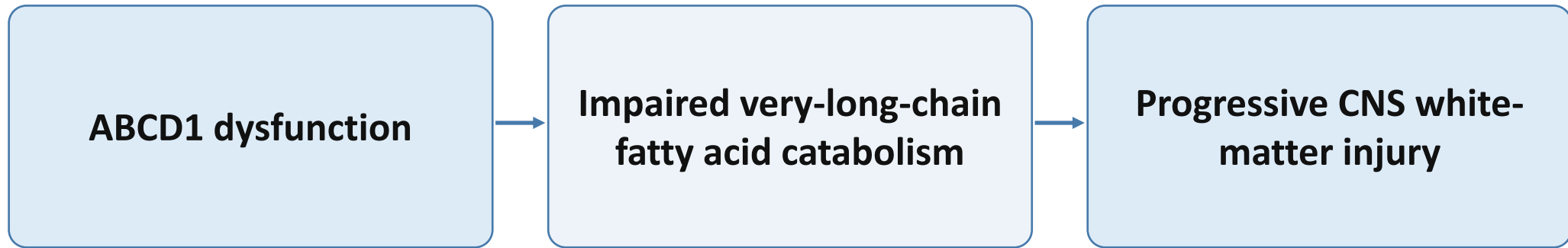
- Krabbe disease causes loss of myelin and oligodendrocytes.
- Neurons and axons are relatively spared early in the process.
- Engorged macrophages form characteristic globoid cells.
- The macrophage reaction accompanies oligodendroglial injury.

Metachromatic leukodystrophy: Stored sulfatides



Metachromatic inclusions occur in macrophages; Glial injury and gliosis accompany the myelin defect.

Adrenoleukodystrophy: A transport defect



Inflammation and gliosis may accompany the white-matter myelin loss.

Four mechanisms, one vulnerable cell system

Immune-mediated myelin injury

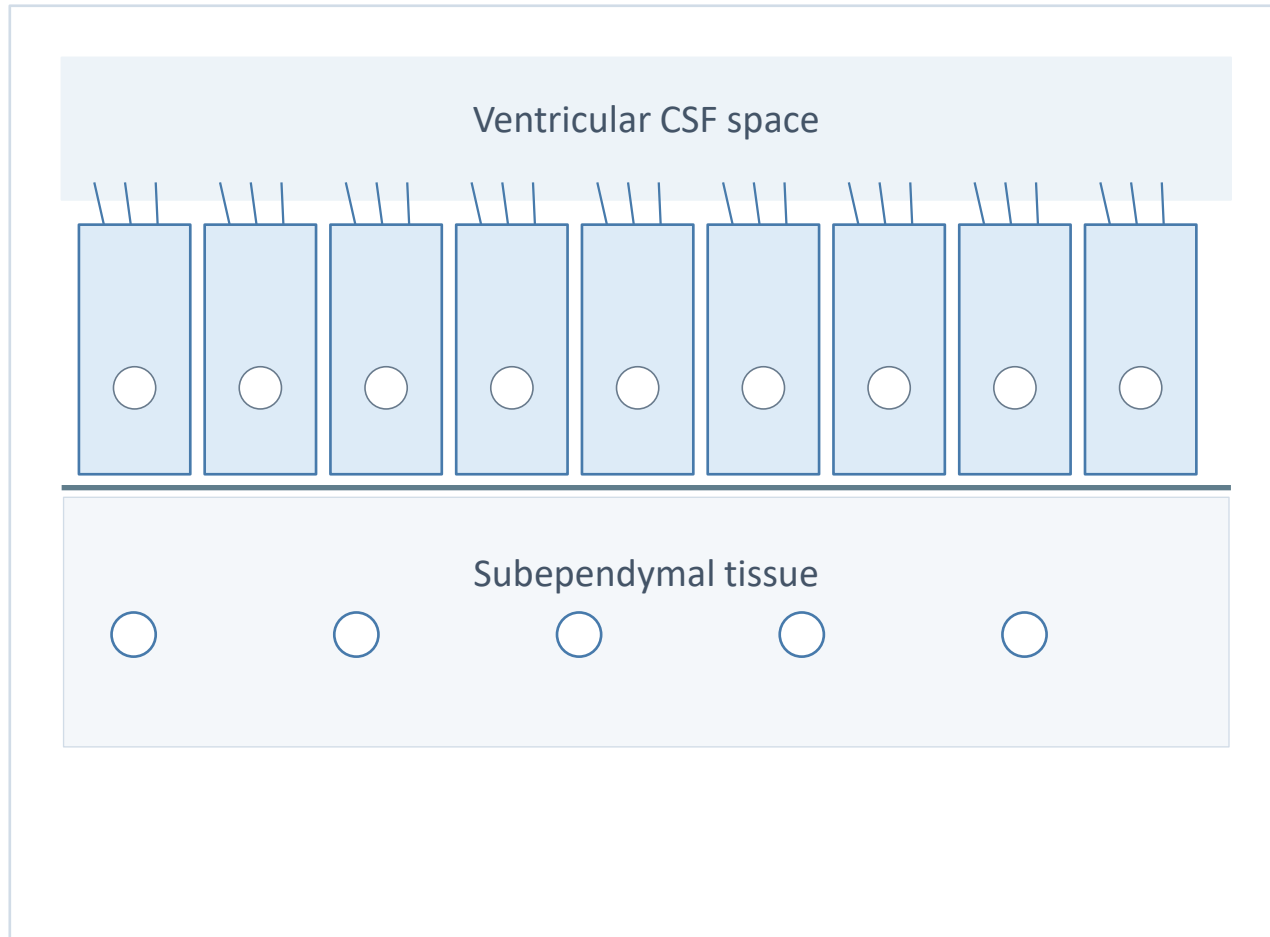
JC virus replication

Inherited myelin instability

Glial protein aggregation

- Immune, infectious, metabolic and degenerative mechanisms differ.
- All can affect oligodendrocyte function or associated myelin.
- An accurate diagnosis requires the disease-specific clue.

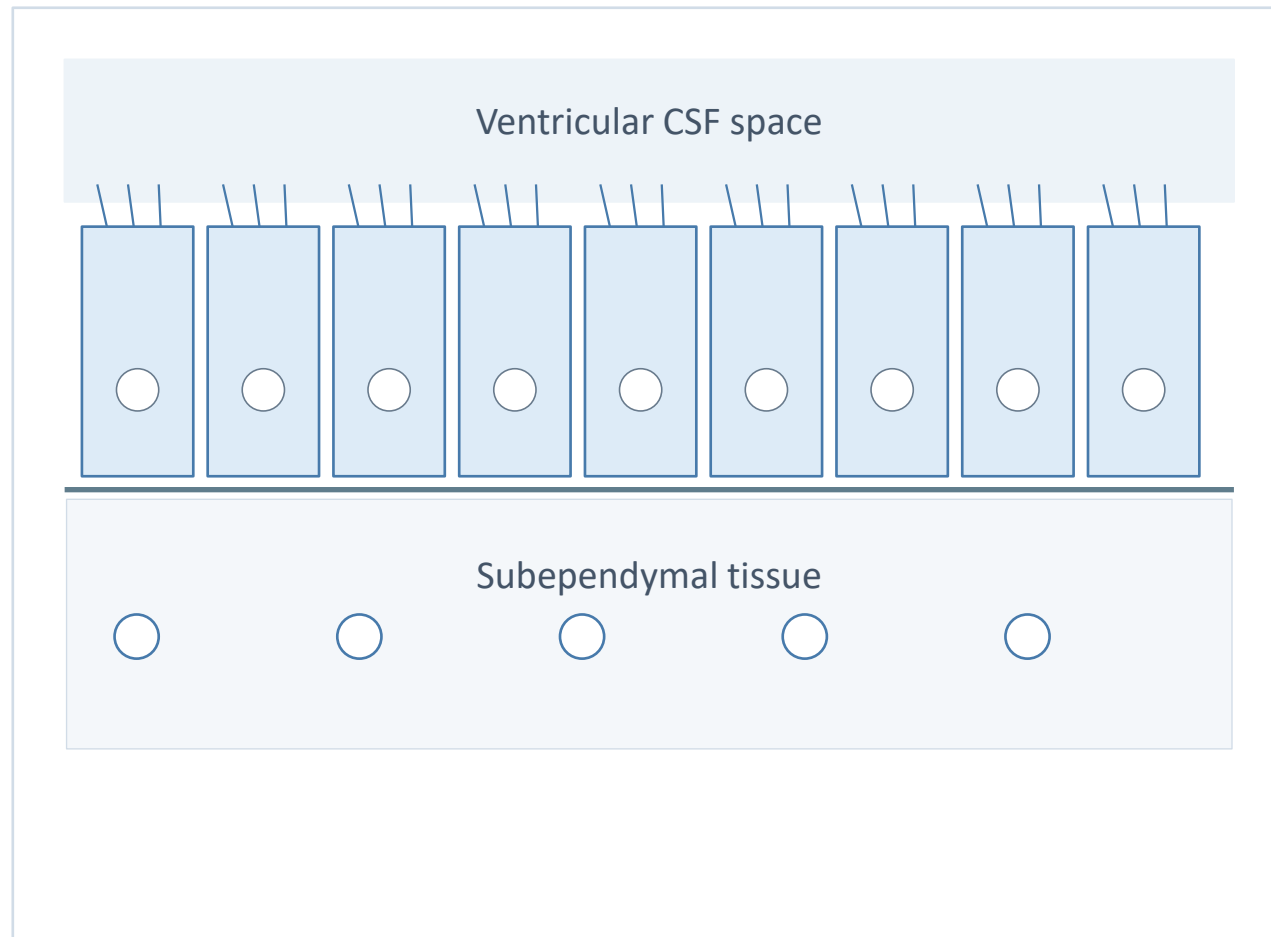
Ependymal cells line the ventricular system



- Ependymal cells are ciliated columnar epithelial cells.
- They form a cellular layer at the ventricular surface.
- Their response differs from the parenchymal astrocytic reaction.

Schematic — not a histologic specimen

Cilia distinguish normal ependymal architecture



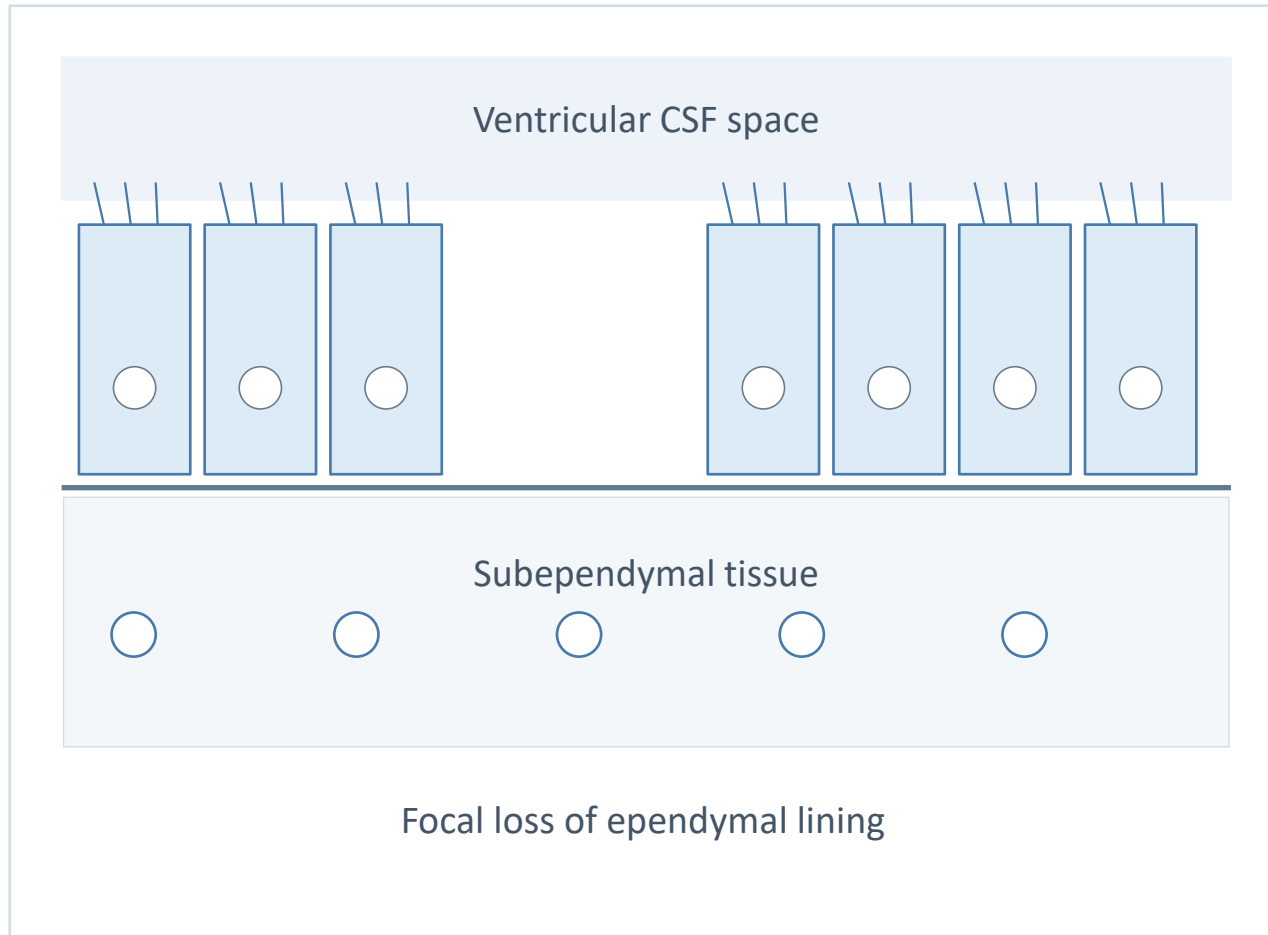
- The ventricular interface is lined by columnar cells.
- Cilia extend toward the ventricular lumen.
- The layer can be disrupted by inflammation or marked ventricular dilation.

Schematic — not a histologic specimen

Ependyma has no stereotyped injury response

- No specific ependymal reaction pattern.
- A damaged lining often reflects the underlying insult rather than a unique ependymal morphology.
- Subependymal astrocytes provide a conspicuous secondary response.

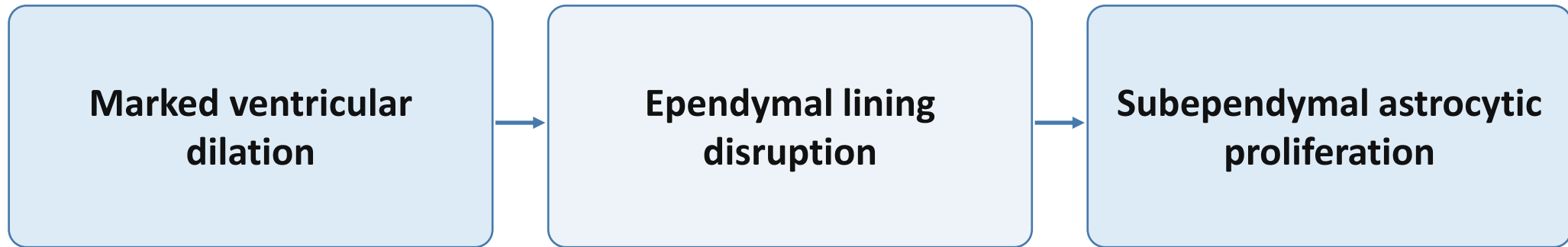
Inflammation may disrupt the ependymal lining



- Inflammatory injury can interrupt the ventricular surface epithelium.
- Loss of lining cells exposes the subjacent tissue.
- Associated subependymal astrocytosis may distort the surface.

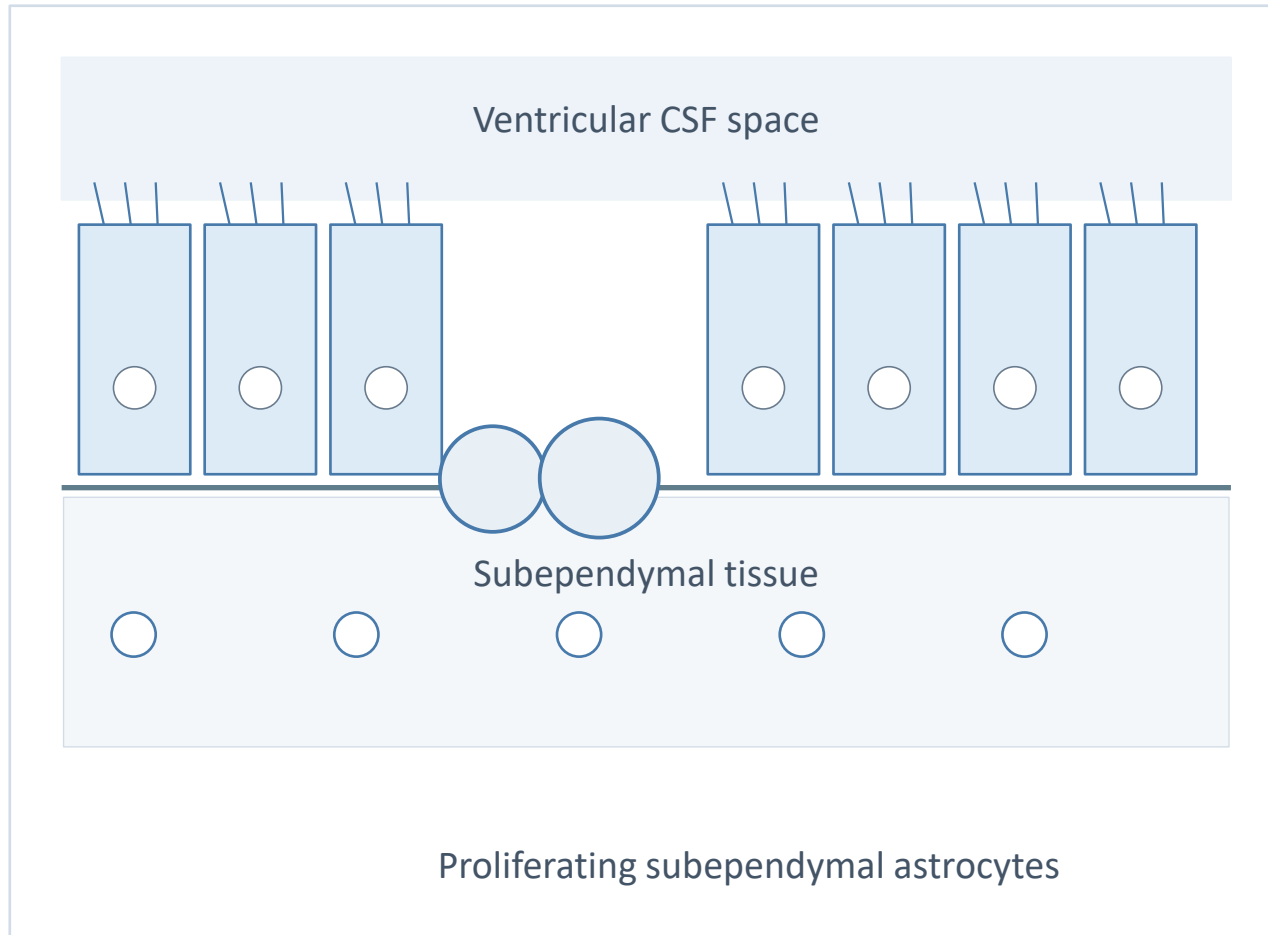
Schematic — not a histologic specimen

Ventricular dilation is another route to disruption



The resulting ventricular surface may become irregular rather than remain smoothly lined.

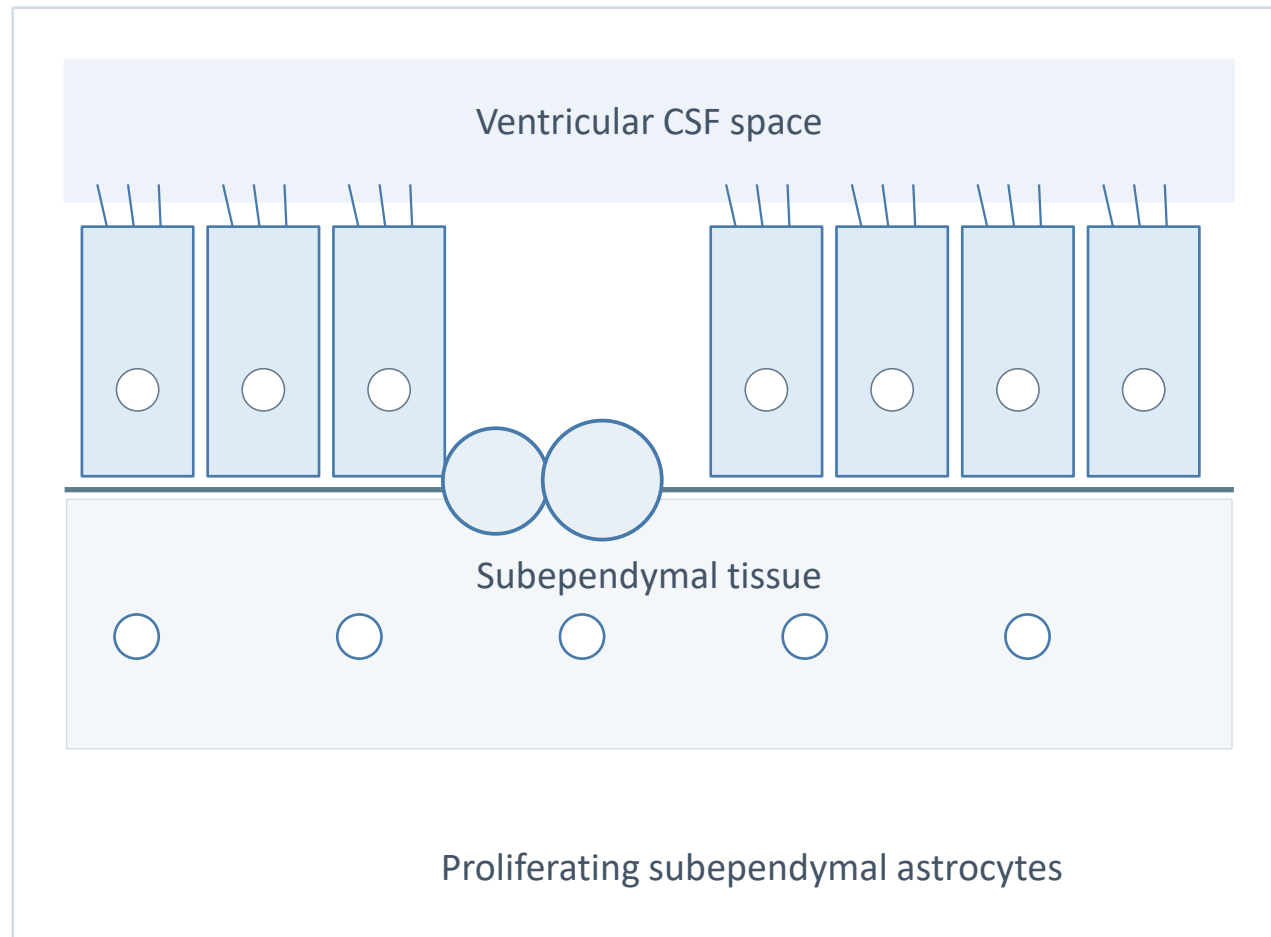
Subependymal astrocytes account for granulations



- The ependymal lining becomes interrupted.
- Subependymal astrocytes proliferate beneath injured areas.
- Small irregularities appear on the ventricular surface.

Schematic — not a histologic specimen

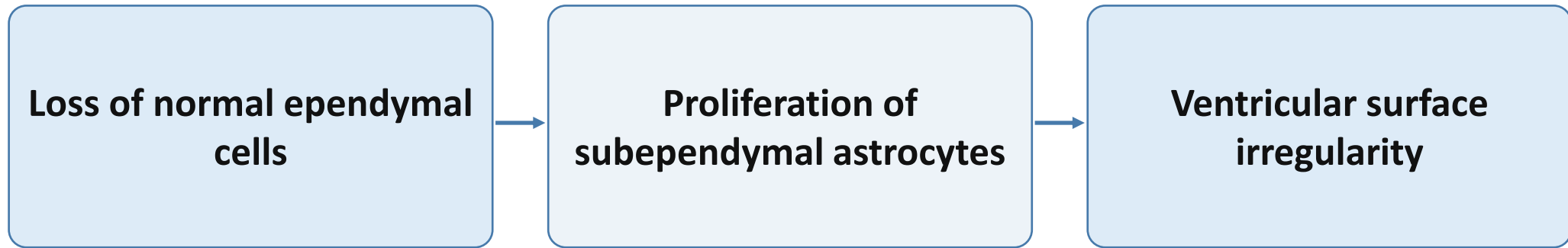
Ependymal granulations are a reactive surface change



- The term describes small ventricular surface irregularities.
- Both prior lining disruption and astrocytic response contribute.
- This reaction should not be conflated with an ependymal neoplasm.

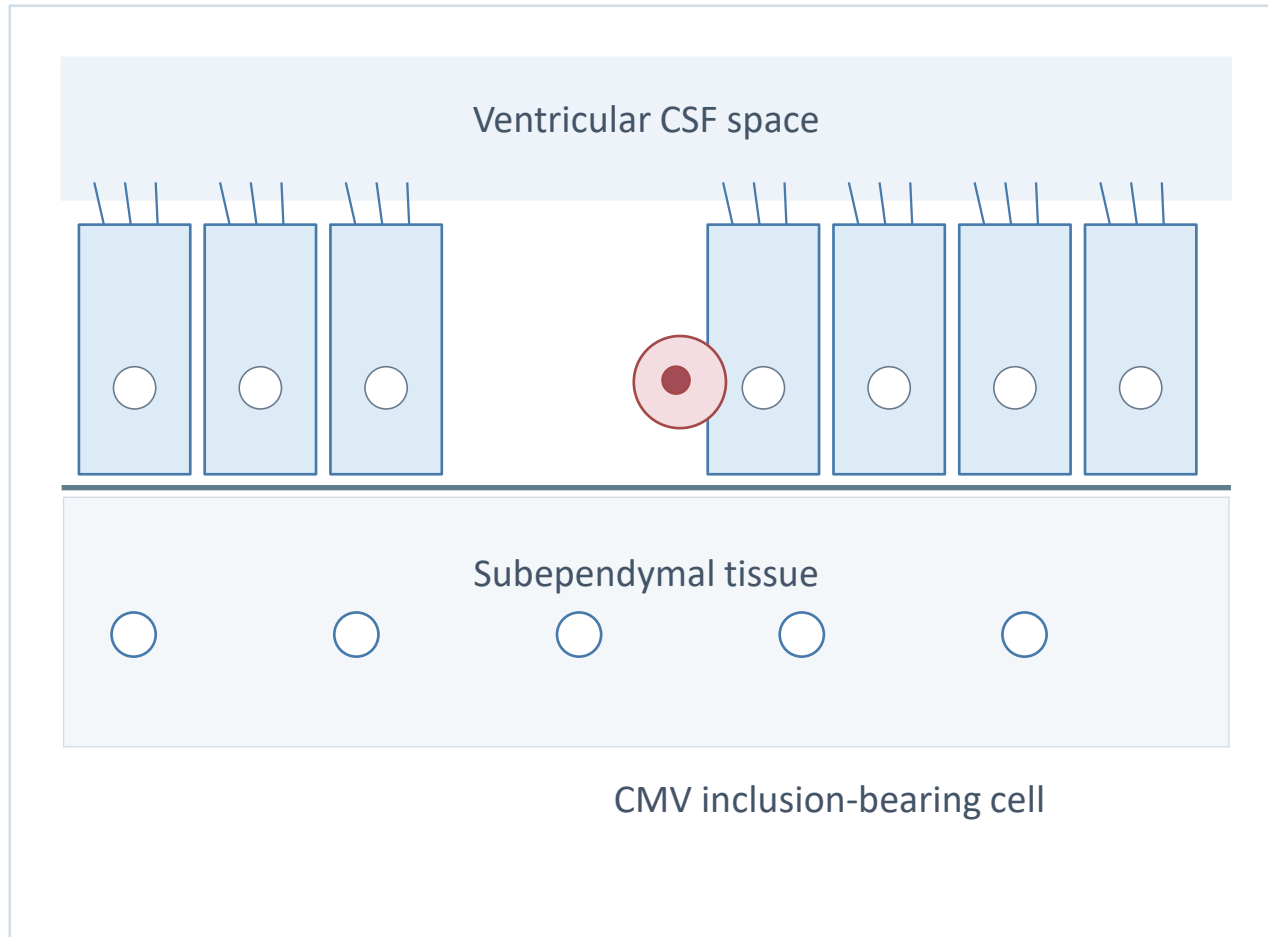
Schematic — not a histologic specimen

Ependymal granulation has two cellular components



The reactive component is predominantly astrocytic, not hyperplasia of injured ependymal cells.

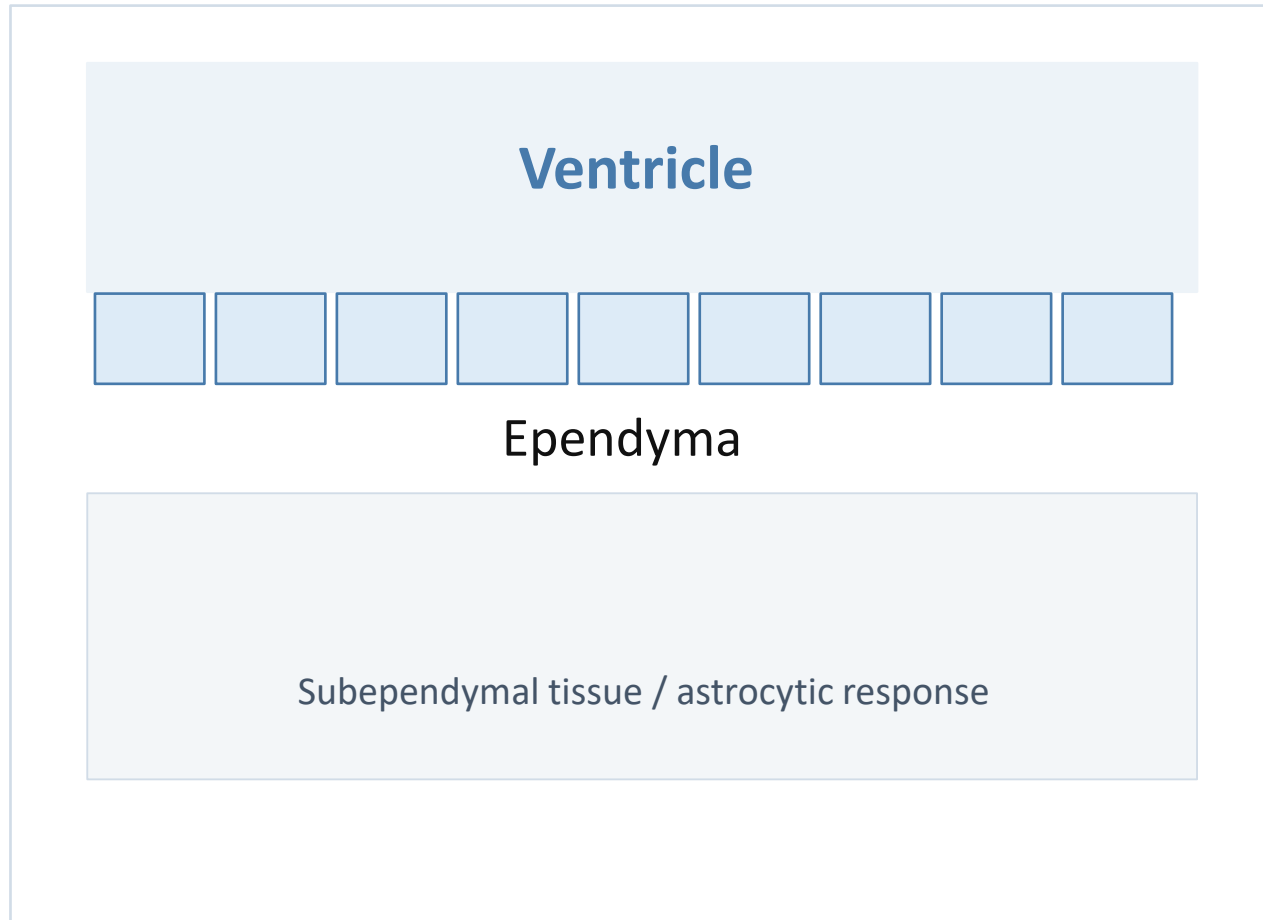
CMV can directly injure the ependyma



- Cytomegalovirus (CMV) is an infectious cause of ependymal injury.
- Viral inclusions may occur within ependymal cells.
- Potentially extensive lining damage.

Schematic — not a histologic specimen

CMV has a subependymal predilection



- The source describes localization of CMV injury to subependymal regions.
- Affected cells may contain recognizable viral inclusions.
- Distribution along the ventricular interface can guide tissue sampling.

Congenital CMV produces periventricular injury

- CMV infection in utero may cause periventricular necrosis.
- Severe cerebral injury can follow.
- Later microcephaly and periventricular calcifications are described.
- This disease context illustrates the vulnerability of the ventricular region.

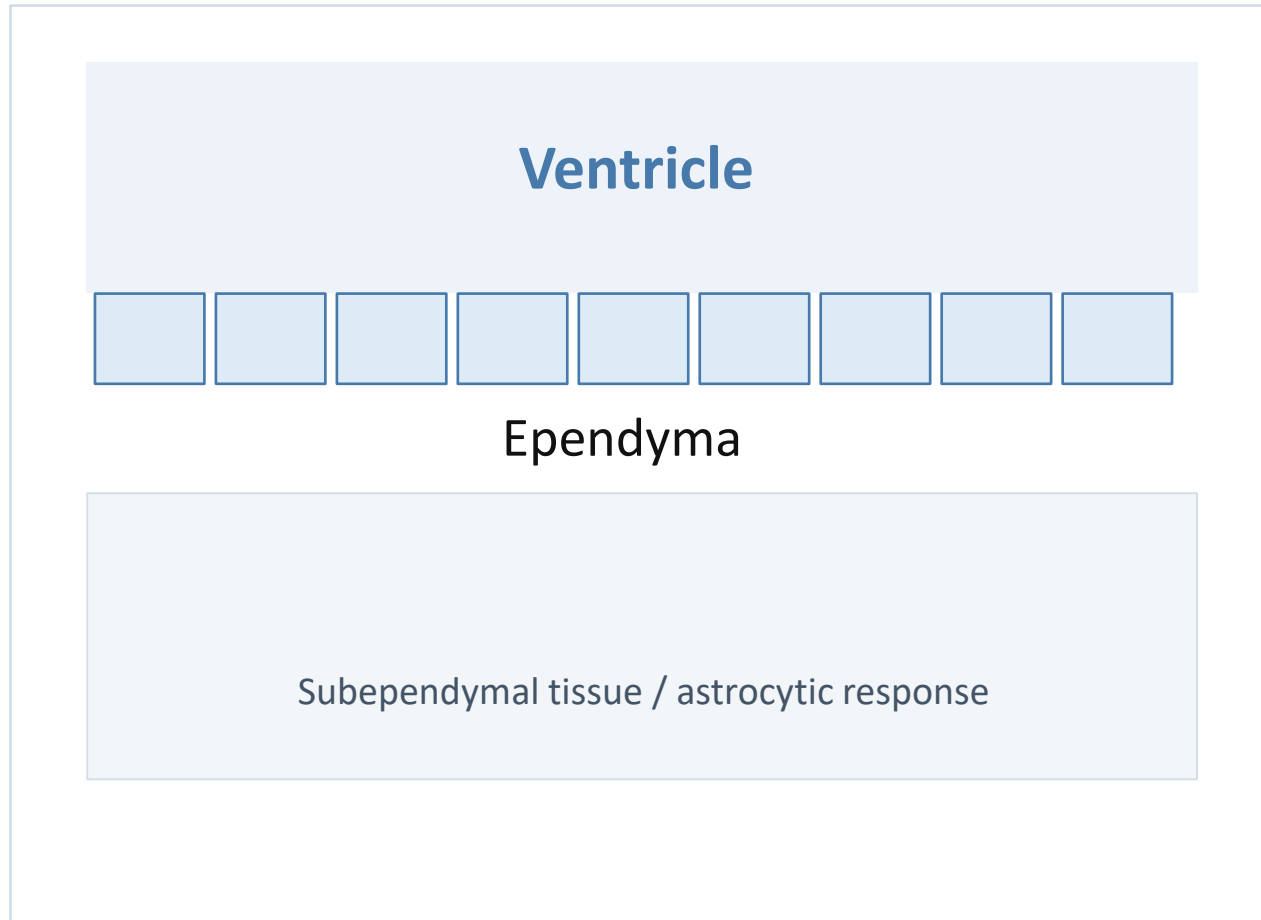
CMV also affects immunosuppressed adults

- CMV is an opportunistic pathogen in immunosuppression.
- The CNS may develop subacute encephalitis.
- Subependymal involvement and viral inclusion-bearing cells are characteristic clues.

Two common contexts of ependymal damage

Setting	Primary injury	Observed consequence
Inflammation / dilation	Lining disruption	Surface granulations with subependymal astrocytes
CMV infection	Viral injury to ependymal cells	Inclusion-bearing cells and ependymal damage

The cell's location shapes injury interpretation



- Ventricular surface injury points toward ependymal involvement.
- Subependymal astrocytosis is a secondary local response.
- Myelin loss deeper in tissue points toward oligodendroglial disease.

Astrocytes contrast with other glial cells

- Reactive astrocytes undergo hypertrophy and hyperplasia (gliosis).
- GFAP expression highlights their cytoplasmic processes.
- Gliosis is a nonspecific but important indicator of CNS injury.
- Oligodendrocytes and ependymal cells usually show less prominent generalized responses.

Microglia contrast with other glial cells

- Microglia act as resident CNS phagocytic cells.
- After injury they can proliferate and form microglial nodules.
- Neuronophagia describes clustering around dying neurons.
- Recruitment of blood-derived macrophages may accompany inflammation.

Different glial cells collaborate in one lesion

Component	Possible role in the same focus
Oligodendrocyte	Myelin production; May be target of damage
Macrophages / microglia	Clear debris and respond to tissue injury
Astrocyte	Reactive gliosis and cellular support
Ependymal cell	Ventricular lining; Damaged in local surface insults

Case: Focal white-matter decline in immunosuppression

Teaching vignette: An immunosuppressed patient develops progressive focal neurologic deficits. White matter shows enlarged oligodendrocyte nuclei with amphophilic inclusions.

What cellular lesion best explains the pattern?

PML: JC-virus–associated oligodendroglial infection and demyelination.

Case: Cytoplasmic inclusions with autonomic failure

Teaching vignette: Progressive parkinsonism and ataxia coexist with autonomic dysfunction.
Tissue shows oligodendrocyte cytoplasmic α -synuclein inclusions.

Which glial proteinopathy is illustrated?

Multiple system atrophy, a glial α -synucleinopathy.

Case: An irregular ventricular surface

Teaching vignette: After marked ventricular enlargement, an irregular ventricular surface is observed where the ependymal lining is interrupted.

Which cell population explains the reactive granulations?

Proliferating subependymal astrocytes.

Case: Viral inclusions at the ventricular interface

Teaching vignette: CNS infection in an immunosuppressed person involves the ventricular and subependymal zones. Ependymal cells contain viral inclusions.

Which infectious agent is highlighted?

Cytomegalovirus (CMV).

Distinguish four characteristic patterns

Pattern	Most informative association
Intranuclear inclusion in oligodendrocyte	JC virus infection / PML
Cytoplasmic α -synuclein in oligodendrocyte	Multiple system atrophy
Ventricular granulation following lining loss	Subependymal astrocytic proliferation
Inclusion-bearing infected ependymal cell	Cytomegalovirus

Interpret the cellular lesion before naming a disease



Example: Nuclear viral inclusion ≠ cytoplasmic protein inclusion ≠ reactive ventricular surface granulation.

Major distinctions to retain

- Oligodendrocytes support many CNS myelin internodes; Injury often produces myelin pathology.
- PML and MSA provide different inclusion patterns in the same glial cell type.
- Ependymal cells may be disrupted by inflammation, dilation, or CMV.
- Ependymal granulations reflect subependymal astrocytic proliferation.

Source and further reading

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).

- Chapter 28 — Cellular pathology of the CNS, p. 1130–1132.
- Disease examples: multiple sclerosis, PML, multiple system atrophy, leukodystrophies and CMV infection.
- Detailed section/page mappings and source provenance are recorded in speaker notes.