Atypical Parkinsonism: "When is it NOT Parkinson's Disease

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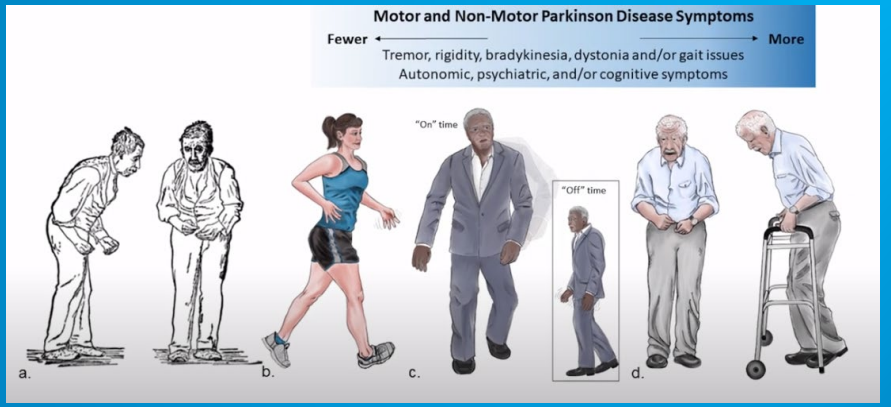
Disclosures

- No pertinent financial disclosures

Objectives

- Review the presentation and pathophysiology of various atypical parkinsonian disorders
- Determine the best workup necessary to differentiate conditions
- Guide management of treatable symptoms

What IS Parkinson's disease?



Motor features

Tremor = 3 – 6 hz, rest more than action
Bradykinesia = slowed, stuttering, smaller
Rigidity = cogwheeling across joints
Postural Instability = retropulsion, inability to stop

Stooped posture
Soft, hoarse voice
Masked face (hypomimia)
Gait festination
Diminished arm swing
Micrographia
Asymmetrical onset

Expected Idopa response

Table 1 *UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria*

STEP 1. Diagnosis of PARKINSONIAN SYNDROME.

BRADYKINESIA (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions).

And at least one of the following:

a. muscular rigidity
b. 4–6 Hz rest tremor
c. postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

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What *else* is Parkinson's disease?

Non-motor features

"the sleep becomes much disturbed…"

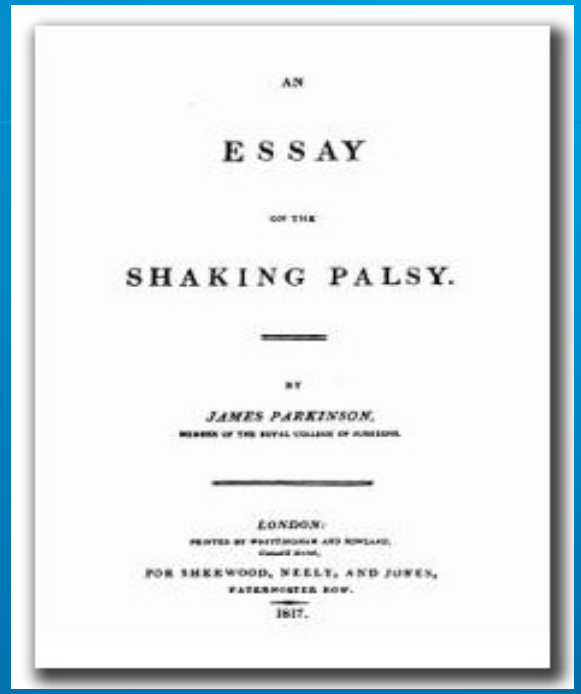
"…constant sleepiness…and other marks of extreme exhaustion…"

"…the power of articulation is lost…"

"…saliva…trickling from the mouth…"

"…the food is with difficulty retained in the mouth…

"…the bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power: the expulsion of the feces from the rectum sometimes requiring mechanical aid…"


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

LONDON:

FOR SHERWOOD, NEELY, AND JONES,

1817.

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What *else* is Parkinson's disease?

Non-motor features

- Disorders of smell
- Sleep disorders
- Mood changes
- Autonomic disorders
- Memory changes
- Speech disorders
- Weight loss/gain
- Sensory changes

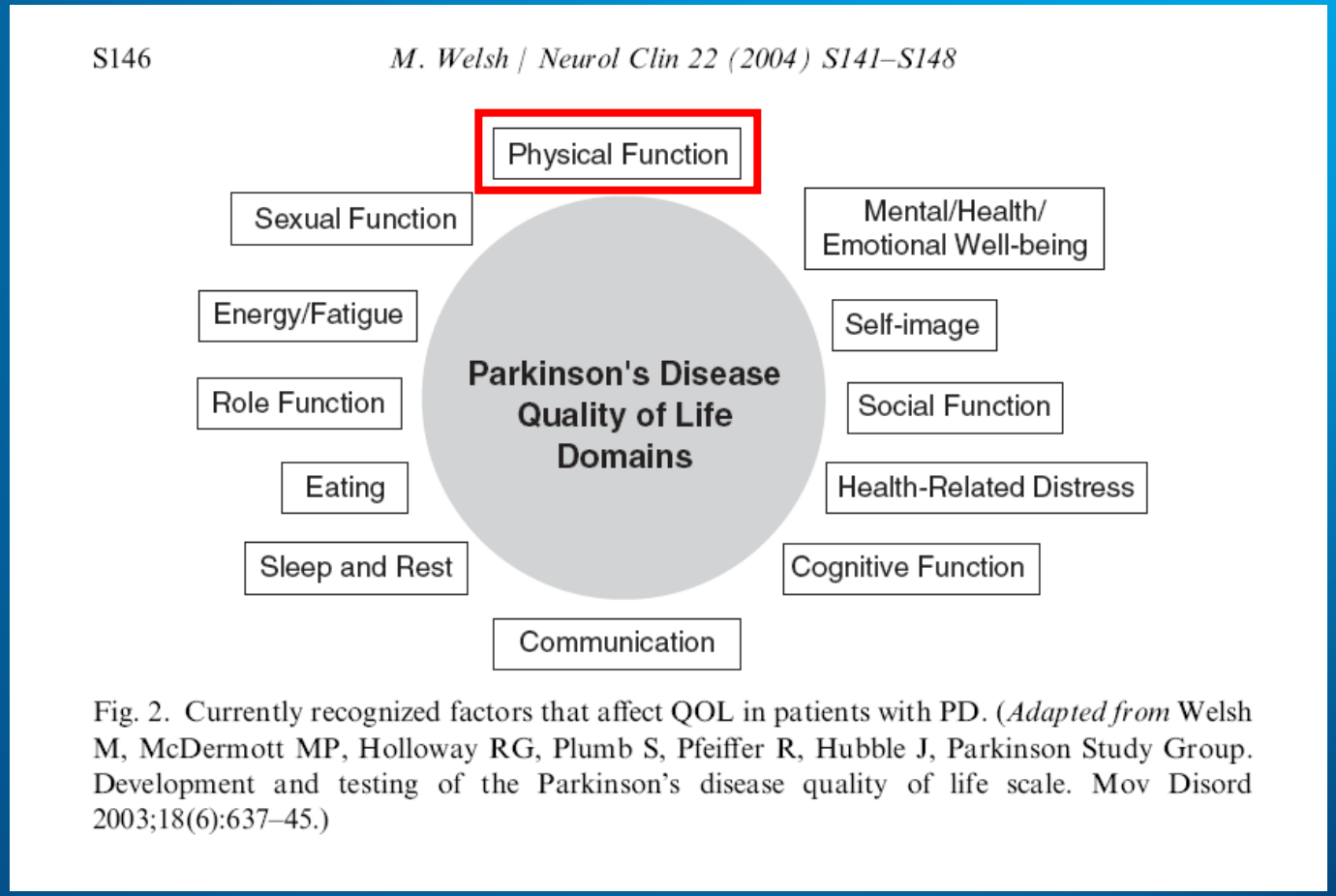

Fig. 2. Currently recognized factors that affect QOL in patients with PD. (*Adapted from* Welsh M, McDermott MP, Holloway RG, Plumb S, Pfeiffer R, Hubble J, Parkinson Study Group. Development and testing of the Parkinson's disease quality of life scale. Mov Disord 2003;18(6):637–45.)

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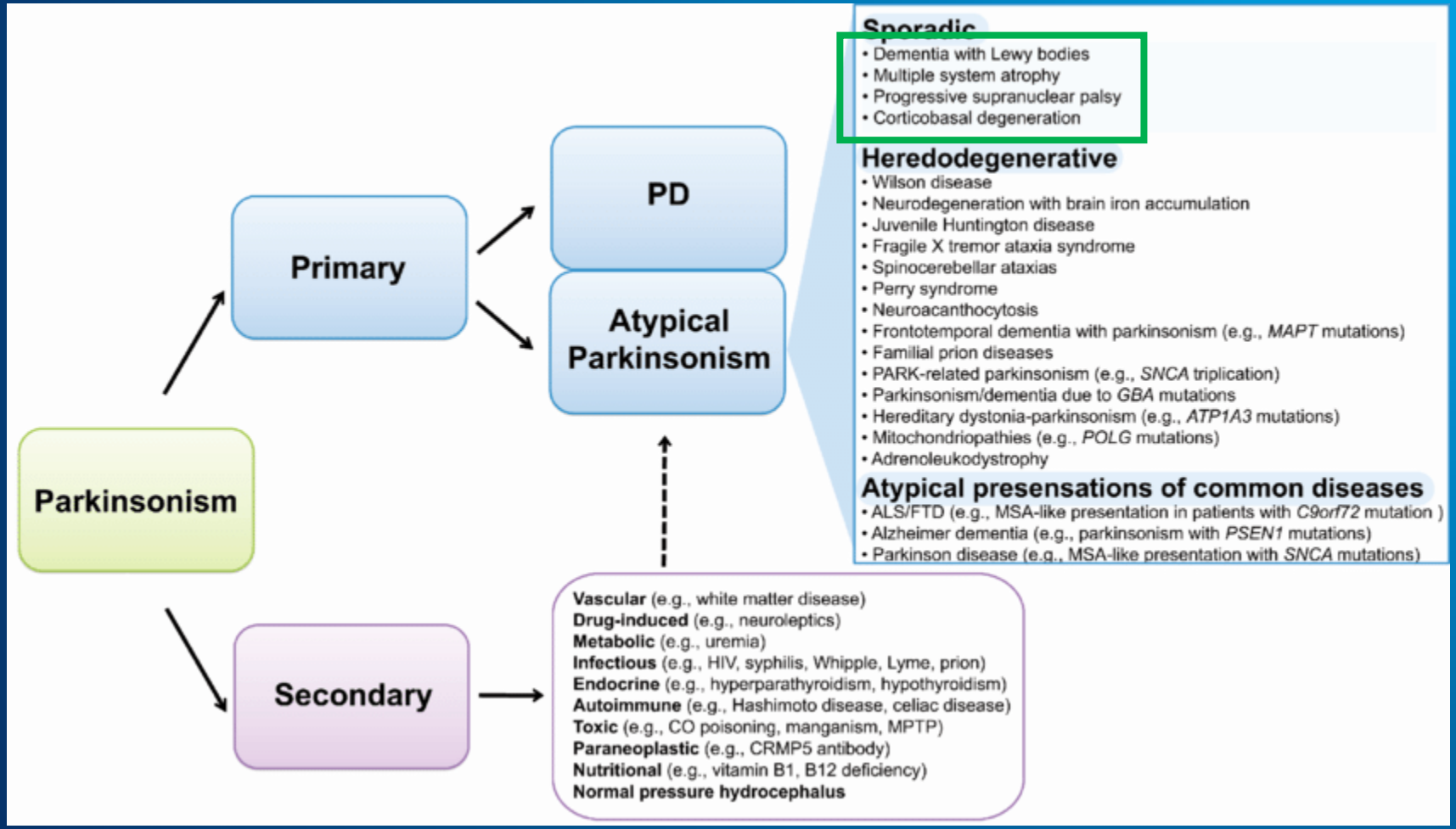
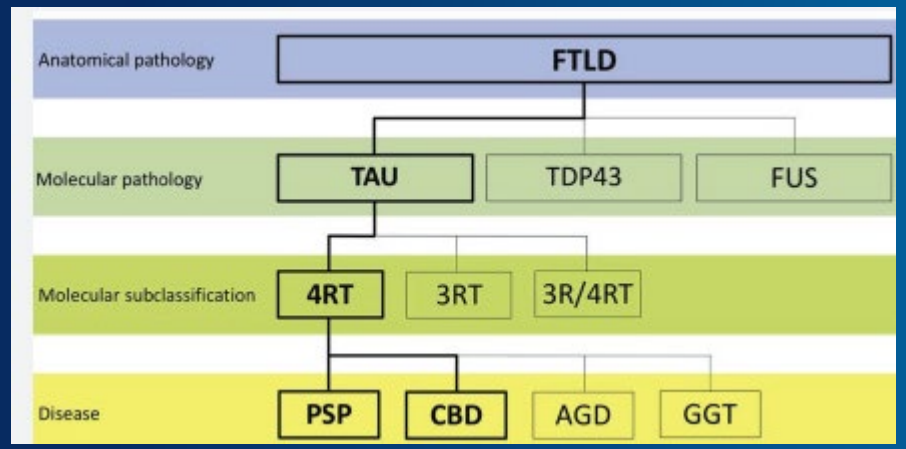
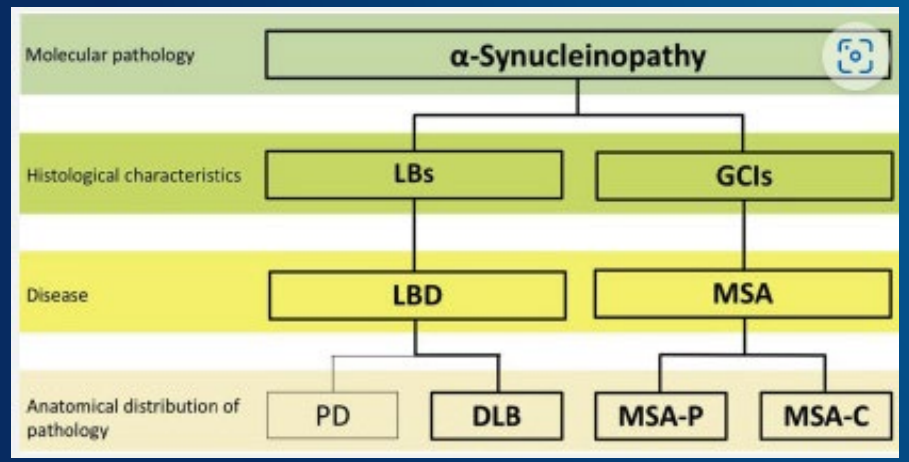
Parkinsonism: the differential diagnosis

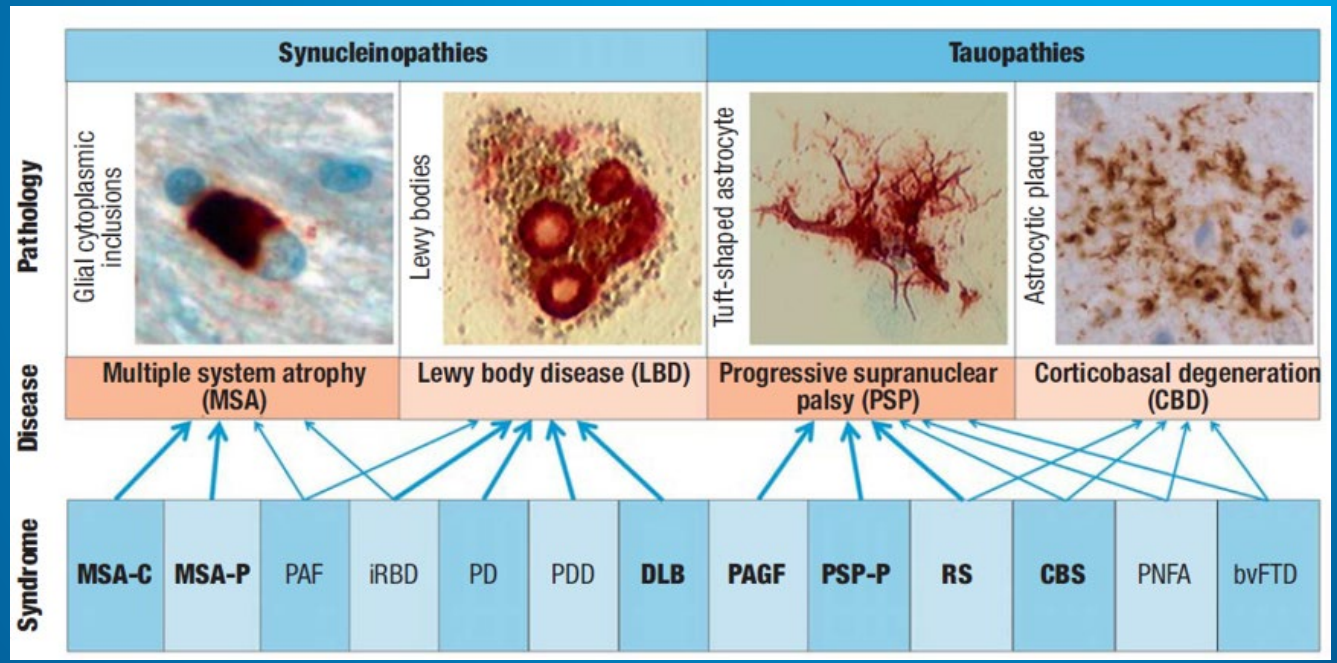


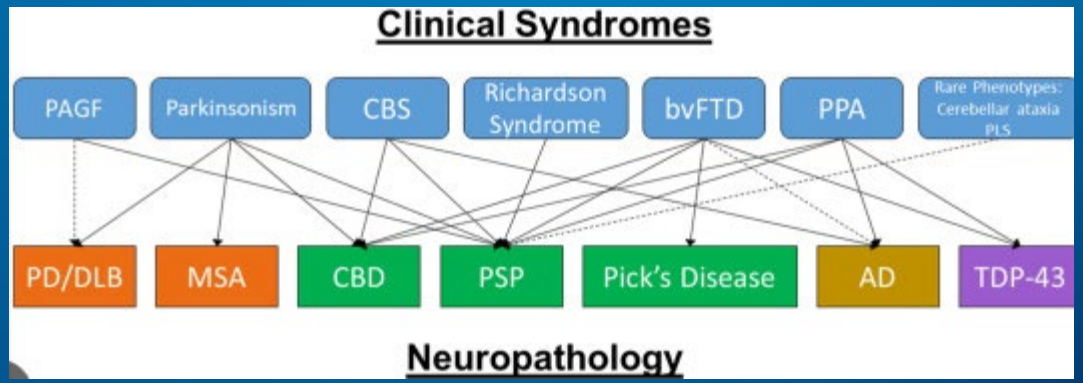
Scholz, Sonja & Bras, Jose. (2015). Genetics Underlying Atypical Parkinsonism and Related Neurodegenerative Disorders. International journal of molecular sciences. 16. 24629-24655. 10.3390/ijms161024629.

Neuropathology and pathophysiology









Respondek G, Stamelou M, Höglinger GU. Classification of atypical parkinsonism per pathology versus phenotype. Int Rev Neurobiol. 2019;149:37-47.

Parkinsonism and Related Disorders, 2020-04-01, Volume 73, Pages 105-116

Dtsch Arztebl Int 2016; 113: 61-9. DOI: 10.3238/arztebl.2016.0061

MSA: the basics

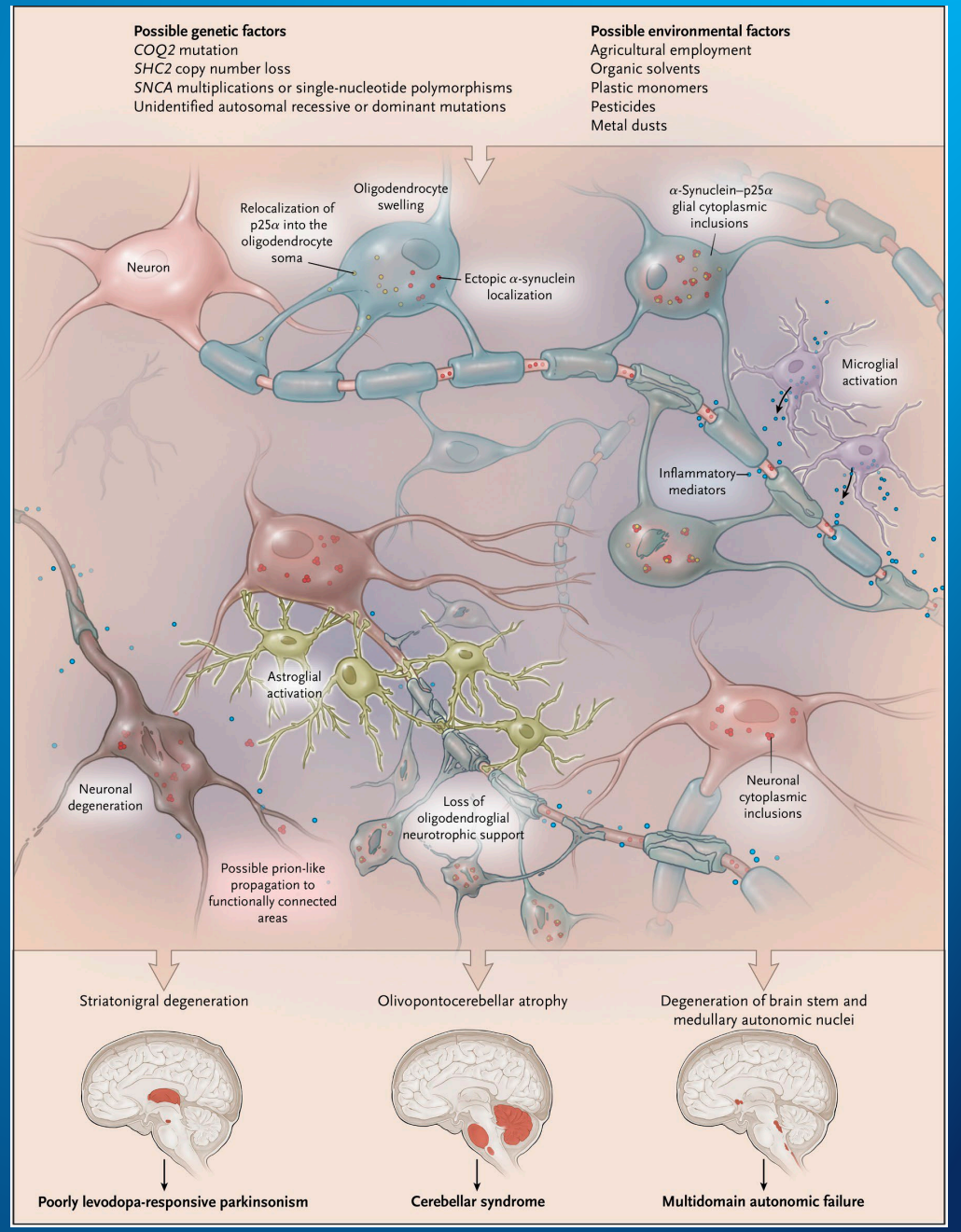
Prevalence: 5/100 000.

Mean age at disease onset: 50s

Disease course: 6 to 10 years, patients die mostly from aspiration or cardiac arrest

Clinical symptoms:
= dysautonomic symptoms are an obligatory component of MSA—especially urinary incontinence, erectile dysfunction, or orthostatic hypotension. Isolated pure autonomic failure (PAF) may precede the motor impairments in MSA.

= MSA-P with predominant parkinsonism
= MSA-C with predominant cerebellar sxs



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N Engl J Med 2015; 372:249-263

MSA: “red flags” and presentation

Rapid clinical deterioration
- Wheelchair within 5 yrs, dependent 10 yrs
- Early postural instability and recurrent falls within 3 years

Eye movement abnormalities
- Gaze-evoked, downbeat and rebound nystagmus

Abnormal facial appearances
- Orofacial dystonia

Limb abnormalities
- Tremulous movements during ballistic aiming movements
- Jerky postural tremor
- Striatal hands
- Contracture of hands and feet

Axial dysfunction
- Severe dysarthria / dysphagia
- Anterocollis, Chin-on-chest posture
- Camptocormia, lateral flexion or Pisa
- Freezing of gait within three years of onset
- A wide-based gait, decreased ten-step tandem gait performance
- Loss of cycling ability

Autonomic dysfunction
- Early severe autonomic dysfunction
- Autonomic dysfunction before Pdism
- Inspiratory stridor or sighs
- Cold hand signs

Cognitive, neuropsychiatric
- Emotional incontinence

Other non-motor symptoms
- Coat hanger pain

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Bhidayasiri R, Sringean J, Reich SG, Colosimo C. Red flags phenotyping: A systematic review on clinical features in atypical parkinsonian disorders. Parkinsonism Relat Disord. 2019 Feb;59:82-92.

MSA: clinical pearls

Often misdiagnosed as a spinal problem or fibromyalgia, it's believed to be caused by poor blood flow in the large muscles of the upper back and neck, caused by disrupted autonomic neurovascular control.

February 25, 2003; 60 (4) NEUROIMAGES

The cold hands sign in MSA

Stephen G. Reich

This “red flag,” which helps to distinguish MSA from PD, consists of cold, dusky, violaceous hands with delayed capillary refill after blanching (figure).

MSA: radiographic pearls

Axial T2

High signal is seen on T2/FLAIR crossing left to right and AP in the pons, creating the hot-cross bun appearance. Signal drop out is also seen in the basal ganglia.

Hot cross bun

Hyperintense putaminal rim

T2

Reversal of the expected magnetic susceptibility pattern within the basal ganglia with more prominent T2* hypointensity within the putamen than the globus pallidus. There is also subtle corresponding decreased T2 signal within the putamen relative to the globus pallidus, and a linear rim of high T2 / FLAIR signal.

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MSA: radiographic pearls

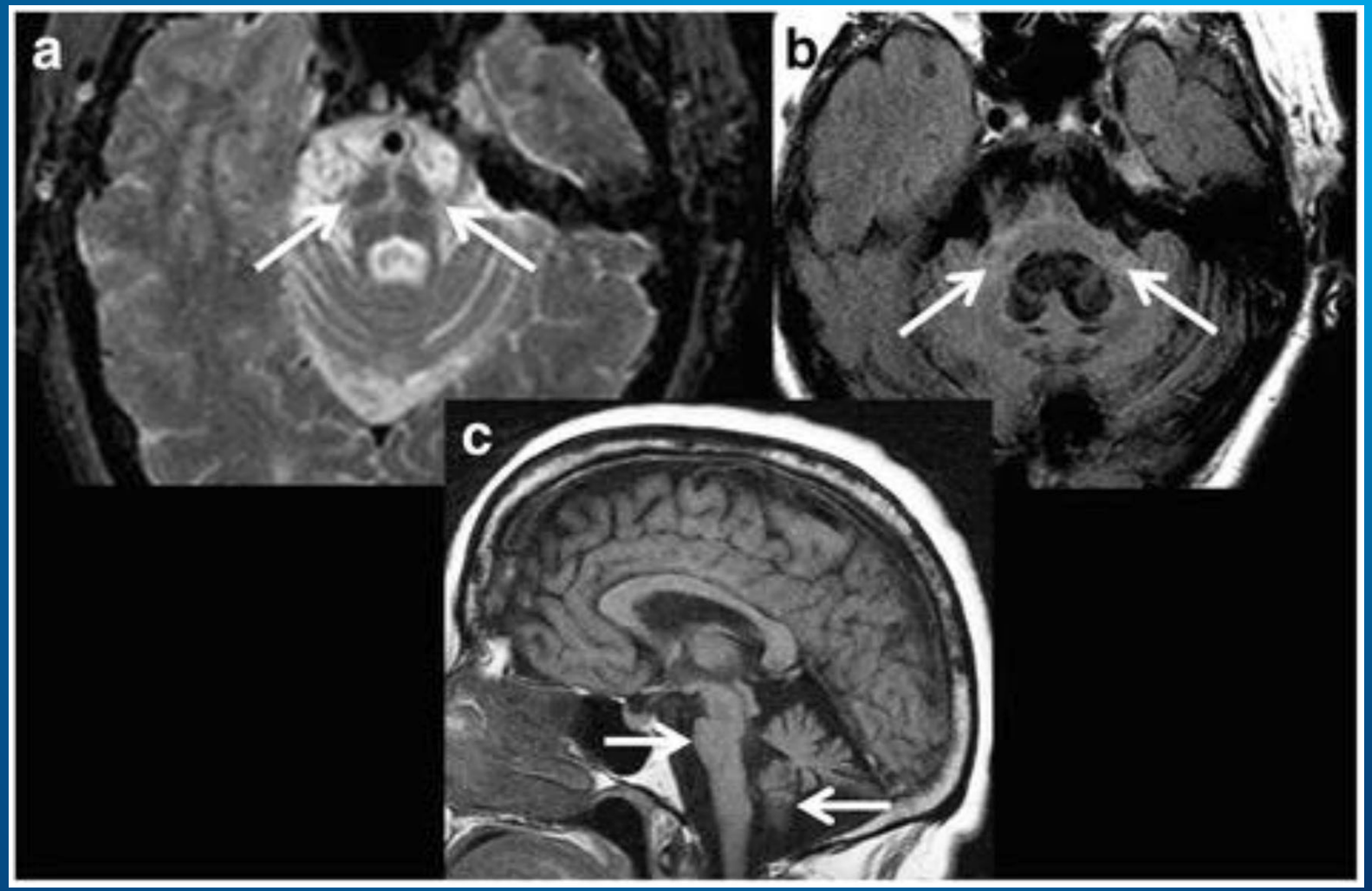
Neuroimaging Advances in Parkinson's Disease and Atypical Parkinsonian Syndromes

Usman Saeed[1], Anthony E. Lang[2,3] and Mario Masellis[1,2,4,5*]

Hot cross bun

MCP Sign

Olivoponto-cerebellar atrophy (OPCA)



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MSA: treatment tips and tricks

For prognosis? Palliative Care

For parkinsonism? Levodopa > amantadine > dopamine agonists

For dystonia? Amantadine + botulinum toxins

For ataxia? PT/OT, no meds

For choking/stridor? Speech therapy + sialorrhea tx (1% atropine, Botox)

For neurogenic bladder? Mirabegron, anti-cholinergics, catheters

For orthostasis?

Non-Rx: 1) avoid rapid postural change, heavy meals, straining while coughing or passing stool, & hot temperatures. 2) add leg crossing, increasing water and salt intake, keeping the head of the bed raised, and using compression stockings or binders

Rx: 1) droxidopa, midodrine, fludrocortisone, pyridostigmine

For reactive hypertension? Short acting clonidine, vasodilators like Nitro paste

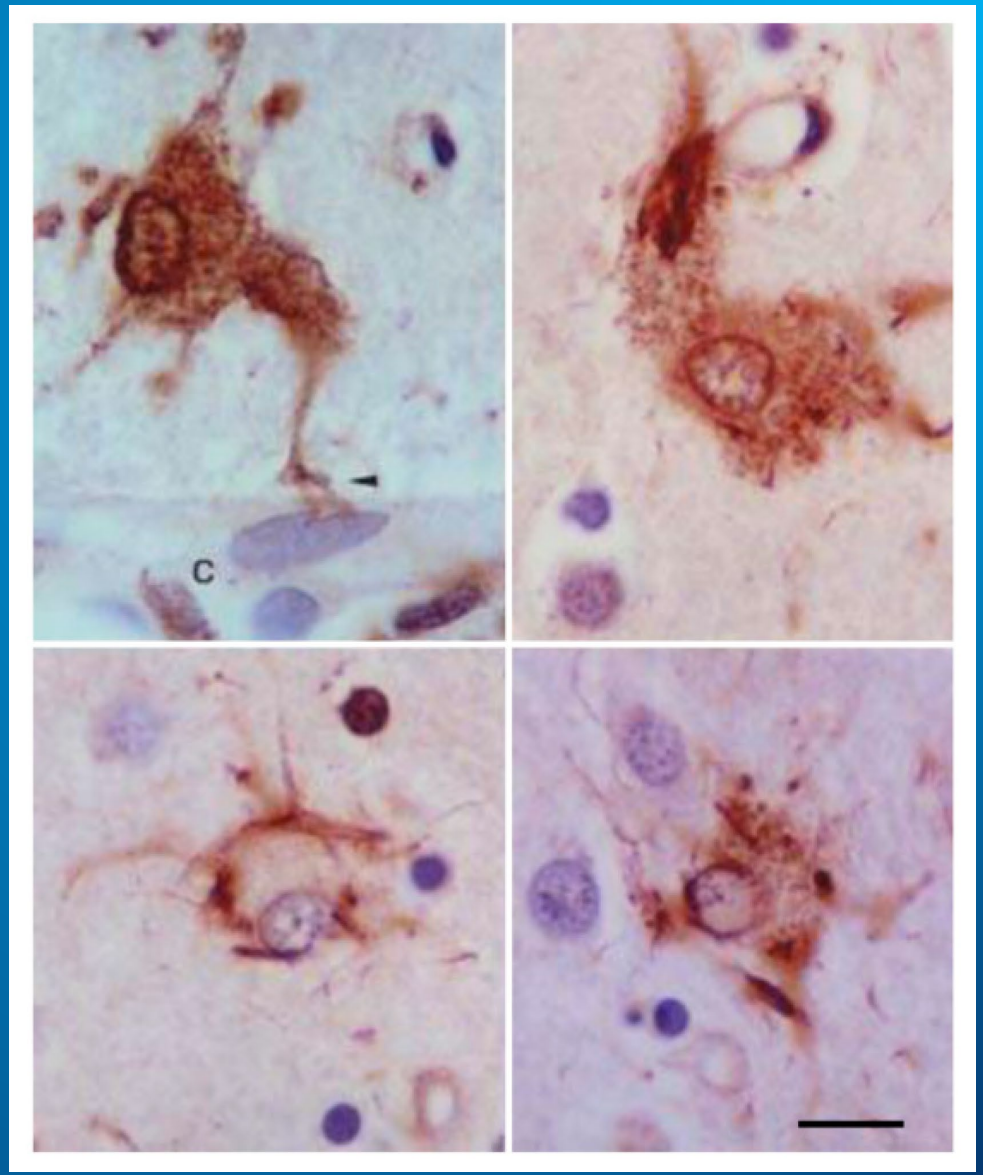
PSP: the basics

Prevalence: 5–10/100 000 persons

Mean age at disease onset: 60s

Disease course: “rule of odds” – year 1, falls; year 3, gaze palsy, year 5, cognitive, years 7-9, near death; patients die mostly from aspiration or falls

Clinical symptoms:
= levodopa-resistant akinetic-rigid symptoms affecting the axial muscles, a tendency to fall backwards, and vertical gaze paresis.
= A frontal lobe syndrome is also typical, with apathy, impaired executive functions, and a “applause sign”
= PSP is initially characterized by asymmetric levodopa-responsive parkinsonism (PSP-P, about 20%), which is clinically indistinguishable from Parkinson’s disease, until the later onset of vertical gaze paresis.



PSP: “red flags” and presentation

Rapid clinical deterioration
- Wheelchair in 5 yrs, dependent in 10 (like MSA)
- Falls within the first year

Eye movement abnormalities
- Giant or macro square wave jerks
- Curved trajectory vertical saccades (Round-the-house sign)
- Slow vertical saccades
- Supranuclear vertical gaze palsy

Abnormal facial appearances
- Dystonic wrinkling of the glabellar region (Procerus or corrugator sign)
- Blepharospasm (& apraxia of eyelid opening)
- Lid retraction (‘Reptilian stare’)
- Transient head deviation

Limb abnormalities
- Tremulous movements during ballistic aiming movements

Axial dysfunction
- Retrocollis with extended body posture
- Freezing of gait within three years of onset
- Robotic voice, dysarthria and dysphagia
- A wide-based gait, lateral instability
- Decreased ten-step tandem gait
- Loss of cycling ability

Cognitive, neuropsychiatric
- Executive dysfunction and apathy within three years of onset
- Apathy and impulsivity (Rocket’s sign)
- Emotional incontinence
- Non-fluent aphasia

Other non-motor symptoms
- Decreased pain sensitivity
- Absent of autonomic symptoms

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Bhidayasiri R, Sringean J, Reich SG, Colosimo C. Red flags phenotyping: A systematic review on clinical features in atypical parkinsonian disorders. Parkinsonism Relat Disord. 2019 Feb;59:82-92.

PSP: clinical phenotypes (most lumping)

Richardson's Syndrome (RS)
- most common subtype of PSP, accounting for about 70% of all cases
- Classic triad of symptoms: postural instability, supranuclear gaze palsy, and

PSP-Parkinsonism (PSP-P)
- subtype of PSP that is characterized by a combination of Parkinsonian features, such as tremors, rigidity, and bradykinesia, along with the classic PSP features
- Greater ldopa response initially, often misdiagnosed as Parkinson's disease

PSP-Corticobasal Syndrome (PSP-CBS)
- subtype combo of PSP and Corticobasal features
- more rigidity, apraxia, and myoclonus; earlier dementia

PSP-Pure Akinesia with Gait Freezing (PSP-PAGF)
- rare subtype of PSP that is characterized by severe akinesia (inability to initiate voluntary movements) and gait freezing

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Multiple sources

PSP: clinical phenotypes (most splitting)

2017 MDS variant PSP clinical presentations with initial predominance

- ocular motor dysfunction (PSP-OM)
- postural instability (PSP-PI)
- parkinsonism resembling idiopathic Parkinson's disease (PSP-P)
- frontal lobe cognitive or behavioral presentations (PSP-F, + bvFTD)
- progressive gait freezing (PSP-PGF)
- corticobasal syndrome (PSP-CBS)
- primary lateral sclerosis (PSP-PLS)
- cerebellar ataxia (PSP-C)
- speech/language disorders (PSP-SL, + nfaPPA)
- progressive apraxia of speech (AOS).

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Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, Mollenhauer B, Müller U, Nilsson C, Whitwell J L, Arzberger T, Englund E, Gelpi E, Giese A, Irwin DJ, Meissner WG, Pantelyat A, Rajput A, van Swieten J C, Troakes C, Antonini A, Bhatia KP, Bordelon Y, Compta Y, Corvol J C, Colosimo C, Dickson DW, Dodel R, Ferguson L, Grossman M, Kassubek J, Krismer F, Levin J, Lorenzl S, Morris HR, Nestor P, Oertel WH, Poewe W, Rabinovici G, Rowe J B, Schellenberg GD, Seppi K, van Eimeren T, Wenning GK, Boxer AL, Golbe LI, Litvan I; Movement Disorder Society-endorsed PSP Study Group. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord. 2017 Jun;32(6):853-864.

PSP: clinical pearls

"Applause sign" helps to discriminate PSP from FTD and PD

The applause sign may rather be the result of the decreased ability to plan a specific program of three claps (because of the frontal dysfunction) associated with an inability to stop an automatic activity once it has been released (because of the dysfunction of the basal ganglia).

Dubois, B. , Slachevsky, A. , Pillon, B. , Beato, R. , Villalponda, J. M. & Litvan, I. (2005). "Applause sign" helps to discriminate PSP from FTDand PD. *Neurology, 64* (12), 2132-2133. doi: 10.1212/ 01.WNL.0000165977.38272.15.

The "bicycle sign" for atypical parkinsonism

- At presentation:

111 patients rode a bicycle
-- 45 developed PD
-- 64 developed atypical Pdism

- At median 30 months:

-- 43/45 PD patients still rode
-- 30/64 aPD patients still rode

- Sensitivity = 52%
- Specificity = 96%

www.thelancet.com **Vol 377 January 8, 2011**

e-Pearl of the Week: Rocket sign

As a result of the frontal lobe disturbance the PSP patient may jump to his or her feet from a sitting position without thinking only to topple backwards into the chair because of postural instability. This is known as the "rocket sign".

Rehman HU. Progressive supranuclear palsy. Postgrad Med J. 2000 Jun;76(896):333-6. doi: 10.1136/pmj.76.896.333. PMID: 10824045; PMCID: PMC1741619.

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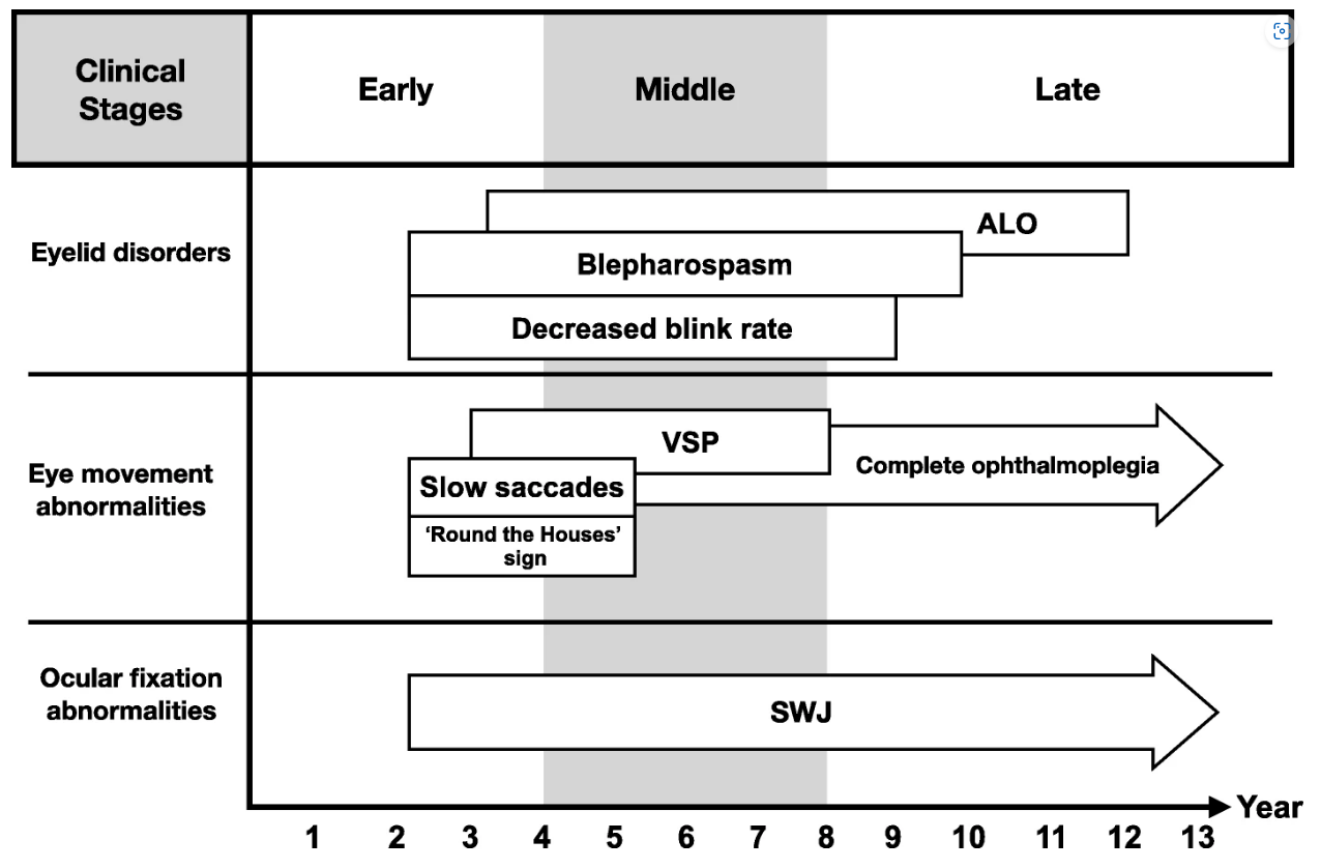
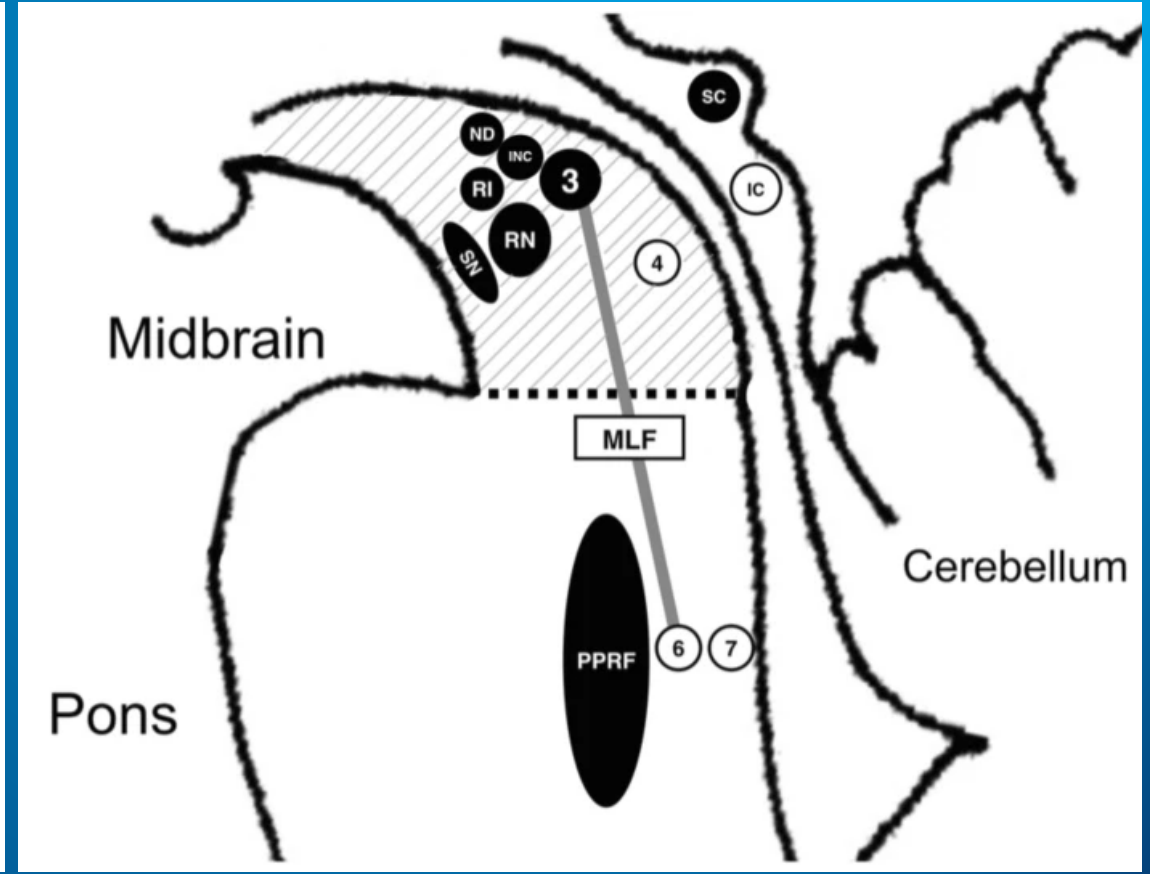
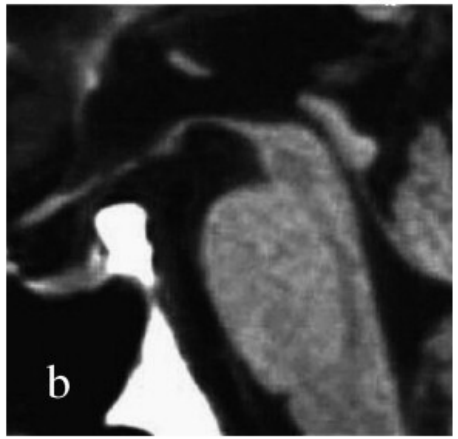
PSP: deeper understanding of the ocular problems



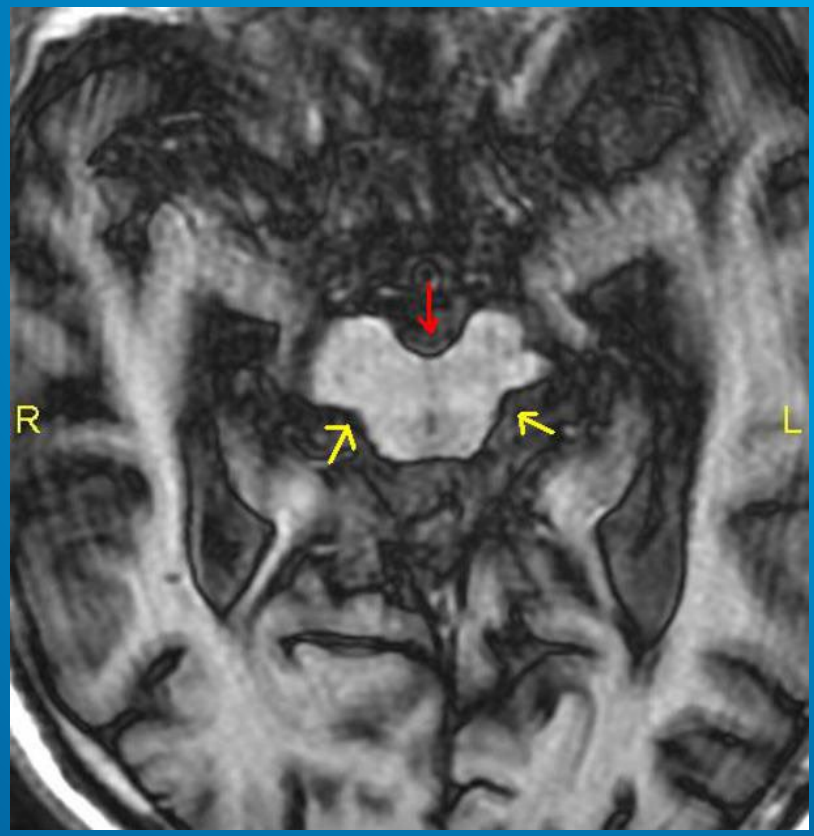


Phokaewvarangkul, O., Bhidayasiri, R. How to spot ocular abnormalities in progressive supranuclear palsy? A practical review. *Transl Neurodegener* **8**, 20 (2019).

PSP: radiographic pearls



(a) Hummingbird, (b) mid-sagittal plain MRI in PSP. The region including the most rostral midbrain, the midbrain tegmentum, the pontine base, and the cerebellum appears to correspond to the bill, crown, body, and wing, respectively, of a hummingbird (i.e., the "hummingbird sign"). Adapted from "Kato N, Arai K, Hattori T. Study of the rostral midbrain atrophy in progressive supranuclear palsy. J Neurol Sci. 2003 Jun 15;210(1–2):57–60. "



•Mickey Mouse appearance: reduction of anteroposterior midline midbrain diameter, at the level of the superior colliculi on axial imaging (from interpeduncular fossa to the intercollicular groove: <12 mm) [6,8]

https://radiopaedia.org/articles/progressive-supranuclear-palsy-1?lang=us

CBD/CBS: the basics

Corticobasal degeneration (CBD) is reserved for the neuropathological diagnosis. Clinically, CBD mostly manifests with a corticobasal syndrome (CBS)…

Prevalence: 1/100 000 persons

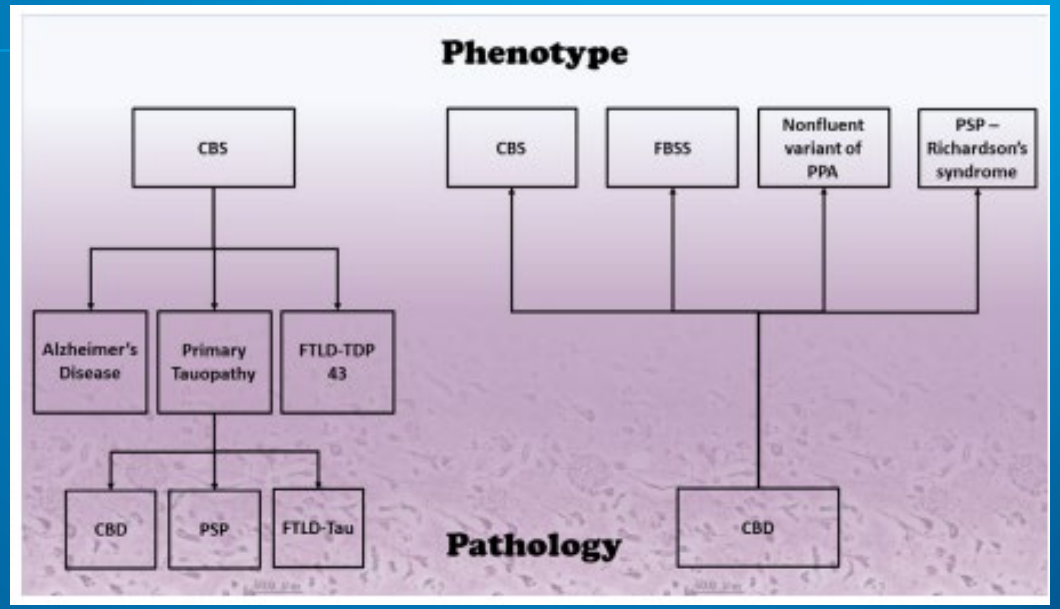
Mean age at disease onset: 50-60s

Disease course: 8-10 years, aspiration is common

Clinical symptoms:
= progressive constellation of symptoms that comprise functional damage to the basal ganglia and the cerebral cortex and appear asymmetrically

The basal ganglia symptoms include akinesia, rigidity, dystonia, and myoclonus, typically resistant to levodopa. Tremor may be present, which is superimposed on myoclonus and therefore appear irregular and jerky.

As the disease progresses, many patients develop a characteristic, fixed dystonia-related posture of the affected arm. Includes apraxia, cortical sensory loss, alien limb phenomenon, pyramidal signs, behavioral disorders, and aphasia



Wilson D, Le Heron C, Anderson T Corticobasal syndrome: a practical guide. *Practical Neurology* 2021;**21:**276-285.

CBD/CBS: “red flags” and presentation

Rapid clinical deterioration
- Wheelchair in 5 yrs, dependent in 10 (like MSA)
- Falls within the first year

Eye movement abnormalities
- Saccadic apraxia

Limb abnormalities
- Jerky dystonic movements (especially when asymmetric)
- Useless arm
- Alien limb phenomenon
- Limb levitation
- Contracture of hands and feet
- Dystonic clenched fist
- Tremulous movements during ballistic aiming movements

Axial dysfunction
- Severe dysarthria and dysphagia within one year of onset
- A wide-based gait with staggering walk and lateral instability
- Decreased ten-step tandem gait performance
- Loss of cycling ability

Cognitive, neuropsychiatric
- Ideomotor apraxia
- Non-fluent aphasia
- Absent of autonomic symptoms

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Bhidayasiri R, Sringean J, Reich SG, Colosimo C. Red flags phenotyping: A systematic review on clinical features in atypical parkinsonian disorders. Parkinsonism Relat Disord. 2019 Feb;59:82-92.

CBD/CBS: clinical phenotypes

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

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

[a] See glossary of terms in appendix e-1 for further explanation of terms used.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA, Kertesz A, Lee SE, Miller BL, Reich SG, Riley DE, Tolosa E, Tröster AI, Vidailhet M, Weiner WJ. Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013 Jan 29;80(5):496-503.

CBD/CBS: clinical pearls

Apraxia may be present in up to 70% of people corticobasal dysfunction

Some exam recommendations:

- **Performing a gesture, miming the use of tools and copying meaningless gestures.**
  = Deficits in these movements → ideomotor apraxia.

- **Performing complex, multistep tasks.**
  = Deficits in these processes → conceptual, or ideational apraxias

- **Performing repetitive distal limb movements (tapping the thumb to each finger in turn)**
  = Deficits such as clumsy or inaccurate movements → limb-kinetic apraxia

(this is a somewhat controversial classification that can be difficult to distinguish from the effects of weakness or bradykinesia)

CBD/CBS: radiographic pearls

Neuroimaging Advances in Parkinson's Disease and Atypical Parkinsonian Syndromes

Usman Saeed[1], Anthony E. Lang[2,3] and Mario Masellis[1,2,4,5]*

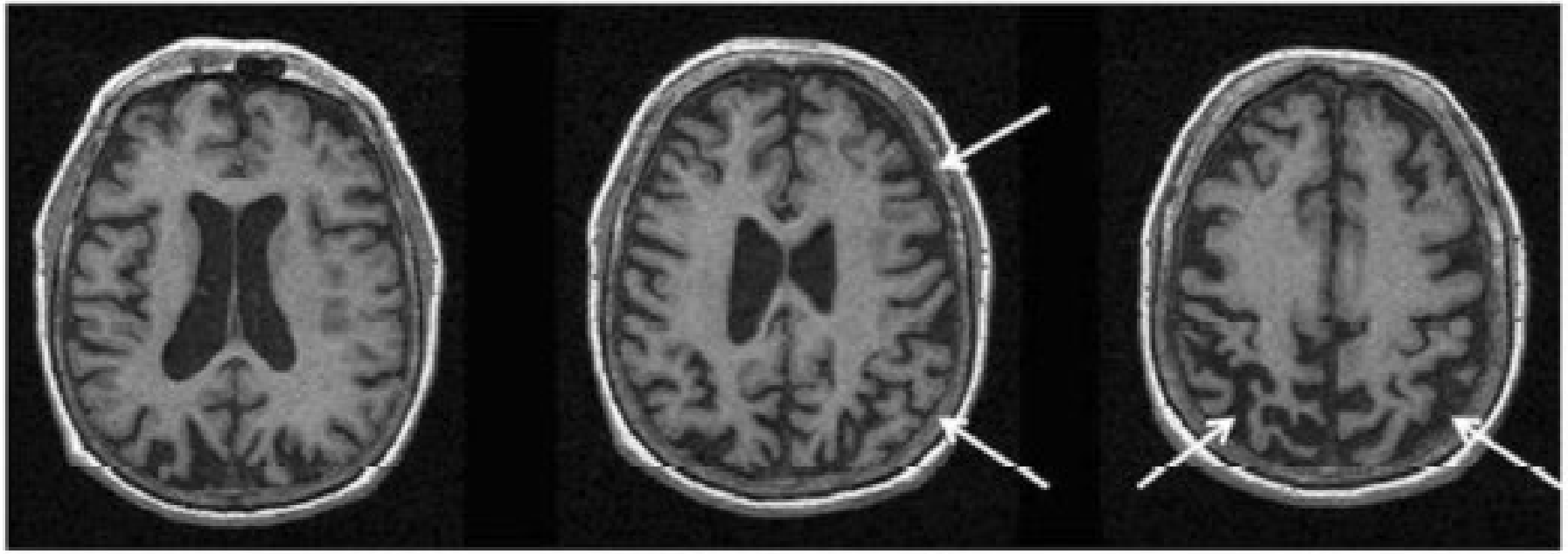


FIGURE 6 | Magnetic resonance imaging of a patient with a pathology-proven diagnosis of corticobasal degeneration. Serial axial T1-weighted sequences are presented showing right greater than left parietofrontal atrophy commonly seen in corticobasal syndrome. Figure reproduced from Saeed et al. (10), under the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

PSP & CBD/CBS: basic treatment tenets

1) Medications: manage specific symptoms such as Parkinsonism, dystonia, and depression.

2) Physical therapy: Physical therapy can help improve mobility, balance, and gait abnormalities.

3) Occupational therapy: Occupational therapy focuses on maintaining independence in daily activities.

4) Speech and swallowing therapy: Speech therapy can help improve speech clarity and develop alternative communication methods. Swallowing therapy aims to prevent aspiration and maintain adequate nutrition and hydration.

5) Neuropsychology: support for mood and cognitive shifts

6) Social work: They can address emotional and psychological aspects, assist with caregiving, and provide guidance on community resources.

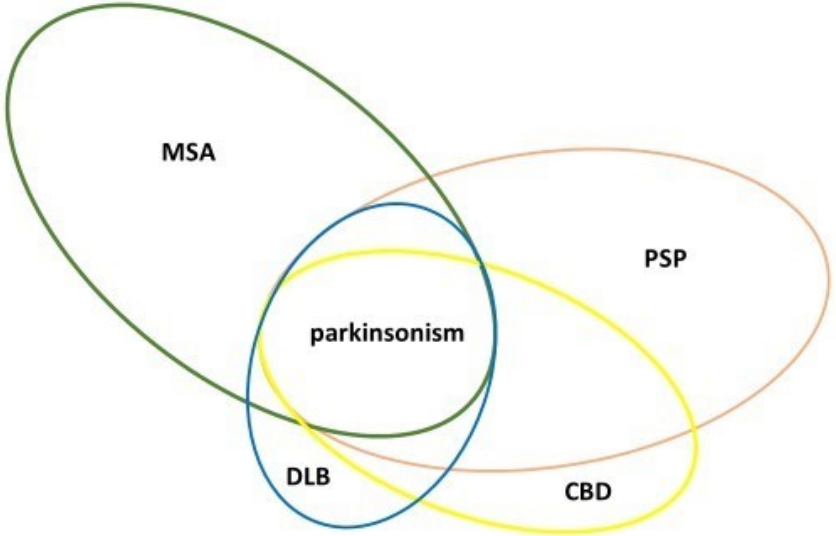
7) Assistive devices: The use of assistive devices can enhance mobility and independence.

8) Research and clinical trials: Participating in research studies and clinical trials can provide access to experimental treatments and contribute to the advancement of knowledge and potential future therapies for PSP and CBS

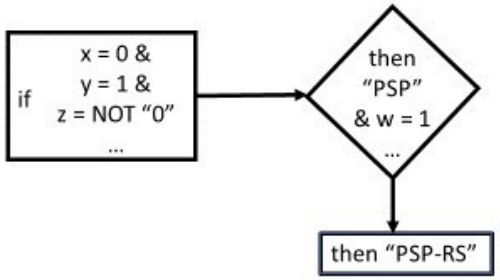
Future direction: can we get better at diagnosis?

Of Criteria and Men – Diagnosing Atypical Parkinsonism: Towards an Algorithmic Approach

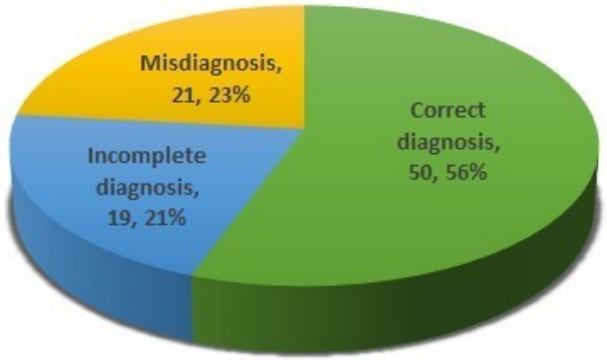
Atypical parkinsonism – a retrospective study 90 patients: 2015-2021



Boolean Diagnostic Algorithm in line with Consensus Criteria



Physician diagnosis compared to algorithm results



Algorithmic tools could be perfected to help regular clinicians use consensus criteria more reliably and quickly

FINAL DIAGNOSIS*

*According to consensus criteria

REM = rapid eye movement; PPA = nonfluent/agrammatic variant of primary progressive aphasia; AOS = apraxia of speech; DLB = dementia with Lewy bodies; MSA = multiple system atrophy; PSP = progressive supranuclear palsy; CBD = corticobasal degeneration

Thank you!

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Dr. Sarah Breaux	Movement Disorder Neurologist
Rachel Rhinehart	Movement Disorder PA
Dr. Colleen Knoop	Movement Disorder NP
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- Palliative Care Team
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- Allied Health Team for PT, OT, Speech, Nutrition

Ochsner