

Multiple System Atrophy

Glial α -synucleinopathy: mechanisms, morphology and clinicopathologic correlation

Striatonigral dysfunction

Olivopontocerebellar dysfunction

Autonomic dysfunction

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

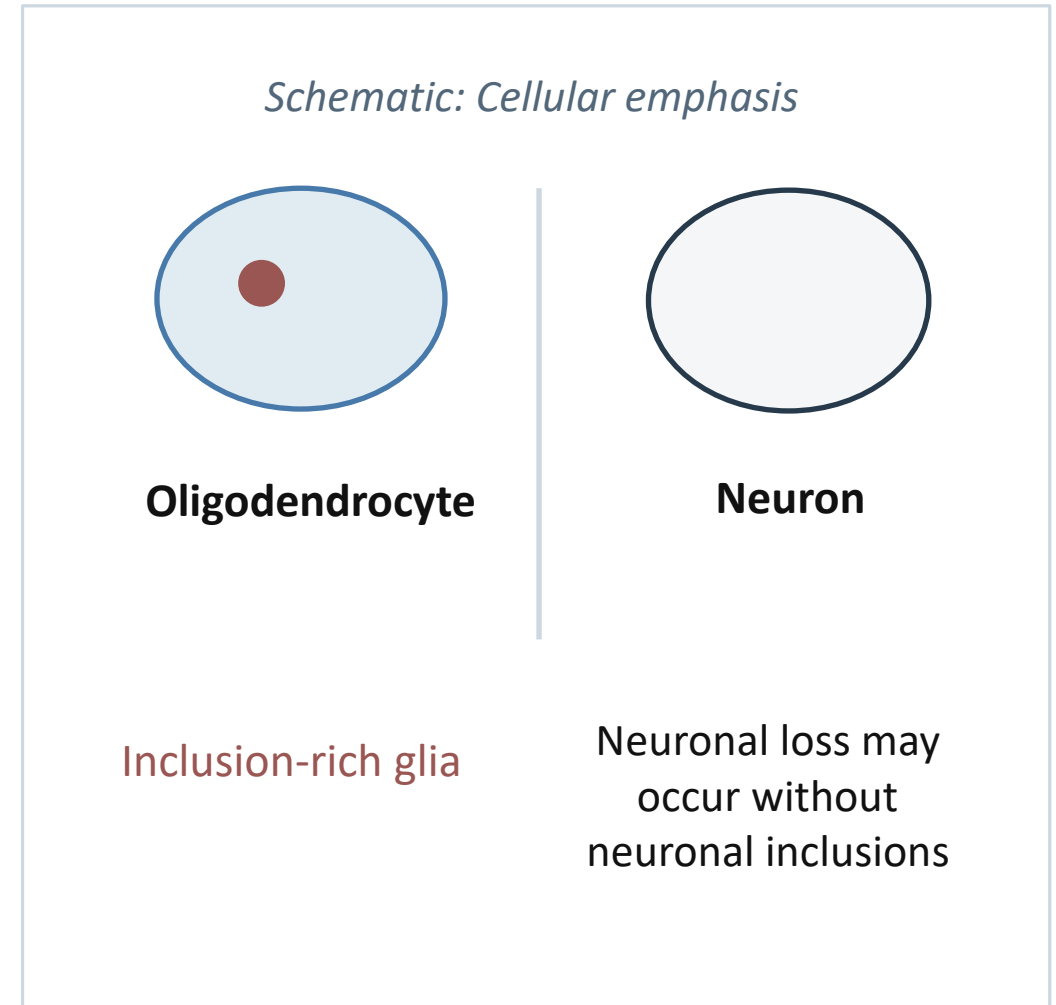
www.abusuraihsakhri.com

Learning outcomes

- Identify the defining glial and white-matter pathology of multiple system atrophy.
- Connect striatonigral, olivopontocerebellar and autonomic degeneration to clinical findings.
- Explain what is known—and what remains unresolved—about α -synuclein accumulation.
- Distinguish MSA from Parkinson disease and tau-associated atypical parkinsonism.

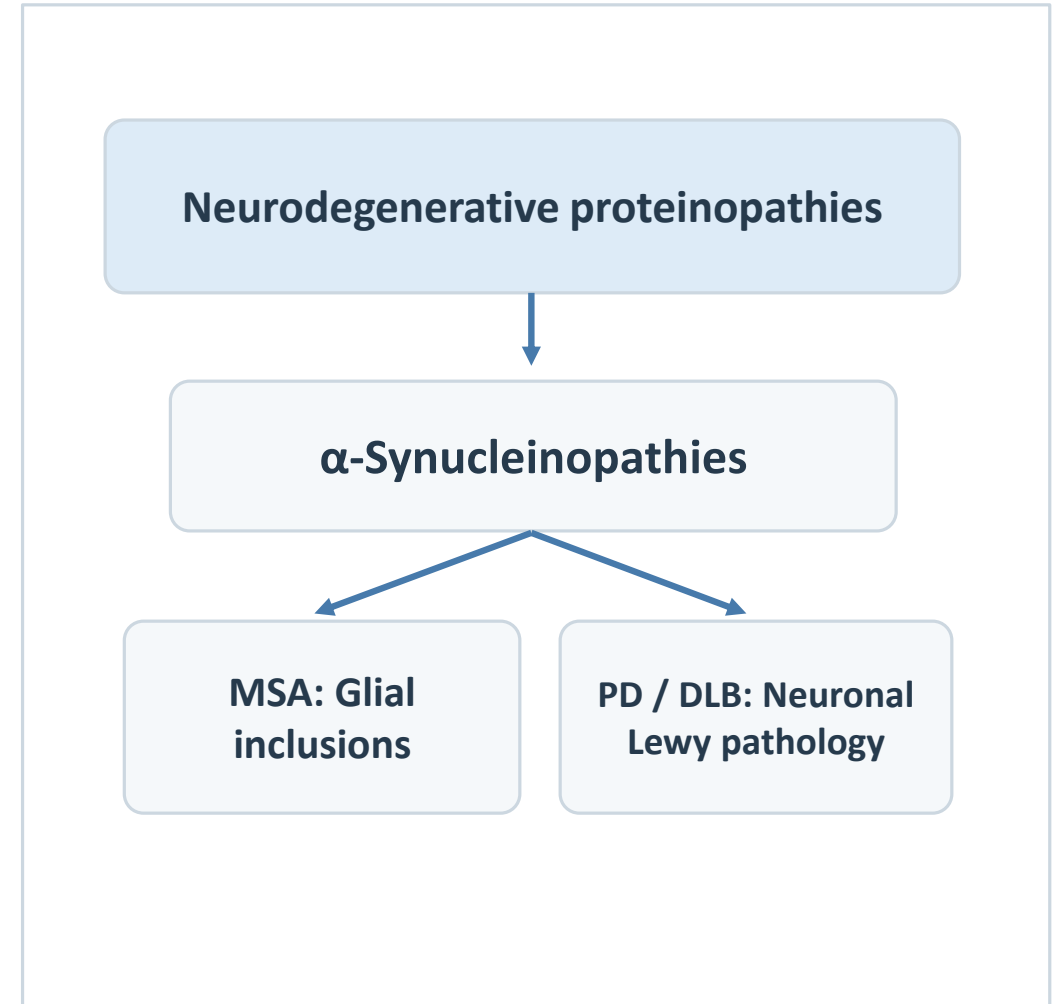
MSA is an oligodendroglial α -synucleinopathy

- MSA is described as a sporadic neurodegenerative disorder.
- Its characteristic inclusions accumulate within oligodendrocyte cytoplasm.
- α -Synuclein is the major protein component of these inclusions.
- The most prominent histopathology involves glia and white-matter tracts.



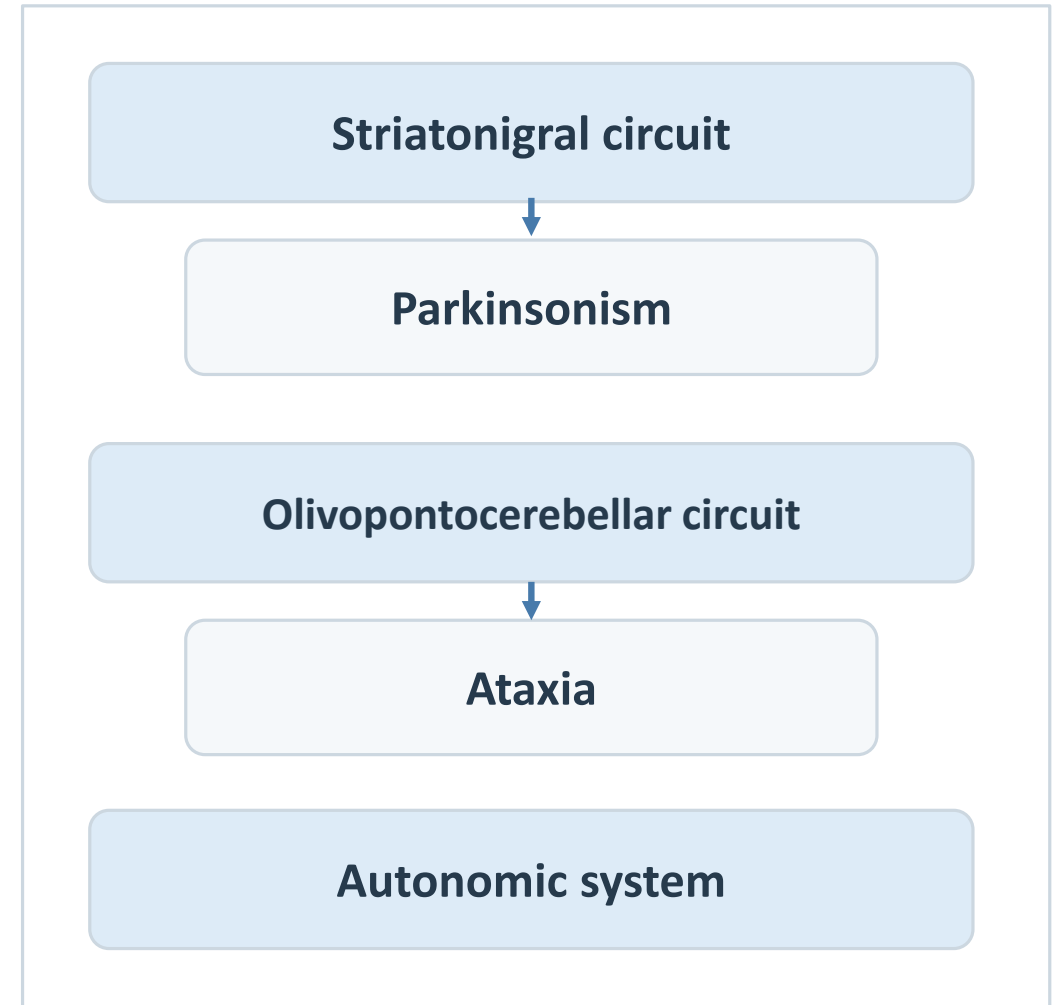
Why MSA is classified as atypical parkinsonism

- Atypical parkinsonian syndromes may have bradykinesia and rigidity plus other neurologic deficits.
- The group is generally much less responsive to L-DOPA than typical Parkinson disease.
- MSA is the α -synucleinopathy within a group that also includes tauopathies PSP and CBD.



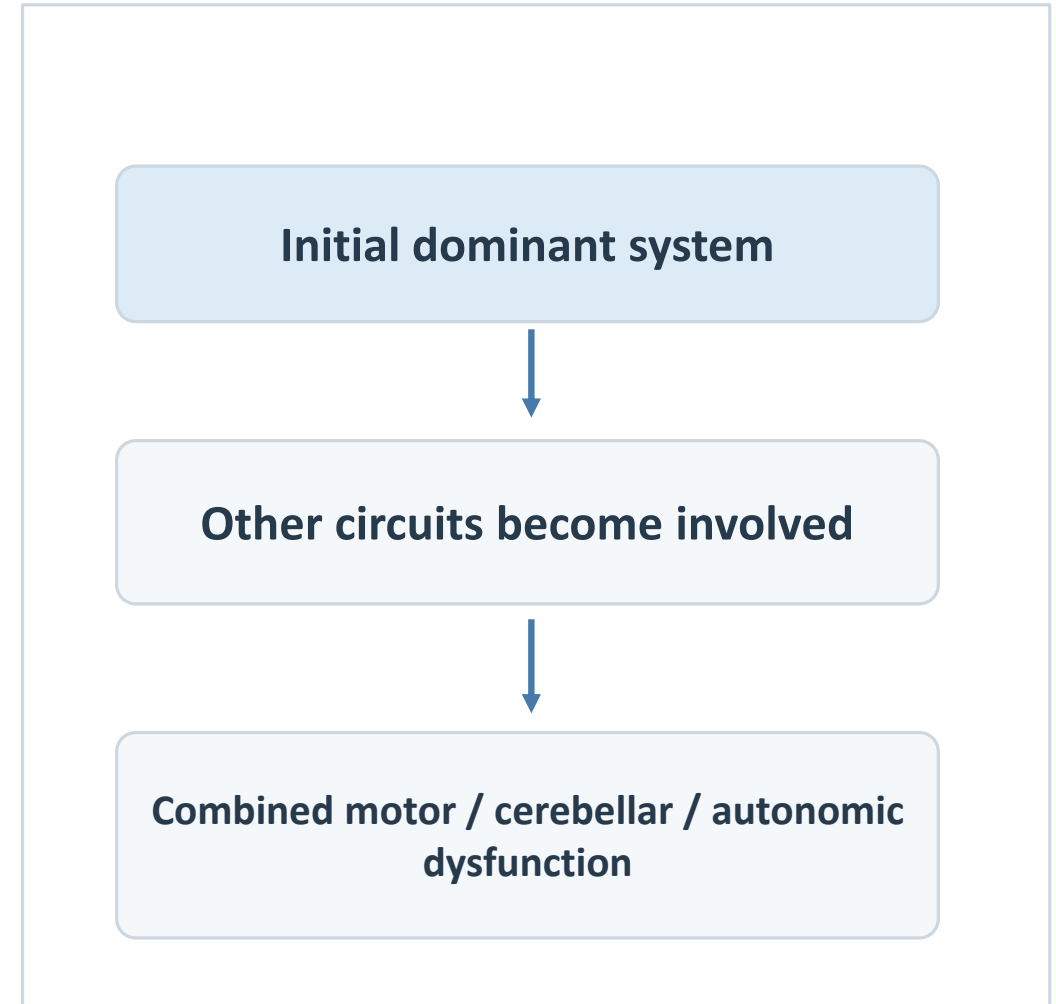
Three neuroanatomic circuits define “multiple”

- Striatonigral circuitry: Dysfunction produces parkinsonism.
- Olivopontocerebellar circuitry: Dysfunction produces ataxia.
- Autonomic pathways, including central elements: Dysfunction produces autonomic failure.



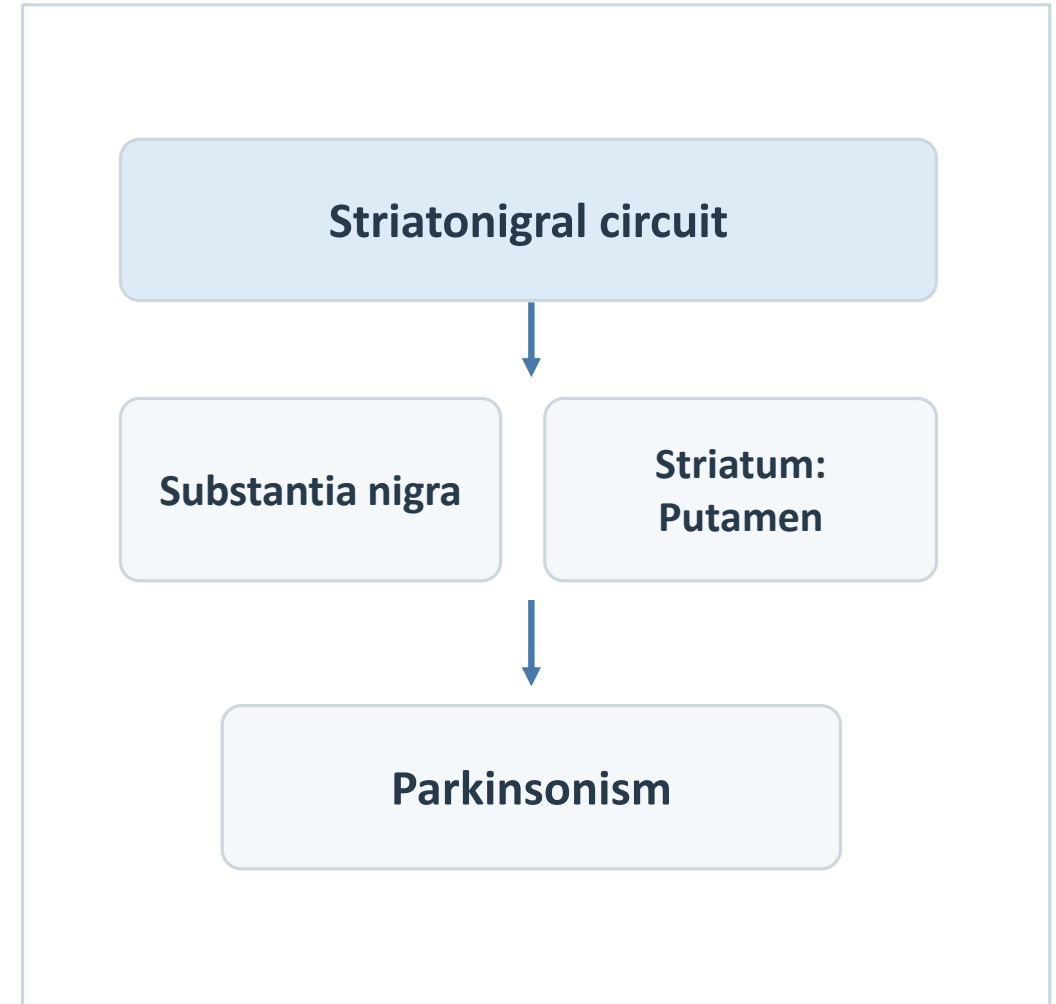
The term “multiple” denotes systems, not separate diseases

- The clinical syndrome integrates involvement of distinct neuroanatomic circuits.
- One circuit may dominate at presentation, even though others are already vulnerable.
- With progression, deficits often extend to other systems.



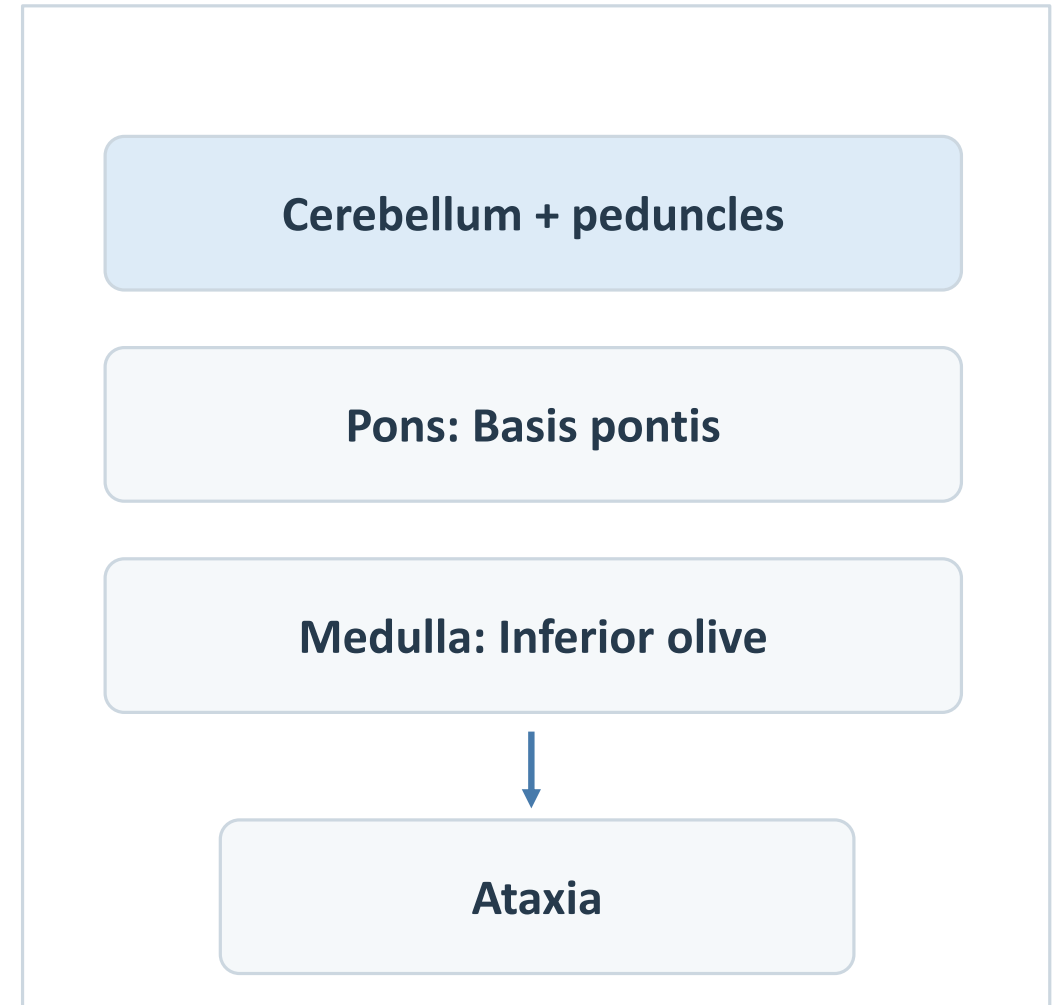
Parkinsonism reflects striatonigral dysfunction

- Striatal and nigral involvement form the motor substrate of parkinsonism in MSA.
- Parkinsonism does not, on its own, identify the underlying proteinopathy.
- Concurrent autonomic or cerebellar abnormalities change the differential diagnosis.



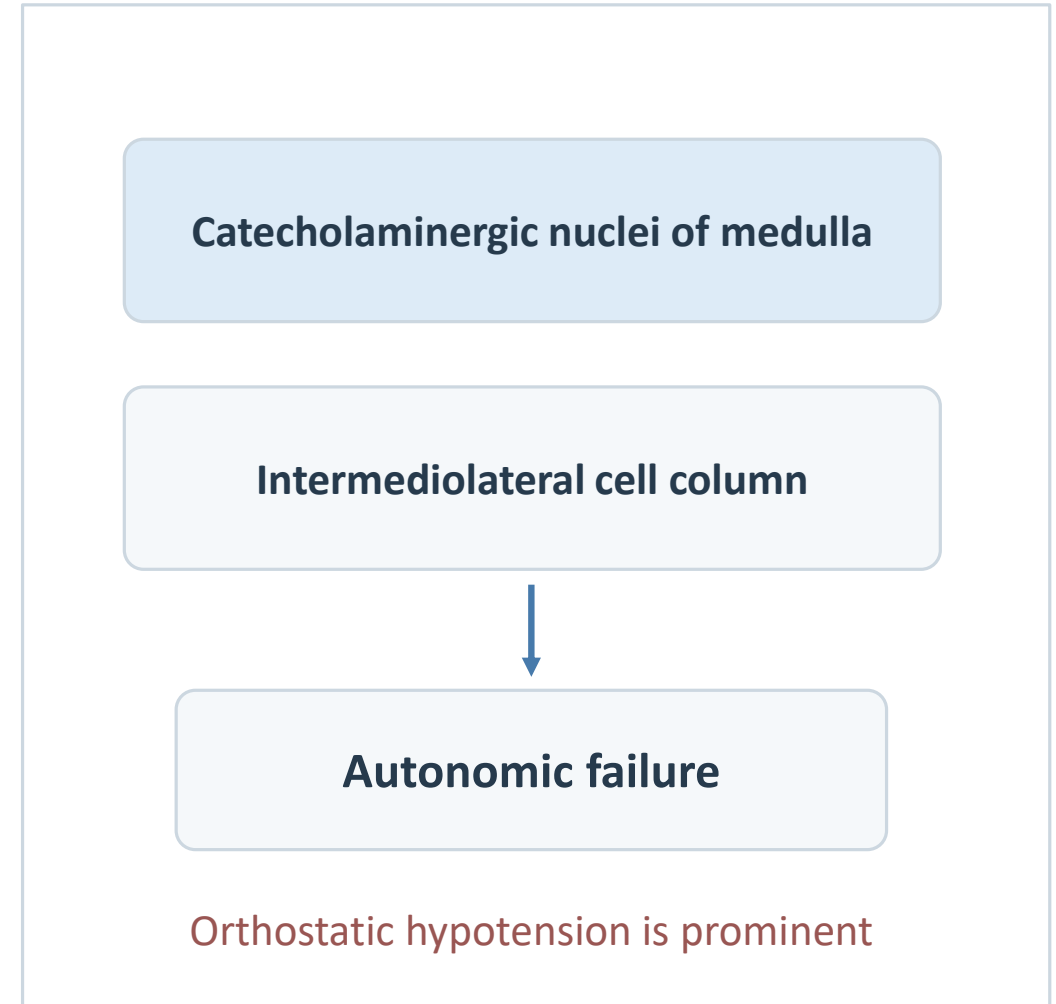
Ataxia reflects olivopontocerebellar dysfunction

- Cerebellar, pontine and olivary degeneration constitutes a second disease axis.
- The source links this anatomic circuit to the ataxic clinical component.
- Ataxia may be the presenting dominant feature.



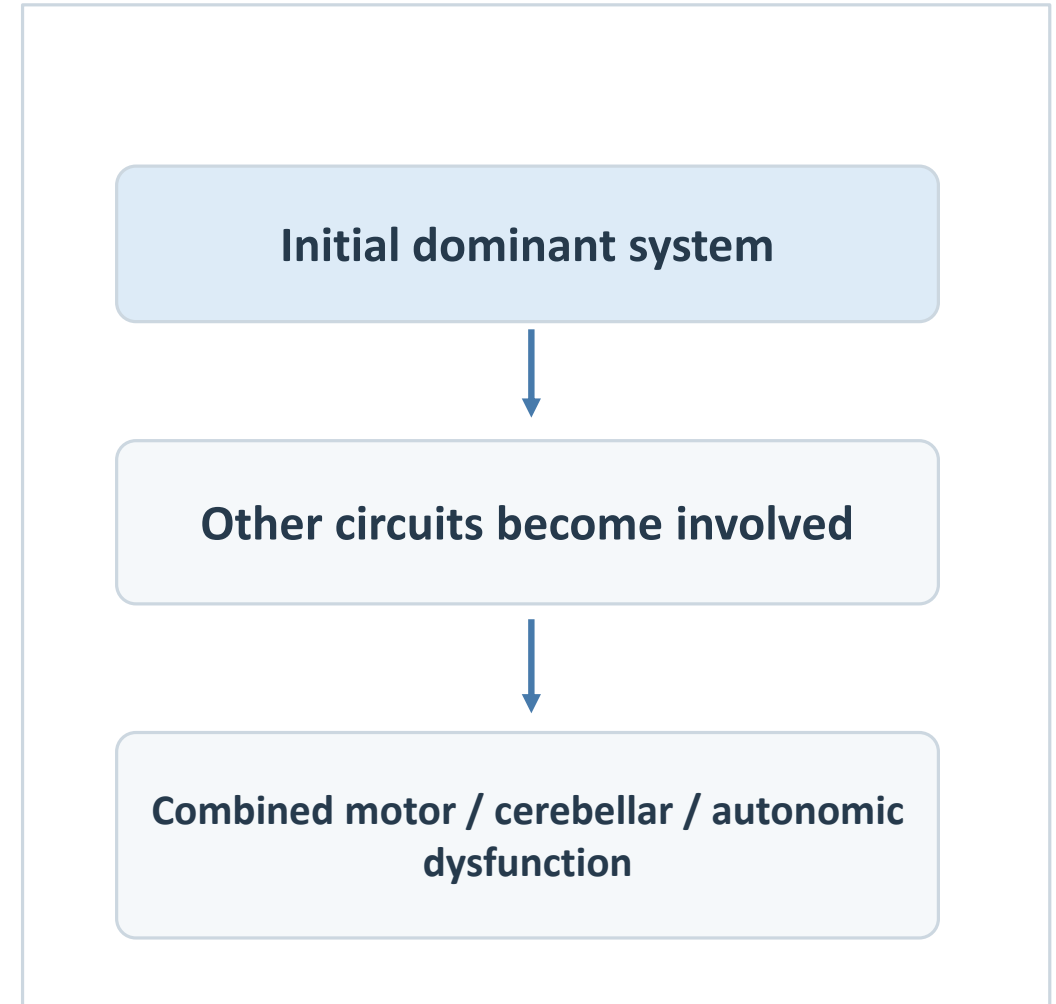
Autonomic failure has a central pathologic substrate

- Autonomic dysfunction in MSA includes degeneration of central autonomic structures.
- The medulla and spinal intermediolateral cell column are specifically implicated.
- Orthostatic hypotension is highlighted as a prominent clinical component.

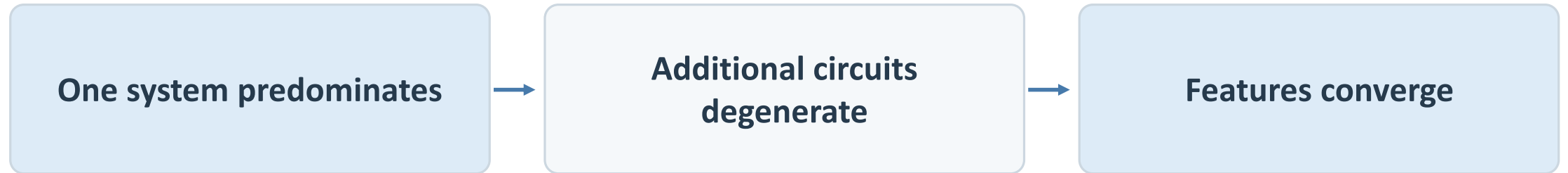


Presentations vary according to early system predominance

- One person may initially have chiefly parkinsonian manifestations.
- Another may initially have chiefly cerebellar manifestations.
- A single dominant phenotype does not imply anatomically isolated disease.



The longitudinal pattern is multisystem involvement



- That the other systems typically become affected as MSA progresses.
- This is a qualitative disease-course description—not a quantified natural-history estimate.

White matter is a primary locus of MSA pathology

- MSA as primarily affecting white matter.
- Oligodendroglial lesions are associated with degeneration of white-matter tracts.
- This contrasts with disorders chiefly recognized by neuronal inclusions.

Oligodendroglial inclusions



White matter tract degeneration

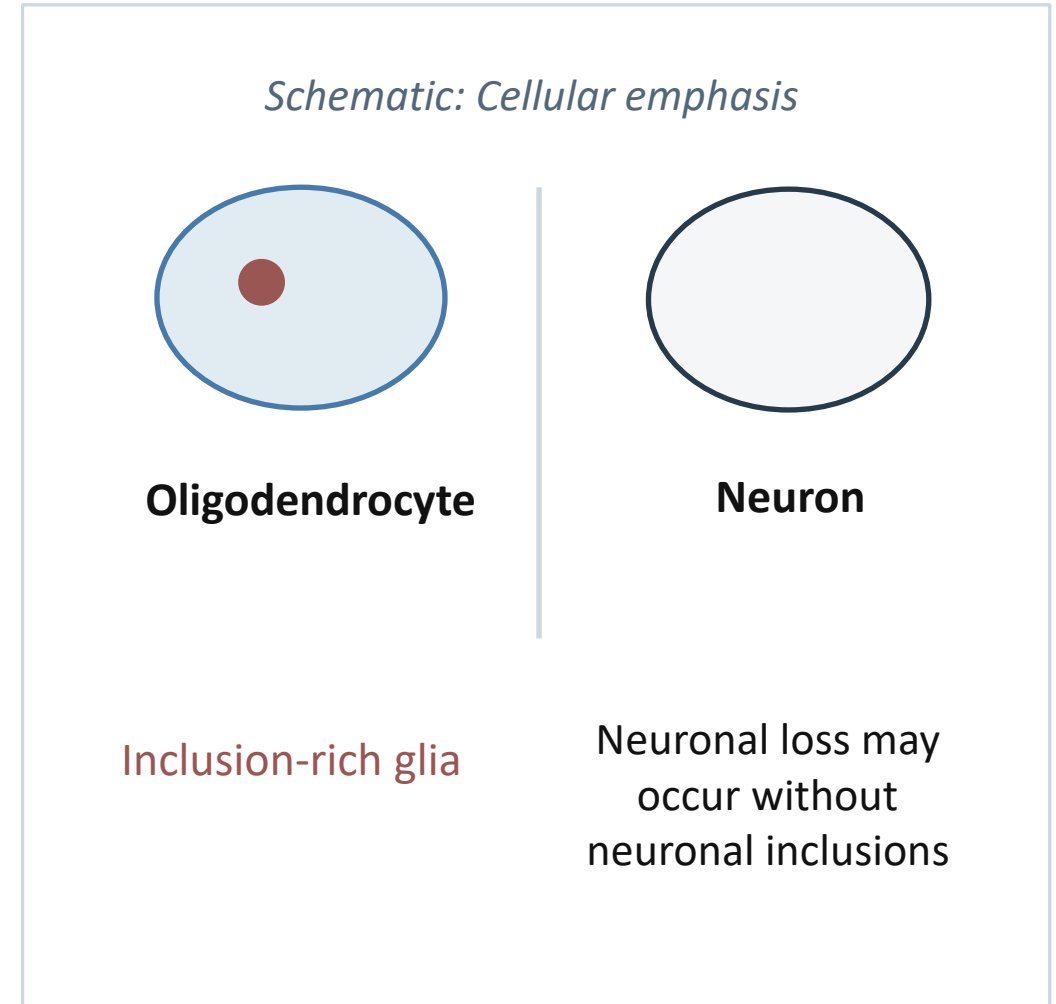


Accompanying neuronal loss

Conceptual relation; Complete causal sequence remains unresolved

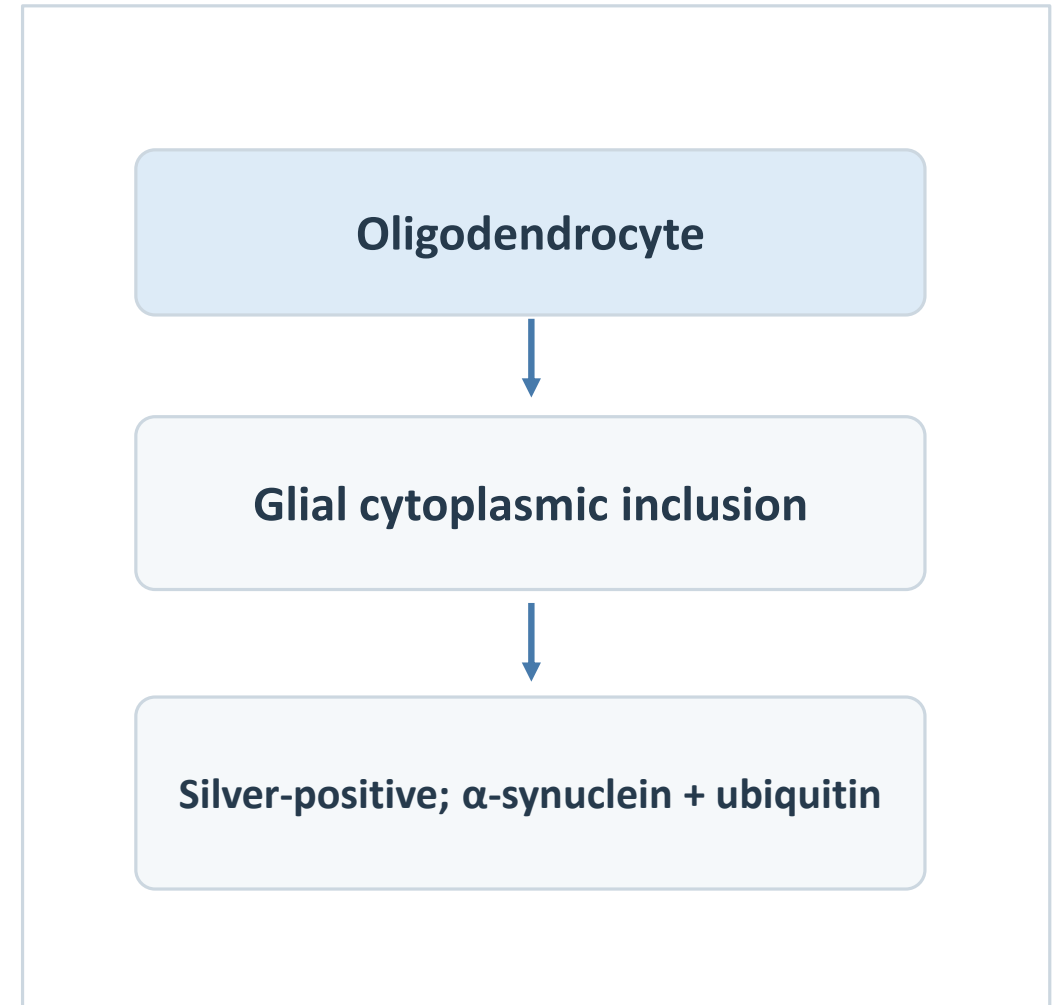
Oligodendrocytes are the principal inclusion-bearing cells

- The defining inclusions occur in the cytoplasm of oligodendrocytes.
- The importance of their glial location is diagnostic, not merely descriptive.
- Degeneration is also seen in neurons, but their inclusions are typically absent.



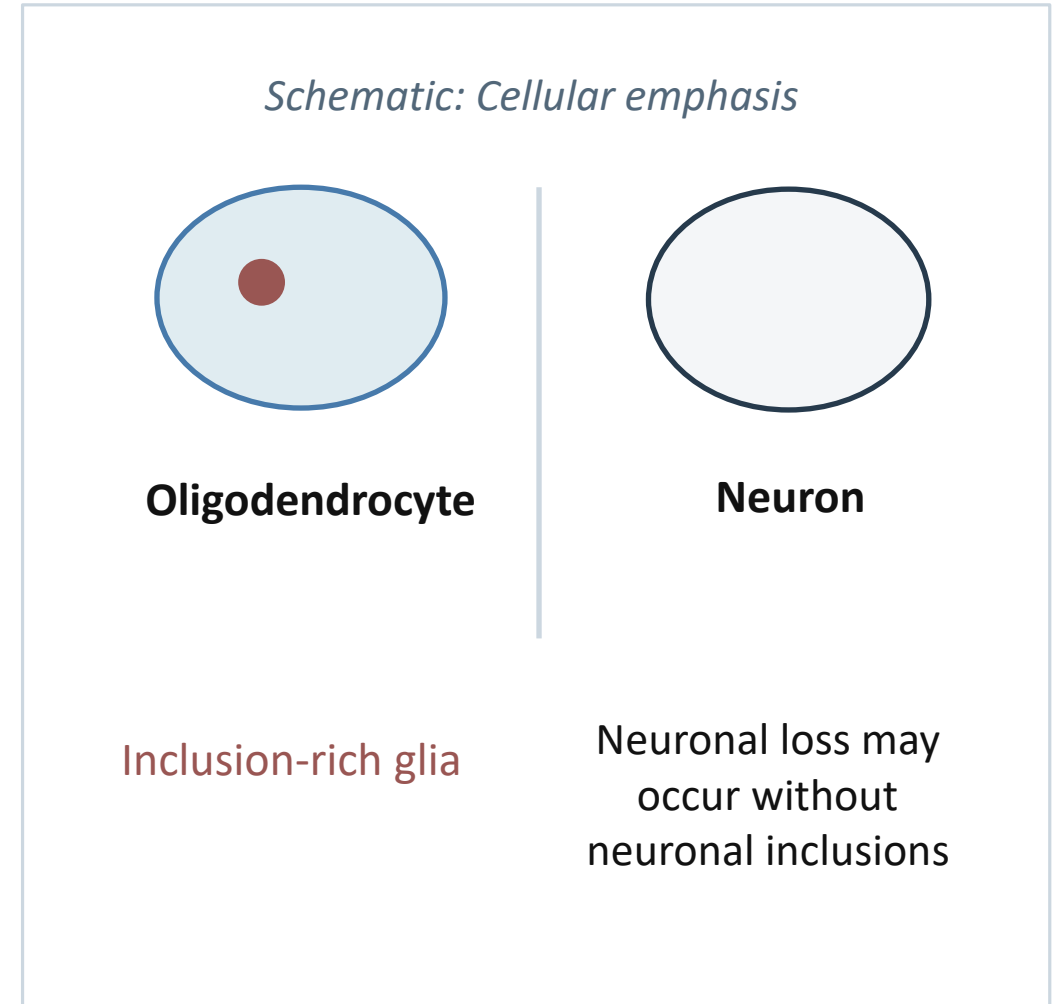
Glial cytoplasmic inclusions are the key lesion

- Glial cytoplasmic inclusions are the diagnostic histologic finding emphasized by Robbins.
- They were first demonstrated with silver impregnation methods.
- They contain aggregated α -synuclein and ubiquitin.



Subcellular localization matters

- The inclusions are cytoplasmic rather than being defined as nuclear deposits.
- The inclusion-bearing cell is oligodendroglial rather than typically neuronal.
- Identifying protein, compartment and cell type separates related neurodegenerative disorders.



α -Synuclein links MSA with Parkinson disease

- In both MSA and Parkinson disease, α -synuclein is an important aggregated protein.
- The protein is normally abundant in neurons and associated with synaptic vesicles.
- Shared protein identity should not be confused with identical disease distribution.

Normal α -synuclein

Predominantly neuronal / synaptic-vesicle associated

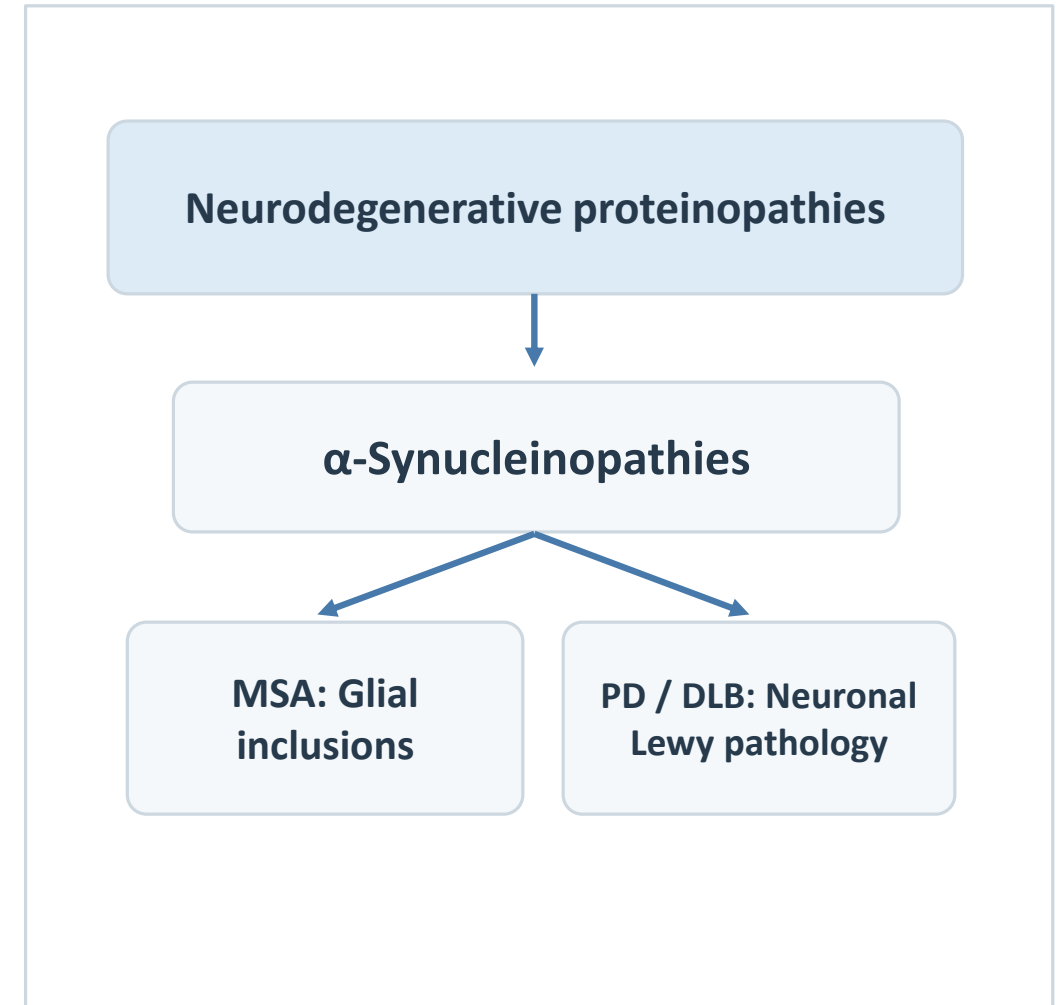


MSA: Oligodendroglial cytoplasmic aggregates

The source of glial α -synuclein is uncertain

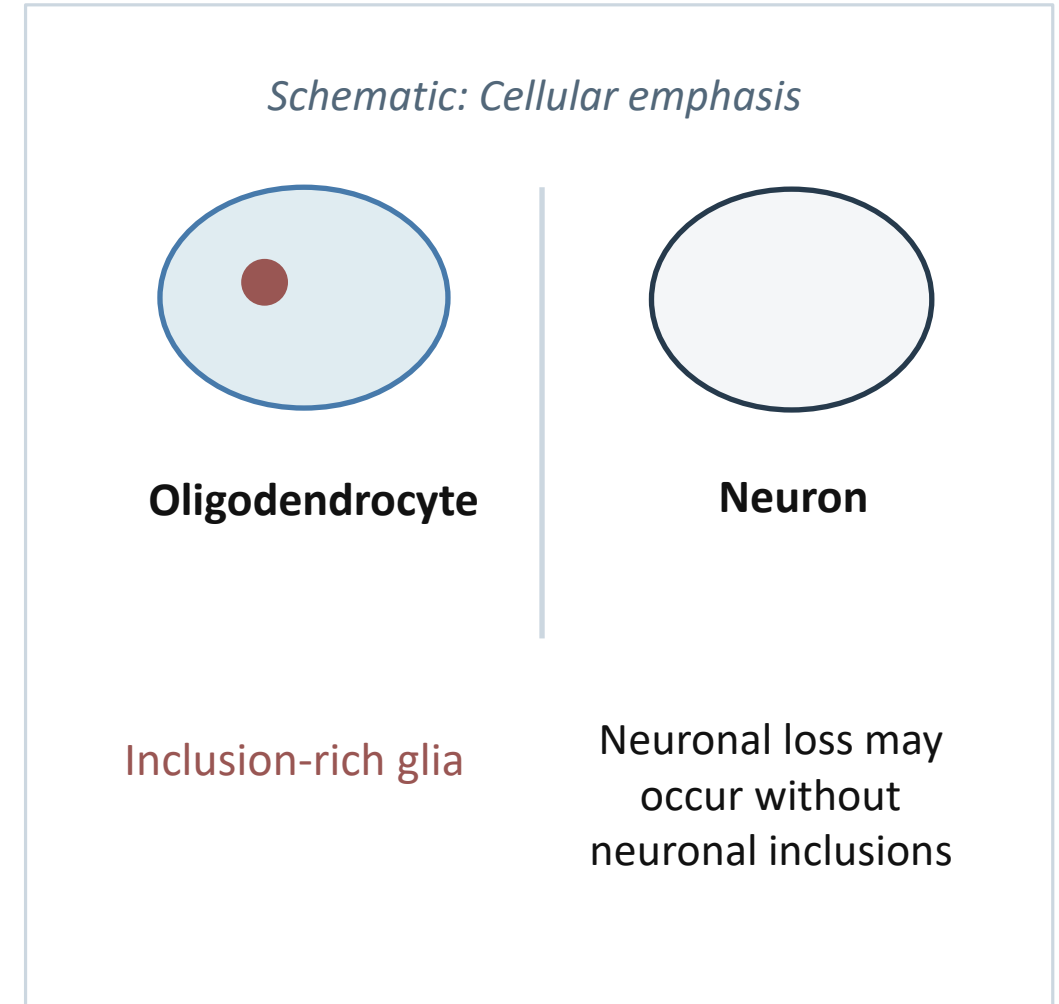
Glial inclusions distinguish MSA from Lewy pathology

- MSA centers on oligodendroglial cytoplasmic inclusions.
- Parkinson disease commonly features neuronal Lewy bodies and Lewy neurites.
- Cellular distribution is therefore crucial when interpreting α -synuclein immunoreactivity.



Neuronal degeneration accompanies glial pathology

- Neuronal degeneration alongside white-matter tract degeneration.
- Neuronal inclusions are typically absent in MSA.
- This combination cautions against interpreting absent neuronal inclusions as absent neuronal injury.



Comparing inclusion-bearing cells

MSA

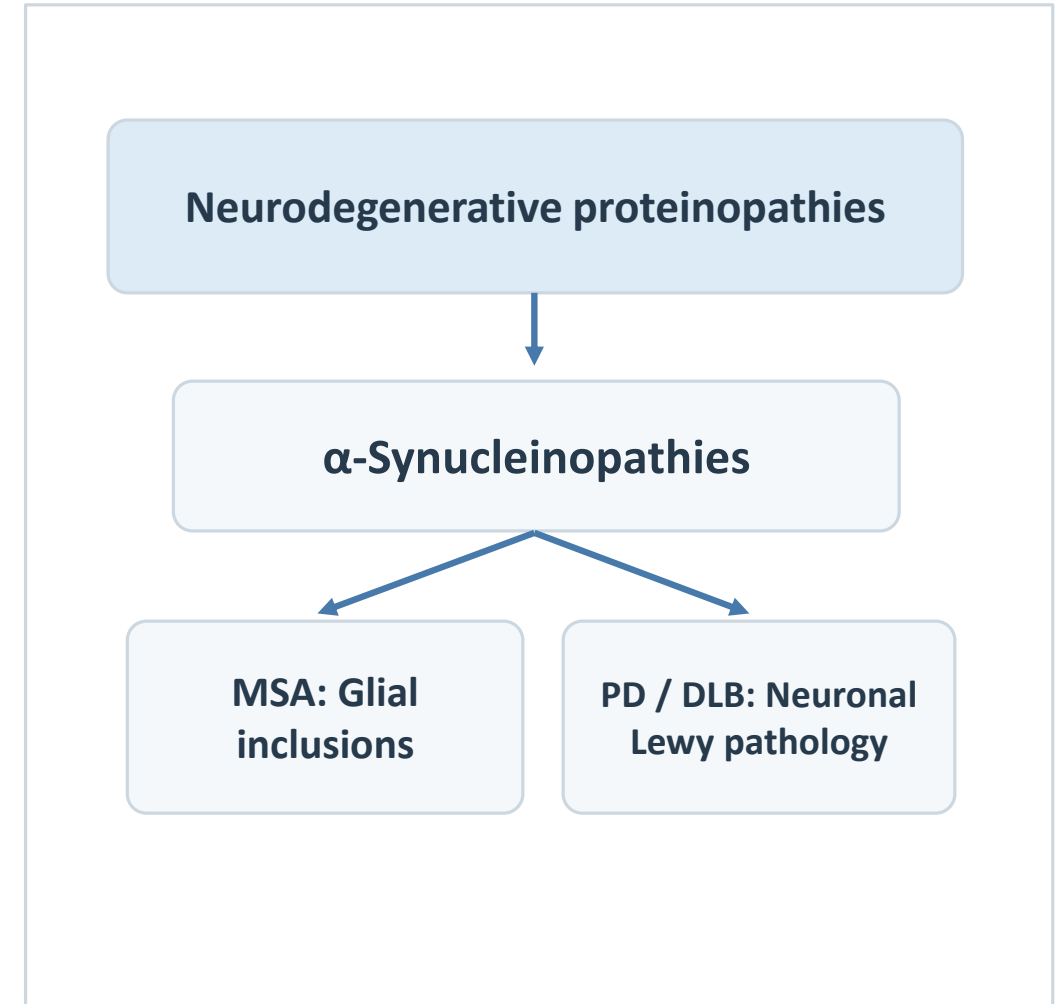
- Predominantly oligodendroglial cytoplasmic inclusions
- Degeneration of white matter tracts

Parkinson disease

- Neuronal Lewy bodies and Lewy neurites
- Prominent substantia nigra neuron loss

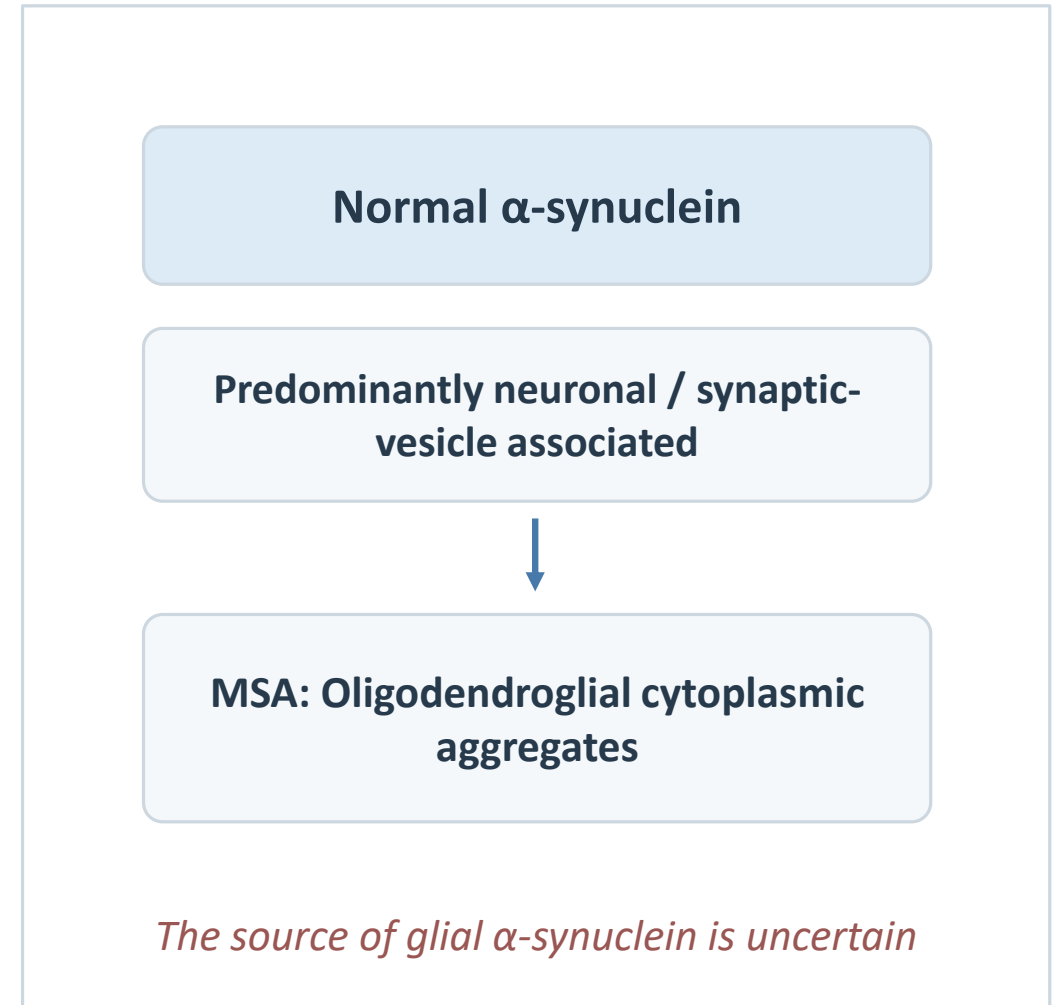
Dementia with Lewy bodies is another α -synucleinopathy

- DLB exhibits α -synuclein-containing neuronal Lewy pathology in cortex and brainstem.
- MSA instead emphasizes oligodendroglial inclusions.
- The shared protein should be interpreted with distribution and cell identity.



α -Synuclein folds differ among disease spectra

- PD and DLB share a molecular α -synuclein fold.
- This fold differs from the α -synuclein fold observed in MSA.
- The statement supports molecular diversity within synucleinopathies; It does not define a routine clinical test.



MSA is described as a sporadic disorder

- The MSA section does not identify an established Mendelian cause.
- It discusses risk-associated polymorphisms near the α -synuclein gene.
- It specifically states that causative mutations in the gene encoding α -synuclein had not been identified for MSA.

Risk association is not monogenic causation

- Polymorphisms near the gene for α -synuclein appear to confer increased MSA risk.
- An association does not establish sufficient or necessary causation.
- This evidence should not be presented as a validated genetic diagnostic test.

Interpreting the genetic statements

Supported by text

- Near-gene polymorphisms appear associated with MSA risk
- The entity is usually sporadic

Not established in text

- A causative SNCA mutation responsible for MSA
- Any clinical genetic cutoff or test sensitivity

Glial inclusions track with disease progression

- The burden of glial cytoplasmic inclusions increases as the disease advances.
- This association links the characteristic lesion to disease activity.
- It does not alone prove that every inclusion directly damages its host cell.

Observation

Inclusion burden rises as disease progresses

Observation

Glial inclusions may occur without neuronal loss

Inclusions may precede overt neuronal loss

- Glial cytoplasmic inclusions can occur without neuronal loss.
- This observation is consistent with a glial-first pathological event.
- Interpretation of event order remains inferential rather than a direct time-lapse demonstration.

Observation

Inclusion burden rises as disease progresses

Observation

Glial inclusions may occur without neuronal loss

What the evidence supports—and does not prove

- Increasing inclusion burden and detection without neuronal loss support an early glial role.
- They do not establish a complete, exclusive causal pathway from aggregate to neuron death.
- The initiating source of the aggregated protein remains unresolved.

Observation

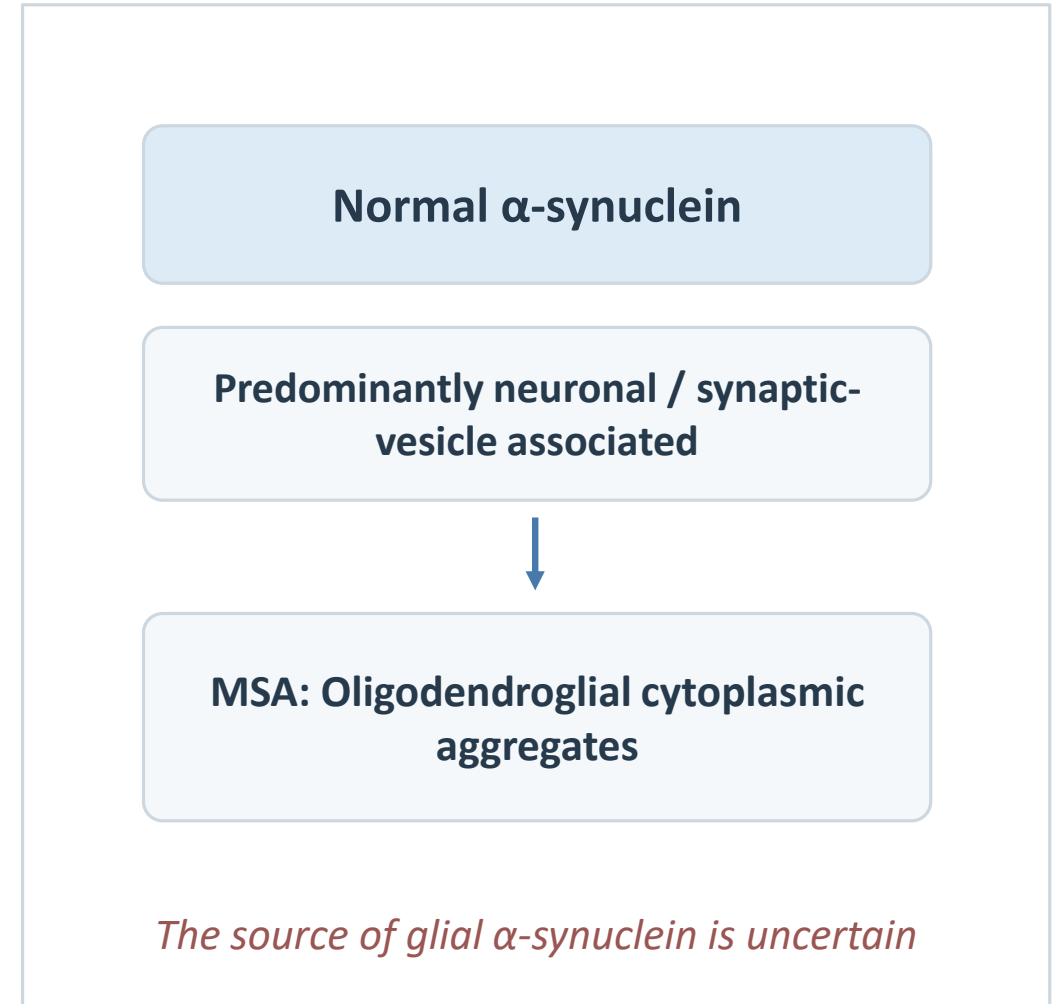
Inclusion burden rises as disease progresses

Observation

Glial inclusions may occur without neuronal loss

α -Synuclein in oligodendrocytes poses a mechanistic puzzle

- α -Synuclein is normally characterized as a neuronal synaptic-associated protein.
- MSA places abundant α -synuclein aggregates within oligodendrocytes.
- The mismatch between normal localization and pathologic compartment raises the question of protein origin.



Oligodendroglial α -synuclein expression is not increased

- Studies showing no α -synuclein expression upregulation in white matter.
- The studies also find no upregulation within oligodendrocytes.
- These observations argue against simple local overexpression as an adequate explanation.

Normal α -synuclein

Predominantly neuronal / synaptic-vesicle associated

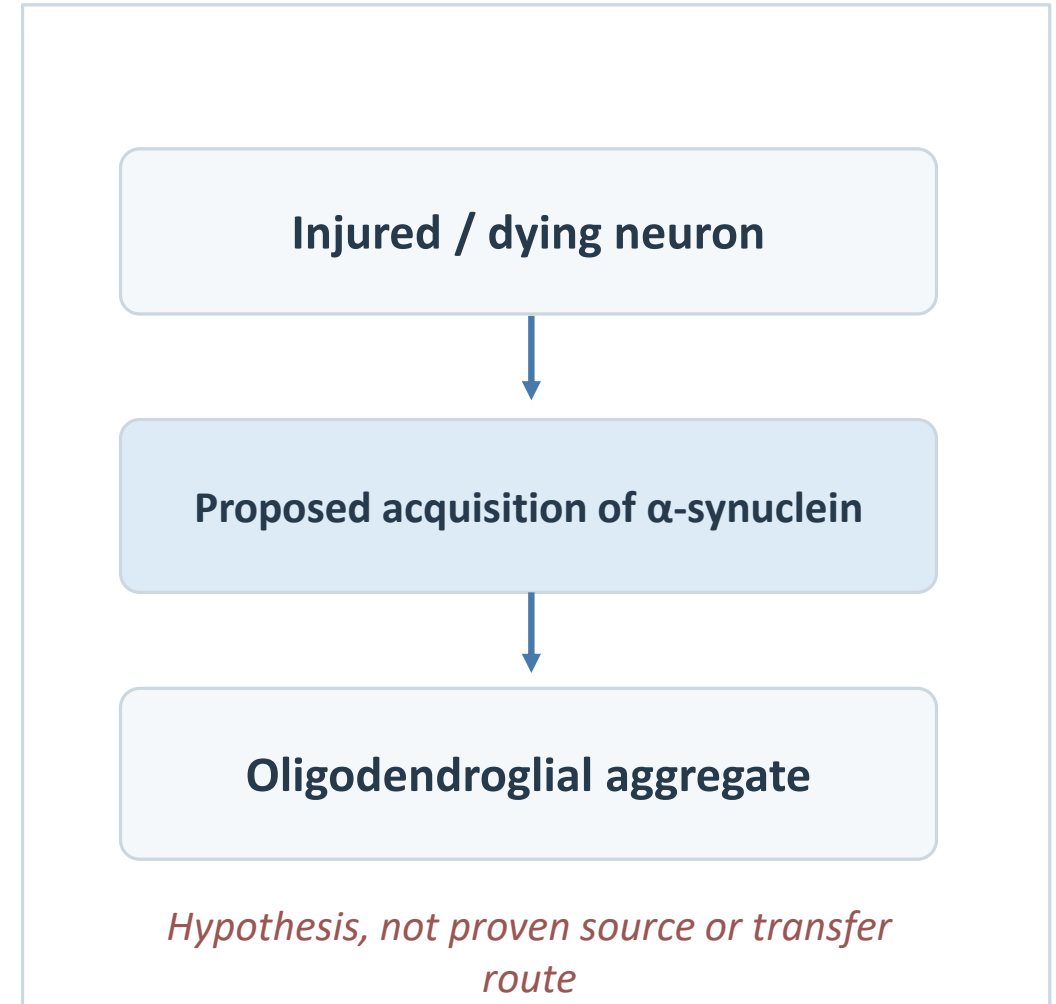


MSA: Oligodendroglial cytoplasmic aggregates

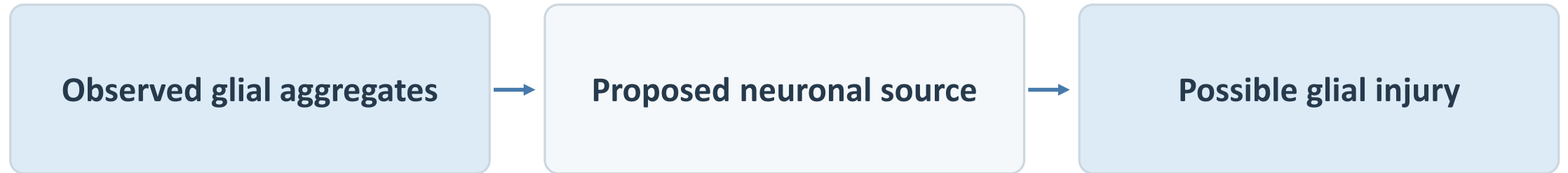
The source of glial α -synuclein is uncertain

Secondary protein acquisition is proposed, not proven

- A hypothesis is that oligodendrocytes acquire α -synuclein from injured or dying neurons.
- The hypothesis is motivated partly by the lack of detected glial upregulation.
- The text does not establish the exact transfer mechanism or causal chronology.



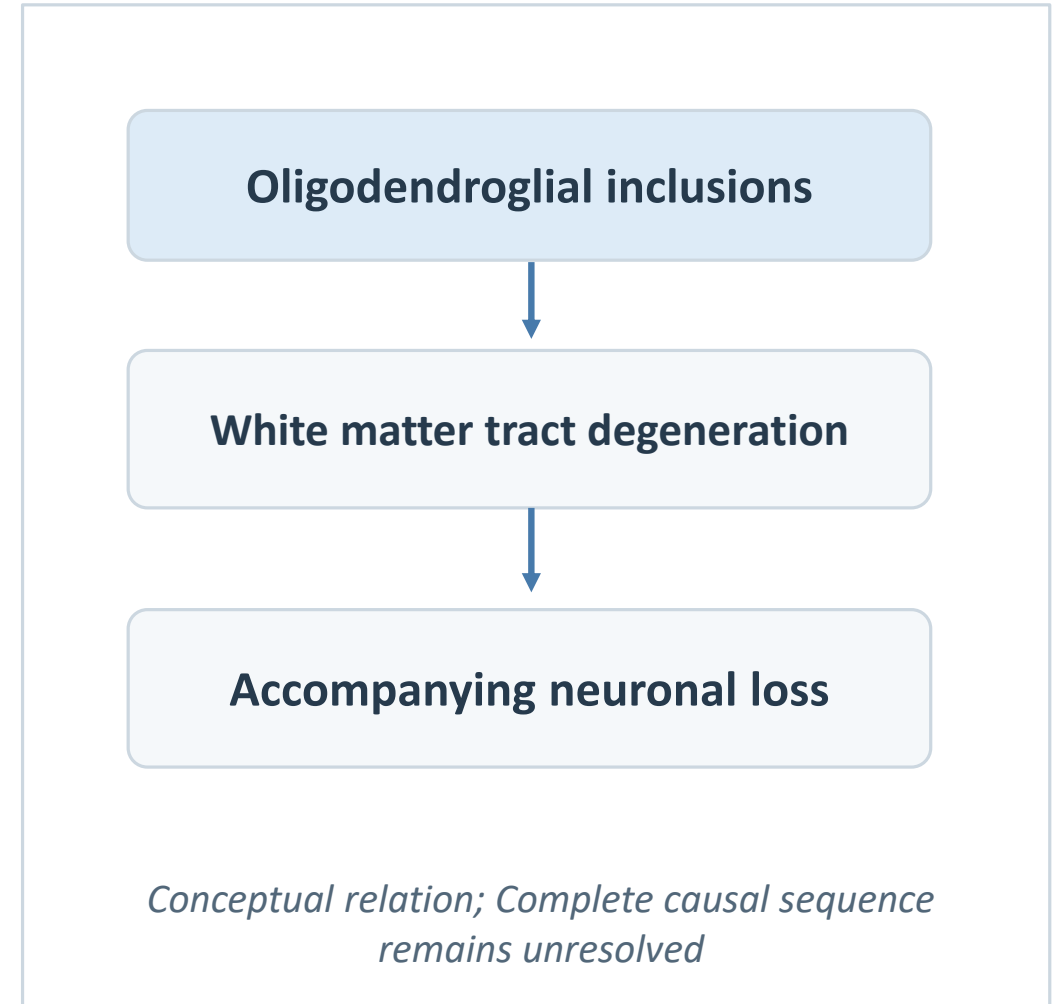
Mechanistic interpretation: Keep certainty levels separate



- Inclusions and selected cellular consequences are observed; Transfer from neurons remains a proposed origin.
- Do not convert this teaching flow into a claim of fully demonstrated causation.

Inclusion-bearing oligodendrocytes are stress-sensitive

- When α -synuclein is present in oligodendrocytes, susceptibility to oxidative stress increases.
- This provides one plausible link between aggregate accumulation and glial vulnerability.
- It does not quantify the contribution of oxidative injury to neuronal loss.



Extracellular matrix interactions are disrupted

- α -Synuclein-containing oligodendrocytes exhibit impaired interaction with the extracellular matrix.
- This is another glial cellular disturbance mentioned by Robbins.
- The contribution of matrix dysfunction to regional neurodegeneration is not fully resolved in the excerpt.

Oligodendroglial inclusions



White matter tract degeneration

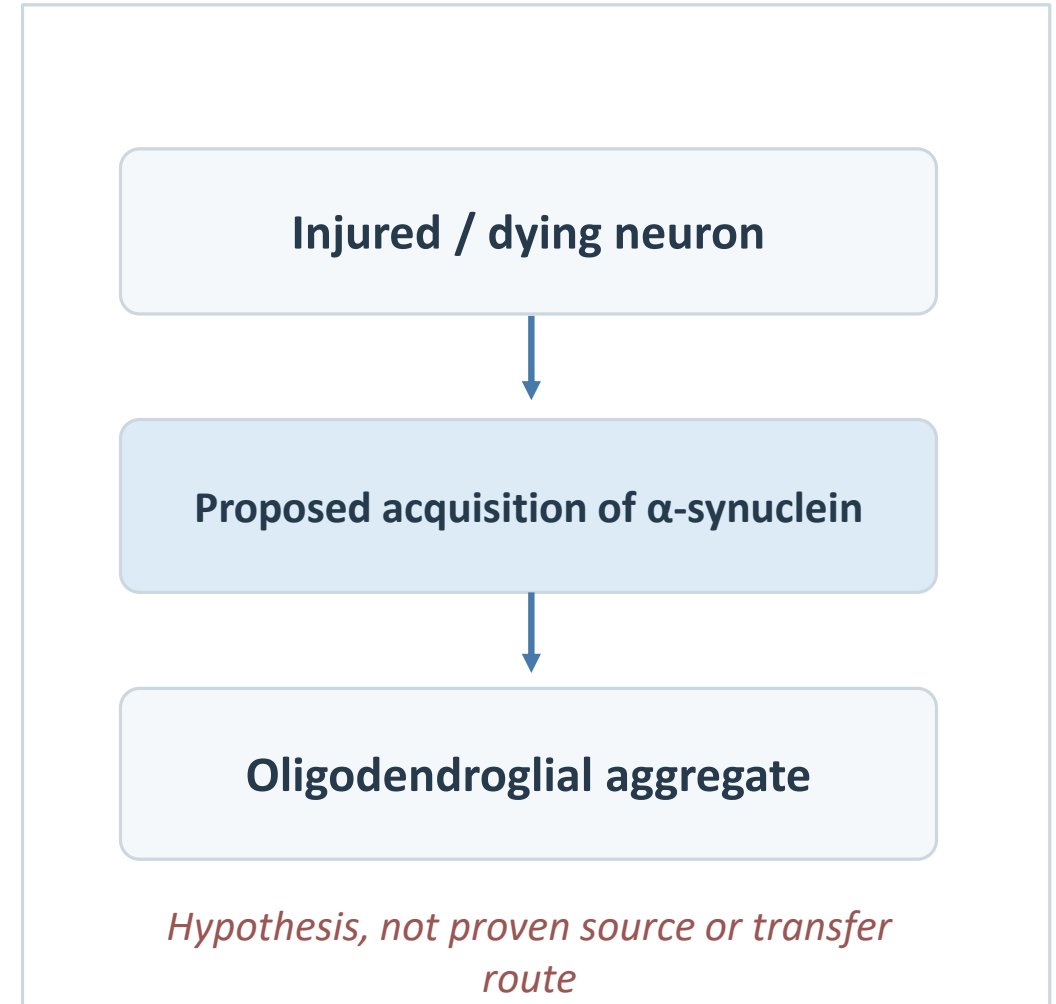


Accompanying neuronal loss

Conceptual relation; Complete causal sequence remains unresolved

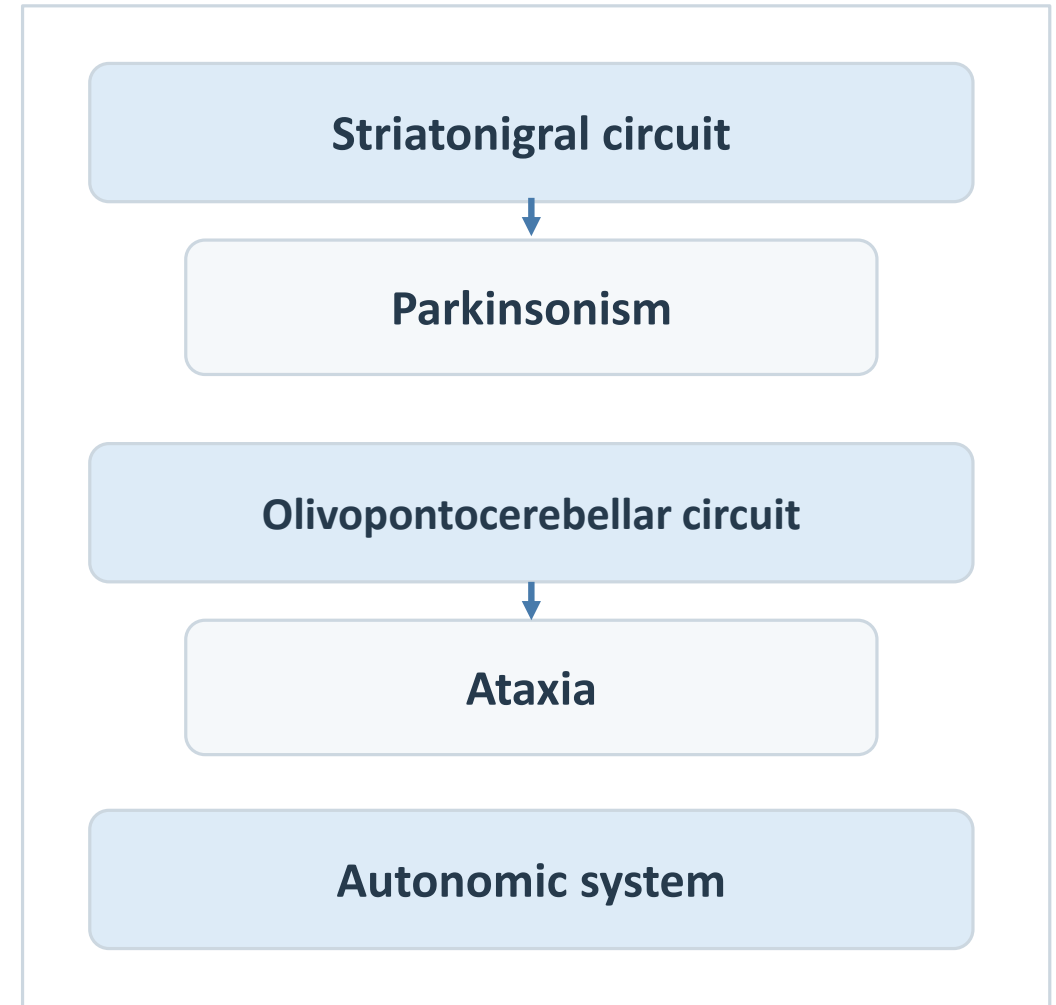
Integrating the MSA pathogenesis model

- Characteristic distribution: α -synuclein aggregates are chiefly oligodendroglial.
- Disease association: Aggregate burden increases with progression.
- Potential injury mechanisms include oxidative vulnerability and impaired matrix interactions.
- The origin of oligodendroglial α -synuclein remains an open question.



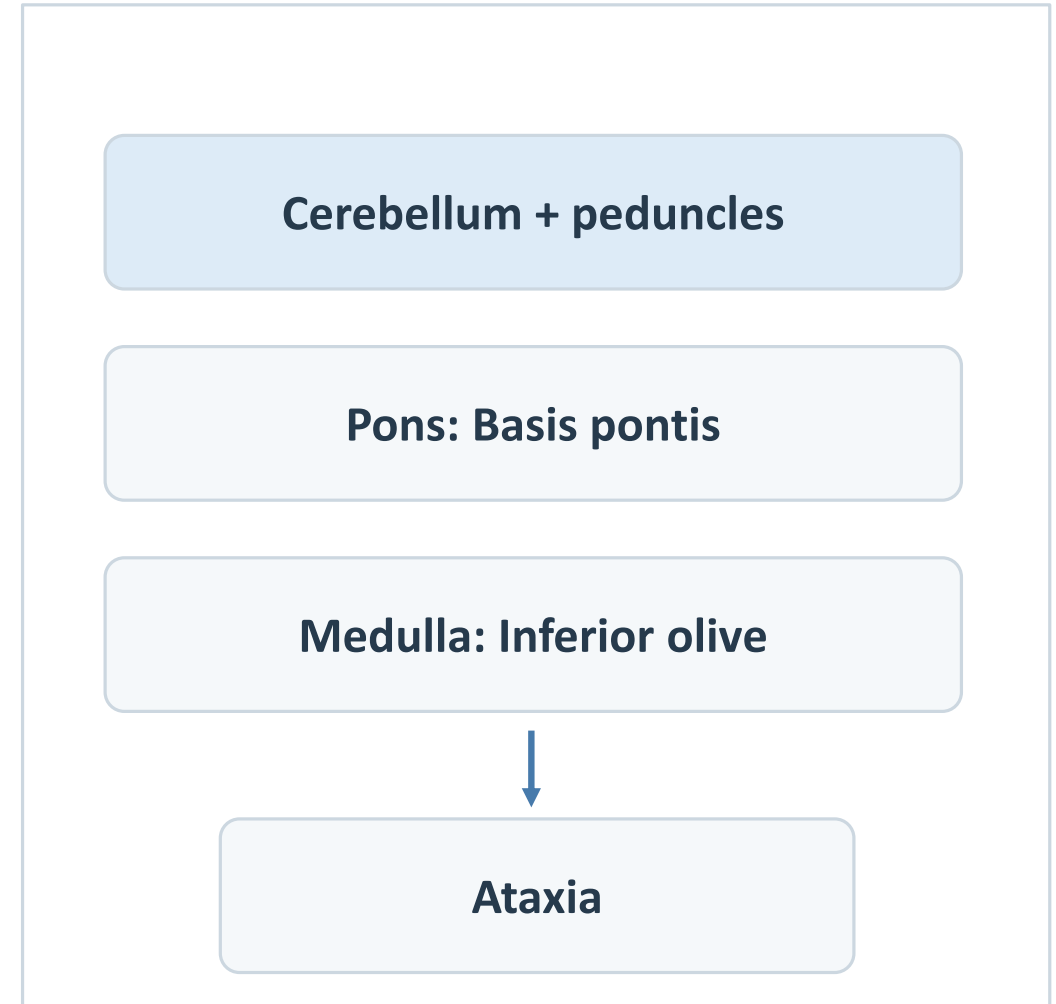
Neuroanatomic distribution predicts the clinical phenotype

- The most involved system in a given case tends to match its clinical presentation.
- Robbins separates cerebellar, parkinsonian and autonomic regional pathology.
- Integrated topography is more informative than one isolated histologic observation.



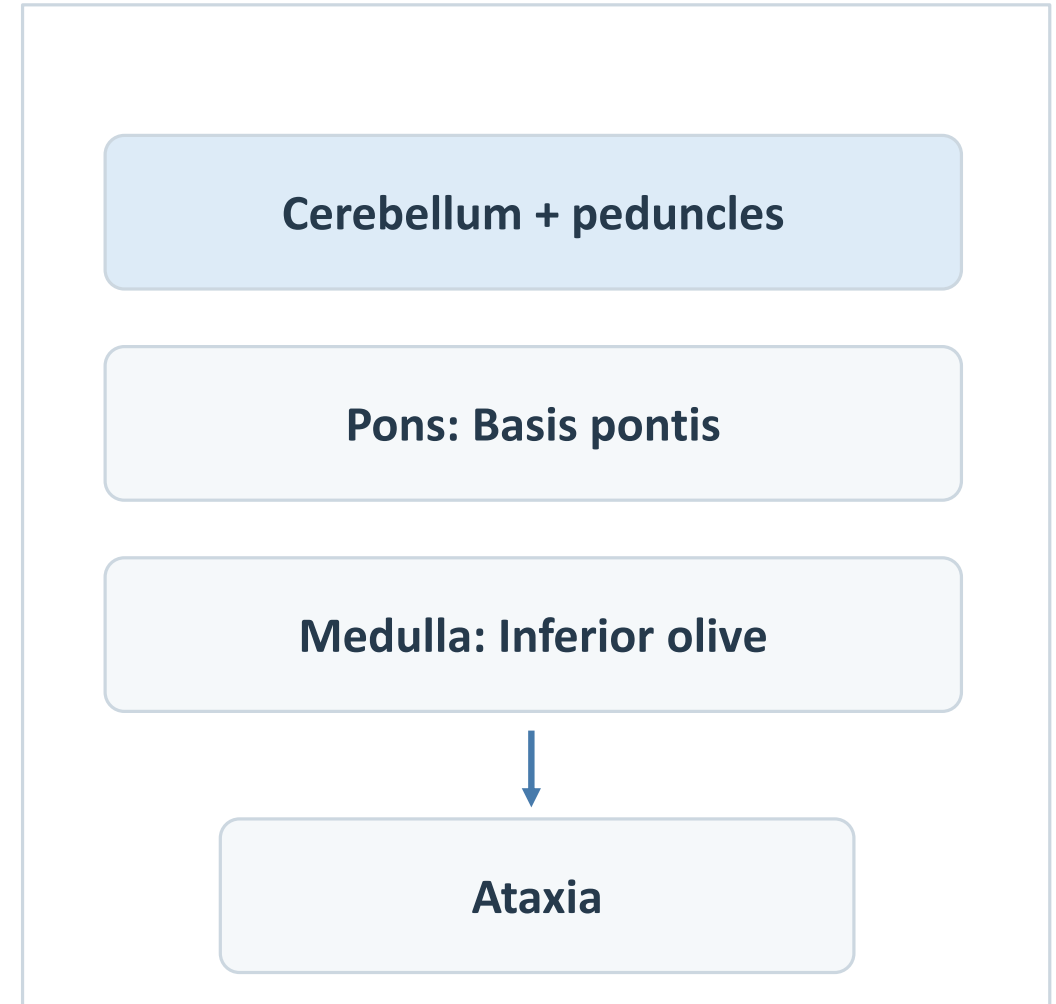
Cerebellar-predominant MSA: Regional atrophy

- Atrophy affects the cerebellum and cerebellar peduncles.
- The pons is involved, especially its base.
- Medullary involvement includes the inferior olive.



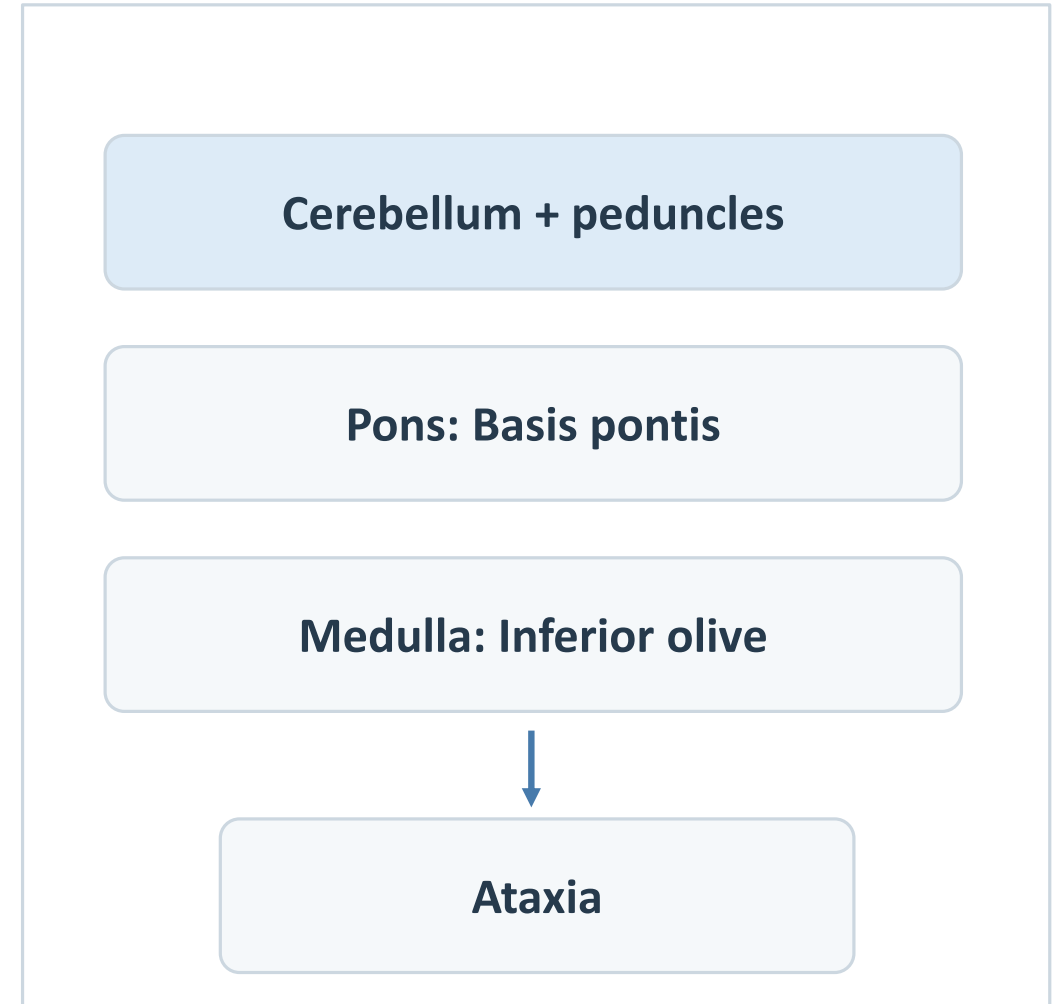
Pontine atrophy especially affects the basis pontis

- The basis pontis is specifically emphasized in the gross morphology description.
- The textbook's Fig. 28.41A depicts severe basis pontis atrophy.
- The current slide uses an editable location schematic rather than reproducing the copyrighted gross image.



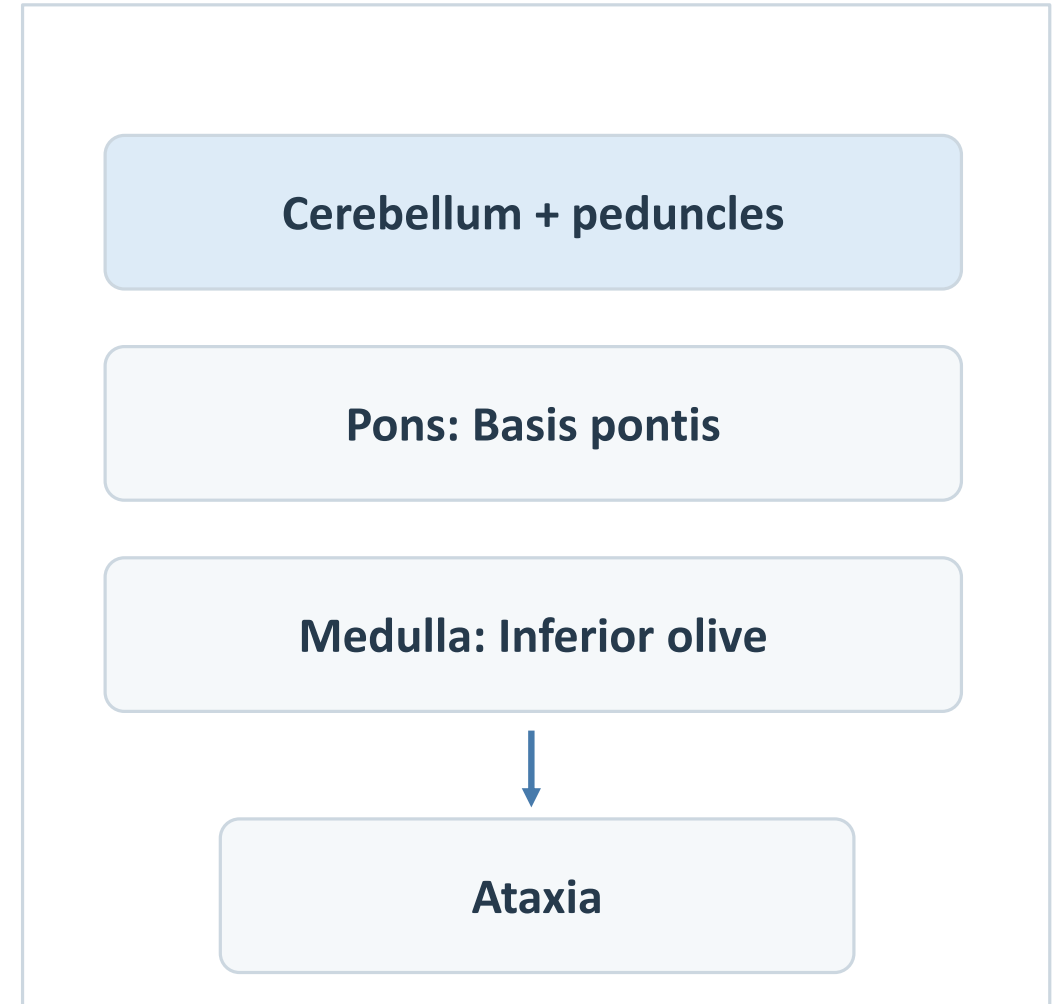
Cerebellar peduncles belong to the atrophic system

- The cerebellar peduncles are included among the atrophic structures in cerebellar forms.
- Their involvement is anatomically consistent with disruption of cerebellar connections.
- No specific tract-by-tract microscopic pattern is specified in the provided text.



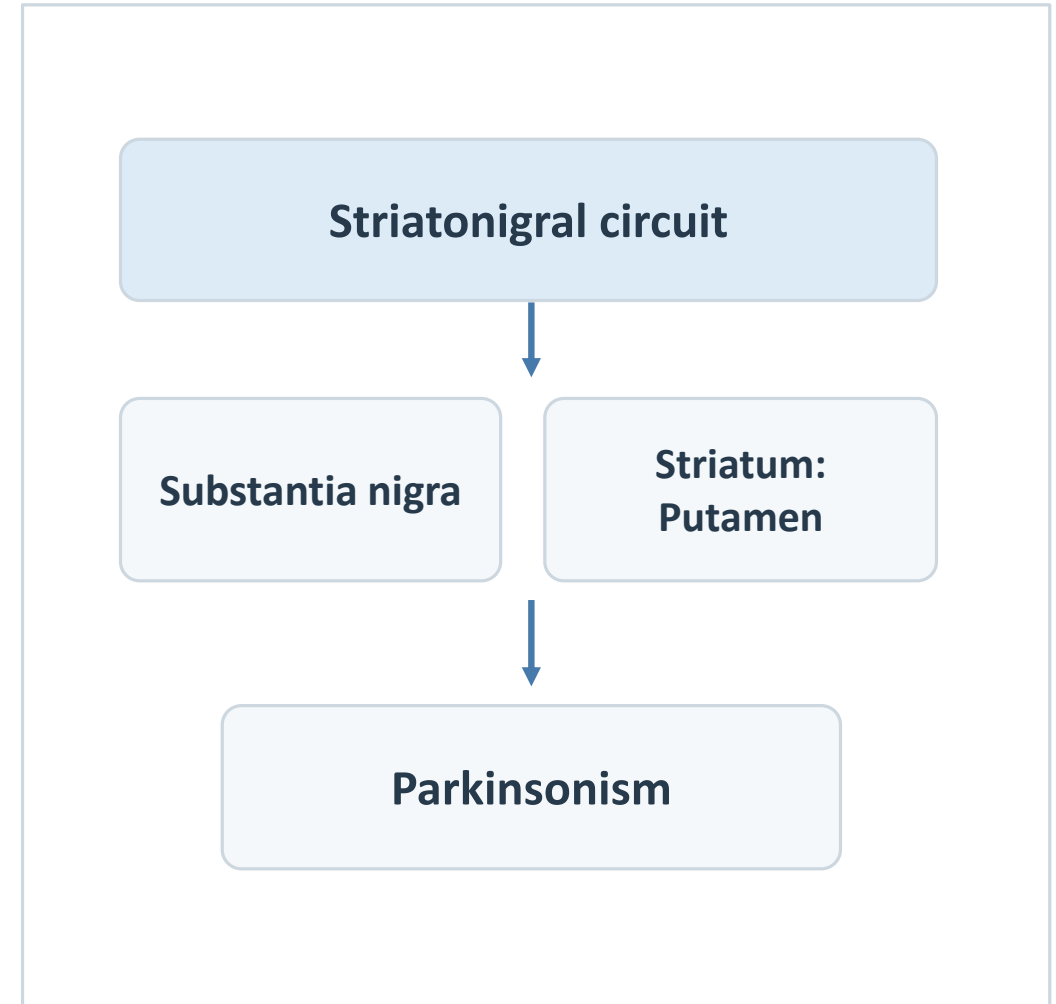
Inferior olivary atrophy identifies medullary involvement

- In cerebellar forms, the medulla may atrophy, especially the inferior olive.
- The inferior olive is part of the olivopontocerebellar distribution named by Robbins.
- This lesion localizes degeneration beyond the cerebellar cortex.



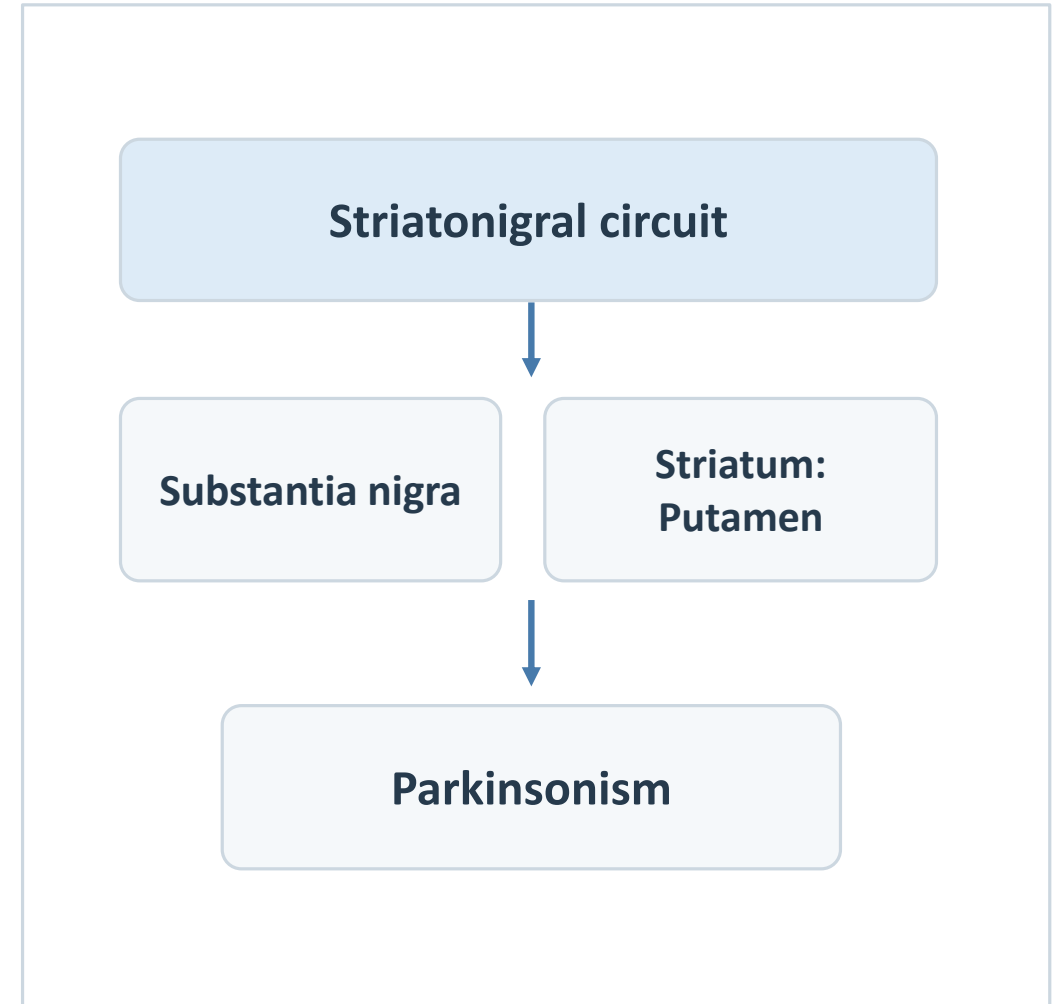
Parkinsonian-predominant MSA: Striatonigral atrophy

- Atrophy involves the substantia nigra and striatum.
- The putamen is particularly emphasized among striatal structures.
- This distribution matches the parkinsonian clinical component.



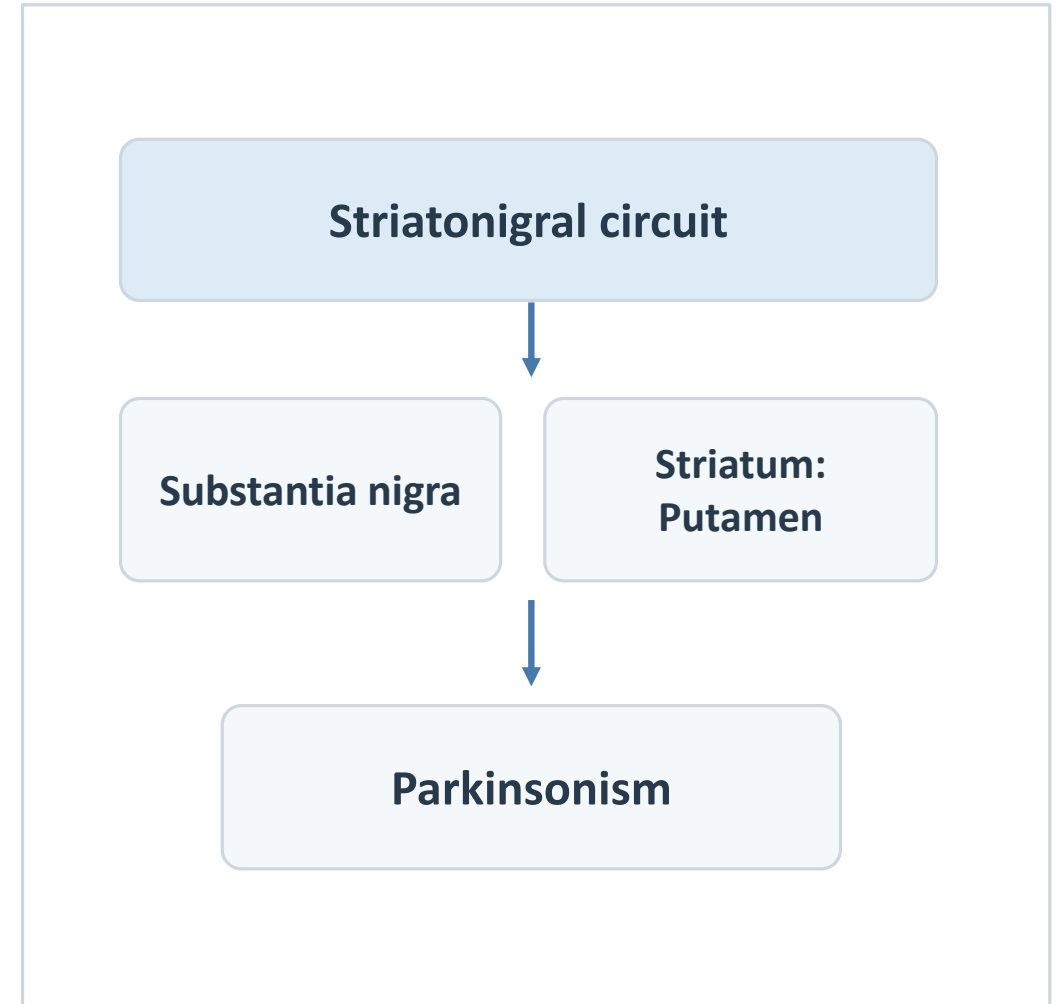
Substantia nigra degeneration is not unique to PD

- The substantia nigra can be affected in both MSA and Parkinson disease.
- In MSA, nigral loss is embedded in a wider oligodendroglial disease process.
- This is why pigment-cell loss or parkinsonism alone cannot distinguish the two entities.



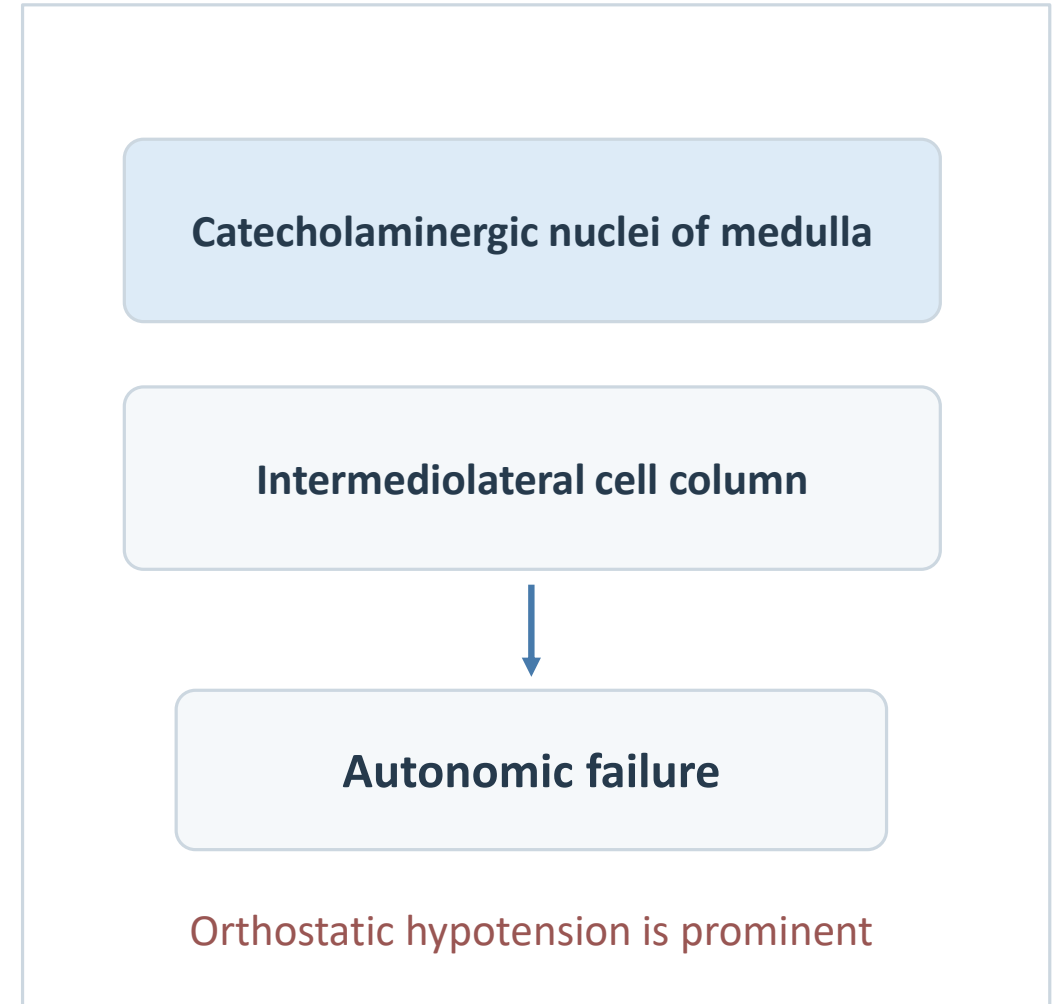
Putaminal involvement characterizes the striatal component

- The striatum—especially the putamen—is an emphasized atrophic site in parkinsonian forms.
- This localization complements nigral degeneration within the striatonigral system.
- Anatomy and glial inclusion pathology must be interpreted together.



Autonomic medullary nuclei contribute to dysfunction

- Loss of catecholaminergic nuclei in the medulla is related to autonomic symptoms.
- This anchors autonomic dysfunction to central nervous system degeneration.
- The source does not specify a single exclusive medullary nucleus as the cause of all symptoms.



The intermediolateral cell column is involved

- Loss in the intermediolateral cell column of the spinal cord.
- This spinal involvement extends MSA pathology beyond supraspinal circuits.
- It contributes to the anatomic explanation for autonomic failure.

Catecholaminergic nuclei of medulla

Intermediolateral cell column

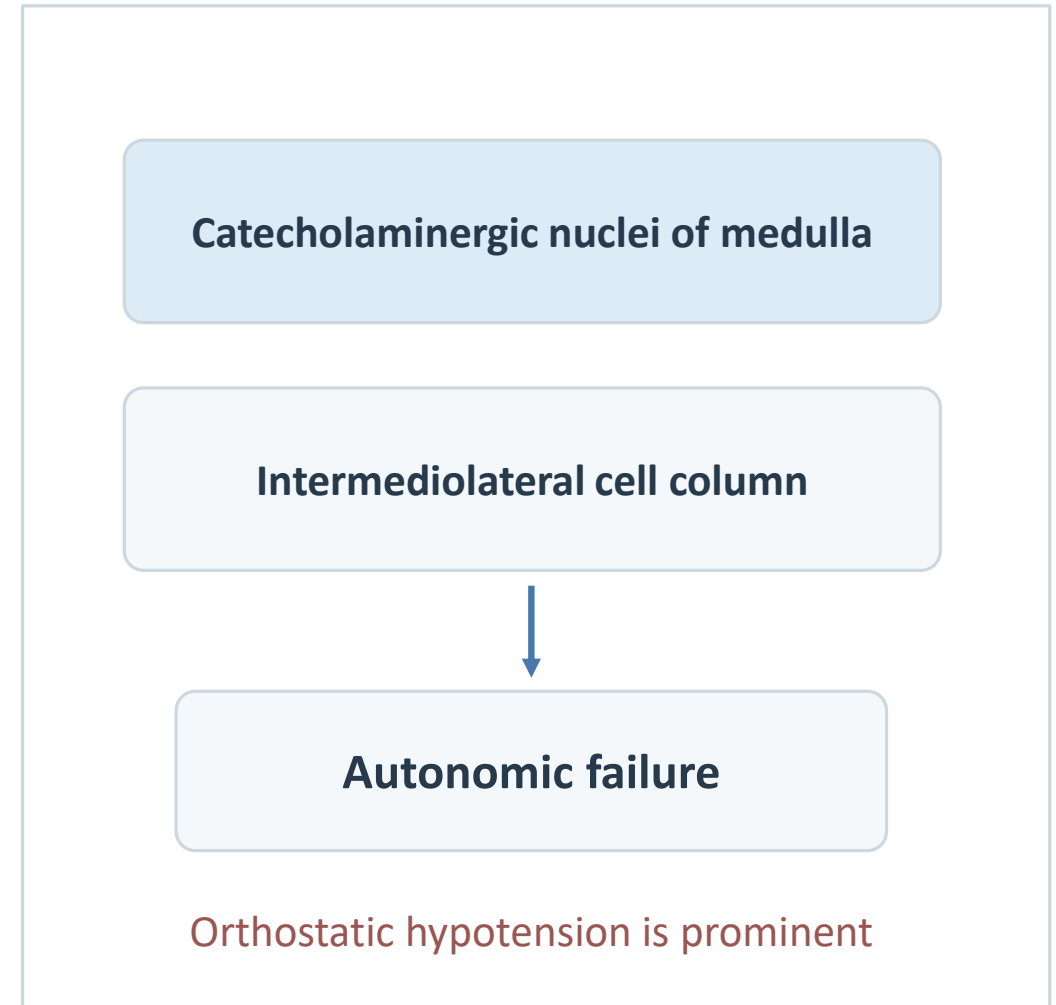


Autonomic failure

Orthostatic hypotension is prominent

Orthostatic hypotension: The highlighted autonomic manifestation

- Orthostatic hypotension is the autonomic symptom specifically highlighted in the MSA overview.
- The source relates autonomic features to degeneration of medullary and spinal central pathways.
- No blood-pressure thresholds or formal diagnostic criteria are supplied by the source passage.



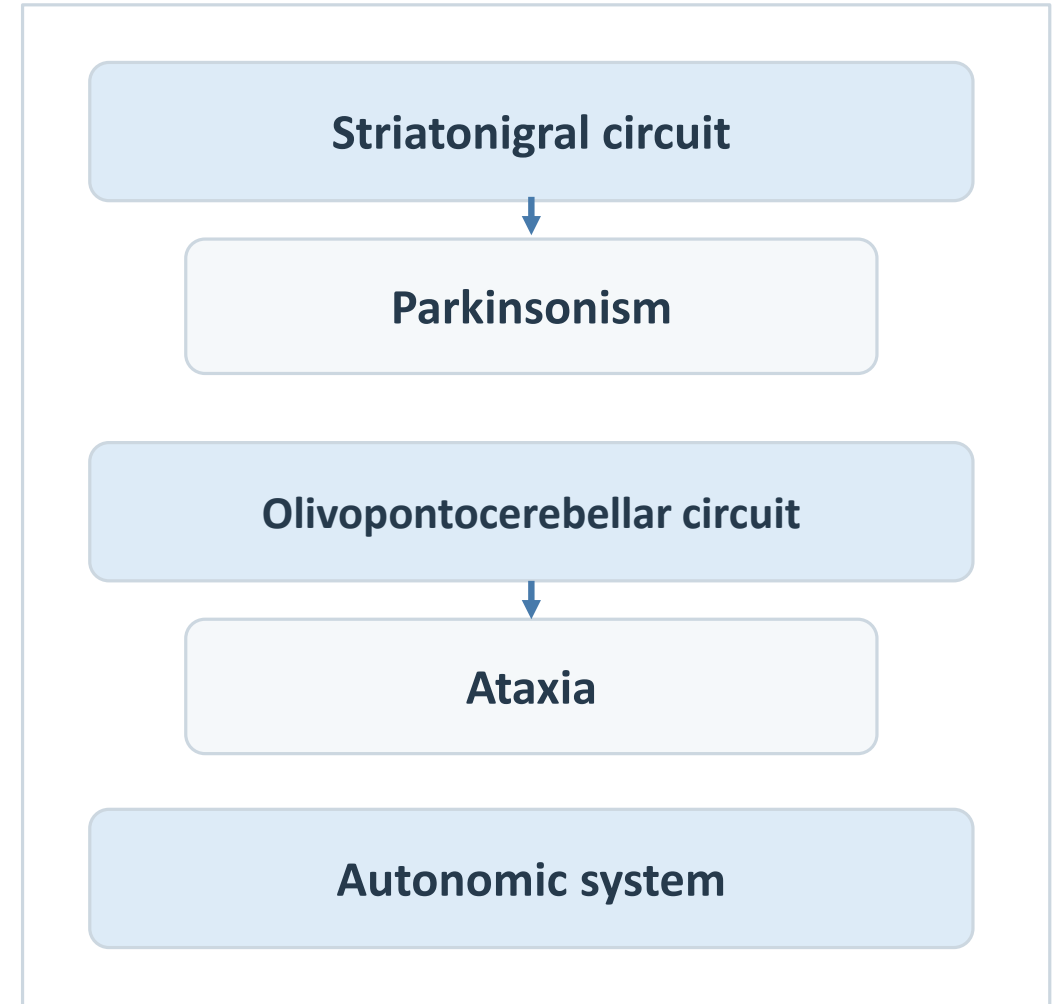
Clinicopathologic localization

System	Prominent pathologic sites	Linked clinical finding
Striatonigral	Substantia nigra; striatum, especially putamen	Parkinsonism
Olivopontocerebellar	Cerebellum; peduncles; basis pontis; inferior olive	Ataxia
Autonomic	Medullary catecholaminergic nuclei; spinal intermediolateral column	Autonomic failure; orthostatic hypotension

Site-to-sign links are from the textbook; This table is an original editable synthesis.

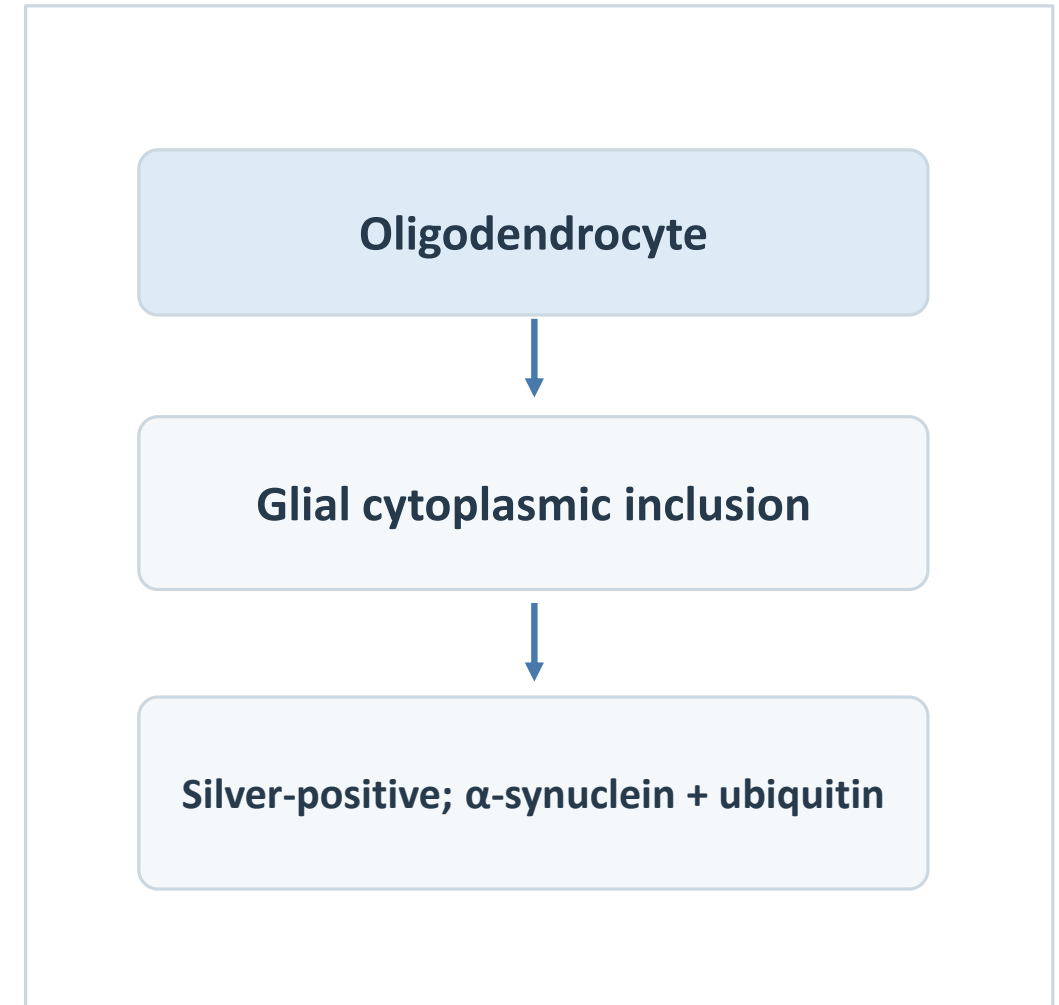
MSA morphology follows the leading clinical syndrome

- Cases with ataxia can show prominent pontocerebellar and olivary atrophy.
- Cases with parkinsonism can show conspicuous striatonigral atrophy.
- The shared inclusion pathology underlies heterogeneous regional expression.



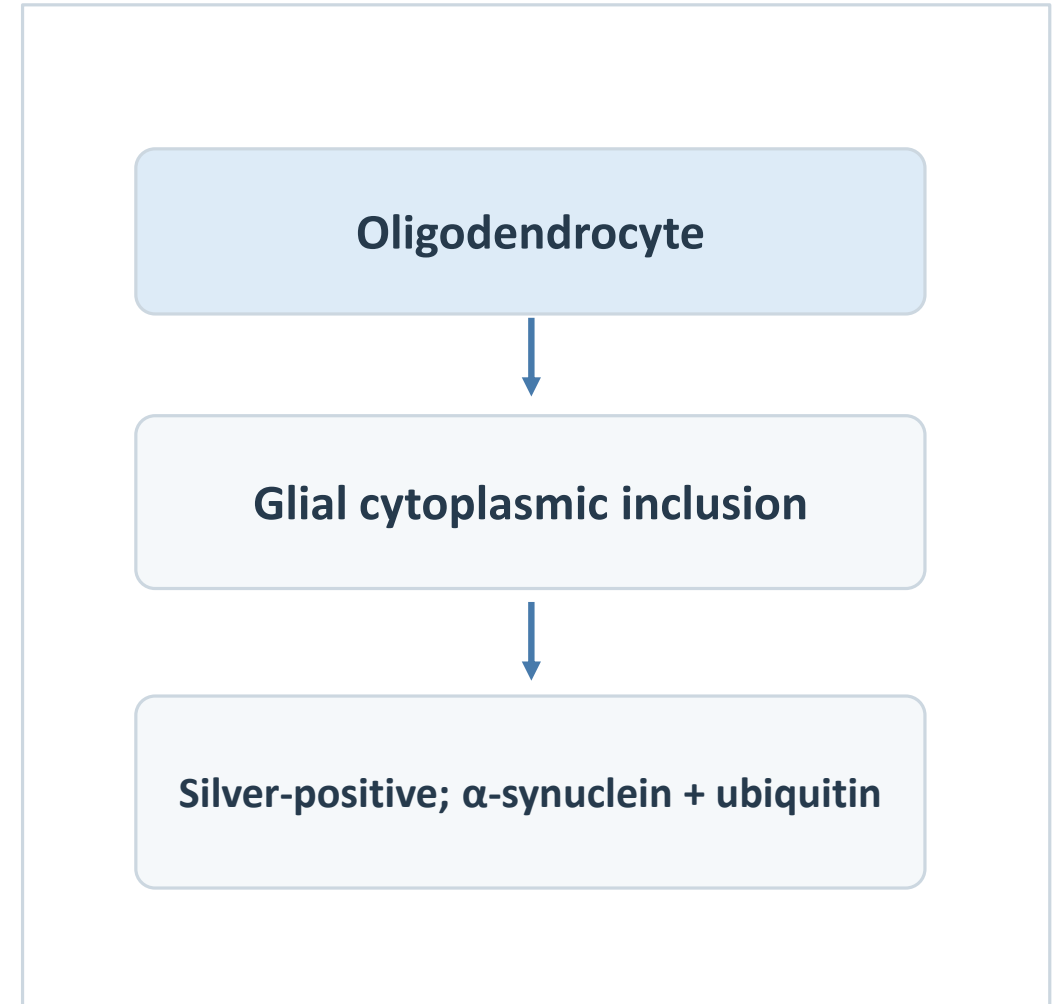
Silver impregnation historically revealed glial inclusions

- Glial cytoplasmic inclusions were originally detected by silver impregnation methods.
- Recognition of the affected glial cell type remains central to their interpretation.
- Silver staining identifies an inclusion but does not independently specify its biochemical components.



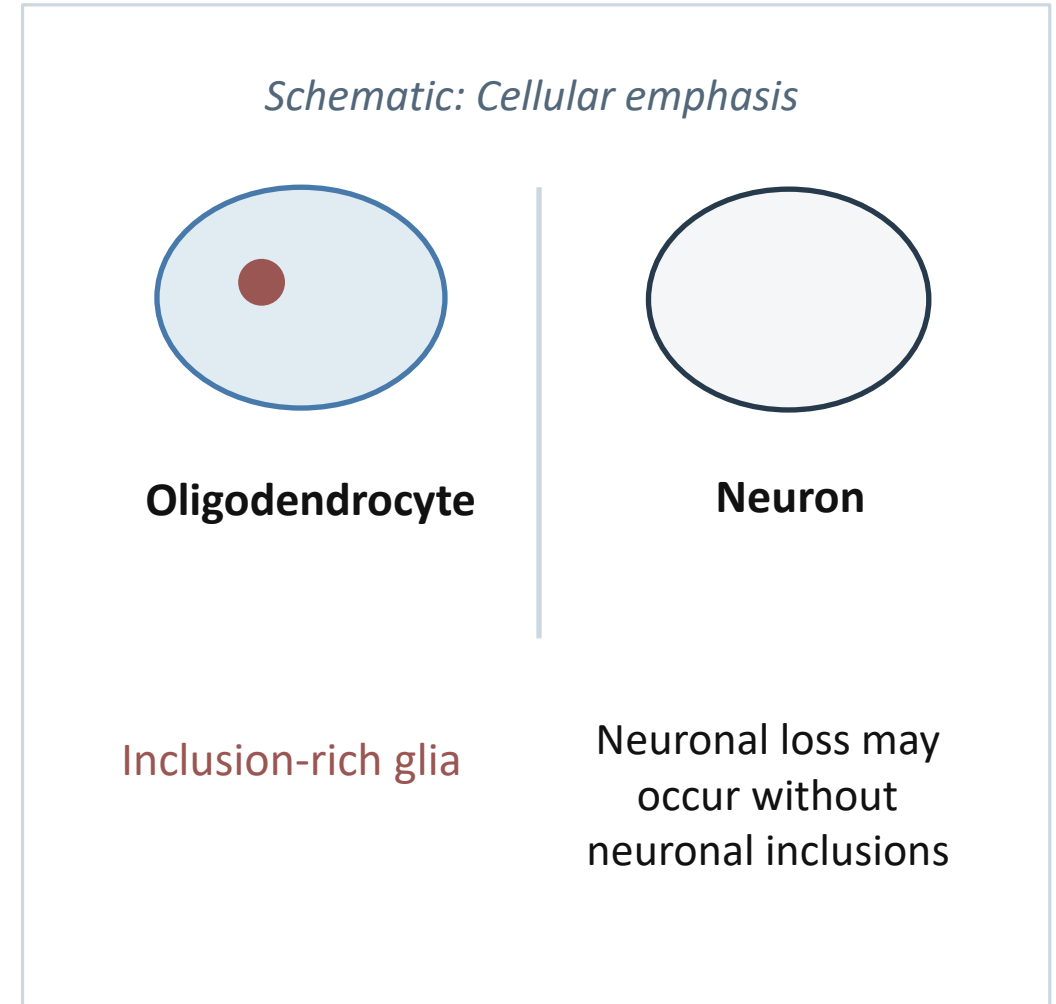
Immunochemical components: α -synuclein and ubiquitin

- α -Synuclein is a principal constituent of the diagnostic glial cytoplasmic inclusion.
- Ubiquitin is also present within these inclusions.
- Robbins Fig. 28.41B depicts α -synuclein-positive oligodendroglial inclusions; No original image is included here.



A schematic is not a diagnostic photomicrograph

- An illustrated oligodendrocyte with intracellular aggregates explains the expected compartment.
- Actual pathology identification requires genuine tissue morphology and appropriate methods.
- No generated or redrawn figure in this deck should be interpreted as an observed patient specimen.



MSA versus Parkinson disease

MSA

- Glial α -synuclein cytoplasmic inclusions
- White-matter involvement with regional neuronal degeneration
- Parkinsonism may coexist with ataxia / autonomic failure

Parkinson disease

- Neuronal Lewy bodies and Lewy neurites
- Nigrostriatal dopamine depletion
- Classic parkinsonism; Initially responds to L-DOPA

MSA versus progressive supranuclear palsy

MSA

- α -Synucleinopathy
- Oligodendroglial cytoplasmic inclusions
- Striatonigral, cerebellar and autonomic involvement

PSP

- Tauopathy
- Tau inclusions in neurons and glia
- Truncal rigidity, falls and impaired voluntary eye movements

MSA versus corticobasal degeneration

MSA

- α -Synuclein-positive glial inclusions
- Prominent white matter / multisystem circuit pathology
- Ataxic and autonomic components are central

CBD

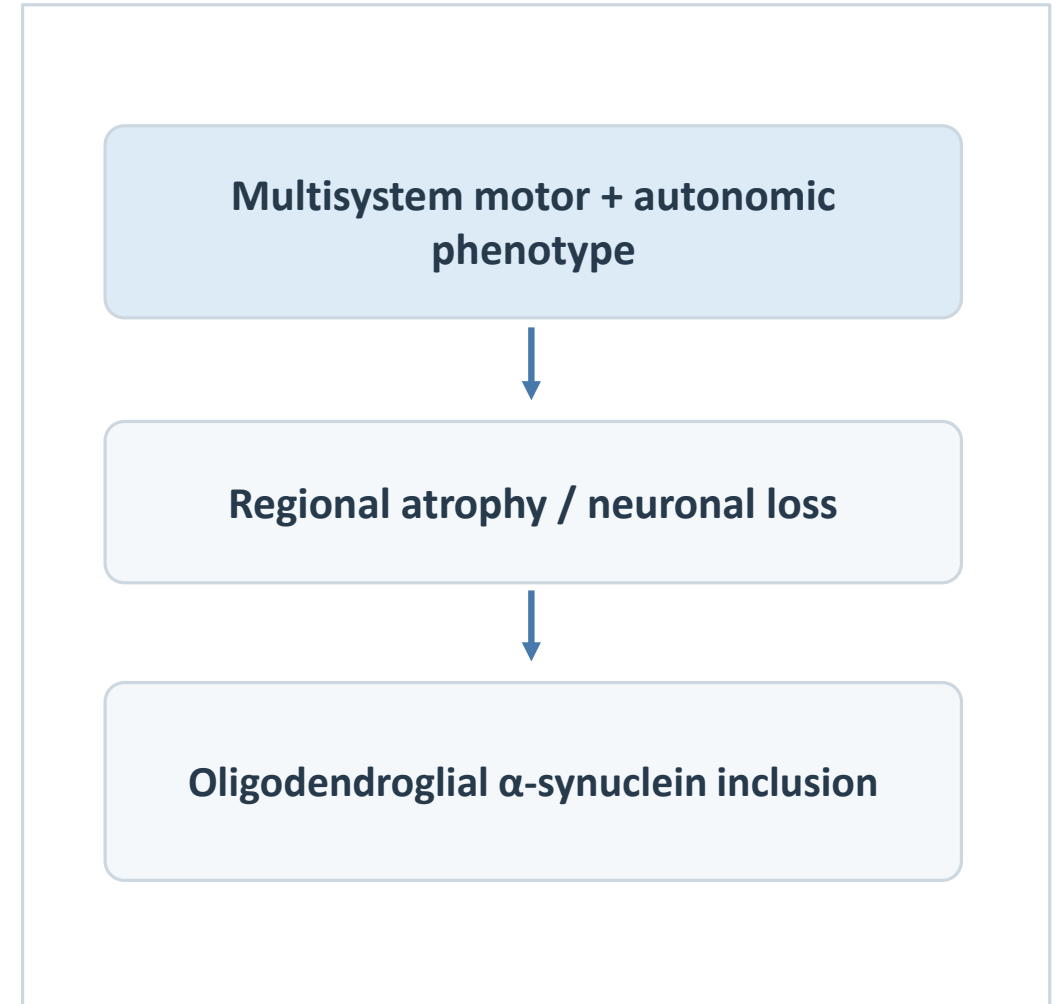
- Tau-positive cortical / glial pathology
- Motor/premotor/anterior parietal cortical atrophy
- Asymmetric motor disturbance with apraxia

Protein and cellular pathology across related disorders

Disorder	Predominant lesion emphasized	Molecular association
MSA	Oligodendroglial cytoplasmic inclusions	α -Synuclein
Parkinson disease	Neuronal Lewy bodies / neurites	α -Synuclein
Dementia with Lewy bodies	Cortical / brainstem neuronal Lewy pathology	α -Synuclein
Progressive supranuclear palsy	Neuronal and glial tau inclusions	Tau
Corticobasal degeneration	Tau-positive cortical and glial pathology	Tau

Pathologic reasoning should be integrated

- Begin by localizing the affected motor, cerebellar and autonomic systems.
- Identify characteristic atrophy and neuronal loss in affected regions.
- Determine the inclusion-bearing cell type and its protein composition.
- Contrast the observed pattern with neuronal Lewy pathology and tauopathies.



Application: Parkinsonism with autonomic failure

Constructed teaching vignette

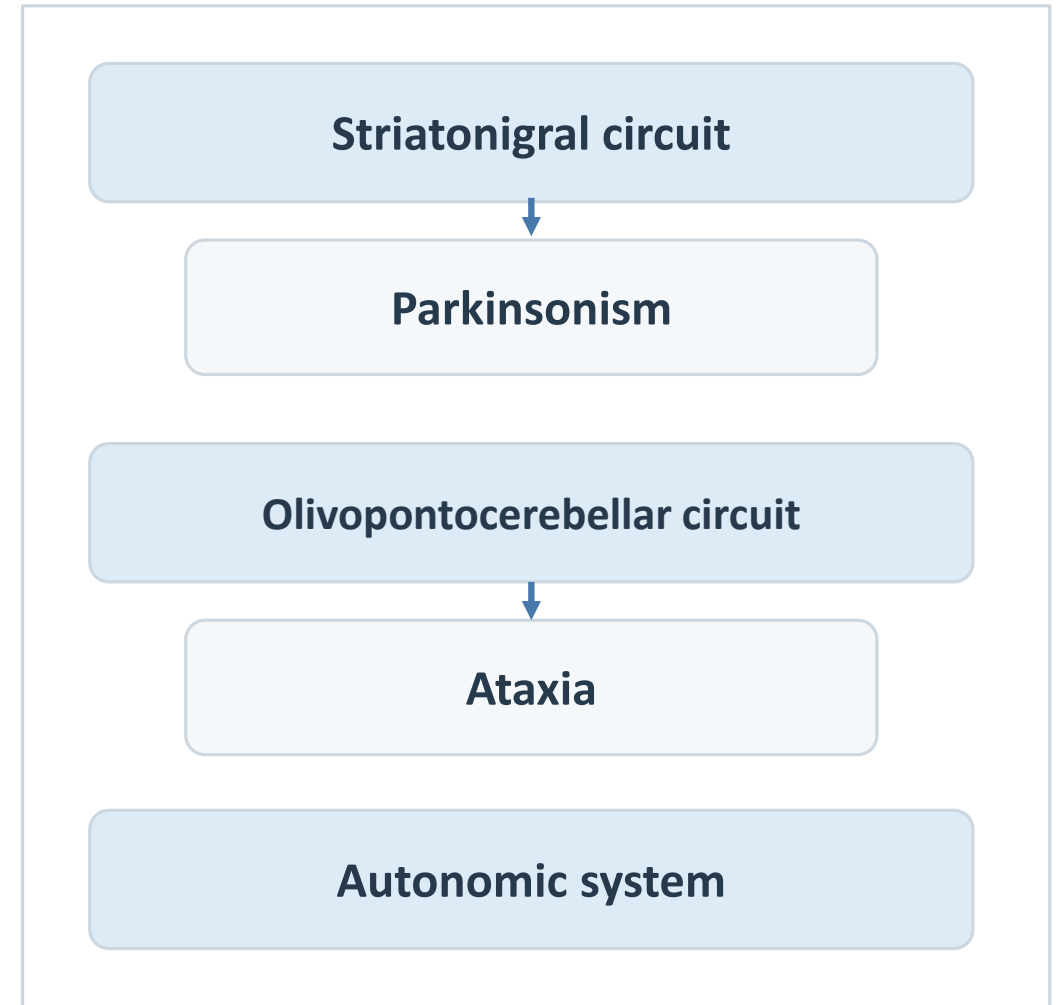
A person develops a progressive hypokinetic-rigid syndrome. Orthostatic symptoms are conspicuous and another motor system becomes involved later.

Question

Which anatomic circuits and proteinopathy should be considered together?

Case interpretation: Multisystem rather than single-system

- Parkinsonism points toward striatonigral dysfunction.
- Autonomic symptoms implicate central autonomic pathways in the MSA framework.
- An MSA pattern is supported by multisystem evolution; The vignette alone is not diagnostic.
- Expected defining pathology would be oligodendroglial α -synuclein inclusions.



Application: Progressive ataxic presentation

Constructed teaching vignette

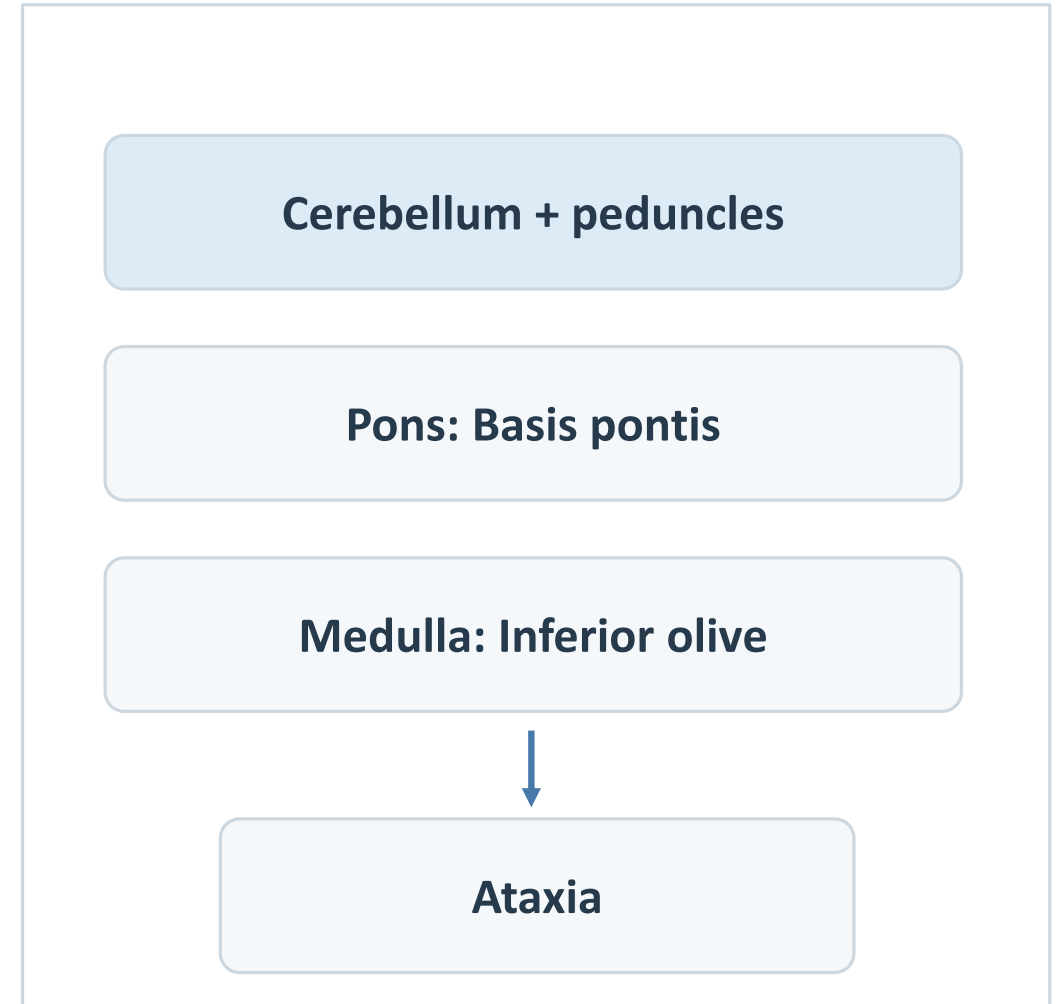
A patient presents with progressive ataxia. Subsequent evaluation documents parkinsonian signs and autonomic impairment. The pathology discussion highlights pontine and olivary atrophy.

Question

Which MSA anatomic distribution is most strongly illustrated?

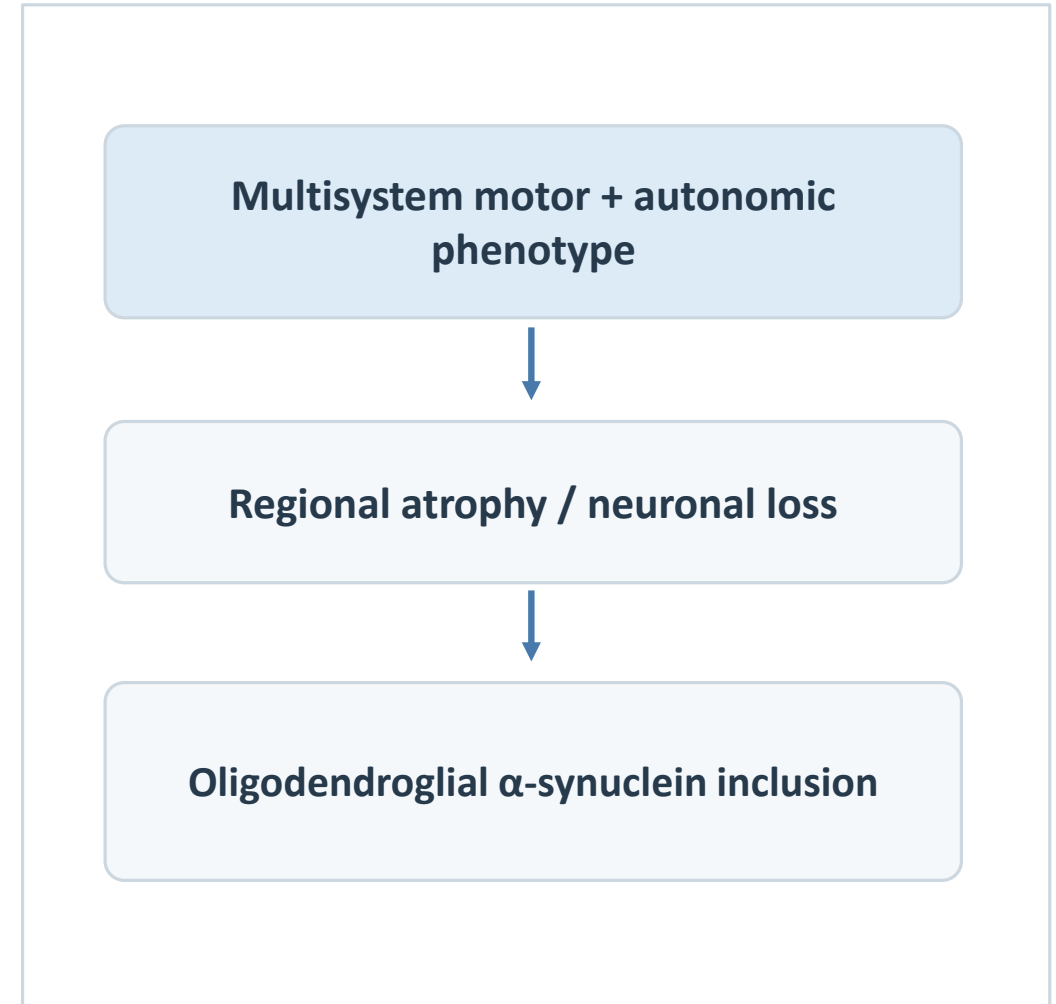
Case interpretation: Olivopontocerebellar emphasis

- Ataxia is linked to the olivopontocerebellar circuit.
- The cerebellum, peduncles, basis pontis and inferior olive are the corresponding regions described.
- Later motor and autonomic deficits are consistent with the multisystem course.
- Glial α -synuclein inclusions remain the defining histologic lesion.



What a pathology report should emphasize

- Identify the sampled structures and their neurodegenerative changes.
- Document oligodendroglial cytoplasmic inclusions and their α -synuclein association.
- Relate striatonigral, olivopontocerebellar and autonomic-region pathology to phenotype.
- Avoid calling the illustrated teaching schematics actual histologic evidence.



Established findings versus unresolved questions

- Established: Oligodendroglial α -synuclein/ubiquitin inclusions and tract degeneration.
- Established: Characteristic clinical–anatomic relations in three major systems.
- Supported association: Inclusion burden increases with progression.
- Unresolved: The initiating source and acquisition route of α -synuclein in oligodendrocytes.

Observation

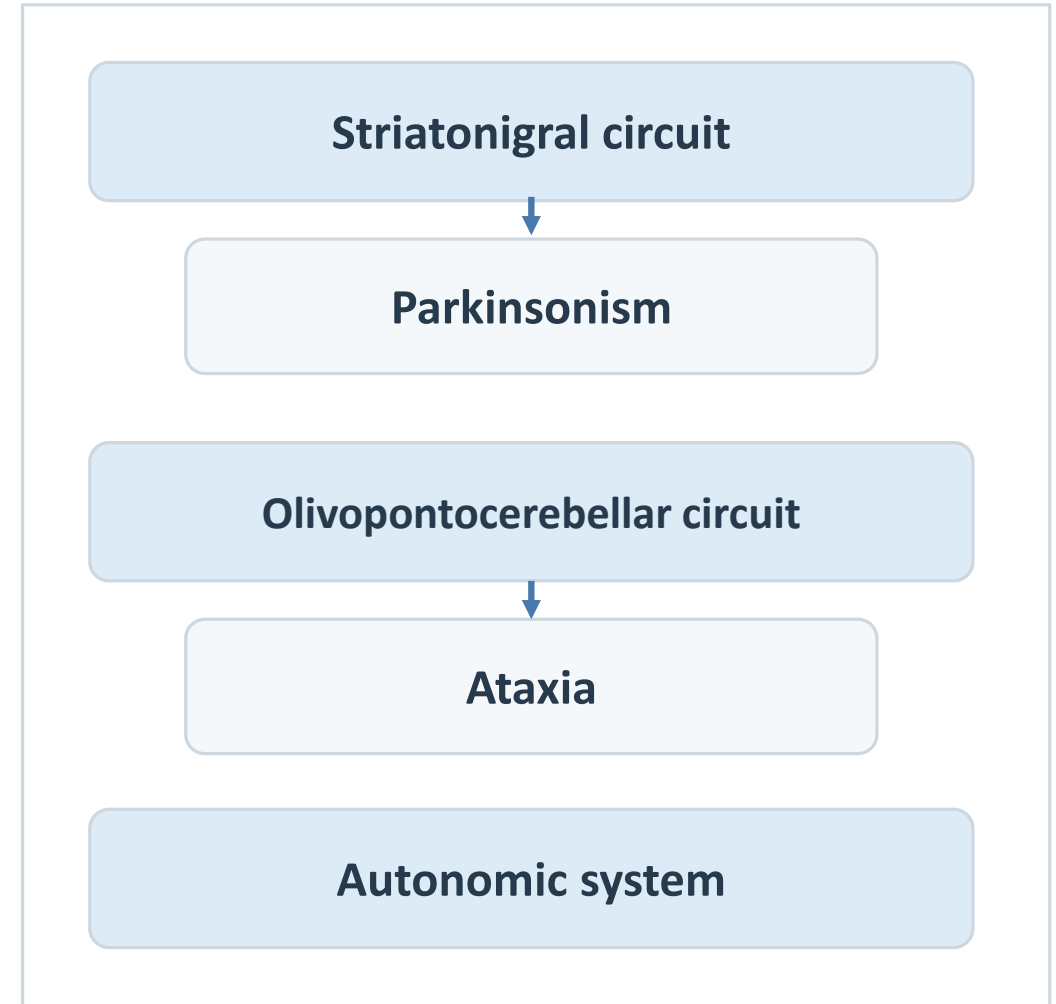
Inclusion burden rises as disease progresses

Observation

Glial inclusions may occur without neuronal loss

Core clinicopathologic synthesis

- MSA is an oligodendroglial α -synucleinopathy with major white-matter pathology.
- Parkinsonism, ataxia and autonomic failure map to distinct but overlapping degeneration patterns.
- The diagnostic glial inclusion must be distinguished from neuronal Lewy bodies.
- Glial protein accumulation is strongly associated with disease, but several mechanistic steps remain uncertain.



Primary references and source limits

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 28, “The Central Nervous System,” pp. 1166–1170.
- MSA section and morphology under “Atypical Parkinsonian Syndromes”; related sections on Parkinson disease, DLB, PSP and CBD.
- Chapter PDFs and the original Fig. 28.41 were not supplied; figures here are original editable schematics—not reproductions of the source.
- Clinical consensus criteria, imaging markers, test performance estimates and treatment guidelines were outside the supplied excerpt and are not asserted here.