Atypical parkinsonism

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Aspen course
2026



Disclosures

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- Off-label medication use

Parkinsonism



- Synucleinopathy
  - Parkinson's Disease (PD)
  - Dementia with Lewy bodies (DLB)
  - Multiple System Atrophy (MSA)

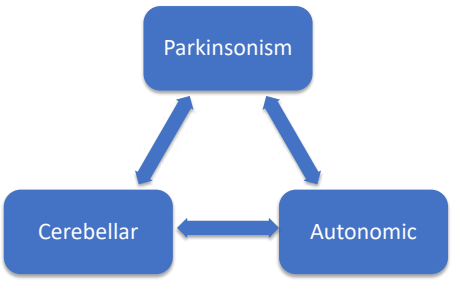
- Tauopathy
  - Progressive Supranuclear Palsy (PSP)
  - Corticobasal syndrome (CBS)
  - Frontotemporal dementia (FTD)

Multiple system atrophy
MSA

MSA terminology

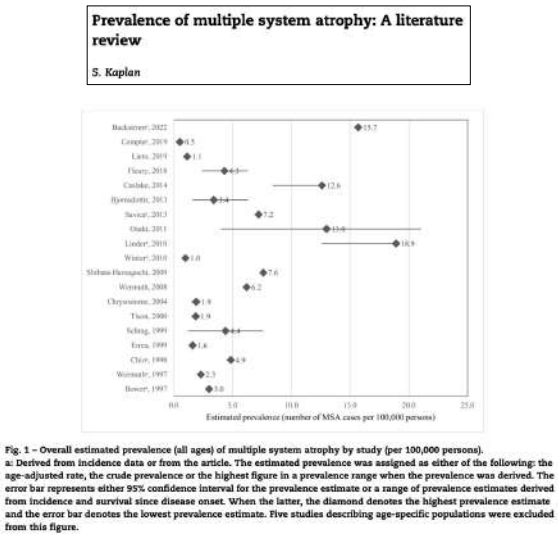
- MSA-Parkinsonism (MSA-P)
- MSA-Cerebellar (MSA-C)

Old terminology
- Striatonigral degeneration (SND)
- Olivopontocerebellar atrophy (OPCA)
- Shy-Drager syndrome (SDS)



MSA epidemiology

- Estimated mean incidence 0.6 to 0.7 cases per 100K person-years (range 0.1-2.4 cases per 100K person-years)
- Estimated point prevalence 3.4 to 4.9 cases per 100K population, increasing to 7.8 per 100K among persons over 40 years
- Parkinsonian > cerebellar subtype in most countries (2-4:1)
  - Cerebellar subtype is more frequent in Japan → genetic or epigenetic factors?
- Disease onset in sixth decade, both sexes equally affected
- Mean survival from symptom onset is 6 to 10 years, few patients survive more than 15 years



Prevalence of multiple system atrophy: A literature review

S. Kaplan

Fig. 1 – Overall estimated prevalence (all ages) of multiple system atrophy by study (per 100,000 persons).
a: Derived from incidence data or from the article. The estimated prevalence was assigned as either of the following: the age-adjusted rate, the crude prevalence or the highest figure in a prevalence range when the prevalence was derived. The error bar represents either 95% confidence interval for the prevalence estimate or a range of prevalence estimates derived from incidence and survival since disease onset. When the latter, the diamond denotes the highest prevalence estimate and the error bar denotes the lowest prevalence estimate. Five studies describing age-specific populations were excluded from this figure.

Fancuilli and Wenning 2015; Kuhnel et al., 2022; Kaplan 2024

MDS diagnostic criteria for MSA

Core diagnostic categories	Supportive clinical features	MRI markers and exclusions
Essential: sporadic, progressive adult onset (>30 years) disease. **Clinically established MSA:** Autonomic dysfunction is required: voiding difficulty with post-void residual ≥100 mL, urinary urge incontinence, or neurogenic OH (≥20/10 mmHg within 3 minutes). **Plus at least one:** poorly L-dopa-responsive parkinsonism or cerebellar syndrome with at least two signs (gait/limb ataxia, cerebellar dysarthria, or oculomotor features). **Also required:** supportive clinical features ≥2, MRI marker ≥1, and no exclusion criteria. **Clinically probable MSA:** At least two - autonomic dysfunction, parkinsonism, or cerebellar syndrome. **Plus :** supportive clinical feature ≥1. MRI marker not required No exclusion criteria.	**Motor features:** • Rapid progression within 3 years • Moderate–severe postural instability • Craniocervical dystonia induced/exacerbated by L-dopa without limb dyskinesia • Severe speech impairment or dysphagia within 3 year • Unexplained Babinski sign • Jerky myoclonic tremor • Postural deformities. **Non-motor features:** • Stridor, inspiratory sighs • Cold discolored hands and feet • Erectile dysfunction below age 60 for clinically probable MSA • Pathologic laughter/crying.	**MSA-P markers:** • Atrophy of putamen, middle cerebellar peduncle, pons, or cerebellum • "Hot cross bun" sign • Increased diffusivity of putamen or middle cerebellar peduncle. **MSA-C markers:** Atrophy of putamen or infratentorial structures (pons and middle cerebellar peduncle) "Hot cross bun" sign Increased diffusivity of putamen. **Exclusion criteria:** Substantial persistent response to dopaminergic medication; unexplained anosmia; fluctuating cognition with early visuoperceptual decline; recurrent visual hallucinations within 3 years; dementia within 3 years; downgaze supranuclear palsy or slowed vertical saccades; MRI suggesting another diagnosis; or an alternative MSA look-alike condition.

Fanciulli & Wenning, 2015; Wenning et al., 2022

MSA – "Red" flags







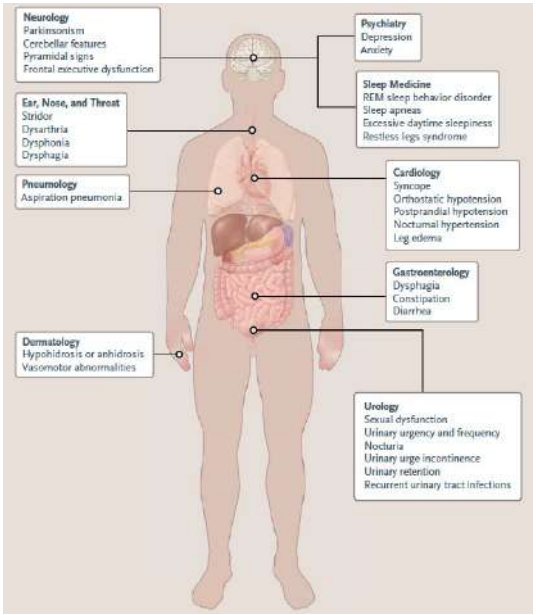


MSA and neuropsychiatric features

- Cognitive - executive dysfunction; dementia 31%
  - Hippocampal alpha-SYN pathology
- Depression
  - ~40-85% have at least mild depression and 1/3rd have moderate to severe depression
- Anxiety
  - Affects ~37%
- Apathy
  - Frequent, ~65%
- Excessive daytime sleepiness
  - More than 25%, unrelated to depression

Miki et al., 2020; Jellinger et al., 2020; Lazzeri et al., 2022

Multidisciplinary presentation of MSA



Faniciulli and Wenning 2015

MSA – Progressive course

Premotor phase
- Primary care clinic – increased visits for hypotension, balance, memory, bladder, dizziness, depression

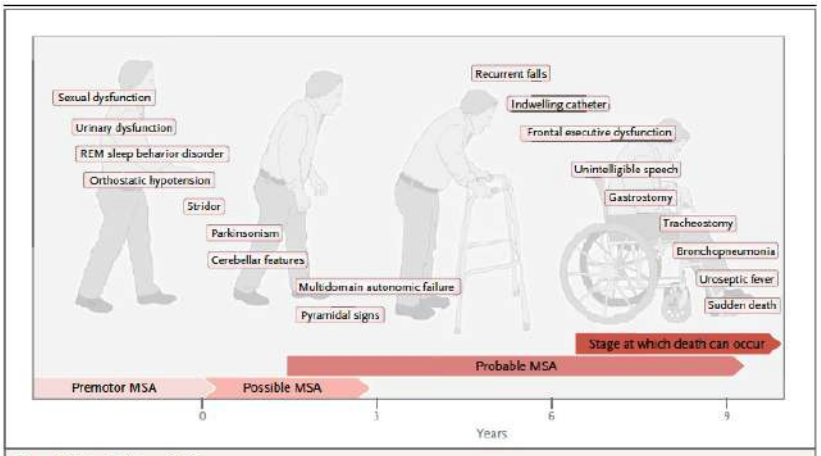


Figure 3. Natural History of MSA.
The premotor phase of MSA can last for months to years. Year 0 denotes the time of onset of motor symptoms. A diagnosis of definite MSA is not possible until the postmortem examination is performed.

Progression
- European MSA natural history study
- ~ 6 years
- Mean 51 mos with global disability 0 → 4
- MSA-P rate more progressive

Faniciulli & Wenning 2015; Schrag et al., 2022; Kuhnel et al., 2022

Multiple system atrophy: advances in pathophysiology, diagnosis, and treatment

Florian Krismer, Alessandra Fanciulli, Wassilios G Meissner, Elizabeth A Coon, Gregor K Wenning

Lancet Neurol 2024; 23: 1252–66

Department of Neurology, Medical University Innsbruck, Innsbruck, Austria (F Krismer PhD, A Fanciulli PhD, Prof G K Wenning PhD*); Centre Hospitalier Universitaire Bordeaux, Service de Neurologie des Maladies Neurodégénératives, Institut des Maladies Neurodégénératives Clinique, French Clinical Research Network for Parkinson's

Multiple system atrophy is an adult-onset, sporadic, and progressive neurodegenerative disease. People with this disorder report a wide range of motor and non-motor symptoms. Overlap in the clinical presentation of multiple system atrophy with other movement disorders (eg, Parkinson's disease and progressive supranuclear palsy) is a concern for accurate and timely diagnosis. Over the past 5 years, progress has been made in understanding key pathophysiological events in multiple system atrophy, including the seeding of α-synuclein inclusions and the detection of disease-specific α-synuclein strains. Diagnostic criteria were revised in 2022 with the intention to improve the accuracy of a diagnosis of multiple system atrophy, particularly for early disease stages. Early signals of efficacy in clinical trials have indicated the potential for disease-modifying therapies for multiple system atrophy, although no trial has yet provided unequivocal evidence of neuroprotection in this rare disease. The advances in pathophysiology could play a part in biomarker discovery for early diagnosis as well as in the development of disease-modifying therapies.

Krismer et al., 2025

Prognosis and survival

- 210 MSA patients → 124 deaths
- Median survival 7 years
- Clinical variables with effect on survival probability at 7 years

TABLE 2 *Multivariate analysis of predictors selected by LASSO regression procedure in the development cohort*

Variable	HR	95% CI	*P*-value
Age at onset	1.75	1.33–2.31	0.0001
MSA subtype (MSA-C)	0.91	0.51–1.65	0.759
Gender (female)	1.02	0.67–1.55	0.935
Early falls ≤3 y (absent)	0.409	0.26–0.64	0.0001
Catheterization ≤3 y (present)	2.25	1.35–3.75	0.002
Dopa response (absent)	1.66	1.03–2.67	0.037
Early OH (present)	2.137	1.33–3.44	0.002
Early urogenital failure (present)	2.11	1.38–3.23	0.001
Parkinsonism at onset (absent)	1.03	0.62–1.74	0.898

Development and Validation of a Prognostic Model to Predict Overall Survival in Multiple System Atrophy

Jolene Eschlboeck, MD,[1] Georg Kraxberger, PhD,[2] Christine Achrainer, MD, PhD,[1,3] Alessandra Fanciulli, MD, PhD,[1] Carolin Ascoregui, MD, PhD,[1,4] Sylvia Boesch, MD,[1] Alice Gerstenhofer, MD, PhD, Beatrice Heim, MD, PhD, Philipp Mahlknecht, MD, PhD, Katharina Marini, MD,[1] Wolfgang Nachbauer, MD, PhD,[1] Christoph Scheffler, MD,[1] Heike Stockner, MD,[1] Werner Poewe, MD,[1] Klaus Seppi, MD,[1] Stefan Kiechl, MD,[1] Gregor Wenning, MD, PhD, MSC,[1,*] Florian Krismer, MD, PhD[1,*] and the EMSA-SG MoS Investigators

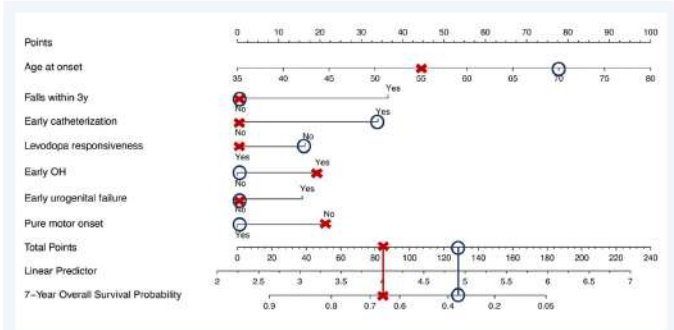


FIG. 1. Nomogram of 7 year overall survival. To use the nomogram, points are assigned to each risk factor. The total number of points determines the 7 year survival probability. For example (red cross), according to the present model, a 58-year-old patient (age at onset points: 44, pure motor presentation at onset points: 21) with MSA featuring parkinsonism with subjective levodopa responsiveness (levodopa responsiveness points: 0) and symptoms of orthostatic hypotension (OH) (early OH points: 19) since 3 years has a 7 year survival probability of ~65% (total points: 84), warranting advanced care planning. In example 2 (blue circle), the survival probability is worse. A 74-year-old women (age at onset points: 78, pure motor presentation at onset points: 0) with MSA featuring cerebellar features since 4 years, experiences now symptoms of parkinsonism with no benefit to levodopa treatment (levodopa responsiveness points: 16). She further reports autonomic failure with recurrent dizziness on standing and symptoms of urogenital failure with incomplete bladder emptying requiring intermittent self-catheterization since 2 years (early OH points: 0, early urogenital failure points: 0, early catheterization points: 34). The patient has a 7 year survival probability of ~35% (total points: 128).

Eschelboeck et al., 2024

Progression modeling

- ASPIRE study
- Early MSA (n=41) and HC (n=20)
- Clinical and biomarker changes at 6 and 12 months
- Survival status at 24 months

- UMSARS I and II, MSA-QoL, MoCA
- MRI regional atrophy, FA/MD
- DaT
- Plasma NfL

- Clinical progression over 6 months best predicted by MRI atrophy of brainstem and pons at baseline and over 12 months, baseline DaT
- Increased mortality and dropout risk linked to high plasma NfL levels

- Sample size calculations / clinical trials



Disease Progression in Multiple System Atrophy: The ASPIRE Multi-Modal Biomarker Study

Margherita Fabbri, Natalia del Campo, Wassilios G. Meissner, Vanessa Rousseau, Agnès Sommet, Pierre Payoux, Pierre Gantet, Amel Drif, Hélène Catala, Claire Thalamas, Christine Tranchant, Franck Durif, Ana Marques, Alexandre Eusebio, Luc Defebvre, Jean-Christophe Corvol, Stephane Thobois, Anthime Flaus, Anne-Gaëlle Corbille, Solène Frismand, Beverley Patterson, Alexandra Foubert-Samier, Anne Pavy-Le Traon, Germain Arribarat, Patrice Péran, PhD, and Olivier Rascol, MD, PhD, for the ASPIRE Study Group

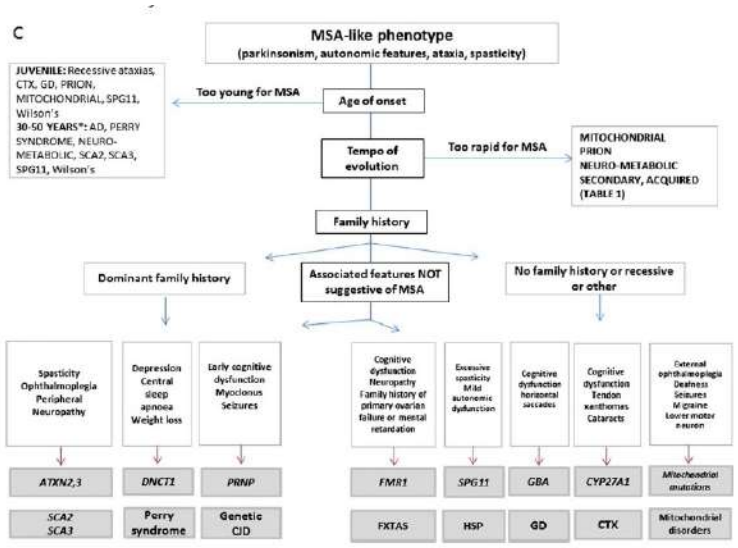
Interpretable Machine Learning Model for Individualized Survival Prediction of Multiple System Atrophy

Xiao Dong, MD, Daji Chen, MD, Linlin Wan, MD, Zhao Chen, MD, Linliu Peng, MD, Zhe Long, MD, Jinze Wu, MD, Riwei Ouyang, MD, Xiafei Long, MD, Ketang Du, MD, Xiaokang Wu, MD, XinYing Xiao, MD, Ruqing He, MD, Daren Zeng, MD, Rong Qiu, PhD, Beisha Tang, MD, and Hong Jiang, MD

Fabbri et al., 2026; Dong et al., 2026

Differential diagnosis

- PD, other atypical parkinsonian syndromes, DLB, cerebellar ataxias, pure autonomic failure



Stamelou et al., 2013; Gallo et al., 2023

Table 1
MSA type C lookalike, genetic etiologies. SCA: spinocerebellar ataxias; CANVAS: cerebellar ataxia with neuropathy and vestibular areflexia syndrome; FXTAS: Fragile X tremor-ataxia syndrome; ARCA: autosomal recessive cerebellar ataxia; LOFA: late-onset Friedreich's ataxia; SPG7, spastic paraplegia 7.

Differential diagnosis	Overlapping features	Clinical Red flags
SCAs (1, 2, 3, 6, 7, 12, 17)	Cerebellar ataxia, parkinsonism, dysphagia, dystonia, autonomic dysfunction, RBD, pyramidal signs	Family history, cognitive impairment, peripheral neuropathy, seizures, visual loss (retinal disease)
ARCA 3	Cerebellar ataxia, hyperreflexia, oculomotor abnormalities, stridor	Slow progression, lower limb spasticity, possible cognitive impairment
LOFA and vLOFA (FNX)*	Cerebellar ataxia, preserved reflexes or hyperreflexia with Babinski sign	Peripheral neuropathy, slow progression, systemic manifestations (cardiomyopathy, scoliosis)
DRPLA (ATN1)	Cerebellar ataxia, choreoathetosis, myoclonus	Epilepsy, dementia, rare extrapyramidal symptoms
LOFA and vLOFA (FXN)	Cerebellar ataxia, retained reflexes	
FXTAS (FMR1)	Cerebellar ataxia, intention tremor, parkinsonism, autonomic dysfunction	Early cognitive dysfunction, peripheral neuropathy, family history of primary ovarian failure or mental retardation
SPG7	Cerebellar ataxia, mixed dysarthria, dysphagia, urinary symptoms, pyramidal signs	Family history, progressive external ophthalmoplegia, visual loss, proximal weakness, mild lower limb spasticity, peripheral neuropathy
CANVAS (RFC1)	Autonomic dysfunction, cerebellar ataxia, scanning dysarthric speech, brisk reflexes, parkinsonism	Spasmodic cough, vestibulopathy, sensory neuronopathy
Mitochondrial disorders	Parkinsonism, ataxia cerebellar, spinocerebellar or sensory ataxia	Many concomitant neurologic and systemic manifestations: neuropathy, myopathy, epilepsy, cognitive impairment, migraine, retinopathy, optic neuropathy, deafness, cardiomyopathy, (lip)etes

Predictors of phenoconversion from PAF to MSA

An update on multiple system atrophy

Iva Stankovic[a], Mechteld Kuijpers[b] and Horacio Kaufmann[b]

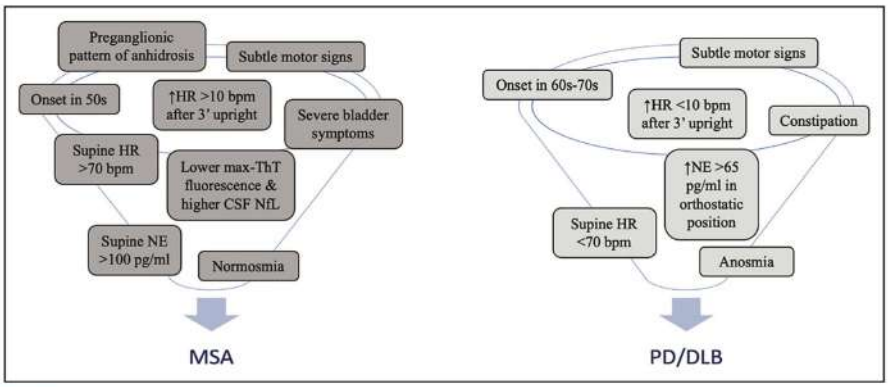


FIGURE 1. Predictors of phenoconversion of pure autonomic failure to MSA. bpm, beats per minute; CSF, cerebrospinal fluid; HR, heart rate; NE, norepinephrine; NfL, neurofilament light chain; pg/ml, picograms per milliliter; ThT, thioflavin.

Stankovic et al., 2024

Anti-IgLON5 and MSA (and DLB)

- Rare autoimmune encephalitis - anti-immunoglobulin-like cell adhesion molecule 5 (IgLON5) disease
- Mimic PSP, CBS, but also MSA and DLB
- MSA-like features: parkinsonism, cerebellar ataxia, severe orthostatic hypotension, acute respiratory failure, sleep parasomnia, vocal cord paralysis, and pyramidal tract signs.
  - Atypical for MSA were myorhythmia, horizontal eye movement restriction, fasciculations, and painful muscle cramps.
- 57 studies with 127 individual case reports of anti-IgLON5 disease (mean age 63 years at diagnosis, median symptom duration 2 years)
  - Cognitive dysfunction was reported in 45% of cases, RBD in 15%, parkinsonism in 14%, respiratory insufficiency in 37%, and bulbar symptoms in 67%



Ono et al., 2024; Vijayaraghavan et al., 2024; McWilliam et al., 2024

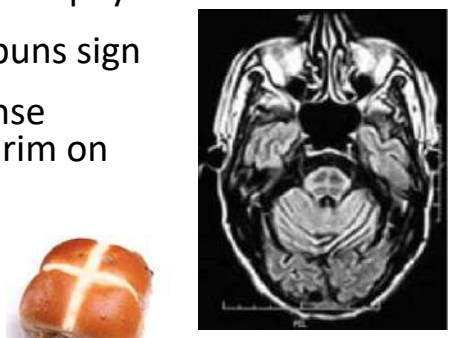
Other investigations

- Sensitivity of clinical diagnosis of MSA ~ 88.2% (mov dis specialists), 64.3% general neurologists
  - Mayo series: 90% autopsy-confirmed were clinically diagnosed with MSA (Koga 2021)
- Brain imaging
  - MR Imaging – may be helpful, not always specific
  - PET/SPECT Imaging – MSA vs. cerebellar ataxias, not among parkinsonian syndromes
- Cardiac sympathetic imaging (MIBG) – preserved postganglionic presynaptic cardiac sympathetic nerve endings in MSA (vs. PD), though overlap present
- Autonomic testing (Valsalva, tilt table, sudomotor, thermoregulatory sweat test) – MSA vs. cerebellar ataxias, but not PD
- Anal sphincter EMG – degeneration of Onuf's nucleus, MSA (vs. PD), though studies limited/nonconfirmatory (Todisco 2022)
- Blood exosomes -immunoprecipitated using neuronal and oligodendroglial markers (PD vs. MSA)?

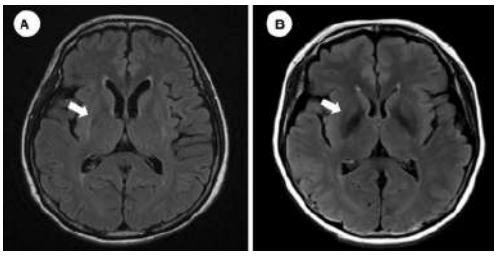
Hughes et al., 2002; Jousta et al., 2014; Kim et al., 2015; Pellechia et al., 2020; Stankovic et al., 2021; Dutta et al., 2021; Koga et al., 2021; Todisco et al., 2022

MSA - Imaging

- Cerebellar atrophy
- Brainstem atrophy
- Hot cross buns sign
- Hyperintense putaminal rim on T2/FLAIR







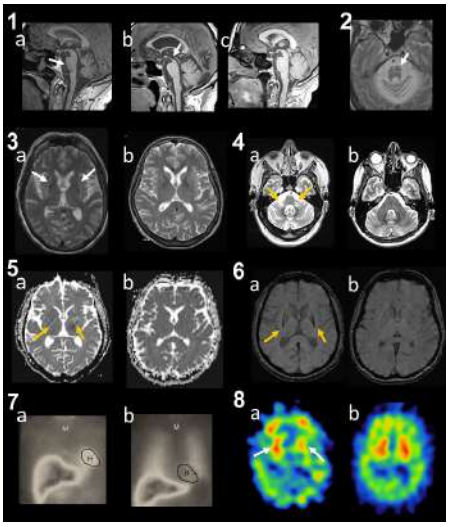
MSA – imaging (2)

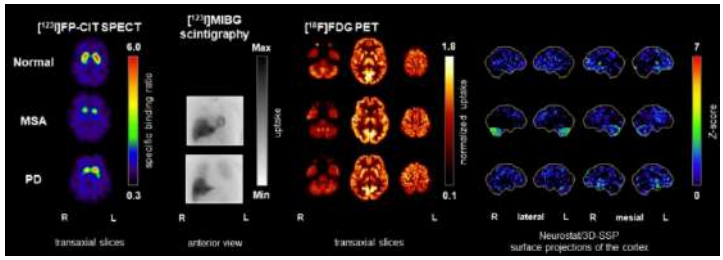
The role of neuro-imaging in multiple system atrophy

Florian Krismer[1] · Klaus Seppi[1,2] · Werner Poewe[1]

Neuroimaging in multiple system atrophy: clinical implications and novel developments

Wolfgang H. Jost[1,2] · Alexander Rau[1] · Joachim Brumberg[1] · Horst Urbach[1] · Philipp T. Meyer[1] · Nils Schröter[1,3]





Krismer et al., 2025; Jost et al., 2025

MSA - Pathology

- Neuronal loss and axonal degeneration, mainly in nigrostriatal and pontocerebellar systems
- Astroglial cytoplasmic inclusions and threads
- Myelin pallor and accompanying gliosis
- Hallmark = cytoplasmic ASYN positive glial cytoplasmic inclusions (GCIs) within oligodendroglial cells

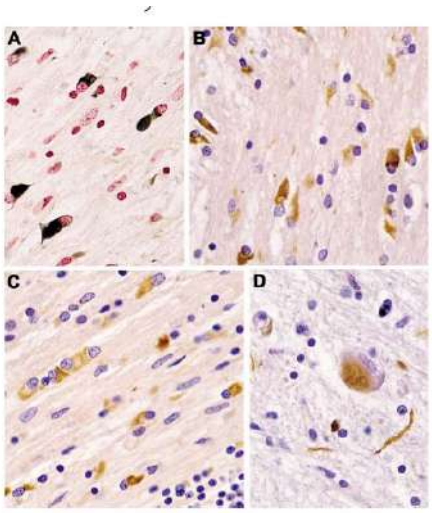
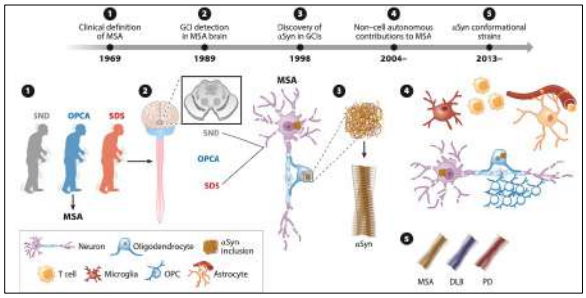


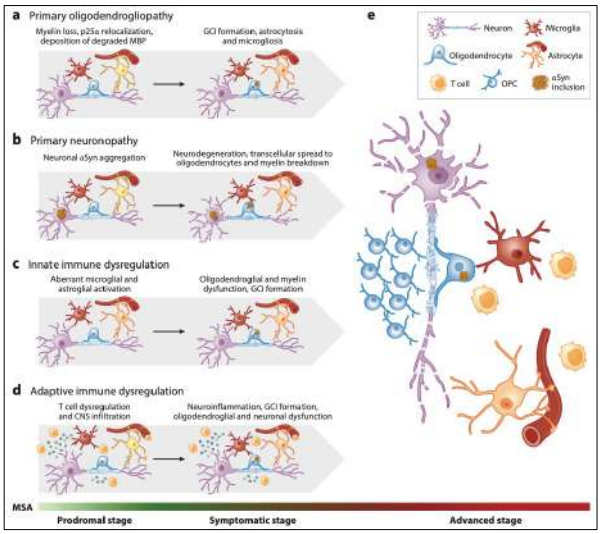
FIG. 1. (A–C) GCIs in MSA: **(A)** in globus pallidus (Gallyas silver impregnation), **(B)** in pontine basis (α-Synuclein) and **(C)** in frontal white matter, anti-ubiquitin. **(D)** Neuronal cytoplasmic inclusion and neurites in pontine basis (α-Synuclein) (GCIs, glial cytoplasmic inclusions). **(A–D)** original magnification ×4,000. From Wenning and Jellinger.[50] [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Armstrong et al., 2007; Jellinger 2014; Kim et al., 2015

A new look at MSA pathology and pathogenesis



- Early-stage MSA brains include diffuse neuronal αSyn accumulation in neurons, glial cytoplasmic and nuclear inclusions, myelin degeneration, astrocytosis, and microgliosis.
- Late-stage pathologies additionally involve the formation of neuronal nuclear and cytoplasmic inclusions. T cell infiltration and proliferation of oligodendrocyte precursors in white matter is observed, but unknown how early it occurs.



Ndayisaba, Halliday, Khurana 2025

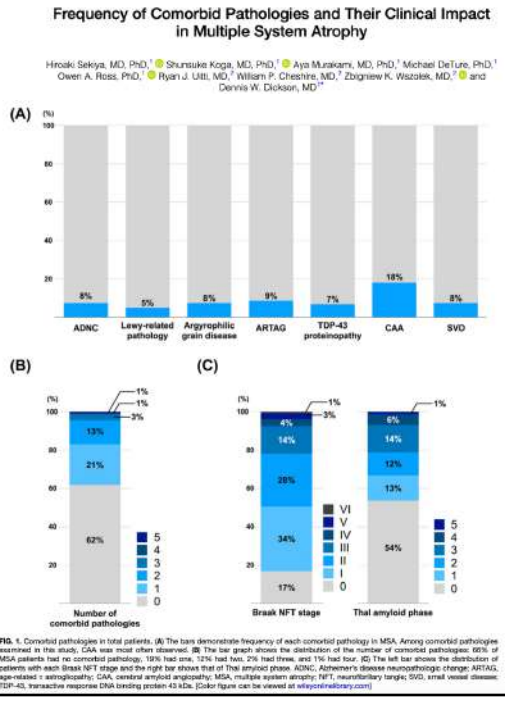
MSA and co-pathology

- 160 autopsy-confirmed MSA cases
- Few co-pathologies (62% w/o significant co-path)
- With advanced AAO and AAD, # co-pathologies, Braak NFT stage and amyloid phase increased, but even in the oldest age group, were infrequent
- ADNC was higher in MSA + cognitive dysfunction, but only found in 15% with relatively low NFT and amyloid

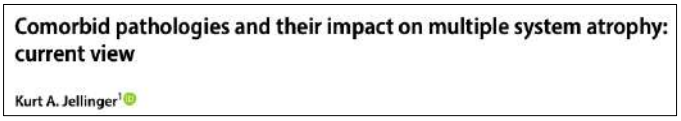
TABLE 1 *Demographic, clinical, and pathological features*

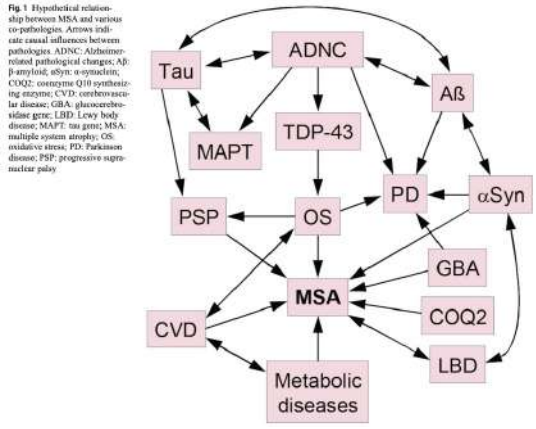
Features	All patients (n = 160)
Female sex	44% (70)
Age at onset (y)	59 ± 9
Age at death (y)	67 ± 8
Disease duration (y)	7 ± 3
Clinical subtype	
MSA-P	79% (126)
MSA-C	21% (34)

Sekiya et al., 2023





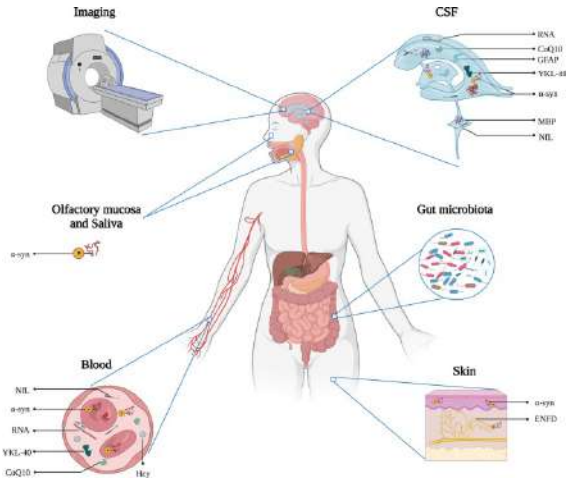


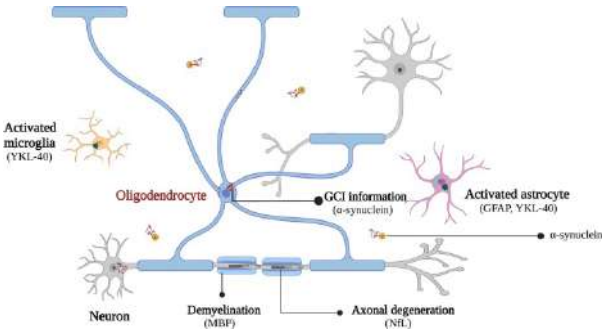


Martinez-Valbuena et al., 2025; Jellinger 2025

MSA and biomarkers

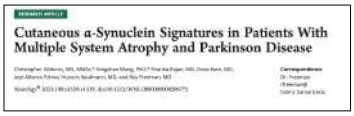
- Fluid
- Tissue
- Gut microbiota
- Imaging

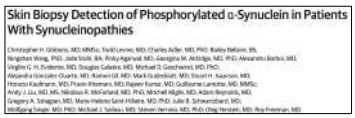




Wan et al., 2023

Phosphorylated a-SYN (skin)


Cutaneous α-Synuclein Signatures in Patients With Multiple System Atrophy and Parkinson Disease


Skin Biopsy Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies

- 31 MSA, 54 PD, 24 HC
- Measured density of intraepidermal, sudomotor, and pilomotor nerve fibers and quantified deposition of phosphorylated ASYN
- PD had reduced nerve fiber densities compared with MSA ($p < 0.05$, all fiber types)
- All MSA and 51/54 with PD had evidence of p-ASYN in at least one skin biopsy, none in controls
- MSA had greater phosphorylated ASYN deposition ($p < 0.0001$) and more widespread peripheral distribution ($p < 0.0001$) than PD
- >90% sensitivity and specificity in distinguishing between MSA and PD

- Multicenter study, 343 participants in primary analysis
- Deposition of p-syn within subepidermal plexus more common in MSA > DLB, PAF, PD

Table 2. Primary Outcomes

Diagnosis	Participants, No.		Proportion of participants positive for P-SYN, % (95% CI)
	P-SYN positive[a]	P-SYN negative[b]	
Synucleinopathy	213	10	95.5 (91.9-97.8)
Parkinson disease	89	7	92.7 (85.6-97.0)
Multiple system atrophy	54	1	98.2 (91.7-99.9)
Dementia with Lewy bodies	48	2	96.0 (86.3-99.5)
Pure autonomic failure	22	0	100 (84.6-100)
No synucleinopathy	4	116	3.3 (1.3-8.0)

Gibbons et al., 2023, 2024

SAA and MSA

- CSF - 22 studies, 1855 synucleinopathies vs 1378 non-synucleinopathies (control) (Grossauer et al., 2023)
- Pooled sensitivity and sensitivity for synucleinopathies vs controls 0.88 and 0.95; less robust for MSA
- Differences in RT-QuIC vs protein misfolding cyclic amplification (PMCA) (better sensitivity for PMCA)
- Structural differences of a-syn aggregates ("strains") in PD and MSA? Different tropism for peripheral tissues?

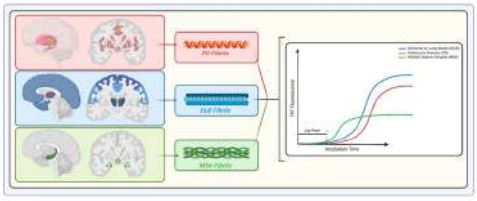


Figure 4. Different synucleinopathies represented in varying brain regions sequestered by contrasting fibril structures. PD, DLB, and MSA are represented in red, blue, and green, respectively. PD is observed in the amygdala, DLB in the cerebral cortex, and MSA in the hippocampus. Each synucleinopathy is associated with a different strain of αSyn fibrils, each with unique biophysical and biochemical properties. In the right-most panel, the varied response to seed amplification assay based on ThT fluorescence is detailed from the differing fibrils associated with each disease. Created with BioRender.com (accessed on 25 June 2023).

α-Synuclein Seed Amplification Assays in the Diagnosis of Synucleinopathies Using Cerebrospinal Fluid—A Systematic Review and Meta-Analysis

α-Synuclein Strains and Their Relevance to Parkinson's Disease, Multiple System Atrophy, and Dementia with Lewy Bodies

Noah J. Cranee, Yann Gambin and Emma Sierecki

Brain-derived and in vitro-seeded alpha-synuclein fibrils exhibit distinct biophysical profiles

Selene Seoyun Lee, Livia Civitelli*, Laura Parkkinen*

- Brain-derived αSyn fibrils from all synucleinopathies display a mixture of 'straight' and 'twisted' microscopic structures.
- However, the PD, PDD, and DLB SAA fibrils had a 'straight' structure, whereas MSA SAA fibrils showed a 'twisted' structure.
- Tubulin polymerization promoting protein (TPPP/p25) as a CSF biomarker specific for MSA vs PD (Zeng, 2026).

Grossauer et al., 2023; Graves et al., 2024; Lee et al., 2025; Zeng et al., 2026

MSA - Treatment

- Motor
  - Parkinsonism - ~1/3 respond to levodopa; watch for OH and facial dyskinesias; gait/safety
  - Ataxia – consider amantadine; address gait/safety
  - Levodopa intestinal gel (small study, Blaise et al., 2022)
- Non-motor
  - Bladder - oxybutynin, tolterodine, solifenacin, etc; botulinum toxin
  - Constipation – polyethylene glycol, bisacodyl, etc; lubiprostone, linaclotide (activates intestinal Cl channels and cGMP)
  - Sleep apnea – CPAP, BIPAP
  - RBD – clonazepam, melatonin
  - Stridor – CPAP, trach (Consensus statement, Cortelli et al., 2019); EMST pilot (Srp et al., 2023)
  - Dysphagia (Consensus statement, Calandra-Buonaura et al., 2021)

Review articles – Grossauer et al., 2022; Stakovic et al., 2024

A strategic approach of the management of sleep-disordered breathing in multiple system atrophy

Anaïs Laga, MD, Fré Bauters, MD, PhD, Katrien Hertegonne, MD, PhD, Peter Tomassen, MD, PhD, Patrick Santens, MD, PhD, Chloé Kastoer, MD, PhD

- Sleep-disordered breathing = stridor, obstructive sleep apnea, and central sleep apnea
- Optimal strategy often remains unclear
- Systematic review with 29 papers included, with a total of 681 patients with MSA and sleep-disordered breathing

- Conflicting results on survival are found for CPAP
- Tracheostomy has a proven survival benefit
- Most beneficial outcomes with tracheostomy-invasive ventilation
- CPAP, other types of positive airway pressure therapy and tracheostomy can control OSA but may exacerbate central sleep apnea
- Lack of sufficient data regarding servoventilation or noninvasive PPV
- Individualized and multidisciplinary approach is mandatory

Treatment modalities:

continuous positive airway pressure,

tracheostomy,

tracheostomy-invasive ventilation,

noninvasive positive pressure ventilation,

adaptive servoventilation,

vocal cord surgery,

botulinum toxin injections,

oral appliance therapy,

cervical spinal cord stimulation,

selective serotonin reuptake inhibitors

Laga et al., 2025

MSA –Treatment (2)

- Orthostatic hypotension
  - Nonpharmacological – fluids, salt, gradual transitions, support hose, abdominal binder, avoid Valsalva, reduce or d/c anti-HTN
  - Pharmacological
    - Fludrocortisone (mineralocorticoid) - 0.1-0.5 mg/day
    - Midodrine (peripheral α1-agonist) - 5-10 mg TID
    - Pyridostigmine (cholinesterase inhibitor) - 30-60 TID
    - Droxidopa (L-DOPS, “prodrug” of NE), up to 600 mg TID
    - Atomoxetine (Shibao et al., 2021, single dose 18 mg)
- Supine hypertension – head up, NTG, clonidine

Recent Advances in Clinical Trials in Multiple System Atrophy

David Bendetowicz[1,2] · Margherita Fabbri[3,4] · Federico Sirna[5] · Pierre-Olivier Fernagut[6] · Alexandra Foubert-Samier[1,2,5] · Tiphaine Saulnier[5] · Anne Pavy Le Traon[3,4] · Cécile Proust-Lima[5] · Olivier Rascol[3,4] · Wassilios G. Meissner[1,2,7]

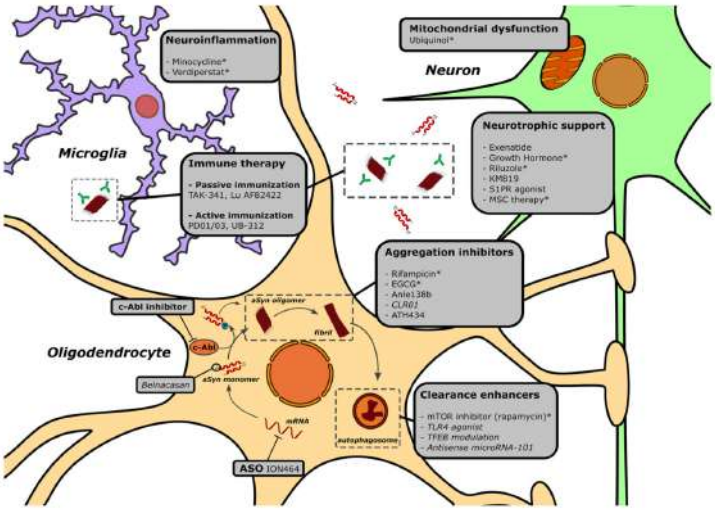


Fig. 1 Illustrated summary of tested compounds and their supposed therapeutic target at the cellular level. Compounds written in italics are currently in the preclinical development stage. Completed trials are indicated by an asterisk

- > 30 compounds tested in MSA clinical trials, but most do not reach primary endpoint
- Endpoint – most often Unified MSA Rating Scale (UMSARS)
- Most target a-synuclein
  - Reduce expression (ASO)
  - Immune (Passive, active)
  - Aggregation inhibitors
  - Clearance enhancer
- Other

Bendetowicz et al., 2024

Ongoing MSA trials

	Study type	Duration	Sample size	Treatment/target	Primary outcome
NCT05109091	DB, PC RCT, Ph2	52 wk	77	ATH434 (iron or a-syn)	Brain MRI iron
NCT05923866	DB, PC RCT, Ph2	28 wk	80	ONO-2808 (a-syn)	Safety, tolerability
NCT04165486	DB, PC RCT, Ph1	36 wk + 96 wk OLE	40	ION464 (a-syn)	Safety, tolerability
NCT04431713	Open label, Ph2	48 wk	50	Exenatide	Change UMSARS total
NCT05167721	DB, PC RCT adaptive Ph2	52 wk	76	Mesenchymal stem cells	Change UMSARS total
NCT05695378	DB, PC RCT, Ph2	40 wk	78	KM-8019 (cell death)	Change DAT
NCT05526391	DB, PC RCT, Ph2	52 wk	138	Tak-341 (a-syn)	Change modified UMSARS
NCT04680065	DB, PC RCT	156 wk	9	AAC2-GDNF	Safety, tolerability
NCT05104476	DB, PC RCT	48-72 wk	64	Lu AF8422 (a-syn)	Change UMSARS total
NCT05698017	DB, shamC RCT, Ph1/2	72 wk	18	Allogenic human oral mucosa stem cells	Safety, tolerability

Modified from Krismer et al., 2025

Safety and efficacy of the anti-α-synuclein monoclonal antibody amlenetug for the treatment of patients with multiple system atrophy (AMULET): a phase 2, randomised, double-blind, multicentre trial

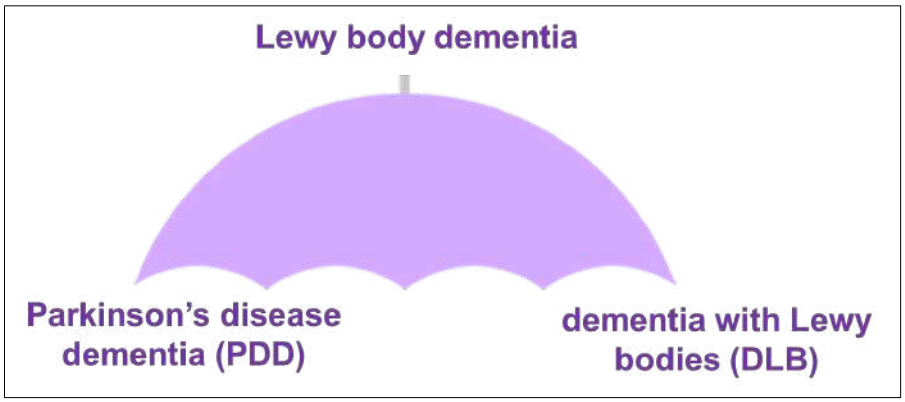
Lotte Kjaersgaard MD [a], Jonas Wiedemann MSc [a], Prof Wolfgang Singer MD [b], Atsushi Takeda MD [c], Anna-Karin Berger PhD [d], Mimi Folden Flensburg DVM PhD [a], Lene Hansen PhD [a], Pekka Kellunki PhD [a], Kristiina Kompus PhD [a], Krishan Nighoh BSc [a], Simon Nitschky Schmidt MSc [a], Mette Nørbæk Jørgensen RN [a], Badil Svanholm Fogh MSc [a], Stefano Zanigni MD PhD [a] ✉, Johan Luthman DDS PhD [a], AMULET Trial Group†

- Amlenetug is an anti-α-synuclein human immunoglobulin G1 monoclonal antibody (mAb) targeting the C-terminus of α-synuclein, with preferential binding to aggregated α-synuclein species.
- RCT at 18 movement disorder and autonomic dysfunction specialist sites, USA and Japan.
- MSA, ages 40–75 years, motor symptom onset in the past 5 year
- Randomly assigned (2:1) to IV amlenetug or placebo every 4 weeks for 48–72 weeks
- 61 received treatment (drug, n=40, placebo, n=21)
- Primary endpoint: change in UMSARS total score (Parts I and II)
- Secondary endpoints: parts of UMSARS, MRI-derived volumes
- Bayesian probability of 89.4% for a true slowing of clinical disease progression did not reach the predefined threshold of 97.5%, and accordingly, the primary endpoint was not met.
- No major treatment side effects
- Planned Phase 3 trial

Kjaersgaard et al., 2026

Dementia with Lewy Bodies DLB

DLB terminology



www.lbda.org

SPECIAL EDITORIAL

The terrorist inside my husband's brain

Susan Schneider Williams, BFA

I am writing to share a story with you, specifically for you. My hope is that it will help you understand your patients along with their spouses and caregivers a little more. And as for the research you do, perhaps this will add a few more faces behind the why you do what you do. I am sure there are already so many.

This is a personal story, sadly tragic and heartbreaking, but by sharing this information with you I know that you can help make a difference in the lives of others.

As you may know, my husband Robin Williams had the little-known but deadly Lewy body disease (LBD). He died from suicide in 2014 at the end of an intense, confusing, and relatively swift persecution at the hand of this disease's symptoms and pathology. He was not alone in his traumatic experience with this neurologic disease. As you may know, almost 1.5 million nationwide are suffering similarly right now.

Although not alone, his case was extreme. Not until the coroner's report, 3 months after his death, would I learn that it was diffuse LBD that took him. All 4 of the doctors I met with afterwards and who had reviewed his records indicated his was one of the worst pathologies they had seen. He had about 40% loss of dopamine neurons and almost no neurons were free of Lewy bodies throughout the entire brain and brainstem.

Robin is and will always be a larger-than-life spirit who was inside the body of a normal man with a human brain. He just happened to be that 1 in 6 who is affected by brain disease.

Not only did I lose my husband to LBD, I lost my best friend. Robin and I had in each other a safe harbor, together, or if he was on the road. We would discuss our joys and triumphs, our fears and insecurities, and our concerns. Any obstacles life threw at us individually or as a couple were somehow surmountable because we had each other.

When LBD began sending a firestorm of symptoms our way, this foundation of friendship and love was our armor.

The colors were changing and the air was crisp; it was already late October of 2013 and our second wedding anniversary. Robin had been under his doctors' care. He had been struggling with symptoms that seemed unrelated: constipation, urinary difficulty, heartburn, sleeplessness and insomnia, and a poor sense of smell—and lots of stress. He also had a slight tremor in his left hand that would come and go. For the time being, that was attributed to a previous shoulder injury.

On this particular weekend, he started having gut discomfort. Having been by my husband's side for many years already, I knew his normal reactions when it came to fear and anxiety. What would follow was markedly out of character for him. His fear and anxiety skyrocketed to a point that was alarming. I wondered privately, Is my husband a hypochondriac? Not until after Robin left us would I discover that a sudden and prolonged spike in fear and anxiety can be an early indication of LBD.

He was tested for diverticulitis and the results were negative. Like the rest of the symptoms that followed, they seemed to come and go at random times. Some symptoms were more prevalent than others, but these increased in frequency and severity over the next

SPECIAL ARTICLE

Twilight and Me: A Soliloquy

By Daniel Alejandro Drubach, MD, FAAN

ABSTRACT

Dementia with Lewy bodies (DLB) is the third most frequent type of dementia. The range of symptoms it causes is quite broad and includes parkinsonism, autonomic dysfunction, cognitive deficits, visual and auditory hallucinations, dream disturbances, and other unusual manifestations such as "sense of presence," Capgras syndrome, and fluctuations in neurologic status. The author, an experienced behavioral neurologist and previous *Continuum* author, has been diagnosed with DLB and assumes the dual role of physician and patient. Each role provides a unique perspective. He discusses the importance of hope and fear in coping with the illness.

INTRODUCTION

My mother had a saying that she would recite when something bad had occurred. It consisted of five words, *de lo malo, lo bueno*, which translates from Spanish as "from the bad, the good." It means extracting the drop of good from anything that is bad; it also assumes that the bad always contains some particle of good.

Despite my mother's precious and desperately necessary optimism, it is hard to find some good in being diagnosed with dementia with Lewy bodies (DLB). It is the third most frequent cause of dementia, following Alzheimer disease and vascular dementia and ahead of frontotemporal dementia. It most frequently affects individuals around the age of 75 and is more common in men than in women. It is a degenerative disorder that courses with relentless progression and for which there is no treatment or cure.

I diagnosed myself with DLB at approximately age 60. Almost immediately after I accepted the news, I decided to give my disease a unique name. I learned early on that the manifestations of the disorder were unique in every individual, and thus I wanted to communicate with my disease in a personal fashion. So I named it Twilight, perhaps because I realized that I am reaching the twilight of my life.

CITE AS:
CONTINUUM (MINNEAP MINN)
2021;27(4):BEHAVIORAL NEUROLOGY AND PSYCHIATRY:1209–1217.

Address correspondence to
Dr Daniel A. Drubach,
Department of Neurology, Mayo Clinic Alix College of Medicine and Science, 200 First St SW, Rochester, MN, 55905. drubach.daniel@mayo.edu.

RELATIONSHIP DISCLOSURE:

DLB epidemiology

- 2nd most frequent neurodegenerative dementia following AD
- 15-20% of late onset dementias
- In population-based and clinic-based studies, represents ~ 4-30% of dementia cases
- May be underrepresented in many clinical studies due to methodological and other issues

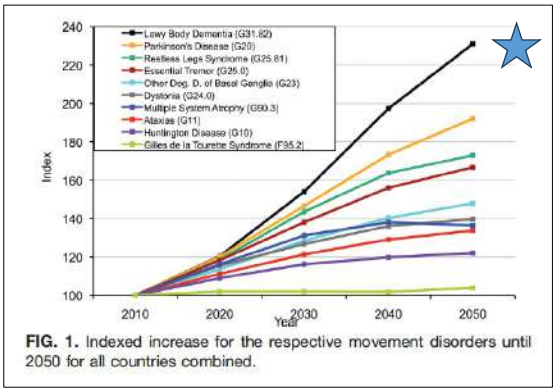


FIG. 1. Indexed increase for the respective movement disorders until 2050 for all countries combined.

Barker et al., 2002; Zaccai et al., 2005; Vann Jones et al., 2014; Desai et al., 2022

Substantial impact

Delayed or misdiagnosis
- Generates confusion for patients and families
- Missed opportunities for management, planning, research studies, and more

Increased disability and decreased quality of life
- Neuropsychiatric symptoms, cognitive fluctuations, motor features, autonomic, and other symptoms
- Cognitive + Motor = "Like having both Alzheimer's and Parkinson's disease"

High economic burden
- Costs of care/month of survival in DLB >> AD

Marked caregiver stress and burden

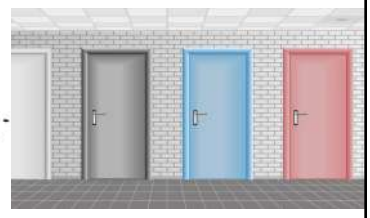
Clinical trial and management challenges – limited medications, side effects, no disease-modifying agents

Mueller et al., 2017; Frazer et al., 2023; Desai et al., 2022; Espinosa et al., 2020; Goldman et al., 2020

Challenges in recognition and diagnosis

- DLB as "the most common dementia people have never heard of"
  - On average, takes 18 months and 3 doctors to receive correct diagnosis
- DLB (and to some degree, PD) may present in numerous ways and thus, to different specialties





Differences in the treatment needs of patients with dementia with Lewy bodies and their caregivers and differences in their physicians' awareness of those treatment needs according to the clinical department visited by the patients: a subanalysis of an observational survey study

Manabu Ikeda[1*], Shunji Toya[2], Yuta Manabe[3], Hajime Yamakage[4] and Mamoru Hashimoto[1,5]

Ikeda et al., 2024

Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

OPEN

McKeith et al., 2017

- Core features
  - Dementia, sufficient to interfere with normal functions or daily activities
  - Fluctuating cognition
  - Recurrent visual hallucinations
  - REM sleep behavior disorder, which may precede cognitive decline
  - Parkinsonism motor features
- Supportive clinical features
  - *Severe sensitivity to antipsychotics, postural instability, repeated falls, syncope or episodes of unresponsiveness, autonomic dysfunction, hypersomnia, hyposmia, hallucinations, delusions, apathy, anxiety, depression*
- Biomarkers
  - *Indicative*
  - *Supportive*

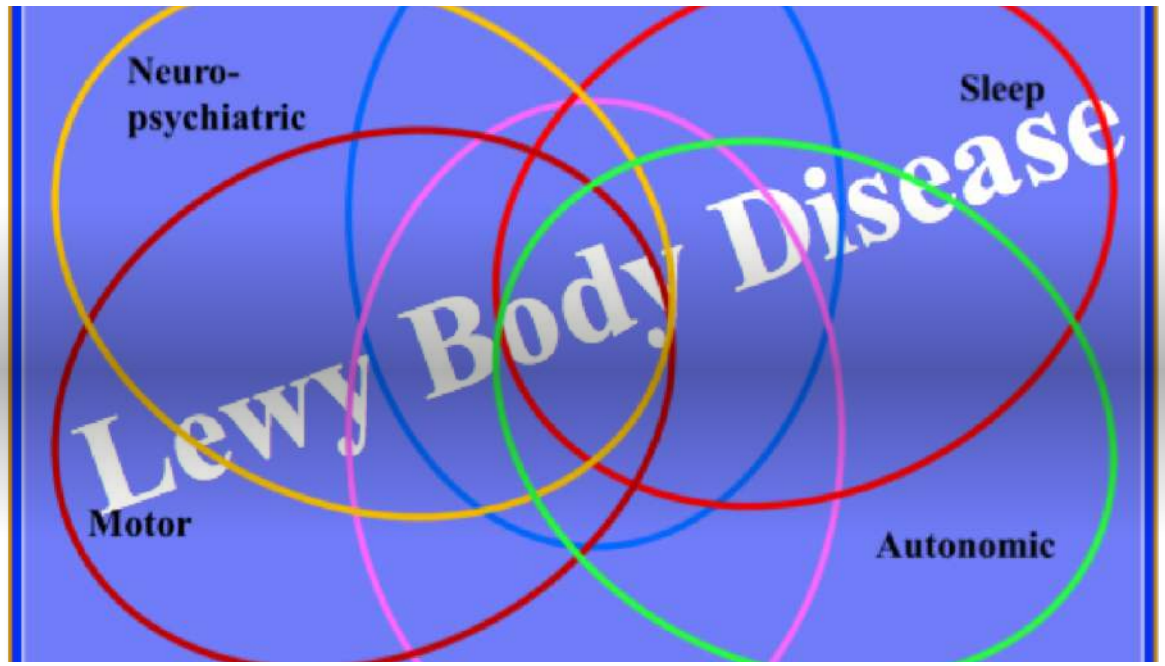
"One year rule"

Indicative biomarkers

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

Supportive biomarkers

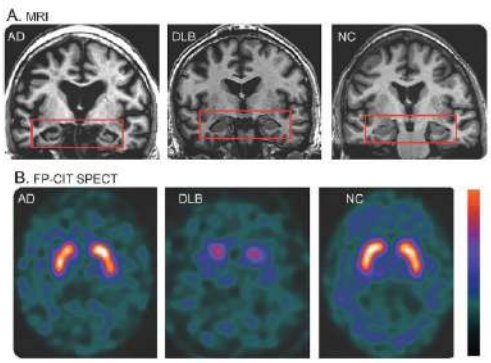
Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.



Courtesy Brad Boeve

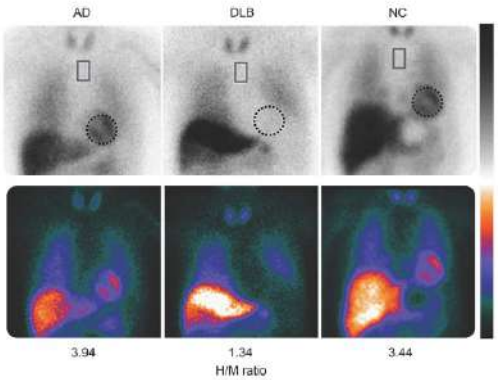
Biomarkers in DLB criteria: AD vs. DLB vs. NC

Figure 1 Coronal T1-weighted MRI and ^{123}Iodine FP-CIT SPECT images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC)



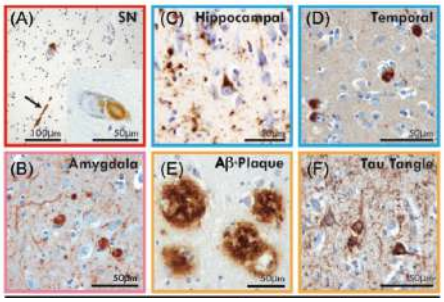
(A) On the MRI, note the relative preservation of medial temporal lobe volume (rectangles) in DLB, which is similar to NC, whereas atrophy is obvious in AD. (B) On the FP-CIT SPECT images, note the minimal uptake in DLB, which is restricted to the caudate (period or full-stop appearance) compared to the robust uptake in the caudate and putamen in AD and NC (comma appearance). Reproduced with permission from Dr. Val Lowe, Mayo Clinic, Rochester, MN.

Figure 2 ^{123}Iodine-metaiodobenzylguanidine myocardial imaging in patients with Alzheimer disease (AD), dementia with Lewy bodies (DLB), and age-matched normal controls (NC)



Images taken 3 hours after injection are shown in 2 color scales, and typical regions of interest are shown on the heart (dotted circle) and upper mediastinum (rectangle). Heart-to-mediastinum (H/M) ratios are standardized to the values comparable to a medium-energy general-purpose collimator condition.[43] Reproduced with permission from Dr. Kenichi Nakajima, Department of Nuclear Medicine, Kanazawa University.

DLB pathology



	Predominant region of LRP	Mild AD Pathology	Intermediate AD pathology	Severe AD pathology
Dementia (DLB or PDD)	Neocortical	DLB	DLB/AD	DLB/AD
	Limbic	DLB	DLB/AD	AD
PD	Brainstem	PD	AD/PD	AD
Preclinical	Amygdala	iLBD	AD	AD
	Olfactory	iLBD	AD	AD
CLINICAL		Not AD	AD	AD

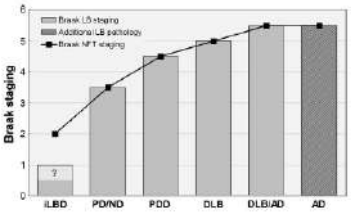
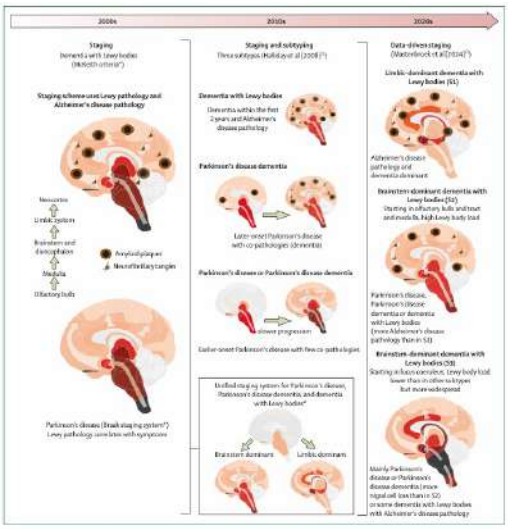


Fig. 1 Spectrum of Lewy body diseases with relations between Braak LB and Braak neuritic (NFT) stages ranging from iLBD to DLB/AD. *LB* Lewy body; *NFT* neurofibrillary tangle; *iLBD* incidental Lewy body disease; *PD* Parkinson disease; *PD/ND* Parkinson disease - not demented; *PDD* Parkinson's disease-dementia; *DLB* dementia with Lewy bodies; *DLB/AD* DLB with Alzheimer disease; *AD* Alzheimer's disease

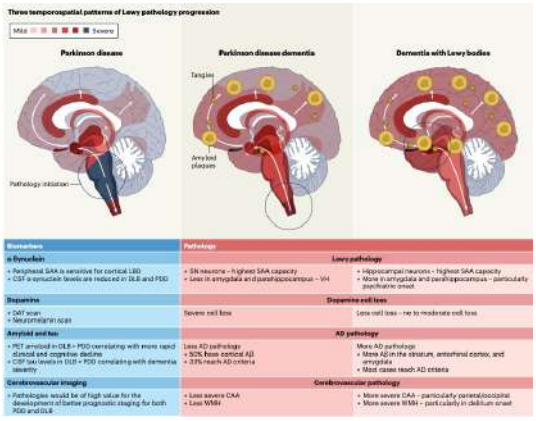
McKeith et al., 2005; McKeith 2007; Jellinger 2018; Goldman…Halliday et al., 2025

DLB and pathologies



Biological effects of pathologies in Lewy body diseases: why timing matters

Dementia with Lewy bodies and Parkinson disease dementia – the same or different and is it important?



Matar and Halliday 2025; Fu and Halliday 2025

Presence of co-pathologies in DLB

TABLE 1 Co-pathology in dementia with Lewy bodies

Type of neurodegenerative condition	Type of pathology	Prevalence in DLB
Alzheimer's disease	Amyloid beta ($A\beta$) plaques Tau neurofibrillary tangles	48% to 88% of individuals with DLB have intermediate- or high-level AD pathology vs 17% to 62% in PDD and 7% to 10% in those with PD who are dementia free[7–10] AD pathology is associated with a greater Lewy pathology burden[11]
TDP-43 and limbic-predominant age-related TDP-43 encephalopathy (LATE)	TDP-43	13% to 60% of individuals with DLB[11–15] More prevalent in the advanced neocortical Lewy pathology (LP) stages, in the presence of AD co-pathology in DLB vs individuals with PD who are dementia-free[11,13,15]
Frontotemporal lobar degeneration (FTLD) tau	Tau	Less prevalent compared to other co-pathologies
Other tau-related neurodegenerative conditions, including aging-related tau astrogliopathy (ARTAG)	Tau	Not studied in DLB alone In Lewy body disease overall (PD + DLB): 31% of participants without AD co-pathology[22] 72% in the presence of AD co-pathology[22]
Cerebrovascular pathology	Microinfarcts Gross infarcts	**Neuropathological** samples[16] Microinfarcts 26.7% Gross infarcts 6.7%[16] **MRI-based samples**[57,62] 18.8% to 27%
	Cerebral amyloid angiopathy (CAA)	**Neuropathological samples** CAA 66.7% none to intermediate AD neuropathological changes vs 94.7% CAA prevalence in individuals with high AD neuropathological changes[13] CAA is highest in DLB (82% to 91%), followed by PDD (50%), and lowest in cognitively unimpaired PD (21.7%)[13,17]
	Cerebral microbleeds (usually associated with CAA)	Are also more frequent in DLB (30% to 45.2%) than in PDD (26.1%), PD (11.5%), and control participants (17.1%)[58–60] However, one study that compared participants with DLB with and without microbleeds did not find differences in florbetapir binding and found that high systolic blood pressure was the factor associated with microbleeds in DLB[61]
	White matter hyperintensity (WMH) burden	It may be ↑ in DLB vs healthy controls,[59,62,66–68] although reports are inconsistent[69–71]

Toledo et al., 2022

Effects of co-pathologies

- Neuropathology studies
  - From NACC database (n=6262) with 0-6 comorbid neuropathologic findings per individual (75.5% with ≥ 2)
  - Presence of AD neuropath changes significantly affected all cognitive domains; presence of LBD affected attention, processing speed, language
- Biomarker studies
  - Amyloid+ (CSF AB1-42, PET) was main predictor of lower cognitive performance when together with Tau+ (CSF p-tau, PET). Tau+ associated with lower frequency of parkinsonism and RBD (Ferreira et al,. 2020)
  - In large cohorts of cognitively impaired individuals, CSF biomarkers detect coexistence of AD and LB pathology in ~20%–25%, independent of primary clinical diagnosis
  - AD-LBD patients showed worse global cognition (attentive/executive and visuospatial functions) and worse motor functions
  - In cognitively unimpaired individuals, concurrent AD-LBD pathologies predicted longitudinal cognitive progression with faster worsening of global cognition, memory, and attentive/executive functions
  - LB-biomarkers (i.e., CSF a-syn SAA) vary with LBD pathological variant (amygdala-predominant)

Disentangling and quantifying the relative cognitive impact of concurrent mixed neurodegenerative pathologies

Carolina Maldonado-Diaz[1] · Satomi Hiya[1] · Raquel T. Yokoda[1] · Kurt Farrell[1,2,3,4,5,6] · Gabriel A. Marx[3,4,5,6,7] · Justin Kauffman[1,2,3,4,5,6] · Elena V. Daoud[8] · Mitzi M. Gonzales[4,10,11] · Alicia S. Parker[10,11] · Leyla Cambeldek[1] · Lakshmi Shree Kulumani Mahadevan[1] · John F. Crary[1,2,3,4,5,6] · Charles L. White III[8] · Jamie M. Walker[3,4,5,11] · Timothy E. Richardson[10]

In vivo detection of Alzheimer's and Lewy body disease concurrence: Clinical implications and future perspectives

Simone Baiardi[1,3] | Oskar Hansson[3,4] | Johannes Levin[5,6,7] | Piero Parchi[1,2]

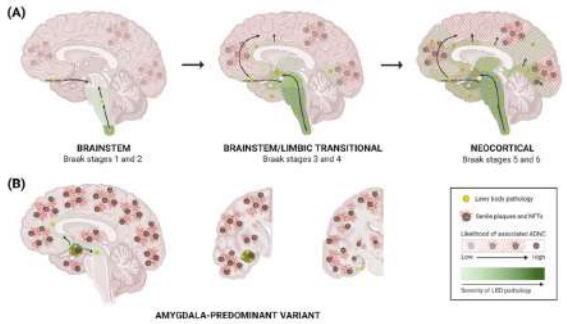


FIGURE 1 Schematic representation of LBD and AD copathology. (A) According to the McKeith/Braak staging, LB pathology initially involves the lower brainstem (left). Then, following an ascending course, it spreads to the limbic regions (middle) and eventually reaches the neocortices (right). As LBD progresses, the likelihood of coexisting AD pathology increases because of the older mean age and a likely synergistic effect between the two pathologies. (B) The amygdala-predominant variant of LBD is almost invariably associated with AD pathology. Besides the amygdala, the area showing the greatest LB pathology load in this variant, LBs can sometimes be detected in the anterior cingulate gyrus, the entorhinal cortex and the upper brainstem (limited to the midbrain). Hemibrain sagittal sections (A, B-left) and coronal sections at the level of the amygdala (B-middle) and hippocampus (B-right). AD, Alzheimer's disease; ADNC, AD neuropathologic change; LB, Lewy bodies; LBD, Lewy body disease; NFTs, neurofibrillary tangles. Figure created with BioRender.com.

Ferreira et al., 2020; Maldonado-Diaz et al., 2024; Baiardi et al., 2024

Cholinergic system (brain & body)

Impaired cholinergic integrity of the colon and pancreas in dementia with Lewy bodies

Niels Okkels,[1,2,3] Jacob Horsager,[1,2] Tatyana D. Fedorova,[1,2] Karoline Knudsen,[1] Casper Skjærbæk,[1,2] Katrine B. Andersen,[1,2] Miguel Labrador-Espinosa,[4,5] Karsten Vestergaard,[6] Janne K. Mortensen,[4,5] Henriette Klit,[7] Mette Møller,[6] Erik H. Danielsen,[8] Erik L. Johnsen,[9] Goran Bekan,[7] Kim V. Hansen,[7] Ole L. Munk,[4] Malene F. Damholdt,[2] Pernille L. Kjeldsen,[4,5] Allan K. Hansen,[1,2] Hanne Gottrup,[3] Michel J. Grothe[4,5] and Per Borghammer[1,2]

Cholinergic changes in Lewy body disease: implications for presentation, progression and subtypes

Niels Okkels,[1,2] Michel J. Grothe,[4,4,5] John-Paul Taylor,[6] Steen Gregers Hasselbalch,[7,8] Tatyana D. Fedorova,[2] Karoline Knudsen,[1] Sygrid van der Zee,[9] Teus van Laar,[9] Nicolaas I. Bohnen,[10,11,12,13,14] Per Borghammer[2,15] and Jacob Horsager[2]

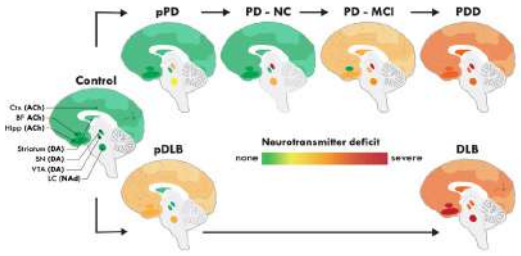


Figure 1 Schematic representation comparing the cell loss seen across dopaminergic (DA), cholinergic (ACh) and noradrenergic syster Parkinson's disease and dementia with Lewy bodies (DLB). Whilst patients with DLB are diagnosed at around the same age as patients Parkinson's disease dementia (PDD), they show more severe cholinergic and noradrenergic loss and less severe dopaminergic loss, especially i nigrostriatal system. Presumably, prodromal Parkinson's disease (pPD) and DLB (pDLB) patients have similar disease durations given the manifest of isolated REM sleep behaviour disorder (iRBD) but pDLB appears more resistant to cell loss, especially across the dopaminergic system. This underpin the range of proposed pDLB phenotypes such as mild cognitive impairment-, delirium- and psychiatric-onset. However, the compens processes are ultimately lost in DLB, which then presents with a devastating cholinergic cell loss and clinical dementia. PD-NC (normal cogni PD-MCI (mild cognitive impairment; BF = basal forebrain; Ctx = cortex; Hipp = hippocampus; LC = locus coeruleus; SN = substantia nigra; VTA = v tegmental area.

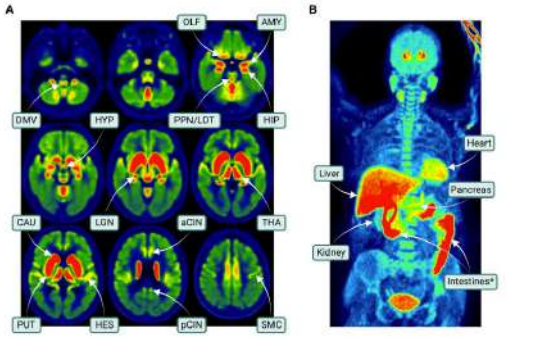


Figure 2 The brain and body visualized using ^{18}F-fluoroetoxybenzovesamicol, a cholinergic PET tracer targeting the vesicular acetylcholine transport- er. (A) Averaged axial slices of tracer uptake in human brains without neurological disease. Brain images are intensity-normalized to a supratentorial white matter region. Red colours indicate standard uptake value ratios >4. (B) Whole-body maximum intensity projection displaying the distribution of tracer in the liver, kidney, heart and pancreas. aCIN = anterior cingulate; AMY = amygdala; CAU = caudate; DMV = dorsal motor nucleus of the vagus and hypoglossal nucleus; HES = Heschl's gyrus; HIP = hippocampus; HYP = hypothalamus; LGN = lateral geniculate nucleus; OLF = olfactory cortex; pCIN = posterior cingulate; PPN/LDT, pedunculopontine and laterodorsal tegmental nuclei; PUT = putamen; SMC = somatomotor cortex; THA = thal- amus. *Proximal small intestines containing excreted tracer; more distal sections of the intestines are not visible on this projection.

Okkels et al., 2023, 2024; Lewis 2023

Noradrenergic system

Locus Coeruleus Pathology Indicates a Continuum of Lewy Body Dementia

Bension S Tilley [1], Shivani R Patel [1], Marc H Goldfinger [1], Ronald K B Pearce [1], Steve M Gentleman [1]

- Neuronal loss in the LC with DLB > PDD > PD > HC
- Potential contributions to neuropsychiatric symptoms

TABLE 1 | Studies involving degeneration of locus coeruleus—noradrenaline system in patients with dementia with Lewy bodies.

Number of Subjects	Mean age in years	Results effects of LC degeneration	References
$N = 26$ DLB/PDD	79	DLB/PDD and AD greater LC damage vs. FTLD, VaD	Haglund et al., 2016
$N = 25$ DLB/PDD	75	DLB/PDD and AD higher LC degeneration vs. FTLD, VaD	Brunnström et al., 2011
$N = 4$ LB PSP	78	LB and neuronal loss in LC	Mori et al., 2002
$N = 9$ DLB	75	Neuronal loss in all DLB cases	Iseki et al., 2001

Tilley et al., 2021; Hansen 2021; Goldstein et al., 2024; Goodheart 2024

Cardiac noradrenergic deficiency revealed by ^{18}F-dopamine positron emission tomography identifies preclinical central Lewy body diseases

David S. Goldstein,[1] Courtney Holmes,[1] Patti Sullivan,[1] Grisel Lopez,[1] Janna Gelsomino,[1] Sarah Moore,[1] Risa Isonaka,[1] Tianxia Wu,[2] and Yehonatan Sharabi[1]

- Assess predictive value of low versus normal cardiac 18F-dopamine PET (index of myocardial content of norepinephrine) in at-risk individuals (prospective, observational study)
- 34 participants with ≥ 3 risk factors (genetics, olfactory, RBD, OH) had serial cardiac 18F-dopa PET at 1.5-year intervals for up to 7.5 years or PD/DLB dx
- 9 participants had low initial myocardial 18F-dopa–derived radioactivity; 25 had normal radioactivity
- At 7 years of follow-up, 8/9 with low initial radioactivity and 1/11 with normal radioactivity were diagnosed with a central LBD (LBD+)

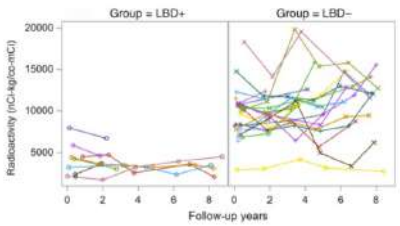
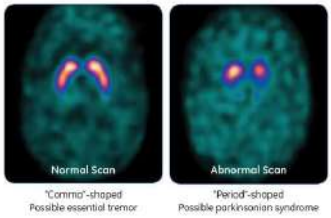


Figure 5. Myocardial ^{18}F-dopamine–derived radioactivity during follow-up.

DLB and dopaminergic dysfunction

- Dopamine transporter imaging (DaT scan) not always “positive” (D-)
- Abnormal scans had a mean sensitivity of 77.7% for detecting clinical probable DLB; specificity of 90.4% for excluding non-DLB dementia (mainly AD); mean value of 85.7% was achieved for overall diagnostic accuracy (McKeith et al., 2007)



- 20% lacking DaT evidence at dementia diagnosis (O’Brien et al., 2014)
- 10% with autopsy diagnosis and negative DaT (Thomas et al., 2017)
- 35% of MCI-LB are D- at presentation

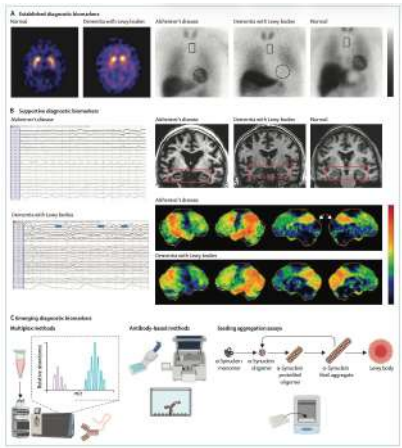
- Sensitivity only 66% in differentiating MCI-LB vs MCI-AD

McKeith et al., 2007; O’Brien et al., 2014; Walker et al., 2015; Chen et al., 2021; Thomas et al., 2017; Donaghy et al., 2023

The quest for biomarkers

Diagnostic and other biomarkers of dementia with Lewy bodies: from research to clinical settings

Angeliki Zarkali, Michael Bartl, Nick C Fox, Louis C S Tan, Brit Mollenhauer, Rimona S Weil



HOT OFF THE PRESS!

Fluid and Tissue Biomarkers of Lewy Body Dementia: Report of an LBDA Symposium

Alpha-synuclein pathology
- CSF seeded aggregation, skin biopsy, submandibular gland, colon biopsy

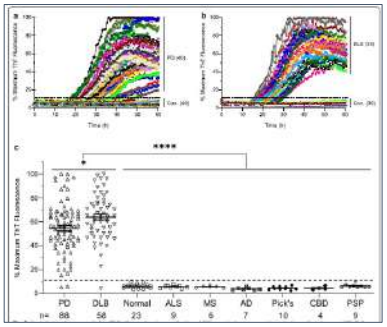
AD pathology
- CSF AB, tau, pTau, NfL
- Plasma AB42/40, tTau/pTau, NfL

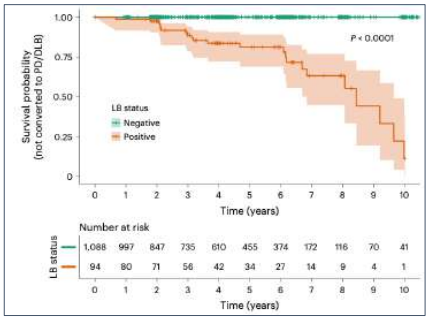
Other mechanisms
- CSF autophagy
- CSF biomarkers NPTX2, VGF
- NfL, inflammation, etc

Scott et al., 2022; Vrillon et al., 2024; Jain et al., 2024; Zarkali et al., 2026

DLB and α-synuclein biomarkers

- CSF αSyn-SAA can reliably detect α-Syn aggregates across different neurodegenerative diseases with dementia if limbic or neocortical stage LB pathology is present, regardless of co-pathology or clinical phenotype
  - Less sensitive to amygdala predominant or brainstem Lewy pathology
- Sensitivity and specificity in CSF samples from autopsy confirmed PD and DLB > 90%
- RT-QuIC identified MCI-LB vs. MCI-AD and unspecified MCI
  - Sensitivity 95%, specificity 97%, accuracy 96%
  - Accuracy 97.3%, 93.7% (in 2 MCI-LB cohorts)
- CSF αSyn-SAA in 1182 cognitively unimpaired
  - Found 8% LB+, 26% Abeta+ (13% also LB+), and 16% tau+
  - LB+ status associated with conversion to PD/DLB





Bongianni et al., 2019; Bargar et al., 2021; Rossi et al., 2021
Hall et al., 2022; Arnold et al., 2022; Concha-Marambio et al., 2023; Pamqvist et al., 2023

Association of CSF α-Synuclein Seeding Amplification Assay Results With Clinical Features of Possible and Probable Dementia With Lewy Bodies

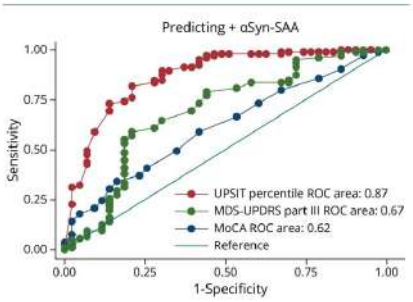
David G. Coughlin, MD, MTR, Karen R. MacLeod, MS, John S. Middleton, MS, Andrea C. Bozoki, MD, James E. Galvin, MD, MPH, David J. Irwin, MD, Carol F. Lippa, MD, Irene Litvan, Oscar L. Lopez, MD, Sarah Berman, Debby W. Tsuang, MD, Cyrus P. Zabetian, MD, MS, Lawrence S. Honig, MD, PhD, Karen S. Marder, MD, Jori E. Fleisher, MD, MSCE, Marwan Sabbagh, MD, Dylan Wint, MD, Angela S. Taylor, Lynn Bekris, PhD, James B. Leverenz, MD, and Douglas Galasko, MD

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Neurology® 2024;103:e209656. doi:10.1212/WNL.0000000000209656

- CSF samples from 191 participants diagnosed with DLB – from DLB Consortium and PDBP
  - Mean age 69.9 ± 6.8, 15% female
- 50 age-matched and sex-matched clinical controls and 49 younger analytical controls
- 72% (137/191) of DLB had positive αSyn-SAAs vs 4% of control groups
- DLB with positive αSyn-SAA had lower MoCA scores, worse parkinsonism on MDS-UPDRS Part 3, greater reports of RBD, worse hyposmia on UPSIT

Figure 1 Receiver Operator Curve Areas for Continuous Variables in Predicting αSyn-SAA Positivity in the Patients With Clinically Diagnosed DLB



Coughlin et al., 2024

Plasma pTau181 Reveals a Pathological Signature that Predicts Cognitive Outcomes in Lewy Body Disease

Carla Abdelnour, MD, PhD, Christina B. Young, PhD, Marian Shahid-Besanti, MSc, Alena Smith, Edward N. Wilson, PhD, Javier Ramos Benitez, Hillary Vossler, Melanie J. Plastini, PhD, Joseph R. Winer, PhD, Geoffrey A. Kerchner, MD, PhD, Brenna Cholerton, PhD, Katrin I. Andreasson, MD, Victor W. Henderson, MD, MS, Maya Yutsis, PhD, Thomas J. Montine, MD, PhD, Lu Tian, PhD, Elizabeth C. Mormino, PhD, and Kathleen L. Poston, MD, MS

- N=565 participants: 94 LBD with normal cognition, 83 LBD with abnormal cognition, 114 with AD, and 274 cognitively normal
- Plasma pTau181 levels, subset had CSF pTau181/Aβ42, CSF Aβ42/Aβ40 or amyloid-β PET
- Plasma pTau181 predicted concurrent ADNC and amyloidosis in LBD with abnormal cognition with 87% and 72% accuracy, respectively
- Higher baseline plasma pTau181 was associated with worse cognitive function (baseline MoCA and CDR-SB) and greater cognitive decline (CDR-SB and memory) over 3 years in those LBD + abnormal cognition

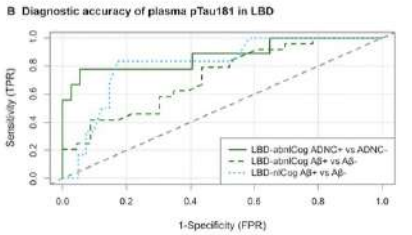


Figure 1: Plasma pTau181 as a diagnostic biomarker in Lewy body disease. A) Comparison of plasma pTau181 levels among

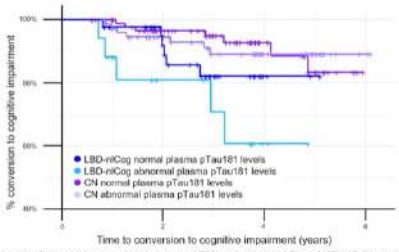


Figure 2: Survival curves of conversion to cognitive impairment (MCI or dementia) in CN and LBD-nlCog participants with normal and abnormal plasma pTau181 levels. LBD-nlCog with normal plasma pTau181 levels (n= 44, dark blue line), LBD-nlCog with

Abdelnour et al., 2024

Clinical effects of Lewy body pathology in cognitively impaired individuals

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Corinne Quadalti, Sebastian Palmqvist, Sara Hall, Marcello Rossi, Angela Mammana, Shorena Janelidze, Sofia Dellavalle, Niklas Mattsson-Carlgren, Simone Baiardi, Erik Stomrud, Oskar Hansson & Piero Parchi

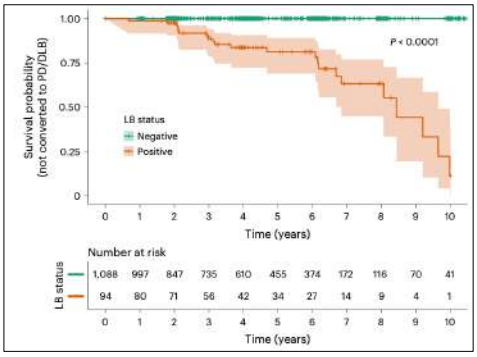
Cognitive effects of Lewy body pathology in clinically unimpaired individuals

Received: 21 January 2023
Accepted: 8 June 2023
Published online: 18 July 2023

Sebastian Palmqvist, Marcello Rossi, Sara Hall, Corinne Quadalti, Niklas Mattsson-Carlgren, Sofia Dellavalle, Pontus Tideman, Joana B. Pereira, Maria H. Nilsson, Angela Mammana, Shorena Janelidze, Simone Baiardi, Erik Stomrud, Piero Parchi & Oskar Hansson

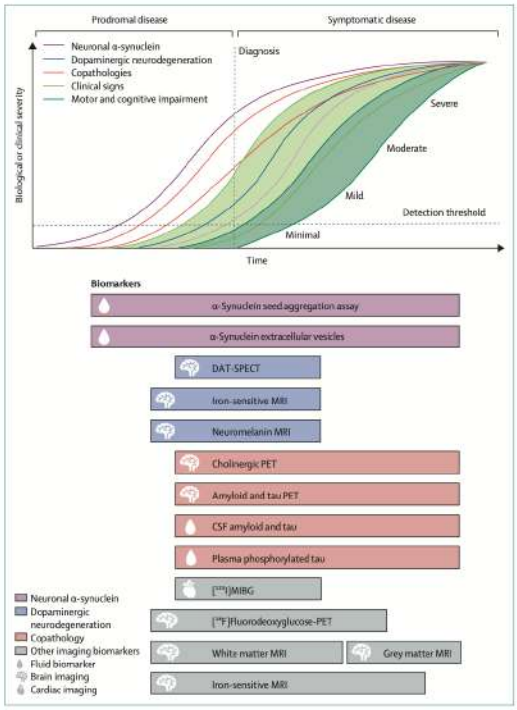
- BioFINDER study
- CSF for SAA in 883 memory clinic patients (MCI or dementia)
- LB pathology (SAA+) in 23%, with only 21% fulfilling clinical criteria for PDD or DLB at baseline
- Among LB+, 48% had AD pathology
- Whole sample, 54% with AD pathology (17% MCI, 24% dementia), LB-
- LB pathology but not Abeta or tau was associated with hallucinations, worse attention/executive, visuospatial and motor function
- LB pathology was also associated with faster cognitive decline, independent of Abeta or tau, cognitive stage or baseline diagnosis

- CSF SAA in In 1182 cog unimpaired
- 8% LB+, 26% Abeta+ (13% also LB+), 16% tau+



Qualdati et al., 2023; Palmqvist et al., 2023

Biomarkers and potential use along disease course



Zarkali et al., 2026

Research criteria for the diagnosis of prodromal dementia with Lewy bodies

Ian G. McKeith, F Med Sci, MD, Tanis J. Ferman, PhD, Alan J. Thomas, PhD, Frédéric Blanc, MD, Bradley F. Boeve, MD, Hiroshige Fujishiro, MD, Kejal Kantarci, MD, MS, Cristina Muscio, PhD, John T. O'Brien, F Med Sci, DM, Ronald B. Postuma, MD, MSc, Dag Aarsland, PhD, Clive Ballard, MD, Laura Bonanni, MD, PhD, Paul Donaghy, PhD, Murat Emre, MD, James E. Galvin, MD, MPH, Douglas Galasko, MD, Jennifer G. Goldman, MD, MS, Stephen N. Gomperts, MD, PhD, Lawrence S. Honig, MD, PhD, Manabu Ikeda, MD, PhD, James B. Leverenz, MD, Simon J.G. Lewis, MD, Karen S. Marder, MD, MPH, Mario Masellis, MD, PhD, David P. Salmon, PhD, John Paul Taylor, MB, BS, PhD, Debby W. Tsuang, MD, Zuzana Walker, MD, and Pietro Tiraboschi, MD, for the prodromal DLB Diagnostic Study Group

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Research diagnostic criteria for mild cognitive impairment with Lewy bodies: A systematic review and meta-analysis

Paul C Donaghy[1] | Claudia Carrarini[2,3] | Daniel Ferreira[4,5] | Annegret Habich[4,6] | Dag Aarsland[7,8] | Claudio Babiloni[9,10] | Ece Bayram[11] | Joseph PM Kane[12] | Simon JG Lewis[13] | Andrea Pilotto[14] | Alan J Thomas[1] | Laura Bonanni[15] | on behalf of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment Lewy Body Dementias Prodromal Working Group

Diagnostic features from the diagnostic criteria for mild cognitive impairment with Lewy bodies (McKeith et al. 2020)[3]

Core clinical features

- Fluctuating cognition with variations in attention and alertness.
- Recurrent visual hallucinations.
- REM sleep behavior disorder.
- One or more spontaneous cardinal features of parkinsonism.

Proposed biomarkers

- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
- Polysomnographic confirmation of REM sleep without atonia.
- Reduced meta-iodobenzylguanidine (MIBG) uptake on myocardial scintigraphy.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; prolonged or recurrent delirium; autonomic dysfunction; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Potential biomarkers of MCI-LB

- Quantitative EEG showing slowing and dominant frequency variability.
- Relative preservation of medial temporal lobe structures on structural imaging.
- Insular thinning and gray matter volume loss on MRI.
- Low occipital uptake on perfusion/metabolism scan.

A diagnosis of probable MCI-LB requires the presence of two core clinical features, or one core clinical feature and one or more proposed biomarkers.

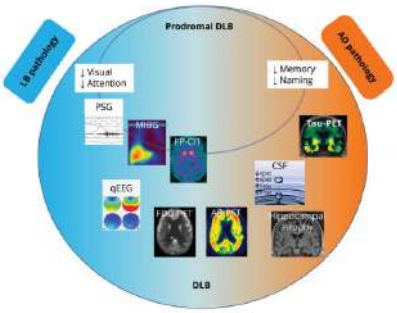
A diagnosis of possible MCI-LB requires the presence of one core clinical feature and no proposed biomarkers, or one or more proposed biomarkers with no core clinical features.

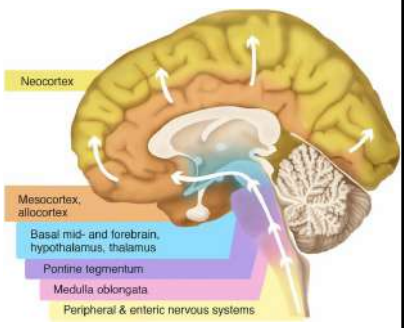
McKeith et al., 2020; Donaghy et al., 2023

Prodromal DLB



- Several possible clinical presentations
  - Mild cognitive impairment
  - Delirium onset
  - Psychiatric-onset
  - RBD
  - Autonomic dysfunction
  - Anosmia
  - Other





Molano et al., 2010, Ferman et al., 2013; Donaghy & McKeith 2014

Biological frameworks and DLB

Implications and opportunities regarding biological frameworks in overt and prodromal dementia with Lewy bodies

Jennifer G. Goldman[1,2] | Bradley F. Boeve[3] | Douglas Galasko[4] | John-Paul Taylor[5] | James E. Galvin[6] | James B. Leverenz[7] | Frederic Blanc[8] | Glenda Halliday[9] | Kejal Kantarci[10] | Afina W. Lemstra[11] | Iracema Leroi[12] | Simon J. G. Lewis[13] | Irene Litvan[14] | Helen Medsger[15] | John O'Brien[16] | Sonja W. Scholz[17,18] | Dag Aarsland[19,20] | Manabu Ikeda[21] | Ian McKeith[5] | Angela Taylor[22]

- National Institute on Aging-Alzheimer's Association
- Neuronal α-synuclein Disease Integrated Staging System
- SynNeurGe

- Discuss the implications of these biological frameworks for the DLB community
- Topics regarding multiple pathologies and neurochemical systems, clinical heterogeneity, and functional impairment, and potential impact on clinical trials and care
- Challenges and opportunities

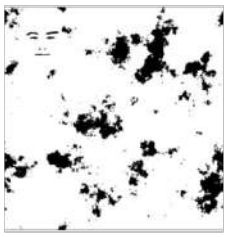
- Multiple pathologies
- Multiple neurochemical systems
- Genetics
- Heterogeneity in prodromal and overt DLB
- Unique clinical features
- Clinical – functional impairment
- Lived experience
- Clinical trial needs

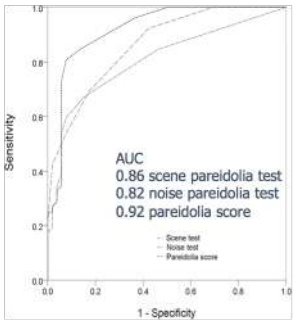
Goldman et al., 2025

Clinical pearls

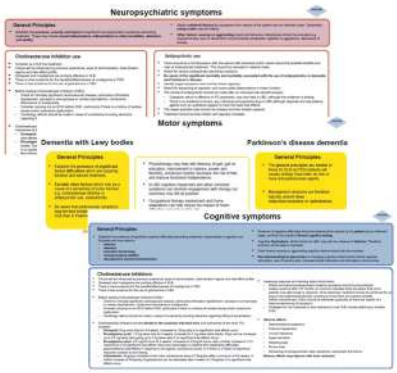
- Clinical neuropsychological profile similar between DLB and PDD
- More differences between LBDs vs. AD

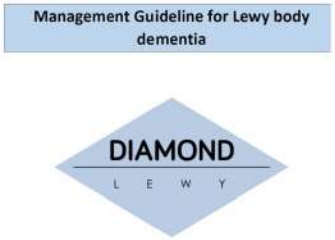
- Noise pareidolia test
  - Evokes visual illusions, surrogate marker for visual hallucinations in DLB
  - Discriminates DLB vs. AD
  - Brief test, good test-retest/inter-rater reliability, moderately correlated with NPI-halluc











Overview Symptom Summaries Reference Guidelines

FIGURE 4 Formats of the management toolkit.

NIHR National Institute for Health Research | Northumberland Tyne and Wear NHS | Newcastle University | UNIVERSITY OF CAMBRIDGE

Taylor, J-P., McKeith, IG. O'Brien, JT. *Management Guideline for Lewy body dementia*. (2019). Available online: https://research.ncl.ac.uk/diamondlewy/managementtoolkit/

DLB treatments

- Motor
  - Careful use of levodopa, monitoring for psychosis and side effects
  - Adjunctive zonisamide (Murata et al., 2018, 2020)

- Non-motor
  - Psychosis – quetiapine, clozapine, pimavanserin (HARMONY trial-PDD); cholinesterase inhibitors; negative study for nelotanserin
  - Depression, anxiety –SSRIs, SNRIs, buproprion, careful use of anxiolytics (benzo)
  - Apathy – similar to PD, tricky!
  - RBD – melatonin, clonazepam; negative study nelotanserin
  - EDS – wakefulness promoting agents – small pilot with armodafinil
  - ANS (OH, GI, GU) – similar to PD and MSA

Molloy et al., 2005, 2006; Goldman et al., 2008; Murata et al., 2018, 2020; Boot et al., 2013; Lapid et al., 2017; Armstrong 2019; Stefani et al., 2021; O'Brien et al., 2021

DLB treatment - dementia

- Cholinesterase inhibitors (rivastigmine and donepezil) - Class I evidence for efficacy
- DLB often greater treatment response than AD, due to profound cholinergic deficits
  - Donepezil approved in Japan
  - Rivastigmine approved in US for PDD
- Memantine – mixed results
- Doses similar to AD and PDD
- Side effects – hypotension, bradycardia, tremor

- Negative trials: intepirdine, irsenontrine (E20207, PDE9 inhibitor)
- Neflamapimod – in OLE, new formulation
- Zervimesine CT1812 – positive

- Cognitive fluctuations – tricky!

Rolinski et al., Cochrane 2012; Goldman & Weintraub 2015; Pagan et al., 2016; Lang et al., 2021; Landry et al., 2022; Pagan et al., 2022; Fallon et al., 2023

Ongoing disease-modifying trials in DLB

	Disease	N*	Intervention	Proposed mechanism	Primary outcome
Phase 4 trials					
NCT06263673	Dementia with Lewy bodies or Parkinson's disease plus glucose intolerance or mild diabetes	18	Dapagliflozin or sitagliptin	SGLT2 inhibitor (dapagliflozin); DPP4 inhibitor (sitagliptin)	Change in MMSE and MDS-UPDRS
Phase 2 trials					
ANeED (NCT04588285)	Dementia or mild cognitive impairment with Lewy bodies	180	Ambroxol	Glucocerebrosidase chaperone	Multiple safety, tolerability, and efficacy measures
RewinD-LB (NCT05869669)	Dementia with Lewy bodies	159	Neflamapimod	p38α MAP kinase inhibitor	Change in CDR-SB
SHIMMER (NCT05225415)	Dementia with Lewy bodies	130	CT1812	Sigma-2 receptor antagonist	Safety and tolerability
NCT06537076	Dementia with Lewy bodies	60	AR1005	Voltage-gated sodium channel antagonist	Change in CDR-SB
NCT04002674	Dementia with Lewy bodies	43	Nilotinib	c-Abl kinase inhibitor	Safety and tolerability
AXON (ACTRN12623000004662)	Dementia with Lewy bodies	32	Ambroxol plus doxycycline	Glucocerebrosidase chaperone (ambroxol), anti-aggregant of α-synuclein and other amyloids (doxycycline)	Safety and tolerability
Phase 1/2 trials					
TZ-DLB (NCT04760860)	Dementia with Lewy bodies	40	Terazosin	PGK1 activator	Safety, tolerability, and brain ATP measured by ^{31}P-MRS
NCT04405596	Dementia with Lewy bodies	15	Ambroxol	Glucocerebrosidase chaperone	Multiple safety, tolerability, and efficacy measures

c-Abl=Abelson murine leukaemia viral oncogene. CDR-SB=clinical dementia rating scale-sum of boxes. DLB-MCI=mild cognitive impairment with Lewy bodies. DPP4=dipeptidyl peptidase-4. MAP=mitogen-activated protein. MDS-UPDRS=Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale. MMSE=mini-mental state examination. ^{31}P-MRS=phosphorous magnetic resonance spectroscopy. PGK1=phosphoglycerate kinase 1. SGLT2=sodium-glucose cotransporter-2. *Estimated or actual enrolment number.

Kalia et al., 2025

Dementia with Lewy Bodies Drug Therapies in Clinical Trials: Systematic Review up to 2022

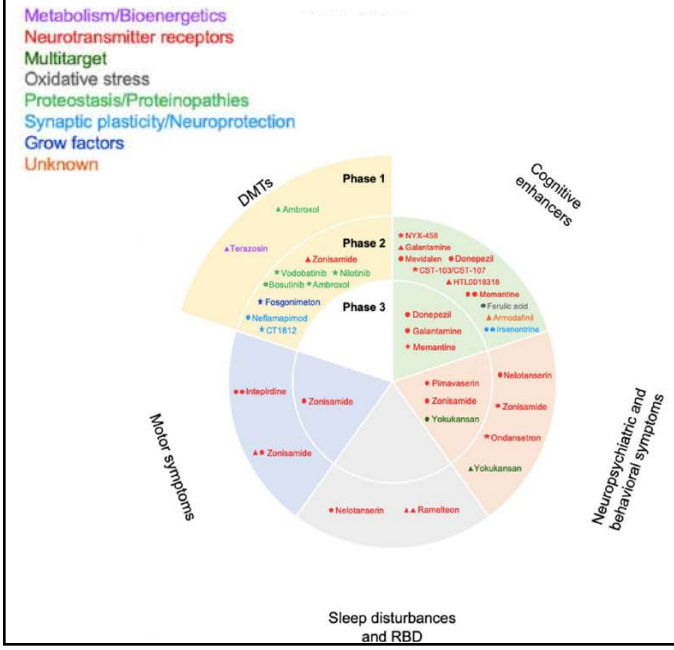


Table 1 General characteristics of clinical trials in DLB as of September 27, 2022

Clinical trial phase	Number of clinical trials	Status			Classification		Repurposed agents
		Completed	Active[a]	Other status	DMT	Symptomatic	
Phase3	7 (17.5%)	6 (86%)	1 (14%)	0	0	7 (100%)	7 (100%)
Phase 2	31 (77.5%)	15 (48.4%)	8 (25.8%)	8[b] (25.8%)	8 (25.8%)	23 (74.2%)	16 (51.6%)
Phase 1	2 (5%)	0	0	2[c] (100%)	2 (100%)	0	2 (100%)
Total	40	21 (52.5%)	9 (22.5%)	10 (27%)	10 (25%)	30 (75%)	25 (65%)

[a]Recruiting, Active/not recruiting
[b]Withdrawn = 3, pending = 2, not recruiting = 2, terminated = 1
[c]Not yet recruiting = 2

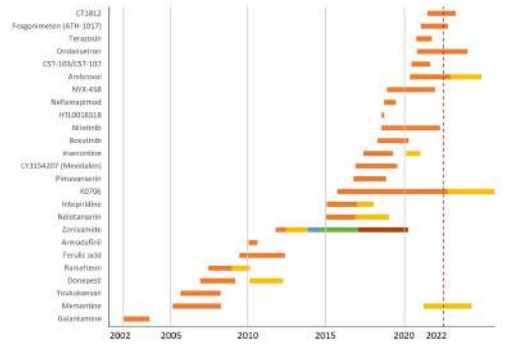


Fig. 2 Evolution of clinical trials for DLB, showing all the agents investigated in DLB clinical trials from 2002 to 2022. *Each color* represents one clinical trial

Abdelnour et al., 2023

Progressive Supranuclear Palsy PSP

PSP - Epidemiology

- Reported to comprise about 5% of parkinsonian patients in a movement disorder clinic
- Crude prevalence of 1.39-14.3 per 100,000 (5-6.4 per 100,000 Kukkle et al., 2026)
- Incidence of 0.3-1.1 cases per 100,000 per year
- Likely underrepresented in many clinical studies due to methodological issues, definitions, lack of autopsy confirmation
- Series mixed regarding M:F

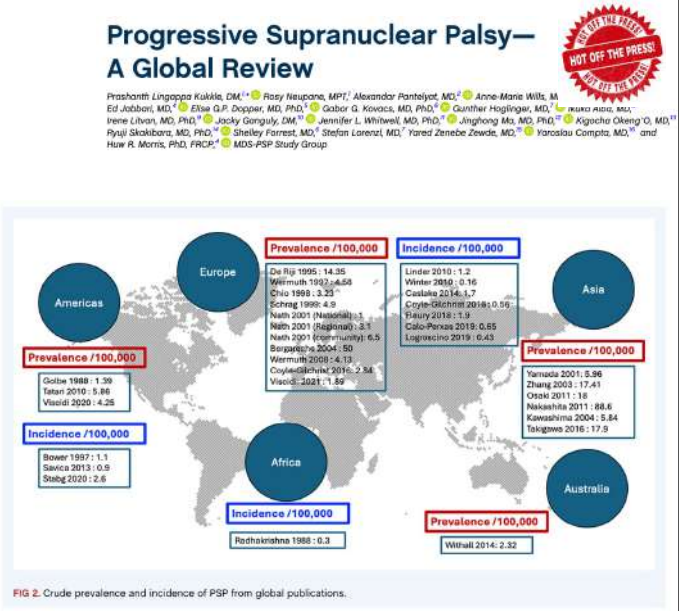


FIG 2. Crude prevalence and incidence of PSP from global publications.

Burn et al., 2000; Williams et al., 2009; Swallow et al., 2022; Lyons et al., 2023; Kukkle et al., 2026

MDS PSP criteria

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

Gunter U. Hoglinger, MD[1,2,*], Gesine Respondek, MD[1,2], Maria Stamelou, MD[3], Carolin Kurz, MD[4], Keith A. Josephs, MD, MST, MSc[5], Anthony E. Lang, MD[6], Brit Mollenhauer, MD[7], Ulrich Muller, MD[8], Christer Nilsson, MD[9], Jennifer L. Whitwell, PhD[10], Thomas Arzberger, MD[2,4,11], Elisabet Englund, MD[12], Ellen Gelpi, MD[13], Armin Giese, MD[11], David J. Irwin, MD[14], Wassilios G. Meissner, MD, PhD[15,16,17], Alexander Pantelyat, MD[18], Alex Rajput, MD[19], John C. van Swieten, MD[20], Claire Troakes, PhD, MSc[21], Angelo Antonini, MD[22], Kailash P. Bhatia, MD[23], Yvette Bordelon, MD, PhD[24], Yaroslau Compta, MD, PhD[25], Jean-Christophe Corvol, MD, PhD[26], Carlo Colosimo, MD, FEAN[27], Dennis W. Dickson, MD[28], Richard Dodel, MD[29], Leslie Ferguson, MD[19], Murray Grossman, MD[14], Jan Kassubek, MD[30], Florian Krismer, MD, PhD[31], Johannes Levin, MD[2,32], Stefan Lorenzl, MD[33,34,35], Huw R. Morris, MD[36], Peter Nestor, MD[37], Wolfgang H. Oertel, MD[38], Werner Poewe, MD[31], Gil Rabinovici, MD[39], James B. Rowe, MD[40], Gerard D. Schellenberg, PhD[41], Klaus Seppi, MD[31], Thilo van Eimeren, MD[42], Gregor K. Wenning, MD, PhD[31], Adam L. Boxer, MD, PhD[39], Lawrence I. Golbe, MD[43], and Irene Litvan, MD[44] for the Movement Disorder Society–endorsed PSP Study Group

2017

- Inclusion criteria
  - Sporadic occurrence
  - Age 40 or older
  - Gradual progression
- Exclusion criteria…
- Supportive features
  - Clinical: levodopa-resistance; hypokinetic, spastic dysarthria; dysphagia; photophobia
  - Imaging: Predominant midbrain atrophy or hypo metabolism; post-synaptic stratal DA degeneration

PSP – Clinical features

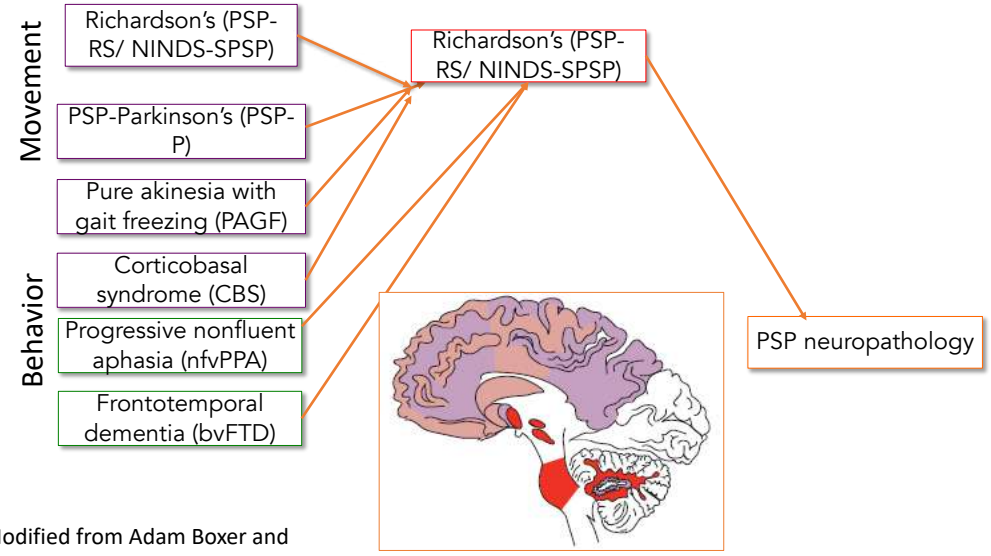
- Progressive disorder
- Age onset ≥ 40
- Parkinsonism, minimal levodopa response
- Often symmetric at onset
- Falls in the first year
- Vertical supranuclear gaze palsy
- Saccade abnormalities (“round the house,” “zig-zag”)
- Dysarthria
- Axial rigidity
- Blepharospasm or apraxia of eyelid opening
- Cognitive and behavioral problems
  - Apathy, depression
- Frontal lobe dysfunction





Abate et al., 2020; Marsili et al., 2020; Rowe et al., 2021; Bower et al., 2022

Multiple phenotypes



Modified from Adam Boxer and Irene Litvan

Williams and Lees 2009; Lopez et al., 2016; McFarland 2017

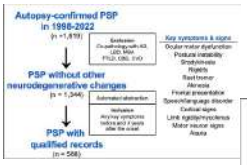
TABLE 5-4 Progressive Supranuclear Palsy Syndromes

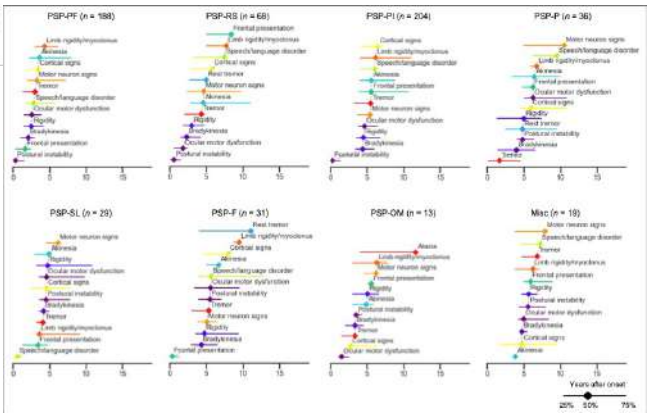
Progressive Supranuclear Palsy (PSP) Syndrome	Clinical Features	Regional Pathology
Classic PSP (Richardson syndrome)	Early gait instability, falls, supranuclear gaze palsy, axial rigidity, dysarthria, dysphagia, progressive dementia	Dentate nucleus, globus pallidus, striatum, midbrain, and superior cerebellar peduncle
PSP-parkinsonism	Tremor, rigid bradykinesia, levodopa responsive,[a] late cognitive decline, longer life expectancy (9 years)	Substantia nigra, subthalamic nucleus
PSP–pure akinesia with gait freezing	Early gait difficulty, freezing of gait/motor block, micrographia, speech impairment, hypophonia, longer disease duration (11–15 years)	Motor cortex, pons, cerebellum
PSP–corticobasal syndrome	Dystonia, dyspraxia, cortical sensory loss, apraxia of speech	Frontal and parietal cortex
PSP–behavioral variant of frontotemporal dementia	Predominant cognitive, personality change, late parkinsonism	Frontotemporal cortex
PSP–primary lateral sclerosis	Bulbar, limb weakness, upper motor neuron signs/spasticity	Frontal predominant, corticospinal tract
PSP-cerebellar	Cerebellar ataxia	Deep cerebellar nuclei

[a] Levodopa response for PSP-parkinsonism wanes later in disease.

McFarland 2017

Phenotypic differences





- 7 subtypes: PSP-PF (postural and frontal dysfunction), PSP-RS, PSP-PI, PSP-P, PSP-SL, PSP-F, and PSP-OM
- PSP-PF (Postural instability and frontal presentation) had rapid progression, shortest median disease duration (6 yrs), and high tau burden in cortical & subcortical regions.
- PSP-F, frontal presentation preceded other symptoms by 4 yrs, 2nd longest disease duration (9 yrs) after PSP-P (10 yrs)

Marchand et al., 2024; Ono et al., 2025 (preprint)

Phenotype influences progression

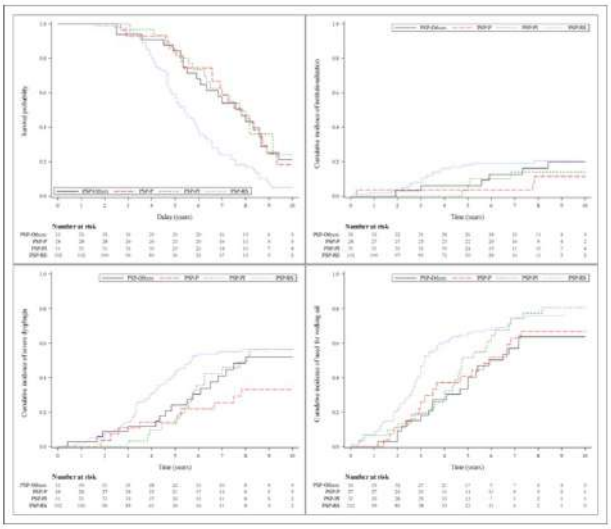
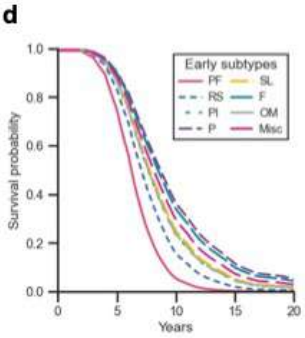


Figure 2. Survival and milestones cumulative incidence curves according to phenotypes groups.

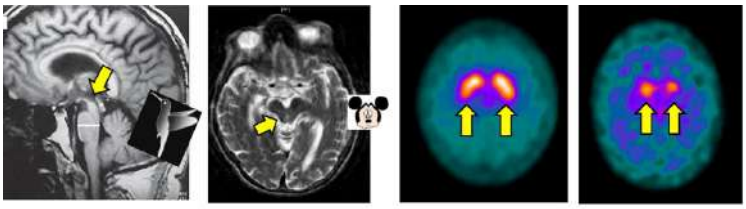


PSP-Richardson – poorer prognosis (Marchand et al., 2024)

PSP-PF (postural instability and frontal) – worse prognosis (Ono et al., 2025)

Marchand et al., 2024; Ono et al., 2025 (preprint)

PSP - Imaging



Hummingbird sign | Mickey Mouse Midbrain | Normal DaTSCAN | PSP DaTSCAN

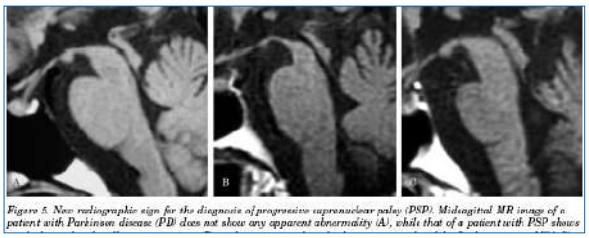
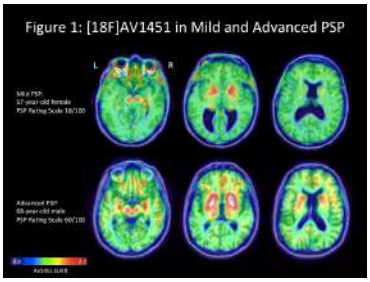


Figure 5. New radiographic sign for the diagnosis of progressive supranuclear palsy (PSP). Midsagittal MR image of a patient with Parkinson disease (PD) does not show any apparent abnormality (A), while that of a patient with PSP shows



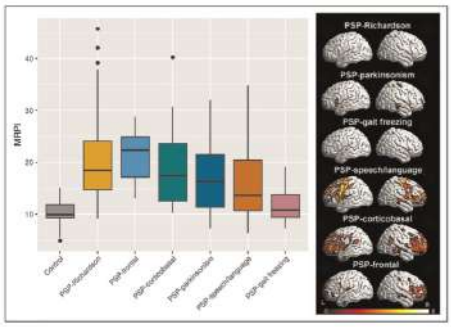


FIGURE 1. Brainstem and cortical findings across progressive supranuclear palsy clinical variants. Left panel shows boxplots of MRI parkinsonism index (MRPI) values across PSP. Right panel shows group-level SPM maps of cortical grey matter loss.

Passamonti et al., 2018; Rowe et al., 2021; Whitwell et al., 2023

Brain Atrophy Does Not Predict Clinical Progression in Progressive Supranuclear Palsy

Andrea Quattrone, MD, PhD,[1,2,3] Nicolai Franzmeier, PhD,[4,5,6] Hans-Jürgen Huppertz, MD,[7] Nicholas Seneca, PhD,[8] Gabor C. Petzold, MD,[9,10] Annika Spottke, MD,[9,11] Johannes Levin, MD,[1,9,12] Johannes Prudlo, MD,[13,14] Emrah Düzel, MD, PhD,[15,16,17] the PASSPORT Study Group, the AL-108-231 Investigators, the Arise Investigators, the Tauros MRI Investigators, the DESCRIBE-PSP group, Günter U. Höglinger, MD[1,5,12*]



- Longitudinal multicohort study
- Baseline clinical severity and regional brain atrophyas predictors of clinical progression in PSP-RS
- PSP-RS patients (n = 309) from the placebo arms of 4 clinical trials and DescribePSP cohort
- Mean PSPRS score increase of 10.3 points/yr
- Frontal lobe volume showed the strongest association with subsequent clinical progression
- However, ML models did not accurately predict individual progression rates (R^2 <0.15)

- Baseline clinical severity and brain atrophy could not predict individual clinical progression → no need for MRI-based stratification in future PSP trials.

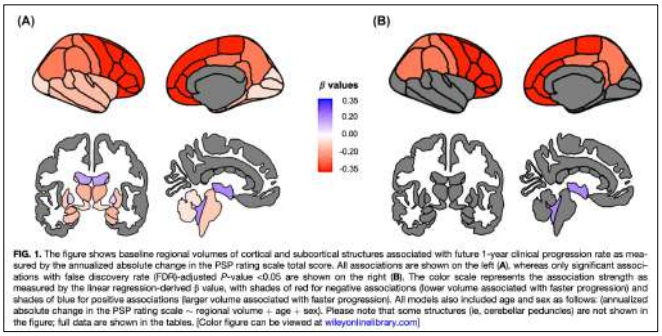


FIG. 1. The figure shows baseline regional volumes of cortical and subcortical structures associated with future 1-year clinical progression rate as measured by the annualized absolute change in the PSP rating scale total score. All associations are shown on the left (A), whereas only significant associations with false discovery rate (FDR)-adjusted *P*-value <0.05 are shown on the right (B). The color scale represents the association strength as measured by the linear regression-derived β value, with shades of red for negative associations (lower volume associated with faster progression) and shades of blue for positive associations (larger volume associated with faster progression). All models also included age and sex as follows: (annualized absolute change in the PSP rating scale ~ regional volume + age + sex). Please note that some structures (ie, cerebellar peduncles) are not shown in the figure; full data are shown in the tables. [Color figure can be viewed at wileyonlinelibrary.com]

Quattrone et al., 2025

PSP – tau, genetics

- MAPT locus
- Most strongly linked with PSP risk
- OR for MAPT H1/H1 carriers is 5.5
- Higher than the OR for APOE e3/e4 genotype for AD

- GWAS studies – additional genetic risk factors (STX6, EIF2AK3, MOBP)

***MAPT* Subhaplotypes in Different Progressive Supranuclear Palsy Phenotypes**

Monica Gagliardi [1,2], Radha Procopio [1,*], Alessia Feliciett [2], Grazia Annesi [3], Mariagrazia Talarico [4], Basilio Vescio [1,4,5], Aldo Quattrone [1,3] and Andrea Quattrone [1,2,3,6]

- Genotyped rs8070723 in 73 PSP patients (47 PSP-RS and 27 PSP variants), S. Italy
- Identified H1 and H2 haplotypes conferring risk (OR, 2.6; 95% CI, 1.4-5.14) and protective effect (OR, 0.37; 95% CI, 0.19-0.69), respectively
- Also identified 18 distinct *MAPT*H1 subhaplotypes, among which H1j displayed a nominally sig reduced risk of PSP

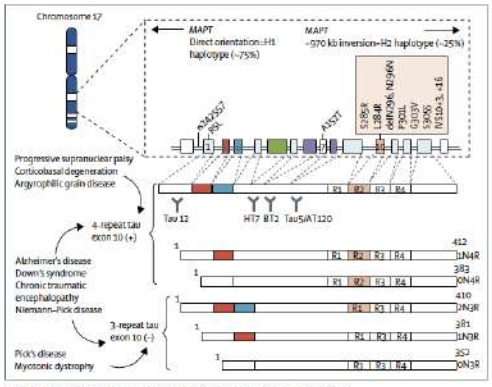
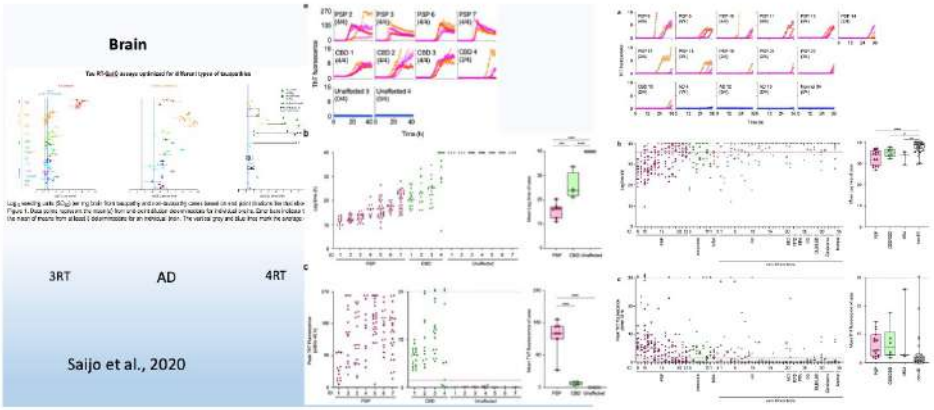


***Figure 3*: The *MAPT* locus, its pathological mutations, and tau protein isoforms**
The *MAPT* locus, located on chromosome 17q21, exists as two major haplotypes, termed H1 and H2. Most people have the H1/H1 haplotype. Mutations producing progressive supranuclear palsy phenotypes are indicated as orange boxes. Alternative splicing of exons 2, 3, and 10 of the *MAPT* gene generates the six isoforms of the encoded tau protein expressed in the human brain. Increased 4 microtubule-binding domain-repeat tau, containing the aminoacids encoded by exon 10, is associated with progressive supranuclear palsy and corticobasal degeneration. An equal ratio of 3-repeat and 4-repeat tau is present in healthy adults and patients with Alzheimer's disease. Binding sites for monoclonal antibodies (tau 12, HT7, BT2, and tau5/AT120), used in CSF tau assays, are indicated. *MAPT*=microtubule-associated protein tau.

Boxer et al., 2017; Litvan et al., 2021; Gagliardi et al., 2025

Tau activity

Ultrasensitive detection and discrimination of tau seeding activities associated with PSP & CBD & other tauopathies



CSF a-synuclein SAA in PSP (and CBS)



Evaluation of Cerebrospinal Fluid α-Synuclein Seed Amplification Assay in Progressive Supranuclear Palsy and Corticobasal Syndrome

David P. Vaughan, MRCPI,[1,2] Riona Furni, MSc,[1,2] Marie Theilmann Jensen, MSc,[1,2] Megan Hodgson, MSc,[1,2]

- 96 CSF samples (PSP, n=59 and CBS, n=37) for α-syn SAA positivity
- 6/59 (10.2%) PSP cases were α-syn SAA positive, including 1 MSA-type positive. PSP cases who were PD-type positive were older with shorter disease than SAA-negative
- 11/37 (29.7%) CBS cases were α-syn SAA positive, including 2 MSA-type positive

CSF α-Synuclein Seed Amplification Assay in Patients With Atypical Parkinsonian Disorders

Chloe Anastassiadis, MSc,[1] Ivan Martinez-Valbuena, PhD,[1] Anna Vasilevskaya, PhD, Simrika Thapa, PhD, Mohsen Hadian, PhD, Alonso Morales-Rivero, MD, Daniela Mora Fisher, MD, Cristina Salvi, MD, Fouad Taghdiri, MSc, MD, Christine Tang, MSc, Danielle Moreno, BSc, Cassandra J. Anor, MA, Karen Mesquita, BSc, Mac Couto, MD, PhD, David F. Tang-Wai, MD, CM, FRCPC, Anthony E. Lang, MD, FRCPC, Susan H. Fox, MB ChB, PhD, Ekaterina Rogaeva, PhD, Gabor G. Kovacs, MD, PhD, FRCPC, and Maria Carmela Tartaglia, MD

Correspondence
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carmela.tartaglia@uhn.ca

- CSF of 40 patients with CBS (19 F, 65.9 ± 8.6 yrs) and 28 with PSP (13 F, 72.5 ± 8.7 yrs old), mostly White (n=50) or Asian (n = 14)
- 28.6% PSP and 35.9% CBS were αSyn-SAA positive
- In young-onset, αSyn-SAA positivity and AD positivity were associated (odds ratio [OR] 8.8, 95% CI 1.2-82.6, $p < 0.05$)
- Significant interaction of αSyn-SAA status by age at onset on CSF Aβ42 levels (β = 0.3 ± 0.1, $p < 0.05$)
- RBD was associated with αSyn-SAA positivity ($p < 0.01$)

Synucleinopathy-like clinical features and biologically defined synuclein seeding in PSP-Parkinsonism: an imperfect match

Received: 19 December 2025
Accepted: 6 May 2026
Cite this article as: Painous, C., Martínez, A., Camara, A. et al.

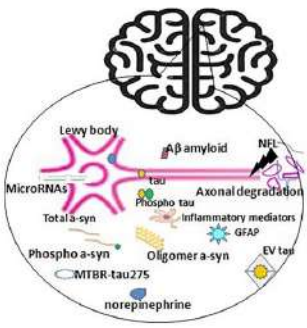
Celia Painous, Andrea Martínez, Ana Campos, Mónel Fernandez, Maria J. Martí, Esteban Muñoz, Almudena Sánchez-Gómez, Alexandra Pérez-Soriano, Alicia Garrido, Carla Varela, Francesc Valldeoriola, Edward Tolosa, Nuria Caballol, Serge Jasmin, Claustre Pont-Sunyer, Tania Delgado, Albert Llado, Jesica Pérez-Montoyo, Lorena de Mena, Laura Naranjo, Raquel Real García, Laura Mellao-Porcel, Ilias Aldecoa, Barcelona PSP Registry Consortium, Joan Santamaria & Yaroslau Compta

- 80 PSP (10 PSP-P, 20 PSP-R, 10 PD, 20 controls)
- α-syn SAA positivity was 100% PD, 100% controls and PSP-RS, 24% PSP-P
- Not all clinically syn-like PSP-P were α-syn SAA positive and vice versa

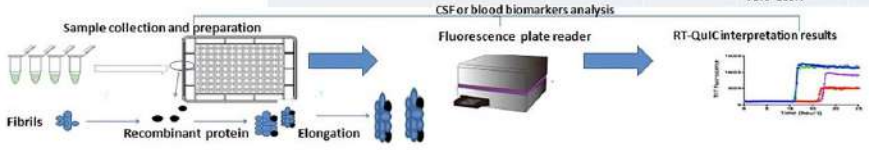
Vaughan et al., 2024; Anastassiadis et al., 2025; Painous et al., 2026

Fluid biomarkers in atypical Parkinsonism: current state and future perspectives

Anastasia Bougea[1] · Carlo Colosimo[2] · Cristian Falup-Pecurariu[3,4] · Giovanni Palermo[4] · Yildiz Degirmenci[5]



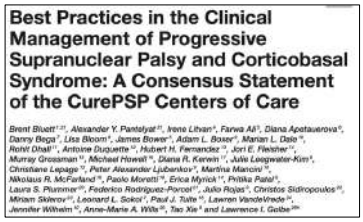
Fluid biomarkers included in the Present review	PSP	CBS	MSA	DLB
CSF or blood amyloid/tau/phospho-tau MTBR-tau275/t-tau /EV tau)	Unhelpful	Positive if AD pathology underlies the CBS	Unclear value	Positive or negative
CSF or blood a-syn (total/phospho/oligomer/Hb-α-syn	Unclear value	Unclear value	Unclear value	Unclear value
CSF or blood NFL	Unclear value	Unclear value	Predictive value	Unclear value
CSF or blood inflammatory mediators	Unclear value	Unclear value	Unclear value	Unclear value
SAA assays in CSF	Usually negative	Usually negative	Usually positive	Usually positive
Plasma norepinephrine	Unhelpful	Unhelpful	for MSA vs. isolated autonomic failure sensitivity: 82%–100%, specificity: 75%–100%	Unhelpful



Bougea et al., 2025

Management

- Motor: Dopaminergic agents, PT, OT
- Dystonia: Botulinum toxin injections
- Speech/swallowing: SLP
- Orthostatic hypotension: Salt, fludrocortisone, midrodrine, droxidopa
- Neurogenic bladder: solifenacin, mirabegron
- Mood: Antidepressants
- Apathy: cholinesterase inhibitors, stimulants
- Cognition: cholinesterase inhibitors, memantine
- Gastroparesis


Best Practices in the Clinical Management of Progressive Supranuclear Palsy and Corticobasal Syndrome: A Consensus Statement of the CurePSP Centers of Care

Bluett et al., 2021

Multidisciplinary care use in neurodegenerative complex diseases: The example of progressive supranuclear palsy and advanced Parkinson's disease in real-life

Margherita Fabbri[a,b], Claudia Ledda[c,d], Tommaso Schirinzi[e], Carlo Alberto Artusi[c,d], Anna Rosa Avallone[f], Henri Zenuni[e], Rosa De Micco[g], Simone Aloisio[g], Ilaria Cani[h,i], Maria Chiara Malaguti[j], Francesca Di Biasio[k], Giovanna Calandra-Buonaura[h,i], Alessandro Stefani[e], Leonardo Lopiano[c,d], Paolo Barone[f], Marina Picillo[f,*], the PSP-NET study group[1]

- Cross-sectional, multicenter observational study (N=129 PSP, 65=APD), Hoehn and Yahr ≥3, matched for sex and age
- Lack of rehabilitation and psychosocial services received
- Over the previous year, 40% of PSP patients did not encounter a PT
- ~33% met a SLP and 5% an OT, psychologist 26.1%, psychiatrist 9.3%, social assistance 6.2%, spiritual care 3.1%, dietician 13.2%
- More than 20% received in-home care and 32% needed home structural changes, with PSP patients requiring greater services

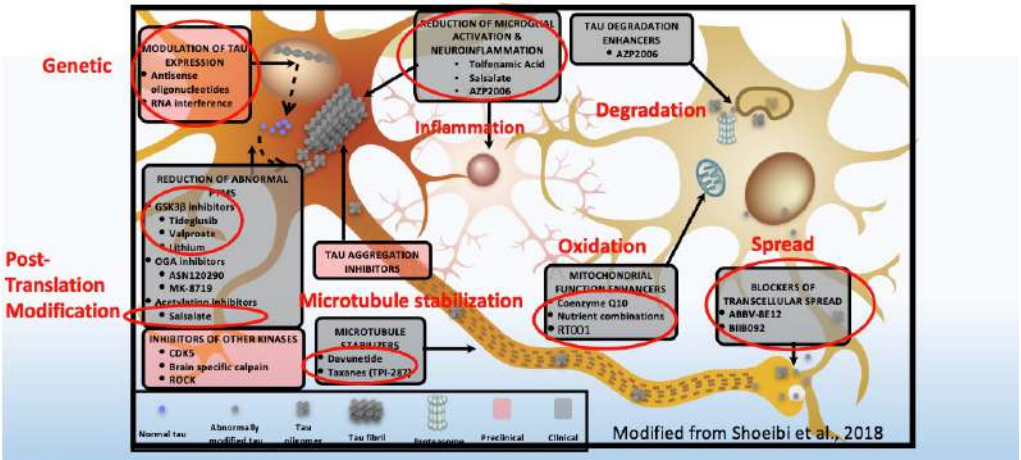
Table 1
Demographic, clinical and therapeutic data of PSP and APD.

Patients' data	PSP N = 129	APD N = 65	p
Age, yrs	71.6 (6.5)	73.2 (8.0)	0.100
Women, n (%)	44 (34.1)	35 (53.8)	0.250
Age at onset, yrs	69.6 (6.9)	61.3 (10.3)	**<0.001**
Disease duration, yrs	2.3 (1.9)	11.8 (6.6)	**<0.001**
LEDD	403 (484)	857 (383)	**<0.001**
S&E	53.0 (26.1)	43.0 (21.7)	**0.024**
MDS-UPDRS part III	NA	47.5 (11.8)	/
PSP-rs	42.5 (17.3)	NA	/
NPI-12			
Total score	16.5 (15.8)	24.7 (18.8)	**0.002**

Fabbri et al,. 2024

PSP is an ideal therapeutic disease to target tau

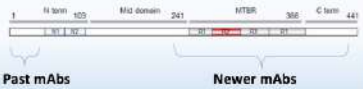
Emerging Disease Modifying Therapeutic Targets in PSP & CBD



OGA=O-linked N-acetylglucosaminidase

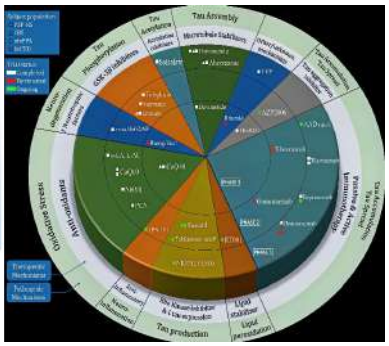
Generations of potential PSP therapeutics

First	Second	Third	Fourth	Fifth
(Neurotransmitter Targeted)	*(Potentially disease modifying)*	*(Anti-tau)*	*(Genetically targeted)*	*(Improved anti-tau)*
Pergolide Tricyclics Idazoxan Donepezil Zolpidem	Riluzole Co-Q10 Davunetide Tideglusib TPI-287 Salsalate Young plasma Tolfenamic Acid RT001 (LPO) AZP2006	BIIB092 (N-term) ABBV-8E12 (N-term)	Antisense oligonucleotides (NIO752) Gene therapy Retroviral (Transposon) Small molecules	MTBR mAbs Anti-aggregation Clearance enhancers Designed molecules *(inflammation modulators)* *Inhibitors of kinases-PTM*



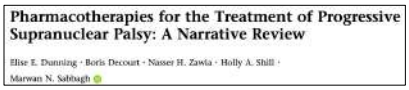
Phase 2 study results:
ABBV-8E12 — Failed
BIIB092— Failed (target engagement)
Combined n ~ 700 patients worldwide

Modified from Adam Boxer



Olfati et al., 2023

Trials and research pipeline


Pharmacotherapies for the Treatment of Progressive Supranuclear Palsy: A Narrative Review

Elise E. Dunning · Boris Decourt · Nasser H. Zawia · Holly A. Shill · Marwan N. Sabbagh

- Agents tried…negative
  - Riluzole, Lithium, Tideglusib (phase 2, GSK-3 inhibitor), Davunetide (phase 2-3, microtubule stabilizer)
  - Microtubule stabilizer, tau active vaccination, tau-aggregation inhibitor, anti-tau monoclonal Ab, inhibitor of tau acetylation
  - Anti-tau antibody
    - Gosuranemab [BIIB092] neg, decreased tau in CSF – Boxer et al., 2019, Dam et al., 2021
    - Tilavonemab [ABBV-8E12] neg, terminated @interim analysis– Hoglinger et al., 2021, no change in tau burden in 2 autopsied cases – Koga et al., 2022
  - Stimulation
    - rTMS cerebellum for postural instability protocol (Dale et al., 2024)
    - DCS prefrontal cortex – negative (Cappiello et al., 2023)

Dunning et al., 2024

Ongoing PSP trials



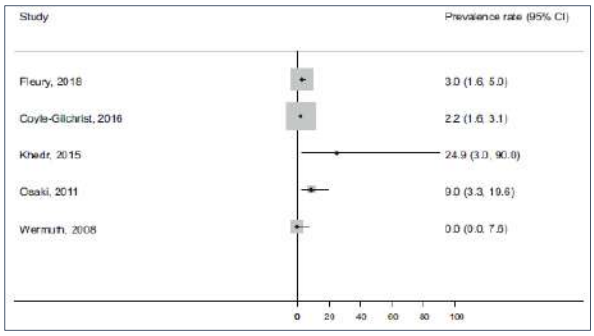
	Study type	Duration	Sample size	Treatment/target	Primary outcome
NCT06235775	DB, PC RCT Ph2	12 mos	75	GV1001	Safety
NCT06355531	DB, PC RCT Ph2	52 wks	220	FNP-223	PSPRS total
NCT04658199	DB, PC RCT Ph1	OLE	19	Long-term UCB0107 (bepranemab)	Adverse effects
NCT06122662	DB, PC RCT Ph2b/3	52 wk	110	AMX0035	PSPRS total
NCT06162013	DB, PC RCT Ph2	78 wk	330	Nicotinamide riboside	PSPRS total
NCT04468932	Crossover	4 wk	30	TMS - cerebellar	Posturography, fNIRS, speech
NCT07264283	DB, PC RCT Ph2	52 weeks	147	LM11A-31	mPSPRS-15
NCT07217665	DB, PC RCT Ph2	52 weeks	146	AADvac1	mPSPRS-15
NCT07498426	DB, PC RCT Ph3 and OLE	72 wk	300	NIO752 (ASO)	mPSPRS-10

Clinicaltrials.gov

Corticobasal degeneration/syndrome CBD/CBS

CBD - Early history/epidemiology

- First described “corticodentatonigral degeneration with neuronal achromasia”
- 3 patients with asymmetric, akinetic-rigid syndrome with cerebral cortical dysfunction
- Widespread deposition of 4-R tau in neurons and glia
- Pathology predicted antemortem in only 25-56% of cases
- Prevalence of 4.9-7.3 per 100,000, incidence 0.62-0.92 per 100,000 per year

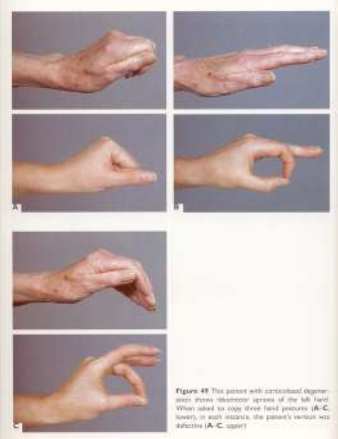


Pooled 2.3 per 100,000/year – Swallow 2022

Rebeiz et al., 1967; Gibb et al., 1989; Swallow et al., 2022

Clinical features

- Gradual onset
- Age ≈ 60 years
- Marked asymmetry
- Parkinsonism
- Apraxia
- Alien limb
- Cortical sensory loss
- Dystonia
- Myoclonus
- Dementia
- Aphasia



Phenotypes and criteria

Table 4 Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration[a]

Syndrome	Features
Probable corticobasal syndrome	Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia	Effortful, agrammatic speech plus at least one of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

Table 5 Diagnostic criteria for corticobasal degeneration[a]

	Clinical research criteria for probable sporadic CBD	Clinical criteria for possible CBD[b]
Presentation	Insidious onset and gradual progression	Insidious onset and gradual progression
Minimum duration of symptoms, y	1	1
Age at onset, y	≥50	No minimum
Family history (2 or more relatives)	Exclusion	Permitted
Permitted phenotypes (see table 4 for criteria)	1) Probable CBS or 2) FBS or NAV plus at least one CBS feature (a–f)	1) Possible CBS or 2) FBS or NAV or 3) PSPS plus at least one CBS feature b–f
Genetic mutation affecting τ (e.g., MAPT)	Exclusion	Permitted

Armstrong et al., 2013

Clinical/pathological correlates

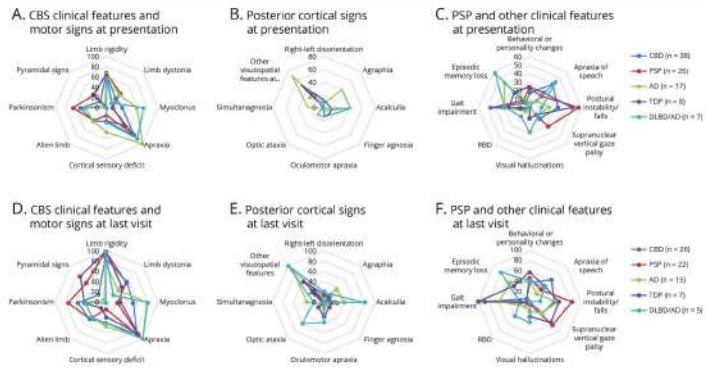
- 113 patients with CBS
- 54% female
- Disease duration 7 +/- 3.7 years
- Age at death 70.5 +/- 9.1 years
- Primary pathological dx
  - 38% CBD, 24% PSP, 15% AD, 9% FTLD with TDP inclusions, 6% DLBD/AD, 8% other
- Regional imaging differences informed neuropathology
  - Cortical GM loss – CBS-AD
  - Premotor WM loss, midbrain/pons atrophy – CBS-PSP
  - Parieto-occipital GM loss – CBS-DLBD/AD
  - Prefrontal GM loss – CBS-FTLD-TDP

Clinicoradiologic and Neuropathologic Evaluation of Corticobasal Syndrome

Dror Shir, MD, Nha Trang Thu Pham, BS, Hugo Botha, MD, Shunsuke Koga, MD, PhD, Naomi Kouri, PhD, Farwa Ali, MBBS, David S. Knopman, MD, Ronald C. Petersen, MD, PhD, Brad F. Boeve, MD, Walter K. Kremers, PhD, Aivi T. Nguyen, MD, Melissa E. Murray, PhD, R. Ross Reichard, MD, Dennis W. Dickson, MD, Neill Graff-Radford, MBBCh, Keith Anthony Josephs, MD, MST, MSc, Jennifer Whitwell, PhD, and Jonathon Graff-Radford, MD

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Figure 1 Radar Charts of Clinical Features by Neuropathology Diagnosis



Shir et al., 2023

Imaging and pathology

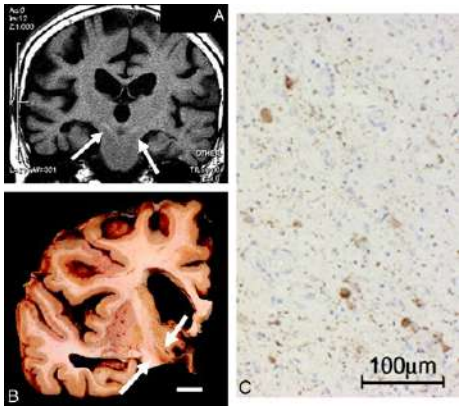
- Imaging
  - Asymmetric fronto-parietal atrophy
  - Often seen on MRI or SPECT
- Pathology
  - Asymmetric fronto-parietal atrophy
  - Ballooned, achromatic neurons containing filamentous 4R-tau aggregates in cortex and striatum
  - "Astroglial plaques"
  - Inclusions in astrocytes and oligodendroglia ("coiled bodies")
  - Tau

Pathomechanisms of cognitive and behavioral impairment in corticobasal degeneration

Kurt A. Jellinger[1]

The enigma of depression in corticobasal degeneration, a frequent but poorly understood co-morbidity

Kurt A. Jellinger[1]



Tokumaru et al., 2009; Jellinger 2023

CBS management

- Symptomatic
- Motor
- Dystonia
- Speech/swallowing
- Mood
- Cognition
- Apathy
- Other

Summary for atypicals

- Keep an eye out for ”red flags”
- Monitor and follow patients over time for changes in their symptoms, responses to therapies, etc
- Re-evaluate diagnoses
- Growing field of biomarkers that distinguish among the atypical parkinsonian syndromes and may have utility for diagnosis and in clinical trials
- Symptomatic therapies as current mainstay, but increasing attention to clinical trials for disease-modifying agents


Thank you for your attention!
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