Associazione Italiana per lo studio del Sistema NeuroVegetativo

Corso di Aggiornamento AINV 2024

La disautonomia nella pratica clinica: diagnosi e strategie terapeutiche

Treia, 4 ottobre 2024

# Pure Autonomic Failure e Alpha-sinucleina

Dott. Luca Baldelli

Dipartimento di Scienze Biomediche e Neuromotorie (DIBINEM) – Università di Bologna

IRCCS Istituto delle Scienze Neurologiche di Bologna

luca.baldelli4@unibo.it

# ♂ 58 yo

## Reason for referral

7 year-history of urinary urgency, frequency and impaired urinary flow, associated with erectile dysfunction

- **Family and medical history:**
  - Not relevant
- **Ongoing therapy:**
  - Atorvastatin 20mg/day
- **Further history:**
  - Episodes of blurred vision and instability when standing, particularly in hot weather and after meals
  - No losses of consciousness

***Orthostatic hypotension?***

***Clinical signs of Parkinsonism / Dementia?***

# ♂ 58 yo

## Reason for referral

7 year-history of urinary urgency, frequency and impaired urinary flow, associated with erectile dysfunction

- **Clinical evaluation:**
  - Neurological examination was normal. MMSE: 30/30.
  - Blood pressure (BP) measurement during standing test revealed Orthostatic Hypotension (OH)

- **Standing test**
  - BP supine: 139/76mmHg HR: 78bpm
  - BP standing 3rd minute: 111/62mmHg HR 83bpm
  - ΔHR/ΔSBP ratio = 0,28 → neurogenic OH

***Isolated neurogenic autonomic failure***

# ♂ 58 yo

## Diagnostic workup

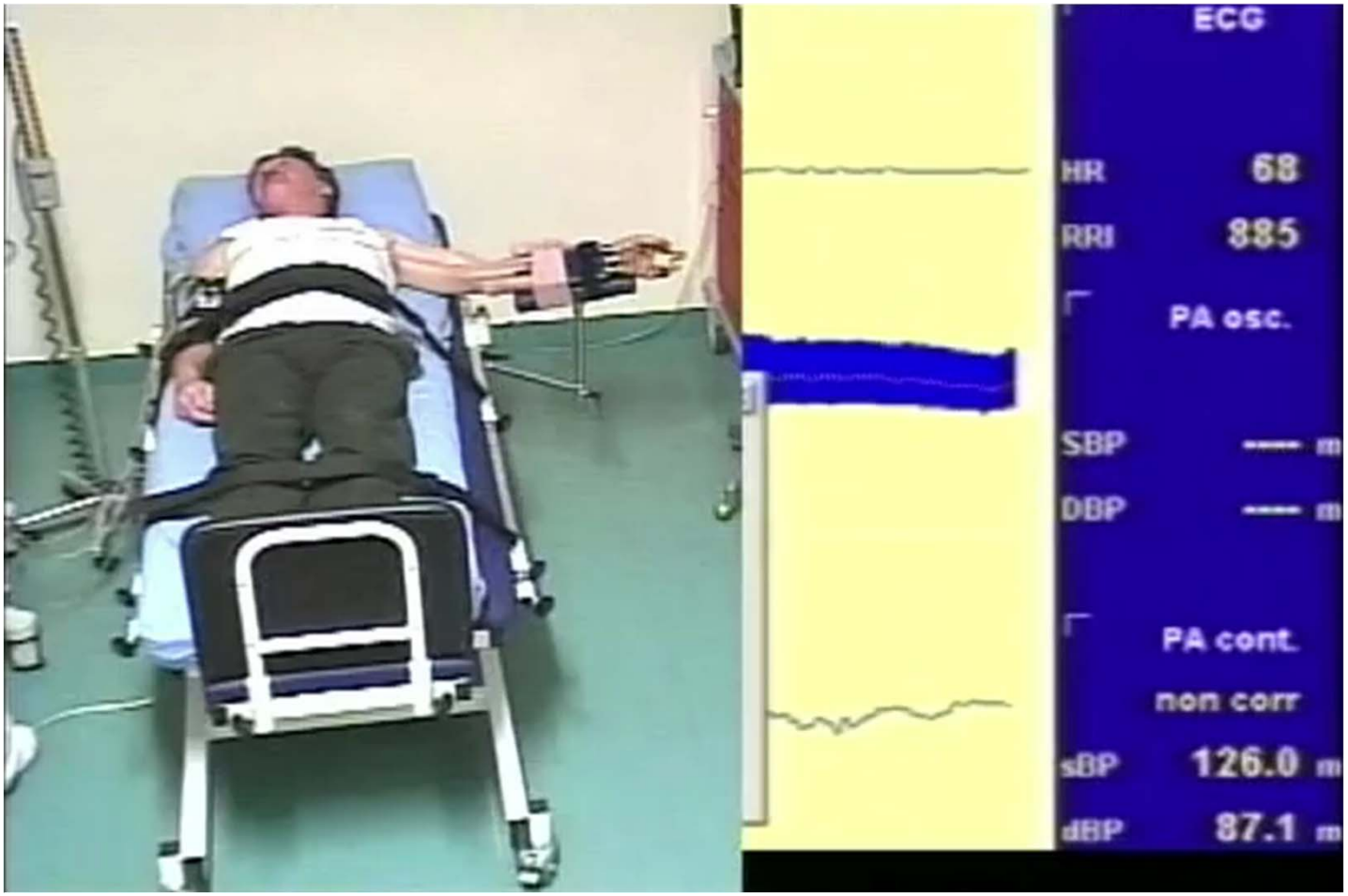
- Urodynamic study consistent with neurogenic bladder. Post-void residual: 160ml.
- Hematological, biochemical, immunological tests (including paraneoplastic, infectious, metabolic and autoimmune screening tests): normal → Secondary causes of OH were excluded
- Antibodies to the neuronal nicotinic acetylcholine receptor: negative
- Cardiological evaluation: negative
- Brain MRI: normal
- Cerebrospinal fluid analysis: normal
- Nerve conduction studies and electromyography (EMG): normal
- vPSG: normal sleep efficiency. Physiological muscular atonia during REM sleep.

***(Pure) neurogenic autonomic failure***

*Goldstein 2009*

# ♂ 58 yo

## Cardiovascular reflexes tests (CRT)



# ♂ 58 yo

## Cardiovascular reflexes tests (CRT)

- CRTs confirmed OH (delayed) and showed absence of phase IV BP overshoot of the Valsalva maneuver, a sign of sympathetic failure.
- Plasma noradrenaline (NA) reported normal values in the supine position with no increase during standing.

## Other autonomic and imaging tests

- A 24 hour-assessment of BP revealed supine systolic hypertension (SH) and absence of the physiological nocturnal decrease of BP (non-dipper pattern).
- Iodine-123 meta-iodobenzylguanidine (MIBG) myocardial scintigraphy showed normal cardiac sympathetic innervation.

***Central (Pure) neurogenic autonomic failure with OH and SH***

*Freeman 2011*

# ♂ 58 yo

## Diagnosis

- Considering the long duration of Autonomic failure, the normal neurological examination after 7 years from autonomic symptoms onset and the results of pharmacological tests, a diagnosis of PAF was made.

## Management

- The patient started treatment with droxidopa and fludrocortisone, with good response

# ♂ 66 yo → Follow-up

- Evaluated at least once a year during the disease course
- 8 years after the onset of autonomic symptoms, he experienced a worsening of autonomic symptoms and complained of less dexterity in his right leg
- During the history update the patient referred since the previous year several episodes where he could shout, kick and punch, referring that he was dreaming of quarreling with someone. He fell from bed during these episodes twice.
- Examination: rigidity and bradykinesia of his right limbs, gait ataxia and bilateral hyper-reflexia with bilateral Babinski sign

***development of parkinsonian, cerebellar and pyramidal signs***

# ♂ 66 yo → Follow-up

## Diagnostic workup

- Brain MRI was repeated and showed thinning of cerebellar peduncles.
- Dopamine transporter imaging (DaTSCAN) showed reduced uptake in the caudate and putamen bilaterally.
- CTRs confirmed previous results, showing a worsening of OH.
- Nocturnal videopolysomnography (VPSG) loss of physiological muscle atonia in REM sleep and absence of stridor

## Management

- Patient started treatment with levodopa without any significant clinical improvement and developed oro-lingual and left hand dyskinesias

***Clinically established MSA with predominant parkinsonism (MSA-P)***

*Wenning 2022*

# MSA Criteria

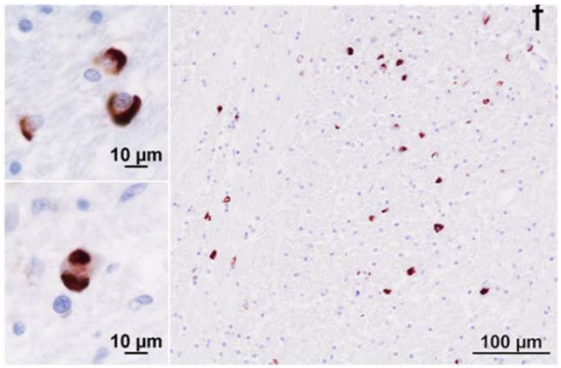
| | | |
|---|---|---|
| **Essential features** | A sporadic, progressive adult (>30 years) onset disease | |
| | **Clinically established MSA** | **Clinically probable MSA** |
| **Core clinical features** | 1. Autonomic dysfunction defined as (at least one is required)<br>○ Unexplained voiding difficulties with post-void urinary residual volume ≥100 mL<br>○ Unexplained urinary urge incontinence<br>○ Neurogenic OH (≥20/10 mmHg blood pressure drop) within 3 minutes of standing or head-up tilt test<br>and at least one of<br>1. Poorly L-dopa-responsive parkinsonism<br>2. Cerebellar syndrome (at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features) | At least two of: |
| **Supportive clinical (motor or non-motor) features** | At least two | **Supportive clinical features**<br>**Supportive motor features**<br>Rapid progression within 3 years of motor onset<br>Moderate to severe postural instability within 3 years of motor onset<br>Craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia<br>Severe speech impairment within 3 years of motor onset<br>Severe dysphagia within 3 years of motor onset<br>Unexplained Babinski sign<br>Jerky myoclonic postural or kinetic tremor<br>Postural deformities<br>**Supportive non-motor features**<br>Stridor<br>Inspiratory sighs<br>Cold discolored hands and feet<br>Erectile dysfunction (below age of 60 years for clinically probable MSA)<br>Pathologic laughter or crying |
| **MRI marker** | At least one | **MRI markers of clinically established MSA**<br>Each affected brain region as evidenced by either atrophy or increased diffusivity counts as one MRI marker.<br>For MSA-P<br>• Atrophy of:<br>○ Putamen (and signal decrease on iron-sensitive sequences)<br>○ Middle cerebellar peduncle<br>○ pons<br>○ Cerebellum<br>• "Hot cross bun" sign<br>For MSA-C<br>• Atrophy of:<br>○ Putamen (and signal decrease on iron-sensitive sequences)<br>○ Infratentorial structures (pons and middle cerebellar peduncle)<br>• "Hot cross bun" sign |
| **Exclusion criteria** | Absence | |

# Subsequent Follow-up

- Over the following three years, he developed hypophonia, symmetrical and severe parkinsonism with camptocormic posture and Pisa syndrome. He became wheelchair bound due to severe gait ataxia and OH
- He died of pneumonia 11 years after autonomic symptom onset

**Neuropathology**

Intracellular protein aggregates of alpha-synuclein in oligodendroglial cells, consistent with GCI, in the white matter of basis pons, mesencephalus, medulla oblongata, thalamus and basal ganglia




***Neuropathologically established MSA***

*Wenning 2022*

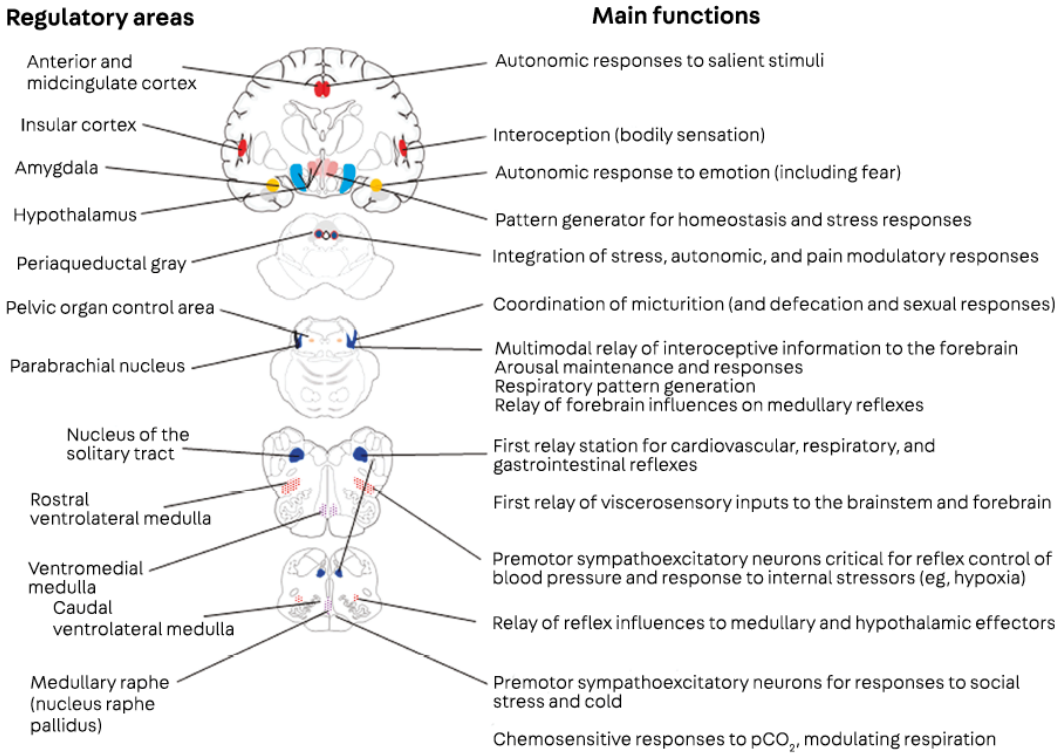
## EARLY CLINICAL MANIFESTATIONS OF ALPHA-SYNUCLEINOPATHIES IS BECOMING A STRONG RESEARCH FOCUS

- Cohort studies of individuals generated novel insight into the conversion of this group into clinically established synucleinopathies.
  - Pure/Isolated autonomic failure (PAF/IAF)

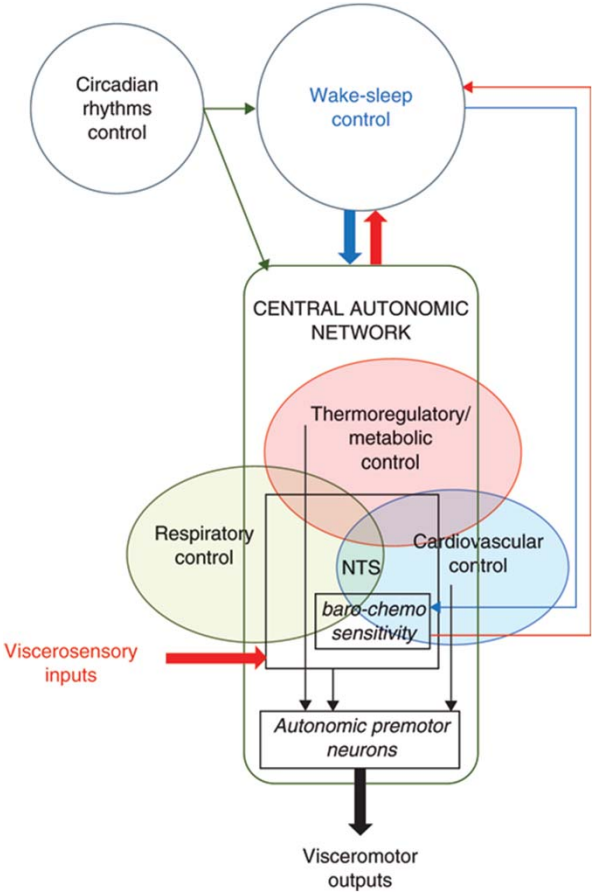
    and….

  - Isolated RBD

# Autonomic nervous system and sleep – Diffuse complexity – 1



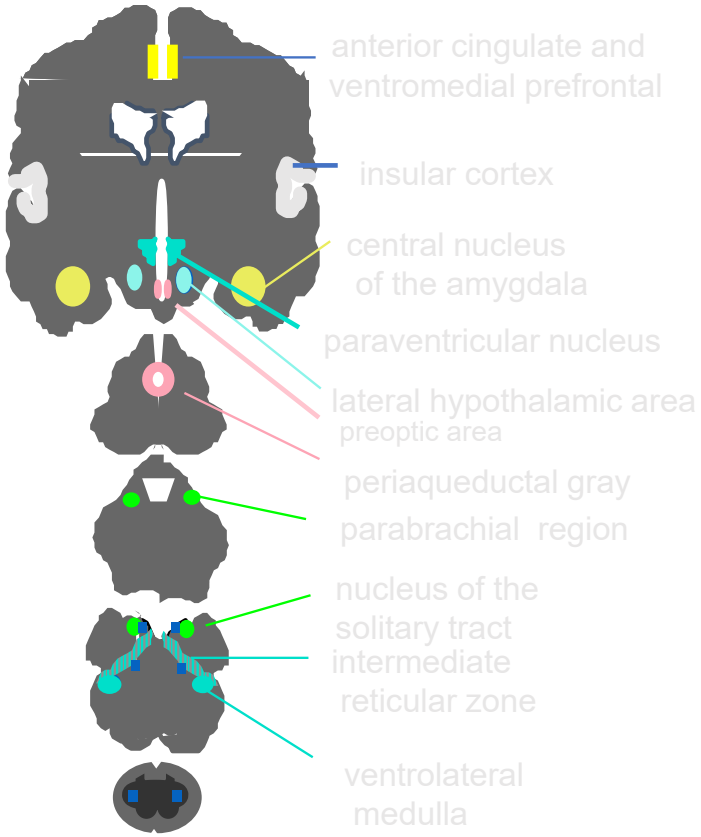

Benarroch, Continuum Neurol, 2020



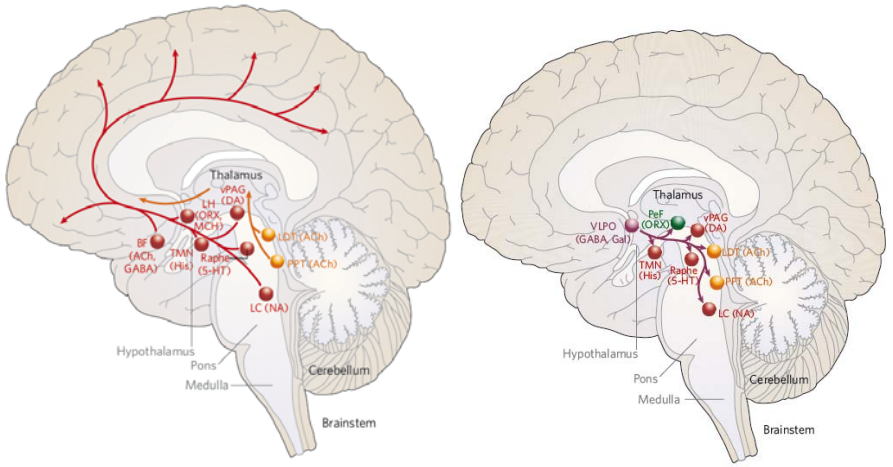

Amici and Zoccoli, in Autonomic Nervous System and Sleep, 2021

# Autonomic nervous system and sleep – Diffuse complexity – 2

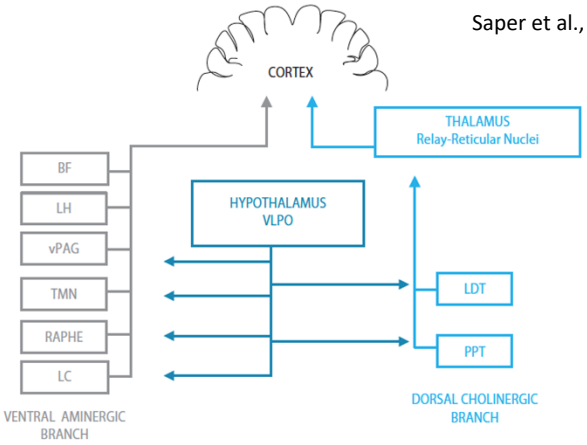
There is a close relationship between the autonomic nervous system and sleep from both biological and clinical perspectives. The neuronal populations participating in the transition from wake to sleep and in the subsequent development of the sleep stages are localized near to and reciprocally interconnected with the ANS areas involved in cardiovascular control.




**Central autonomic network**

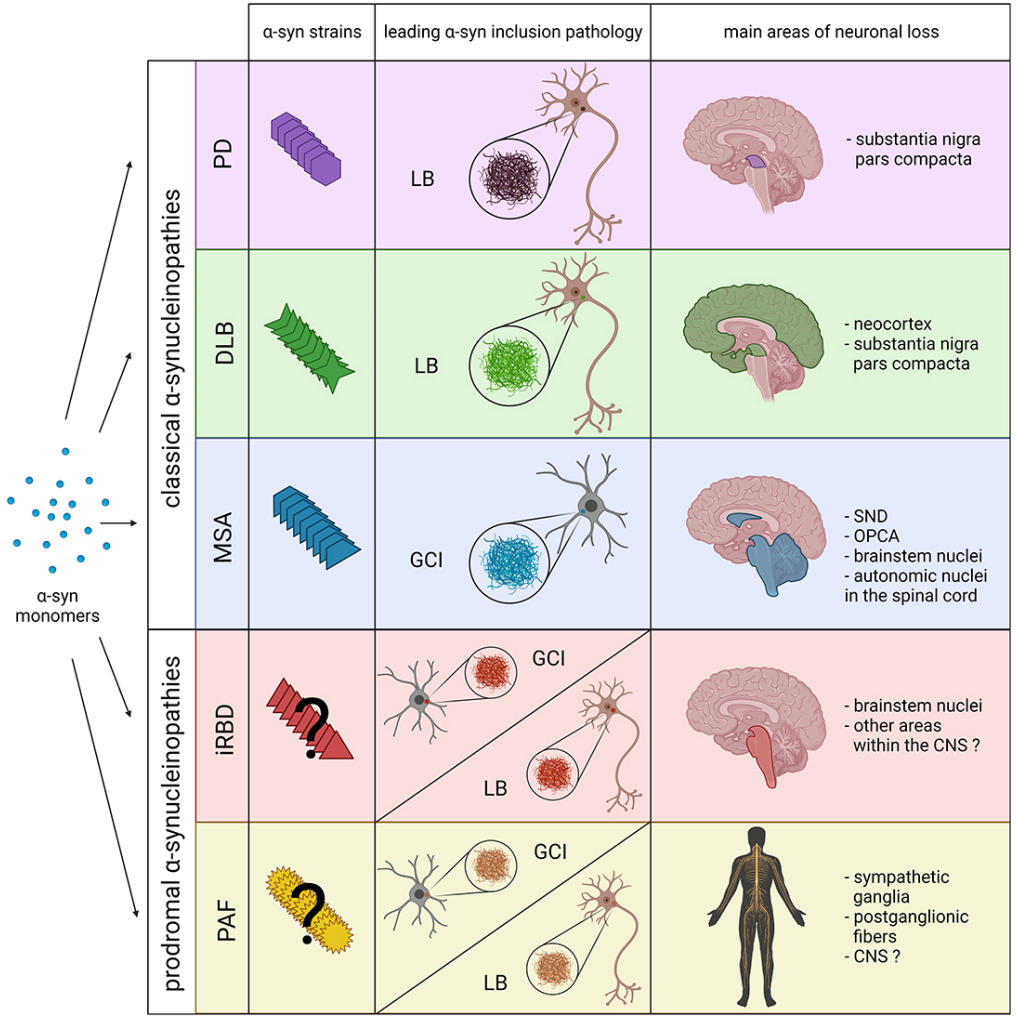



Saper et al., Nature 2005

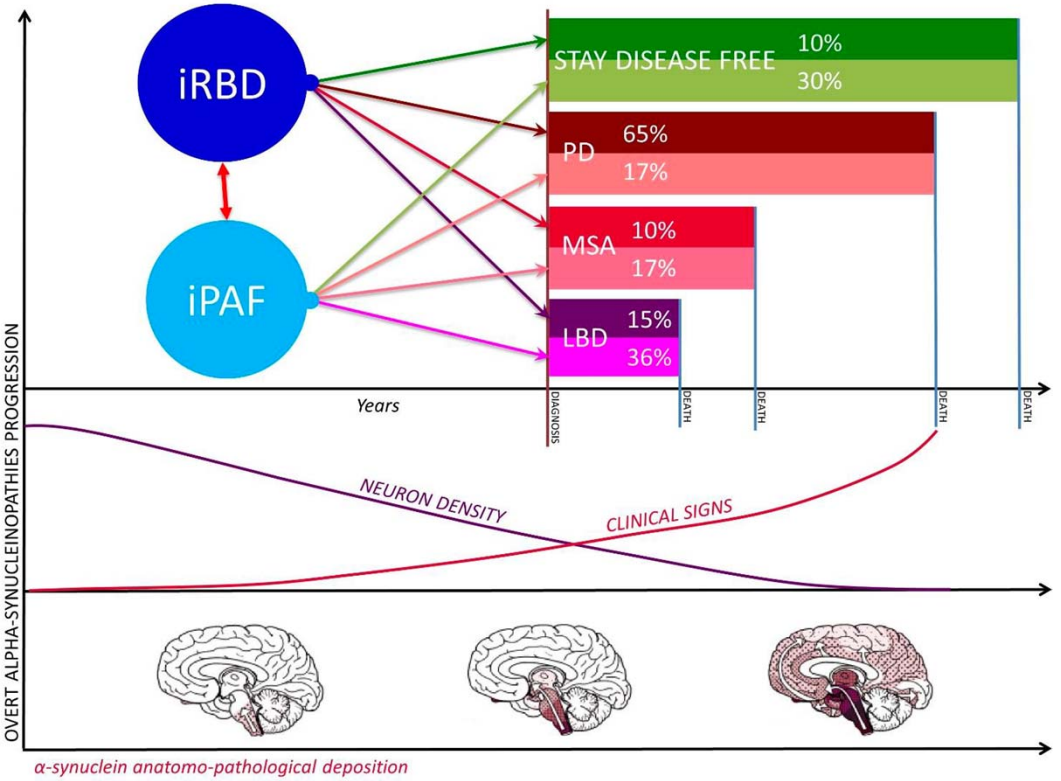



Montagna et al., 2008

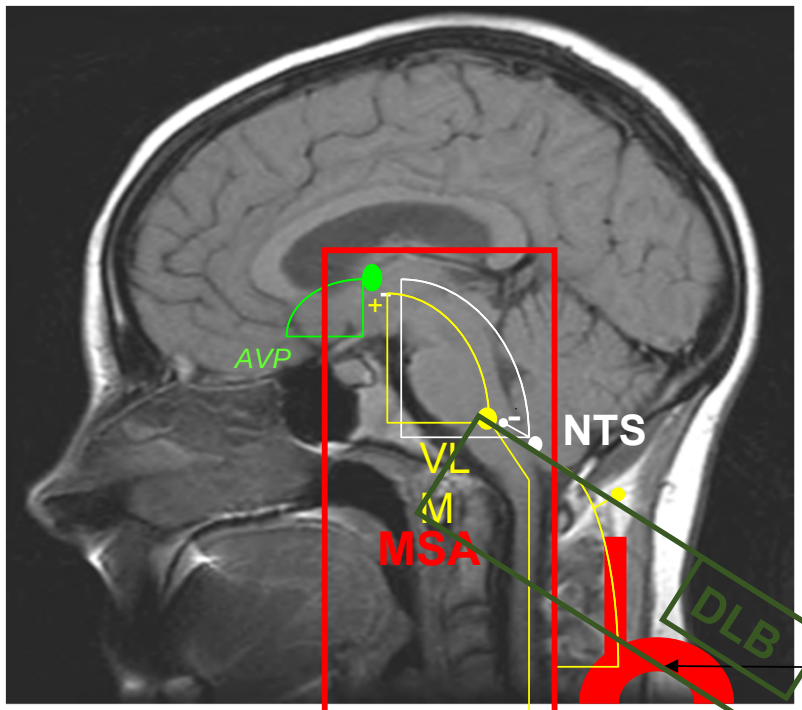
# Alpha-synucleinopathies

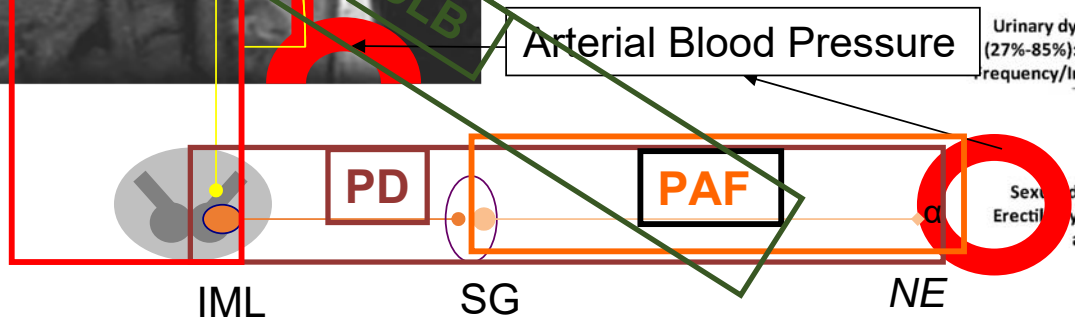


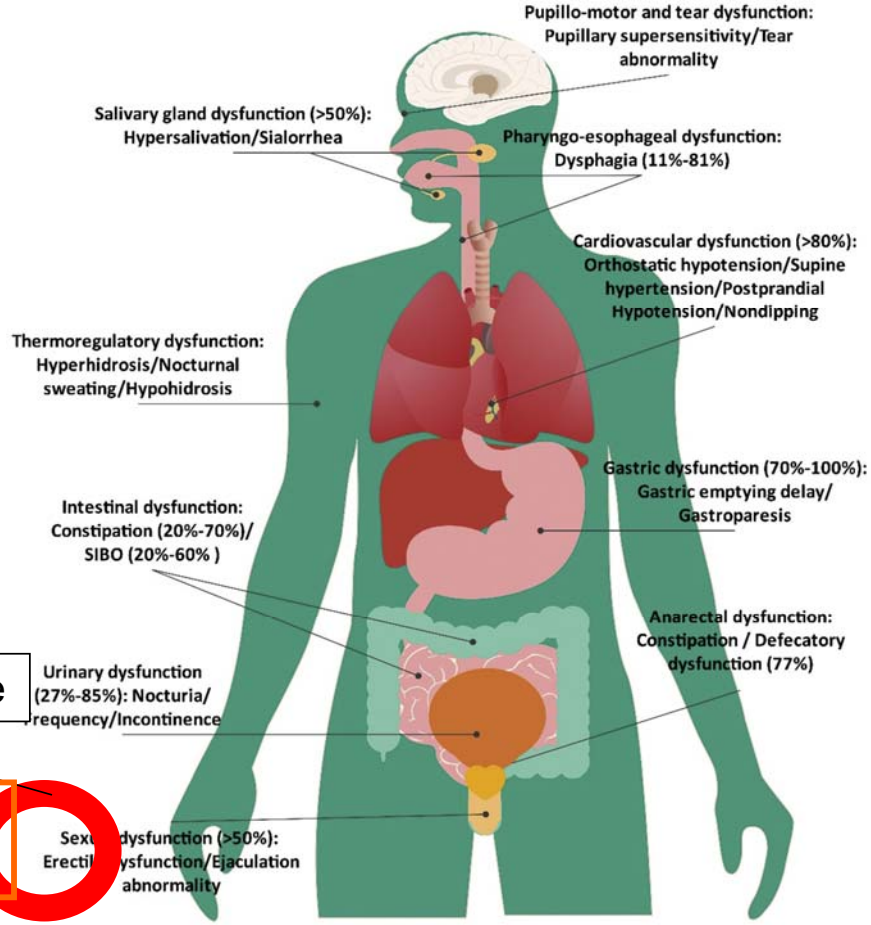

Malfertheiner, Front Neurol, 2021



# Autonomic impairment in alpha-synucleinopathies



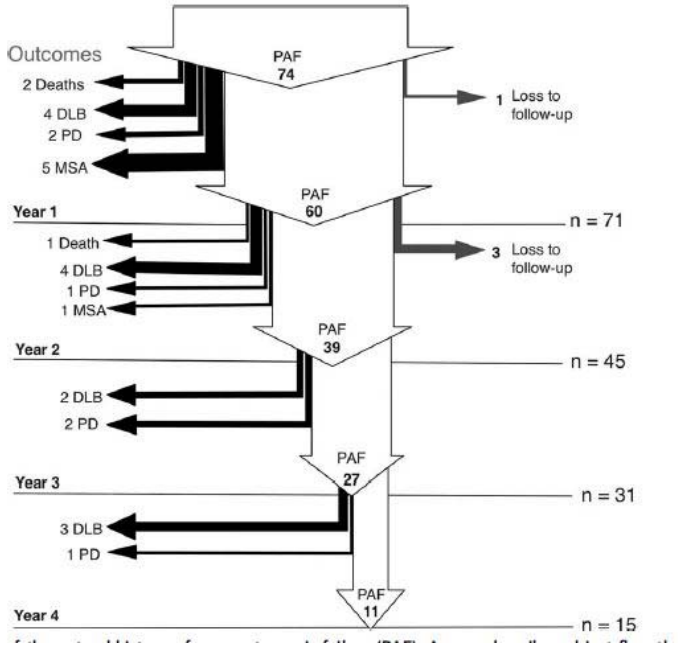




Chen et al., Neurobiol Dis, 2020

# PREMOTOR

## Natural History of Pure Autonomic Failure: A United States Prospective Cohort

Horacio Kaufmann, MD,[1] Lucy Norcliffe-Kaufmann, PhD,[1]
Jose-Alberto Palma, MD, PhD,[1] Italo Biaggioni, MD,[2] Phillip A. Low, MD,[3]




Prospective study
- 100 consecutive patients with IAF
- 74 subjects longitudinally followed up
- 34% of cumulative incidence of phenoconversion during a limited 4-year follow-up period (around 14% per year)

## Pure autonomic failure

Predictors of conversion to clinical CNS involvement

Wolfgang Singer, MD
Sarah E. Berini, MD
Paola Sandroni, MD
Robert D. Fealey, MD
Elizabeth A. Coon, MD
Mariana D. Suarez
Eduardo E. Benarroch, MD
Phillip A. Low, MD

Retrospective cohort study
- 318 patients with a nOH diagnosis at the initial evaluation
- 79 subjects followed up for at least 3-years
- Estimated conversion rate between 12% and 48% (38/318 and 38/79)

# Pure autonomic failure

## Predictors of conversion to clinical CNS involvement

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Neurology 2017;88:1129-1136

**Table 2** Predictors of conversion to multiple system atrophy (MSA) and to Parkinson disease (PD)/dementia with Lewy bodies (DLB)

| | MSA converters (n = 22) | Stable PAF (n = 41) | Odds ratio |
|---|---|---|---|
| CASS vagal score <2, n (%) | 15 (68) | 13 (33) | 4.3 (1.4–13.1) |
| Preganglionic sweat loss pattern, n (%) | 14 (78) | 15 (45) | 4.2 (1.1–15.5) |
| Severe bladder dysfunction, n (%) | 11 (55) | 3 (8) | 14.7 (3.4–63.8) |
| Supine NE >100 pg/mL, n (%) | 16 (89) | 7 (28) | 20.6 (3.7–113.7) |
| Subtle motor signs, n (%) | 7 (32) | 5 (12) | 3.4 (0.9–12.3) |
| | PD/DLB converters (n = 11) | Stable PAF (n = 41) | Odds ratio |
| CASS total score <7, n (%) | 8 (89) | 9 (24) | 25.8 (2.8–234.8) |
| Orthostatic NE rise >65 pg/mL, n (%) | 7 (100) | 11 (44) | 18.9[a] (6.4–55.8) |
| Subtle motor signs, n (%) | 5 (45) | 5 (12) | 6.0 (1.3–27.2) |

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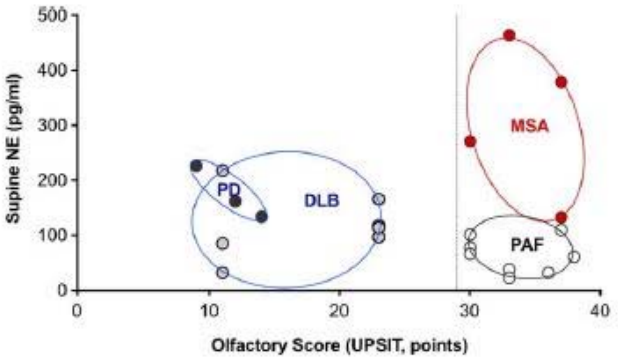
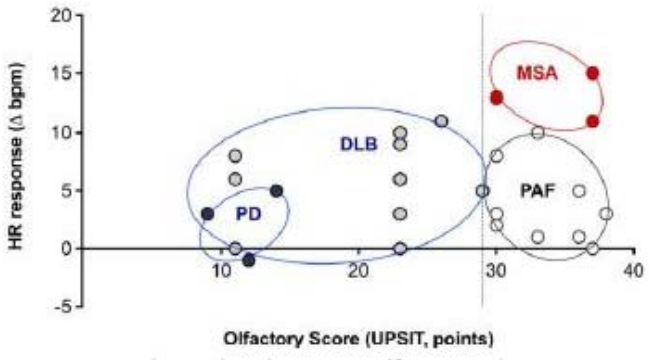



## Risk Prediction for Phenoconversion

- Probable RBD strongly associated with phenoconversion (OR: 7.1, CI: 1.5–33.5)
- Probable RBD + deficits in olfaction (UPSIT<30) → phenoconversion to PD/DLB (OR: 6.3, CI: 1.3–29).
- Probable RBD + preserved olfaction (UPSIT>30) → phenoconversion to MSA (OR: 22.5, CI: 3.8–51).
- Supine HR>70bpm + supine plasma NE>110pg/ml → phenoconversion to MSA (OR: 18, CI:1.9–66).
- Supine HR<70bpm + HR response to tilt<10bpm → phenoconversion to PD/DLB (OR: 4.8, CI: 1.4–16).

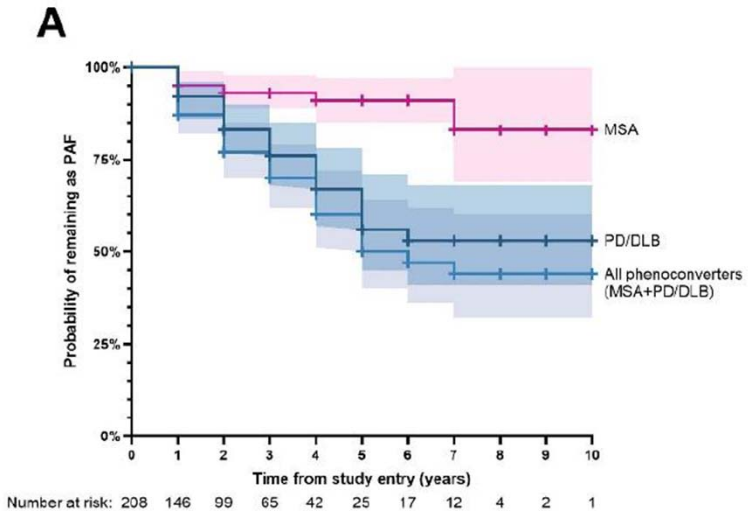
# Phenoconversion in pure autonomic failure: a multicentre prospective longitudinal cohort study

Patricio Millar Vernetti,[1] Lucy Norcliffe-Kaufmann,[1] Jose-Alberto Palma,[1] Italo Biaggioni,[2] Cyndya A. Shibao,[2] Amanda Peltier,[2] Roy Freeman,[3] Christopher Gibbons,[3] David S. Goldstein,[4] Phillip A. Low,[5] Wolfgang Singer,[5] Elizabeth A. Coon,[5] Mitchell G. Miglis,[6] Gregor K. Wenning,[7] Alessandra Fanciulli,[7] Steven Vernino,[8] Rebecca A Betensky[9] and Horacio Kaufmann[1]

***Brain. 2024***

209 participants with PAF with a median disease duration of 6 years (IQR: 3-10)
143 (68%) had evidence of subtle motor signs

**146 participants completed baseline**
**33**% phenoconverted (median of 6 years after enrollment)
PD n=20, 42%
DLB n=17, 35%
**MSA n=11**, 23% (7 MSA-P, 4 MSA-C)



**Phenoconversion in pure autonomic failure: a multicentre prospective longitudinal cohort study**

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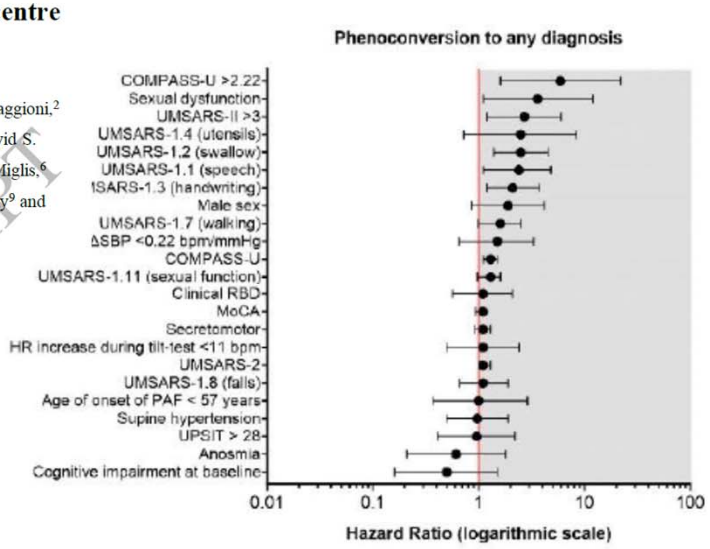
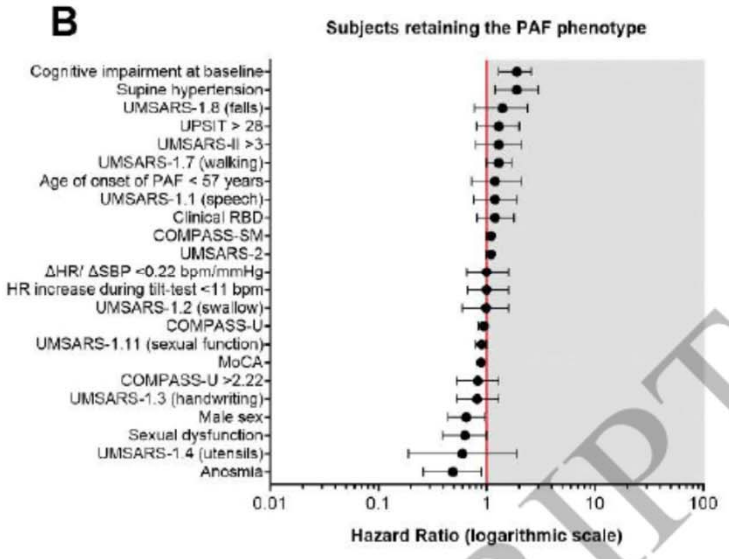
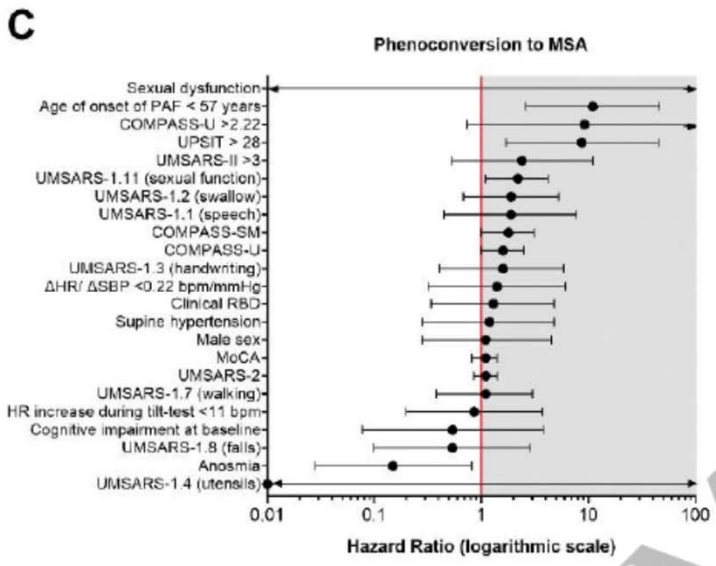
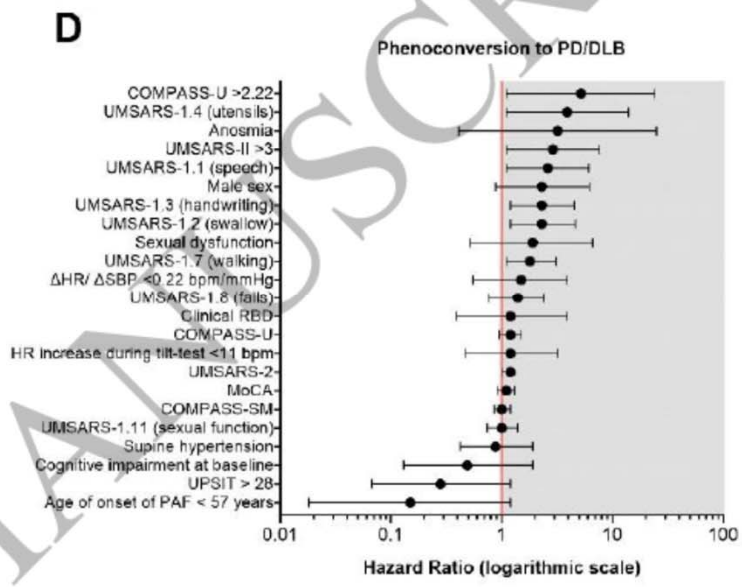
Urinary symptoms were important predictors of phenoconversion, especially to MSA.



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# The natural history of idiopathic autonomic failure

## The IAF-BO cohort study

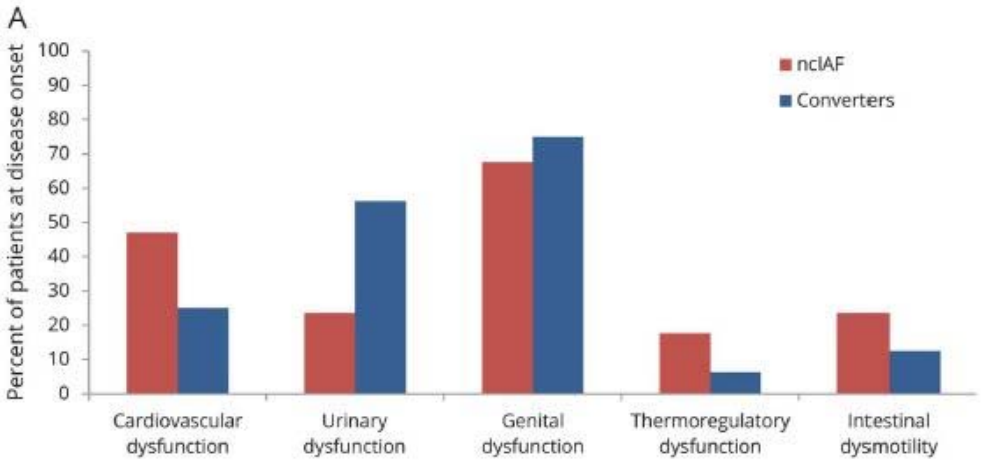
Giulia Giannini, MD,* Giovanna Calandra-Buonaura, MD, PhD,* Gian Maria Asioli, MD, Annagrazia Cecere, MSc, Giorgio Barletta, MSc, Francesco Mignani, MSc, Stefano Ratti, MD, Pietro Guaraldi, MD, PhD, Federica Provini, MD, PhD, and Pietro Cortelli, MD, PhD

**Correspondence**
Dr. Cortelli
pietro.cortelli@uni

*Neurology*® 2018;91:e1245-e1254. doi:10.1212/WNL.0000000000006243

Retrospective study

- 98 patients showing IAF
- 50 patients with a 5-year history of IAF longitudinally followed up and without subtle nonspecific neurologic deficits at the time of enrolment
- 16 (32%) of phenoconversion to a manifest central nervous system synucleinopathy
- 10 patients with MSA, 2 DLB, 1 PD, 3 undefined parkinsonism.

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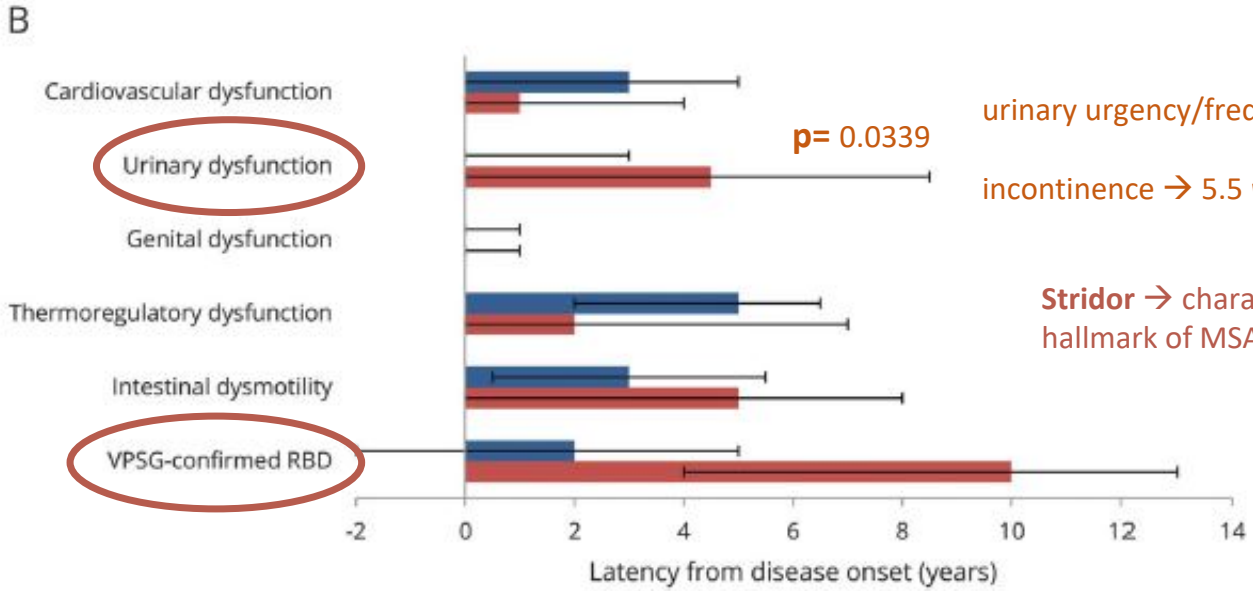
**The converters group more frequently presented with urinary dysfunction (75.0% vs. 32.4%, p = 0.035)**




**p=** 0.0339

urinary urgency/frequency → 0 *vs.* 4.5 y (p = 0.0480)

incontinence → 5.5 *vs.* 13 y (p = 0.0357)

**Stridor** → characteristic of converters groups, i.e., a hallmark of MSA

**p= 0.0281**

**Table 4** Variables associated with conversion to other synucleinopathies in the univariate Cox regression analysis

| Variable | n | Unadjusted hazard ratio (95% CI) | *p* Value |
|---|---|---|---|
| Age at disease onset, y | 50 | 1.03 (0.97–1.08) | 0.378 |
| Sex | | | |
| Female | 11 | 0.22 (0.03–1.69) | 0.147 |
| Male | 39 | 1.0 (reference) | |
| Clinical variables at onset | | | |
| Early symptomatic nOH | 30 | 0.84 (0.28–2.50) | 0.750 |
| Early urgency/frequency | 18 | 2.90 (0.91–9.26) | 0.073 |
| Early urinary retention | 13 | 2.16 (0.54–8.67) | 0.278 |
| Early incontinence | 5 | 3.39 (0.83–13.87) | 0.090 |
| Early VPSG-confirmed RBD[a] onset | 7 | 8.05 (1.48–43.84) | 0.016 |
| Cardiovascular reflex test results | | | |
| Supine resting SBP, mm Hg | 50 | 0.99 (0.96–1.01) | 0.280 |
| Δ3-min SBP, mm Hg | 50 | 1.02 (0.99–1.04) | 0.097 |
| Supine resting DBP, mm Hg | 50 | 0.99 (0.96–1.04) | 0.960 |
| Δ3-min DBP, mm Hg | 50 | 1.02 (0.98–1.07) | 0.245 |
| Supine resting HR, bpm | 50 | 1.03 (0.97–1.08) | 0.392 |
| Δ3-min HR, bpm | 50 | 0.98 (0.92–1.05) | 0.629 |
| Supine rest HR >70 bpm | 16 | 1.11 (0.40–3.05) | 0.841 |
| Δ3-min HR >10 bpm | 17 | 1.03 (0.37–2.89) | 0.958 |
| VR ≥1.25 | 14 | 3.33 (1.24–8.97) | 0.017 |

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*Neurology*® 2018;91:e1245-e1254. doi:10.1212/WNL.0000000000006243

- **VR ≥1.25** → associated with phenoconversion
- **MIBG-SPECT** → normal heart-to-mediastinum ratio in 6 patients (4 patients with MSA and 2 with ncIAF) and a reduced ratio in 21 (3 patients with PD, 2 with DLB, and 16 with ncIAF).

frontiers in Neurology

CASE REPORT
published: 26 May 2017
doi: 10.3389/fneur.2017.00225

# Iodine-123-meta-iodobenzylguanidine Myocardial Scintigraphy in Isolated Autonomic Failure: Potential Red Flag for Future Multiple System Atrophy

*Francesca Baschieri[1†], Giovanna Calandra-Buonaura[2,3†], Annagrazia Cecere[2,3], Giorgio Barletta[2,3], Manuela Contin[2,3], Piero Parchi[2,3] and Pietro Cortelli[2,3*]*

*[1] Clinica Neurologica, Dipartimento di Medicina, Università degli Studi di Perugia, Ospedale S. Maria della Misericordia, Perugia, Italy, [2] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy, [3] IRCCS, Institute of Neurological Sciences, Bellaria Hospital, Bologna, Italy*

Pure autonomic failure is challenging as it can be the presenting feature of a central nervous system syncleinopathy such as Parkinson's disease (PD) or multiple system atrophy (MSA). Because the prognosis of MSA and PD is so different, predictive features for a possible conversion can be extremely valuable. In this paper, we report three cases (two with autopsy-proven diagnosis) that had isolated AF for many years before converting to MSA or PD. Of all the tests that were performed during the premotor stage, Iodine-123-meta-iodobenzylguanidine (MIBG) myocardial scintigraphy was predictive of the conversion to MSA. We suggest that MIBG myocardial scintigraphy, when performed in patients with isolated AF, may be a valuable predictor of conversion to MSA. On the contrary, the role of such test in parkinsonian patients irrespective of the presence of AF is still to be clarified.

long-standing isolated autonomic failure that converted to MSA after 8 and 11 years from symptom onset

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https://doi.org/10.1007/s10286-023-00987-1

RESEARCH ARTICLE

# Cardiac $^{18}$F-dopamine positron emission tomography predicts the type of phenoconversion of pure autonomic failure

Abhishek Lenka[1,2] · Risa Isonaka[1] · Courtney Holmes[1] · David S. Goldstein[1]

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## Abstract

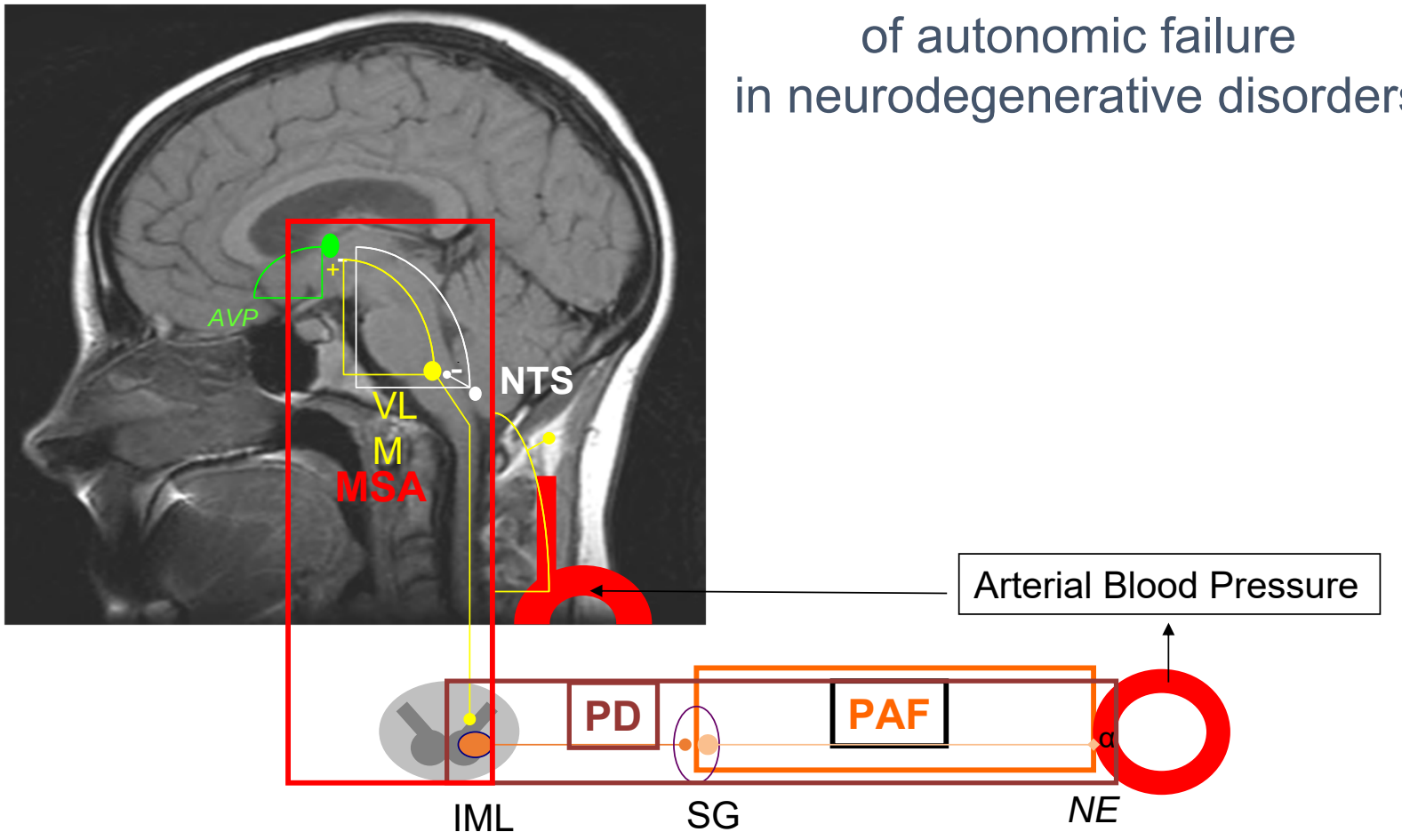
**Purpose** Pure autonomic failure (PAF) is a rare disease characterized by neurogenic orthostatic hypotension (nOH), no known secondary cause, and lack of a neurodegenerative movement or cognitive disorder. Clinically diagnosed PAF can evolve ("phenoconvert") to a central Lewy body disease [LBD, e.g., Parkinson's disease (PD) or dementia with Lewy bodies (DLB)] or to the non-LBD synucleinopathy multiple system atrophy (MSA). Since cardiac $^{18}$F-dopamine-derived radioactivity usually is low in LBDs and usually is normal in MSA, we hypothesized that patients with PAF with low cardiac $^{18}$F-dopamine-derived radioactivity would be more likely to phenoconvert to a central LBD than to MSA.

**Methods** We reviewed data from all the patients seen at the National Institutes of Health Clinical Center from 1994 to 2023 with a clinical diagnosis of PAF and data about $^{18}$F-dopamine positron emission tomography (PET).

**Results** Nineteen patients (15 with low $^{18}$F-dopamine-derived radioactivity, 4 with normal radioactivity) met the above criteria and had follow-up data. Nine (47%) phenoconverted to a central synucleinopathy over a mean of 6.6 years (range 1.5–18.8 years). All 6 patients with low cardiac $^{18}$F-dopamine-derived radioactivity who phenoconverted during follow-up developed a central LBD, whereas none of 4 patients with consistently normal $^{18}$F-dopamine PET phenoconverted to a central LBD ($p=0.0048$), 3 evolving to probable MSA and 1 upon autopsy having neither a LBD nor MSA.

**Conclusion** Cardiac $^{18}$F-dopamine PET can predict the type of phenoconversion of PAF. This capability could refine eligibility criteria for entry into disease-modification trials aimed at preventing evolution of PAF to symptomatic central LBDs.

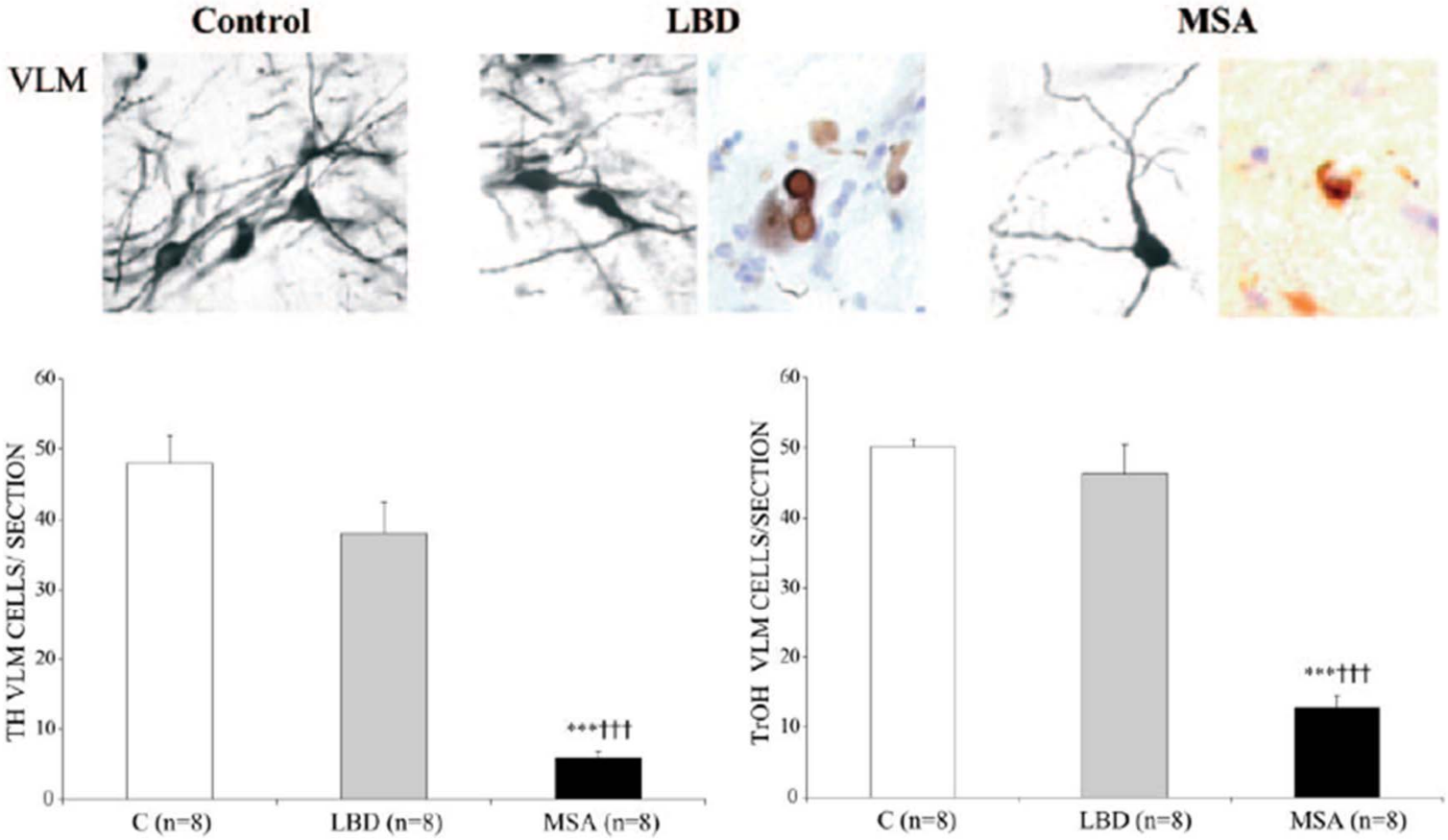
# Main substrates of autonomic failure in neurodegenerative disorders



doi:10.1093/brain/awh376 *Brain* (2005), **128**, 338–344

# Involvement of medullary regions controlling sympathetic output in Lewy body disease

Eduardo E. Benarroch,[1] Ann M. Schmeichel,[1] Phillip A. Low,[1] Bradley F. Boeve,[1,2] Paola Sandroni[1] and Joseph E. Parisi[1,3]



Clin Geriatr Med 36 (2020) 53–67
https://doi.org/10.1016/j.cger.2019.09.002

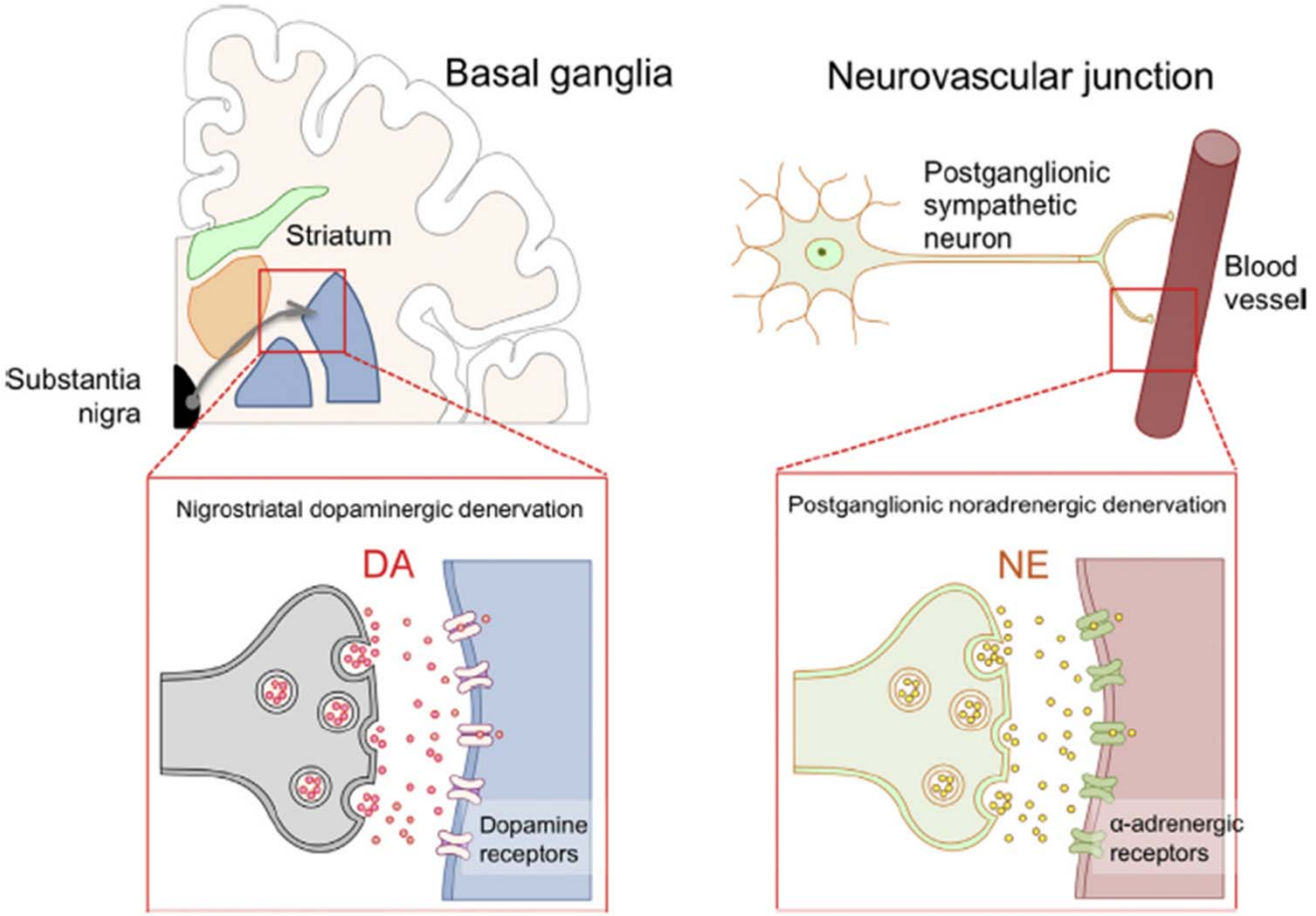



**Fig. 1.** Neurotransmitter disorders in Parkinson disease. Neurogenic orthostatic hypotension can be understood as a neurotransmitter disorder, similar to the motor dysfunction. Nigrostriatal dopaminergic denervation causing defective dopamine (DA) release results in the movement disorder, whereas postganglionic sympathetic denervation causing defective norepinephrine (NE) release when standing causes neurogenic orthostatic hypotension.

# The role of autonomic testing in the differentiation of Parkinson's disease from multiple system atrophy

Kurt Kimpinski [a], Valeria Iodice [b], Duane D. Burton [c], Michael Camilleri [d], Brian P. Mullan [e], Axel Lipp [f], Paola Sandroni [g], Tonette L. Gehrking [g], David M. Sletten [g], J.E. Ahlskog [g], Robert D. Fealey [g], Wolfgang Singer [g], Phillip A. Low [g,*]

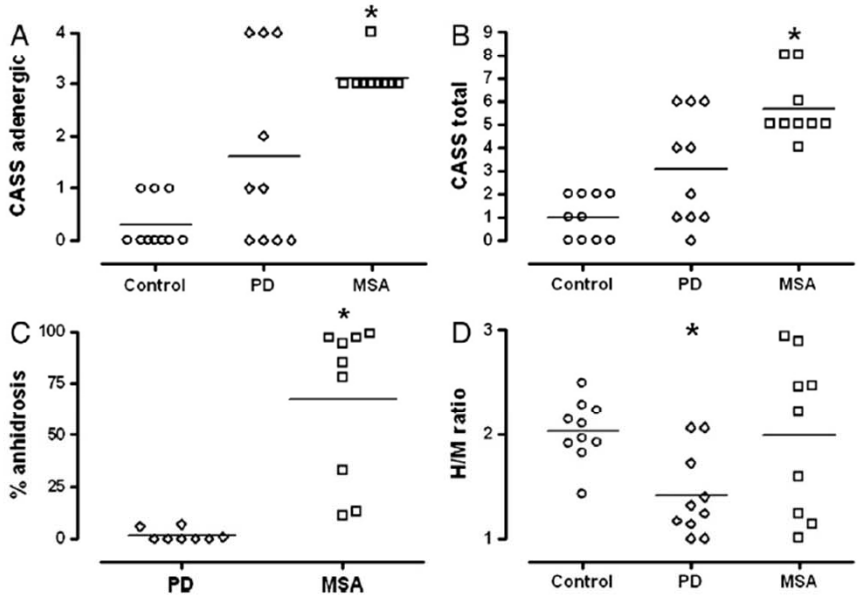



**Fig. 1.** Comparison of specific autonomic tests in the differentiation of control, PD and MSA patients. CASS scores for all three groups (control n = 10; PD n = 10; MSA n = 9) are broken down into adrenergic (A), and CASS total (B) scores. MSA patients exhibited significantly higher adrenergic and overall autonomic dysfunction compared to controls and PD patients as shown by their respective CASS scores (Kruskal–Wallis one-way analysis of variance, *$p < 0.001$ for both CASS adrenergic and CASS total scores). There was a significant increase in % anhidrosis on TST in MSA (n = 9) versus PD (n = 8) patients (C; Mann–Whitney U test, *$p < 0.001$). Heart to mediastinal (H/M) ratios for $I^{123}$ MIBG uptake at 4 h (D) are shown for control (n = 10), PD (n = 10) and MSA (n = 9) groups. Cardiac uptake of $I^{123}$ MIBG was significantly reduced as indicated by lower H/M ratios for PD patients versus controls (Kruskal–Wallis one-way analysis of variance, *$p = 0.025$). There were no significant differences in $I^{123}$ MIBG uptake when comparing MSA to PD or control groups. Data are expressed as scatter plots with each individual symbol representing a single patient and the horizontal line representing the mean of the corresponding group.

Journal of the Neurological Sciences 317 (2012) 92–96

J Neural Transm (2010) 117:69–76
DOI 10.1007/s00702-009-0313-y

MOVEMENT DISORDERS - ORIGINAL ARTICLE

# Comprehensive autonomic assessment does not differentiate between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy

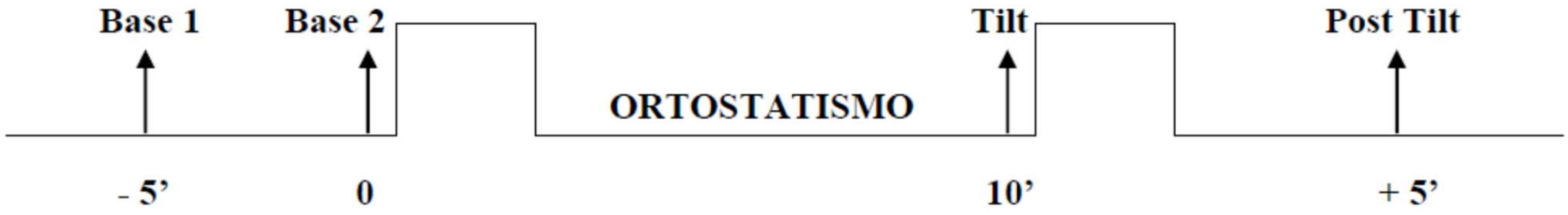
Manja Reimann · Claudia Schmidt · Birgit Herting · Silke Prieur · Susann Junghanns · Katherine Schweitzer · Christoph Globas · Ludger Schoels · Heinz Reichmann · Daniela Berg · Tjalf Ziemssen

**Abstract** Differential diagnosis of parkinsonian syndromes is a major challenge in movement disorders. Dysautonomia is a common feature but may vary in clinical severity and onset. The study attempted to find a pattern of autonomic abnormalities discriminative for patients with different parkinsonian syndromes. The cross-sectional study included 38 patients with multiple system atrophy (MSA), 32 patients with progressive supranuclear palsy (PSP), 26 patients with idiopathic Parkinson's disease (IPD) and 27 age-matched healthy controls. Autonomic symptoms were evaluated by a standardized questionnaire. The performance of patients and controls was compared on five autonomic function tests: deep breathing, Valsalva manoeuvre, tilt-table testing, sympathetic skin response, pupillography, and 24-h ambulatory blood pressure monitoring (ABPM). Disease severity was significantly lower in IPD than PSP and MSA. Except for pupillography, none of the laboratory autonomic tests distinguished one patient group from the other alone or in combination. The same was observed on the questionnaire. Receiver operating characteristic curve revealed discriminating performance of pupil diameter in darkness and nocturnal blood pressure change. The composite score of urogenital and vasomotor domains significantly distinguished MSA from IPD patients but not from PSP. Our study supports the observation that even mild IPD is frequently indistinguishable from more severe MSA and PSP. Thus, clinical combination of motor and non-motor symptoms does not exclusively point at MSA. Pupillography, ABPM and the questionnaire may assist in delineating the three syndromes when applied in combination.

# DOSAGGIO DELLE CATECOLAMINE

**Procedura :**

**Preparare una siringa da 10ml con Soluzione fisiologica per il lavaggio della stessa. Incannulare la vena. Preparare 4 provette Preparare un contenitore con del ghiaccio. Lasciare il soggetto in posizione supina per almeno 20 minuti; aspirare 1ml di sangue e buttarlo via, aspirare 4 ml di sangue, versarlo nella provetta precedentemente preparata, mettere il prelievo nel contenitore con il ghiaccio. Lavare la cannula con soluzione fisiologica. I prelievi in totale sono 4: 2 prelievi di base a distanza di 5 minuti, 1 prelievo al 10° minuto in ortostatismo, 1 prelievo al 5° minuto dopo il ritorno in clinostatismo.**



**Catecolamine**
**Ortostatismo**

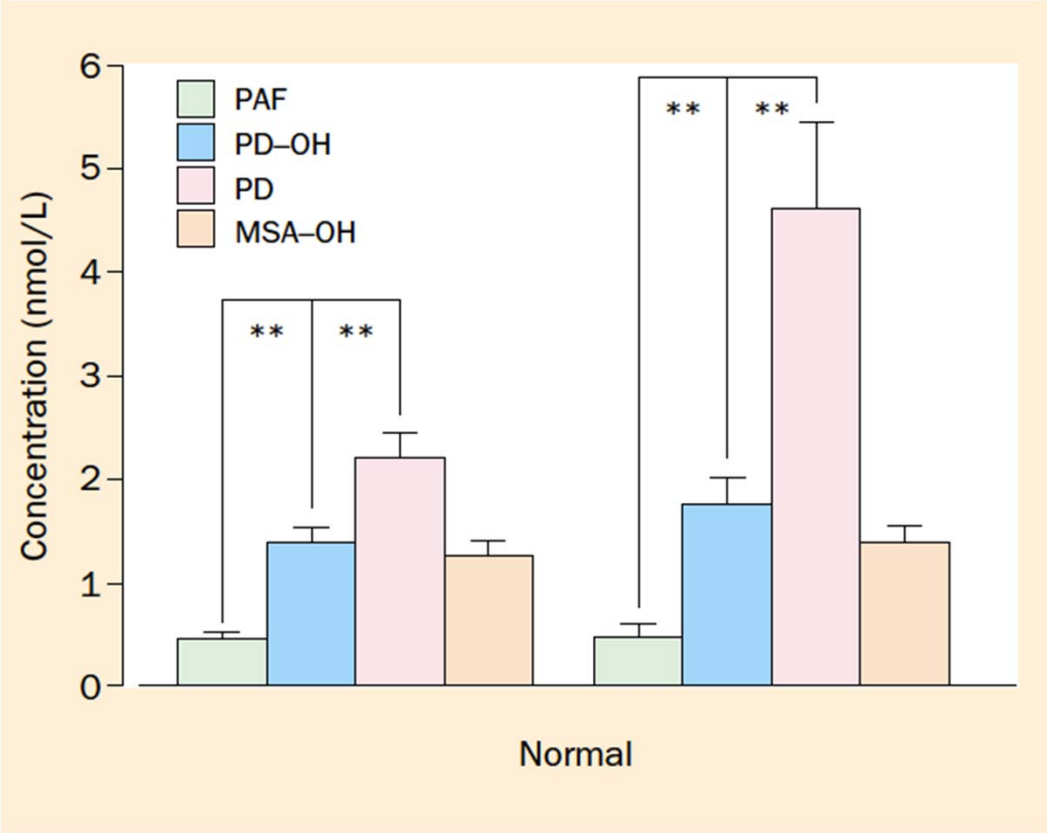



*Figure 5. Concentrations of norepinephrine in the plasma during supine rest and after 5 min of standing in patients with pure autonomic failure (PAF), PD with or without orthostatic hypotension (OH), and multiple system atrophy (MSA) with OH. Note blunted orthostatic increment in plasma noradrenaline concentration in PAF, PD–OH, and MSA–OH but not in PD without OH.*

**Goldstein. Lancet 2003; 2:669 - 676**

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# Intrasubject reproducibility of supine norepinephrine plasma concentrations in patients with cardiovascular sympathetic failure

Giannicola Carrozzo [a,b], Mitchell G. Miglis [c], Manuela Contin [a], Ilaria Cani [a,b], Pietro Cortelli [a,b], Pietro Guaraldi [a,*], Giovanna Calandra-Buonaura [a,b]

[a] IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
[b] Department of Biomedical and NeuroMotor Sciences (DIBINEM), Alma Mater Studiorum, University of Bologna, Bologna, Italy
[c] Department of Neurology and Neurological Sciences, Stanford Medical Center, Palo Alto, CA, USA

ARTICLE INFO

*Keywords:*
Catecholamines
Norepinephrine
Parkinson's disease
Dementia with Lewy bodies
Multiple system atrophy
Pure autonomic failure

ABSTRACT

*Background:* Plasma levels of the catecholamine norepinephrine (NE) has emerged as a useful tool to help differentiate pre- and post-ganglionic disorders in patients with cardiovascular autonomic failure (AF). However, data on intrasubject reliability in individuals with these conditions are limited. We evaluated the intrasubject reproducibility of supine plasma NE levels drawn across two consecutive time points under controlled conditions during head-up table testing in a large cohort of patients with alpha-synucleinopathies and both pre- and post-ganglionic cardiovascular AF.

*Methods:* Antecubital venous blood drawn via an indwelling cannula with the subject supine was assayed for plasma level of catecholamines. We collected two consecutive samples, the first after 20 min of supine rest (NE1) and the second 5 min later (NE2), from a group of 279 participants including 57 with Parkinson's disease/Lewy body dementia (44 M; 65.5 ± 11.1 y), 131 with multiple system atrophy (81 M; 63.2 ± 8.5 y), 41 with pure autonomic failure (25 M, 65.1 ± 9.3 y), and 50 healthy controls (27 M; 46.7 ± 19.4 y).

*Results:* We found no difference between NE1 and NE2 ($p = 0.645$), with a mean intrasubject reproducibility (NE maximum − NE minimum) × 100 / NE maximum) of 11.5 % ± 10.64. This finding was confirmed when controlling for diagnosis ($p = 0.669$), gender ($p = 0.493$), age ($p = 0.865$), disease duration ($p = 0.596$) or considering all factors together ($p = 0.527$).

*Conclusions:* We found excellent test-retest reliability of consecutive supine NE measurements in patients with alpha-synucleinopathies and cardiovascular AF, independent of age, gender and disease duration. This lends evidence to support the use of a single supine NE measurement in these conditions.

# Cardiovascular autonomic testing performed with a new integrated instrumental approach is useful in differentiating MSA-P from PD at an early stage

Francesca Baschieri [a, 1], Giovanna Calandra-Buonaura [a, b, 1], Andrea Doria [a], Francesca Mastrolilli [c], Aldopaolo Palareti [d], Giorgio Barletta [a, b], Laura Solieri [a, b], Pietro Guaraldi [e], Paolo Martinelli [a], Pietro Cortelli [a, b, *]

[a] *Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy*
[b] *IRCCS, Institute of Neurological Sciences, Bellaria Hospital, Bologna, Italy*
[c] *Department of Neurology, Lewisham and Greenwich NHS Trust, Queen Elizabeth Hospital, London, UK*
[d] *Department of Computer Science and Engineering, University of Bologna, Bologna, Italy*
[e] *Public Local Health Authority of Modena and Bologna, Italy*

Parkinsonism and Related Disorders 21 (2015) 477–482

## Highlights

- Cardiovascular autonomic failure may be present in MSA-P and PD at an early stage.
- Orthostatic hypotension did not discriminate MSA-P from PD patients.
- A new instrumental approach made cardiovascular tests reliable and reproducible.
- Cardiovascular autonomic tests discriminated MSA-P from PD patients.
- Sensitivity and specificity (CI) for HUTT + VM were 91% (0.76–0.98) and 92% (0.83–0.97).

**Predicting phenoconversion in pure autonomic failure**

Elizabeth A. Coon, Jay N. Mandrekar, Sarah E. Berini, et al.

*Neurology* 2020;95;e889-e897 Published Online before print June 16, 2020
DOI 10.1212/WNL.0000000000010002

| | Stable PAF (n = 208) | Phenoconversion to MSA (n = 34) | Phenoconversion to PD/DLB (n = 33) |
|---|---|---|---|

| | Phenoconversion to PD/DLB | |
|---|---|---|
| | Odds ratio | *p* Value |
| Subtle motor signs at presentation | 8.3 (3.0–22.9) | <0.0001 |
| Dream enactment behavior presentation | 7.0 (1.7–29.7) | 0.0079 |
| Constipation at presentation | 2.1 (1.0–4.5) | 0.0479 |
| Age at onset | 1.0 (1.0–1.1) | 0.0324 |

PD/DLB

| Subtle motor signs at presentation | Dream enactment behavior | Age at onset ≥65 y | Probability |
|---|---|---|---|
| **0** | 0 | 0 | 0.0568 |
| **0** | 0 | 1 | 0.1362 |
| **0** | 1 | 0 | 0.2747 |
| **0** | 1 | 1 | 0.4980 |
| **1** | 0 | 0 | 0.2998 |
| **1** | 0 | 1 | 0.5286 |
| **1** | 1 | 0 | 0.7292 |
| **1** | 1 | 1 | 0.8758 |

**Predicting phenoconversion in pure autonomic failure**

Elizabeth A. Coon, Jay N. Mandrekar, Sarah E. Berini, et al.
*Neurology* 2020;95;e889-e897 Published Online before print June 16, 2020
DOI 10.1212/WNL.0000000000010002

| | Stable PAF (n = 208) | Phenoconversion to MSA (n = 34) | Phenoconversion to PD/DLB (n = 33) |
|---|---|---|---|

| | Phenoconversion to MSA | |
|---|---|---|
| | Odds ratio | *p* Value |
| Subtle motor signs at presentation | 22.1 (8.6–57.0) | <0.0001 |
| Supine norepinephrine ≥100 pg/mL | 15.9 (2.1–123.0) | 0.0079 |
| Severe bladder symptoms at presentation | 8.4 (3.6–19.7) | <0.0001 |
| Dream enactment behavior presentation | 6.8 (1.6–28.6) | 0.0090 |
| Preganglionic sweat loss on TST | 5.4 (2.3–12.5) | <0.0001 |
| Constipation at presentation | 2.9 (1.4–6.0) | 0.0054 |
| Norepinephrine rise >65 pg/mL | 3.7 (1.3–10.7) | 0.0171 |
| Heart rate change at 1 minute of tilt | 1.0 (1.0–1.1) | 0.0266 |
| Supine norepinephrine level | 1.0 (1.0–1.0) | 0.0136 |

MSA

| Subtle motor signs at presentation | Supine norepinephrine ≥100 pg/mL | Severe bladder symptoms at presentation | Probability |
|---|---|---|---|
| 0 | 0 | 0 | 0.0018 |
| 0 | 0 | 1 | 0.0329 |
| 0 | 1 | 0 | 0.0489 |
| 0 | 1 | 1 | 0.4864 |
| 1 | 0 | 0 | 0.1045 |
| 1 | 0 | 1 | 0.6826 |
| 1 | 1 | 0 | 0.7645 |
| 1 | 1 | 1 | 0.9836 |

# ANS and Sleep - Autonomic impairment impact on iRBD – 1

- Autonomic impairment is a frequent collateral finding in iRBD patients.
- The co-occurrence of these disorders could arise from degeneration of adjacent structures controlling REM sleep and ANS in the brainstem.

| Study identifier | No. of subjects | Questionnaire used | Results |
|---|---|---|---|
| Questionnaire-based studies | | | |
| Ferini-Strambi et al. [53] | 318 iRBD vs 318 HC | SCOPA-AUT | Total score (iRBD vs HC): 12.44 ± 6.99 vs 8.90 ± 6.45 ($p < 0.0001$)<br>Gastrointestinal (iRBD vs HC): 3.53 ± 2.84 vs 1.68 ± 1.93 ($p < 0.0001$)<br>Urinary (iRBD vs HC): 4.79 ± 3.11 vs 3.87 ± 3.18 ($p < 0.0001$)<br>Cardiovascular (iRBD vs HC): 0.68 ± 1.15 vs 0.48 ± 0.89 ($p < 0.005$) |
| Aguirre-Mardones et al. [54] | 44 iRBD vs 40 HC | SCOPA-AUT | Total score (iRBD vs HC): 17.68 ± 9.99 vs 14.0 ± 8.27 ($p = 0.071$) |
| Frauscher et al. [59] | 15 iRBD vs 15 PD vs 15 HC | COMPASS | Total score (iRBD vs HC): 23.3 ± 10.6 vs 11.5 ± 5.8 ($p < 0.001$) |
| Postuma et al. [56] | 91 iRBD of which 32 pRBD vs HC | UMSARS | SBP drop (mmHg) (iRBD vs HC): 10.2 ± 13.8 vs 3.2 ± 8.1 ($p = 0.012$)<br>Erectile dysfunction (iRBD vs HC): 0.45 ± 1.02 vs 1.82 ± 1.45 ($p < 0.001$)<br>Constipation (iRBD vs HC): 0.156 ± 0.41 vs 0.65 ± 0.83 ($p = 0.004$) |
| Li et al. [55] | 43 iRBD of which 18 pRBD | SCOPA-AUT | iRBD with higher scores in the cardiovascular and gastrointestinal domains were more likely to progress (HR = 4.46, 95% CI 1.64–12.10, $p = 0.003$) |

| Study identifier | No. of subjects | Results |
|---|---|---|
| Cardiovascular reflex tests | | |
| Lee et al. 2015 [61] | 13 iRBD vs HC | HUT ¦ SBP (mmHg) (iRBD vs HC): 101.12 ± 17.80 vs 129.27 ± 21.81 ($p < 0.05$);<br>DBP (mmHg): 58.35 ± 10.36 vs 69.07 ± 13.10 ($p = 0.02$)<br>HR response (iRBD vs HC): 6.01 ± 3.95 vs 10.92 ± 4.31 ($p < 0.05$)<br>VR (iRBD vs HC): 1.38 ± 0.18 vs 1.55 ± 0.21 ($p = 0.03$) |
| Ferini-Strambi et al. 1996 [60] | 10 iRBD and 4 pRBD vs 14 HC | Abnormal BP and HR responses on HUT in 4 iRBD and 1 pRBD; abnormal VM profile and deep breathing response compared to HC |
| Frauscher et al. 2012 [59] | 15 iRBD vs 15 PD vs 15 HC | Standing test ¦ ΔSBP (mmHg) (iRBD vs HC): −0.3 ± 9.1 vs 7.6 ± 10.4 ($p = 0.034$); ΔDBP: 0.9 ± 8.4 vs 8.3 ± 10.2 ($p = 0.041$)<br>VR (iRBD vs HC): 1.34 ± 0.20 vs 1.52 ± 0.22 ($p = 0.015$) |
| Heart rate variability studies | | |
| Ferini-Strambi et al. 1996 [60] | 10 iRBD and 4 pRBD vs 14 HC | Reduced HR variability during nighttime |
| Lanfranchi et al. 2007 [64] | 10 iRBD vs 10 HC | RR interval, HF, and HFnu components decreases from NREM to REM did not change in iRBD (Interaction $p < 0.05$). LFnu (interaction $p < 0.001$), LF/HF (interaction $p < 0.001$), and respiratory frequency (interaction $p < 0.05$) remained stable in iRBD |
| Postuma et al. 2010 [65] | 42 RBD vs 42 HC of which 21 pRBD | Reductions in RR-standard deviation (24.6 ± 2.2 vs. 35.2 ± 3.5 ms, $p = 0.006$), VLF (238.6 ± 6 99.6 vs. 840.1 ± 188.3 $ms^2$, $p < 0.001$), and LF (127.8 ± 26.3 vs. 288.7 ± 66.2 $ms^2$, $p = 0.032$) in chi? |
| Sorensen et al. 2012 [66] | 11 iRBD vs 30 PD vs 17 HC | Attenuated HR response to arousals or LMs during sleep in PD and iRBD compared to HC |
| Sorensen et al. 2013 [67] | 11 iRBD vs 23 PD vs 10 HC | VLF ($ms^2$) (iRBDvs HC): 47 ± 34 vs 158 90 ($p < 0.006$) |

Chiaro et al., Clin Aut Res, 2018

October 19, 2023 RESEARCH ARTICLE

## Frequency of Orthostatic Hypotension in Isolated REM Sleep Behavior Disorder: The North American Prodromal Synucleinopathy Cohort

Jonathan Elliott, Mohini D Bryant-Ekstrand, Allison T Keil, Brittany R Ligman, Miranda M Lim, Jennifer Zitser, Emmanuel H During, Jean-Francois Gagnon, Erik K St Louis, Julie A Fields, Daniel E Huddleston, Donald L Bliwise, Alon Y Avidan, Carlos H Schenck, Jennifer McLeland, Susan R Criswell, Albert A Davis, Aleksandar Videnovic, Joyce K Lee-Iannotti, Ronald Postuma, Bradley F Boeve, Yo-El Ju, Mitchell G Miglis, for North American Prodromal Synucleinopathy (NAPS) Consortium

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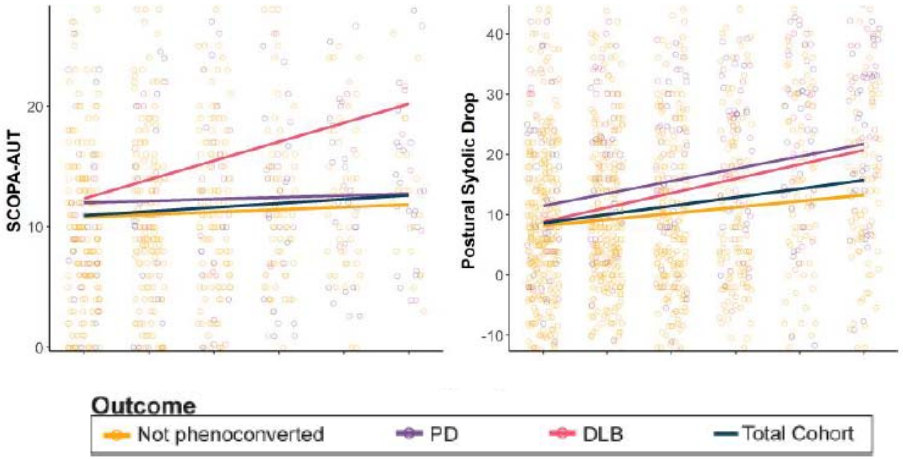
# ANS and Sleep - Autonomic impairment impact on iRBD – 2

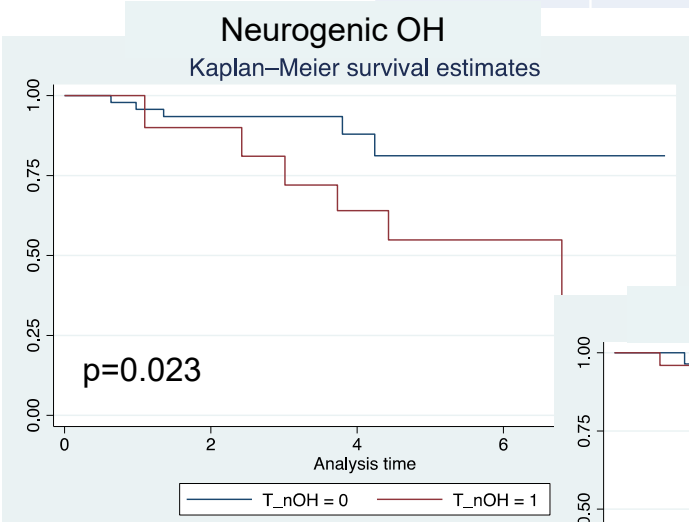
## Progression of clinical markers in prodromal Parkinson's disease and dementia with Lewy bodies: a multicentre study

Stephen Joza,[1] Michele T. Hu,[2] Ki-Young Jung,[3] Dieter Kunz,[4] Ambra Stefani,[5] Petr Dušek,[6] Michele Terzaghi,[7,8] Dario Arnaldi,[9,10] Aleksandar Videnovic,[11] Mya C. Schiess,[12] Wiebke Hermann,[13] Jee-Young Lee,[14] Luigi Ferini-Strambi,[15] Simon J. G. Lewis,[16] Laurène Leclair-Visonneau,[17,18] Wolfgang H. Oertel,[19,20] Elena Antelmi,[21] Friederike Sixel-Döring,[19,22] Valérie Cochen De Cock,[23,24] Claudio Liguori,[25,26] Jun Liu,[27] Federica Provini,[28,29] Monica Puligheddu,[30] Alessandra Nicoletti,[31] Claudio L. A. Bassetti,[32] Jitka Bušková,[33] Yves Dauvilliers,[34] Raffaele Ferri,[35] Jacques Y. Montplaisir,[36,37] Michael Lawton,[38] Han-Joon Kim,[3] Frederik Bes,[4] Birgit Högl,[5] Karel Šonka,[6] Giuseppe Fiamingo,[7,8] Pietro Mattioli,[9] Maria Lorena Lavadia,[11] Jessika Suescun,[12] Kyung Ah Woo,[14] Sara Marelli,[15] Kaylena Ehgoetz Martens,[39] Annette Janzen,[19] Giuseppe Plazzi,[29,40] Brit Mollenhauer,[22,41] Mariana Fernandes,[25] Yuanyuan Li,[27] Pietro Cortelli,[28,29] Michela Figorilli,[30] Calogero Edoardo Cicero,[31] Carolin Schaefer,[32] Lily Guiraud,[34] Giuseppe Lanza,[35,42] Jean-François Gagnon,[36,37] Jun-Sang Sunwoo,[43] Abubaker Ibrahim,[5] Nicola Girtler,[9,10] Claudia Trenkwalder,[22,41] Luca Baldelli,[28,29] Amelie Pelletier,[1,36] and Ronald B. Postuma[1,36] for the International REM Sleep Behavior Disorder Study Group

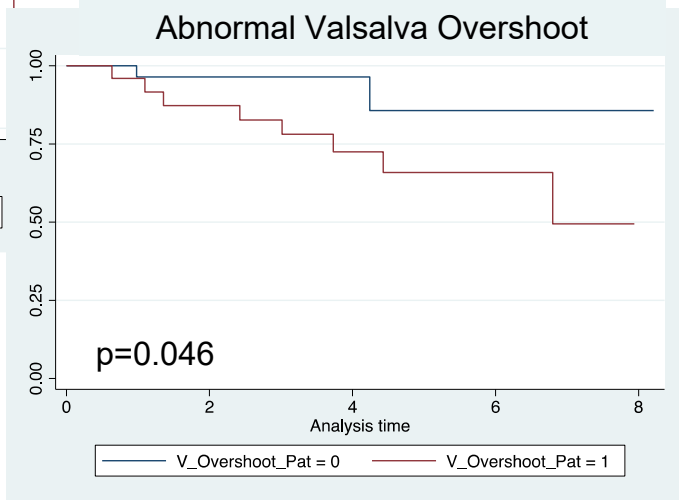
BRAIN 2023: 00; 1–15




| Bologna iRBD Cohort | | |
|---|---|---|
| # iRBD → | Converters | FU |
| 64 | 12 | ~5y |




Baldelli et al., in review



# ANS – Cognition – Dementia with Lewy Bodies

Neurol Sci (2012) 33:469–473
DOI 10.1007/s10072-011-0746-6

BRIEF COMMUNICATION

## Standing worsens cognitive functions in patients with neurogenic orthostatic hypotension

R. Poda · P. Guaraldi · L. Solieri · G. Calandra-Buonaura · G. Marano · R. Gallassi · P. Cortelli

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PLOS ONE

## Cognitive Function in Peripheral Autonomic Disorders

**Pietro Guaraldi[1,2]*, Roberto Poda[1,2], Giovanna Calandra-Buonaura[1,2], Laura Solieri[1,2], Luisa Sambati[1,2], Roberto Gallassi[1,2], Pietro Cortelli[1,2]**

1 IRCCS, Institute of Neurological Sciences of Bologna, Bologna, Italy, 2 Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

***Conclusions:*** these data demonstrate that patients with PAF and AAN present a normal sitting global cognitive evaluation. However, their executive functions worsen significantly during the orthostatic challenge, possibly because of transient frontal lobes hypoperfusion.

# ANS – Cognition – Causal Link

1. CI should probably be considered more a transient symptom of OH than a chronic effect
2. Low blood pressure can decrease cerebral blood flow leading to functional and ultimately structural damage (white matter abnormalities)
3. The neurodegenerative process leading to CI or dementia syndromes involved also the areas devoted to cardiovascular autonomic control, so that neurodegeneration can be the cause of both CI and OH.

# ANS – Cognition – Causal Link ?

## Cognitive profile in idiopathic autonomic failure: relation with white matter hyperintensities and neurofilament levels

Ilaria Cani[1,2], Luisa Sambati[2], Fiorina Bartiromo[2], Gian Maria Asioli[1], Simone Baiardi[2,3], Laura M. B. Belotti[2], Giulia Giannini[1,2], Pietro Guaraldi[2], Corinne Quadalti[2], Luciano Romano[1], Raffaele Lodi[1,2], Piero Parchi[2,3], Pietro Cortelli[1,2], Caterina Tonon[1,2] & Giovanna Calandra-Buonaura[1,2]

**Abstract**

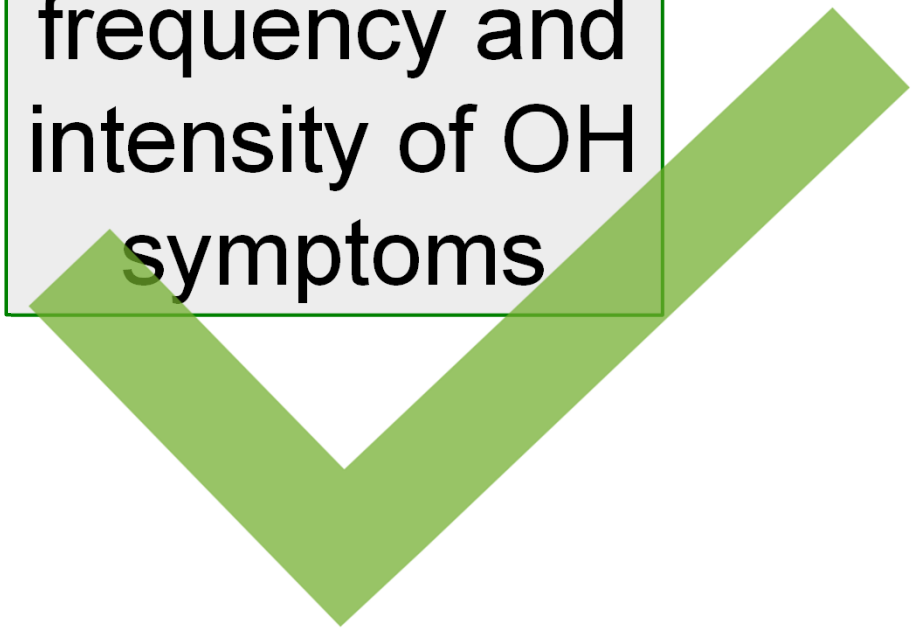
**Objective**: To disclose the nature of cognitive deficits in a cohort of patients with idiopathic autonomic failure (IAF) by exploring the relation among cognitive functions, cardiovascular autonomic failure (AF) and clinical progression to another α-synucleinopathy (phenoconversion). **Methods**: We retrospectively identified all patients with a clinical diagnosis of IAF who underwent a comprehensive neuropsychological evaluation, clinical examination and cardiovascular autonomic tests from the IAF-BO cohort. Brain magnetic resonance imaging (MRI) studies and cerebrospinal fluid (CSF) analysis, including neurofilament light chain (NfL), Alzheimer disease core biomarkers, and α-synuclein seeding activity were further evaluated when available. Correlations among cognitive functions, clinical features, cardiovascular AF, cerebral white matter hyperintensities (WMH) load, and CSF biomarkers were estimated using Spearman correlation coefficient. **Results**: Thirteen out of 30 (43%) patients with IAF displayed cognitive deficits (CI) mainly concerning executive functioning. Seven out of 30 (23%) met the criteria for mild cognitive impairment (MCI). The diagnosis of CI and MCI was not associated with phenoconversion or autonomic function parameters, including duration and severity of neurogenic orthostatic hypotension, presence and severity of supine hypertension, and nocturnal dipper profile. Twenty patients underwent a brain MRI and CSF analysis. MCI was related to WMH load ($r = 0.549$) and NfL levels ($r = 0.656$), while autonomic function parameters were not associated with either WMH or NfL levels. **Interpretation**: Cardiovascular AF and phenoconversion, underlying the spreading of neurodegeneration to the central nervous system, were not independent drivers of cognitive dysfunction in IAF. We identified WMH load and NfL levels as potential biomarkers of the neural network disruption associated with cognitive impairment in patients with IAF.

# Take Home Messages

1. Isolated (Pure) Autonomic failure is a (prodromal) synucleinopathy with involvement of the peripheral ANS
2. Conversion time to an overt central neurodegenerative disease can be long, but present.
3. Further involvement of motor, cognitive and sleep domains increases the risk of conversion.

# Q&A: WHICH ARE THE AIM OF OH TREATMENT?

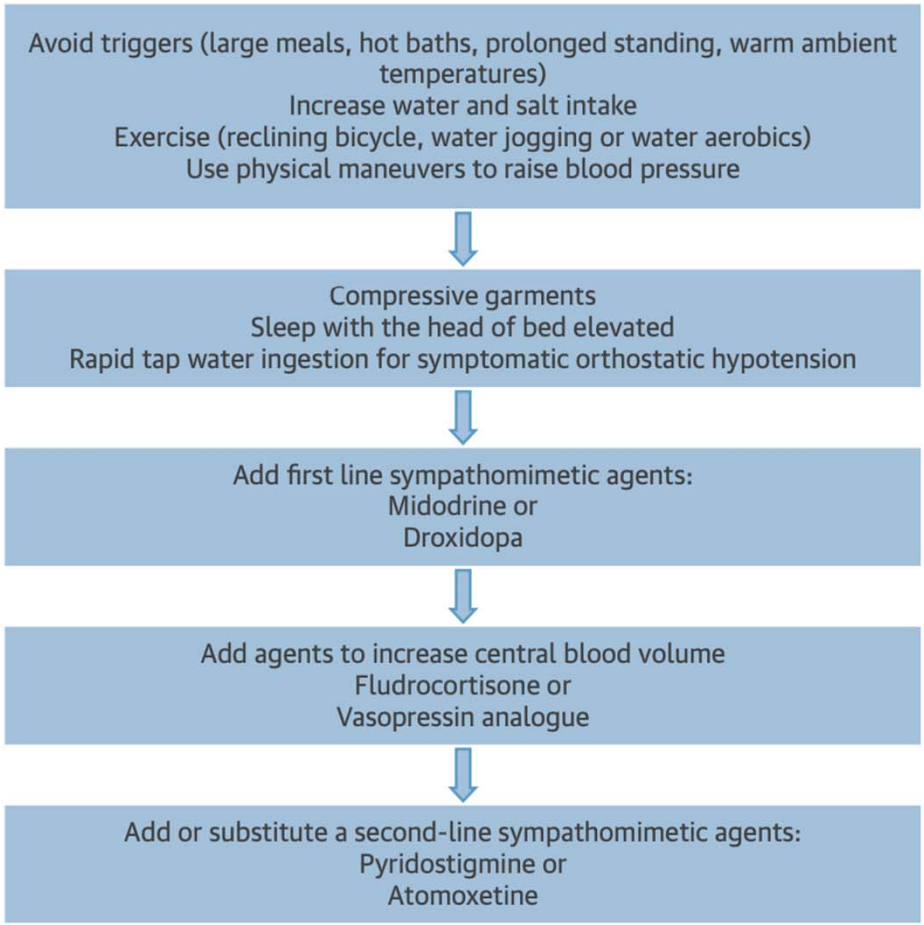
Reduce frequency and intensity of OH symptoms



# Therapeutic goals


- **Reduce recurrence and severity of postural symptoms**
- **NO need to recover normotension**
- **In non neurogenic OH find and (if possible) trat the cause**

**FIGURE 4** **The Treatment Algorithm for Neurogenic Orthostatic Hypotension**




Nonpharmacological and pharmacological interventions to treat neurogenic orthostatic hypotension.

# A four step process for treating OH

**1.Medication Review**

Modify or remove medications that can cause or worsen OH

**2.Non-Pharmacologic Measures**

Fluid, salt, compression stockings, abdominal binders, exercise

**3.Pharmacologic Measures**

Fludrocor□ sone, midodrine, droxidopa, pyridos□ gmine

**4.Combination Pharmacologic Measures**

*Gibbons et al. 2017*

# A four step process for treating OH

**1.Medication Review**

Modify or remove medications that can cause or worsen OH

- **Alpha-1 adrenergic antagonists**
- **Dopaminergic agents**
- **Antidepressants (particularly tricyclic agents)**
- **Anticholinergics Anti-hypertensive agents Preload reducers**
- **Diuretics**
- **Nitrates**
- **Phosphodiesterase E5 inhibitors**
- **Vasodilators**
- **..**

*Gibbons et al. 2017*

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*Gibbons et al. 2017*

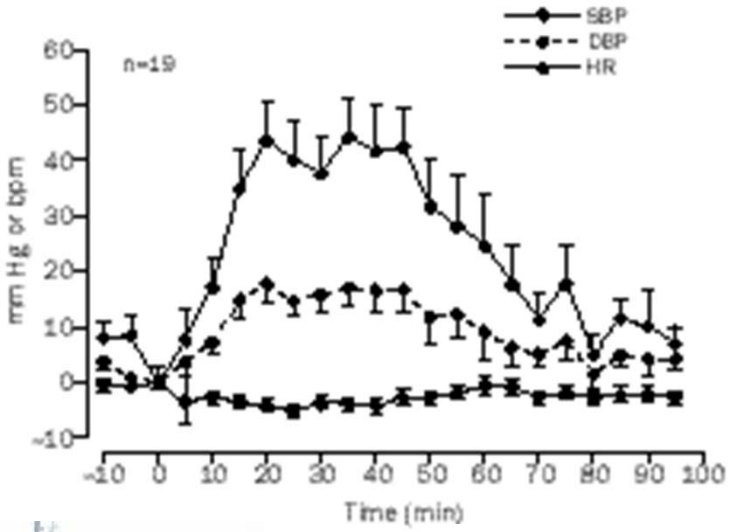
# A four step process for treating OH

**2.Non-Pharmacologic Measures**

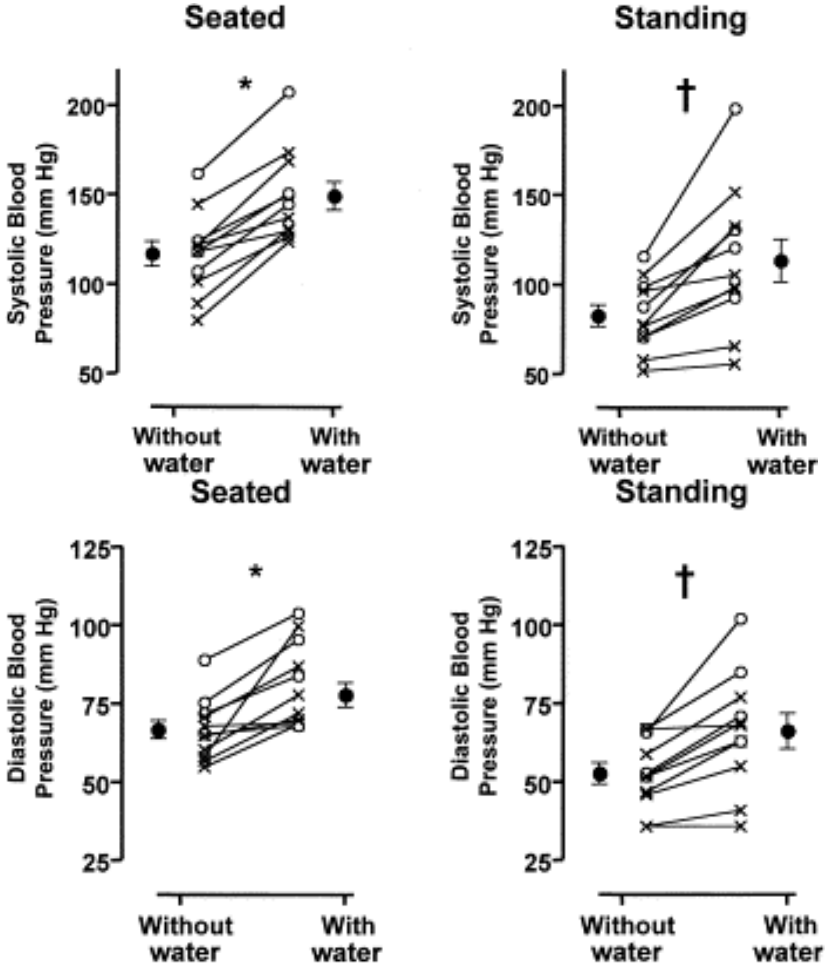
- **Increase water intake (2-2,5 L/day)**
- **Adequate salt intake**
- **Use compression garments (abdominal binders)**
- **Elevate the had of the bed for sleeping**
- **Physical conditioning**
- **Eat small meals with less carbohydrates**
- **Avoid increases in body temperature**
- **Avoid straining or maneuvers that increase intrathoracic pressure**

*Gibbons et al. 2017*

# Water pressure effect

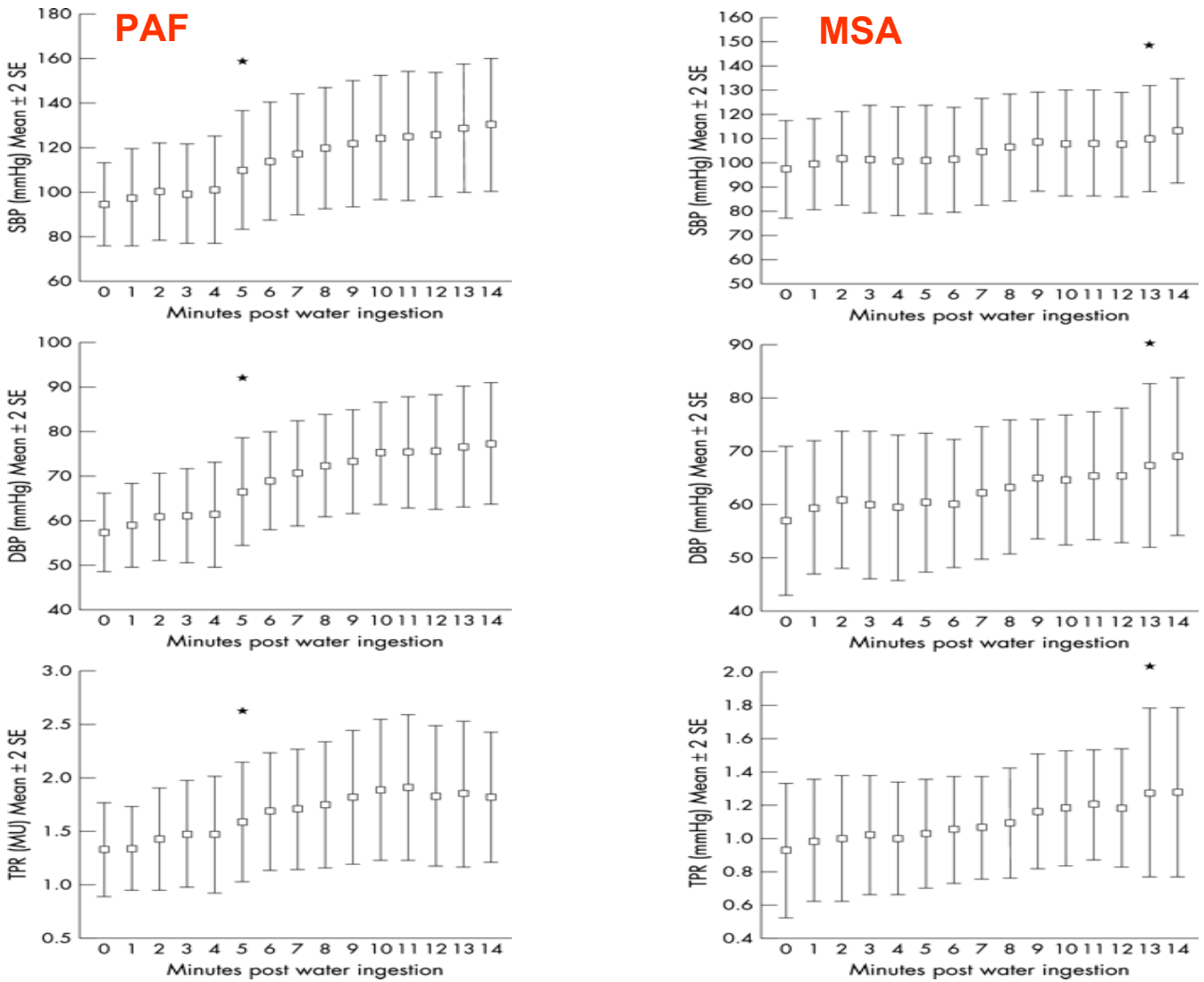






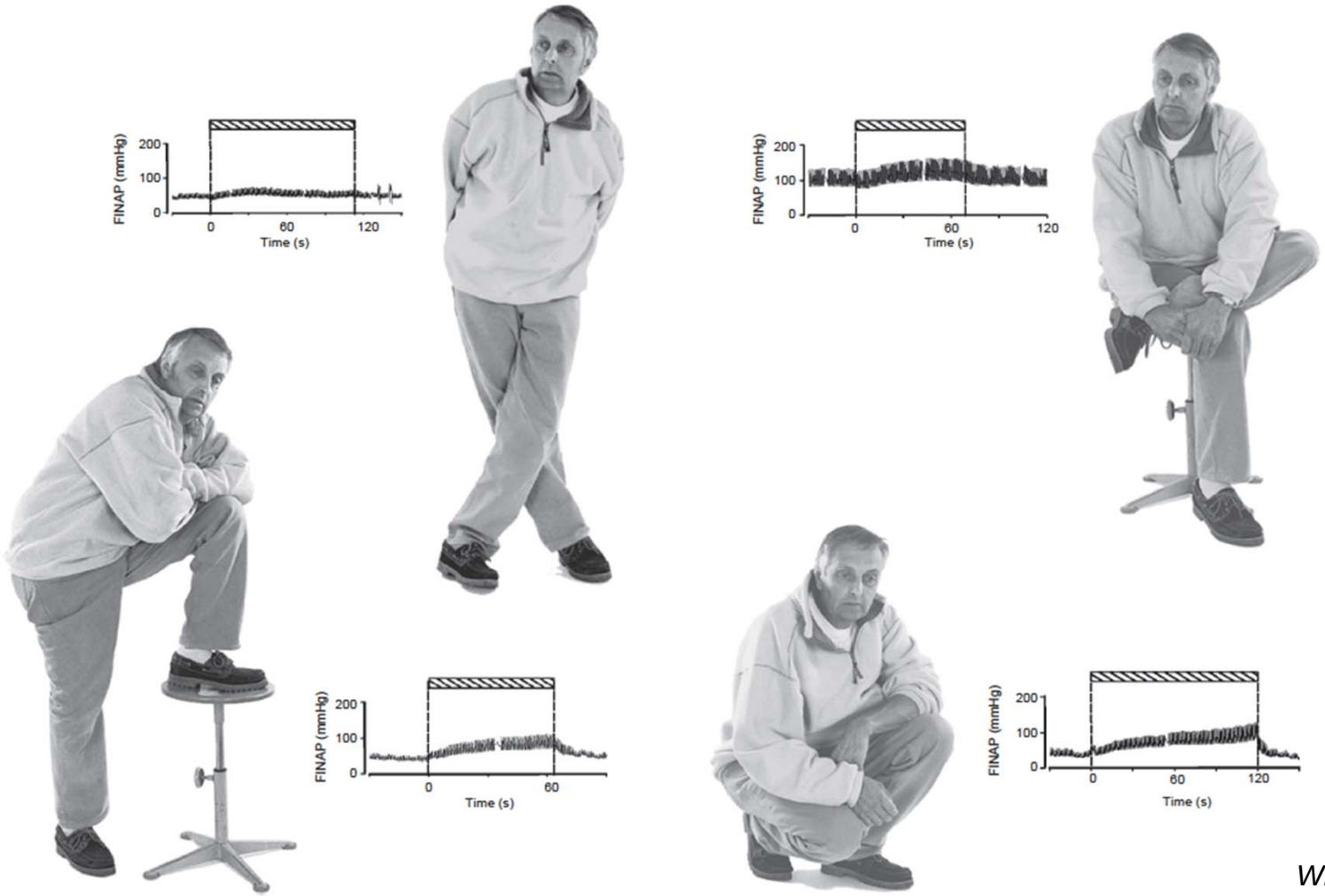

*Jordan J et al. Lancet 1999; Shannon et al. Am J Med*

## Parametri emodinamici durante ingestione di ACQUA




*Young TM 2004*

# Physical counter-maneuvers




*Wieling et al 2015*

# Elevate the had of the bed for sleeping

# Efficacy of Servo-Controlled Splanchnic Venous Compression in the Treatment of Orthostatic Hypotension

## A Randomized Comparison With Midodrine

Luis E. Okamoto, André Diedrich, Franz J. Baudenbacher, René Harder, Jonathan S. Whitfield, Fahad Iqbal, Alfredo Gamboa, Cyndya A. Shibao, Bonnie K. Black, Satish R. Raj, David Robertson, Italo Biaggioni

**See Editorial Commentary, pp 310-311**

***Abstract***—Splanchnic venous pooling is a major hemodynamic determinant of orthostatic hypotension, but is not specifically targeted by pressor agents, the mainstay of treatment. We developed an automated inflatable abdominal binder that provides sustained servo-controlled venous compression (40 mm Hg) and can be activated only on standing. We tested the efficacy of this device against placebo and compared it to midodrine in 19 autonomic failure patients randomized to receive either placebo, midodrine (2.5–10 mg), or placebo combined with binder on separate days in a single-blind, crossover study. Systolic blood pressure (SBP) was measured seated and standing before and 1-hour post medication; the binder was inflated immediately before standing. Only midodrine increased seated SBP (31±5 versus 9±4 placebo and 7±5 binder, $P$=0.003), whereas orthostatic tolerance (defined as area under the curve of upright SBP [$AUC_{SBP}$]) improved similarly with binder and midodrine ($AUC_{SBP}$, 195±35 and 197±41 versus 19±38 mm Hg×minute for placebo; $P$=0.003). Orthostatic symptom burden decreased with the binder (from 21.9±3.6 to 16.3±3.1, $P$=0.032) and midodrine (from 25.6±3.4 to 14.2±3.3, $P$<0.001), but not with placebo (from 19.6±3.5 to 20.1±3.3, $P$=0.756). We also compared the combination of midodrine and binder with midodrine alone. The combination produced a greater increase in orthostatic tolerance ($AUC_{SBP}$, 326±65 versus 140±53 mm Hg×minute for midodrine alone; $P$=0.028, n=21) and decreased orthostatic symptoms (from 21.8±3.2 to 12.9±2.9, $P$<0.001). In conclusion, servo-controlled abdominal venous compression with an automated inflatable binder is as effective as midodrine, the standard of care, in the management of orthostatic hypotension. Combining both therapies produces greater improvement in orthostatic tolerance.

***Clinical Trial Registration***—URL: https://www.clinicaltrials.gov. Unique identifier: NCT00223691.

**(*Hypertension*. 2016;68:418-426. DOI: 10.1161/HYPERTENSIONAHA.116.07199.)** ● **Online Data Supplement**

**Key Words:** autonomic nervous system ■ blood pressure ■ hemodynamic ■ midodrine ■ orthostatic hypotension ■ splanchnic circulation

**Unità di Esplorazione Funzionale del Sistema Nervoso Vegetativo**

# CONSIGLI PRATICI PER I PAZIENTI CON IPOTENSIONE ORTOSTATICA

## *Comportamenti da evitare*

- Alzarsi improvvisamente in piedi soprattutto al risveglio;
- Rimanere a lungo in piedi fermi;
- Rimanere a lungo sdraiati durante il giorno;
- Sforzi prolungati (aumento pressione addominale) durante la minzione e la defecazione;
- Elevate temperature ambientali (inclusi bagni e docce caldi);
- Sforzi fisici intensi;
- Pasti molto abbondanti e ricchi di carboidrati (gli alimenti contenenti carboidrati come la pasta, il pane e i dolci sono quelli che più accentuano il calo pressorio);
- L'alcool è un vasodilatatore e può, pertanto peggiorare l'ipotensione ortostatica;
- Farmaci con proprietà vasodepressorie

## *Comportamenti da adottare*

- Al risveglio è opportuno sedersi sul letto per alcuni minuti, quindi mettere le gambe giù dal letto rimanendo ancora seduti per qualche minuto ed infine alzarsi. Se l'ipotensione è molto marcata al mattino è consigliabile assumere la terapia e fare colazione seduti a letto e attendere 30-60 min. prima di alzarsi;
- dieta ricca di fibre, un buon apporto di liquidi ed eventualmente l'utilizzo di lassativi. Particolarmente indicato è l'utilizzo di Movicol (macrogol 3350/elettroliti) bust. 1 o 2 bust. al giorno da portare a 1 bust al giorno una volta ottenuto un buon risultato e successivamente a 1 bust. a giorni alterni o ogni 2-3 giorni. Il Movicol non funziona se non si assume almeno 1,5 lt di acqua al giorno;
- pasti frazionati e frequenti riducendo i carboidrati specialmente a pranzo;
- apporto di sale nella dieta di almeno 8 grammi al giorno; se non si trovano in commercio le compresse di sale, salare i cibi, e introdurre nella dieta prosciutto crudo, salatini a bastoncino ricoperti di sale o aggiungere all'acqua preparati a base di elettroliti come Reidrax bust. 1 bust. sciolta in 500cc. di acqua;
- bere almeno 2-2,5 litri di liquidi al giorno;
- bere rapidamente 500 cc d'acqua aumenta la pressione arteriosa e può essere usata come strategia per contrastare l'ipotensione ortostatica sintomatica
- dormire in "head up tilt" cioè con la testa sollevata rispetto ai piedi. Per questo è necessario inclinare tutto il letto ponendo zoccoli di legno di altezza da 15 a 30 cm sotto i piedi del letto dalla parte della testa. Generalmente ci si abitua rapidamente ma un cuscino posizionato all'altezza delle gambe in modo da tenerle parzialmente sollevate può essere utile;
- Esercitare una costante ma non intensa attività fisica. Il nuoto, in un ambiente controllato, può essere ben tollerato ma occorrono precauzioni soprattutto nel momento in cui si esce dall'acqua. Il vogatore è un ottimo ausilio per l'attività fisica perché si utilizza in posizione seduta e offre l'opportunità di rinforzare i muscoli addominali
- In estate mantenere una temperatura più bassa nell'ambiente in cui si trascorre la maggior parte del tempo (aria condizionata) e nella scelta del luogo di vacanza è consigliabile optare per la montagna. Il condizionamento dell'ambiente diventa ancora più importante in presenza di febbre

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Bologna
Istituto delle Scienze Neurologiche
Istituto di Ricovero e Cura a Carattere Scientifico
UOC Clinica Neurologica Rete Metropolitana NEUROMET
Direttore: Prof. Pietro Cortelli
ALMA MATER STUDIORUM
UNIVERSITA' DI BOLOGNA

***Manovre fisiche che riducono il calo pressorio in posizione eretta e da usare al primo sintomo di bassa perfusione cerebrale (visione offuscata, dolore al collo a mantellina o qualsiasi sintomo che si dimostri poi scomparire in posizione supina)***

- piegarsi in avanti come per allacciarsi una scarpa, e/o stare su di un piede appoggiando l'altro su di una superficie più alta come una sedia.
- accovacciarsi piegando le ginocchia ("squatting")
- incrociare le gambe "a forbice";
- contrarre la muscolatura addominale, delle gambe e dei glutei quando si è in piedi e anche quando si incrociano le gambe;
- piegare la testa a livello del cuore quando si è in piedi o seduti

### *Da considerare*

- L'utilizzo di calze elastiche e/o indumenti di supporto quali la panciera. Le calze devono essere a compressione graduata ed esercitare una pressione a livello della caviglia di 30- 40 mmHg (calze antiembolo a compressione graduale, collant o monocollant destro e sinistro classe KL2 a punta aperta).
- può essere utile avere a disposizione una sedia pieghevole a bastone tipo sedia da pescatore, da utilizzare quando i sintomi legati a caduta della pressione possono verificarsi fuori di casa.

### *In caso di rilievo di elevata pressione arteriosa in posizione supina*

- non allarmarsi e assumere la posizione eretta; in alternativa ricordarsi che bere un bicchiere d'acqua zuccherata, fare uno spuntino dolce con 1/2 bicchiere di vino o piccola dose di super-alcoolico sono manovre sufficienti per ridurre la pressione arteriosa

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- se l'ipertensione supina è cronica prima di addormentarsi la sera prevenire ipertensione con bicchiere d'acqua zuccherata o spuntino dolce con 1/2 bicchiere di vino o piccola dose di super-alcoolico

# A four step process for treating OH

**1.Medication Review**

Modify or remove medications that can cause or worsen OH

**2.Non-Pharmacologic Measures**

Fluid, salt, compression stockings, abdominal binders, exercise

**3.Pharmacologic Measures**

Fludrocortisone, midodrine, droxidopa, pyridostigmine

*Gibbons et al. 2017*

# A four step process for treating OH

## 3.Pharmacologic Measures

- **Midodrine**
  - a 1-adrenoreceptor agonist
  - 2.5-7.5 mg TID (waking hours)
  - side effects: supine hypertension, skin itching, and urinary retention. Caution in patients with heart failure and chronic renal failure
- **Droxidopa**
  - pro-drug that is converted into norepinephrine
  - 100-600 mg TID (waking hours)
  - side effects: headache, dizziness, nausea, fatigue, and supine hypertension. Caution in patients with heart failure and chronic renal failure

*Gibbons et al. 2017*

# Midodrina (Gutron)

**Pro-drug later converted to desmo-glymidodrine, selective 1-adrenergic agonist.**

Effective in tp of NOH by increasing total peripheral resistances.

- Few OL and DB studies. "Disappointing" results from systematic reviews.
- Lack of studies on long-term efficacy

Rapidly absorbed gastrointestinally.
**Peak 30 min. Half-life: 3-4 h.**
Does not pass blood-brain barrier

**Daily dose: cp 2.5 mg >> max 30 mg/day in 3 administrations.**
**Do not take more than 4-5 h before bedtime**

**Side effects:** urinary retention, itching, piloerection, irritability
Insomnia.
Do not use in ischemic heart disease/urinary retention
Renal excretion (keep renal function monitored).

# L-threo DOPS (Droxidopa)

## Synthetic aminoacid >> decarbossilated into Norepinephrine

Effective on symptoms of NOH vs. placebo

(no comparative studies with midodrine available)

Approved by FDA

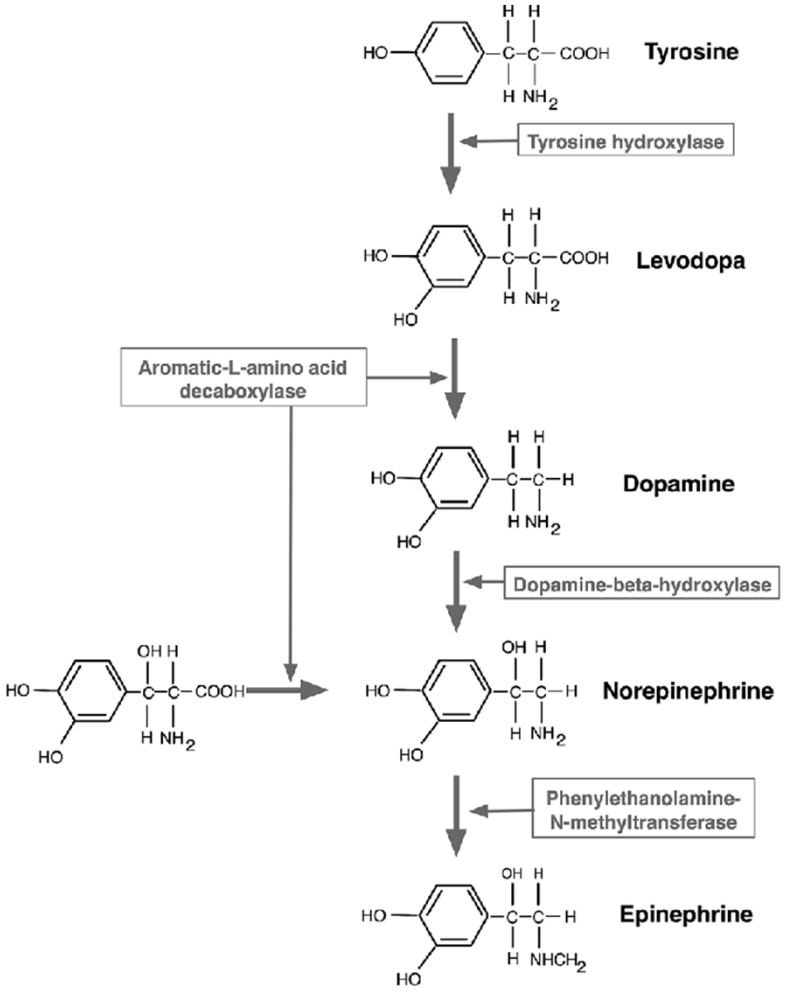
NOT marketed in Europe.

**Dosage: 100mgx3 to 600mgx3/day**

**Starting by increasing by 100 mgTID/24-48h**

**Side effects: hypertension**

Less likely to cause clinostatic hypertension



# A four step process for treating OH

## 3.Pharmacologic Measures

- **Fludrocortisone**
  - Mineralcorticoid expanding intravascular blood volume
  - 0.1–0.2 mg/day
  - side effects: supine hypertension, hypokalemia, and edema. Caution in patients with congestive heart failure.

- **Pyridostigmine**
  - acetylcholinesterase inhibitor potentiates neurotransmission at peripheral cholinergic synapses amplifying the increased sympathetic nerve activity in response to orthostatic stress.
  - 30–60 mg once to three times per day
  - side effects: abdominal cramps, diarrhea, sialorrhea, excessive sweating, and urinary incontinence.

*Gibbons et al. 2017*

# Fludrocortisone

**mineralcorticoide, favorisce riassorbimento di sodio a livello renale e determina espansione volume plasmatico aumentando così PA**

**Poor evidence of efficacy in OH treatment**

**Does NOT have specific indication**

**Long duration**

**Easily causes clinostatic hypertension**

**Dosage: 0.1-0.3 mg/day to be increased gradually.**

**Side effects:** hydro-saline retention, oedema, hypoK, peripheral oedema, congestive heart failure >> frequently discontinued (1/3 pc)

Contraindicated in cardiopathic patients.

Requires K+ monitoring before and after tp and K+ supplementation

# AMPRELOXETINE
## Inibitore elettivo del reuptake della NA

**potent selective NE reuptake inhibitor (NRI).** Inhibition of norepinephrine transport mechanism increases synaptic NE released from the system > useful for tapping "residual sympathetic tone."

Used in ADHD and Fibromyalgia

**One administration per day**
**Dose: 2 to 50 mg/day (20 mg/day)**

**Half-life (t1/2): 30-40 hours, reaches steady state within 6 days.**

Improved safety profile compared to other mechanisms of action (nausea, dry mouth, headache, dizziness, somnolence, fatigue, diarrhea, insomnia, vomiting, syncope, seizures, constipation, hyponatremia, hyperhidrosis, urinary retention, and decreased appetite)

**More than 90% eliminated through metabolism and CYP1A2**

# Theravance Biopharma Ampreloxetine Phase 3 Program for the Treatment of Symptomatic nOH

February 2021

Study 0169

SEQUOIA

An ampreloxetine study for symptomatic nOH

Study 0170

REDWOOD

An ampreloxetine study for symptomatic nOH

Study 0171

OAK

An ampreloxetine study for symptomatic nOH

# Blood pressure and pharmacodynamic response of ampreloxetine, a norepinephrine reuptake inhibitor, in patients with symptomatic neurogenic orthostatic hypotension

Horacio Kaufmann, Roy Freeman, David Bourdet, Ross Vickery, Lucy Kaufmann, Tadhg Guerin, Annamaria Takats, Pietro Guaraldi, Alexandru Barboi, Valeria Iodice, Robert Iansek, and Italo Biaggioni

**Background:** Ampreloxetine is a selective norepinephrine reuptake inhibitor recently investigated in a Phase 3 program for the treatment of symptomatic neurogenic orthostatic hypertension (nOH) in patients with primary autonomic failure (MSA, PD, and PAF). The purpose of this study was to evaluate the pharmacodynamic and blood pressure (BP) response to ampreloxetine.

**Methods:** Patients with nOH were enrolled in sequential Phase 3 trials. Patients received ampreloxetine (10 mg) or placebo once-daily for 4 weeks in a randomized double-blind placebo-controlled study [SEQUOIA]. All patients then received ampreloxetine during a 16-week open-label phase followed by a 6-week withdrawal study where patients were randomized to placebo or ampreloxetine (10 mg) [REDWOOD]. Plasma concentrations of norepinephrine (NE) and its main neuronal metabolite 3,4-dihydroxyphenlglycol (DHPG) were measured at baseline and after ampreloxetine administration. Standing and supine BP were also assessed.

**Results:** Ampreloxetine administration was associated with a 48% increase ($p<0.05$) in plasma NE levels and a concomitant 22% decline ($p < 0.05$) in plasma DHPG during the initial 4-week study. No change in aplasma NE or DHPG levels was observed after placebo administration. Continued administration of ampreloxetine for an additional 4 weeks was associated with a further 10% increase in NE plasma levels and 13% decline in DHPG. Similar changes in plasma NE and DHPG levels were observed in MSA and PD/PAF patients. Standing BP (3 min) was maintained in the ampreloxetine-treated patients at the conclusion of the 6-week randomized withdrawal treatment period; standing systolic BP was 8.6 mmHg [95% CI: 0.8, 16.3; $p<0.05$] higher in the ampreloxetine-treated patients relative to placebo. The effect of ampreloxetine on standing systolic BP (3 min) was most pronounced in patients with MSA; standing systolic BP was 15.7 mmHg [95% CI: 3.2, 28.1; $p < 0.05$) higher in the ampreloxetine-treated patients with MSA relative to placebo. No clinically relevant changes were observed in supine BP between treatment groups.

**Conclusions:** Ampreloxetine induces persistent elevation of plasma NE and reductions in DHPG that are consistent with reduced neuronal reuptake and metabolism of NE. The resulting pressor effect of ampreloxetine is most pronounced in patients with MSA.

**Theravance Biopharma, Inc. Announces Results from Study 0170, a Second Phase 3 Study of Ampreloxetine, in Patients with Symptomatic Neurogenic Orthostatic Hypotension (nOH)**

- *Results from Study 0170 show a benefit in study patients with multiple system atrophy (MSA)*
- *Company beginning discussions with potential strategic partners and planning health authority interactions to expedite ampreloxetine as a possible treatment option for patients with symptomatic nOH*
- *Company remains focused on respiratory therapeutics, value creation for shareholders and reiterates plan to be sustainably cash-flow positive by the second half of the year*

DUBLIN, April 4, 2022 /PRNewswire/ -- Theravance Biopharma, Inc. ("Theravance Biopharma" or the "Company") (NASDAQ: TBPH) today announced results from the second Phase 3 study, Study 0170 (n=128 out of n=154 planned), assessing the durability of clinical effect of ampreloxetine compared to placebo for the treatment of symptomatic nOH. Study 0170 was a 22-week Phase 3 study comprised of a 16-week open-label period followed by a 6-week double-blind, placebo-controlled, randomized withdrawal period. The primary endpoint of treatment failure at week 6 of the randomized withdrawal period was defined as a worsening of both Orthostatic Hypotension Symptom Assessment Scale (OHSA) question #1 and Patient Global Impression of Severity (PGI-S) scores by 1.0 point.

The primary endpoint was not statistically significant for the overall population of patients which included patients with Parkinson's disease (PD), pure autonomic failure (PAF) and MSA (odds ratio=0.6; p-value=0.196). The odds ratio suggests that patients receiving ampreloxetine had a 40% reduction in the odds of treatment failure compared to placebo.

The pre-specified subgroup analysis by disease type suggests the benefit seen in patients receiving ampreloxetine was largely driven by MSA patients (n=40). An odds ratio of 0.28 (95% CI: 0.05, 1.22) was observed in MSA patients indicating a 72% reduction in the odds of treatment failure with ampreloxetine compared to placebo. The benefit to MSA patients was observed in multiple endpoints including OHSA composite, Orthostatic Hypotension Daily Activities Scale (OHDAS) composite, Orthostatic Hypotension Questionnaire (OHQ) composite and OHSA #1 (see figure below). Notably, patients withdrawn to placebo had a clinically relevant decrease in standing blood pressure; there was no decrease for patients remaining on ampreloxetine. While the same benefit was not apparent in patients with PD or PAF, the Company continues to analyze the data to better understand this observation. Throughout the study, there was no indication of worsening of supine hypertension based on 24-hour monitoring. Data suggest that ampreloxetine was well-tolerated and no new safety signals were identified.

| DRUG | MECHANISM OF ACTION | DOSE |
|---|---|---|
| Etilefrine | α and β adrenergic agonist | 2.5 – 5mg TID |
| Yohimbine | α2 adrenergic receptor antagonist | 6mg/day to 4mg TID |
| Desmopressin NOCTURIA | Synthetic vasopressin analogue (action on V2 receptors in renal collecting tubules) | Nasal spray (10-40 mcg) or orally 100-400 mcg/day |
| Erythropoietin ANEMIA | Increases production of red blood cells | 25 to 75 units/Kg 3 times/week |
| Octreotide (somatostatin analogue) POST-PRANDIAL HYPOTENSION | Inhibits the release of vasoactive gastrointestinal peptides in response to food ingestion | 50 mcg subcutaneously 30 min before each meal |
| Acarbose POST-PRANDIAL HYPOTENSION | Alpha-glucosidase inhibitor and hypoglycemic agent | 50mg before meal |

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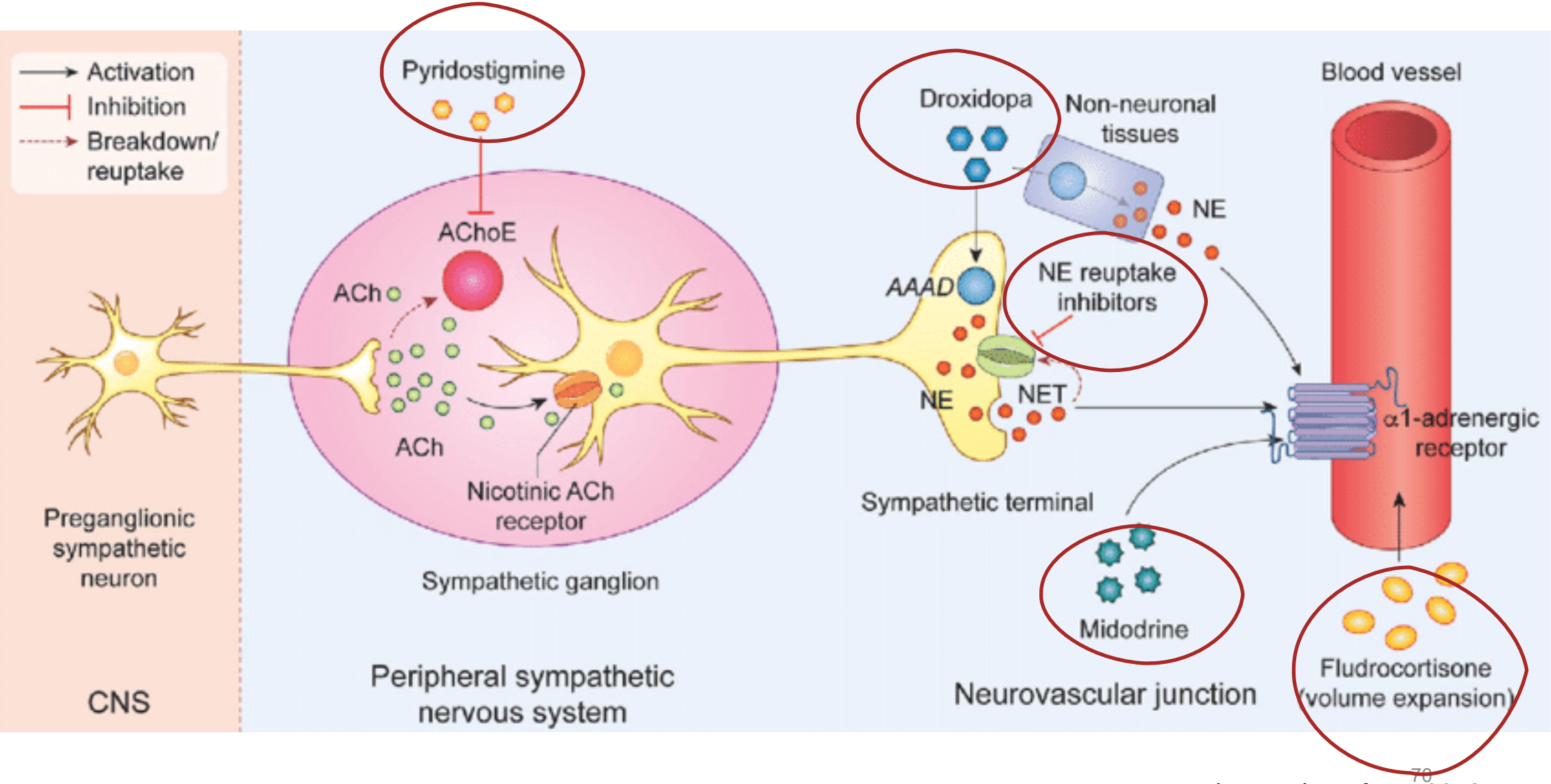
**4.Combination Pharmacologic Measures**

*Gibbons et al. 2017*




*Palma and Kaufman 2018*

| DRUG | MECHANISM OF ACTION | DOSE | SIDE EFFECTS |
|---|---|---|---|
| Midodrine<br>FDA APPROVED | Peripheral α1-adrenergic agonist → arterial and venous vasoconstriction | 2.5-10 mg, 2-3 times/day (no later than 4 p.m. to avoid supine hypertension at night-time) | Supine hypertension, headache, goose bumping, scalp itching, urinary urgency or retention |
| Droxidopa<br>FDA APPROVED | Norepinephrine precursor | 100-600 mg, 3 times/day | Supine hypertension, headache, dizziness, nausea |
| Fludrocortisone<br>OFF-LABEL | Increase renal sodium and water reabsorption → volume expansion | 0.1-0.2 mg, once daily | Supine hypertension, headache, worsening heart failure, edema, hypokalemia |
| Pyridostigmine<br>OFF-LABEL | Inhibitor of cholinesterase → enhances signal transmission in the autonomic ganglia while upright | 30-60 mg, 2-3 times/day | Bradycardia, increased salivation, abdominal cramps, diarrhoea |

# Pharmacologic treatment – *what's new?*

- **Norepinephrine reuptake inhibitors**
  - ✓ Atomoxetine
  - ✓ Ampreloxetine

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BRIEF REPORT

# Implanted System for Orthostatic Hypotension in Multiple-System Atrophy

Jordan W. Squair, Ph.D., Maxime Berney, M.D., Mayte Castro Jimenez, M.D., Nicolas Hankov, M.Sc., Robin Demesmaeker, Ph.D., Suje Amir, M.Sc., Aurelie Paley, M.Sc., Sergio Hernandez-Charpak, M.Sc., Gregory Dumont, Ph.D., Leonie Asboth, Ph.D., Gilles Allenbach, M.D., Fabio Becce, M.D., Patrick Schoettker, M.D., Gregoire Wuerzner, M.D., Julien F. Bally, M.D., Grégoire Courtine, Ph.D., and Jocelyne Bloch, M.D.

## SUMMARY

Orthostatic hypotension is a cardinal feature of multiple-system atrophy. The upright posture provokes syncopal episodes that prevent patients from standing and walking for more than brief periods. We implanted a system to restore regulation of blood pressure and enable a patient with multiple-system atrophy to stand and walk after having lost these abilities because of orthostatic hypotension. This system involved epidural electrical stimulation delivered over the thoracic spinal cord with accelerometers that detected changes in body position. (Funded by the Defitech Foundation.)

From the Center for Neuroprosthetics and the Brain Mind Institute, School of Life Sciences, Swiss Federal Institute of Technology (EPFL) (J.W.S., N.H., R.D., S.A., A.P., S.H.-C., G.D., L.A., G.C., J.B.), the Department of Clinical Neuroscience (J.W.S., N.H., R.D., S.A., A.P., S.H.-C., G.D., L.A., G.C., J.B.), the Service of Neurosurgery (J.W.S., G.C., J.B.), the Service of Nephrology and Hypertension (M.B., G.W.), the Service of Neurology (M.C.J., J.F.B.), the Department of Diagnostic and