**Table S1.** Comprehensive comparison of MSA, PD, PSP, and LBD, integrating symptoms, treatments, and key distinctions in the pathophysiology [13,15,226–241]. The table combines clinical and mechanistic perspectives, outlining shared features, distinctive red flags that aid classification, and key pathophysiological differences. These dimensions together underscore how variations in protein aggregation, neuronal targets, and systemic involvement may correspond to distinct modes of ecosystem failure.

| | Clinical Overview | | | Pathophysiological Overview | | |
|---|---|---|---|---|---|---|
| **Disease** | **Shared Symptoms** | **Distinguishing Features** | **Other Clinical Features/Management** | **Protein Aggregation & Neuronal Targets** | **Pathophysiological Modifiers** | **Etiology** |
| **MSA** | Parkinsonism; autonomic dysfunction; ataxia | Early severe autonomic failure; poor response to PD meds; stridor | Rapid progression; cold, clammy skin; severe sleep apnea; speech therapy beneficial; bladder meds often required | $\alpha$-syn in oligodendrocytes ⟶ glial cytoplasmic inclusions; widespread basal ganglia, cerebellum, brainstem | Strong neuroinflammation; severe autonomic failure | Mostly sporadic; some genetic risks; undefined environmental triggers |
| **PD** | Tremor, bradykinesia, rigidity; parkinsonism | Tremor at rest; good levodopa response | Hyposmia; micrographia; daytime sleepiness; DBS in selected cases; bladder/voice issues later | $\alpha$-syn in neurons ⟶ Lewy bodies; dopaminergic loss in substantia nigra | Milder neuroinflammation; moderate autonomic involvement | Sporadic; LRRK2, SNCA mutations; pesticides/environmental links |
| **PSP** | Parkinsonism; poor coordination; impaired eye movements | Early balance problems; vertical gaze palsy | Personality change; dysphagia; frequent falls; speech slow/slurred; bladder less affected | Tau in neurons and glia ⟶ neurofibrillary tangles; basal ganglia & brainstem targets | Inflammation around tau deposits; less autonomic dysfunction | Largely sporadic; some genetic risk factors |
| **LBD** | Parkinsonism; cognitive fluctuations; hallucinations | Early cognitive decline; prominent hallucinations/delusions | Capgras syndrome; REM sleep disturbance; cholinesterase inhibitors helpful; bladder manageable with meds | -syn in cortical & subcortical neurons ⟶ Lewy bodies | Synaptic dysfunction; variable autonomic symptoms | Similar to PD; genetic predisposition; environmental links less defined |