# Early Diagnosis of Multiple System Atrophy

**Amy E Brown, MD, MS,**
**Assistant Professor of Neurology,**
**Vanderbilt University Medical Center**

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# Disclosures

I have received financial fundings for clinical trials related to MSA from Alterity therapeutics, Lundbeck, Ono Pharmaceutical, Teva Pharmaceuticals and Yoda Therapeutics

I have also received industry-related research funding from the below companies:

- CHDI (HD)
- F. Hoffmann-La Roche (HD)
- Neurocrine Biosciences (HD)
- Novartis (PSP, HD)
- Orphalan (Wilson's disease)
- Sage Therapeutics (PD, HD)
- UniQure (HD)

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# Objectives

1. Describe the MDS-MSA Criteria for Diagnosis
2. Key Elements of the Clinical History and Examination in diagnosing MSA

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# Parkinsonism

## Hypokinetic syndrome

- Resting tremor
- Muscular rigidity
- Bradykinesia/akinesia
- Postural instability

## Atypical parkinsonism

Parkinsonian syndrome with atypical features, such as:

- Early dementia
- Frequent falls
- Ocular dysmotility
- Ataxia
- Prominent dysautonomia
  - Urinary incontinence
  - Orthostatic hypotension

Paralysis Agitans. *(After St. Leger.)*

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# Why identify atypical parkinsonism?

Progression and subsequent functional decline is often more rapid than PD

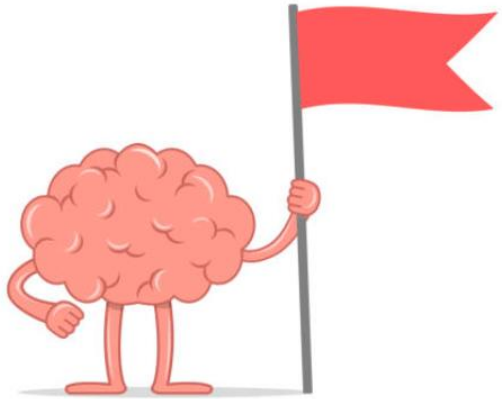
Treatment with standard therapies frequently lacks efficacy and often have complications

Complex care needs – Benefit from a multidisciplinary approach

# “Red flags” to suggest atypical parkinsonism

These diagnoses remain primary based on clinical evaluation, so pay attention to red flags when looking at parkinsonian patients:

- Rapid disease progression
- Early gait instability / falls
- Absence or paucity of tremor
- Irregular jerky tremor, myoclonus
- Autonomic failure
- Poor or absent response to levodopa
- Pain / Dysesthesia
- Pyramidal tract / cerebellar signs
- Severe dysarthria, dysphonia, stridor



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# Multiple systems atrophy (MSA)

## Clinical variable presentation of:

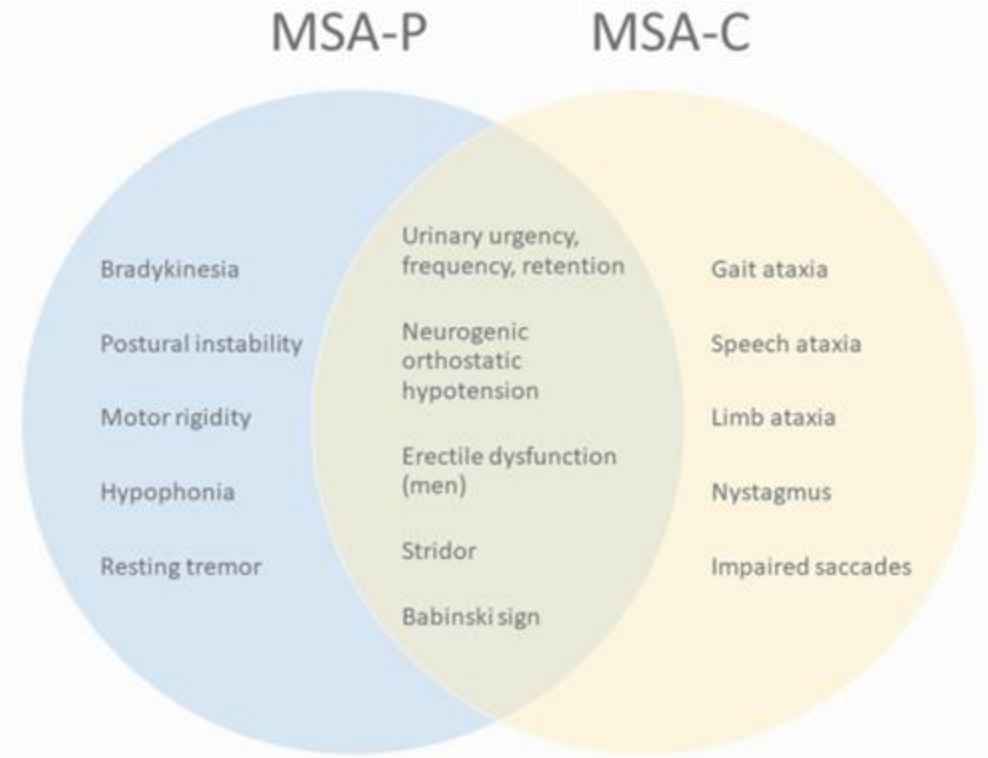
- Parkinsonian motor symptoms
- Cerebellar/ataxic symptoms
- Pyramidal signs
- Autonomic dysfunction

## Over the years, different diagnostic terms:

- Shy-Drager syndrome
- Olivopontocerebellar atrophy
- Striatonigral degeneration

## Median age of onset: 58 years old

## Mean survival from diagnosis: 6-10 years (faster than PD)

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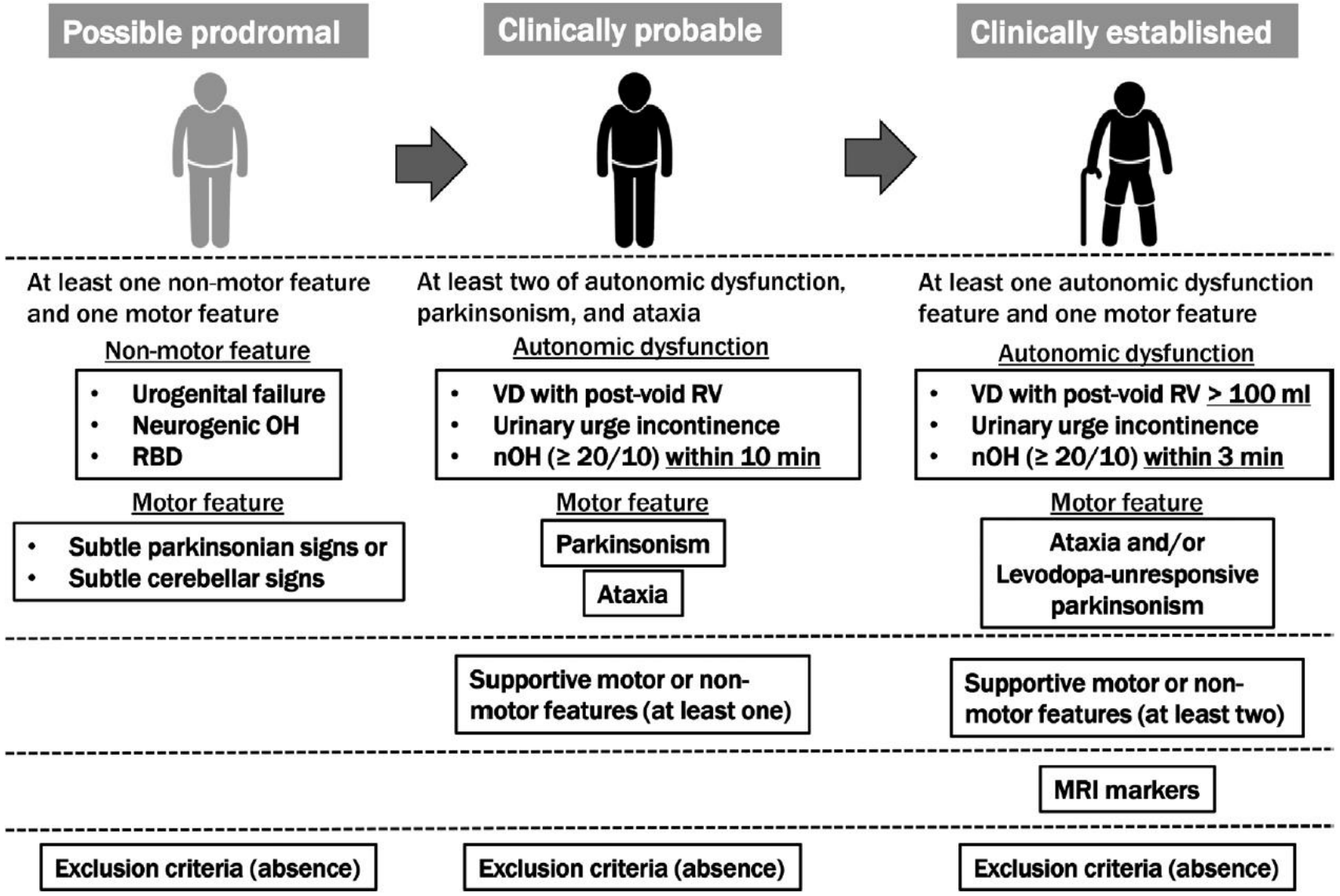
# MDS Criteria for the Diagnosis of MSA

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# Prodromal and early signs of MSA

## Prodromal symptoms

- REM sleep behavioral disorder
- Autonomic failure
  - Pure autonomic failure – syndrome with orthostatic hypotension, reduction in sweating, and pathologically with degeneration of peripheral autonomic neurons
  - Central noradrenergic failure - an increase in heart rate after 3 minutes of standing up from supine position (postganglionic sympathatic neurons are preserved in MSA )
- Urinary retention  (up to 20%)
- (Normal smell)

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# MDS-MSA: Clinically established MSA

| | | | |
|---|---|---|---|
| **Core clinical features** | **Autonomic dysfunction (at least 1 feature)** | Unexplained voiding difficulties with post-void urinary residual volume ≥ 100mL | |
| | | Unexplained urinary urge incontinence | |
| | | Neurogenic OH<br>≥20/10 mmHg Blood pressure drop within 3 minutes of standing or head-up tilt test | |
| | AND | | |
| | **Poor l-dopa responsive parkinsonism** | < 30% improvement in MDS-UPDRS III after l-dopa intake | |
| | OR | | |
| | **Cerebellar syndrome (at least 2 features)** | Gait ataxia | Cerebellar dysarthria |
| | | Limb ataxia | Oculomotor features |
| **Supportive clinical features** | ≥ 2 features | | |
| **MRI marker** | ≥ 1 features | | |

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# Clinically established MSA

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| | | Limb ataxia | Oculomotor features |
| **Supportive clinical features** | ≥ 2 features | | |
| **MRI marker** | ≥ 1 features | | |

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# Case #1 : Poor Levodopa Response


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# Clinically established MSA

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| **MRI marker** | ≥ 1 features | | |

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# Case #2 : Gait ataxia


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# Clinically established MSA

| | | | |
|---|---|---|---|
| **Core clinical features** | **Autonomic dysfunction (at least 1 feature)** | Unexplained voiding difficulties with post-void urinary residual volume ≥ 100mL | |
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| | OR | | |
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| | | Limb ataxia | Oculomotor features |
| **Supportive clinical features** | ≥ 2 features | | |
| **MRI marker** | ≥ 1 features | | |

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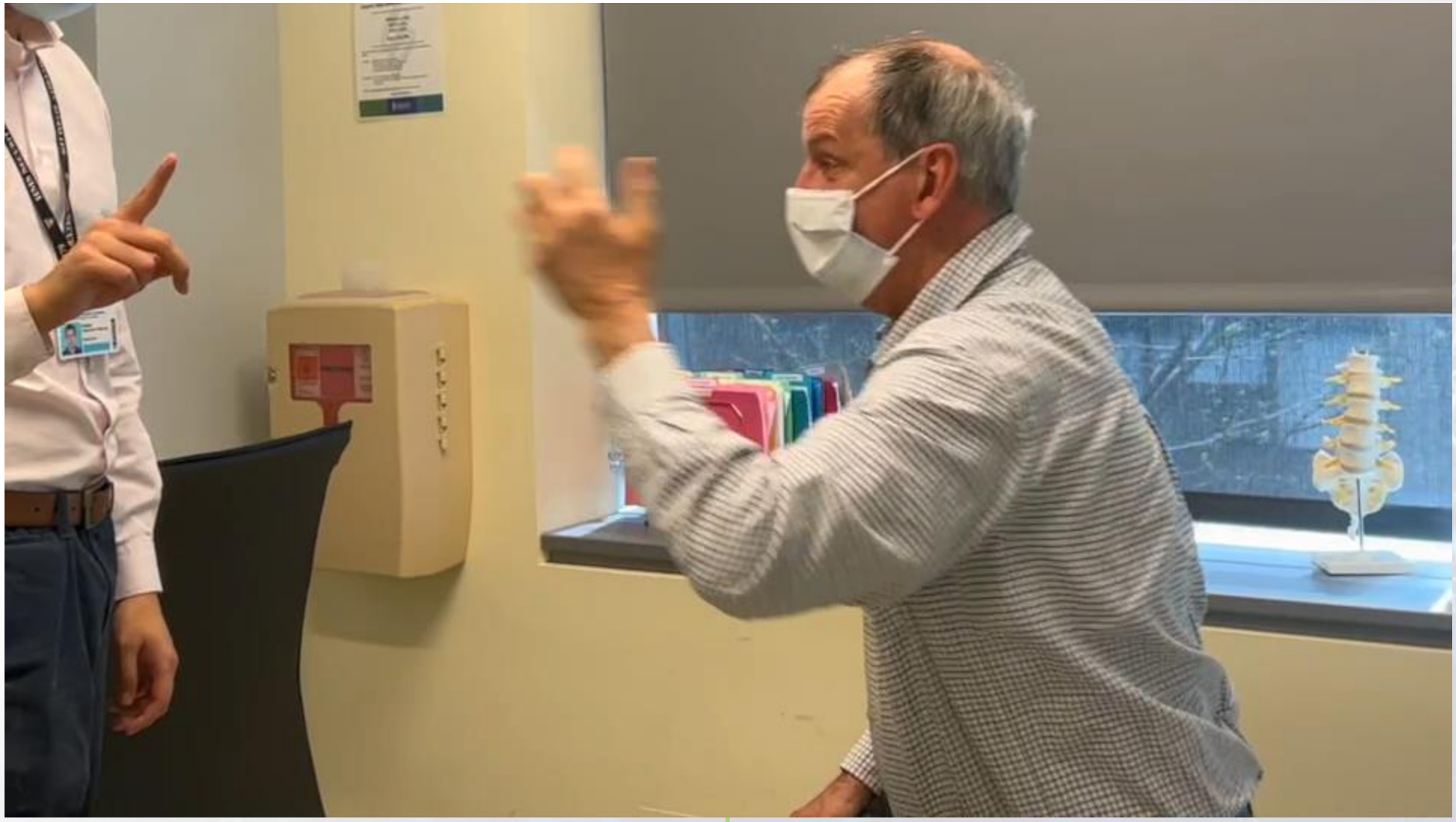
# Case #2 : Limb ataxia



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# Clinically established MSA

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| | | Limb ataxia | Oculomotor features |
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| **MRI marker** | ≥ 1 features | | |

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# Case #2 : Cerebellar dysarthria

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# Clinically established MSA

| | | | |
|---|---|---|---|
| **Core clinical features** | **Autonomic dysfunction (at least 1 feature)** | Unexplained voiding difficulties with post-void urinary residual volume ≥ 100mL | |
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| | OR | | |
| | **Cerebellar syndrome (at least 2 features)** | Gait ataxia | Cerebellar dysarthria |
| | | Limb ataxia | Oculomotor features |
| **Supportive clinical features** | ≥ 2 features | | |
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# Oculomotor features


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# Clinically established MSA

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| **Supportive clinical features** | ≥ 2 features | | |
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# Supportive clinical features

- Rapidly progression within 3 years of motor onset
- Moderate to severe postural instability within 3 years of motor onset
- Severe speech impairment within 3 years of motor onset
- Severe dysphagia within 3 years of motor onset
- Craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia
- Unexplained Babinski skin
- Jerky myoclonic postural or kinetic tremor
- Postural deformities
- Stridor
- Inspiratory sighs
- Cold discolored hands and feet
- Erectile dysfunction (below age of 60 years)
- Pathological laugher or crying

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# Jerky myoclonic postural or kinetic tremor

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- Jerky myoclonic postural or kinetic tremor
- **Postural deformities**
- Stridor
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# Postural deformities


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# Supportive clinical features

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- Postural deformities

- **Stridor**
- Inspiratory sighs
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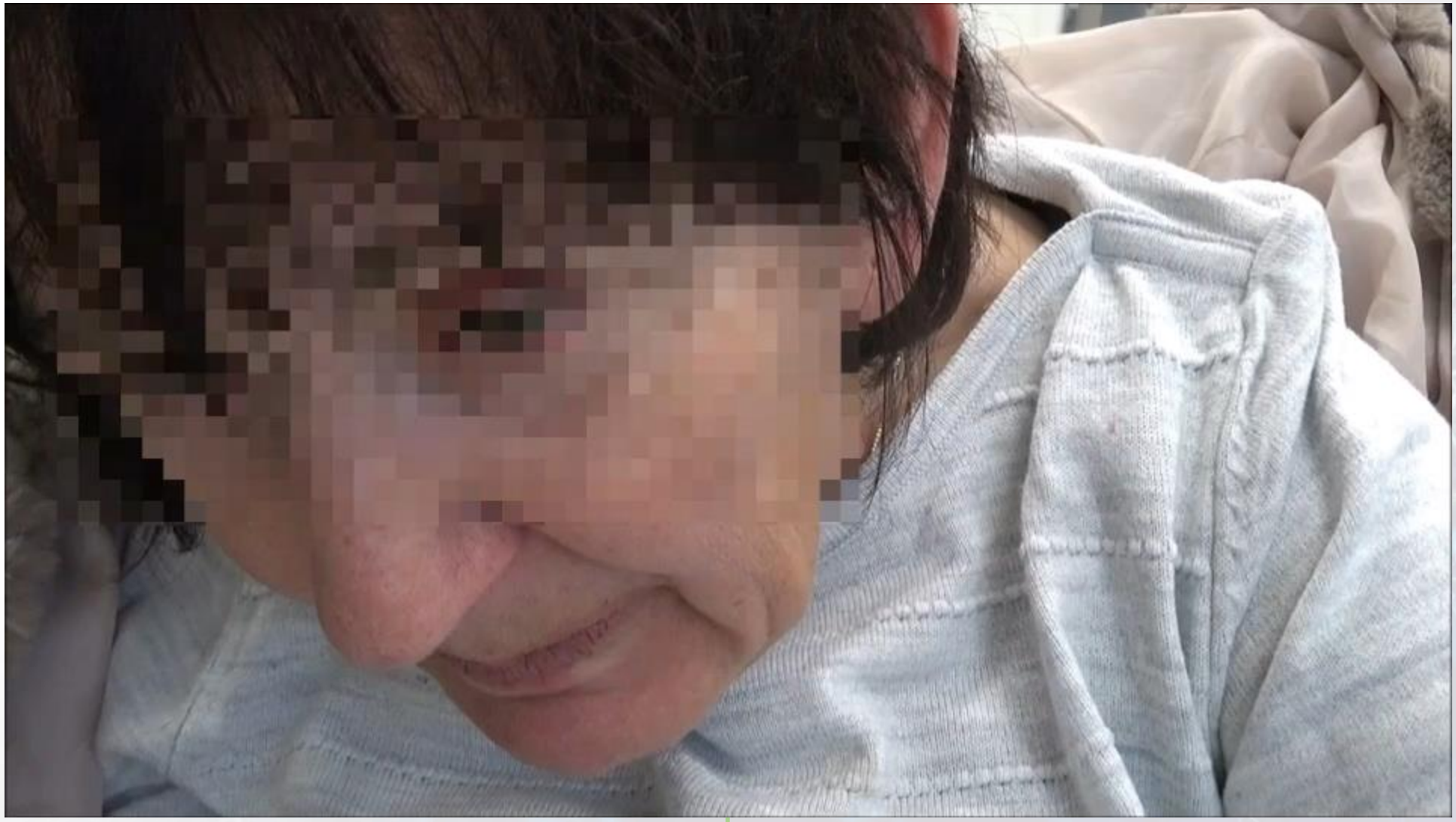
# Stridor



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# Inspiratory sighs

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# Supportive clinical features

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- Moderate to severe postural instability within 3 years of motor onset
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- Postural deformities
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- Inspiratory sighs
- Cold discolored hands and feet
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- Pathological laugher or crying

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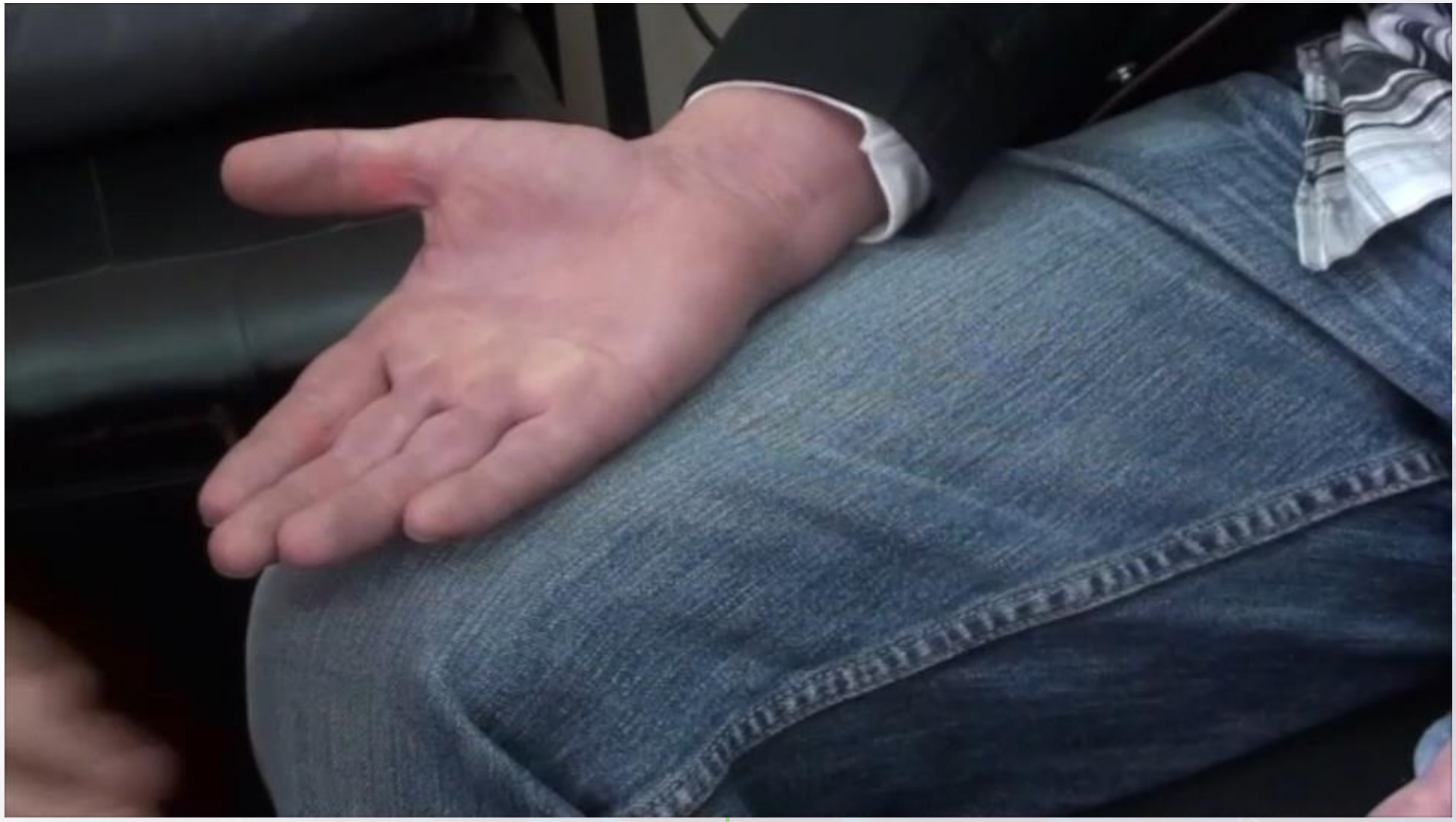
# Purple glove sign



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# Clinically established MSA

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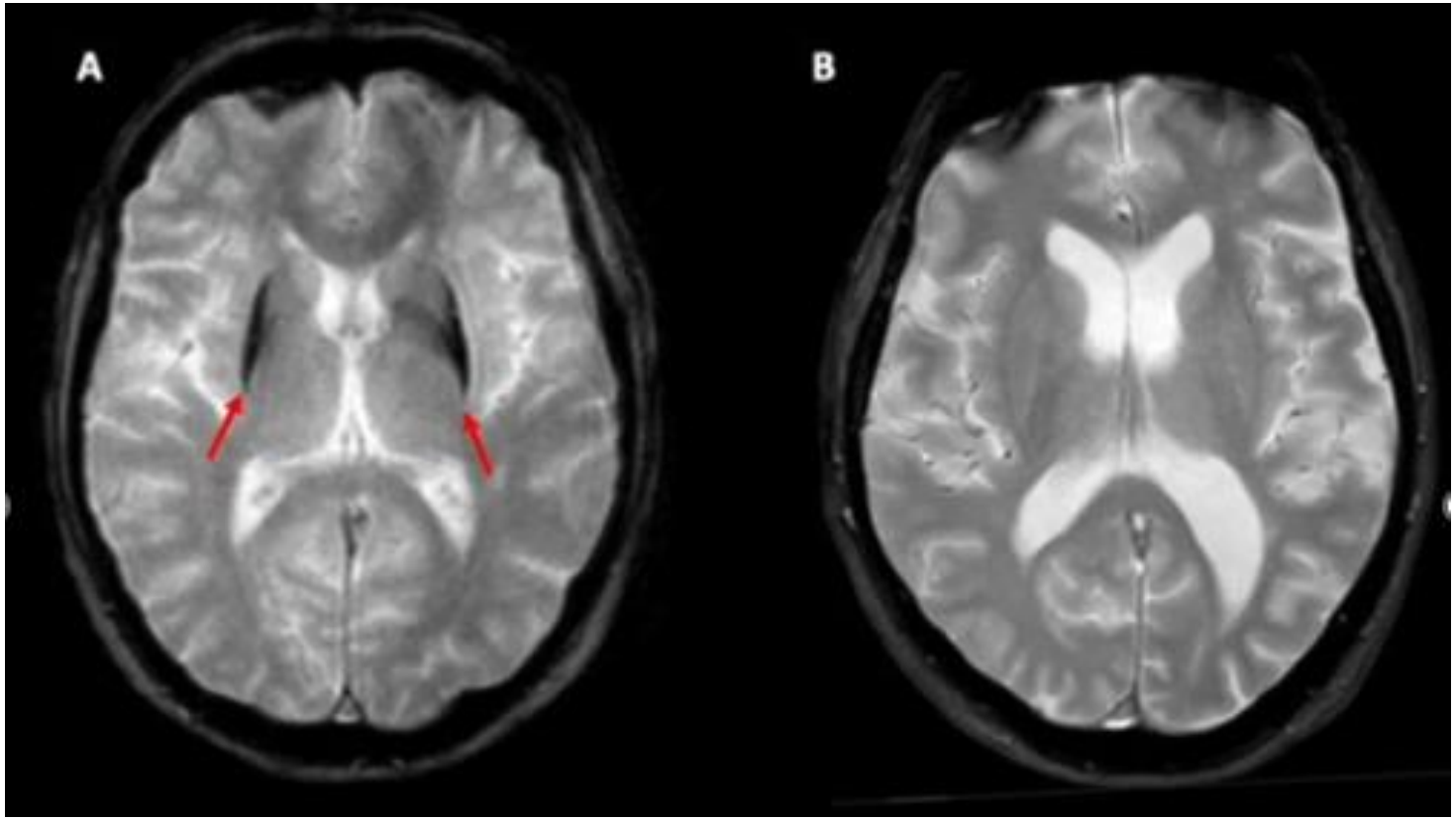
# MRI Marker




Hypointensities on susceptibility-weighted imaging T2 and putaminal atrophy in patient with MSA (A) compared to healthy control (B)

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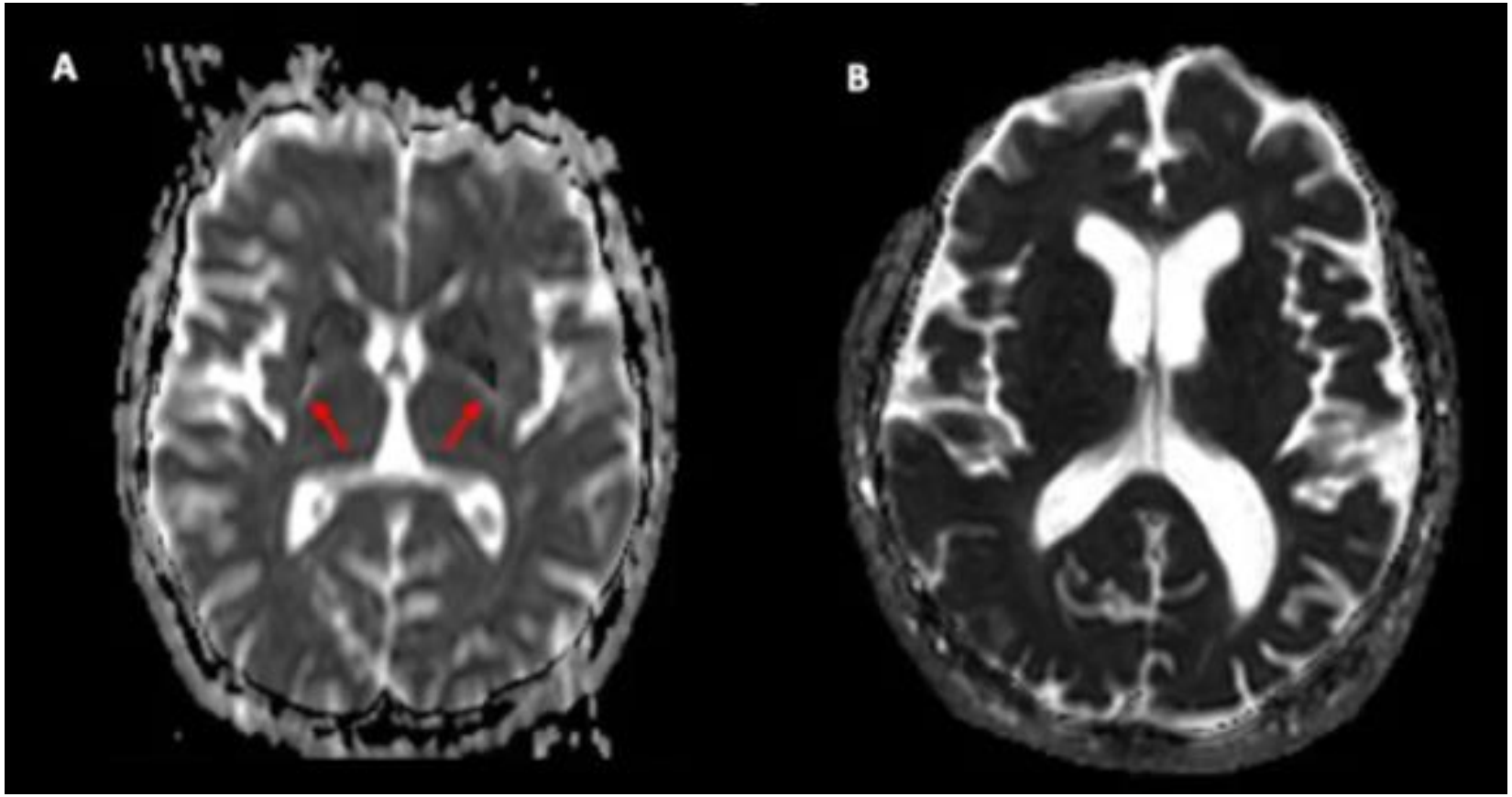
# MRI Marker




Diffuse hyperintensities (ADC map) in both posterior putamina in a patient with MSA-P (A) compared to health control (B)

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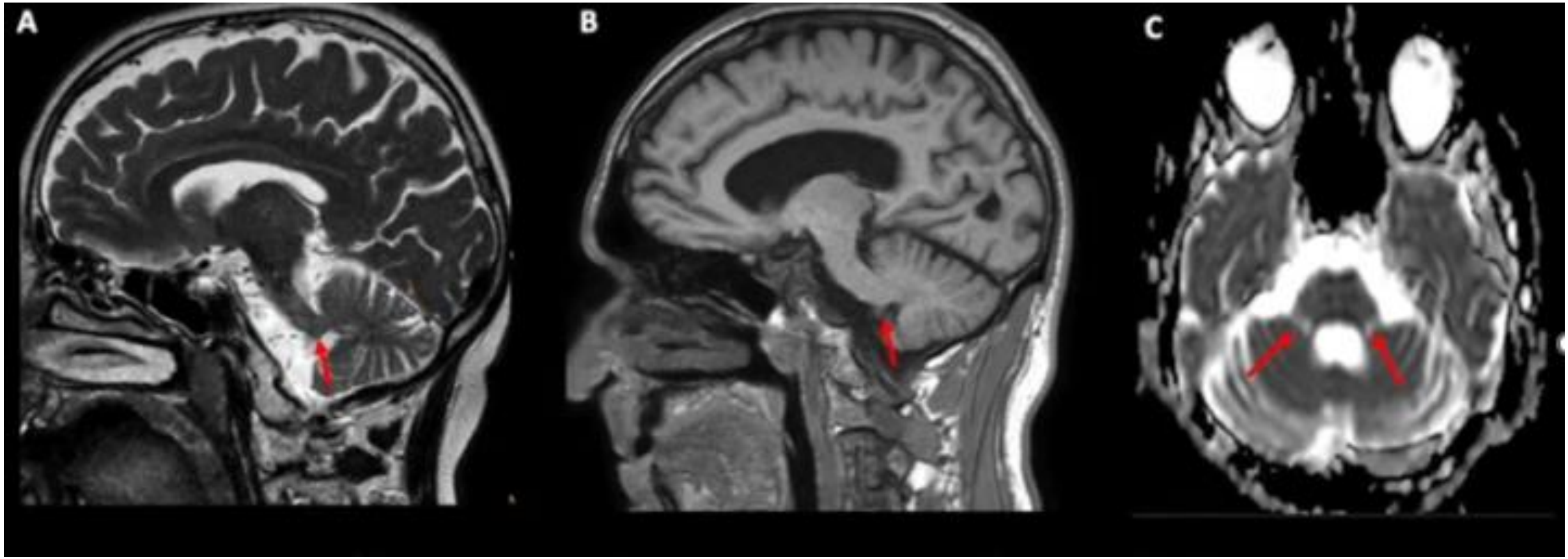
# MRI Findings




Atrophy in the middle cerebral peduncle in a patient with MSA-C (A) compared to health control (B).
C) Diffuse hyperintensities in the middle cerebral peduncle of this MSA patient indicating increased diffusivity

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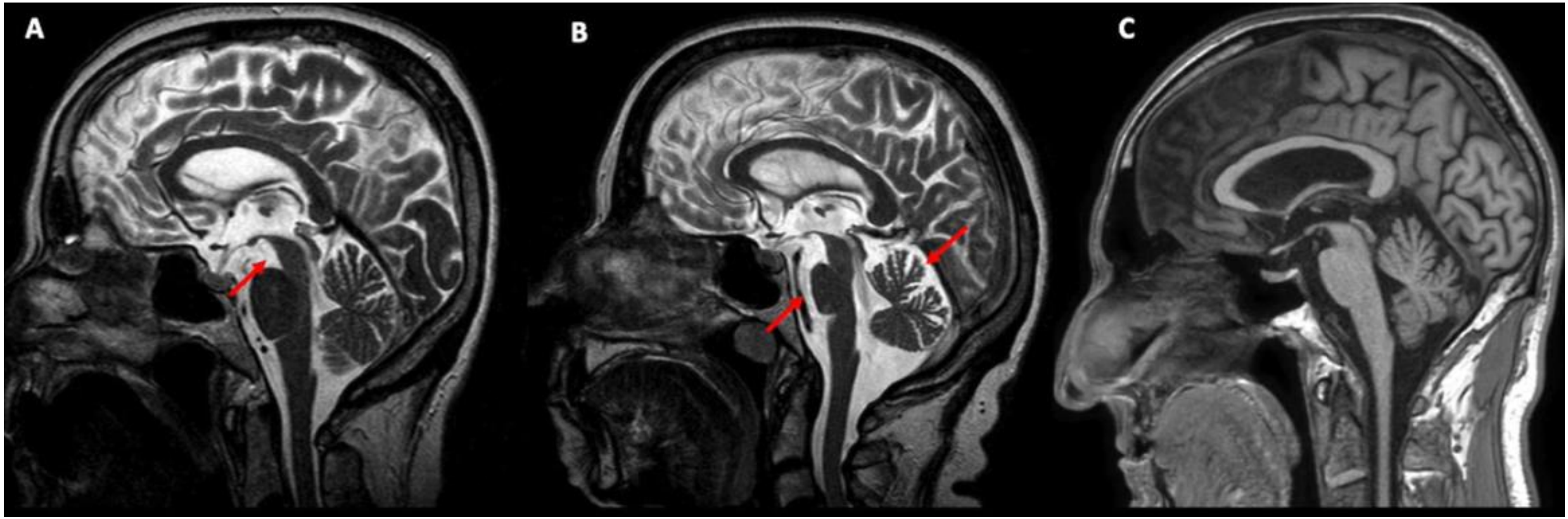
# MRI Findings




A) Atrophy of the midbrain in PSP (hummingbird sign)
B) Pontocerebellar atrophy in MSA-C
C) No atrophy in patient with PD

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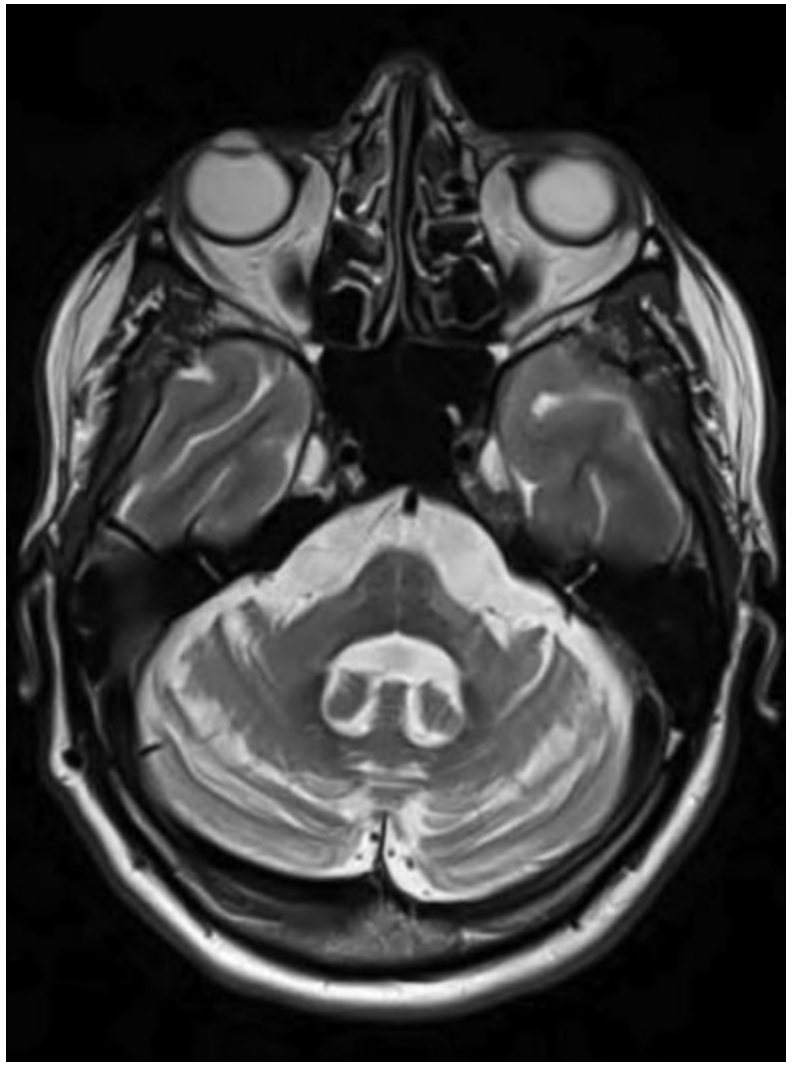
# MRI Findings



Hot cross bun sign (T2 weighted)

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# Clinically probable MSA

| | | | |
|---|---|---|---|
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| | OR | | |
| | **Cerebellar syndrome (at least 1 features)** | Gait ataxia | Cerebellar dysarthria |
| | | Limb ataxia | Oculomotor features |
| **Supportive clinical features** | **≥ 1 features** | | |
| **MRI marker** | **0 features** | | |

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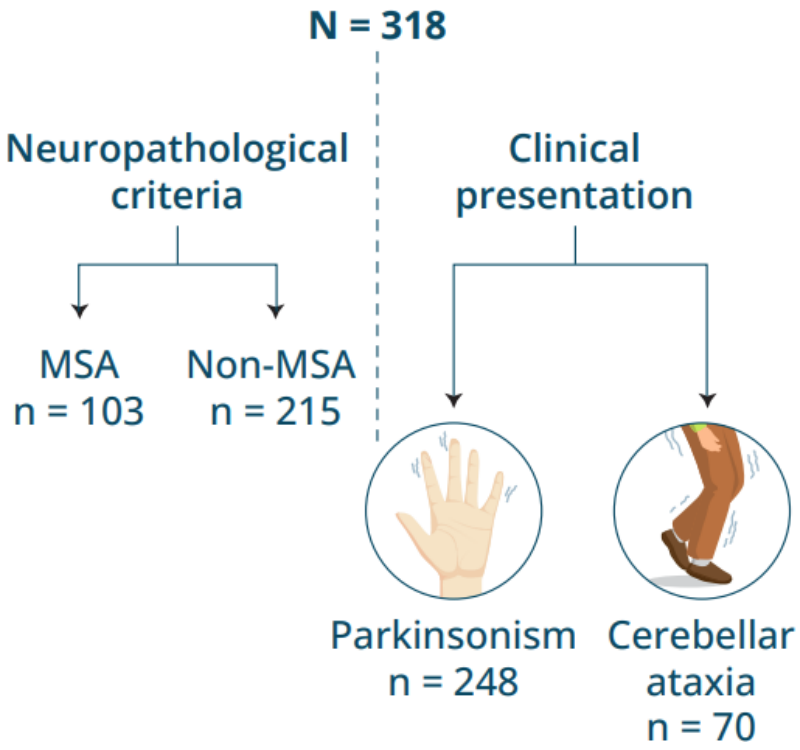
# Accuracy of the MDS-MSA criteria

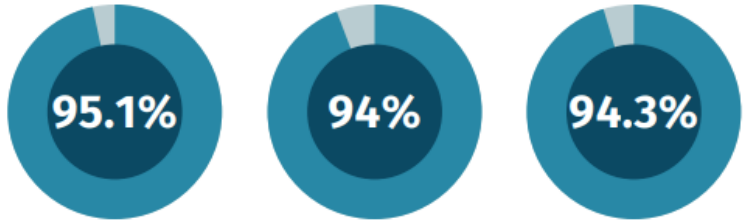
## MDS-MSA diagnostic criteria




## Clinically established MDS-MSA


Specificity

## Clinically probable MDS-MSA




Sensitivity | Specificity | Accuracy

## Advantages in clinical practice

MDS-MSA criteria outperformed the diagnosis by previous criteria and clinicians

MDS-MSA criteria diagnostic accuracy did not differ according to clinical presentation (parkinsonism and ataxia)

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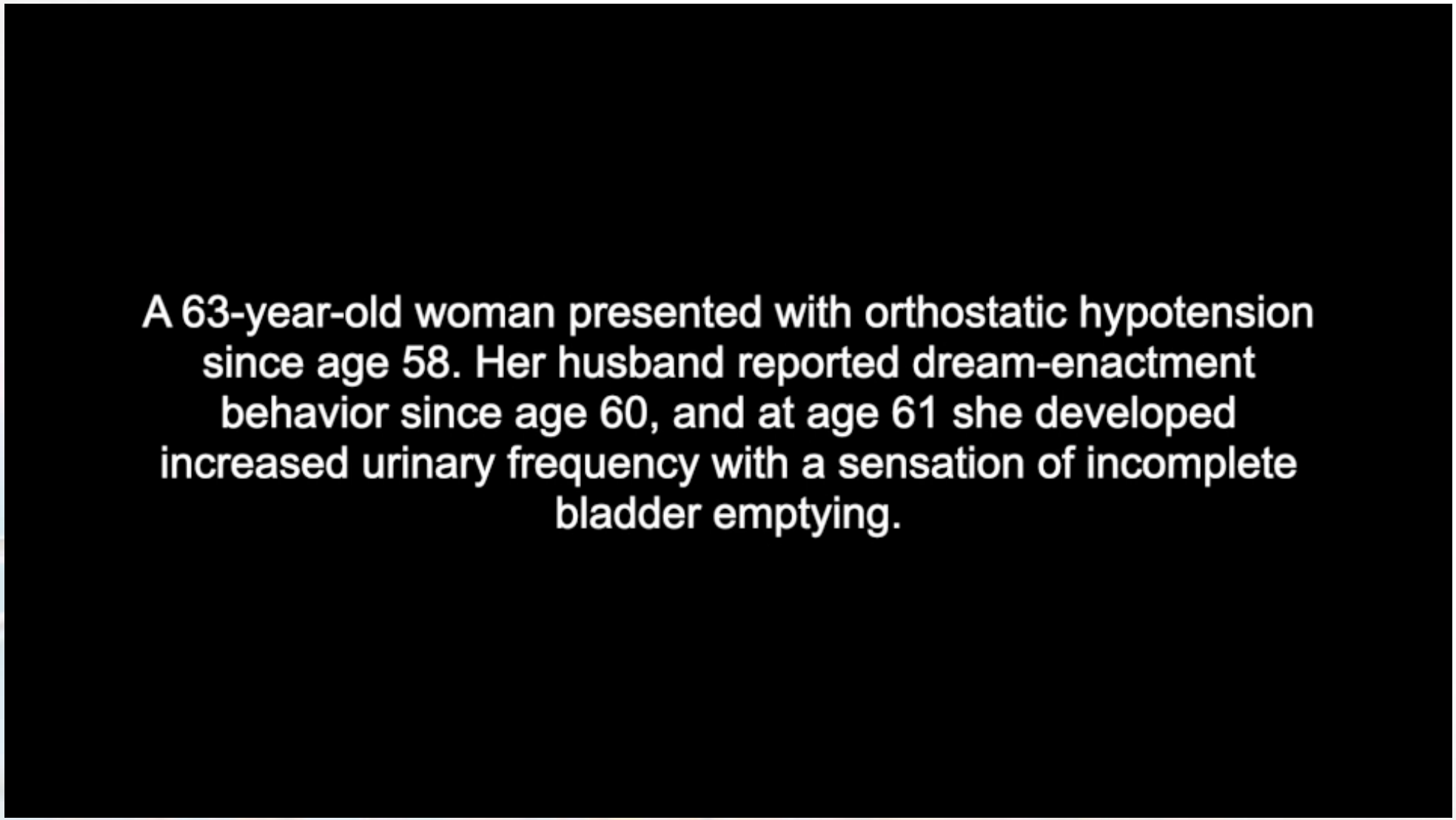
# Case Example #3

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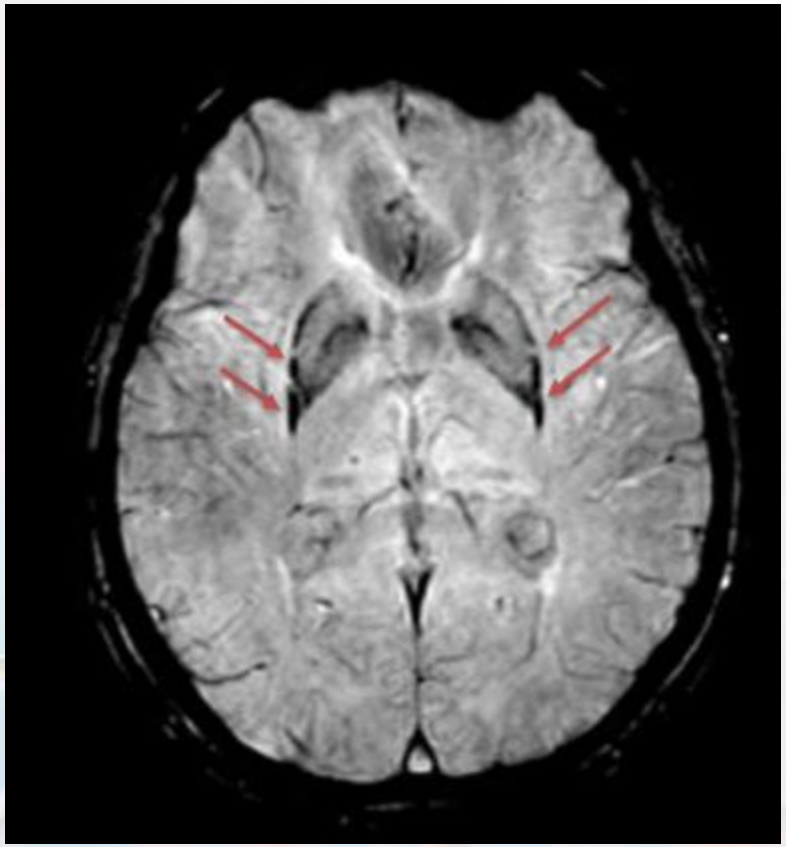
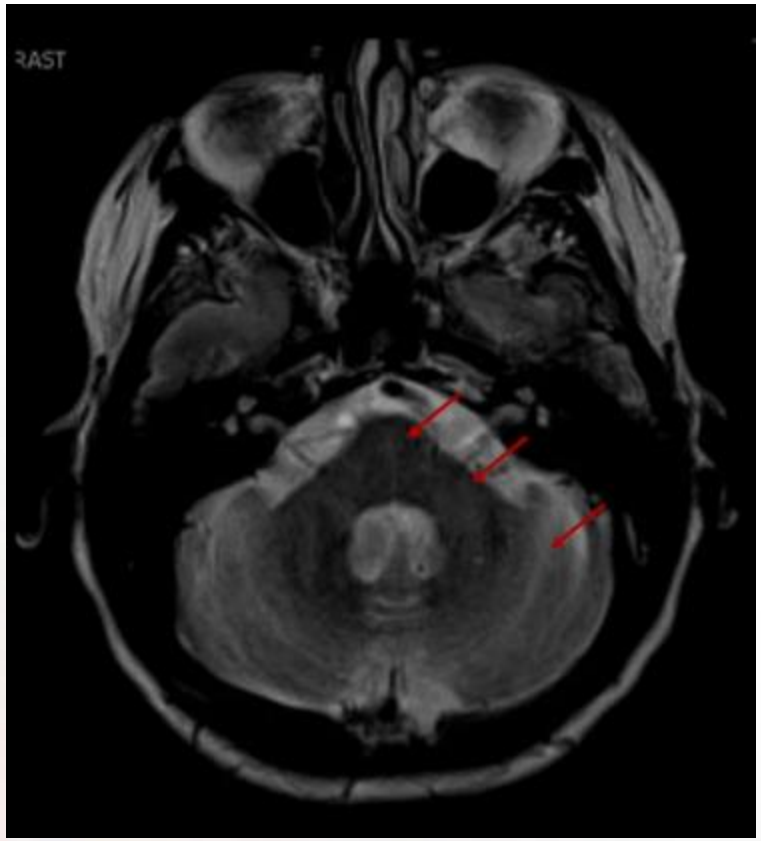
# Case Example



Decreased signal in the dorsolateral putamen on SWI



Atrophy of the pons with longitudinal hyperintensity
Atrophy of the Middle cerebellar peduncles with diffuse hyperintensity signal
Atrophy of the cerebellum

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# Case Example


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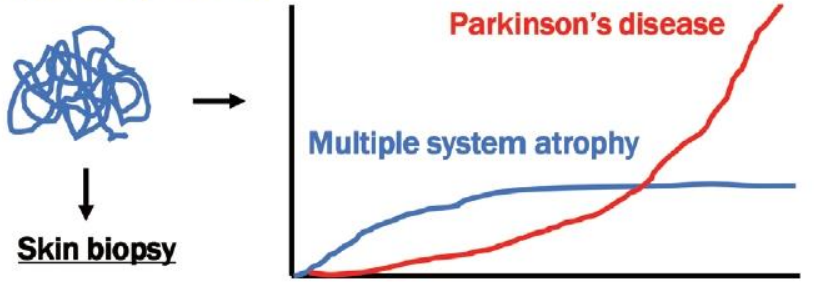
# Novel Markers

**A. Neuronal and oligodendroglial loss marker**

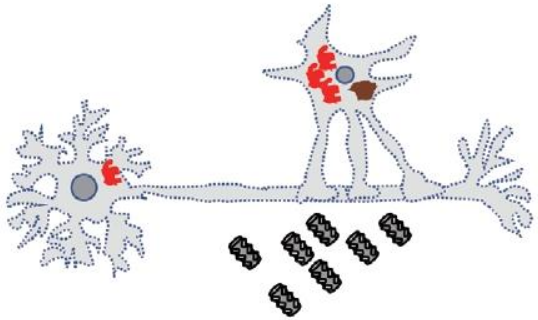
MSA-type α-synuclein

Protein misfolding cyclic amplification




Pathological α-synuclein detection

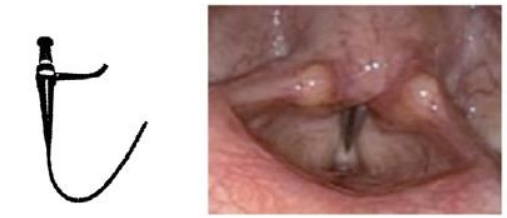
**B. Neuronal injury marker**



Plasma and CSF neurofilament light chain↑

**C. Abnormal laryngeal marker**

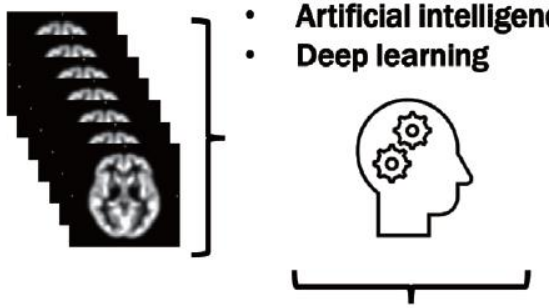
Flexible fiberoptic video rhinolaryngoscopy evaluation of a swallowing task



Laryngeal motion abnormalities in 93% of patients with MSA and 1.8% of patients with PD

**D. Novel imaging marker**

- Machine learning
- Artificial intelligence
- Deep learning



- Accuracy↑
- Individual analysis

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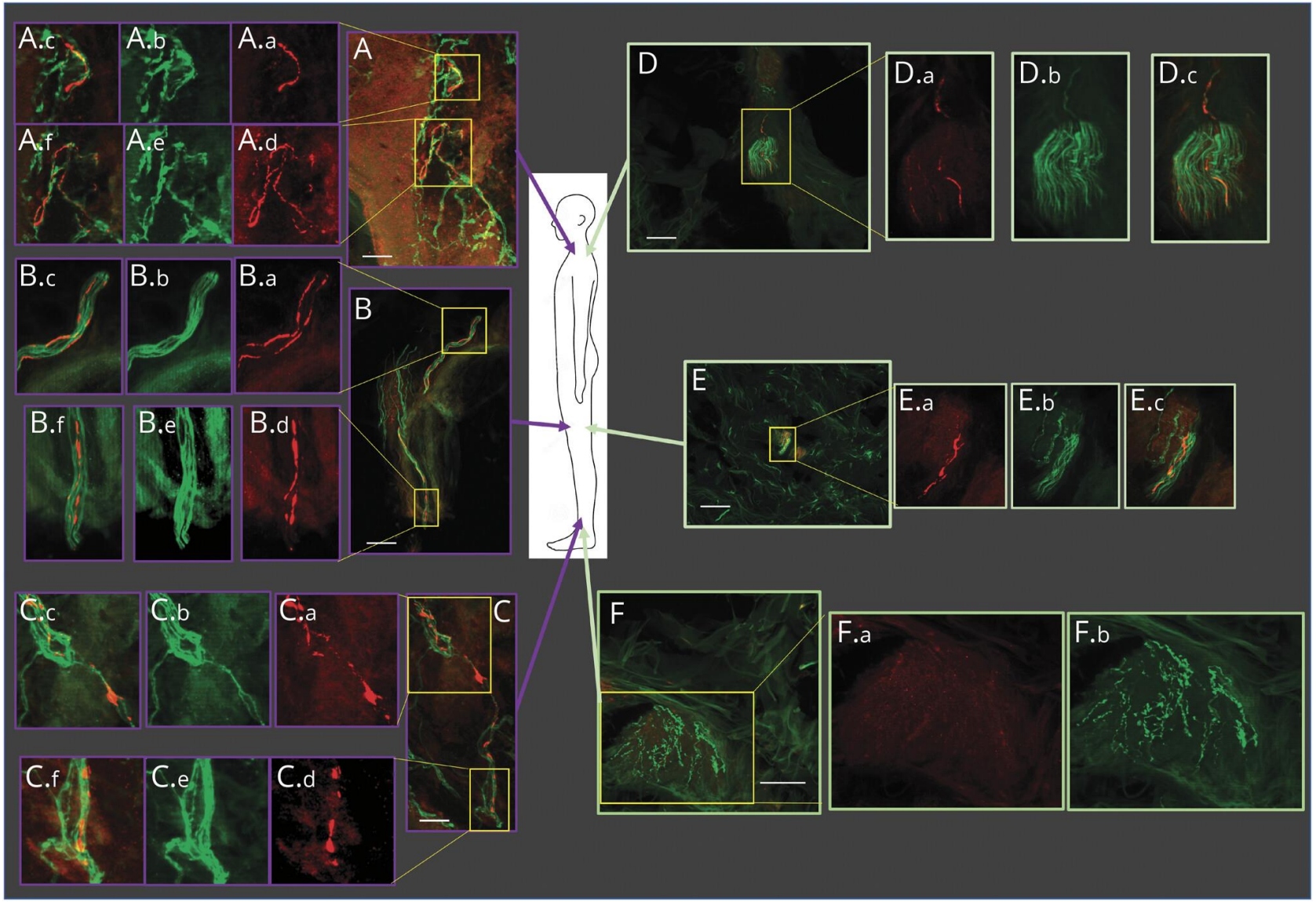
# Novel Markers: Skin Biopsy

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# Supportive Care

- Ideally establish patient with a multidisciplinary team
- Trial of levodopa (30-60% of patients have a response):
  - You need to balance between benefit of therapy and development of motor complications earlier in MSA, ex dyskinesias (involving jaw/face) and orthostatic hypotension
- Respond poorly to DBS
- Treating orthostatic hypotension:
  - Conservation methods: Oral hydration, Increased salt intake, Compression stockings, Abdominal binder.
  - Pharmacological therapy: Midodrine, Droxidopa, Fludrocortisone, pyridostigmine. (Can also try fluoxetine, atomoxetine, yohimbine) .
  - Treat supine hypertension also! Goal is less than 180mmHg when laying flat. May need low dose nifedipine or losartan.
- Neurogenic bladder: antispasmodics or botulinum toxin injections. May need to self catharize or suprapubic catheter.
- Bulbar Symptoms: Early referral to SLP and voice banking
- Sleep: RBD – Clonazepam, melatonin. Treat sleep apnea, hypoventilation

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# Questions