Atypical Parkinsonism

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Introduction

The diagnosis of Parkinson disease in the early stages can be challenging.

Symptoms overlap with other movement disorders such as essential tremor and atypical parkinsonian disorders.

Differentiating atypical parkinsonism from Parkinson disease is important.
Helps predict how well patients will respond to therapy.

How the disease will progress.

what the prognosis is compared to idiopathic Parkinson disease.
Parkinsonism Diagnostic Criteria

- Tremor at rest
- Bradykinesia
- Rigidity
- Loss of postural reflexes
- Flexed posture
- Freezing (motor blocks)
Definite: At least two of these features must be present, one of them being 1 or 2.

Probable: Feature 1 or 2 alone is present.

Possible: At least two of features 3 to 6 must be present.
Queen Square Brain Bank Criteria

- Presence of Bradykinesia and of either:
  - 1- Resting tremor 4-6Hz
  - 2- Extrapyramidal rigidity
  - 3- Postural instability not caused by visual, cerebellar, vestibular, or proprioceptive dysfunction.
Features of typical PD
At least 3

- Unilateral onset
- Excellent response to levodopa (70%-100%)
- Development of dyskinesia
- Levodopa response for 5 yrs or more
- Clinical course of 10 yrs or more
Progressive disorder

Rest tremor present

Persistent asymmetry affecting side of onset most
Exclusion

- Pyramidal signs
- Stepwise deterioration
- Repeated head injury
- History of encephalitis or oculogyric crisis
- Neuroleptic treatment at onset
- Strictly unilateral features after 3 yrs
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic dysfunction
- Early severe cognitive dysfunction
- Early freezing & postural falls
- Negative response to levodopa
- Imaging evidence of communicating hydrocephalus
# Parkinson’s Disease Diagnostic Criteria

<table>
<thead>
<tr>
<th>Required Criterion</th>
<th>Parkinsonism: Bradykinesia with at least 1 of rest tremor or rigidity</th>
</tr>
</thead>
</table>
| **Diagnostic Categories** | 1. Clinical Established PD: Parkinsonism + absence of absolute exclusion criteria + ≥2 supportive criteria + no red flags  
2. Clinically Probable PD: Parkinsonism + absence of absolute exclusion criteria + presence of red flags counterbalanced by supportive criteria |
| **Supportive Criteria** | 1. Clear and dramatic response to dopaminergic therapy  
2. Presence of levodopa-induced dyskinesias  
3. Rest tremor documented on examination  
4. Presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy |
| **Absolute Exclusion Criteria** | 1. Unequivocal cerebellar abnormalities,  
2. Downward supranuclear gaze palsy or selective slowing of downward vertical saccades,  
3. Diagnosis of probable bvFTD or PPA,  
4. Parkinsonian features restricted to LEs for >3 years,  
5. Drug-induced parkinsonism,  
6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease,  
7. Unequivocal cortical sensory loss |
| **Red Flags** | 1. Rapid progression,  
2. No progression,  
3. Early bulbar dysfunction,  
4. Inspiratory respiratory dysfunction,  
5. Severe autonomic failure in first 5 years,  
6. Recurrent falls within 3 years of onset,  
7. Disproportionate anterocollis or contractures of hands/feet within first 10 years,  
8. Absence of common nonmotor features within 5 years,  
9. Otherwise unexplained pyramidal tract signs,  
10. Bilateral symmetric parkinsonism |

RED FLAGS

- Early autonomic dysregulation.
- Early postural instability.
- Symmetric onset.
- Brainstem symptoms & signs.
- Pyramidal signs.
- Early cognitive decline.
- Early visual hallucinations.
- Stimulus-sensitive myoclonus.
- Vertical gaze palsy.
- Ataxia.
- Inspiratory stridor
- Sleep apnea
- Cortical sensory deficit.
- Poor response to levodopa.
- Motor apraxia
- Early freezing of gait
- Blepharospasm
- Saccadic intrusions
- Apraxia of lid opening
- Alien limb phenomena
Pathological Classification

TDP-43 Proteinopathies

Taupathies
PSP/CBS-CBD

Synucleinopathies
MSA/DLB

Nerve cells in cerebral cortex
Cortical Lewy body (Hematoxylin and eosin stain)
Progressive Supranuclear Palsy

- Disorder of Tau protein aggregation.
- Sporadic; familial PSP reported.
- More often in men @ mean age of 63 yrs.
- Classic picture: early gait & balance impairment, early freezing, gaze palsy, parkinsonism (axial > appendicular), spastic dysarthria, dysphagia.
Average annual incidence rate has been estimated to be 5.3 new cases per 100 000 person-years (Bower et al., 1997).

The prevalence, after age adjustment to the US population, has been estimated to be 1.39 per 100 000 (Golbe et al., 1988).
Degeneration of multiple neurotransmitter systems.

Neuronal loss, gliosis and neurofibrillary tangles in the prefrontal area, substantia nigra, subthalamic nucleus, globus pallidus and superior colliculus.
Diagnosis of PSP should be considered in all patients presenting with:

1- Parkinsonism
2- NOT responding to levodopa
3- Early postural instability, falls & freezing
4- Slowing of vertical saccades (downward>upward)
5- Supranuclear vertical gaze palsy

6- Pronounced saccadic intrusions on primary gaze fixation

7- Rapid onset of dysarthria/dysphagia

8- Early executive dysfunction, apathy, & depression
Clinical signs:

- Procerus sign: Worried/astonished look
- Rocket sign (darting out of the wheel chair without regard for safety)
- Applause sign: (frontal disinhibition and perseverance)
- Asymmetric apraxia with arm levitation (overlap with CBS)
Tremor at rest may be present in 5-10% of patients.

Dystonic posturing

Retrocollis
Characteristic eye movement abnormalities:

- Slowing of vertical saccades (down>up), (OKN)
- Apraxia of gaze initiation,
- Saccadic pursuit, poor convergence and square wave jerks).
Blepharospasm

Apraxia of eyelid opening or closure (Levator inhibition)

Reduced blinking
Speech abnormalities are common with spastic dysarthria, hypophonia or ataxic speech.

Patients can be uninhibited in stuffing their mouth and are at a higher risk of dysphagia and aspiration pneumonia.

Pseudobulbar symptoms in PSP patients are characterized chiefly by dysarthria, dysphagia, and “emotional incontinence”
Sleep abnormalities such as:

- Primary and secondary insomnia
- Sleep problems were correlated with worsening dementia.
- Day time hypersomnia

Another study showed marked reduction in percentage of REM sleep ([Montplaisir et al., 1997](#)).
Involvement of substantia innominate and onuf’s nucleus results in:

- Urinary urgency and
- Urine incontinence.
Possible PSP:
- Gradually progressive disorder
- Onset at age 40 or later
- Either vertical (upward or downward gaze) supranuclear palsy or both, slowing of vertical saccades
prominent postural instability with falls in the first year of disease onset

No evidence of other diseases that could explain the foregoing features, as indicated by mandatory exclusion criteria
Probable PSP

- Gradually progressive disorder
- Onset at age 40 or later
- Vertical (upward or downward gaze) supranuclear palsy and prominent postural instability with falls in the first year of disease onset
- No evidence of other disease that could explain the foregoing features, as indicated by mandatory exclusion criteria
Definite PSP

- Clinically probable or possible PSP and histopathologic evidence of typical PSP

Mandatory exclusion criteria are the following:

- Recent history of encephalitis
- Alien limb syndrome, cortical sensory deficits, focal frontal or temporoparietal atrophy
- Hallucinations or delusions unrelated to dopaminergic therapy
- Cortical dementia of Alzheimer type
Prominent, early cerebellar symptoms or prominent, early unexplained dysautonomia (marked hypotension and urinary disturbances)

Severe asymmetric parkinsonian signs

Neuroradiologic evidence of relevant structural abnormality

Whipple disease, confirmed by polymerase chain reaction, if indicated
Supportive criteria for PSP are as follows:

- Symmetric akinesia or rigidity, proximal more than distal
- Abnormal neck posture, especially retrocollis
- Poor or absent response of parkinsonism to levodopa therapy
- Early dysphagia and dysarthria
- Early onset of cognitive impairment including at least two of the following:
- Apathy
- Impairment in abstract thought
- Decreased verbal fluency
- Utilization or imitation behavior
- Frontal release signs
Videos
Multiple Phenotypes: Subtypes

1- Classic phenotype: Richardson syndrome
2- Parkinson disease-like: PSP parkinsonism
3- Pure akinesia (no appendicular rigidity): PSP-pure akinesia with gait freezing
4- Asymmetric parkinsonism: PSP-corticobasal syndrome
5- Frontal-predominant dementia: PSP-frontotemporal dementia
6- PSP with speech/language dysfunction (PSP-PNFA)

7- PSP with cerebellar ataxia (PSP-C)

8- PSP with primary lateral sclerosis (PSP-PLS)
Richardson Syndrome

- Mean age of onset is around 65 years
- Early postural instability (backward falls)
- Early personality changes (apathy)
- Visual disturbances
- Generalized slowness
Characteristic eye movement abnormalities:

1. Saccadic intrusions on primary gaze fixation.
2. Early loss of downward optokinetic nystagmus.
3. Slowing of vertical saccades (downward > upward).
4. Eventually vertical and horizontal gaze palsy.
5- Involuntary persistence of ocular fixation
6- Difficulties in maintaining eye contact
7- Difficulties in reading
8- Diplopia & Blurred vision
9- Convergence insufficiency
10- Bilateral impairment of the antisaccade task
The ophthalmoparesis can be overcomed by the oculocephaletic maneuvre.

Later on, vestibular-ocular reflex will be lost, to the extent the paresis will shift to plegia.

This will not be overcomed by oculocephaletic maneuvre which indicates nuclear involvement.
Eyelid movements:
- Lid retraction,
- Blepharospasm,
- Apraxia of eyelid opening,
- Reduced blink rate, impaired blink reflexes.
Eye motility: decreased saccade velocity, abnormal vertical saccades more than horizontal, impaired antisaccades, vertical supranuclear gaze palsy, impaired smooth pursuit with catch-up saccades, square wave jerks, convergence insufficiency, persistent ocular fixation, difficulty suppressing vestibulo-ocular reflexes.

Other findings: constriction of pupils in the dark.
Differential: Vertical Ophthalmoparesis

- CBD
- DLB
- Wernike’s encephalopathy
- Dorsal midbrain syndrome
- Prion disease
- Post-encephalitic parkinsonism
- Whipples disease
- Niemann-Pick type C
- Progressive subcortical gliosis
- Gaucher disease
- Kufo-Rakeb syndrome (PARK9; secondary to mutation in ATP13A2 gene on chromosome 1p36)
- Stiff-person syndrome
- Primary pallidal degeneration
- Paraneoplastic syndrome
- Valproate toxicity
Panel: Potential causes of eye movement abnormalities, postural instability, and parkinsonism that are not due to progressive supranuclear palsy

- Dementia with Lewy bodies
- Multiple system atrophy
- Cerebrovascular disease
- Aortic surgery and hypoxic damage
- Frontotemporal dementia associated with chromosome 17
- Ubiquitin-positive frontotemporal lobar degeneration
- Neuropsyphilis
- Motor neuron disease with congophilic angiopathy
- Amyotrophic lateral sclerosis
- Antiphospholipid syndrome
- Prion disease
- Lytico–Bodig disease
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- Whipple’s disease
- Neimann–Pick disease type C
Development of these eye movement abnormalities is associated with midbrain atrophy ("Penguin/Hummingbird sign").

Cognitive deficits typically affects speed processing speed.

Memory impairment & severe visuospatial dysfunction are unusual.
Postural instability is usually abnormal in PSP-Richardson in relation to mild bradykinesia.

In contrast to PD, DLB, MSA, patients with PSP-Richardson only rarely develop severe autonomic dysfunction.

Cerebellar ataxia is unusual and more common in MSA.
Patients usually become dependent on others for care 3-4 yrs after disease onset.

Speech often becomes unintelligible.

Recurrent choking can lead to frequent aspiration pneumonia.

Mean disease duration is about 7 yrs.
PSP-Parkinsonism

- In contrast to PSP-Richardson, PSP-Parkinsonism patients develop bradykinesia & severe limb rigidity at disease onset.
- Asymmetric presentation.
- Associated with a jerky action or rest tremor.
- Axial rigidity is an early feature.
- More benign and less tau pathology.
Response to levodopa is a feature of early progressive PSP-P at a stage when postural instability, frontal cognitive impairment & vertical gaze palsy is uncommon.

Mentioned above are markers of disease severity which occur early in PSP-Richardson and later in PSP-P.

Disease duration to death is about 3 yrs.
Helpful pointers for PSP-P:

1- Rapid progression
2- Prominent axial symptoms
3- Suboptimal response to levodopa.
4- Drug-induced dyskinesias are unusual
PSP- Pure Akinesia with Gait Freezing

- Isolated bradykinesia, predominantly affecting gait leading to freezing of gait.
- Gait unsteadiness may develop up to 2 yrs after the freezing of gait & gait initiation failure develops.
- Early hypophonia, hypomimia, and micrographia
Axial rigidity with increasing neck stiffness in the absence of limb rigidity is a distinctive feature.

Supranuclear vertical gaze palsy and blepharospasm develop late.

In contrast to PSP-R, cognitive deficits & bradyphrenia are not prominent, but may occur late.

Mean disease duration is about 10 yrs.
PSP-Corticobasal Syndrome

- Unilateral ideomotor apraxia
- Non-levodopa responsive parkinsonism
- Myoclonus
- Dystonia
- Alien hand phenomenon
Non-motor features:

- Aphasia
- Cortical sensory deficit
- Visuospatial deficits
These patients develop the behavior variant FTD:

1. Progressive personality change
2. Disinhibition
3. Change in eating habit
4. Stereotypical behavior
5. Apathy
Others develop the progressive non-fluent aphasia (apraxia of speech) (PSP-PNFA).

These patients usually develop typical motor symptoms of PSP more than 5 yrs after presentation.
<table>
<thead>
<tr>
<th></th>
<th>Richardson's syndrome</th>
<th>PSP-P</th>
<th>PSP-PAGF</th>
<th>PSP-CBS</th>
<th>PSP-PNFA</th>
<th>Parkinson's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rigidity</strong></td>
<td>Axial much more than limb</td>
<td>Axial less than or the same as limb</td>
<td>Axial</td>
<td>Yes</td>
<td>Sometimes</td>
<td>Limb much more than axial</td>
</tr>
<tr>
<td><strong>Bradykinesia</strong></td>
<td>Mild</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Yes</td>
<td>Mild</td>
<td>Moderate</td>
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<tr>
<td><strong>Tremor</strong></td>
<td>No</td>
<td>Yes/no (rest or jerky postural)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (at rest)</td>
</tr>
<tr>
<td><strong>Early falls</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Early postural instability</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td><strong>Early cognitive decline</strong></td>
<td>Often</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Early abnormalities of eye movement</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Response to levodopa</strong></td>
<td>No</td>
<td>Often</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td><strong>Hyposmia</strong></td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Cardiac MIBG</strong></td>
<td>Normal</td>
<td>Normal*</td>
<td>Normal*</td>
<td></td>
<td></td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

PSP = progressive supranuclear palsy. CBS = corticobasal syndrome. PAGF = pure akinesia with gait freezing. PNFA = progressive non-fluent aphasia. MIBG = $^{111}$I-labelled meta-iobenzyl/guanidinium. --- = unknown. *Author’s unpublished data.

Table 1: Clinical features of Richardson’s syndrome, PSP-PAGF, PSP-CBS, PSP-PNFA, and Parkinson’s disease
<table>
<thead>
<tr>
<th>Structure</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex</td>
<td>Dysexecutive syndrome; progressive non-fluent aphasia; perseveration; impulsivity</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>Alien limb</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>Rigidity; bradykinesia; postural instability; dystonia</td>
</tr>
<tr>
<td>Extranigral midbrain dopamine neurons</td>
<td>No response to levodopa</td>
</tr>
<tr>
<td>Periaqueductal grey and raphe nucleus</td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>Dentate nucleus</td>
<td>Gaze fixation (excess of square wave jerks)</td>
</tr>
<tr>
<td>Pontine and medullary nuclei</td>
<td>Dysarthria; dysphagia</td>
</tr>
<tr>
<td>riMLF (premotor burst neurons)</td>
<td>Slow saccades</td>
</tr>
<tr>
<td>Cholinergic neurons of the lower pontine reticular formation</td>
<td>No startle response; oculomotor dysfunction</td>
</tr>
</tbody>
</table>

riMLF = rostral interstitial nuclei of the medial longitudinal fasciculus.

*Table 2: Clinical and anatomical correlations of progressive supranuclear palsy-tau pathology*
Differential Diagnosis

- CBS
- PD
- NPH
- Wilson disease
- Alzheimer’s disease
Whipple’s disease
multi-infarct dementia
midbrain tumors
prion disease and syringomyelia
Niemann-Pick type C
Video: midbrain tumor
MRI can help exclude some of the above disorders.

Midbrain (A-P) diameter less than 17 mm may be helpful with the right clinical picture.

Contrast to PD patients (mean 18.5 mm), PSP patients had a significantly lower diameter (13.4 mm) on axial T2-weighted MRI.
“Hummingbird sign”, “Penguin sign” and “Mickey mouse brain”, “Morning glory”

Midsagittal MRI, the average midbrain area of patients with PSP was 56 mm$^2$, which was significantly smaller than that of patients with PD (103 mm$^2$) or MSA-P (97.2 mm$^2$)
Using diffusion-weighted MRI (DWI-MRI)

Using voxel-based morphometry:

CBD patients had marked asymmetric (L > R) pattern of atrophy involving premotor cortex, superior parietal lobules, and striatum,

PSP was characterized by atrophy of the midbrain, pons, thalamus, and striatum.
Treatment Paradigm

- Supportive therapy:

- Pharmacologic

- Multidisciplinary team: PT, OT, Speech pathologist, social worker, etc.
The dopaminergic meds do not improve symptoms in PSP to the same extent as PD.

There is minimal benefit in PSP-P, which may diminish for months to years.

Levodopa responsiveness can be tested by administering escalating doses (with COMT) up to 1200 mg/d for at least 1 month.
Dopamine agonists are less effective, with high profile side-effects.

- Amantadine is occasionally helpful in improving motor symptoms including:
  1. Gait freezing
  2. Dysphagia
  3. Sialorrhea
Anticholinergics should be avoided as they may worsen cognition.

Antispasmodics for the treatment of overactive urinary bladder (solifenacin) M3 antagonist.

Botulinum toxin used for blepharospasm, limb dystonia, apraxia of eyelid opening, and neurogenic bladder.
Mood and cognitive issues should be addressed.

Donepezil performed poorly in a clinical trial with worsening of motor scores.

Rivastigamine trial could be attempted.
Evaluation for swallowing difficulties is recommended.

PEG tube placement not just for dysphagia but also for addressing nutritional needs.
Future Directions

- Drugs targeting dopaminergic, cholinergic (Physostigmine, Donepezil, Rivastigmine) or GABAergic (Zolpidem, Gabapentin) deficits are not clinically effective in PSP.
- Lithium (FAILED)
- Tideglusib (GSK-3b inhibitor) (FAILED)
- Davunetide (FAILED)
A phase III trial with CoQ10 (FAILED)
Rasagiline (FAILED)
Other inhibitors of Tau aggregation:
Methylene blue (under investigation)
Microtubule stabilizers (Taxol, Epothilone D and TPI-28) (under investigation)
Corticobasal Syndrome/Degeneration

- Rare, progressive neurodegenerative disorder
- Multiple phenotypes/overlap between PSP, FTD (Pick's), Alzheimer.
- Age of onset is in the 5th to 7th decade.
- Predominance in women?
Classic presentation:
- Asymmetric parkinsonism
- Myoclonus (stimulus-sensitive)
- Dystonia
- Ideomotor apraxia & cortical sensory loss
- Alien limb phenomena
Language disturbances:

- Mild impairment to severe progressive non-fluent aphasia or even complete mutism.
- Visual neglect with agnosia and or optic ataxia is seen at times.
- Apathy, irritability and depression are common.
Asymmetric onset of dystonia mostly in upper limbs or hemi-dystonia along with myoclonus involving upper limbs and face can be seen.

Myoclonus can be focal with action or can be stimulus-sensitive.

Upper motor neuron signs can be present.

Dysarthria and dysphagia.
Eye motility:

- Impaired convergence
- Increased horizontal saccade latency with preserved saccade velocity.
- Impairment of upward gaze or vertical saccades.
Video
Many Faces of CBD

- Typical corticobasal syndrome
- CBD-FTD
- CBD-Aphasia/Apraxia of speech
- CBD-PSP-like syndrome
- CBD-Posterior cortical atrophy
Diagnosis

- Definitive diagnosis is always histopathological.
- MRI Brain is obtained to rule out secondary etiologies.
- Cortical atrophy in frontal and parietal areas along with ballooned and achromatic neurons seen on microscopy.
Probable CBS: asymmetric presentation and at least two of:

a) limb rigidity or akinesia,
b) limb dystonia,
c) limb myoclonus, plus two of:
d) Orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Possible CBS  Symmetric and characterized by at least one of:

a) limb rigidity or akinesia,
b) limb dystonia,
c) limb myoclonus, plus one of:
d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome (FBS): characterized by two of:

a) Executive dysfunction,
b) Behavioral or personality changes,
c) Visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia (naPPA),

characterized by 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 (PSPS): characterized by 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
More specific clinical research criteria for probable sporadic CBD are:

- Presentation with insidious onset and gradual progression
- A one-year minimum duration of symptoms
- Age ≥50 years at onset
- Permitted phenotypes are probable CBS, or FBS or naPPA plus at least one CBS feature (a to f above)
Management

- Trial of levodopa at 1,000-1,200 mg but the response may be lacking or diminishes with time.

- Myoclonus: valproic acid, clonazepam or levatiracetam.

- Dystonia can respond to botulinum toxin injection.

- Speech therapy (dysphagia management), physical and occupational therapy.
Future Directions

- Disease-modifying treatment is not yet available for CBD.

- Ongoing placebo controlled Phase I trial, testing the efficacy of TPI 287 (a microtubule inhibitor) in patients with 4 R tauopathies.
Multiple System Atrophy

- Rare adult onset neurodegenerative disorder.
- Age at onset: 53 – 65 yrs.
- More common in males than females.
- Sporadic disease; nevertheless genetic factors play an etiologic role in some families.
Pathogenic mechanisms underlying MSA remain partially unclear.

Evidence suggests that it is an oligodendroglialopathy.

Possible genetic factors: COQ2 mutation, SHC2 copy number loss, SNCA multiplications or SNP’s.
Possible genetic factors: COQ2 mutation, SHC2 copy number loss, SNCA multiplications or SNP’s.

Possible environmental factors: agricultural employment, organic solvents, plastic monomers, pesticides and metal dusts.
Subtypes:

- MSA-Parkinsonism (MSA-P)
- MSA-Cerebellar (MSA-C)
Early autonomic dysfunction preceding motor symptoms.

The diagnosis is considered when parkinsonism is associated with:

1- Early urinary urgency
2- Early postural hypotension
3- Constipation
4- Early REM sleep behavior disorder
5- Early erectile dysfunction
6- Sleep apnea
7- Early morning headaches
8- Nocturnal inspiratory stridor
9- Levodopa-induced facial/axial dyskinesias
Early postural dizziness
“Coat hanger pain”
Pyramidal signs
Cerebellar signs
Fasciculations (LMN)
Anterocollis
Nasal type dysarthria
Poor response to levodopa
Severe thermoregulatory disturbances
Cold hands & feet
Supine hypertension
poor lacrimation and salivation
Panel 1: Features predating the onset of classic motor signs in multiple system atrophy and their pathophysiological substrates

Erectile dysfunction
- Intermediolateral cell columns of the S2–S4 spinal cord
- Onuf’s nucleus
- Mesocortical and mesolimbic pathways with paraventricular nucleus of the hypothalamus

Urinary dysfunction
Main contributors
- Locus caeruleus
- Pontine micturition centre
- Putamen and substantia nigra
- Cerebellar Purkinje cells
- Dorsal motor nucleus of the vagus
- Intermediolateral cell columns of the S2–S4 spinal cord
- Onuf’s nucleus

Less contributory
- Frontal cortex
- Postganglionic cholinergic fibres

Orthostatic hypotension
- Medullary cardiovascular centre (solitary tract nucleus, area reticularis superficialis ventrolateralis, arcuate nucleus, dorsal nucleus of the vagus)
- Intermediolateral cell columns of the thoracic cord
- Sympathetic ganglia
- Postganglionic adrenergic fibres
Respiratory dysfunction
Nocturnal stridor and obstructive sleep apnoea
• Degeneration of the nucleus ambiguus, leading to vocal cord abductor muscle atrophy and paralysis
• Degeneration of serotonergic neurons in medullary raphe
• Dystonia in adductor vocal cord muscles during inspiration
• Degeneration of brainstem cholinergic neurons originating from the pedunculopontine nucleus and laterodorsal tegmental nuclei

Central hypoventilation
• Degeneration of the nucleus tractus solitarius, pre-Bötzinger complex, medullary raphe and arcuate nucleus

Rapid eye movement sleep behaviour disorder
• Pedunculopontine nucleus
• Locus caeruleus-subcaeruleus complex

Excessive daytime sleepiness
• Impairment of neuronal system involved in wakefulness regulation, such as the hypocretin and dopamine periaqueductal grey systems

Impairments in odour detection, identification, and discrimination
• Olfactory bulb and rhinencephalon
• Secondary effect of autonomic failure on the nasal mucosa
• Cerebellar degeneration disturbances in processing odour-related information
<table>
<thead>
<tr>
<th></th>
<th>RBD</th>
<th>ED</th>
<th>UD</th>
<th>OH</th>
<th>RD/stridor</th>
<th>Smell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premotor MSA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Premotor PD</td>
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<td>PAF</td>
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Non-motor symptoms that are present in each disorder and well documented in published work are represented by +; non-motor symptoms that occur rarely, are not prominent or that might be absent are represented by −. MSA = multiple system atrophy. PD = Parkinson’s disease. PAF = pure autonomic failure. RBD = rapid eye movement sleep behaviour disorder. ED = erectile dysfunction. UD = urinary disturbances. OH = orthostatic hypotension. RD/stridor = respiratory dysfunction/stridor.

Table: Symptoms in premotor multiple system atrophy, premotor Parkinson’s disease, and pure autonomic failure
Parkinsonism is seen in 90% of cases.

76% of patients with MSA-C have parkinsonism and 54% of MSA-P patients have cerebellar symptoms.

Tremor is seen in 80% of MSA patients and is more common in MSA-P.
The parkinsonism of MSA is usually symmetric.

Approx thirty percent responds to levodopa.

Bradykinesia & rigidity progress faster than PD.

Postural instability & falls emerge within the first 3 yrs of disease onset.
Cognitive dysfunction (prefrontal) more severe in MSA-P than MSA-C.

Pseudobulbar affect more in MSA-C.

Polyminimyoclonus is seen.

Jerky myoclonic action tremor, stimulus-sensitive distal myoclonus is more common in MSA-P.
Cerebellar dysfunction with:
- Intention tremor
- Gait and appendicular ataxia
- Dysarthria
- Sustained gaze-evoked nystagmus with hypometric saccades is present.
Dystonia can be seen in the form of:

- Laryngeal stridor and facial dystonia (levodopa-induced).
- Anterocollis, camptocormia and truncal dystonia (“Pisa syndrome”).
- Contractures of hands or feet.
Figure. Patient presenting tonic flexion of trunk and head toward the left along with a slight backward axial rotation.
REM sleep behavioral disorder can be seen in 70%.

Central and obstructive sleep apnea can increase risk of sudden death.
Eye motility:

- Spontaneous or gaze-evoke nystagmus
- Square-wave jerks
- Slow and hypometric saccades
- Reduced vestibulo-ocular reflex suppression, reduced vertical gaze, impaired smooth pursuit.
Diagnostic Criteria

- A definite diagnosis requires the neuropathologic findings of widespread and abundant CNS-synuclein–positive glial cytoplasmic inclusions (Papp–Lantos inclusions).

- Neurodegenerative changes in striatonigral or olivopontocerebellar structures.
Probable MSA:

- A sporadic, progressive, adult (>30 y)–onset disease characterized by:
  - Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males)
Or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic and

- Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)
Possible MSA:

A sporadic, progressive, adult (>30 y)–onset disease characterized by
- Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) and
• At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder)

• At least one of the additional features shown in table 3
Additional features of possible MSA

Possible MSA-P or MSA-C
- Babinski sign with hyperreflexia
- Stridor
Possible MSA-P

- Rapidly progressive parkinsonism
- Poor response to levodopa
- Postural instability within 3 y of motor onset
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
- Dysphagia within 5 y of motor onset
- Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
- Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-C

- Parkinsonism (bradykinesia and rigidity)
- Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
- Hypometabolism on FDG-PET in putamen
- Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET
Supporting features:

- Orofacial dystonia
- Disproportionate antecollis
- Camptocormia (severe anterior flexion of the spine) and/or Pisa syndrome (severe lateral flexion of the spine)
- Contractures of hands or feet
• Contractures of hands or feet • Inspiratory sighs
  • Severe dysphonia
  • Severe dysarthria sclerosis

• New or increased snoring
  • Cold hands and feet • Pathologic laughter or crying
Non-supporting features:

- Classic pill-rolling rest tremor
- Clinically significant neuropathy
- Hallucinations not induced by drugs
- Onset after age 75 y
- Family history of ataxia or parkinsonism
- Dementia (on DSM-IV)
- White matter lesions suggesting multiple
Neuroimaging

- MSA-P: T2 MRI: putaminal atrophy, lateral rim hyperintensity

MSA-C: atrophy of the medulla, MCP, pons, inferior olives, cerebellum, “hot cross buns” sign
Autonomic studies reveal early abnormalities compared to PD:

- Orthostatic hypotension
- Abnormal QSART testing
- Urinary residual volume more than 100 ml.
- Abnormal norepinephrine levels along and an abnormal composite autonomic score (CASS score).
MIBG scintigraphy reveals preserved uptake in MSA compared to PD.

EMG: External anal sphincter denervation.
The median survival of either phenotypes is about 8 yrs.

Factors predicting short disease survival:

1- Early autonomic failure.
2- Older age of onset. Usually age of onset: 50’s
3- Short interval from disease onset to frequent falling.
4- Cognitive disability.
5- Unintelligible speech.
6- Severe dysphagia.
7- Dependence on wheelchair for mobility.
8- Urinary catheter use.
9- Lack of admission to a nursing home facility.
Management

- Multidisciplinary team approach.

- **Dopaminergic meds:**
  - Only 30% of patients respond to levodopa with short-lived benefit.
  - Dosing is limited by nausea, hypotension and hallucinations.
Approx one-third of patients with MSA-P will benefit.

Levodopa/carbidopa (Sinemet 100/25 po tds) to start low by ½ tab and titrate slowly over a weekly period to the target dose.

Can reach upto 1200mg/d, according to the best response/ emerging side effects.
There is no specific therapy for cerebellar symptoms.

Dystonia can be treated with botulinum toxin injections.
Autonomic Dysfunction:

Management of orthostatic hypotension is critical.

Non-pharmacologic approach:
1- increasing dietary salt intake.
2- Avoid caffeinated drinks.
3- D/c or reduce the dose of any antihypertensive meds.

4- Getting up slowly from a seated/lying position.

5- Wearing thigh-high compression stockings.

6- Leg elevation while lying.

7- Monitoring for supine hypertension.
Pharmacologic:

- Fludrocortisone: (Florinef): Increases blood volume.
- Midodrine: Increases peripheral vascular resistance.
- If both are ineffective, indomethacin/pyridostigmine can be used.
Droxdopa: alpha/beta adrenergic agonist

Converts to norepinephrine by dopa decarboxylase.

Dose: 100 mg po tds.

Last dose to be given 3 hrs prior to sleep to avoid supine hypertension.
Urologic Symptoms:

- Urinary retention or incontinence are usually present early in MSA.
- Urodynamic studies determines the type of neurogenic urinary bladder.
- Bladder spasticity responds to peripherally acting anticholinergic agents or botulinum toxin.
- Occasionally, intermittent or suprapubic catheterization maybe required.
REM-BD can respond to clonazepam or melatonin.

Sleep study with management of obstructive sleep apnea.
Supportive therapy including allied health care team:

- Tracheostomy/gastrostomy maybe considered in selected patients with:
  - Cervical, laryngeal, & pharyngeal dystonia causing upper airway obstruction.

- These procedure will improve the quality of life.
Tracheostomy:

- May effectively relieve airway obstruction at the laryngeal level
- Does not eliminate the risk of sudden death due to fatal sleep apnea.
Referral should be sent to Urology for management of sexual dysfunction and urinary abnormalities.

Physical, speech and occupational therapies are part of rehabilitation with this progressive disorder.
Future Directions

- No clinical trials have proven efficacy for MSA progression.
- MSA specific biomarkers are essential to facilitate the early identification of patients in disease-modifying clinical trials.
- Enrollment of patients in disease-modifying clinical trials.
- Blood and CSF alpha-synuclein levels (not sensitive and specific)
Riluzole, Minocycline, Rifampicin or Rasagiline have not shown any benefit.

A global MSA registry (GLOMSAR) has been established to facilitate accelerated interventional target delivery, biomarker development and early patient recruitment.
Atypical parkinsonism can present initially as idiopathic PD (PSP & MSA).

Close follow up is crucial.

Don’t rush into conclusions and send patients for DBS in the very early stages.

Currently, no effective Rx that alter the natural history of disease or alter survival.
Current therapies only focus on symptomatic management.

Clinical trials have been limited by poor funding, small size, & lack of biomarkers.

Recent breakthrough in genetics, molecular biology, & neuroimaging will help in developing targeted therapies with disease-modifying properties.
Thank You

References:

- Principles and practice of Movement Disorders; Fahn, Jankovic & Hallett

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