Parkinsonismi e diagnosi differenziale

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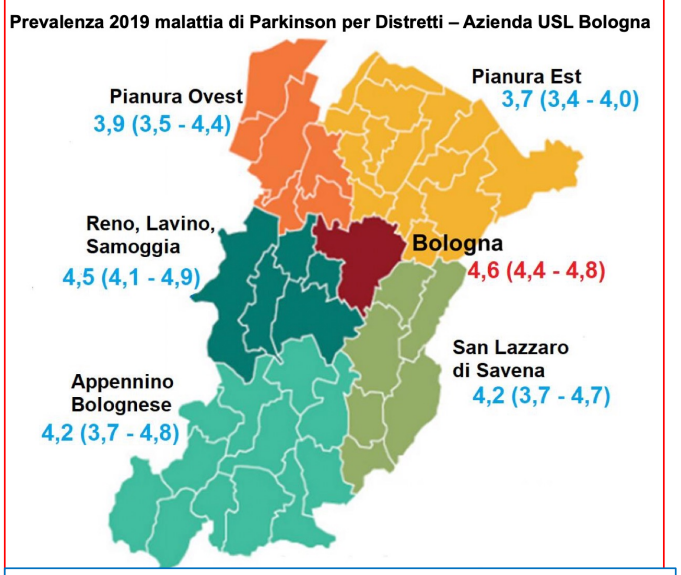
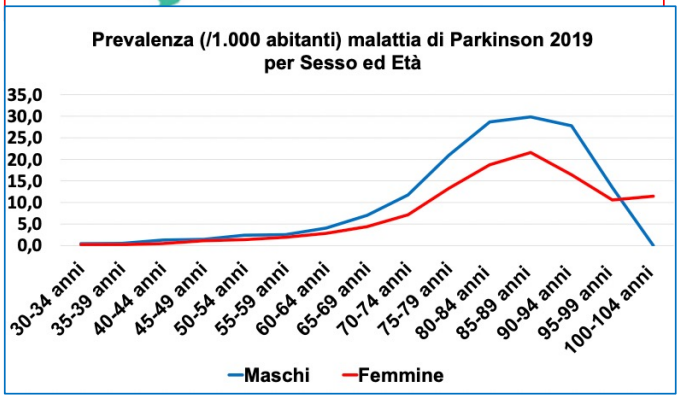
Parkinon's disease

Prevalenza 2019
malattia di Parkinson
4,3 (IC 95% 4,2 – 4,4)





MSA: Multiple system atrophy is a progressive sporadic neurodegenerative disease that clinically presents with autonomic failure, parkinsonism, and a cerebellar syndrome in various combinations and pathologically with glial cytoplasmic inclusions and neuronal loss predomi-nantly in striatonigral and olivopontocerebellar sys-tems.

MSA-P; MSA-C. Prevalence 1-5 casi/100.000; Mean DD 7-9 years

PSP: PSP is a neuropathologically defined disease entity (intracerebral aggregation of the microtubule-associated protein tau, predominantly involving isoforms with four microtubule-binding repeats (4R-tau), in neurofibrillary tangles, oligodendrocytic coils, and, specifically, astrocytic tufts.

cumulative prevalence 2.3 to 10.6 cases per 100.000 , >55 years 7/100.000 Mean DD 6 years

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   - If 1 red flag is present, there must also be at least 1 supportive criterion
   - If 2 red flags, at least 2 supportive criteria are needed
   - No more than 2 red flags are allowed for this category

Supportive criteria

(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

☐ 2. Presence of levodopa-induced dyskinesia

☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Red flags

- ☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
- ☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
- ☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
- ☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- ☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  - a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  - b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
- ☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
- ☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
- ☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

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Absolute exclusion criteria: The presence of any of these features rules out PD:

- ☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
- ☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
- ☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
- ☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
- ☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
- ☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
- ☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
- ☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
- ☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy

CME

Gregor K. Wenning, MD,PhD,[1*] Iva Stankovic, MD,PhD,[2*] Luca Vignatelli, MD,PhD,[3] Alessandra Fanciulli, MD,PhD,[1] Giovanna Calandra-Buonaura, MD,PhD,[3,4] Klaus Seppi, MD,PhD,[1] Jose-Alberto Palma, MD,PhD,[5] Wassilios G. Meissner, MD,PhD,[6,7] Florian Krismer, MD,PhD,[1] Daniela Berg, MD,PhD,[8,9] Pietro Cortelli, MD,PhD,[3,4] Roy Freeman, MD,[10] Glenda Halliday, MD,[11] Günter Höglinger, MD,PhD,[12,13] Anthony Lang, MD,[14] Helen Ling, MD,PhD,[15,16] Irene Litvan, MD,[17] Phillip Low, MD,[18] Yasuo Miki, MD,PhD,[15,19] Jalesh Panicker, MD,FRCP,[20,21] Maria Teresa Pellecchia, MD,PhD,[22] Niall Quinn, MD,FRCP,[20] Ryuji Sakakibara, MD,PhD,[23] Maria Stamelou, MD,PhD,[24,25] Eduardo Tolosa, MD,PhD,[26,27] Shoji Tsuji, MD,PhD,[28,29] Tom Warner, MD,PhD,[15] Werner Poewe, MD,[1] and Horacio Kaufmann, MD[5*]

Movement Disorders, Vol. 37, No. 6, 2022

Neuropathologically established MSA

Widespread and abundant CNS α-synuclein positive glial cytoplasmic inclusions associated with neurodegenerative changes in striatonigral or olivoponto-cerebellar structures

Clinically established MSA

Clinically probable MSA

Possible prodromal MSA

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Postuma, et al. 2015

Essential features for clinical MSA diagnosis: Sporadic, progressive, adult (> 30 years) onset disease

Clinically established MSA	• **Core clinical features** Autonomic dysfunction: at least one of voiding difficulties with postvoid urinary residual volume > 100 ml, urinary urge incontinence or neurogenic OH And at least one of poorly L-Dopa-responsive parkinsonism and/or cerebellar syndrome • **≥ 2 supportive clinical features** • **≥ 1 brain MRI marker** • **Absence of exclusion criteria**
Clinically probable MSA	• **Core clinical features** At least two of: - autonomic dysfunction (at least one of voiding difficulties with postvoid urinary residual volume, urinary urge incontinence or delayed neurogenic OH) - parkinsonism - cerebellar syndrome • **≥ 1 supportive clinical feature** (excluding erectile dysfunction alone) • **Absence of exclusion criteria**

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Supportive motor features	Rapid progression within 3 years of motor onset	**Supportive non-motor features**	Stridor
	Moderate to severe postural instability within 3 years of motor onset		Inspiratory sighs
	Craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia		Cold discolored hands and feet
	Severe speech impairment within 3 years of motor onset		Erectile dysfunction (below age of 60 years for clinically probable MSA)
	Severe dysphagia within 3 years of motor onset		Pathologic laughter or crying
	Unexplained Babinski sign		
	Jerky myoclonic postural or kinetic tremor		
	Postural deformities		

Exclusion criteria
Substantial and persistent beneficial response to dopaminergic medications
Unexplained anosmia on olfactory testing
Fluctuating cognition with pronounced variation in attention and alertness and early decline in visuoperceptual abilities
Recurrent visual hallucinations not induced by drugs within 3 years of disease onset
Dementia according to DSM-V within 3 years of disease onset
Downgaze supranuclear palsy or slowing of vertical saccades
Brain MRI findings suggestive of an alternative diagnosis (eg, PSP, multiple sclerosis, vascular parkinsonism, symptomatic cerebellar disease, etc.)
Documentation of an alternative condition (MSA look-alike, including genetic or symptomatic ataxia and parkinsonism) known to produce autonomic failure, ataxia, or parkinsonism and plausibly connected to the patient's symptoms

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

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Suggestive of PSP

TABLE 5

Degrees of diagnostic certainty, obtained by combinations of clinical features and clinical clues

Diagnostic Certainty	Definition	Combinations	Predominance Type	Abbreviation
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	def. PSP
Probable PSP	Highly specific, but not very sensitive for PSP	(O1 or O2) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
	Suitable for therapeutic and biological studies	(O1 or O2) + A1	PSP with progressive gait freezing	prob. PSP-PGF
		(O1 or O2) + (A2 or A3)	PSP with predominant parkinsonism	prob. PSP-P
		(O1 or O2) + C2	PSP with predominant frontal presentation	prob. PSP-F
Possible PSP	Substantially more sensitive, but less specific for PSP	O1	PSP with predominant ocular motor dysfunction	poss. PSP-OM
	Suitable for descriptive epidemiological studies and clinical care	O2 + P3	PSP with Richardson's syndrome	poss. PSP-RS
		A1	PSP with progressive gait freezing	poss. PSP-PGF
		(O1 or O2) + C1	PSP with predominant speech/language disorder[a]	poss. PSP-SL
		(O1 or O2) + C3	PSP with predominant CBS[a]	poss. PSP-CBS

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The basic features B1+B2+B3 (see Table 1) apply for all probable, possible, and suggestive criteria. Core clinical features are defined by their functional domain (ocular motor dysfunction [O], postural instability [P], akinesia [A], and cognitive dysfunction [C]), and stratified by presumed levels of certainty (1 [highest], 2 [mid], 3 [lowest]) they contribute to the diagnosis of PSP (see Table 2). Supportive clinical clues (CC) are presented in Table 3. Operationalized definitions of clinical features and clinical clues are given in Table 4.

[a]Probable 4R-tauopathy (i.e., either PSP or CBD).

Basic features

B1: Mandatory inclusion criteria	**1**	Sporadic occurrence *
	2	Age 40 or older at onset ** of first PSP-related symptom ***
	3	Gradual progression of PSP-related symptoms ***

Core clinical features

	Functional Domain			
Levels of Certainty	**Ocular Motor Dysfunction**	**Postural Instability**	**Akinesia**	**Cognitive Dysfunction**
Level 1	**O1**: Vertical supranuclear gaze palsy	**P1**: Repeated unprovoked falls within 3 years	**A1**: Progressive gait freezing within 3 years	**C1**: Speech/language disorder, i.e., nonfluent/ agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	**O2**: Slow velocity of vertical saccades	**P2**: Tendency to fall on the pull-test within 3 years	**A2**: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2**: Frontal cognitive/behavioral presentation
Level 3	**O3**: Frequent macro square wave jerks or "eyelid opening apraxia"	**P3**: More than two steps backward on the pull-test within 3 years	**A3**: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	**C3**: Corticobasal syndrome

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Supportive features

Clinical Clues	Imaging Findings
CC1: Levodopa-resistance	**IF1**: Predominant midbrain atrophy or hypometabolism
CC2: Hypokinetic, spastic dysarthria	**IF2**: Postsynaptic striatal dopaminergic degeneration
CC3: Dysphagia	
CC4: Photophobia	

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B2: Mandatory exclusion criteria[a]	Clinical findings	
	1	Predominant, otherwise unexplained impairment of episodic memory, suggestive of AD
	2	Predominant, otherwise unexplained autonomic failure, e.g., orthostatic hypotension (orthostatic reduction in blood pressure after 3 minutes standing ≥30 mm Hg systolic or ≥15 mm Hg diastolic), suggestive of multiple system atrophy or Lewy body disease
	3	Predominant, otherwise unexplained visual hallucinations or fluctuations in alertness, suggestive of dementia with Lewy bodies
	4	Predominant, otherwise unexplained multisegmental upper and lower motor neuron signs, suggestive of motor neuron disease (pure upper motor neuron signs are *not* an exclusion criterion)
	5	Sudden onset or step-wise or rapid progression of symptoms, in conjunction with corresponding imaging or laboratory findings, suggestive of vascular etiology, autoimmune encephalitis, metabolic encephalopathies, or prion disease
	6	History of encephalitis
	7	Prominent appendicular ataxia
	8	Identifiable cause of postural instability, e.g., primary sensory deficit, vestibular dysfunction, severe spasticity, or lower motor neuron syndrome

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Supportive criteria
(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

☐ 2. Presence of levodopa-induced dyskinesia

☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Parkinsonism

Bradykinesia: slowness of movement AND decrement in amplitude or speed (or progressive hesitations/halts) as movements are continued.

Bradykinesia can be evaluated by using finger tapping, hand movements, pronation-supination movements, toe tapping, and foot tapping.

Although bradykinesia also occurs in voice, face, and axial/gait domains, limb bradykinesia must be documented to establish a diagnosis of PD.

Core clinical features MSA: parkinsonism

- **bradykinesia** = slowness of movement and decrement in amplitude or speed (or progressive hesitations or halts) as movements are continued

PLUS

- **rigidity** = velocity-independent resistance to passive movement not solely reflecting failure to relax that may be accompanied by cogwheel phenomenon

OR

- **tremor** = rhythmic or arrhythmic involuntary movement in arms or legs.

A total of 12 (6 clinicopathological) studies were included

Feature	Prevalence in MSA
Resting tremor	12.5%-39% (definite)
Pill rolling tremor	8% (definite)
Asymmetry at onset	39%
Persistent asymmetry	35%

PSP-P: parkinsonism

Core clinical features

	Functional Domain			
Levels of Certainty	**Ocular Motor Dysfunction**	**Postural Instability**	**Akinesia**	**Cognitive Dysfunction**
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Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. Operationalized definitions of the core clinical features are provided in Table 4.

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MSA: levodopa response

Poorly L-Dopa-responsive parkinsonism

LD Response: 42.5%–56.7% of MSA-P patients and 12.9%–25% of MSA-C patients associated with motor fluctuations and dyskinesia (3.5± 2.7 years and 3.2 ± 2.3 years) (Wenning et al., 2013; Low et al., 2015).

Poor L-dopa responsiveness (for clinically established MSA): Defined by history or as <30% improvement on the MDS-UPDRS III on up to 1000 mg L-dopa as needed or tolerated for at least a month as judged by a movement disorder specialist.

- Motor complications (Wenning et al., 2013):
    - wearing-off fluctuations in 23%
    -off-period dystonia in 20%
    - on–off fluctuations in 14%
    -peak-dose dyskinesia in 11%

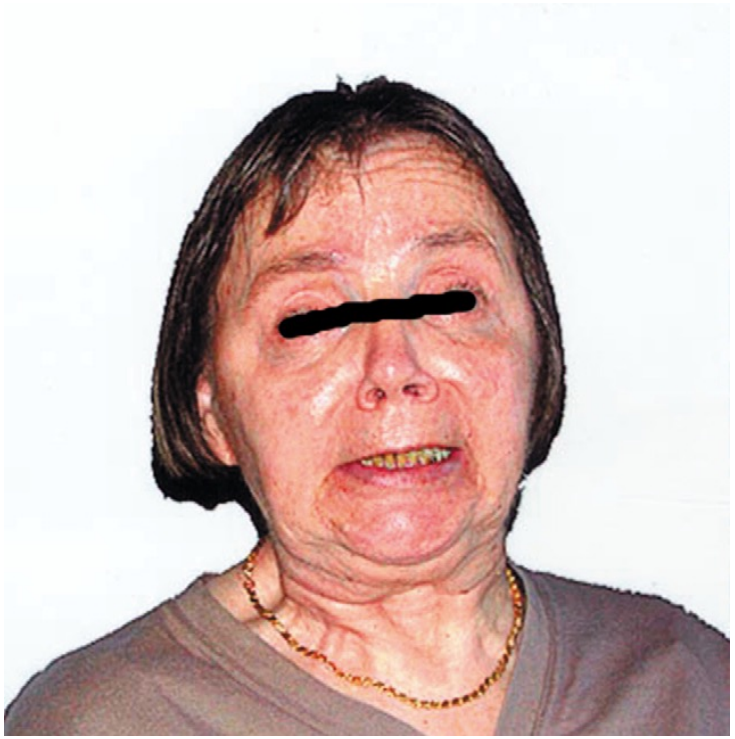
Dyskinesia is usually **focal, asymmetric, and dystonic** affecting **the cranio-cervical or hands/feet regions** vs the generalized choreatic limb dyskinesia typical of patients with PD (Wenning et al., 1994; Boesch SM et al., 2002).

- Patients with young-onset MSA more frequently have a good response to L-Dopa, L-Dopa-induced dyskinesia, and dystonic features compared to patients with the classic disease onset in the 6th decade of life (Batla et al., 2018).

Supportive clinical motor features for MSA

Craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia	Involuntary dystonic movements of the face induced or exacerbated by L-dopa in the absence or presence of very mild limb dyskinesia.

Focal dystonic postures affecting the face, neck, or limbs prior to the initiation of L-Dopa were recorded in up to half of MSA patients, even preceding parkinsonism in some (Wenning et al., 1997).



MSA : levodopa response

Exclusion criteria
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Unexplained anosmia on olfactory testing
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PSP: levodopa response

Around 30 % of PSP patients experience a mild to modest but transient beneficial effect of levodopa on akinesia and rigidity, possibly leading to fewer falls. A minority of PSP patients develop levodopa- induced dyskinesias, which predominantly involve the face.

Akinesia

A1	Progressive gait freezing within 3 years	Sudden and transient motor blocks or start hesitation are predominant within 3 years after onset of PSP-related symptoms, progressive and not responsive to levodopa; in the early disease course, akinesia may be present, but limb rigidity, tremor, and dementia are absent or mild.
A2	Parkinsonism, akinetic-rigid, predominantly axial and levodopa resistant	Bradykinesia and rigidity with axial predominance, and levodopa resistance (see Clinical Clue CC1 for operationalized definition).
A3	Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	Bradykinesia with rigidity and/or tremor, and/or asymmetric predominance of limbs, and/or levodopa responsiveness (see Clinical Clue CC1 for operationalized definition).

Levodopa resistance is defined as improvement of the MDS-UPDRS motor scale by ≤30%; to fulfill this criterion patients should be assessed having been given at least 1,000 mg (if tolerated) at least 1 month OR once patients have received this treatment they could be formally assessed following a challenge dose of at least 200 mg.

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Quantitative Assessment of Motor Response to a Low Subacute Levodopa Dose in the Differential Diagnosis of Parkinsonisms at Disease Onset: Data from the BoProPark Cohort

Manuela Contin[a,b,*], Giovanna Lopane[a], Pietro Cortelli[a,b], Luisa Sambati[a,b], Susan Mohamed[a] and Giovanna Calandra-Buonaura[a,b]

Abstract.

Background: Differential diagnosis between Parkinson's disease (PD) and atypical parkinsonisms (APs) may be difficult at disease onset. The response to levodopa (LD) is a key supportive feature but its definition is largely empirical. Studies evaluating this issue by quantitative tests are scanty.

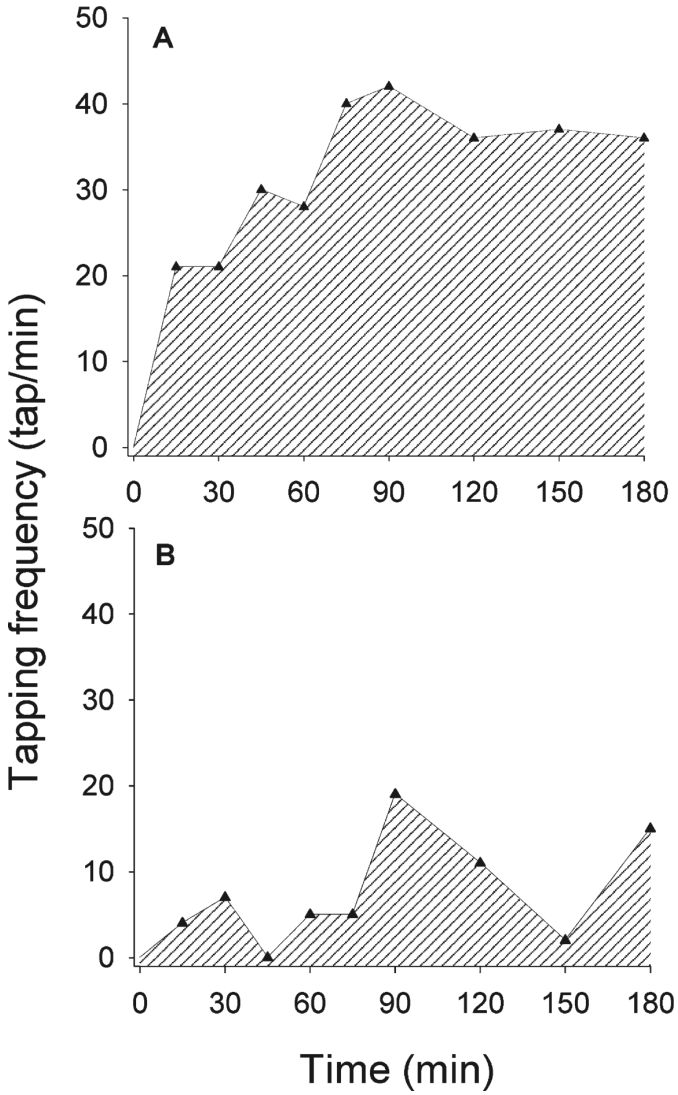
Objective: We aimed to assess the utility of a subacute low LD dose kinetic-dynamic test in the differential diagnosis between PD and APs. It was applied at the baseline of a prospective follow-up in patients with parkinsonian signs within three years of disease motor onset ("BoProPark" cohort) and eventually diagnosed as PD or APs according to consensus criteria.

Methods: Patients under at least 3-month LD therapy received a first morning fasting dose of LD/benserazide or carbidopa (100/25 mg) and underwent simultaneous serial assessments of plasma LD concentration and alternate finger tapping frequency up to 3 h. The main outcome was the extent of LD motor response, calculated by the area under the 3 h tapping effect–time curve (AUC_ETap). A receiver operating characteristic (ROC) curve analysis was performed to establish the optimal AUC_ETap cut-off to differentiate PD and APs.

Results: The first 100 consecutive "BoProPark" patients were analyzed. Forty-seven patients were classified as possible, 37 as probable PD and 16 as APs. AUC_ETap medians were similar in the PD subgroups but reduced to a third in APs ($p < 0.001$). The optimal AUC_ETap cut-off value was >2186 [(tap/min) x min], with a sensitivity of 92% and a specificity of 75%. Accuracy of the test was 0.85 (95% CI 0.74–0.95), $p < 0.0001$.

Conclusion: The estimation of 3 h AUC_ETap after a subacute low LD dose proved a reliable, objective tool to assess LD motor response in our cohort of patients. AUC_ETap value rounded to ≥2200 supports PD diagnosis, while lower values may alert to AP diagnoses.

J Parkinsons Dis. 2021; 11(2): 811–819.



MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
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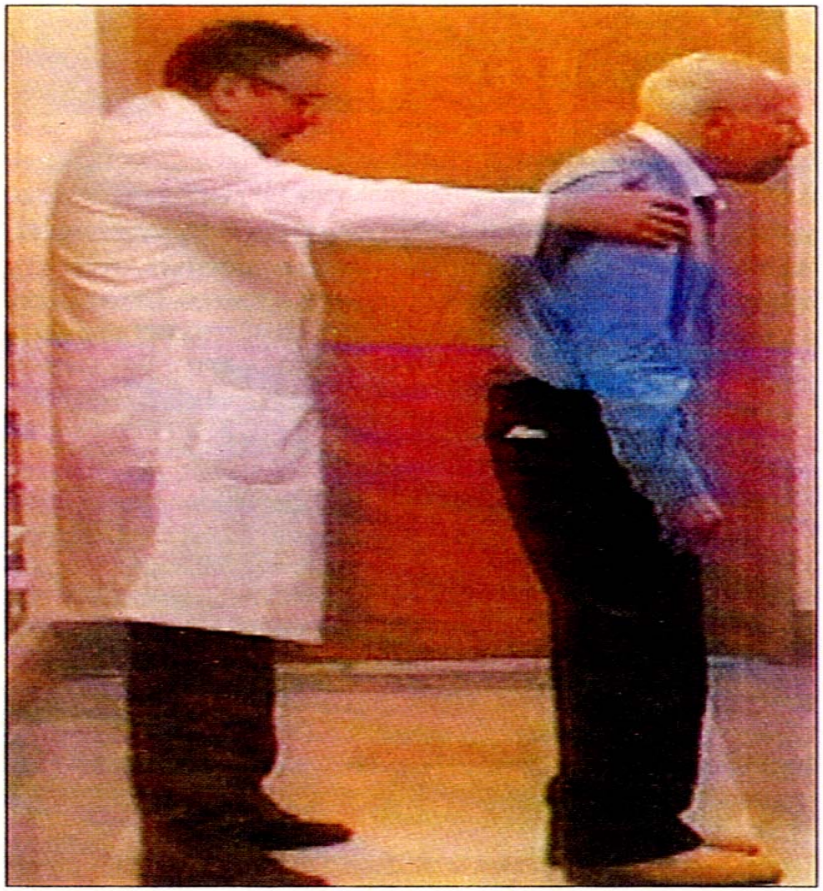
and Günther Deuschl, MD[18]

Red flags

- ☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
- ☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
- ☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
- ☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- ☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  - a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  - b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
- ☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
- ☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
- ☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Movement Disorders, Vol. 30, No. 12, 2015

Pull test



0 Normale:

Nessun problema. Il recupero avviene con uno o due passi.

1 Minimo:

Dai 3 ai 5 passi, ma il paziente recupera senza aiuto.

2 Lieve:

Più di 5 passi, ma il soggetto recupera senza aiuto.

3 Moderato:

Sta in piedi senza problemi di stabilità ma la risposta posturale è assente; cade se non sorretto dall'esaminatore

4 Grave:

Molto instabile, tende a perdere l'equilibrio spontaneamente o con solo una lieve pressione sulle spalle

Supportive clinical motor features for MSA

Rapid progression within 3 years of motor onset	Needs help with some chores or greater disability within 3 years of motor onset assessed by history. Rate of progression is rapid in comparison to what a movement disorder specialist would anticipate for Parkinson's disease.

Rapid progression, defined as reaching Hoehn and Yahr stage ≥ 3 within three years from onset, DD PD vs MSA (sensitivity: 69%; **specificity: 90%)** (Colosimo et al., 1995)

Moderate to severe postural instability within three years from motor onset	Deficient postural response defined as at least three steps backwards or tendency to fall if not caught by examiner upon pull test within 3 years of motor onset.

Compared to PD: postural instability within the first 3 years of disease is suggestive of MSA (sensitivity: 27%–45%, **specificity: 88.7%**), in the first year from motor onset sensitivity: 23.5%, **specificity: 94%.** (Osaki et al., 2009; Respondek et al., 2017). Median latency to falls was shorter in MSA (24 months) than in PD (118 months) (Wenning et al., 1999).

Core clinical features

	Functional Domain			
Levels of Certainty	**Ocular Motor Dysfunction**	**Postural Instability**	**Akinesia**	**Cognitive Dysfunction**
Level 1	**O1**: Vertical supranuclear gaze palsy	**P1**: Repeated unprovoked falls within 3 years	**A1**: Progressive gait freezing within 3 years	**C1**: Speech/language disorder, i.e., nonfluent/ agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	**O2**: Slow velocity of vertical saccades	**P2**: Tendency to fall on the pull-test within 3 years	**A2**: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2**: Frontal cognitive/behavioral presentation
Level 3	**O3**: Frequent macro square wave jerks or "eyelid opening apraxia"	**P3**: More than two steps backward on the pull-test within 3 years	**A3**: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	**C3**: Corticobasal syndrome

Mov Disord. 2017 June ; 32(6): 853–864. doi:10.1002/mds.26987.

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Red flags

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- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Movement Disorders, Vol. 30, No. 12, 2015

Red Flag for PD: *disproportionate anterocollis (dystonic)* (Tinazzi et al. MDCP 2022) or *contractures of hand or feet within the first 10 y*

Supportive MSA motor features, at least one of :

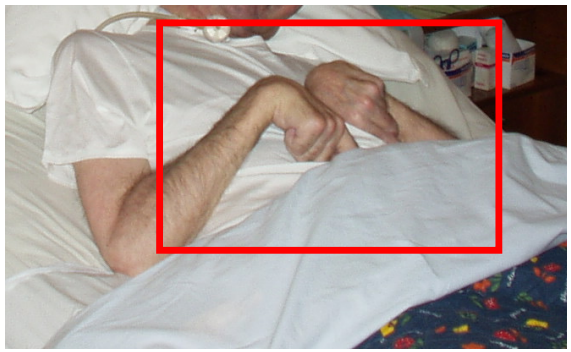
Disproportionate anterocollis or laterocollis = marked neck anteroflexion or lateroflexion, may be partially overcome by voluntary or passive movement

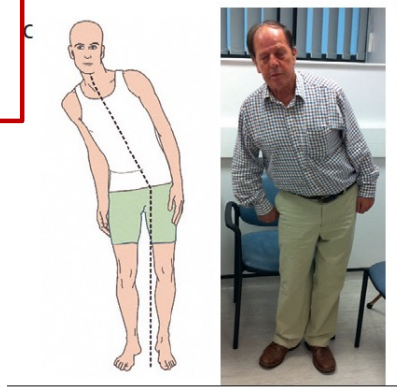
Contractures of hands or feet

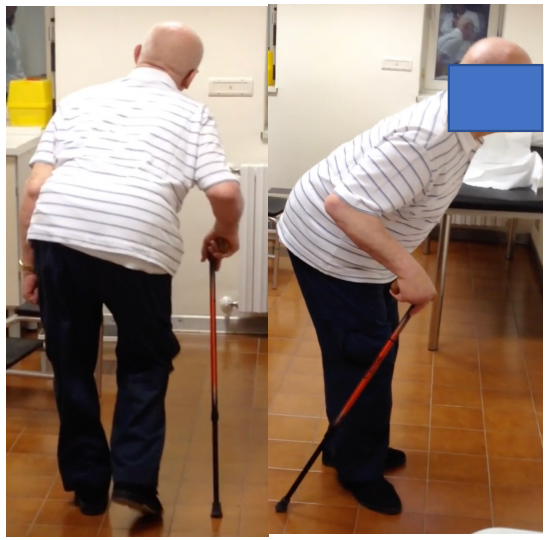
Pisa syndrome = severe lateral flexion of the spine

Camptocormia = severe anterior flexion of the spine

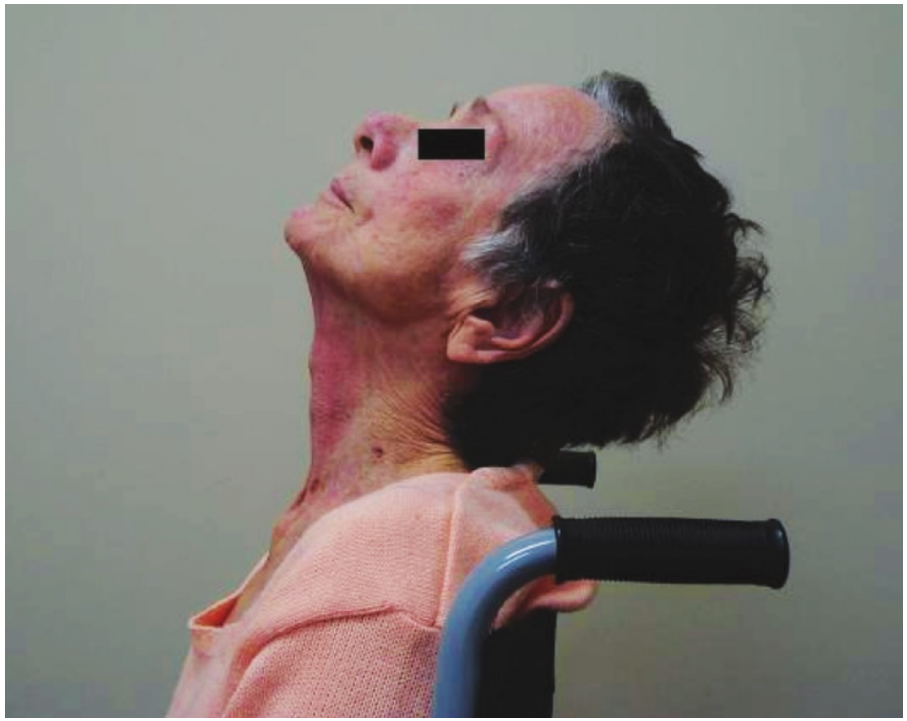
Geser F, Wenning GK Journal für Neurologie, Neurochirurgie und Psychiatrie 2004; 5 (2): 56-62 ©







Nuchal dystonia with retrocollis may be helpful to raise suspicion about PSP, but no clear evidence suggesting that it would indeed contribute reliable information to substantiate the diagnosis of PSP.



Red Flag for PD: Inspiratory respiratory dysfunction defined as either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs

Supportive MSA non motor features

Stridor (Cortelli et al. Neurology 2019)

Inspiratory sighs

Dysphagia and PD patients:

- Prevalence of oropharyngeal dysphagia based on subjective outcomes is **35%** and on objective measures is **82%** (Kalf et al. 2012).
- Only **20-40% of PD** patients are aware of their swallowing dysfunction, and **less than 10%** of PD patients report spontaneously about dysphagia.
- Signs of penetration and/or aspiration may be present in **20%** of patients without any complaint of swallowing difficulties (silent aspiration)(Rodrigues et al. 2011)

MSA patients:

- Prevalence ranging from 31% to 78% (Calandra-Buonaura et al. 2021)
- Occurrence of severe dysphagia within 3 years of motor onset is a clinical supportive feature of MSA (Wenning et al. 2022)

		MSA lookalikes	
The frequency of clinical features	**MSA *n* = 160**	**LBD *n* = 26**	**PSP *n* = 13**
Parkinsonism (tremor, bradykinesia, rigidity or positive pull test), % (*n*)	93.8 (150/160)	100 (26/26)	100 (13/13)
Tremor			
Resting, % (*n*)	27.5 (44/160)	53.8 (14/26)*	30.8 (4/13)
Typical pill-rolling, % (*n*)	3.8 (6/160)	26.9 (7/26)**	0 (0/13)
Postural/action, % (*n*)	33.1 (53/160)	42.3 (11/26)	23.1 (3/13)
Intention, % (*n*)	18.8 (30/160)	11.5 (3/26)	0 (0/13)
Bradykinesia, % (*n*)	80 (128/160)	96.2 (25/26)	84.6 (11/13)
Rigidity, % (*n*)	76.9 (123/160)	96.2 (25/26)	92.3 (12/13)
Positive pull test, % (*n*)	31.3 (50/160)	26.9 (7/26)	23.1 (3/13)
Early positive pull test within 3 years of onset, % (*n*)	9.3 (15/160)	0 (0/26)	7.7 (1/13)
Gait freezing, % (*n*)	15.0 (24/160)	34.6 (9/26)	23.1 (3/13)
Early gait freezing within 3 years of onset, % (*n*)	3.8 (6/160)	0 (0/26)	0 (0/13)
Ataxia, % (*n*)	62.5 (100/160)	3.8 (1/26)**	23.0 (3/13)*
Early ataxia within 3 years of onset, % (*n*)	36.8 (59/160)	0 (0/26)**	7.7 (1/13)
Stridor, % (*n*)	31.8 (51/160)	7.7 (2/26)*	0 (0/13)*
Dysphagia within 5 years of onset, % (*n*)	46.2 (74/160)	15.4 (4/26)**	23.1 (3/13)
Falls, % (*n*)	82.5 (132/160)	61.5 (16/26)*	100 (13/13)
Early falls within 3 years of onset, % (*n*)	42.5 (68/160)	15.4 (4/26)*	38.5 (5/13)
Vertical gaze palsy, % (*n*)	20.6 (33/160)	15.4 (4/26)	61.5 (8/13)**
Hyperreflexia with Babinski reflex, % (*n*)	32.5 (52/160)	15.4 (4/26)	23.1 (3/13)
Frontal release signs, % (*n*)	10.6 (17/160)	7.7 (2/26)	23.1 (3/13)
Impairment of frontal lobe function, % (*n*)	13.1 (21/160)	11.5 (3/26)	7.7 (1/13)
Depression, % (*n*)	44.4 (71/160)	42.3 (11/26)	53.8 (7/13)
Hallucination, % (*n*)	5 (8/160)	34.6 (9/26)**	15.4 (2/13)
REM sleep behaviour disorder, % (*n*)	41.3 (66/160)	34.6 (9/26)	7.7 (1/13)

PSP patients:

- Dysphagia is also a common feature in PSP occurring in up to 80% of patients (Litvan et al. 1996)
- "Otherwise unexplained difficulty in swallowing, severe enough to request dietary adaptations" is a clinical clues in PSP criteria (Hoglingher et al. 2017)

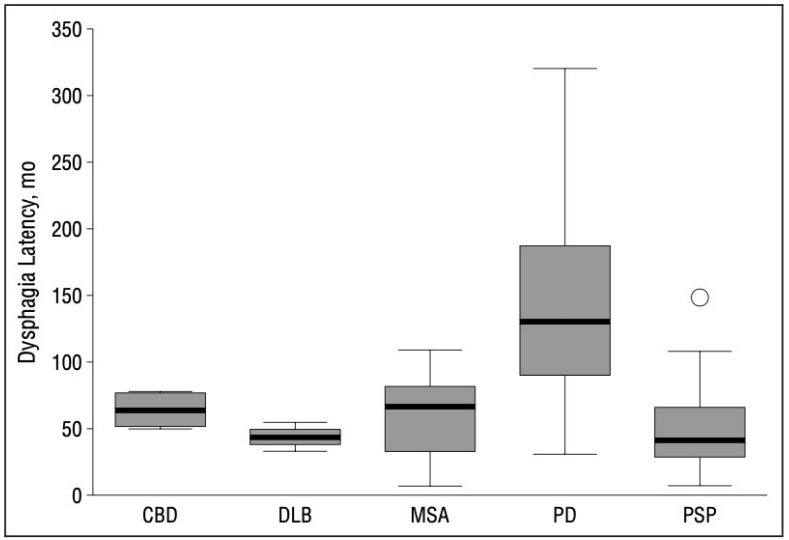


Figure 2. *Latencies to dysphagia after disease onset in postmortem-confirmed parkinsonian disorders. Frequencies of dysphagia: corticobasal degeneration (CBD), n=4; dementia with Lewy bodies (DLB), n=3; multiple system atrophy (MSA), n=11; Parkinson disease (PD), n=7; and progressive supranuclear palsy (PSP), n=20. The horizontal lines indicate median values; boxes, 25th to 75th percentile; error bars, lowest and highest values within 1.5 times the values observed in the percentile boxes; and circle, a single case exceeding 1.5 times the values observed in the percentile box.*

Muller et al.2001

Dysarthria:

Red flag for PD: Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y

Supportive feature of MSA: Severe speech impairment within 3 years of motor onset Slow, slurred, or dysphonic speech severe enough to require occasional repetition of statements during interview within 3 years of motor onset.

Clinical clues for PSP Hypokinetic, spastic dysarthria: slow, low volume and pitch, harsh voice.

Severe speech impairment within 3 years of motor onset	Slow, slurred, or dysphonic speech severe enough to require occasional repetition of statements during interview within 3 years of motor onset.

Neurogenic OH

Red Flag for PD: severe autonomic failure in the first 5 y of disease. This can include: Orthostatic hypotension—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction,

Exclusion criteria for PSP: Predominant, otherwise unexplained autonomic failure, e.g., orthostatic hypotension, suggestive of multiple system atrophy or Lewy body disease

Neurogenic OH and delayed neurogenic OH are core clinical features for clinically established and clinically probable MSA.

Neurogenic orthostatic hypotension in early stage Parkinson's disease: New insights from the first 105 patients of the BoProPark study

Francesca Baschieri [a,b], Luisa Sambati [a,b], Pietro Guaraldi [b], Giorgio Barletta [a,b], Pietro Cortelli [a,b], Giovanna Calandra-Buonaura [a,b,*]

Parkinsonism and Related Disorders 93 (2021) 12–18

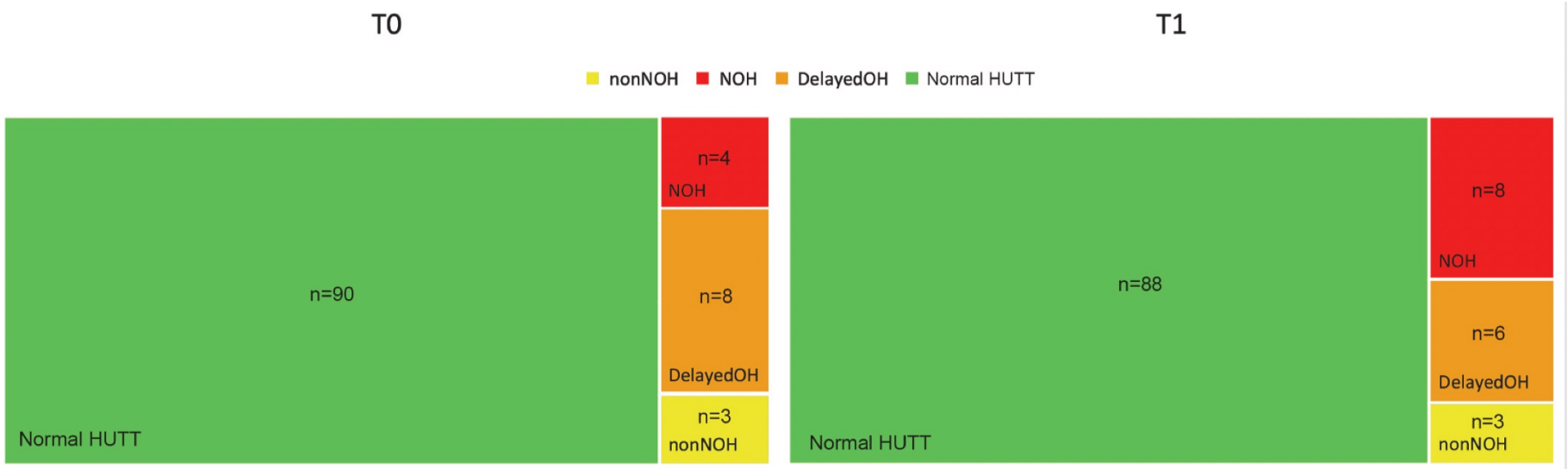


Fig. 1. Title: Longitudinal prevalence of orthostatic hypotension in Parkinson's disease
Legend: OH = orthostatic hypotension; NOH = neurogenic OH; nonNOH = non-neurogenic OH; HUTT = head-up tilt test; n = number of subjects.

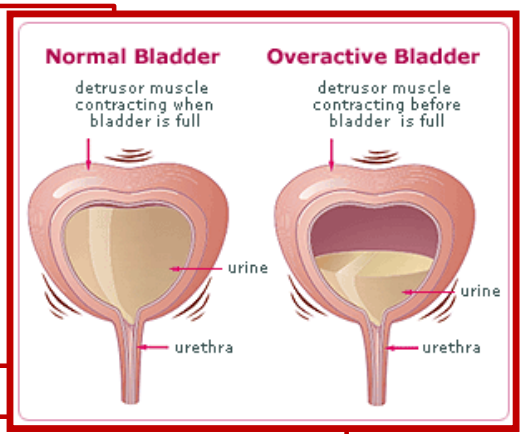
Core clinical features for MSA: autonomic urinary dysfunction

Storage dysfunction

Frequency

Urgency

Urinary incontinence



Clinically established MSA: voiding difficulties with postvoid urinary residual volume > 100 ml, urinary urge incontinence

Clinically probable MSA: voiding difficulties with postvoid urinary residual volume, urinary urge incontinence

Voiding dysfunction

Incomplete bladder emptying with postvoid urinary residual volume > 100 ml

Symptoms: hesitancy, intermittent urinary stream or poor flow, sensation of incomplete bladder emptying, double voiding.

Early presentation of urinary retention in multiple system atrophy: can the disease begin in the sacral spinal cord?

Jalesh N. Panicker[1,2] · Sara Simeoni[1] · Yasuo Miki[3,4] · Amit Batla[2,5] · Valeria Iodice[2,6] · Janice L. Holton[3] · Ryuji Sakakibara[7] · Thomas T. Warner[3]

Journal of Neurology (2020) 267:659–664

Abstract

Lower urinary tract (LUT) dysfunction presents early in multiple system atrophy (MSA), usually initially as urinary urgency, frequency and incontinence, and voiding difficulties/urinary retention becomes apparent over time. We have observed a subset of patients who instead presented initially with urinary retention requiring catheterisation. At presentation, these patients had only subtle neurological signs that would not fulfil the diagnostic criteria of MSA; however, the anal sphincter electromyography (EMG) was abnormal and they reported bowel and sexual dysfunction, suggesting localisation at the level of the sacral spinal cord. They subsequently developed classical neurological signs, meeting the diagnostic criteria for probable MSA. One patient was confirmed to have MSA at autopsy. We postulate that in a subset of patients with MSA, the disease begins in the sacral spinal cord and then spreads to other regions resulting in the classical signs of MSA. The transmissibility of alpha-synuclein has been demonstrated in animal models and the spread of pathology from sacral cord to other regions of the central nervous system is therefore plausible. Patients presenting with urinary retention and mild neurological features would be an ideal group for experimental trials evaluating neuroprotection in MSA

Lower urinary tract (LUT) symptoms suggestive of urogenital failure are the sole initial manifestation of MSA in 18% of patients, with a mean onset of **2.8 years** prior to the onset of motor symptoms (Sakakibara et al. 2019).

Significantly elevated PVR is the most specific sign of bladder dysfunction in MSA versus PD (sensitivity: 34%, specificity: 95%), but is not useful to distinguish MSA from PSP (Han et al., 2005; Kim et al., 2015; Kim et al., 2018). Patients with SAOA usually develop overactive bladder symptoms .

Urinary urge incontinence is more sensitive but less specific for the diagnosis of MSA (sensitivity: 48%, specificity: 34%) (Fanciulli et al., 2019)

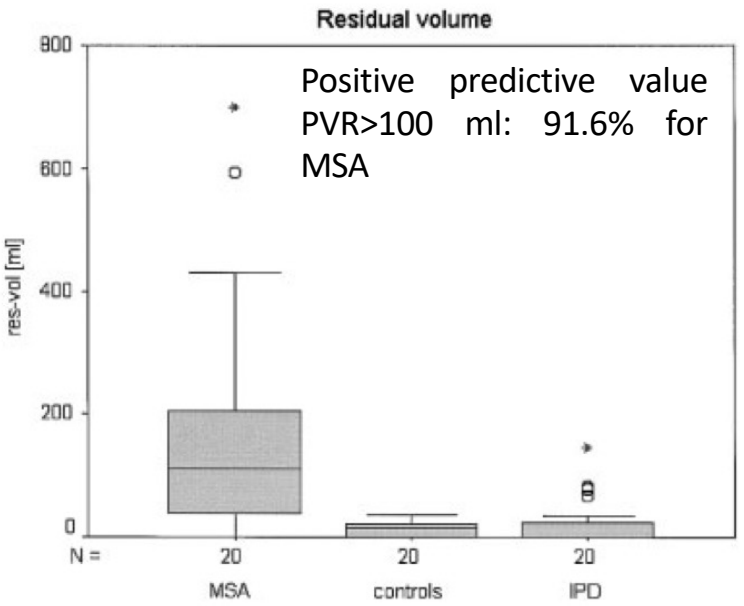


FIG. 1. Box plots showing median and 25/75 percentile of residual bladder volume in subjects with multiple system atrophy (MSA), Parkinson's disease, and healthy controls.

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Absolute exclusion criteria: The presence of any of these features rules out PD:

- ☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
- ☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
- ☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
- ☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
- ☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
- ☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
- ☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
- ☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
- ☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Core clinical features for MSA: cerebellar syndrome

At least two (for clinically established) or at least one (for clinically probable MSA):

- gait ataxia (36 to 64% of MSA)
- limb ataxia (47-53%)
- cerebellar dysarthria (49-69%)
- oculomotor dysfunction = sustained nystagmus (gaze-evoked horizontal or downbeat) or saccadic hypermetria.

B2: Mandatory exclusion criteria[a]	Clinical findings	
	1	Predominant, otherwise unexplained impairment of episodic memory, suggestive of AD
	2	Predominant, otherwise unexplained autonomic failure, e.g., orthostatic hypotension (orthostatic reduction in blood pressure after 3 minutes standing ≥30 mm Hg systolic or ≥15 mm Hg diastolic), suggestive of multiple system atrophy or Lewy body disease
	3	Predominant, otherwise unexplained visual hallucinations or fluctuations in alertness, suggestive of dementia with Lewy bodies
	4	Predominant, otherwise unexplained multisegmental upper and lower motor neuron signs, suggestive of motor neuron disease (pure upper motor neuron signs are *not* an exclusion criterion)
	5	Sudden onset or step-wise or rapid progression of symptoms, in conjunction with corresponding imaging or laboratory findings, suggestive of vascular etiology, autoimmune encephalitis, metabolic encephalopathies, or prion disease
	6	History of encephalitis
	7	Prominent appendicular ataxia
	8	Identifiable cause of postural instability, e.g., primary sensory deficit, vestibular dysfunction, severe spasticity, or lower motor neuron syndrome

Mov Disord. 2017 June ; 32(6): 853–864. doi:10.1002/mds.26987.

Exclusion criteria
Substantial and persistent beneficial response to dopaminergic medications
Unexplained anosmia on olfactory testing
Fluctuating cognition with pronounced variation in attention and alertness and early decline in visuoperceptual abilities
Recurrent visual hallucinations not induced by drugs within 3 years of disease onset
Dementia according to DSM-V within 3 years of disease onset
Downgaze supranuclear palsy or slowing of vertical saccades
Brain MRI findings suggestive of an alternative diagnosis (eg, PSP, multiple sclerosis, vascular parkinsonism, symptomatic cerebellar disease, etc.)
Documentation of an alternative condition (MSA look-alike, including genetic or symptomatic ataxia and parkinsonism) known to produce autonomic failure, ataxia, or parkinsonism and plausibly connected to the patient's symptoms

Ocular motor dysfunction		
O1	Vertical supranuclear gaze palsy	A clear limitation of the range of voluntary gaze in the vertical more than in the horizontal plane, affecting both up- and downgaze, more than expected for age, which is overcome by activation with the vestibulo-ocular reflex; at later stages, the vestibulo-ocular reflex may be lost, or the maneuver prevented by nuchal rigidity.

Parkinsonism & Related Disorders
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O2	Slow velocity of vertical saccades	Decreased velocity (and amplitude) of vertical greater than horizontal saccadic eye movements; this may be established by quantitative measurements of saccades, such as infrared oculography, or by bedside testing; gaze should be assessed by command ("Look at the flicking finger") rather than by pursuit ("Follow my finger"), with the target >20 degrees from the position of primary gaze; to be diagnostic, saccadic movements are slow enough for the examiner to see their movement (eye rotation), rather than just initial and final eye positions in normal subjects; a delay in saccade initiation is not considered slowing; findings are supported by slowed or absent fast components of vertical optokinetic nystagmus (i.e., only the slow following component may be retained).

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O3	Frequent macro square wave jerks or "eyelid opening apraxia"	Macro square wave jerks are rapid involuntary saccadic intrusions during fixation, displacing the eye horizontally from the primary position, and returning it to the target after 200 to 300 milliseconds; most square wave jerks are <1 degree in amplitude and rare in healthy controls, but up to 3 to 4 degrees and more frequent (>10/min) in PSP.[50] "Eyelid opening apraxia" is an inability to voluntarily initiate eyelid opening after a period of lid closure in the absence of involuntary forced eyelid closure (i.e., blepharospasm); the term is written in quotation marks because the inability to initiate eyelid opening is often attributed to activation of the pretarsal component of the orbicularis oculi (i.e., pretarsal blepharospasm) rather than failure to activate the levator palpebrae.

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Vascular parkinsonism

Rektor et al 2018

Table 2
Clinical and imaging features in post-stroke and insidious VaPark subtypes and mixed VaPark/neurodegenerative parkinsonism.

Diagnosis	Onset	Clinical presentation	Associated features	MRI findings
Acute/subacute Post-stroke VaPark	Acute/ Subacute	4–6 Hz resting/postural tremor (+/−) Rigidity with cogwheeling (−/+) Lower body predominance (−) Levodopa response (+) Dementia (−) Upper motor neuron signs (−/+)	Asymmetry of neurological involvement, robust dopaminergic responsiveness	Contralateral stroke in substantia nigra or nigrostriatal pathway region
Insidious VaPark	Insidious	Tremor (−) Rigidity with cogwheeling (−) Predominance on lower body (+) Levodopa response (−) Dementia (+/−) Upper motor neuron signs (+)	Predominantly symmetrical neurological involvement, cognitive or urinary symptoms	Deep white matter hyperintensities
Mixed neurodegenerative parkinsonism and CVD (mixed PD/CVD)	Insidious	4-6 Hz resting/postural tremor (+/−) Rigidity with cogwheeling (+) Predominance on lower body (−/+) Levodopa response (+) Dementia (−/+) Upper motor neuron signs (−)	Symmetrical or asymmetrical neurological involvement, cognitive or urinary symptoms	Deep white matter hyperintensities and/or strokes, lacunar infarcts

Legend: (+) sign present; (−) sign absent; (−/+) sign can be present or absent, more likely absent; (+/−) sign can be present or absent, more likely present.

The typical clinical picture of the insidious onset of VaP:

- **Gait disorder**
- **Early postural instability with falls**
- **Predominance of lower body rigidity**
- Other signs that could be associated : corticospinal and cerebellar signs (es. Upper motor sign), cognitive impairment, urinary incontinence, pseudobulbar signs (dysphagia, dysarthria) or involuntary laughter or crying

Non-supportive features: responsiveness to levodopa, classic 4-5 Hz pill rolling resting tremor or visual hallucinations.

Normal pressure hydrocephalus

	International Guidelines (2005)[3]	Japanese Guidelines (2012)[4]
Clinical features		
Probable	Gait/balance disturbance and at least one of the following: a. Cognitive impairment b. Urinary incontinence/ urgency	At least two of the clinical triad: a. Gait disturbance b. Cognitive impairment c. Urinary incontinence
Possible	Symptoms of either: a. Incontinence and/or cognitive impairment in the absence of gait/ balance disturbance b. Gait disturbance alone	Same as probable
Brain imaging		
Probable	Ventriculomegaly (EI > 0.3) and at least one of the following: a. Narrow callosal angle b. Enlargement of the temporal horns c. Periventricular signal changes not attributable to ischemic changes or demyelination	Ventriculomegaly (EI > 0.3) and narrowing of the sulci over the high convexity/DESH
Possible	Ventriculomegaly (EI > 0.3)	Ventriculomegaly (EI > 0.3)
Duration of symptoms	>3 months	NA
Age	>40 years	>60 years
Comorbidities	No other condition	Other neurological condition possible (but "mild")
Opening pressure	70–245 mm H_2O	≦200 mm H_2O

Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; EI, Evans index; DESH, disproportionately enlarged subarachnoid space hydrocephalus; NA: not available.

Gait is "shuffling," "magnetic," and "wide-based."
Typical features:
-External rotation in foot posture
-Poor foot clearance (festination, shuffling, tripping)
- Notable difficulty turning on the body's - long axis (multistep turns)
- Gait initiation failure or freezing of gait
With disease progression, the patient's gait deteriorates finally becoming broad-based, slow, short-stepped, and glue-footed (a gait disturbance of the astasia-abasia type).

Dysequilibrium is usually worse with the eyes closed, but patients require a broad standing base even with their eyes open.
Motor abnormalities in the upper limbs are either mild or absent and generally restricted to bradykinesia.
The slowness of gait and in the movements of both upper and lower limbs can improve following shunting.

Conclusions

-Response to levodopa could be present also in atypical parkinsonism but it is usually not sustained

- Some Signs are more frequent in atypical parkisnonism

- Some Signs occurr ealy in the disease course in atypical parkinsonism

- In presence of postural instability in the first years of the disease or severe gait impairment atypical parkisnonism should be excluded.