European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

DG ‚Atypical Parkinsonism'
14. April 2020

Joint webinar series

Recognizing atypical parkinsonism

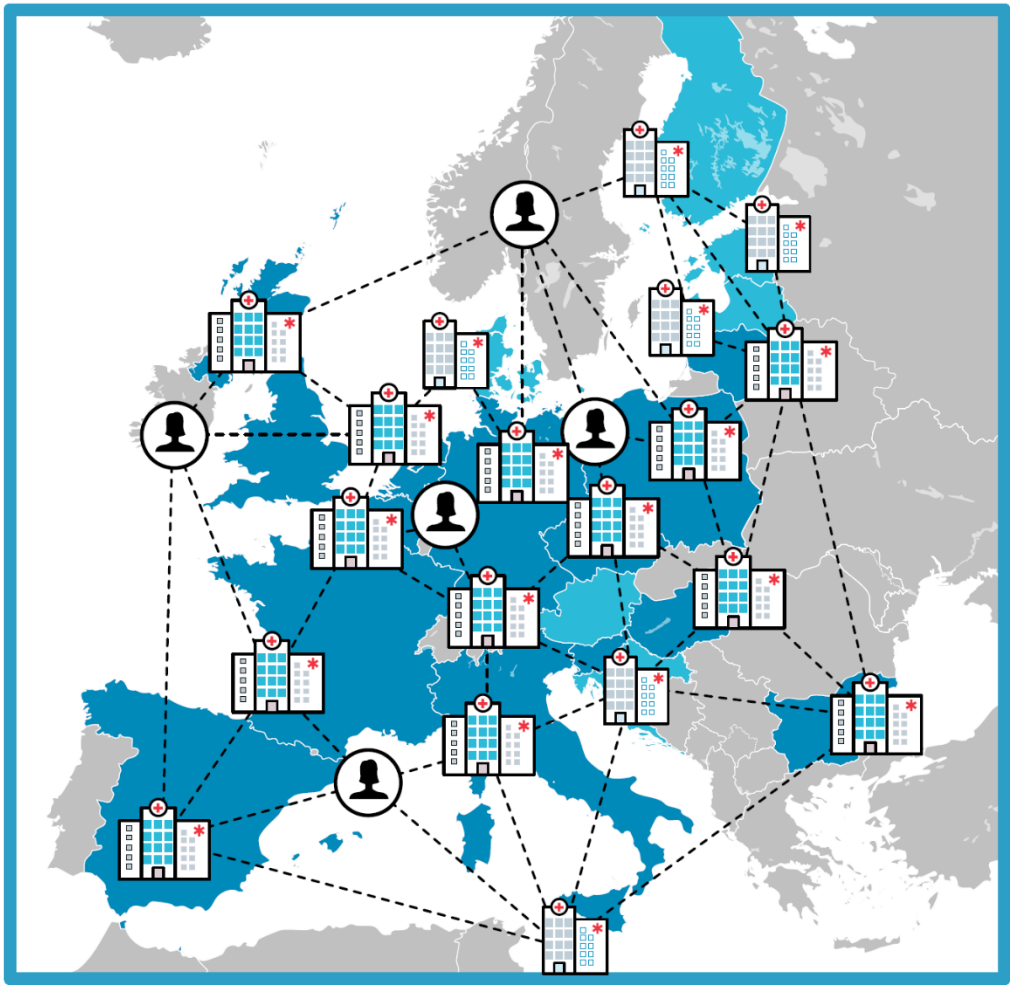
Wassilios Meissner
University Hospital Bordeaux, France

General information about the webinars

- RARE neurological, neuromuscular and movement disorders
- 30-35min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- Target audience: neurologists, residents, paediatric neurologists, geneticists and other para-medical personnel involved in patient care
- Recorded Webinar and presentation to be found at the latest 2 weeks after on: http://www.ern-rnd.eu/education-training/past-webinars/
- For more information on this diseases group visit: http://www.ern-rnd.eu/disease-knowledge-hub/msa/
- Post-webinar survey (2-3min): satisfaction, topic/speaker ideas for next webinars

European Reference Network for RARE Neurological Diseases (ERN-RND)

- **Countries with Full Members**
- **Countries with Affiliated Partners**



ERN-RND covers 6 disease groups:

1. Ataxia and HSP
2. Leukodystrophies
3. Dystonias /NBIA/Paroxysmal disorders
4. Chorea and HD
5. FTD
6. Atypical Parkinsonism

Speaker: Wassilios Meissner

- **Current position**: Director of the Expert Centre for Parkinson's disease (PD) at the University Hospital Bordeaux and co-chair of:
  - French Reference Center for Multiple System Atrophy (MSA)
  - MDS-sponsored MSA Study Group and
  - Atypical Parkinsonism Disease Group of ERN-RND.
- **Training**: medical degree from the Humboldt University Berlin in Germany (1997) and residency at the Charité University Hospital in Berlin and the University Hospital Bordeaux → Board Certification in Neurology in 2005
- **Professor of Neurology** since 2012 at the University of Bordeaux
- **Publications**:
  >150 peer-reviewed publications in the field of movement disorders, mostly dealing with PD and MSA, 100 invited lectures in more than 20 countries.
- **Research focus**: biological and clinical markers of disease progression in PD and MSA, and development of new preclinical models and treatments with a translational approach.
  Recently completed a phase 1 trial with two vaccines directed against alpha-synuclein in MSA patients within the framework of the European SYMPATH consortium.
- Coordinates the European ARTEMIS consortium that evaluates the efficacy of distinct strategies targeting alpha-synuclein in preclinical models of MSA.

Financial disclosures (past 12 months)

Teaching honoraria from UCB and Boehringer Ingelheim

Consultancy for Lundbeck and Biohaven

Fees for editorial activities from Springer Nature and Elsevier

Question 1 (single choice)

What is your professional background?

A. Neurology resident/fellow
B. Neurologist
C. Movement disorder specialist
D. General practitioner
E. Other medical specialty
F. Allied health professional
G. Other

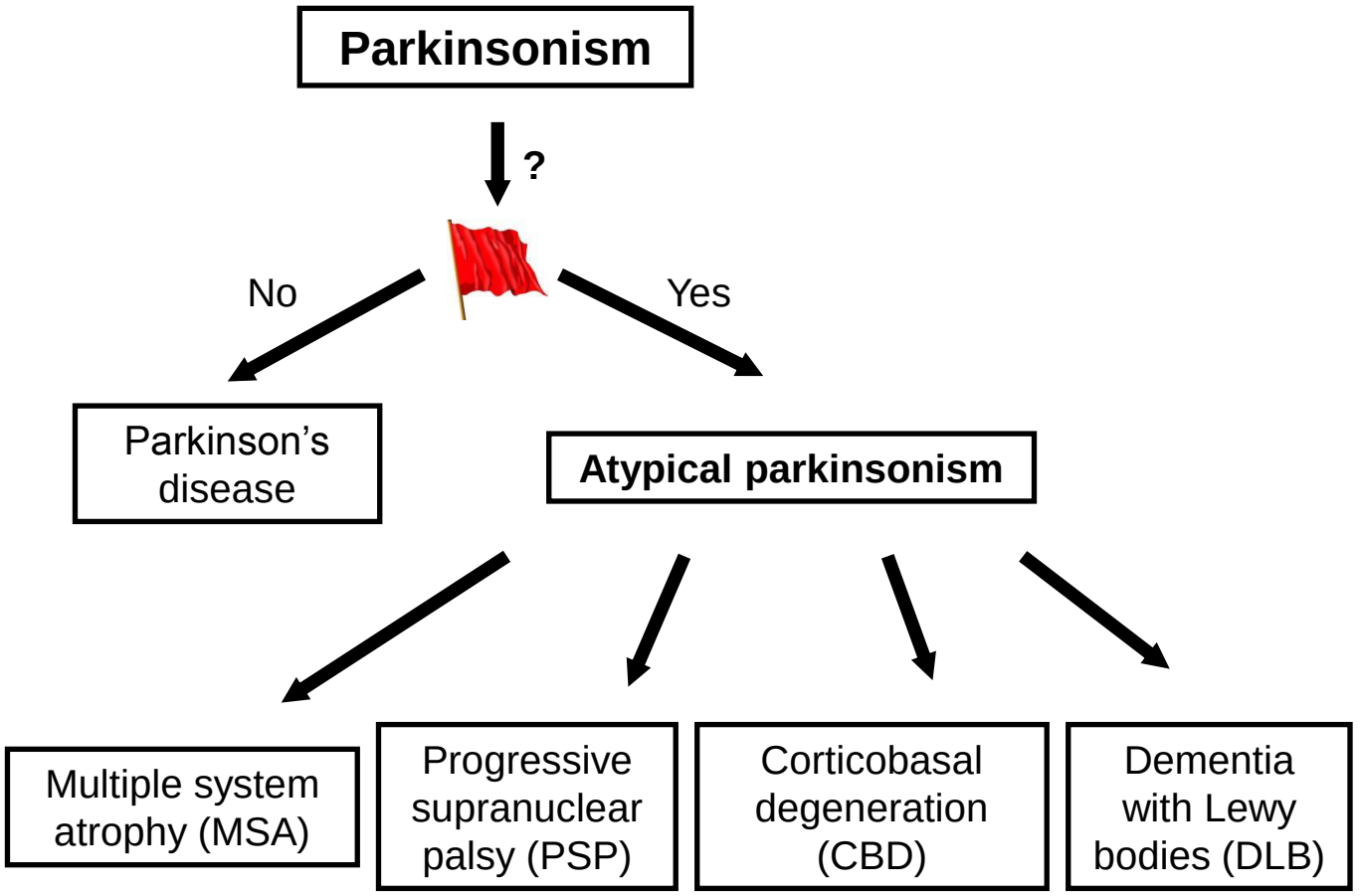
Webinar outline

- Focus on multiple system atrophy (MSA) and progressive supranuclear palsy (PSP)
- Each chapter will start with an introductory slide, followed by a description of core clinical features (with emphasis on red flags), paraclinical tests (e.g. imaging, autonomic function testing, fluid biomarkers) and diagnosis criteria
- Some treatment considerations will be provided at the end of each chapter

Learning objectives

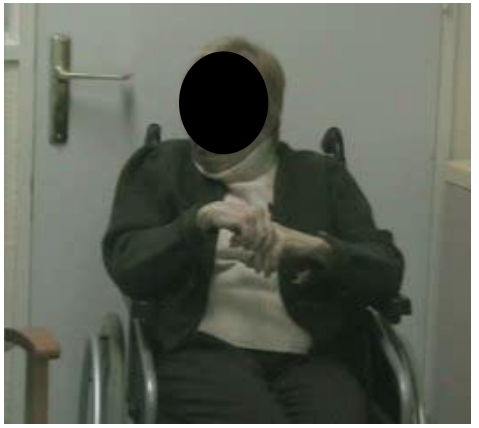
By the end of this webinar you will be able to:

- discuss the clinical features of MSA and PSP
- recognize typical MRI features of both disorders
- describe additional ancillary investigations to support their diagnosis, and
- explain available therapeutic options

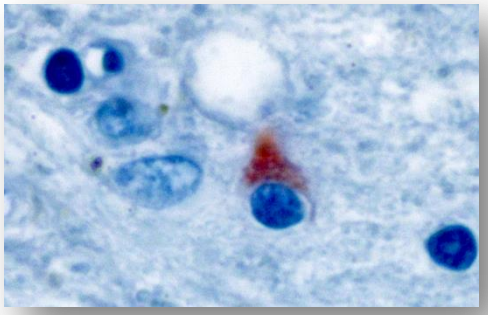

Parkinsonism
?
No
Yes
Parkinson's disease
Atypical parkinsonism
Multiple system atrophy (MSA)
Progressive supranuclear palsy (PSP)
Corticobasal degeneration (CBD)
Dementia with Lewy bodies (DLB)

Clinical presentation of MSA

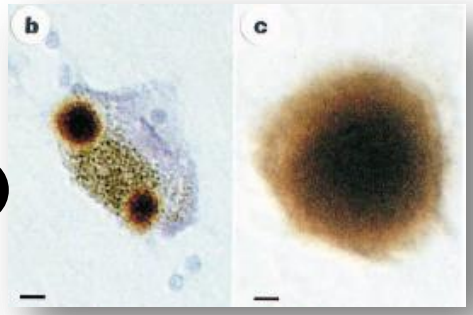
- Prevalence: 2-5/100 000
- Parkinsonism with weak l-dopa response
- Cerebellar signs
- Autonomic failure
- Rapid progression (survival = 6-10 years)

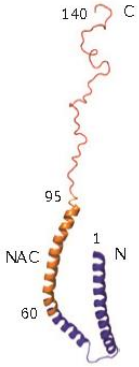


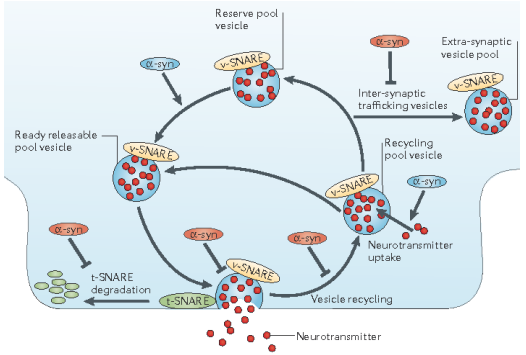
GCIs in MSA



Lewy bodies in PD



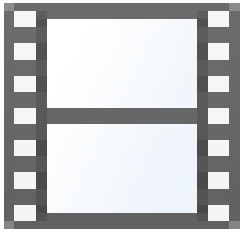




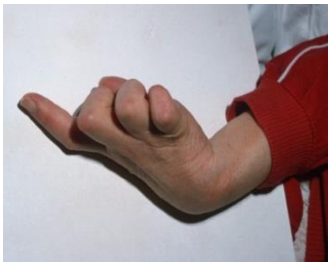
Spillantini et al., 1997; Lashuel et al., 2013

MSA – motor signs

- L-dopa induced orofacial dyskinesias (*risus sardonicus*)
- Axial dystonia (Pisa syndrome, camptocormia)
- Disproportional antecollis
- Early postural instability with falls
- “Jerky tremor”
- Early dysphagia and/or dysarthria

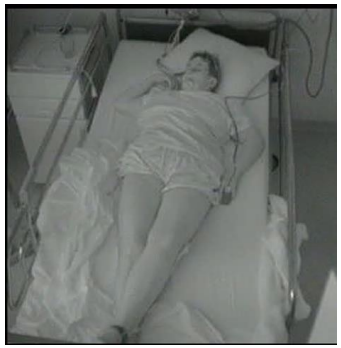


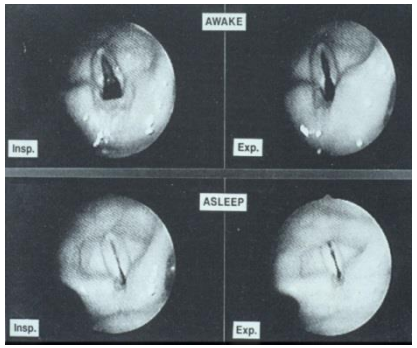
Wenning et al., 1996

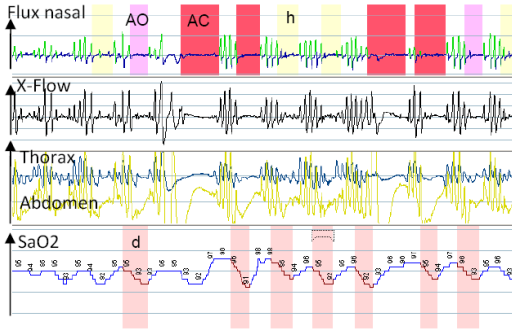


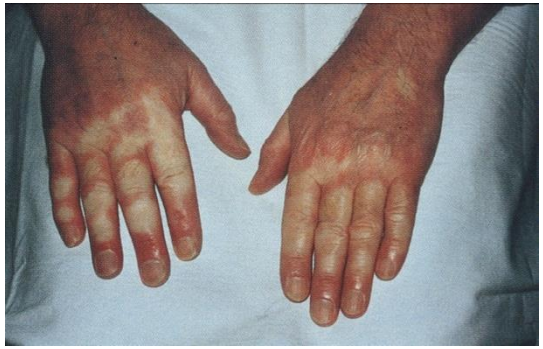
MSA – non-motor signs

- Emotional instability
- Autonomic failure
  - OH, urinary dysfunction, constipation, Raynaud syndrome
- Sleep disturbances
  - RBD, respiratory, stridor









Isozaki et al., 1996

Second consensus statement on the diagnosis of multiple system atrophy

- Diagnosis of MSA-P and MSA-C with 3 degrees of certitude
- Inclusion of additional features (clinical, imaging)

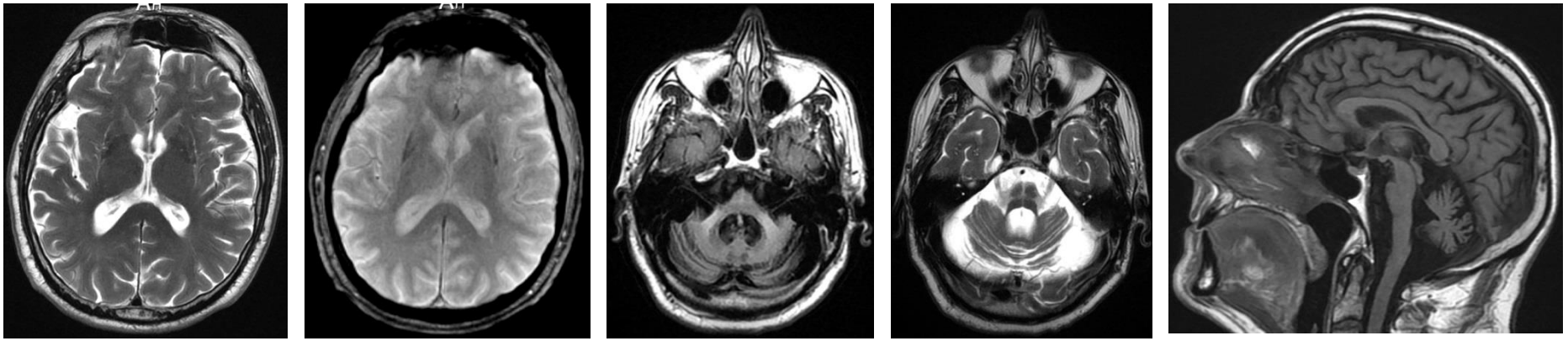
Gilman et al., 2008

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	

MSA = multiple system atrophy; MSA-P = MSA with predominant parkinsonism; MSA-C = MSA with predominant cerebellar ataxia; FDG = [^{18}F]fluorodeoxyglucose.

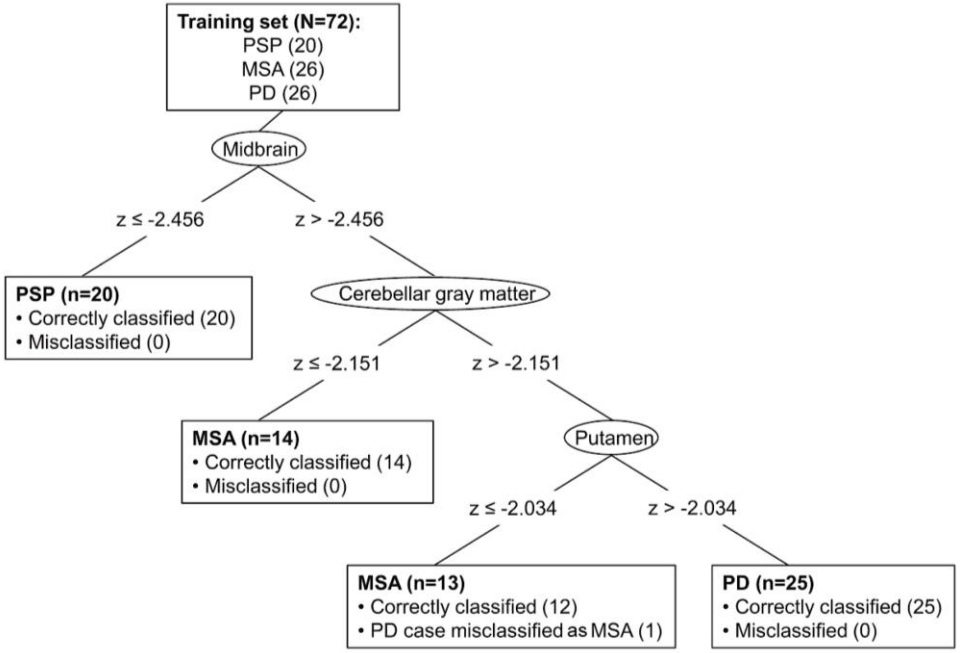
Gilman et al., 2008

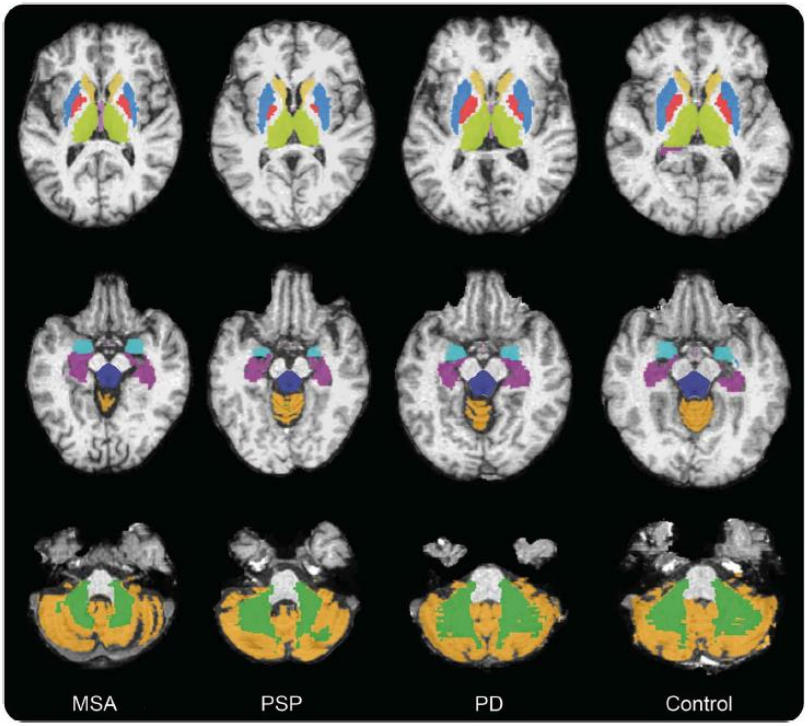
Paraclinical investigations – MRI



- Hypersignal of lateral putaminal border
- Hypointensity of postero-lateral putamen (T2/FLAIR, T2*)
- Hypersignal of middle cerebellar peduncles (MCP)
- “Hot cross bun sign”
- Atrophy of putamen, MCP, pons or cerebellum

Diagnostic potential of automated subcortical volume segmentation in atypical parkinsonism



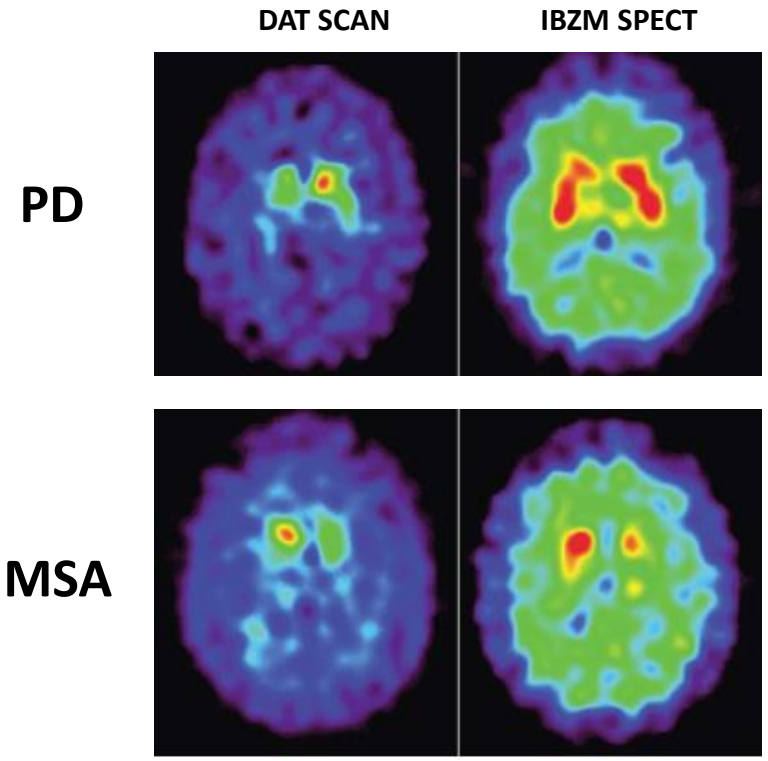


Increase of MSA diagnosis accuracy at first visit from 65 to 100%.

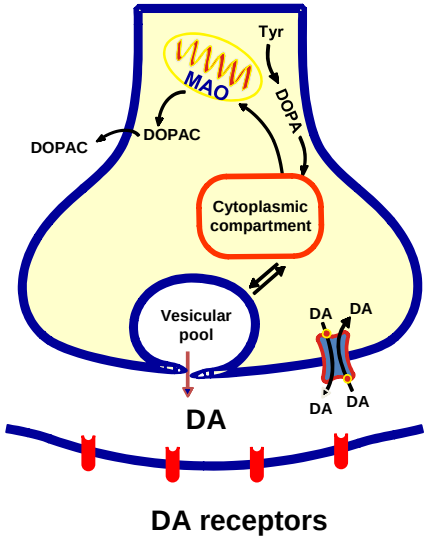
Scherfler et al., 2016

Imaging of the DA system

Pre and postsynaptic involvement



Plotkin et al., 2005



Parkinsonism and Related Disorders xxx (xxxx) xxx–xxx

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journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Dopamine transporter imaging for the diagnosis of multiple system atrophy cerebellar type

Sylvain Vergnet[a], Florent Hives[b], Alexandra Foubert-Samier[a,c], Pierre Payoux[b,d], Philippe Fernandez[e,f,g], Marie Meyer[e,f,g], Julia Dupouy[h], Christine Brefel-Courbon[h], Fabienne Ory-Magne[h], Olivier Rascol[i,j], François Tison[a,k,l], Anne Pavy-Le Traon[j], Wassilios G. Meissner[a,k,l,m,*]

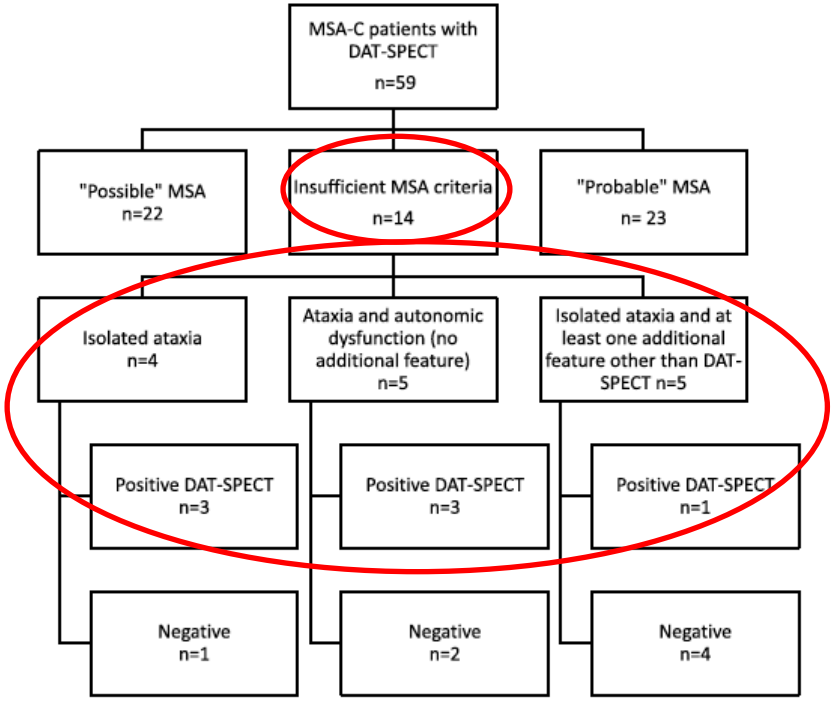
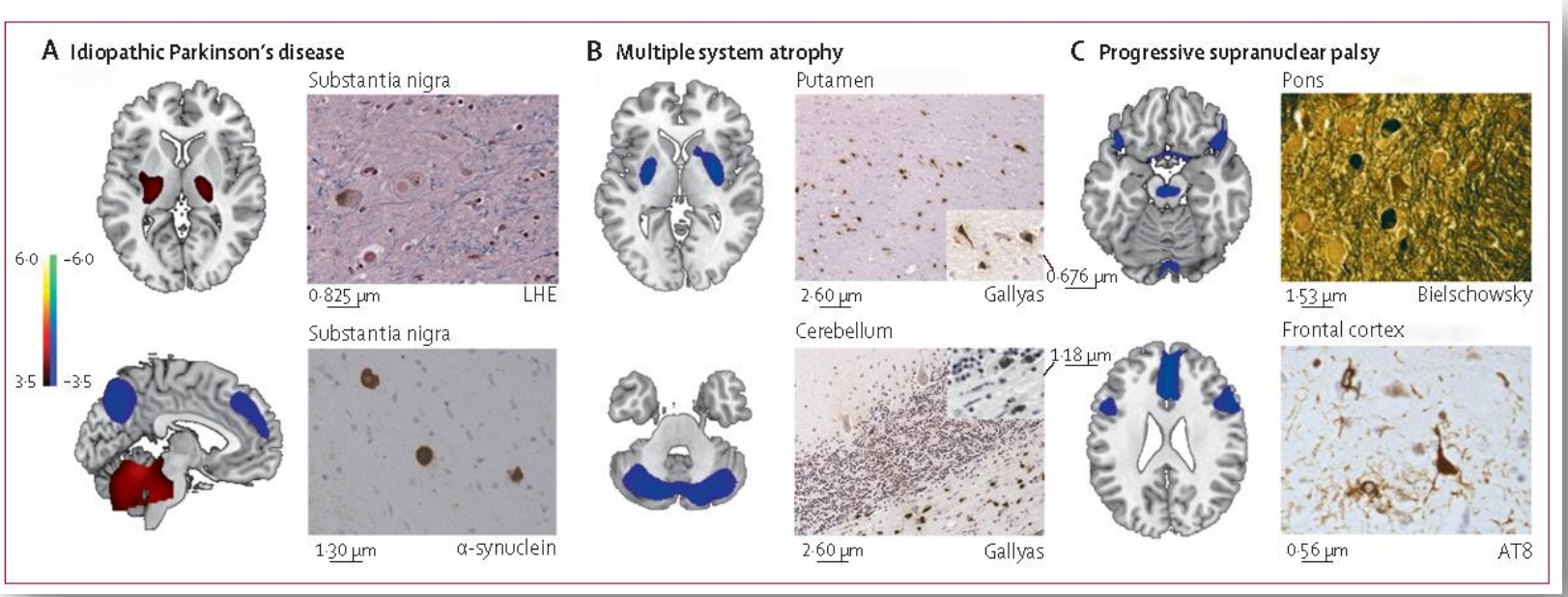


Fig. 2. Diagnostic certitude before performing DAT-SPECT.

6/14 (43%) with “possible” MSA-C diagnosis because of pos. DAT-SPECT.

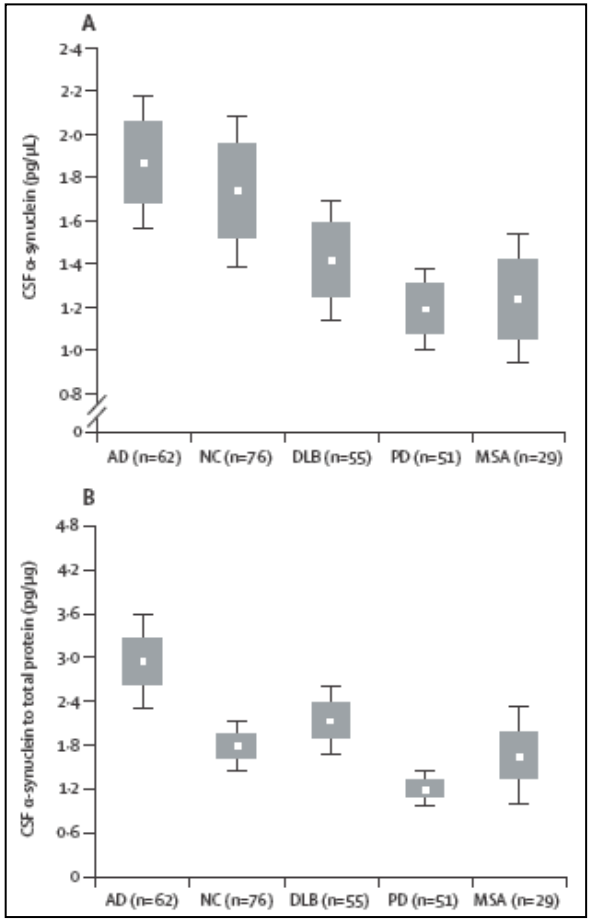
FDG-PET – Disease-related metabolic patterns



Specific MSA-related pattern with decreased metabolism in the putamen and cerebellum.

Eckert et al. 2005, 2008; Tang et al. 2010; Niethammer et al. 2012

Fluid biomarker in MSA – α-synuclein levels in CSF



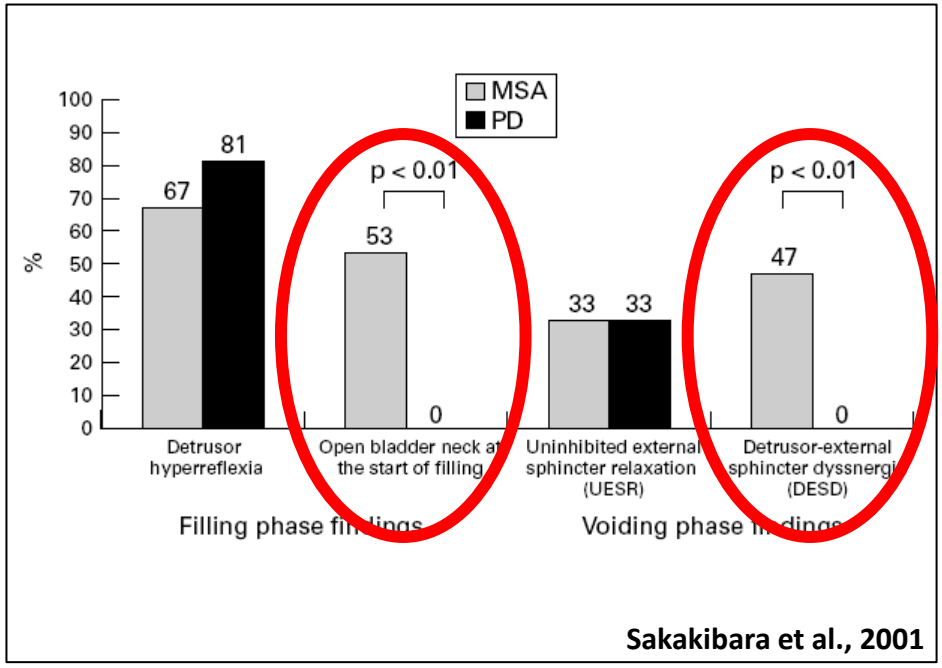
Most studies have reported decreased total α-synuclein levels in MSA. No difference between MSA and PD.

Aerts et al., 2012; Mollenhauer et al., 2011; Shi et al., 2011; Hall et al., 2012; Wang et al., 2012; Tateno et al., 2012; Mondello et al., 2014; Herbert et al., 2014; Magdalinou et al., 2015

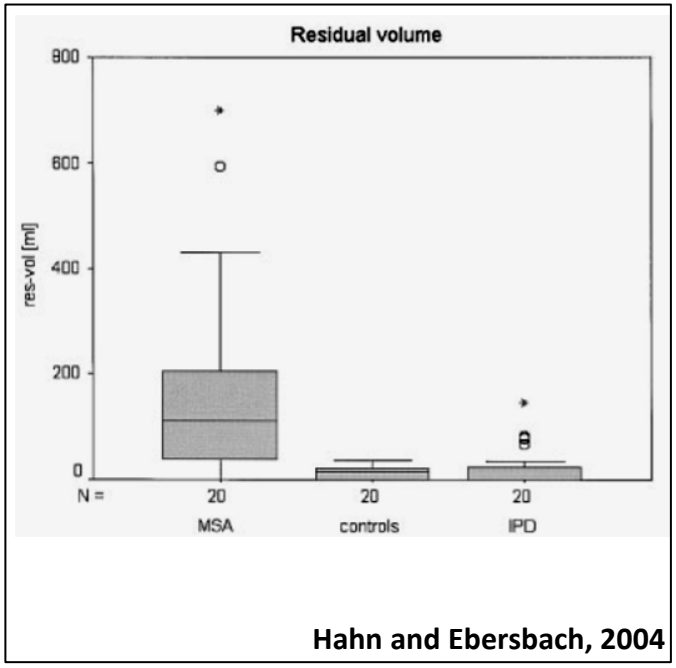
Proteins reflecting neurodegeneration

Tau↑/↔	Abdo 2007, Süssmuth 2010, Hall 2012, Herbert 2014, 2015 ↑ vs PD Abdo 2004, Mollenhauer 2007, 2011, Shi 2011, Magdalinou 2014 ↔ vs PD
Neurofilament ↑	Holmberg 1998, 2001, Brettschneider 2006, Abdo 2007, Hall 2012, Herbert 2015, Magdalinou 2015, Hansson 2017 ↑ vs PD Constantinescu 2010 ↔ vs PD
MBP ↑	Abdo 2007 ↑ vs PD
GFAP ↔	Holmberg 1998, Abdo 2004, Constantinescu 2010, Süssmuth 2010 ↔ PD
NSE ↑	Abdo 2004 ↑ vs PD
S-100 ↔	Abdo 2004 ↔ PD
Aβ42 ↔	Holmberg 2003 ↓ vs PD Verbeek 2004, Mollenhauer 2007, Süssmuth 2010, Shi 2011, Hall 2012, Magdalinou 2015 ↔ PD

Urinary dysfunction – differences between PD and MSA

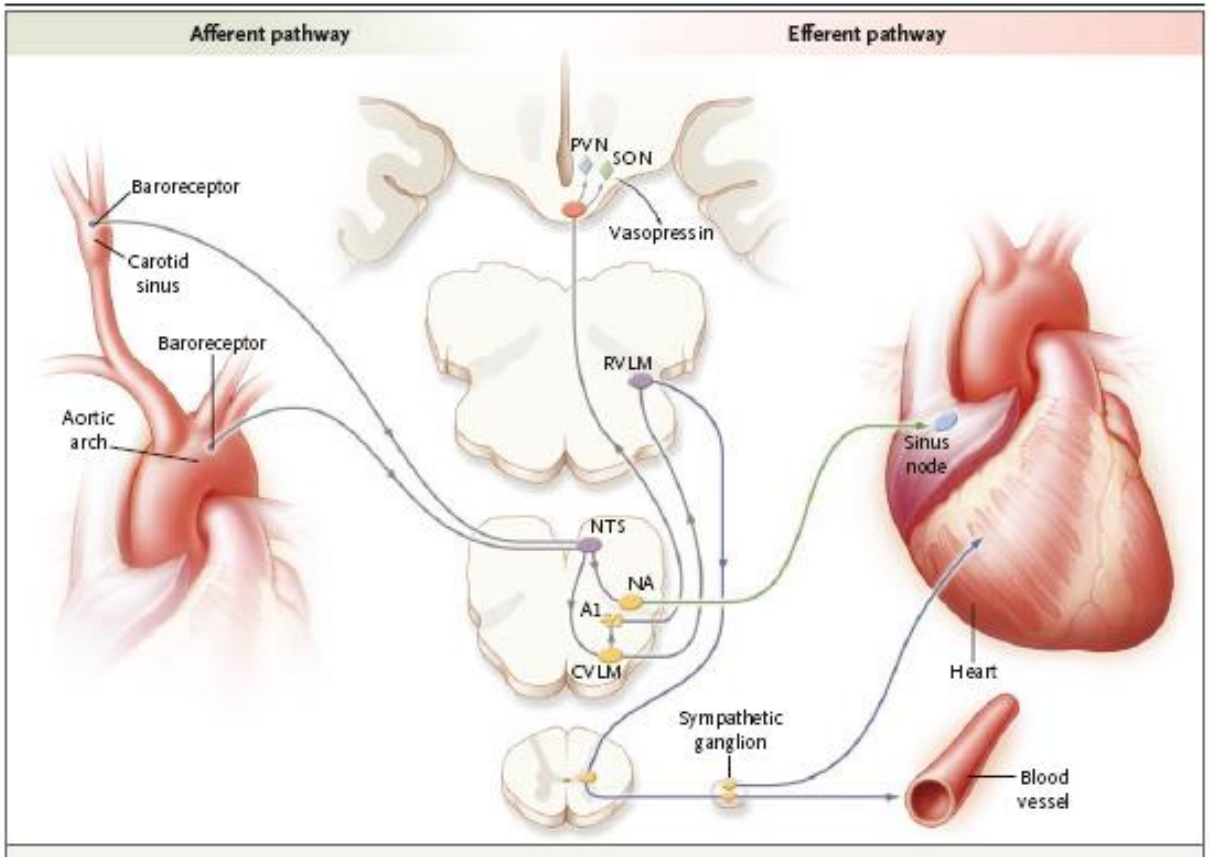


Sakakibara et al., 2001



Hahn and Ebersbach, 2004

Pathophysiology of cardiovascular autonomic failure



Freeman, 2008

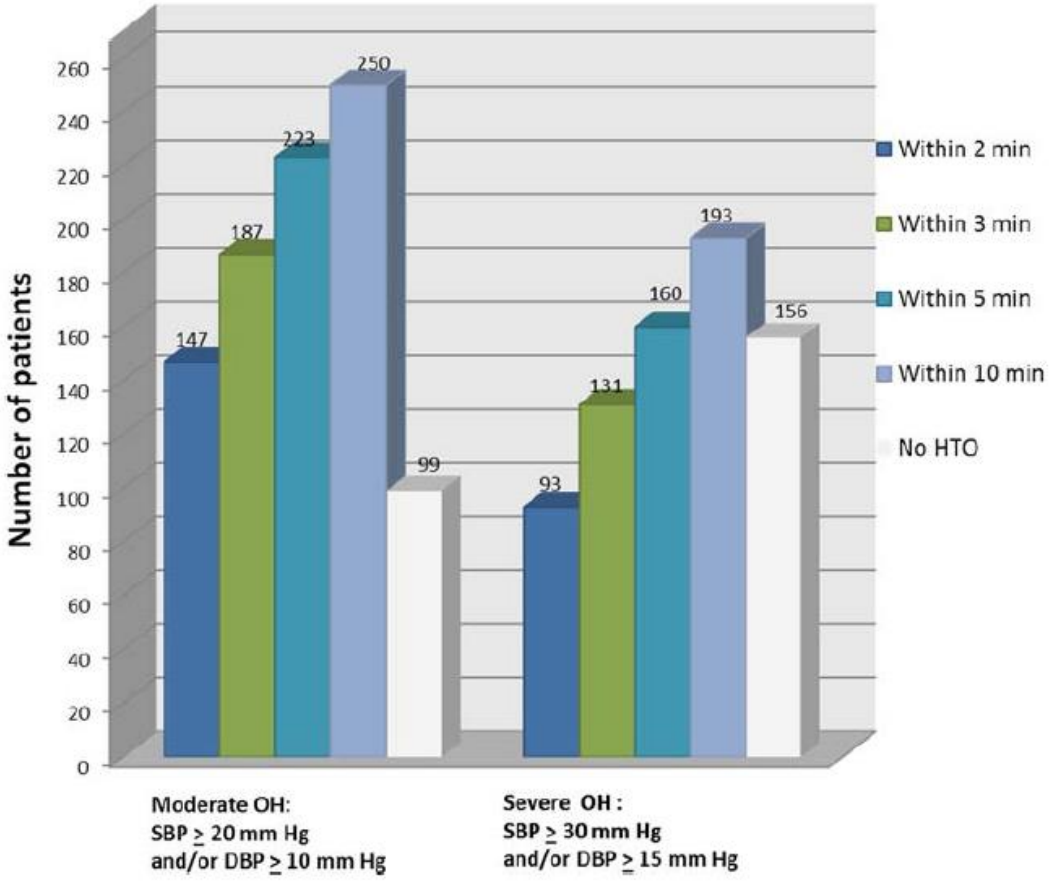
Autonomic

RESEARCH PAPER

New insights into orthostatic hypotension in multiple system atrophy: a European multicentre cohort study

A Pavy-Le Traon,[1,2] A Piedvache,[3] S Perez-Lloret,[4,5] G Calandra-Buonaura,[6,7] V Cochen-De Cock,[1,8] C Colosimo,[9] P Cortelli,[6,7] R Debs,[1] S Duerr,[10] A Fanciulli,[10] A Foubert-Samier,[11,12,13] A Gerdelat,[1] T Gurevich,[14] F Krismer,[10] W Poewe,[15] F Tison,[11,12,13] C Tranchant,[16] G Wenning,[10,15] O Rascol,[1,4] WG Meissner,[11,12,13] on behalf of the European MSA Study Group

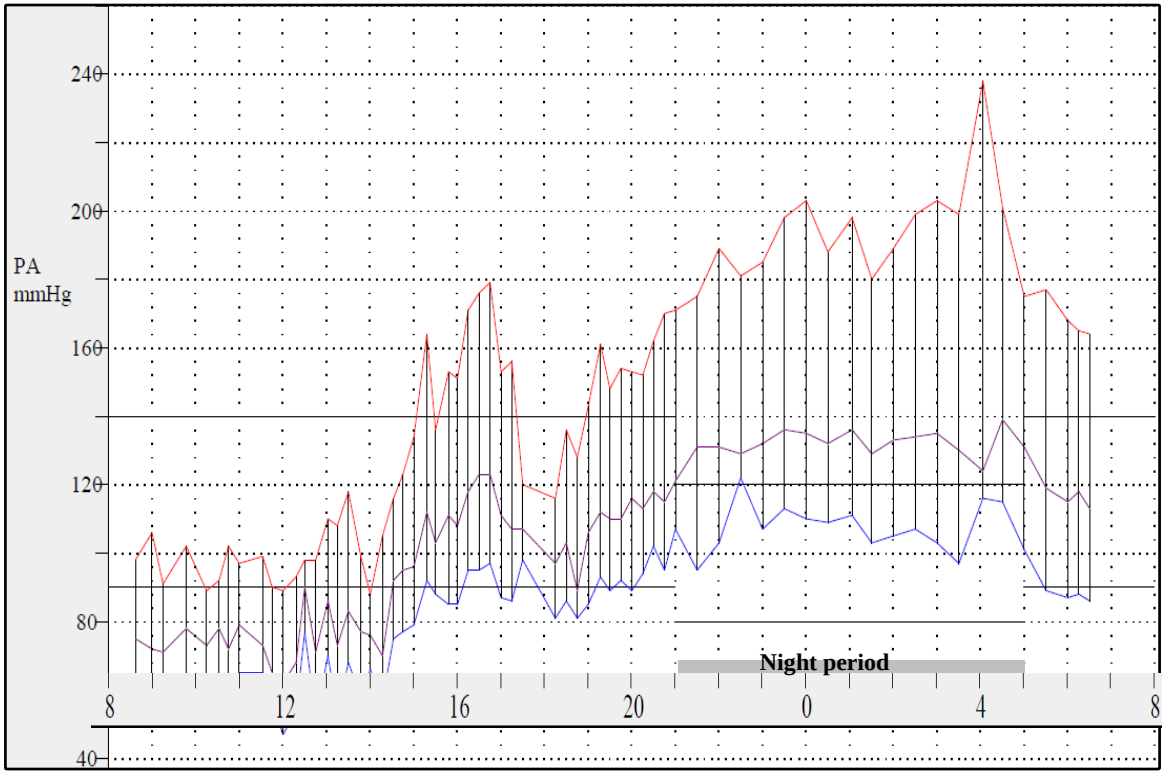
Measuring BP for 10 minutes increases sensitivity for detecting OH!



Pavy-Le Traon et al., 2016

Evaluation of cardiovascular autonomic failure

Ambulatory BP monitoring



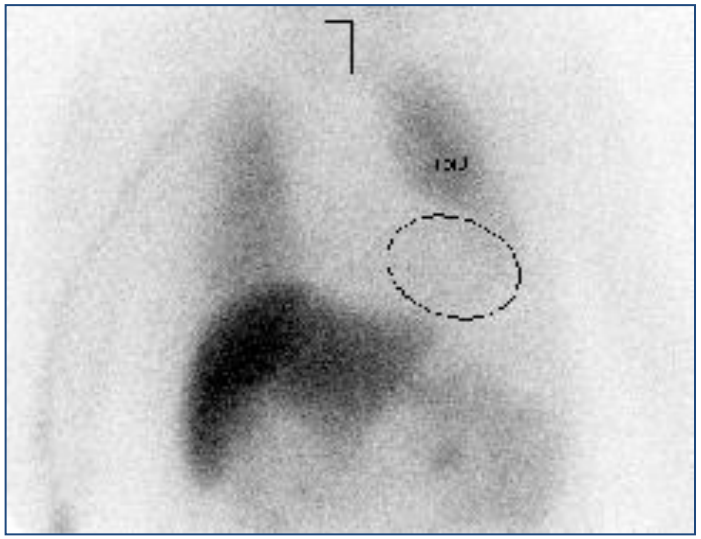
Neurogenic orthostatic hypotension and supine hypertension in chronic CV autonomic failure.

Courtesy Dr A. Pavy-Le-Traon, Toulouse

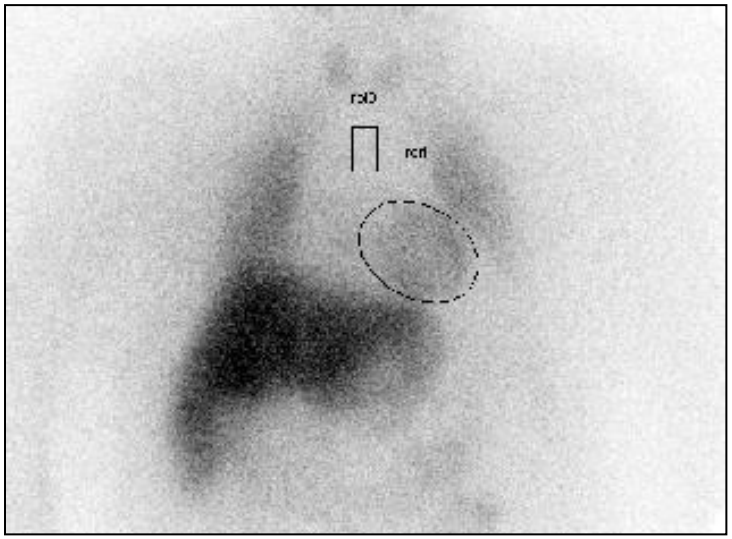
Evaluation of cardiovascular autonomic failure

MIBG SPECT

PD



MSA



MIBG uptake is reduced in PD indicating postganglionic denervation.

Braune et al., 1999

Question 2 (multiple right)

What are useful imaging modalities to support the diagnosis of MSA?

A. Dopamine transporter (DAT) SPECT
B. MRI
C. MIBG SPECT
D. FDG-PET
E. IBZM SPECT

Treatment – motor symptoms

- L-dopa (transient, but some patients with sustained response)
- Amantadine
- DBS = no
- Focal dystonia (limbs): Botulinum toxin
- Drooling: Be careful with botulinum toxin!
- Physiotherapy, speech therapy
- Walking aids/wheel chair
- Adjustment of environment to increasing disability
- PEG?

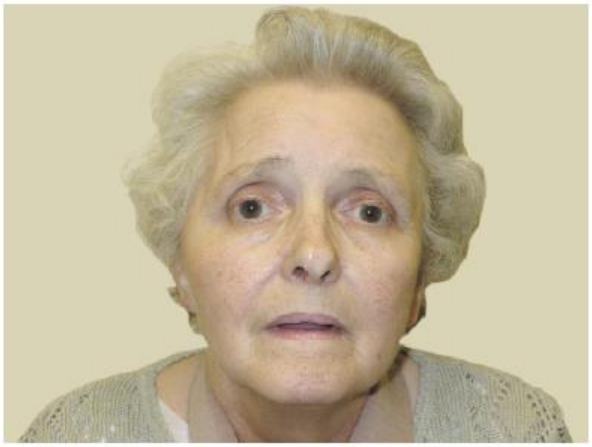
Treatment – non-motor signs

- Autonomic symptoms
  - OH (non-pharmacological, midodrine, fludrocortisone, droxidopa, other)
  - Urinary disturbances (anticholinergics, intermittent catherization)
  - Other (e.g. constipation)
- Mood disorders
- Stridor and sleep apnea (CPAP, trachestomy)

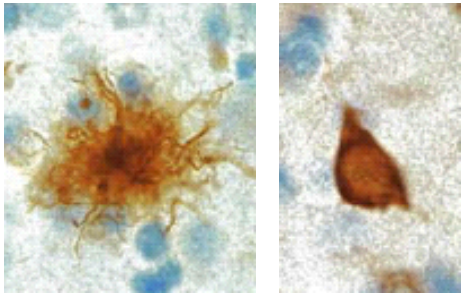
Progressive supranuclear palsy

Clinical signs

- Axial parkinsonism, weak l-dopa response
- Early postural instability and falls
- Vertical gaze palsy
- Early cognitive dysfunction (apathy, executive dysfunction)



Intraglial tau inclusions



Burn et al., 2002

Clinical spectrum of PSP

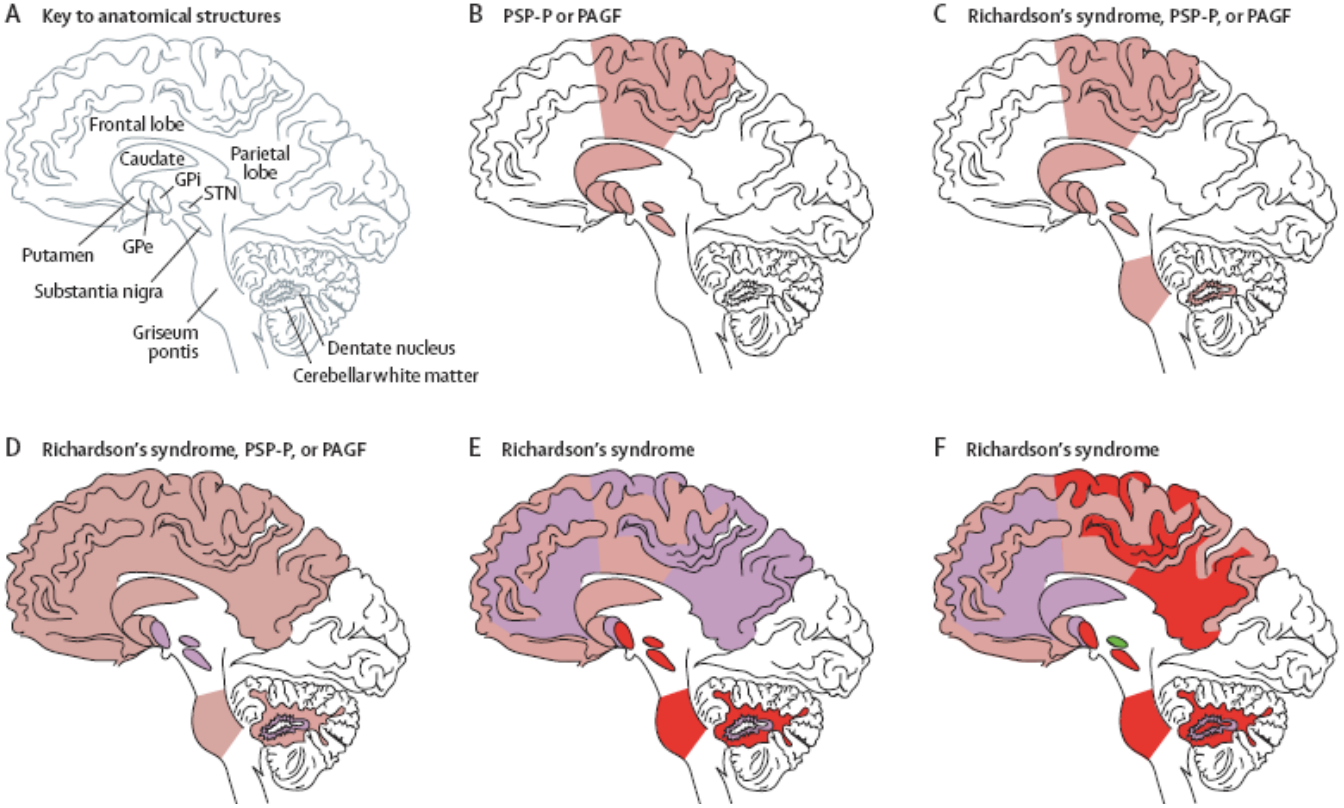
	Richardson's syndrome	PSP-P	PSP-PAGF	PSP-CBS	PSP-PNFA	Parkinson's disease
Rigidity	Axial much more than limb	Axial less than or the same as limb	Axial	Yes	Sometimes	Limb much more than axial
Bradykinesia	Mild	Moderate	Moderate	Yes	Mild	Moderate
Tremor	No	Yes/no (rest or jerky postural)	No	No	No	Yes (at rest)
Early falls	Yes	No	No	Sometimes	Sometimes	No
Early postural instability	Yes	No	Yes	..	..	No
Early cognitive decline	Often	No	No	No	Yes	No
Early abnormalities of eye movement	Yes	No	No	No	Sometimes	No
Response to levodopa	No	Often	No	No	No	Usually
Hyposmia	No	No	..	..	..	Yes
Cardiac MIBG	Normal	Normal*	Normal*	..	..	Abnormal

PSP=progressive supranuclear palsy. CBS=corticobasal syndrome. PAGF=pure akinesia with gait freezing. PNFA=progressive non-fluent aphasia. MIGB=^{123}I-labelled meta-iodobenzylguanidine. ..=unknown. *Author's unpublished data.

Table 1: **Clinical features of Richardson's syndrome, PSP-PAGF, PSP-CBS, PSP-PNFA, and Parkinson's disease**

Williams and Lees, 2009

Clinical spectrum of PSP



Williams and Lees, 2009

Question 3 (single right)

What is the most frequent PSP predominance type ?

A. PSP with predominant parkinsonism (PSP-P)
B. PSP with Richardson's syndrome (PSP-RS)
C. PSP with progressive gait freezing (PSP-PGF)
D. PSP with predominant corticobasal syndrome (PSP-CBS)
E. PSP with predominant speech/language disorder (PSP-SL)

New consensus diagnosis criteria

TABLE 2. Core clinical features

Levels of Certainty	Functional Domain			
	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

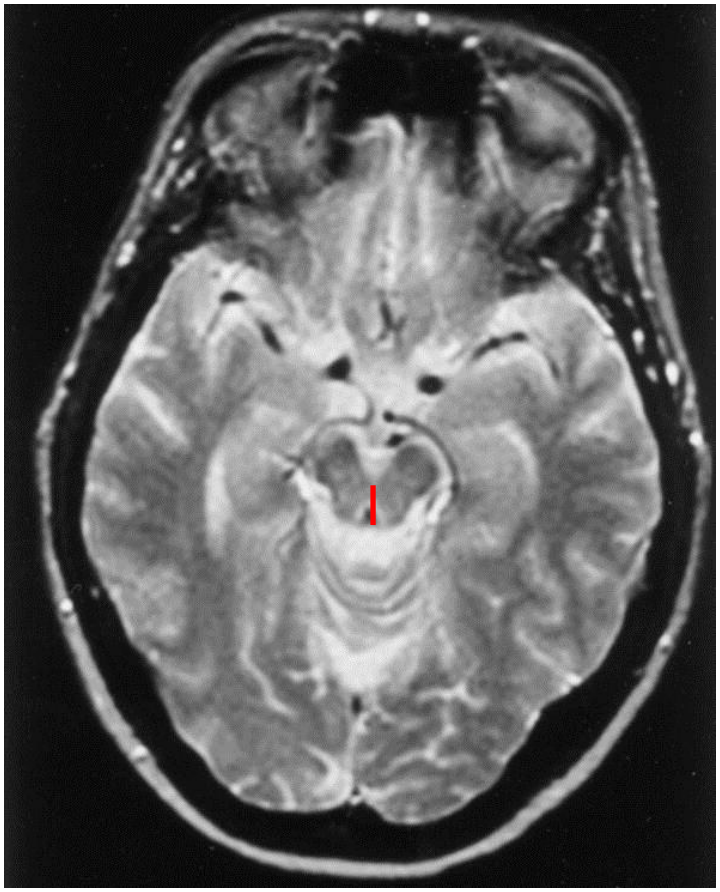
Hoeglinger et al., 2017

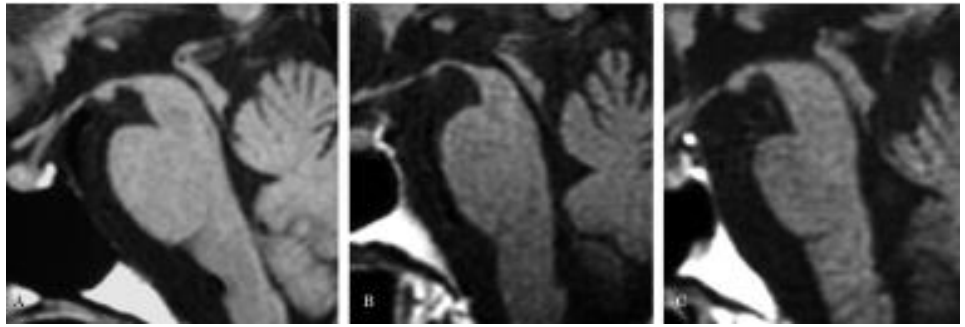
New consensus diagnosis criteria

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 *Suitable for therapeutic and biological studies*	(O1 or O2) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
		(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 *Suitable for descriptive epidemiological studies and clinical care*	O1	PSP with predominant ocular motor dysfunction	poss. PSP-OM
		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
Suggestive of PSP	Suggestive of PSP, but not passing the threshold for possible or probable PSP *Suitable for early identification*	O2 or O3	PSP with predominant ocular motor dysfunction	s.o. PSP-OM
		P1 or P2	PSP with predominant postural instability	s.o. PSP-PI
		O3 + (P2 or P3)	PSP with Richardson's syndrome	s.o. PSP-RS
		(A2 or A3) + (O3, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with predominant parkinsonism	s.o. PSP-P
		C1	PSP with predominant speech/language disorder	s.o. PSP-SL
		C2 + (O3 or P3)	PSP with predominant frontal presentation	s.o. PSP-F
		C3	PSP with predominant CBS	s.o. PSP-CBS

Hoeglinger et al., 2017

Paraclinical investigations – MRI



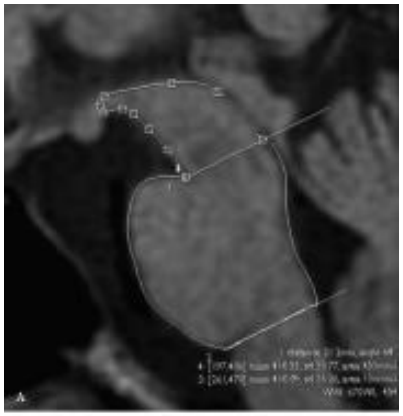


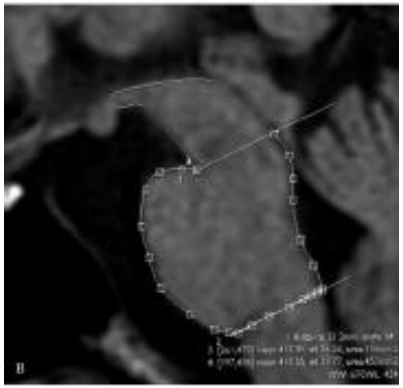
- Midbrain atrophy (diameter<17mm)
- “Mickey mouse sign”
- “Hummingbird sign”
- “Morning glory sign”

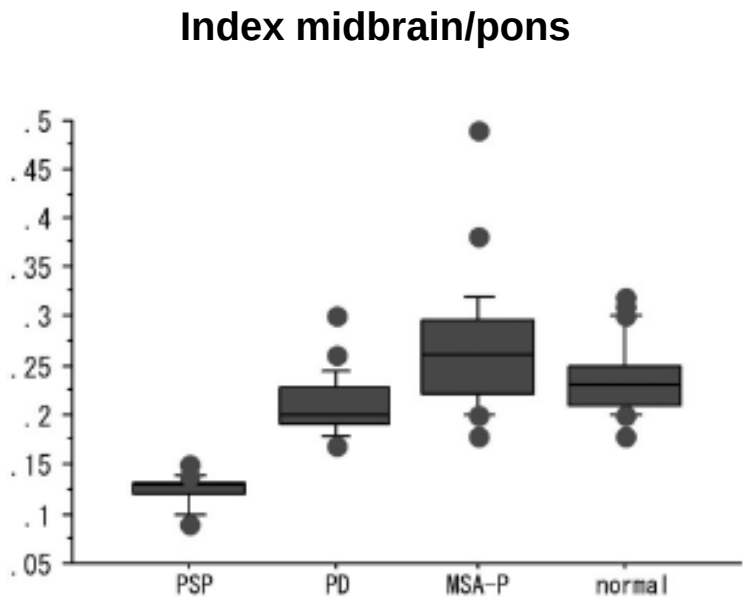
- Pallidal and putaminal atrophy
- Atrophy of superior cerebellar peduncle

Schrag et al, 2001; Oba et al., 2005

Paraclinical investigations – MRI





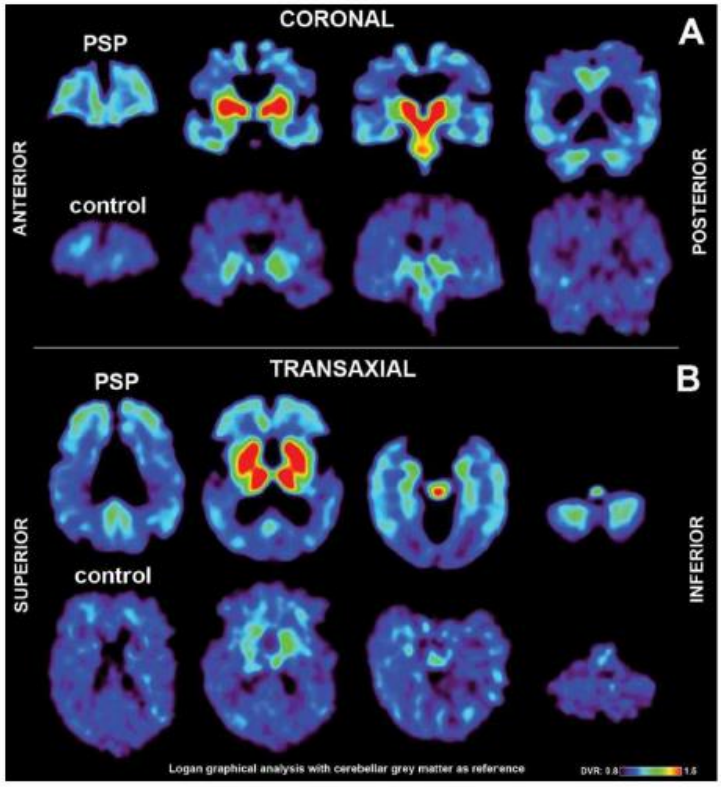


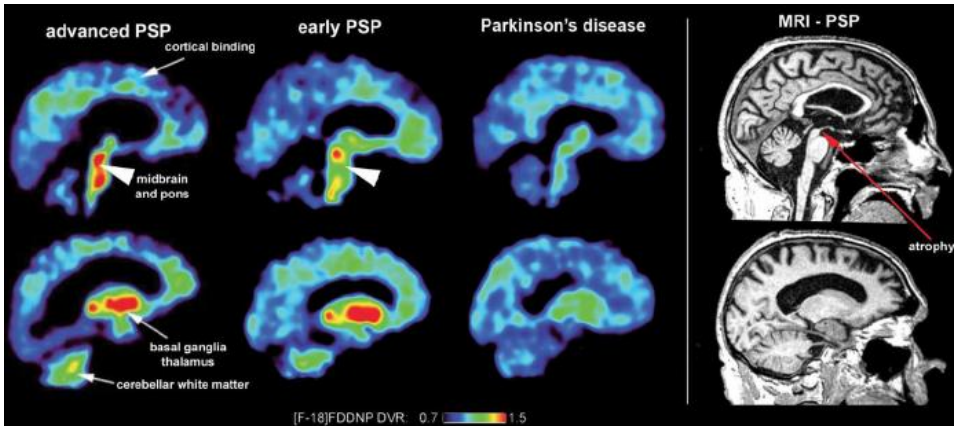
For an index < 0.015, sensitivity and specificity are 100% for the diagnosis of PSP.

Oba et al., 2005

Paraclinical investigations

18F-FDDNP pTau PET

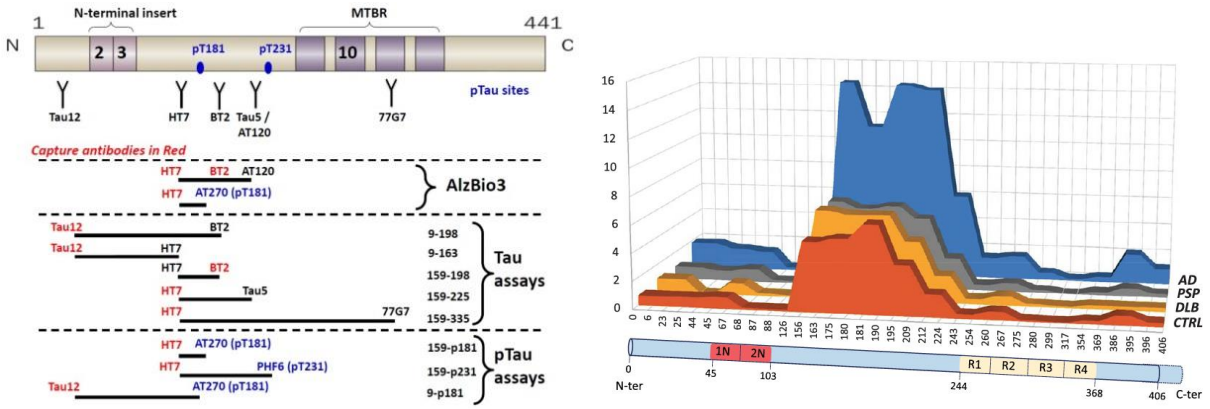




Current ligands show limited binding to 4R tau and have therefore limited interested for the diagnosis of PSP/CBD.

Kepe et al., 2013

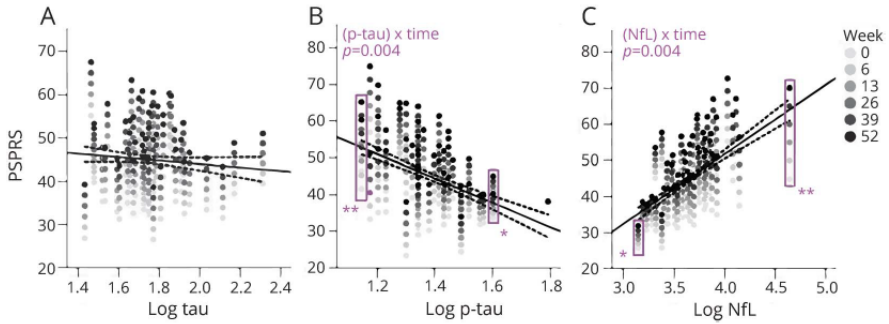
Fluid biomarker in PSP



pTau181 CSF levels inconsistent across studies, but potential for more detailed tau profiling.

Meredith et al., 2013, Barthelemy et al., 2016

Figure 1 Progressive Supranuclear Palsy Rating Scale (PSPRS) change predicted by baseline CSF biomarker concentration



Baseline NfL and pTau181 CSF levels predict progression of PSPRS.

Rojas et al., 2018

Treatment – motor signs

- L-dopa = transient response in PSP-P (less effective/ineffective in other forms)
- Botulinum toxin injection may be considered for eyelid opening apraxia
- PPN-DBS = no consistent effect
- Modest benefit of coenzyme Q10 in small trial, not confirmed in larger RCT; all other RCT were negative
- Physiotherapy, speech therapy
- Adjustment of environment to increasing disability
- Eye prisms are sometimes useful
- Place of PEG?

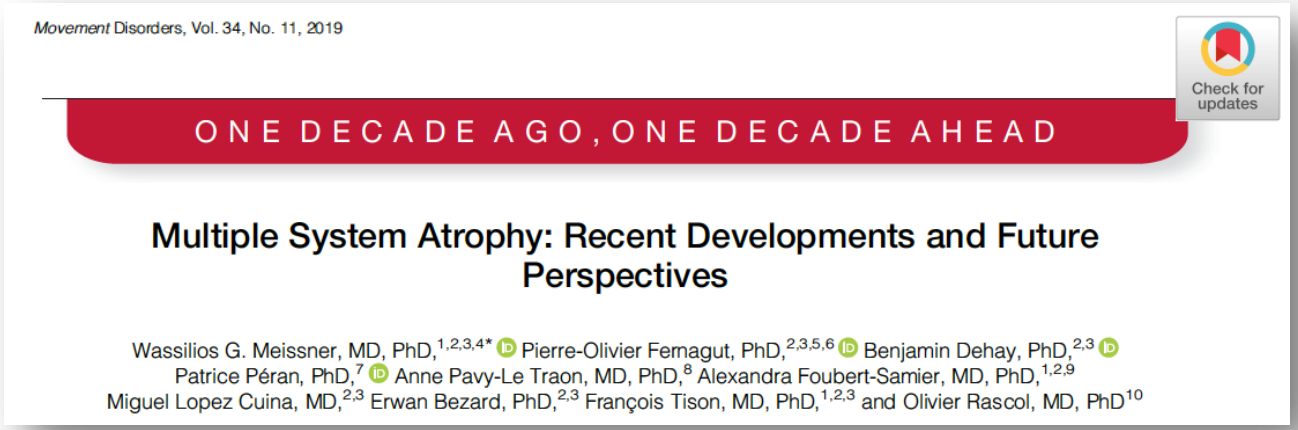
Treatment – non-motor signs

- Mood disorders (antidepressants, psychological support)
- Apathy
- Behavioral disturbances
- Cognitive impairment
- Autonomic dysfunction

Key Points /Conclusions

- The differential diagnosis between atypical parkinsonian disorders can be challenging in early disease stages.
- The screening for clinical red flag signs is key, while they sometimes only emerge after several years.
- Imaging may provide guidance, but can be normal in early disease stages.
- Some symptomatic treatments are available, especially for autonomic dysfunction.
- Disease-modifying/neuroprotective strategies remain an unmet need.

Two recent reviews on MSA and PSP for further reading...

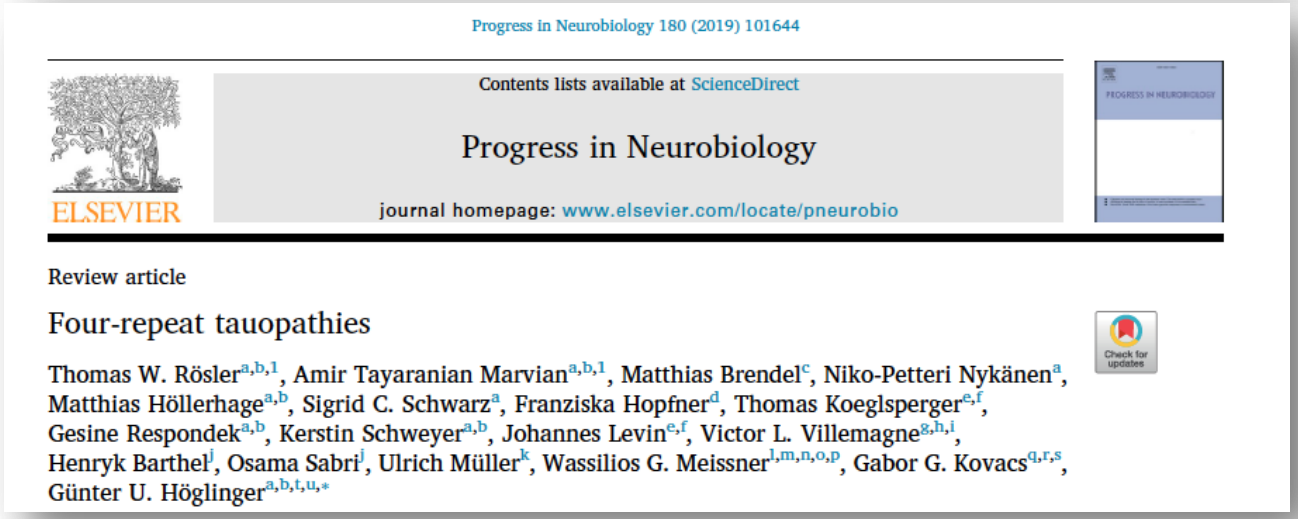


Movement Disorders, Vol. 34, No. 11, 2019

ONE DECADE AGO, ONE DECADE AHEAD

Multiple System Atrophy: Recent Developments and Future Perspectives

Wassilios G. Meissner, MD, PhD,[1,2,3,4*] Pierre-Olivier Fernagut, PhD,[2,3,5,6] Benjamin Dehay, PhD,[2,3] Patrice Péran, PhD,[7] Anne Pavy-Le Traon, MD, PhD,[8] Alexandra Foubert-Samier, MD, PhD,[1,2,9] Miguel Lopez Cuina, MD,[2,3] Erwan Bezard, PhD,[2,3] François Tison, MD, PhD,[1,2,3] and Olivier Rascol, MD, PhD[10]



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Review article

Four-repeat tauopathies

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Joint webinar series

THANK YOU

Next Webinar: 'Hypomyelination'

21. April 2020, 15-16h CET