Autonomic dysfunction in Parkinson's disease

PAOLA SANDRONI MD, PHD
PROFESSOR OF NEUROLOGY
MAYO CLINIC ROCHESTER MN
USA

BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

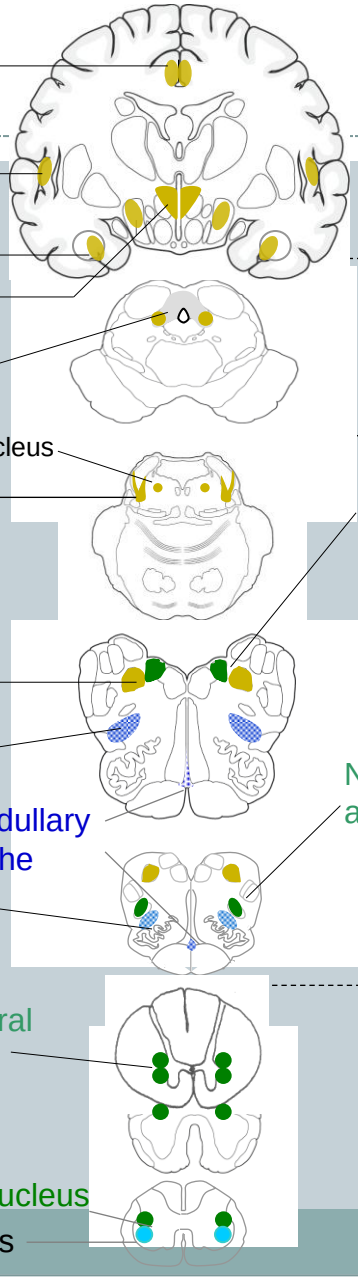
Introduction

- PD is the most common synucleinopathy
- Although motor manifestations dominates the clinical picture, non-motor ones have become increasingly recognized as playing a critical role in the patients' quality of life
- Autonomic dysfunction is a well known non-motor manifestation with multisystem involvement in various degree of severity

Pathology

- Autonomic involvement in PD, DLB, MSA and PAF result from distinct patterns of abnormal alpha-synuclein aggregation throughout the central and peripheral autonomic networks.
- The pathologic hallmarks of PD and DLB are the Lewy bodies and neurites; in MSA are oligodendroglial cytoplasmic inclusions and in PAF are peripheral neuronal cytoplasmic inclusions.

Central Autonomic Network



Level-Specific Function

Behavioral Arousal
Interoceptive awareness
Emotion
Stress responses
Homeostasis

Integration of autonomic function with arousal and pain modulation,

-Tonic control of blood pressure
-Respiratory rhythms
-Autonomic reflexes
- circulation,
- respiration
- micturition
- gastrointestinal

Segmental sympathetic and sacral (micturition, defecation, erection) reflexes

Benarroch EE, Mayo Foundation

Insula, cingulate cortex and amygdala

- Involvement of the insular cortex in PD has been related to non-motor symptoms including autonomic dysfunction and arousal
- Accumulation of alpha-synuclein in the left posterior insula has been correlated to presence of orthostatic hypotension
- Ant. Cingulate projects to ant. Insula as well as to subcortical autonomic structures and modulates autonomic responses depending on behavioral state.
- Sub – and pregenual portions are associated with cardiovagal responses
- Dorsal anterior cingulate cortex is associated with sympathetic activation triggered by behavioral arousal
- Amygdala is involved in prodromal DLB but its correlation with autonomic dysfunction has not been fully elucidated

Coon et al. Mov Disorders 2018

Hypothalamus

- Dorsomedial nucleus: sympathoactivation in response to cold (and stressors)
- Lateral hypothalamic area: sympathoexcitation due to behavioral arousal
- Anterior/preoptic area: heat-sensitive neurons that activate heat loss responses
- Lewy body are present in hypothalamus in PD, resulting in disordered thermoregulation

Coon et al. Mov Disorders 2018
Dayan et al. Neurology 2018

Brainstem

- PAG, pontine A5, VLM, raphe: control micturition, wakefulness, cardiovascular and cardiorespiratory manifestations. Involvement is max in MSA, but present also in DLB and PD to a lesser degree
- DMV: preganglionic vagal innervation, mediated by ENS in the gut. Involved in early stages of PD.
- Nucleus ambiguus: relatively spared in Lewy body disorders, but affected in MSA

Benarroch et al. 2000-2014

Peripheral Autonomic Structures

- ENS and autonomic ganglia: largely spared in MSA, but affected in DLB and PD
- Braak's hypothesis: alpha-synuclein deposition starts in ENS and spread to central structures via vagus nerve.
- Rostrocaudal gradient (from submandibular gland to rectum) corresponds to vagal innervation from DMV, but does not parallel neuronal loss
- Early ENS involvement explains constipation preceding PD diagnosis by several years
- Upper GI symptoms explained by ENS receiving vagal input from DMV.

Dickson et al. Acta Neuropath 2008

Peripheral Neurons

Sympathetic	Parasympathetic
• Loss of fibers to sweat glands, heart, blood vessels • Abnormal deposits noted in skin biopsies and adrenal medulla	• Alpha-synuclein deposits in cranial and sacral autonomic ganglia in PD

Different central structure involvement in synucleinopathies

TABLE 1. Key central autonomic structures affected in synucleinopathies

Structure	MSA	PD/DLB	PAF
Hypothalamus	++	+	–
Periaqueductal gray	++	+	–
Ventrolateral medulla	+++	+	–
Medullary raphe	++	+	–
Dorsal motor nucleus of vagus	++	+++	–
Nucleus ambiguus	++	+	–
Pontine micturition center	++	–	–
Sacral preganglionic neurons	+	+	–
Onuf nucleus	++	+	–

DLB, dementia with Lewy bodies; PAF, pure autonomic failure.

Cersosimo et al. Clin Neurol 2013

Different peripheral structure involvement in synucleinopathies

TABLE 2. Key peripheral autonomic structures affected in synucleinopathies

Structure	MSA	PD/DLB	PAF
Enteric nervous system	–/?	++	–/?
Postganglionic sympathetic neurons	+	++	+++
Cholinergic sudomotor	+/–	+	++
Noradrenergic cardiac	+/–	+++	++
Noradrenergic vasomotor	–	+	++
Adrenal gland	–	+	–
Postganglionic parasympathetic neurons	–/?	++	–/?
Submandibular gland	–/?	++	–/?
Pelvic ganglia	–/?	+	–/?
Gonadal tissue	–/?	+	–/?

DLB, dementia with Lewy bodies; PAF, pure autonomic failure.

Summary

- Lewy body pathology start earlier in periphery and move centrally
- MSA: brunt of pathology is central and more severe

Clinical manifestations: cardiovascular

- OH: up to 56% of PD have OH symptoms as opposed to 16% age matched controls
- Genetic forms: if Lewy body pathology there is autonomic dysfunction, o/w profile is normal (i.e. PARK2)
- Can be asymptomatic
- Key features: cerebral hypoperfusion, postprandial effect, meds can amplify abnormality. Worsens with disease progression (multifactorial too: volume status, activity level etc.)
- Supine hypertension - Exercise induced hypotension
- Malignant PD: more OH and cognitive dysfunction

Asahina et al. J Neurol Neurosurg Psychiatry 2013
Coon et al. Mov Disorders 2018
Cheiban et al. Mov.Disorders 2018

Effect of L-Dopa

- Not much is written, though it is talked about a lot.
- Duodenal infusion of L-dopa produced mean 24 mmHg drop in orthostatic BP in 9 subjects with severe Parkinson's
- Blood pressure fluctuates more in PD patients with motor fluctuations (25 mmHg vs 12 mmHg) [Pursiainen, 2007]

Pursiainen et al. 2000 and 2007

Dysautonomia in PD: structural/functional alterations

- In a recent study (Chung et al. Neurology, Feb. 2019) compared patients with de novo PD and divided them in 2 groups, with mod/severe dysautonomia vs. a group w/o or with mild sxs
- The dys group had poorer cognitive efficiency, particularly executive function, and there was evidence of disrupted white matter connectivity activity in the frontal subcortical and posterior cortical regions

Orthostatic Hypotension Management: As Simple as ABC

- **A**bdominal binder
- **B**olus treatment (2 x 8oz glasses of water)
- **B**ed up (head of bed elevated 4 inches)
- **C**ountermaneuvers. Physical countermaneuver raise standing BP
- **D**rugs
  - Midodrine
  - Fluodrocortisone
  - Pyridostigmine
  - Droxidopa
  - Atomoxetine (NE reuptake inhibitor)
- **E**ducation (recognize subtle symptoms and orthostatic stressors)
- **F**luids and salt

- Supine HTN: losartan, captopril, hydralazine at bedtime

Modified from: Figueroa et al 2010

Clinical manifestations: gastrointestinal

- Upper GI: reduced saliva production (sialorrhea due to ineffective and less frequent swallowing), gastroparesis (nausea, vomiting, early satiety, bloating), loss of appetite (L-dopa worsens these as well), dysphagia (due to oropharyngeal as well as esophageal dysmotility)
- Difficulty with pills, coughing, prolonged chewing…
- Lower GI: constipation is present in up to 90% of patients, pseudoobstruction-pattern

Treatment: upper GI

- Postural and behavioral changes during meals
- Modified meal consistency
- Expiratory muscles training and video-assisted swallowing therapy
- Botox for sialorrhea (avoid antiAch due to side effects) and distal esophagus
- Eventually PEG/PEJ
- Promotility agents for gastroparesis are dopamine-blockers…cholinergic enhancers, serotonin agonist (cisapride, tegaserod) and motilin receptor agonist (erythromycin)

Larson JM et al. J. Neurogastroenetrol. Motil 2010
Sanger GJ et al. Nat Rev Gastroenterol Hepatol 2016

Treatment: lower GI

- Dietary modifications, probiotics, exercise, fluids
- Bulk laxatives, osmotic laxatives (magnesium etc.)
- Stimulant laxatives (senna)
- Can add glycerol suppository or clonidine
- Cl-channel activators: lubiprostone
- Serononin agonists: prucalopride, mosapride (5-HT4)
- In development: ghrelin agonist (relamorelin), ileal bile acid transporter inhibitor (elobixibat)
- Diarrhea: usually due to overflow from obstruction

Chey WD et al. Am J Gastroenterol 2011
Corsetti M, Tack J. Expert Opin Pharmacother 2014
Camiller M et al. Neurogastroeneterol Motil 2015

Clinical manifestations: genitourinary

- Present in 50% of PD cases.
- Difficult to assess precisely due to age-related pathology and idiopathic forms present in otherwise normal subjects
- Frequency, npcturia, urgency, incontinence are most common symptoms; voiding difficulties may be present in more advanced cases
- ED: age-matched subjects 3 times more likely to develop PD if present than those in whom is absent. Multifactorial as well.

How do your treat an overactive bladder?

- Behavioral

  Fluid schedules

  Treat pelvic floor , constipation

  Timed/Prompted voiding

  Absorbent garments
- Anti-muscarinic Medications: Ditropan™, Detrol ™, Vesicare ™, Enablex ™, Oxytrol ™, Gelnique ™, Toviaz ™, oxybutynin

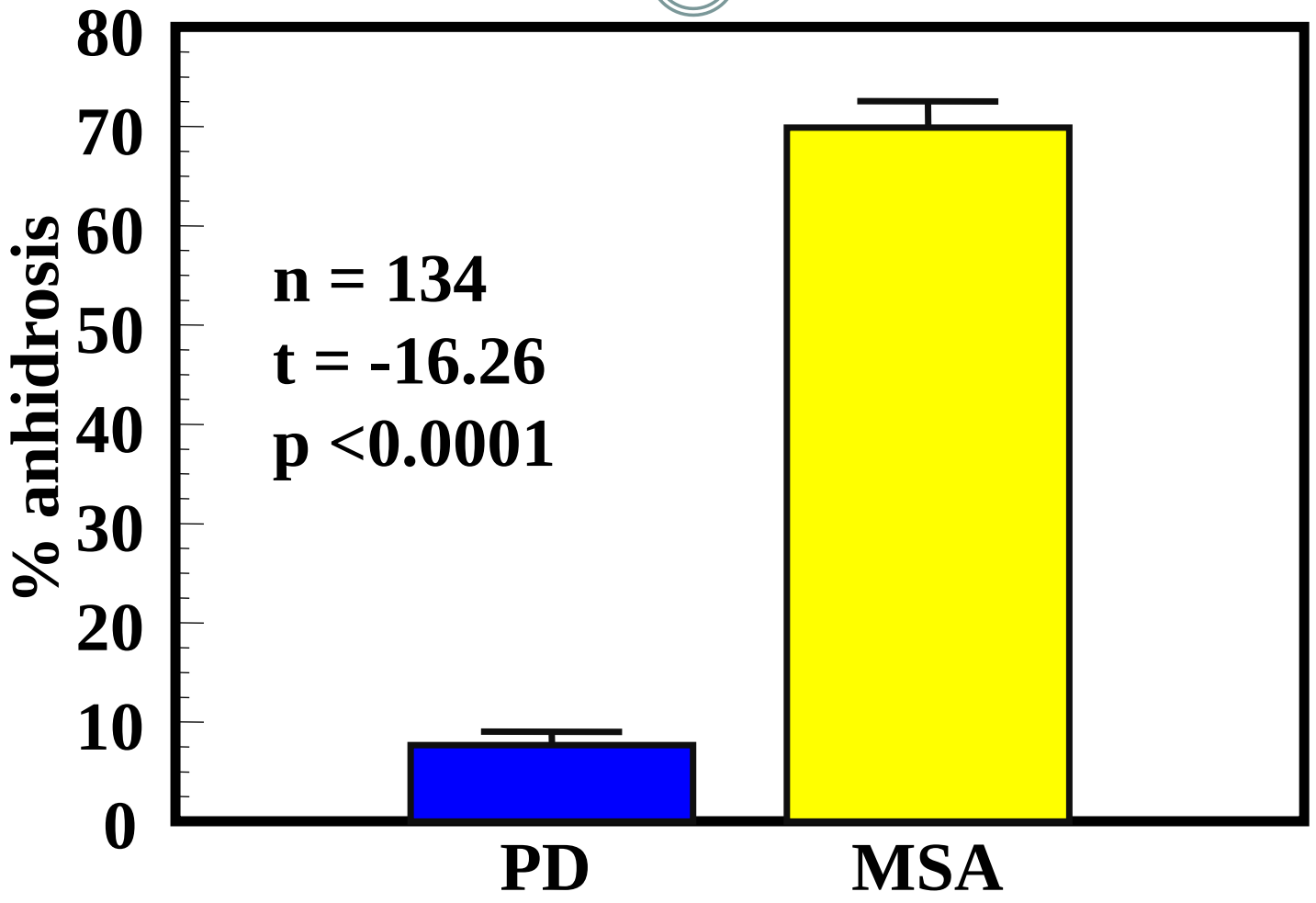
Bladder tips

- Evaluation: Post void residual volume (by ultrasound) or urodynamic studies
- Urgency: can be treated by medications such as oxybutnin (Ditropan), tolteradine (Detrol), solifenacin (Vesicare), etc.
- Retention: can try meds like alpha-blockers (terazosin) but usually difficult to tolerate due to orthostatic hypotension

Clinical Manifestations: sweating

- 30-55% of PD patients have sweat abnormalities
- Hyperhidrosis: usually upper body, often associated with on/off and dyskinesia.
- Hypo/anhidrosis: more length-dependent pattern.
- Heat intolerance may be present

TST: MSA vs. PD
(% anhidrosis)



Fealey, pers. communication

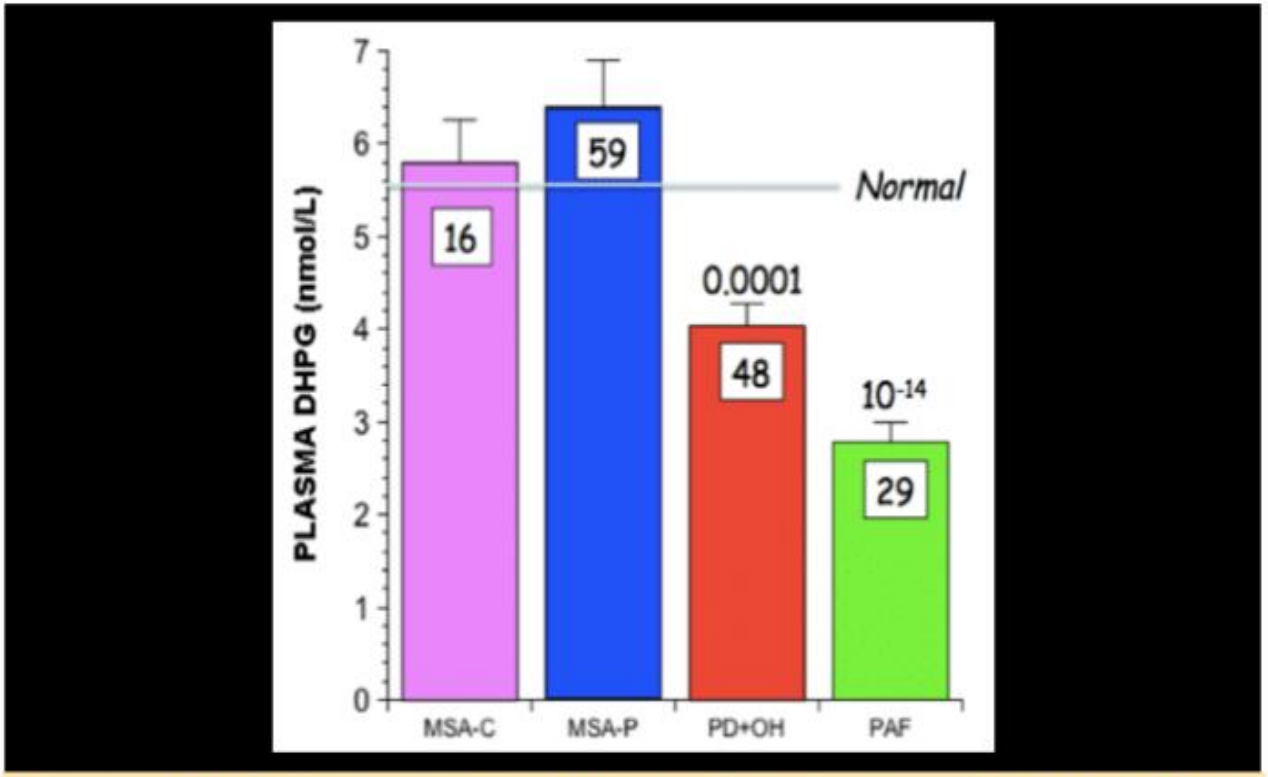
Clinical Manifestations: pupil

- Rarely noted on exam; little if any clinical significance

Evaluations

- Tilt study, Valsalva maneuver, metronomic breathing
- 24 hours blood pressure/holter monitoring
- Plasma catecholamines
- MIBG Cardiac scintigraphy
- GI motility
- Urodynamic study, sphincter EMG
- Sweat testing
- Skin biopsy

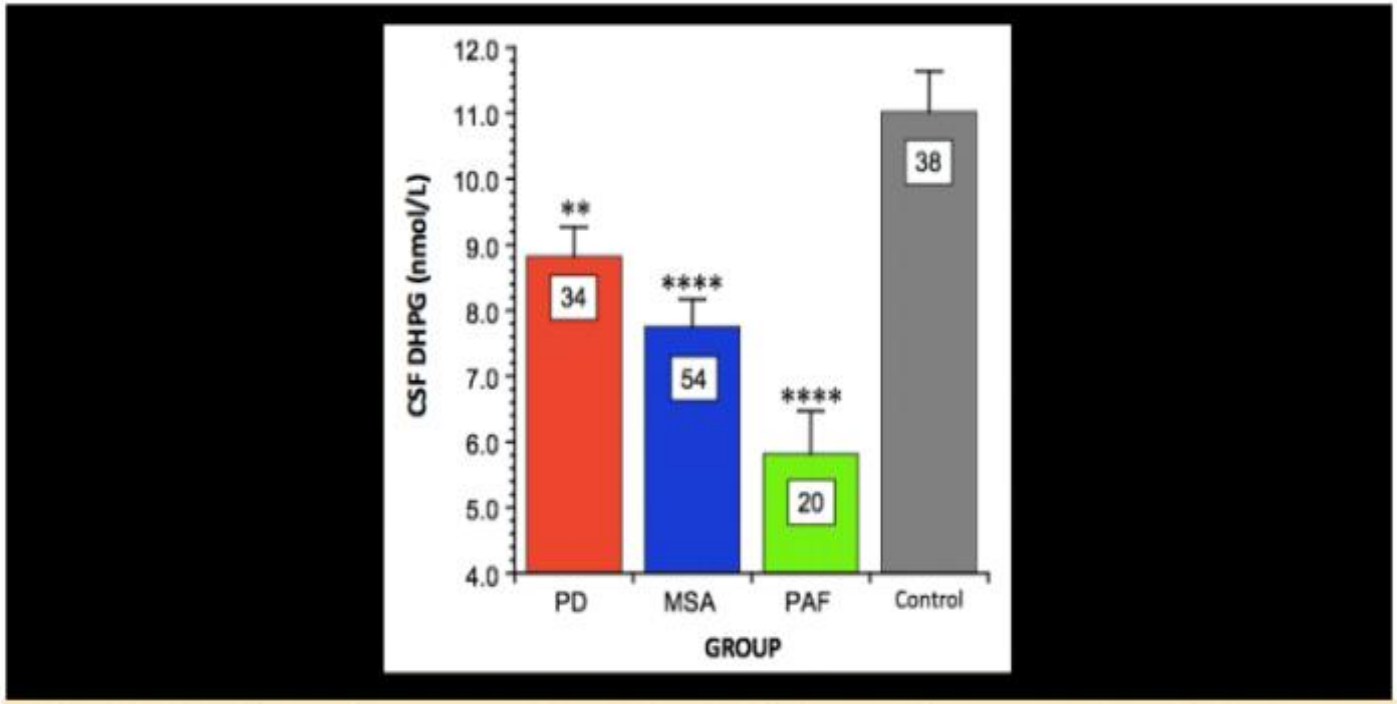
Catecholamines in synucleinopathies: plasma levels



Plasma DHPG is normal in MSA, often decreased in PD+OH, and almost always decreased in PAF

Courtesy of:
Goldstein DS

Catecholamines in synucleinopathies: CSF levels



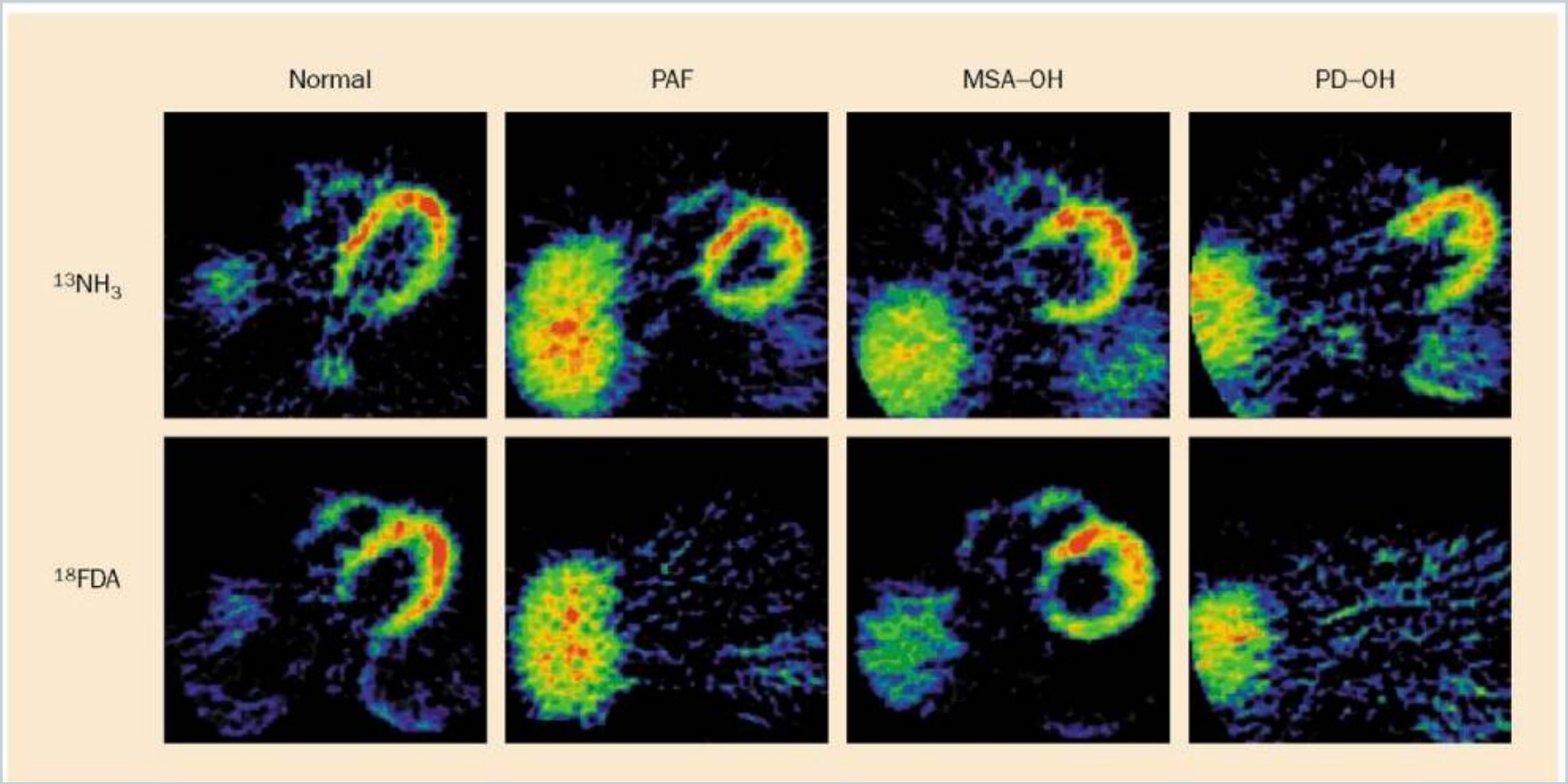
CSF DHPG is decreased in PD, MSA, and especially PAF.

Courtesy of:
Goldstein DS

Functional Imaging: heart and brain

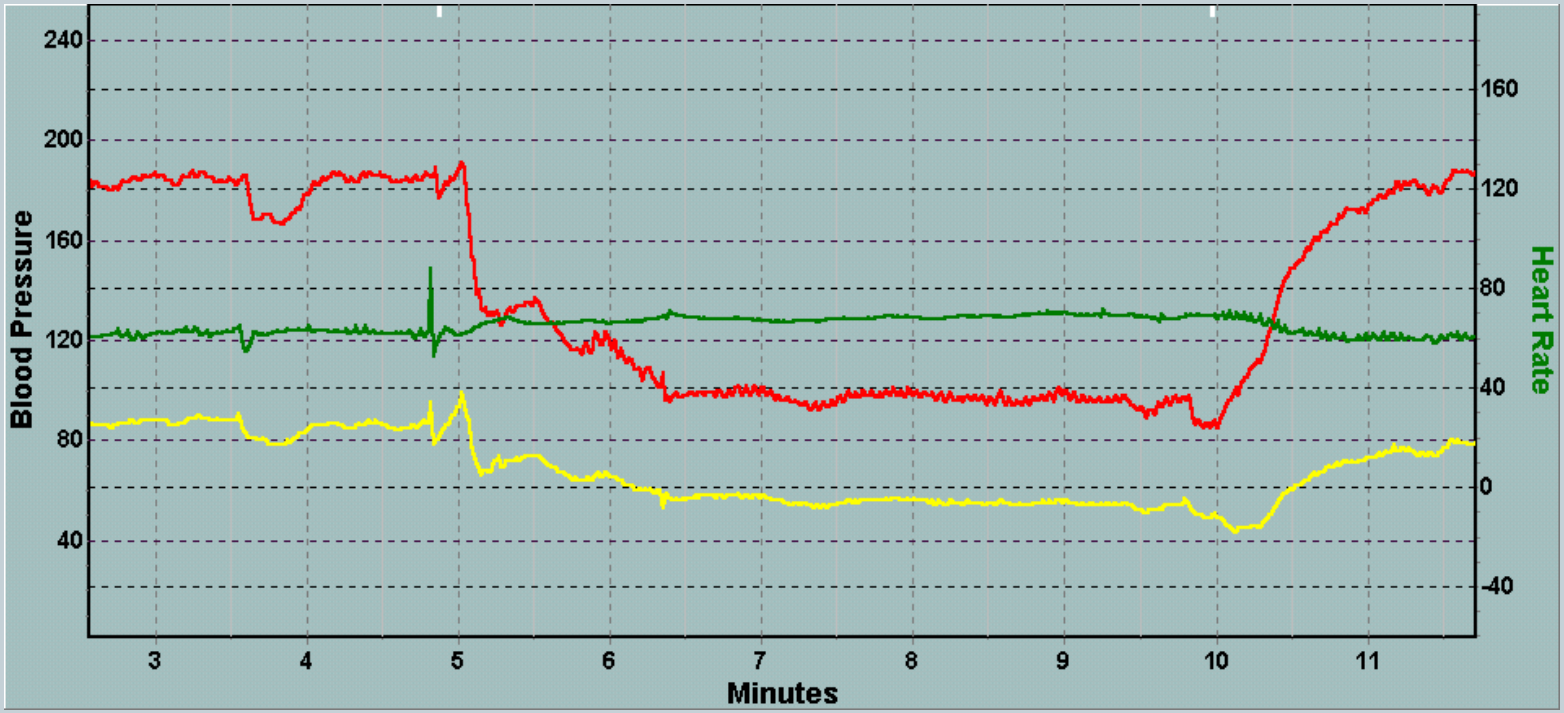
- I-MIBG or fluorodopamine cardiac scanning will be abnormal in peripheral autonomic disorders, PAF and Parkinson: normal in MSA
- F-DOPA PET, DAT scan: abnormal in PD, not PAF or MSA

MIBG in Synucleinopathies



Goldstein Compr Physiol 2014

HUT: MSA (note resting HTN)



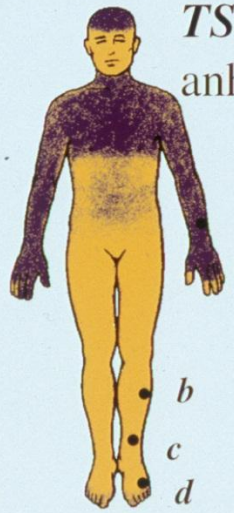
TST\QSART:
Determine site of autonomic failure

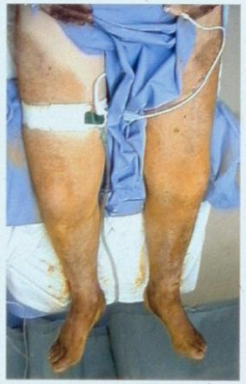
QSART (ul/cm²)

- b) 2.61 (prox leg)
- c) 1.94 (distal leg)
- d) 0.54 (foot)

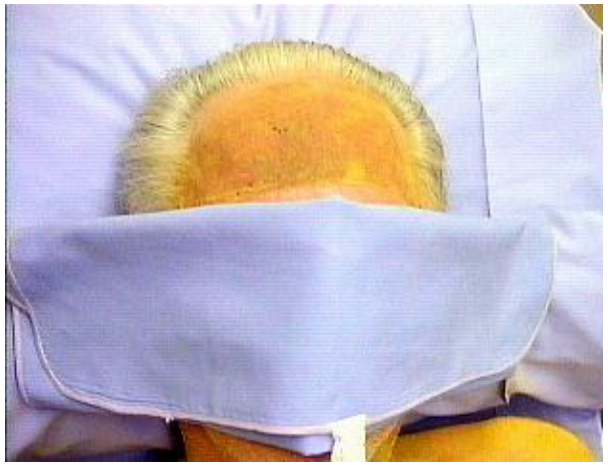
Conclusion: Results compatible with a **preganglionic** lesion primarily

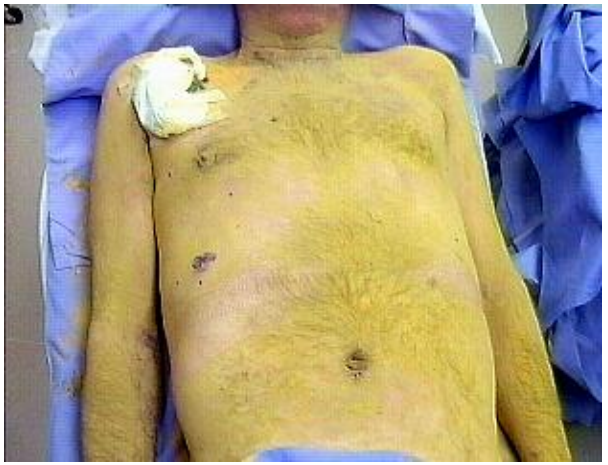
TST: segmental anhidrosis

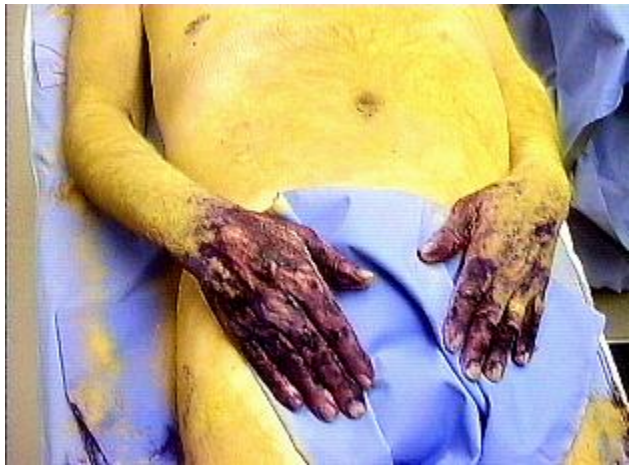


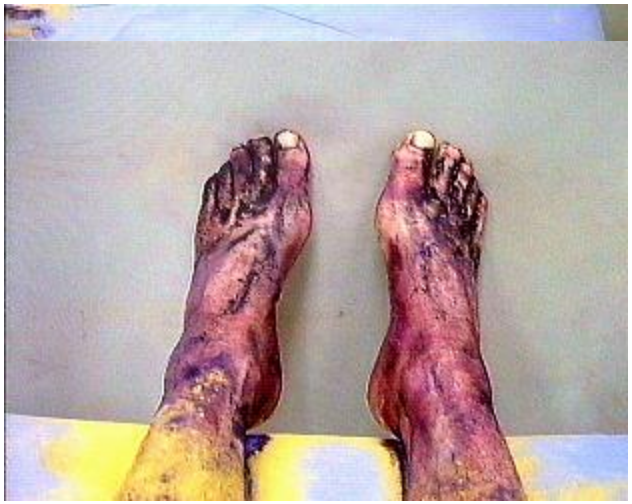


TST Digital Photos: MSA patient









What's the nature of the problem?