Sabato 2 marzo 2019

QUARTA SESSIONE: Disturbi del Movimento
Moderatore senior: **Roberto Eleopra**, *Milano*
Moderatore young: **Giulia Paparella**, *Roma*

9.00 Argomenti di pratica clinica
HOT TOPIC 1: Management del Morbo di Parkinson in fase iniziale
Leonardo Lopiano, *Torino*
HOT TOPIC 2: Management della disautonomia nei Disturbi del Movimento
Pietro Cortelli, *Bologna*

9.30 Novità sull'argomento in fatto di terapia
Giovanni Palermo, *Pisa*

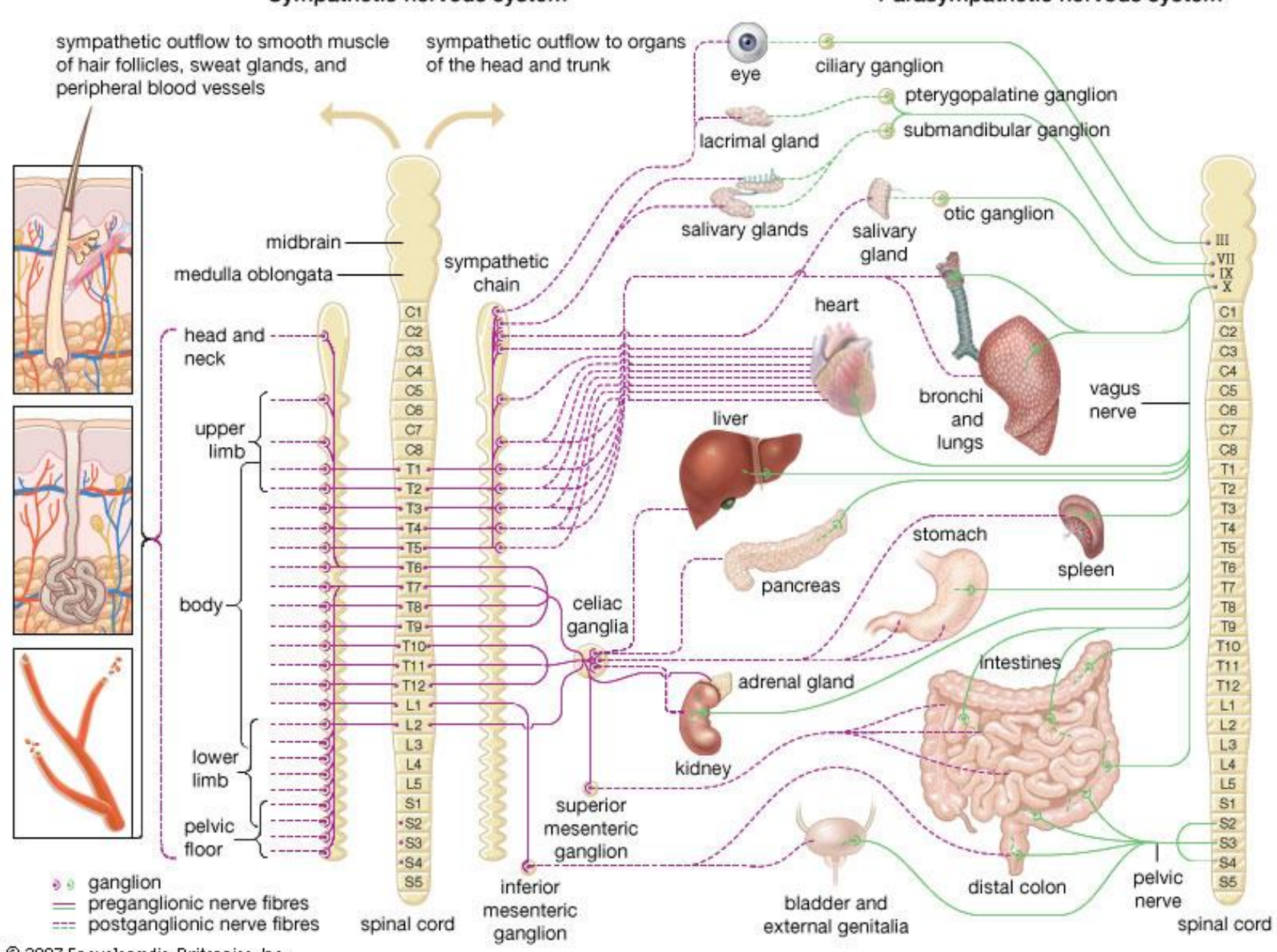
9.50 Caso clinico

10.05 Discussione interattiva

10.30 Neuroquiz a tempo

11.00 Pausa caffé

Pietro Cortelli
IRCCS Istituto delle Scienze Neurologiche di Bologna
DIBINEM, Alma Mater Studiorum - Università di Bologna



Autonomic manifestations of Parkinson's disease.

Manifestation	Pathophysiology	Anatomica substrate (α-SYN associated neuropathology)
Orthostatic hypotension	Impaired sympathetic vasoconstriction	Sympathetic ganglia, followed by IML and in some cases rostral VLM
Urinary urgency and urge incontinence	Detrusor overactivity	Impaired dopaminergic control at the basal-ganglia–frontal circuits (?)
Sexual dysfunction	Erectile dysfunction, Changes in libido	Involvement of pelvic nuclei and ganglia (?), Dopaminergic dysregulation in the hypothalamus, ventral striatum and frontal lobe (?)
Dry mouth	Impaired cranial parasympathetic output to salivary glands	Submandibular glands,Submandibular ganglion, Salivatory nucleus
Drooling	Impaired swallowing	Dysfunction of the swallowing central pattern generator
Oropharyngeal dysphagia	Impaired coordination of activity of pharyngeal and upper esophageal muscles	Dysfunction of the swallowing central pattern generator (PPN)
Upper gastrointestinal dysmotility	Impaired vagal control of smooth muscle relaxation and contraction in the esophagus and stomach	Myenteric plexus, Dorsal motor nucleus of the vagus
Constipation	Impaired local peristaltic reflexes in the intestine and colon	Myenteric plexus (rostrocaudal gradient).
Defecatory dysfunction	Contraction of the puborectal muscle during evacuation	Dysfunction of the al rectoanal reflex
Hyperhidrosis	Sympathoexcitation during “off-periods”, Compensatory	Thermoregulatory pathways (?), Skin sympathetic denervation (?)

Come si definisce ipotensione ortostatica?

Definizione

Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome

Roy Freeman · Wouter Wieling · Felicia B. Axelrod · David G. Benditt · Eduardo Benarroch · Italo Biaggioni · William P. Cheshire · Thomas Chelimsky · Pietro Cortelli · Christopher H. Gibbons · David S. Goldstein · Roger Hainsworth · Max J. Hilz · Giris Jacob · Horacio Kaufmann · Jens Jordan · Lewis A. Lipsitz · Benjamin D. Levine · Phillip A. Low · Christopher Mathias · Satish R. Raj · David Robertson · Paola Sandroni · Irwin Schatz · Ron Schondorff · Julian M. Stewart · J. Gert van Dijk

Clin Auton Res (2011) 21:69–72
DOI 10.1007/s10286-011-0119-5

1. L'ipotensione ortostatica (orthostatic hypotension, OH) è una riduzione sostenuta della pressione sistolica di almeno 20 mmHg o della pressione diastolica di almeno 10 mmHg entro 3 minuti di ortostatismo o di un TILT-test inclinato almeno a 60°.

1. L'OH è un segno clinico e può decorrere sintomatica o asintomatica.

2. Nei pazienti con **ipertensione supina**, una riduzione della pressione sistolica di 30 mmHg può essere un criterio più appropriato per la diagnosi di OH poiché l'intensità della caduta della pressione arteriosa dipende dal valore basale della pressione.

Clin Auton Res (2011) 21:69–72
DOI 10.1007/s10286-011-0119-5

CONSENSUS STATEMENT

Variabili confondenti:

1. *Età:* la caduta della pressione aumenta con l'età, è maggiore nei pazienti anziani.
2. *Ipertensione supina:* la caduta della pressione può rispettare i criteri della OH anche se i valori pressori rimangono superiori alla norma
3. *Variabilità diurna:* la OH è più comune e grave al mattino
4. *Ingestione di cibo:* in particolare i pazienti con disautonomia possono presentare cadute significative di pressione dopo i pasti
5. *Farmaci:* diuretici, antiipertensivi, alfa-antagonisti (es. farmaci per ipertrofia prostatica), antidepressivi (in particolare i triciclici), neurolettici, inibitori della 5-fosfodiesterasi (per disfunzione erettile) dopamino agonisti e levo-dopa, ecc..
6. *Altri fattori:* idratazione, temperatura ambientale, allettamento prolungato

Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome

Clin Auton Res (2011) 21:69–72
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CONSENSUS STATEMENT

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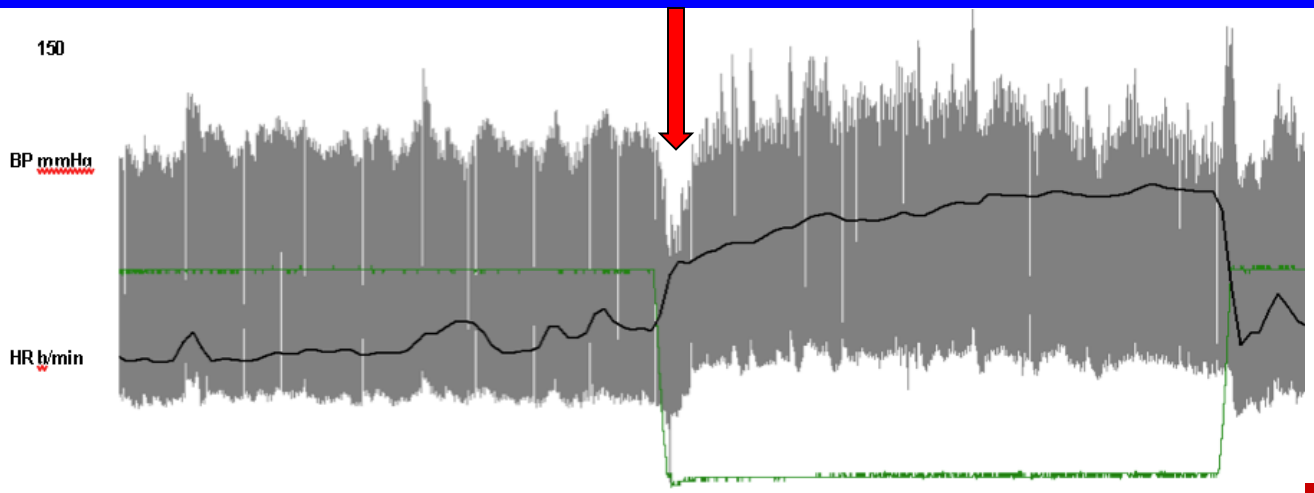
Ipotensione ortostatica iniziale

1. Esagerata caduta transitoria della pressione (> 40 mmHg di sistolica and/or > 20 mmHg di diastolica) ***entro 15 s di ortostatismo***
2. Si può osservare solo attraverso una misurazione battito a battito della PA
3. Può essere causa di sincope



Clin Auton Res (2011) 21:69–72
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CONSENSUS STATEMENT

Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome

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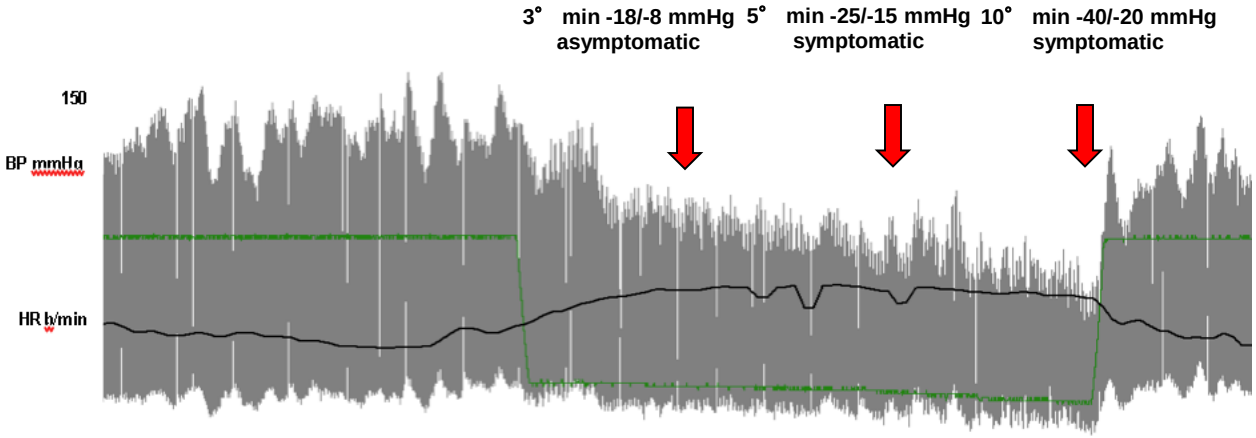
Ipotensione ortostatica ritardata

1. Ipotensione ortostatica sintomatica ***dopo 3 minuti di ortostatismo***
2. Il significato clinico di questa non è noto (forma lieve e precoce di insufficienza simpatica ?)
3. Può essere rilevata aumentando oltre i 3 minuti il tempo di stress ortostatico



Parkinsonism and Related Disorders xxx (2011) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Review

Prevalence of orthostatic hypotension in Parkinson's disease: A systematic review and meta-analysis☆

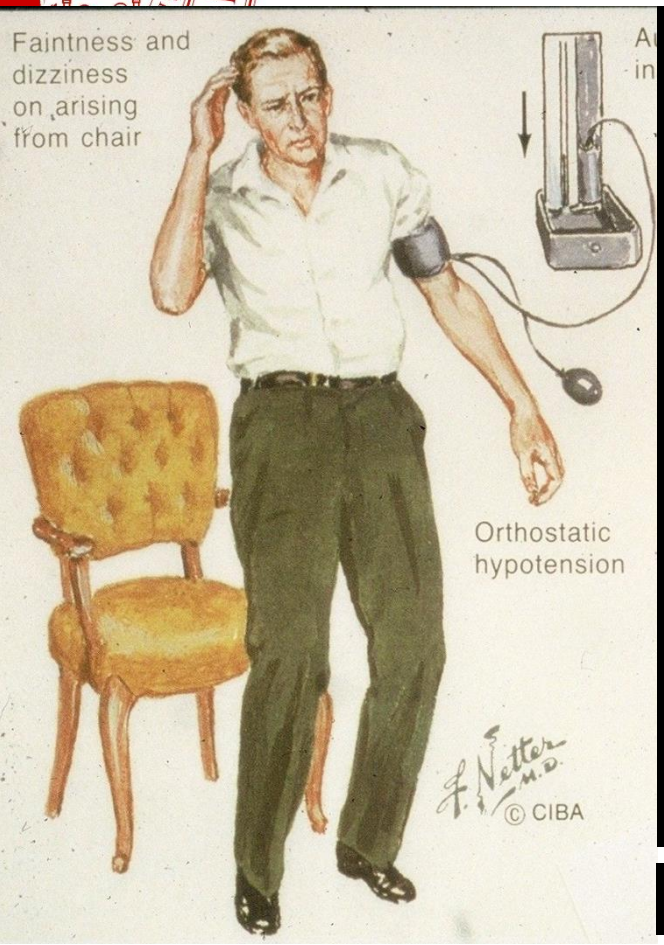
Daan C. Velseboer [a,*], Rob J. de Haan [b], Wouter Wieling [c], David S. Goldstein [d], Rob M.A. de Bie [a]

A B S T R A C T

Background: Although orthostatic hypotension (OH) is recognized as one of the main non-motor symptoms of Parkinson's disease (PD), there is inconsistent evidence about the prevalence of OH in PD. To estimate the prevalence of OH in PD more precisely we conducted a systematic review of the literature.
Methods: From PubMed and Embase searches with predefined inclusion criteria, we identified studies published up till December 2009. Prevalence numbers from studies were pooled using a non-linear random-effects meta-analysis.
Results: We found 25 studies from which the prevalence of OH could be calculated. The pooled estimate of the point prevalence of OH in PD was 30·1% (95% CI: 22·9% to 38·4%). We found a large statistical heterogeneity between studies which could not be reduced by several subgroup analyses.
Conclusions: The estimated prevalence of OH in PD is 30%. However, due to the large heterogeneity between studies this pooled estimate should be interpreted with caution. More data from unselected population-based cohorts are needed.

Come sospettare la presenza di ipotensione ortostatica neurogena?

Orthostatic Hypotension



Symptoms

- ✓Dizziness, lightheadedness
- ✓blurred vision
- ✓difficulties to concentrate
- ✓cognitive impairment
- ✓coat-hanger-like neck pain
- ✓Nausea, headache, palpitations
- ✓Weakness, fatigue, lethargy
- ✓Syncope

Very rare symptoms: angina pectoris, oliguria

ANScovery System

SparkBio

COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 117 (2014) 267–276

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journal homepage: www.intl.elsevierhealth.com/journals/cmpb

A new integrated instrumental approach to autonomic nervous system assessment

CrossMark

I. Corazza[a,*,1], *G. Barletta*[b,c,1], *P. Guaraldi*[b,c], *A. Cecere*[b,c], *G. Calandra-Buonaura*[b,c], *E. Altini*[a], *R. Zannoli*[a], *P. Cortelli*[b,c]

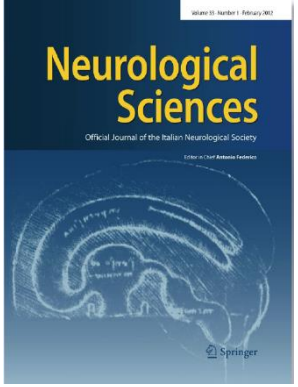
[a] *Experimental, Diagnostic and Specialty Medicine Department, University of Bologna, Italy*
[b] *Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy*
[c] *IRCCS, Institute of Neurological Sciences of Bologna, Bologna, Italy*

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



- Orthostatic hypotension was associated with a significant worsening of cognitive performances, affecting both global cognitive functioning and specific tasks, mainly exploring executive functions
- The assessment of cognitive function in patients with neurogenic orthostatic hypotension should be performed considering the body's position of the subject

Table 2 Mean results to the neuropsychological assessments while supine (Supine) and during head-up tilt (HUT)

Neuropsychological test	Supine results (mean ± SD)	HUT results (mean ± SD)	*p* value
BMDB FR	2.02 ± 0.60	1.19 ± 0.53	0.005*
AVLT			
Short-term	38.85 ± 5.30	38.15 ± 7.17	0.68
Long-term	7.06 ± 2.44	6.64 ± 2.75	0.54
Immediate visual memory	21.52 ± 2.20	19.59 ± 1.65	0.03*
Visual search (Barrage test)	−0.16 ± 1.34	2.65 ± 4.10	0.03*
Verbal abstract thinking (Analogies test)	17.85 ± 1.84	14.95 ± 3.33	0.02*
Time reactions to visual stimuli			
Reaction time (ms)	441.59 ± 66.26	451.83 ± 96.53	0.80
Omission errors	0.00 ± 0.00	0.20 ± 0.42	0.16
Assessment errors	1.60 ± 1.58	2.00 ± 1.41	0.16
Total errors	1.60 ± 1.58	2.20 ± 1.32	0.06
Finger tapping test			
1 session	82.40 ± 26.06	85.20 ± 26.64	0.65
2 session	76.60 ± 27.53	82.60 ± 29.83	0.51
3 session	82.70 ± 27.16	81.20 ± 28.89	0.59
Mean	80.56 ± 25.95	83.00 ± 27.95	0.96
MAP (mmHg)	106 ± 17	70 ± 15	
HR (bpm)	64 ± 8	74 ± 10	

BMDB FR final result of Brief Mental Deterioration battery, *HR* heart rate, *MAP* mean arterial pressure

* Statistically significant

Cognitive and PAF

OPEN ACCESS Freely available online

January 2014 | Volume 9 | Issue 1 | e85020

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.

Neurol Sci
DOI 10.1007/s10072-014-1686-8

REVIEW ARTICLE

Orthostatic hypotension and cognitive impairment: a dangerous association?

Luisa Sambati · Giovanna Calandra-Buonaura · Roberto Poda · Pietro Guaraldi · Pietro Cortelli

Received: 5 August 2013 / Accepted: 12 February 2014

REVIEW

'Under pressure': is there a link between orthostatic hypotension and cognitive impairment in α-synucleinopathies?

Sean J Udow,[1,2,3,4] Andrew D Robertson,[4] Bradley J MacIntosh,[4] Alberto J Espay,[5] James B Rowe,[6,7] Anthony E Lang,[3,8,9] Mario Masellis[1,2,3,4,10]

Udow SJ, *et al*. *J Neurol Neurosurg Psychiatry* 2016;**87**:1311–1321. doi:10.1136/jnnp-2016-314123

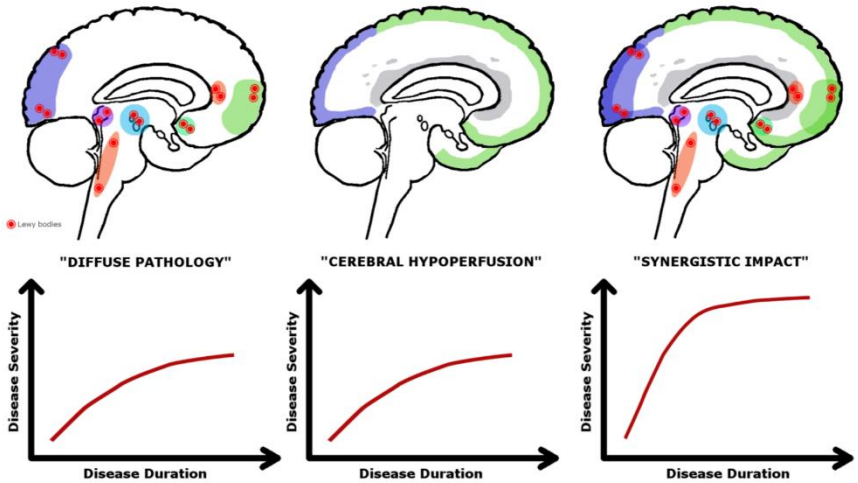
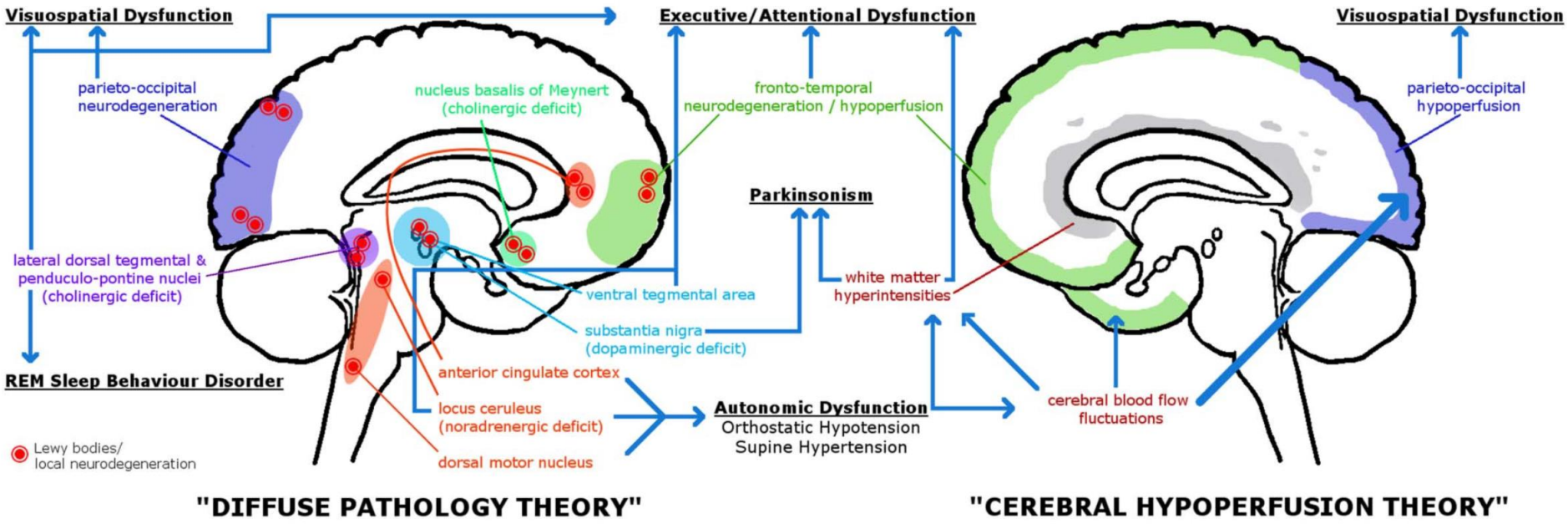


Figure 3 A graphical representation of the synergistic effect caused by contributions from the 'diffuse neuropathology theory' and 'cerebral hypoperfusion theory'. It is likely that the pathophysiologic mechanisms underlying each theory interact with each other, where diffuse neuropathology causes OH and cognitive impairment, OH contributes to cognitive impairment and OH contributes to worsening of neuropathology. Together, these mechanisms increase the rate and severity of disease progression. OH, orthostatic hypotension.



La nOH è sempre associata a ipertensione supina?

Come definisco ipertensione supina in presenza di nOH?

Clin Auton Res
DOI 10.1007/s10286-015-0336-4

RESEARCH ARTICLE

Supine hypertension in Parkinson's disease and multiple system atrophy

Alessandra Fanciulli[1,2] · Georg Göbel[3] · Jean Pierre Ndayisaba[1] · Roberta Granata[1] · Susanne Duerr[1] · Stefano Strano[4] · Carlo Colosimo[5] · Werner Poewe[1] · Francesco E. Pontieri[2,6] · Gregor K. Wenning[1]

Abstract

Objective Supine hypertension (SH) is a feature of cardiovascular autonomic failure that often accompanies orthostatic hypotension and may represent a negative prognostic factor in parkinsonian syndromes. Here we investigated the frequency rate as well as the clinical and tilt test correlates of SH in Parkinson's disease (PD) and multiple system atrophy (MSA).

Methods 197 PD (33 demented) and 78 MSA (24 MSA-Cerebellar, 54 MSA-Parkinsonian) patients who had undergone a tilt test examination were retrospectively included. Clinical-demographic characteristics were collected from clinical records at the time of the tilt test examination.

Results SH (>140 mmHg systolic, >90 mmHg diastolic) occurred in 34 % of PD patients ($n = 66$, mild in 71 % of patients, moderate in 27 %, severe in 2 %) and 37 % of MSA ones ($n = 29$, mild in 55 % of patients, moderate in 17 %, severe in 28 %). No difference was observed in SH frequency between demented versus gender-, age- and disease duration-matched non-demented PD patients, or between patients with the parkinsonian (MSA-P) versus the cerebellar (MSA-C) variant of MSA. In PD, SH was associated with presence of cardiovascular comorbidities ($p = 0.002$) and greater systolic ($p = 0.007$) and diastolic ($p = 0.002$) orthostatic blood pressure fall. Orthostatic hypotension ($p = 0.002$), and to a lesser degree, lower daily dopaminergic intake ($p = 0.01$) and use of anti-hypertensive medications ($p = 0.04$) were associated with SH in MSA.

Interpretation One-third of PD and MSA patients suffer from mild to severe SH, independently of age, disease duration or stage. In PD, cardiovascular comorbidities significantly contribute to the development of SH, while in MSA, SH appears to reflect cardiovascular autonomic failure.

Electronic supplementary material The online version of this article (doi:10.1007/s10286-015-0336-4) contains supplementary material, which is available to authorized users.

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Clinical Autonomic Research (2018) 28:355–362
https://doi.org/10.1007/s10286-018-0529-8

CONSENSUS STATEMENT

Consensus statement on the definition of neurogenic supine hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS)

Endorsed by the European Academy of Neurology (EAN) and the European Society of Hypertension (ESH)

Alessandra Fanciulli[1] · Jens Jordan[2] · Italo Biaggioni[3] · Giovanna Calandra–Buonaura[4,5] · William P. Cheshire[6] · Pietro Cortelli[4,5] · Sabine Eschlboeck[1] · Guido Grassi[7,8] · Max J. Hilz[9,10] · Horacio Kaufmann[11] · Heinz Lahrmann[12] · Giuseppe Mancia[13] · Gert Mayer[14] · Lucy Norcliffe–Kaufmann[11] · Anne Pavy–Le Traon[15,16] · Satish R. Raj[17] · David Robertson[3] · Isabel Rocha[18] · Walter Struhal[19] · Roland Thijs[20,21] · Konstantinos P. Tsioufis[22] · J. Gert van Dijk[21] · Gregor K. Wenning[1]

Abstract

Purpose Patients suffering from cardiovascular autonomic failure often develop neurogenic supine hypertension (nSH), i.e., high blood pressure (BP) in the supine position, which falls in the upright position owing to impaired autonomic regulation. A committee was formed to reach consensus among experts on the definition and diagnosis of nSH in the context of cardiovascular autonomic failure.

Methods As a first and preparatory step, a systematic search of PubMed-indexed literature on nSH up to January 2017 was performed. Available evidence derived from this search was discussed in a consensus expert round table meeting in Innsbruck on February 16, 2017. Statements originating from this meeting were further discussed by representatives of the American Autonomic Society and the European Federation of Autonomic Societies and are summarized in the document presented here. The final version received the endorsement of the European Academy of Neurology and the European Society of Hypertension.

Results In patients with neurogenic orthostatic hypotension, nSH is defined as systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg, measured after at least 5 min of rest in the supine position. Three severity degrees are recommended: mild, moderate and severe. nSH may also be present during nocturnal sleep, with reduced-dipping, non-dipping or rising nocturnal BP profiles with respect to mean daytime BP values. Home BP monitoring and 24-h-ambulatory BP monitoring provide relevant information for a customized clinical management.

Conclusions The establishment of expert-based criteria to define nSH should standardize diagnosis and allow a better understanding of its epidemiology, prognosis and, ultimately, treatment.

Definitions

Supine hypertension

In patients with proven nOH, nSH is defined as systolic BP of ≥ 140 mmHg and/or diastolic BP of ≥ 90 mmHg, measured after at least 5 min of rest in the supine position.

We propose the following ranges to define the severity of nSH in autonomic failure:

- Mild nSH: systolic BP values of 140–159 mmHg or diastolic BP values of 90–99 mmHg.
- Moderate nSH: systolic BP values of 160–179 mmHg or diastolic BP values of 100–109 mmHg.
- Severe nSH: systolic BP values of ≥ 180 mmHg or diastolic BP values of ≥ 110 mmHg.

Nocturnal hypertension

Patients with cardiovascular autonomic failure frequently show nSH also during sleep, i.e. nocturnal hypertension,

Clinical Autonomic Research (2018) 28:355–362

with loss of the physiological nocturnal BP fall at night of ≥ 10% while supine and asleep (dipping). Two main pathological nocturnal BP profiles are distinguished:

- Reduced-dipping: characterized by a mean nocturnal BP reduction of < 10% with respect to mean daytime BP values.
- Non-dipping or rising: when the mean BP does not decrease or even increases during the night with respect to daytime [7, 8].

La nOH è un segno ma mi aiuta nel sospettare la diagnosi giusta?

Clin Auton Res (2006) 16 : 46–54
DOI 10.1007/s10286-006-0317-8

RESEARCH ARTICLE

David S. Goldstein

Orthostatic hypotension as an early finding in Parkinson's disease

- Early if the pt had OH before,concurrent with, or starting within 1 year after onset of a symptomatic movement disorder
- MSA excluded with myocardial PET; OH documented by autonomic testing
- Among the 35 PD+OH 60% had documentation of OH as an early finding. In 4 OH had preceded parkinsonism, and in 4 others, OH had dominated the early clinical picture, even after cessation of levodopa treatment.

NEUROLOGY 2004;63:1093–1095

Autonomic failure as the initial presentation of Parkinson disease and dementia with Lewy bodies

Horacio Kaufmann, MD; Kirsty Nahm, MD; Dushyant Purohit, MD; and David Wolfe, MD

ORIGINAL CONTRIBUTION

Orthostatic Hypotension in De Novo Parkinson Disease

Arch Neurol. 2003;60:1400-1404

Ubaldo Bonuccelli, MD; Claudio Lucetti, MD; Paolo Del Dotto, MD; Roberto Ceravolo, MD; Gianna Gambaccini, MD; Silvia Bernardini, MD; Giuseppe Rossi, PhD; Alberto Piaggesi, MD

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Hughes et al JNNP 1992

Step 2 Exclusion criteria for Parkinson's Disease

9) Early severe autonomic involvement

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

No more than 2 red flags are allowed for this category

Supportive criteria

(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:

a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).

b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

☐ 2. Presence of levodopa-induced dyskinesia

☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

Absolute exclusion criteria: The presence of any of these features rules out PD:

- ☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
- ☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
- ☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
- ☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
- ☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
- ☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
- ☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
- ☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
- ☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

Red flags

- ☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
- ☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
- ☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
- ☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- ☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  - a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  - b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
- ☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
- ☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
- ☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

Diagnostic Algorithm for interpreting OH

Is OH persistent and consistent ?

YES

Possible OH

NO

If episodic & unexpected consider neurocardiogenic syncope or other cause of TLoC

Is identifiable a cause of OH ?

- Drugs (vasodilators, chemiotherapeutics etc)
- Hypovolemia (dehydration, blood loss, adrenal insufficiency)
- Cardiac pump failure (heart block, aortic stenosis)
- Venous pooling (Prolonged recumbency, severe varicosities)
- Peripheral neuropathy (diabetes, amyloidosis, alcohol)
- CNS lesions (spinal cord injury,syringomyelia)

Is identifiable a cause of OH ?

YES

Treat underlying cause

NO

Possible neurogenic OH (go to autonomic lab)

Possible neurogenic OH ?

- Cardiovascular reflex tests
- Beat-to-beat responses to Valsalva
- Orthostatic plasma NE
- Orthostatic vascular resistence

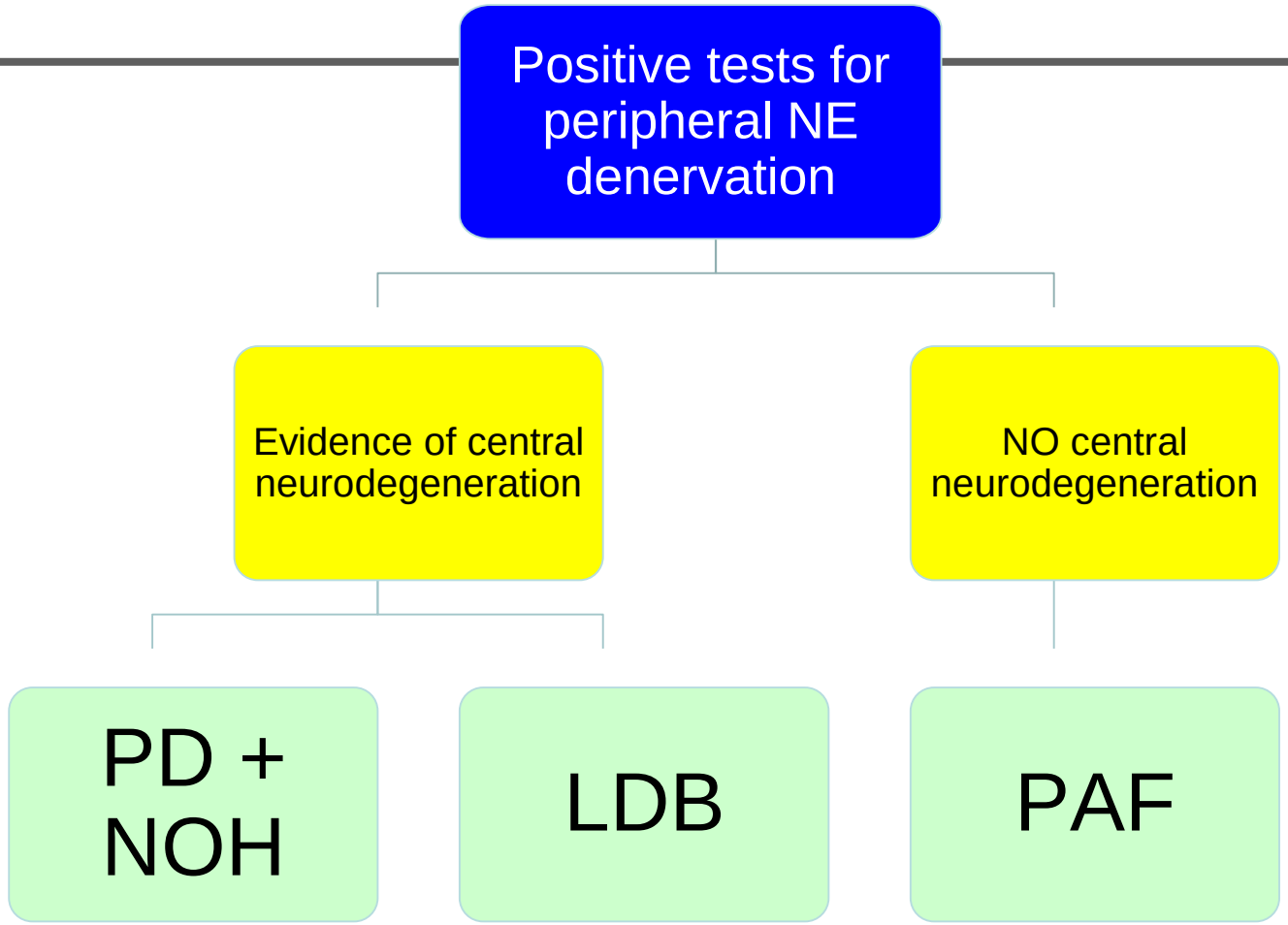
YES → Neurogenic OH

NO → Rule out hypovolemia or other non-neurogenic causes

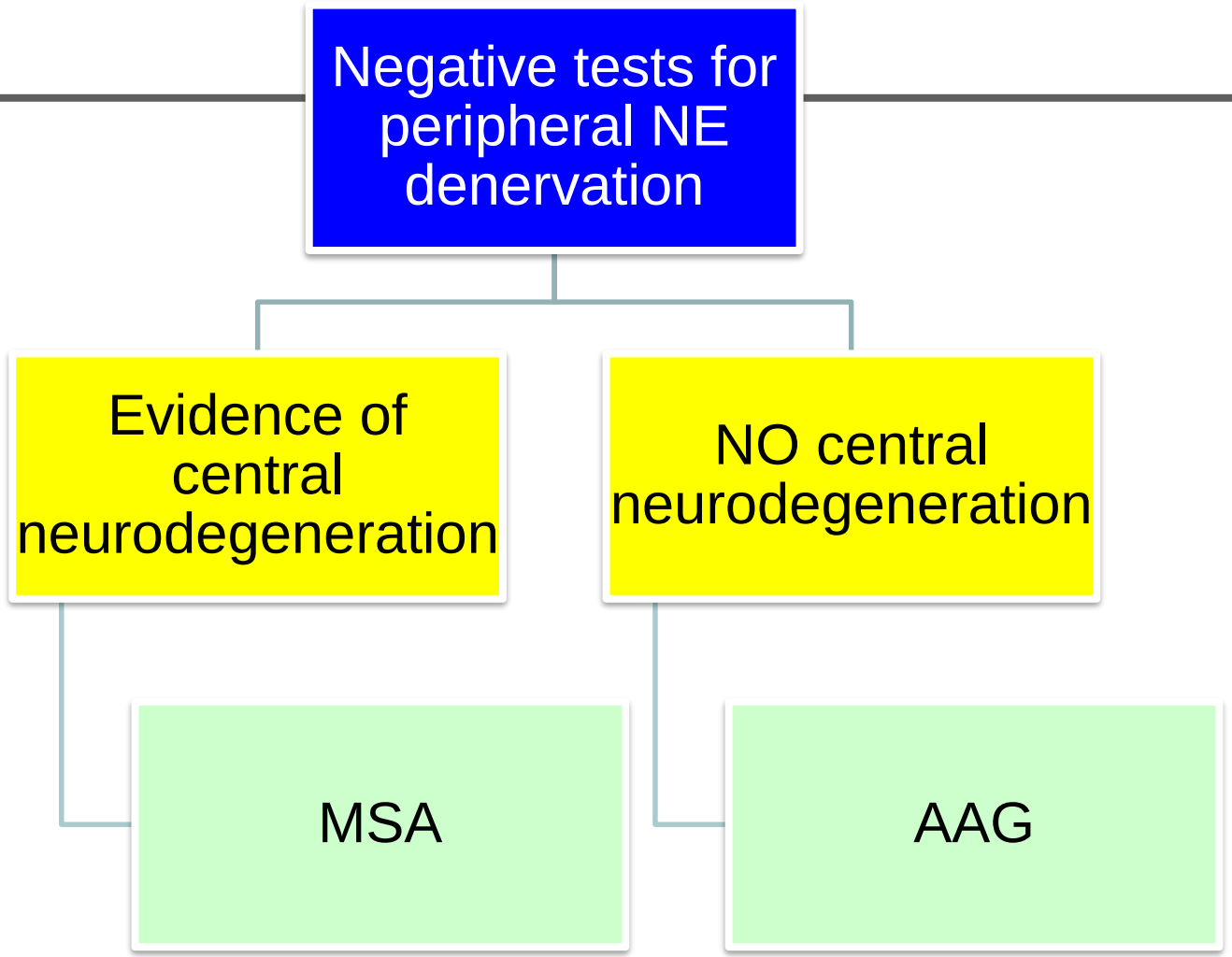
Is peripheral NE denervation present ?

- Cardiac sympathetic neuroimaging (MIBG)
- Supine plasma catechol
- Neuropharmacologic probes (infusion of NE)
- Cardiovascular reflex tests ?

Positive tests for peripheral NE denervation

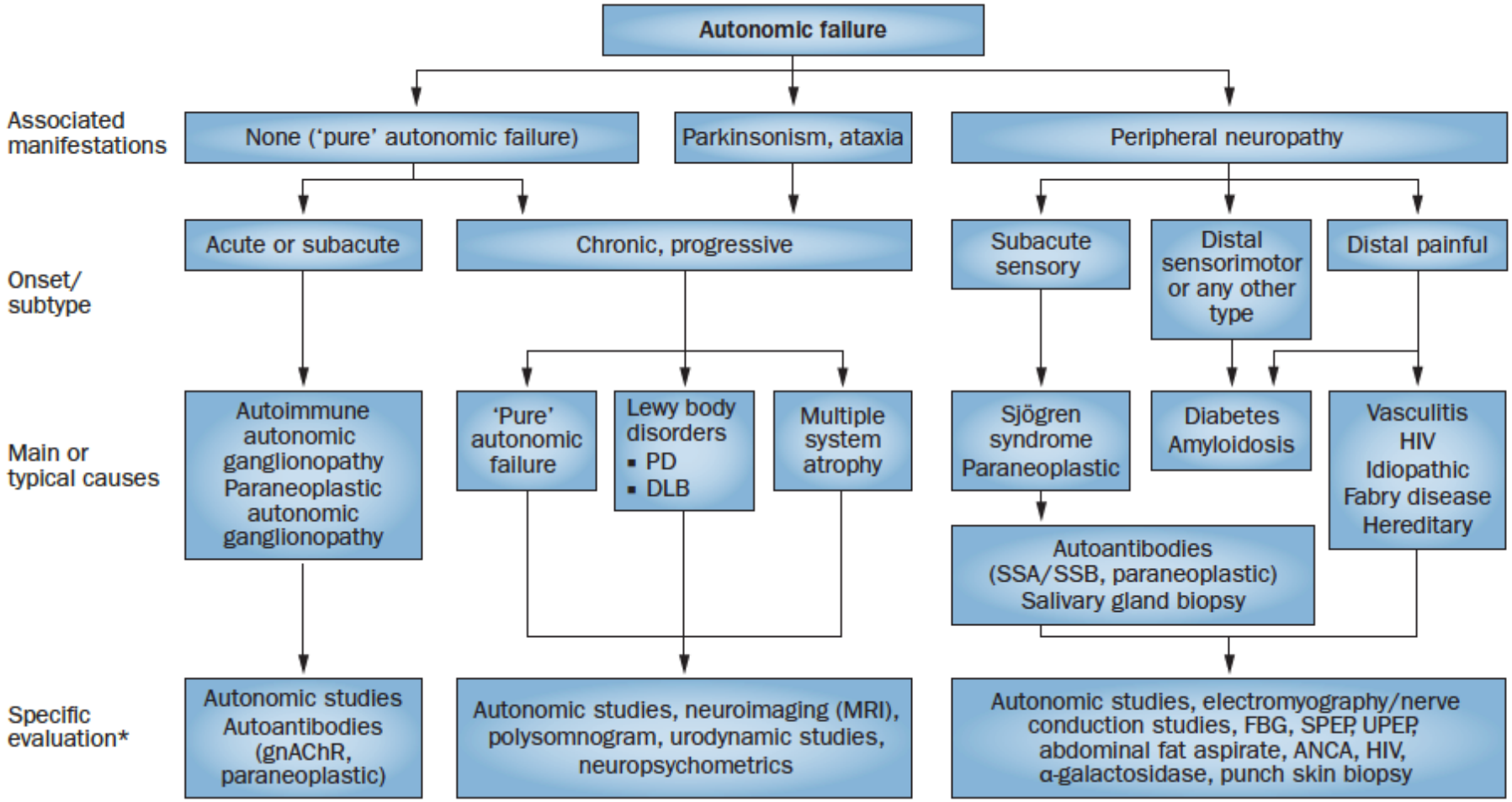


Negative tests for peripheral NE denervation



Evaluating the main causes of AF

Eduardo E. Benarroch Nat. Rev. Neurol. **10**, 396–407 (2014);



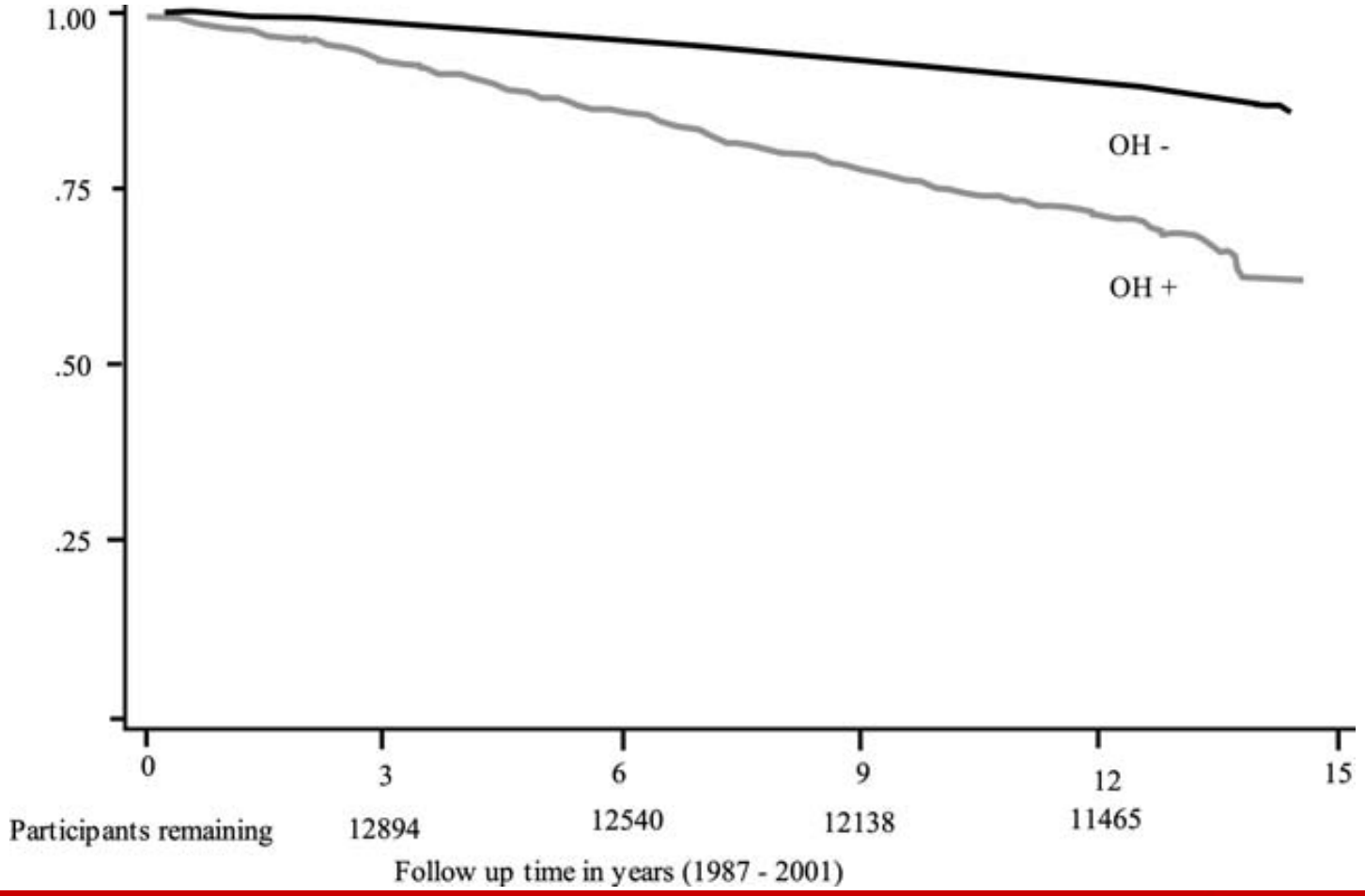
Perché è importante sapere se un pz ha nOH?

Importance of diagnosing OH

- OH may underlie **symptoms of cerebral hypoperfusion**
- OH is a **risk factor for falls** (Ooi WL, 2000)
- OH is an **independent predictor of all cause of mortality** (Masaki 1998, Rose 2006)
- OH is **predictor** in elderly people
  - **of ischemic stroke** (Eigenbrodt 2000)
  - **of white matter findings on cerebral MR** (Longstreth 1996)
- The **risk of vascular death** associated with OH is especially high among **diabetic** pts (Luukinen 2005)

Prognosi ipotensione ortostatica

Rose et al. Circulation 2006



RESEARCH ARTICLE

Autonomic Dysfunction in Parkinson's Disease: A Prospective Cohort Study

Aristide Merola, MD, PhD [1]*, Alberto Romagnolo, MD,[2] Michela Rosso, MD,[1] Ritika Suri, MD,[1] Zoe Berndt, MD,[1] Simona Maule, MD,[3] Leonardo Lopiano, MD, PhD,[2] and Alberto J. Espay, MD, MSc [1]

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[2]*Department of Neuroscience "Rita Levi Montalcini", University of Turin, Torino, Italy*
[3]*Department of Medical Sciences, Autonomic Unit and Hypertension Unit, University of Turin, Torino, Italy*

ABSTRACT: **Background**: Dysautonomia is a frequent and disabling complication of PD, with an estimated prevalence of 30-40% and a significant impact on the quality of life.

Objectives: To evaluate the rate of progression of dysautonomia and, in particular, orthostatic hypotension, in a cohort of unselected PD patients, and assess the extent to which the progression of dysautonomia affects activities of daily living, health-related quality of life, and health care utilization in PD.

Methods: We recruited 131 consecutive patients into a 12-month, prospective, observational cohort study. Clinical measures included the International Parkinson and Movement Disorder Society/UPDRS, the Scale for Outcomes in Parkinson Disease-Autonomic, the Orthostatic Hypotension Symptoms Assessment, and orthostatic blood pressure measurements. Health care utilization was quantified as the number of hospitalizations, emergency room visits, and outpatient clinic evaluations.

Results: The overall severity of autonomic symptoms, as measured by the the Orthostatic Hypotension Symptoms Assessment total score, worsened by 20% over 12 months ($P < 0.001$), with an overall increase in orthostatic hypotension prevalence from 31.1% to 46.7% ($P < 0.001$). Worsening of autonomic symptoms was independently associated with deterioration in daily living activities ($P = 0.021$) and health-related quality of life ($P = 0.025$) adjusting for disease duration, cognitive impairment, and motor severity. Regardless of symptomatic status, orthostatic hypotension was associated with greater deterioration in daily living activities, health care utilization, and falls ($P \leq 0.009$) compared to patients without orthostatic hypotension.

Conclusions: The severity of autonomic symptoms progressed by 20% over 1 year and was independently associated with impairments in daily living activities and health-related quality of life. Symptomatic and asymptomatic orthostatic hypotension were both associated with increased prevalence of falls and health care utilization.

Key Words: Parkinson's disease; autonomic; orthostatic hypotension; supine hypertension

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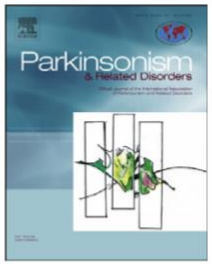

Orthostatic hypotension in Parkinson disease: Impact on health care utilization

Aristide Merola [a, *], Russell P. Sawyer [a], Carlo Alberto Artusi [b], Ritika Suri [a], Zoe Berndt [a], Jose' Ricardo Lopez-Castellanos [a], Jennifer Vaughan [a], Joaquin A. Vizcarra [a], Alberto Romagnolo [b], Alberto J. Espay [a]

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ABSTRACT

Introduction: Orthostatic hypotension (OH) represents a frequent yet overlooked source of disability in Parkinson disease (PD). In particular, its impact on health care utilization has been insufficiently examined. We sought to determine the differential health care utilization in PD patients with (PDOH+) and without OH (PDOH−).

Methods: We quantified the emergency room (ER) visits, hospitalizations, outpatient clinic evaluations, phone calls, and e-mails from PD patients on whom supine and orthostatic blood pressure (BP) measurements were obtained during routine clinical practice between June 2013 and July 2016. Comparative costs between PDOH+ and PDOH− were adjusted for age, disease duration, motor severity, levodopa equivalent daily dose, and Montreal Cognitive Assessment.

Results: From a total of 317 PD patients, 29.3% were classified as PDOH+ ($n = 93$) and 70.6% as PDOH− ($n = 224$) over 30.2 ± 11.0 months, in which there were 247 hospitalizations, 170 ER visits, 2386 outpatient evaluations, and 4747 telephone calls/e-mails. After-adjusting for relevant covariates, PDOH+ was associated with more hospitalization days (+285%; $p = 0.041$), ER visits (+152%; $p = 0.045$), and telephone calls/e-mails than PDOH− (+142%; $p = 0.009$). The overall health care-related cost in PDOH+ was 2.5-fold higher than for PDOH− ($25,205 ± $6546 vs. $9831 ± $4167/person/year; $p = 0.037$).

Conclusion: OH increases health care utilization in PD independently from age, disease duration, motor severity, dopaminergic treatment, and cognitive function.

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

Orthostatic hypotension in Parkinson's disease: Does it matter if asymptomatic?

Aristide Merola [a, *], Alberto Romagnolo [b], Michela Rosso [a], José Ricardo Lopez-Castellanos [a], Benjamin D. Wissel [a], Sydney Larkin [a], Andrea Bernardini [b], Maurizio Zibetti [b], Simona Maule [c], Leonardo Lopiano [b], Alberto J. Espay [a]

ABSTRACT

Introduction: Orthostatic hypotension (OH) may frequently be asymptomatic in patients with Parkinson's disease (PD). However, the relationship between symptomatic/asymptomatic status and functional disability remains unclear.

Methods: Using orthostatic blood pressure (BP) measurements and the Orthostatic Hypotension Symptom Assessment (OHSA) questionnaire, 121 consecutive PD patients without history of chronic hypertension and not taking alpha-adrenergic antagonists for bladder disorders were classified according to (1) OH symptomatic status, based on presence/absence of orthostatic symptoms (symptomatic OH: OHSA item 1 ≥ 1), and (2) OH severity, based on the magnitude of BP fall on the lying-to-standing test: OH- (<20/10 mmHg); moderate OH+ ($\geq$20/10 mmHg but < 30/15 mmHg); and severe OH+ ($\geq$30/15 mmHg). The primary endpoints were the activities of daily living/instrumental activities of daily living (ADL/iADL) and the Ambulatory Capacity Measure (ACM). Secondary endpoints included PD quality of life (PDQ-8) and prevalence of falls.

Results: The overall prevalence of OH+ was 30.6% (37/121 patients), with 62.2% symptomatic (23/37) and 37.8% asymptomatic (14/37). Symptomatic and asymptomatic OH + patients had similar impairments in ADL/iADL and ACM, significantly worse than OH- ($p \leq 0.035$). There was a trend for worse ADL/iADL and ACM scores in severe OH + compared to moderate OH+, but both were worse than OH- ($p \leq 0.048$). Symptomatic and asymptomatic OH + showed similar impairment in PDQ-8 and higher prevalence of falls compared to OH-.

Conclusions: Asymptomatic OH+ was associated with similar impairments in ADL/iADL and ACM than symptomatic OH+. These findings support screening for OH in PD patients regardless of postural lightheadedness.

Journal of Neurology
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ORIGINAL COMMUNICATION

Cardiovascular autonomic neuropathy and falls in Parkinson disease: a prospective cohort study

Alberto Romagnolo[1] · Maurizio Zibetti[1] · Aristide Merola[2] · Daniela Canova[1] · Marianna Sarchioto[3] · Elisa Montanaro[1] · Carlo Alberto Artusi[1] · Fabrizio Vallelonga[4] · Simona Maule[4] · Leonardo Lopiano[1]

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Abstract

Background Falls represent one of the main complications of Parkinson's disease (PD), significantly lowering quality of life. Cardiovascular autonomic neuropathy (cAN) is one of the key contributing factors to PD-associated falls. However, a direct quantification of its impact on the risk of falling in PD is still lacking. In this 12-month prospective study, we sought to evaluate the association between cAN and falls.

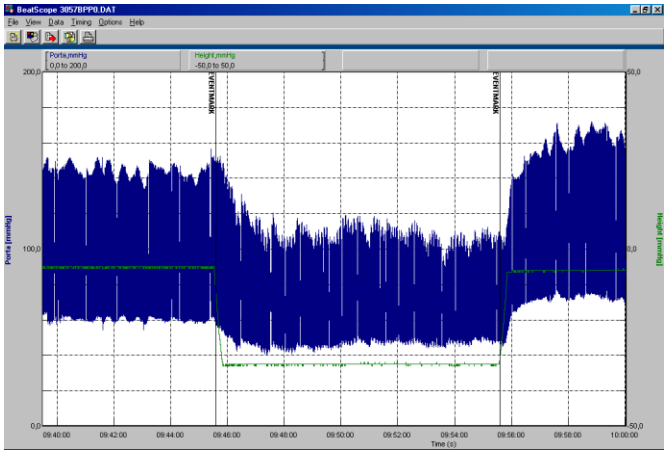
Methods Fifty consecutive patients were evaluated with a standardized battery of autonomic testing, Unified Parkinson's Disease Rating Scale, push and release (P&R) test, timed up and go test, freezing of gait (FOG) questionnaire, Montreal cognitive assessment (MoCA). Dyskinesia severity and presence of REM sleep behavioral disorder (RBD) were additionally considered. Patients were followed-up for 12 months.

Results We observed a 38% prevalence of cAN. At baseline, 36% of patients reported at least one fall in the previous 6 months. This figure increased to 56% over the follow-up. After adjusting for age, disease duration, axial symptoms, MoCA and dopaminergic treatment, cAN was significantly associated with a 15-fold (OR 15.194) higher probability of falls; orthostatic hypotension (OH), the most common expression of cAN, with a 10-fold probability (OR 10.702). In addition P&R test (OR 14.021), RBD (OR 5.470) and FOG (OR 1.450) were independently associated with greater probability of falls.

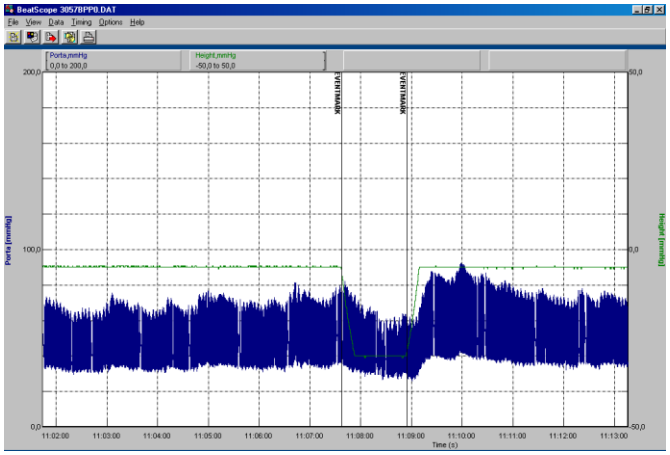
Conclusions cAN, including but not limited to OH, is a strong independent predictor of falls in PD. Future research endeavors clarifying to what extent pharmacological and non-pharmacological treatments targeting autonomic dysfunctions might reduce the risk of falls are warranted.

Head-up tilt test

PRIMA



DOPO 100 mg of LDOPA



ARTICLE

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

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

Abstract

Objective

To retrospectively describe clinical and instrumental features of a cohort of patients with at least a 5-year history of idiopathic autonomic failure (IAF) longitudinally evaluated at the Autonomic Unit of the University of Bologna (IAF-Bo cohort).

Methods

We identified patients with at least a 5-year history of IAF who were referred to our department from 1989 to 2016 and evaluated at least once a year during the disease course. Clinical and instrumental data were collected from medical records. Clinical variables were categorized as early if presenting within 3 years from disease onset. Predictors associated with conversion to other synucleinopathies were identified in a Cox regression analysis.

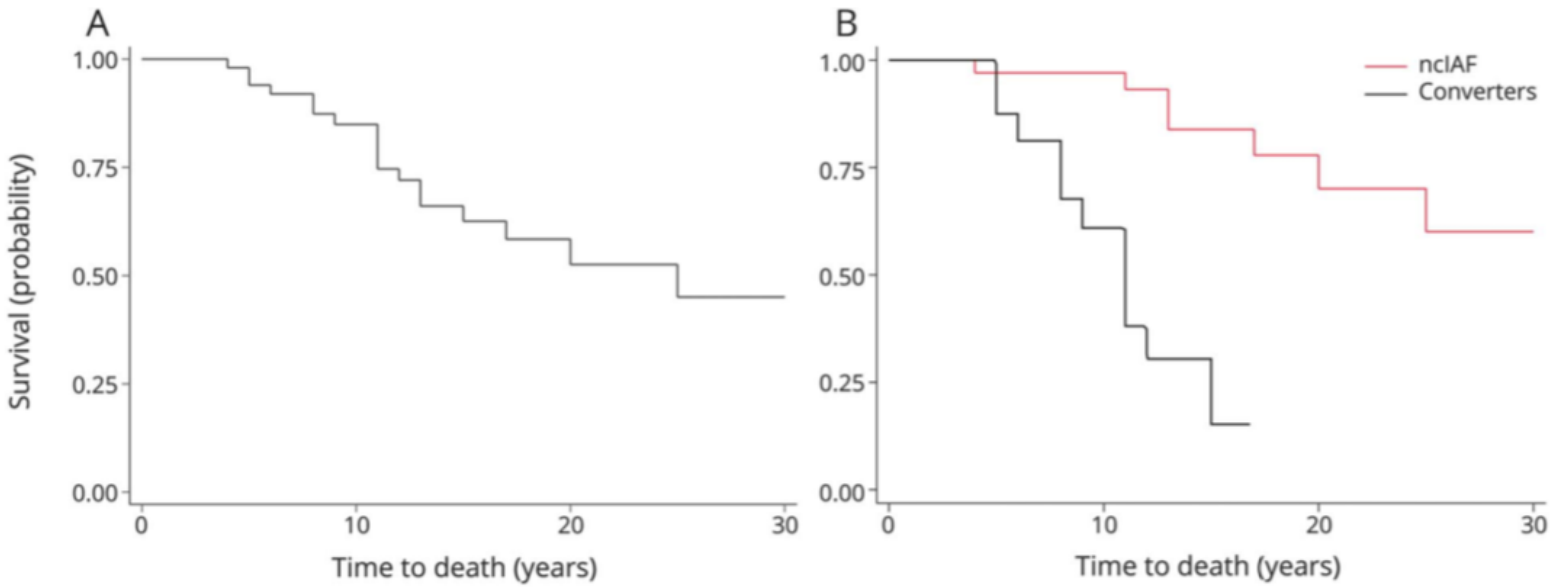
Results

The IAF-Bo cohort included 50 patients (39 male, 19 deceased at the last follow-up). At the last follow-up visit, 34 patients retained IAF phenotype (ncIAF group), while 16 developed a CNS synucleinopathy (converters group). Specific clinical and instrumental features were represented differently in the converters and ncIAF groups. The converters group showed a higher risk of death than the ncIAF group. Early onset of urinary dysfunction, early onset of REM sleep behavior disorder, and a Valsalva ratio ≥1.25 were identified as variables associated with phenoconversion.

Conclusions

This is one of the largest studies on the natural history of a cohort of patients with at least a 5-year history of IAF, showing a percentage of phenoconversion of 32%. We demonstrated that specific clinical and instrumental features entail an increased probability of phenoconversion. These findings could contribute to a better definition of the nature of IAF and to the identification of early markers of phenoconversion.

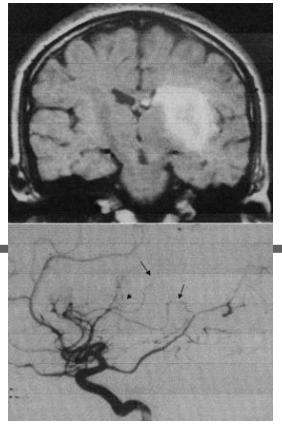
Figure 1 Kaplan-Meier survival curves for probability of death from symptom onset



(A) Survival analysis in all patients with a 5-year history of idiopathic autonomic failure (IAF). (B) Survival analysis in those with nonconverter IAF phenotype (nclAF group) and those phenoconverted into other synucleinopathies (converters group) at the last follow-up visit.

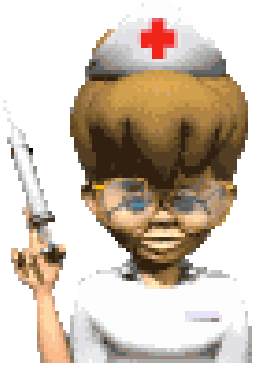
Perché è importante sapere se un paziente con nOH sia anche un iperteso in posizione supina?

Importance of diagnosing SH



- It is unclear to what extent supine hypertension contributes to morbidity and mortality in such patients
- Does SH carry the same risks of chronic hypertension?
- Debate continues on the ‘safe’ upper limits of supine hypertension and the use of anti-hyper drugs at night
- How much harm result from SH in autonomic failure?
  - Left ventricular hypertrophy
  - Case reports of Hemorrhagic stroke

Treatment



A double face dilemma!!!

TERAPIA FARMACOLOGICA

Farmaco Anti-ipertensivo

Peggioramento dell'ipotensione ortostatica

Peggioramento dell'ipertensione clinostatica

Farmaco ipertensivante

So what ??

We treat OH vigorously, even at the exspense of worsened SHyper

The correctness of this practice remains to be established !!!

Disautonomia urinaria

SINTOMATOLOGIA UROLOGICA

Sindrome urgenza/frequenza:

- Urgenza minzionale
- Aumento frequenza minzionale

Incontinenza urinaria da urgenza

- Svuotamento vescicale incompleto
- Ritenzione urinaria

Table 3 Comparison of lower urinary tract function in DLB, AFPD, PAF, PD and MSA (see text)

Disease	LUT symptoms	Urinary incontinence (storage dysfunction)	PVR>100 ml (voiding dysfunction)	No. of patients	Reference	Detrusor overactivity (central type)	Low compliance (preGGL type)	Bethanechol supersensitivity (denervation) (postGGL type)	Neurogenic change of sphincter MUPs (denervation) (Onuf's nucleus)	No. of patients	Reference
MSA	96%	63%	52%	121	9	56%	31%	19%	93%	121	9, 11
DLB	100%	91%	27%	11	-	71%	29%	2/2	2/3	7	-
AFPD	100%	43%	29%	7	19	86%	14%	1/3	4/4	7	19
PAF	100%	33%	33%	6	17	67%	33%	2/3	¾	6	17
PD	53–70%	25–28%	0%	115	18	81%	0%	Not performed	5%	21	11

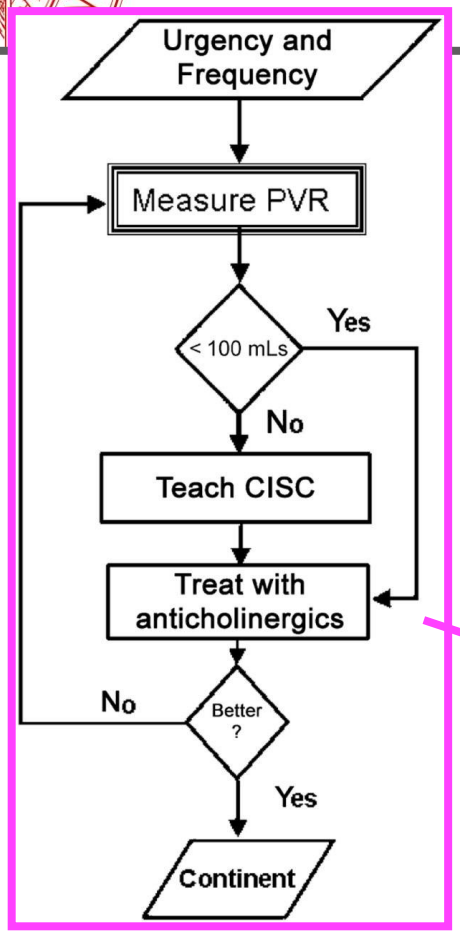
AFPD, autonomic failure with Parkinson's disease; DLB, dementia of Lewy body type; GGL, ganglion; LUT, lower urinary tract; MSA, multiple system atrophy; MUP, motor unit potential; PAF, pure autonomic failure; PD, Parkinson's disease; PVR, post-void residual.

da : Sakakibara R. et al. JNNP 2005

Trattamento della disfunzione urinaria

- Iperreflessia detrusoriale
- Dissinergia sfinterico-detrusoriale
- Ridotta attività detrusoriale

Bladder Dysfunction



Algorithm for management of neurogenic incontinence.
PVR = postvoid residual; CISC = clean intermittent self-catheterization.

Generic Name	Trade Name in the United States	Dose (mg)	Frequency	Elimination Half-life of Drug (Hours)
Propantheline	Pro-Banthine	7.5–15.0	Tid 30 min ac and qhs	<2
Tolterodine	Detrol	1–2	bid	2.4
Tolterodine	Detrol LA	2–4	od	8.4
Trospium	Sanctura	20	bid	20
Oxybutynin	Ditropan	2.5–5.0	bid to tid	2.3
Oxybutynin XL	Ditropan XL	5–30	od	13.2
Darifenacin	Enablex	7.5–15.0	od	13–19
Solifenacin	Vesicare	5–10	od	40–68

ac = before meals; bid = 2 times daily; od = daily; tid = 3 times daily; qhs = each bedtime; qid = 4 times daily.

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