New diagnostic tools for idiopathic Parkinson disease and Parkinsonian Disorders

Irene Litvan, M.D.
Tasch Professor in PD Research
University of California San Diego,
USA
ilitvan@ucsd.edu

UC San Diego
School of Medicine

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Learning Objective

To learn novel tools to accurately diagnose Parkinsonian Disorders

Key Message:

- Diagnosis remains clinical and requires knowledge of:
  - –
  - –
  - –
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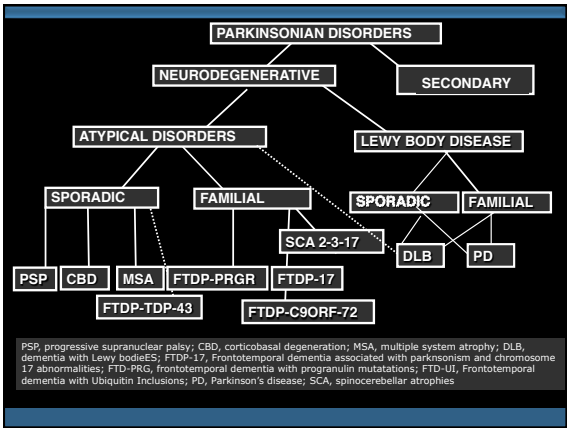
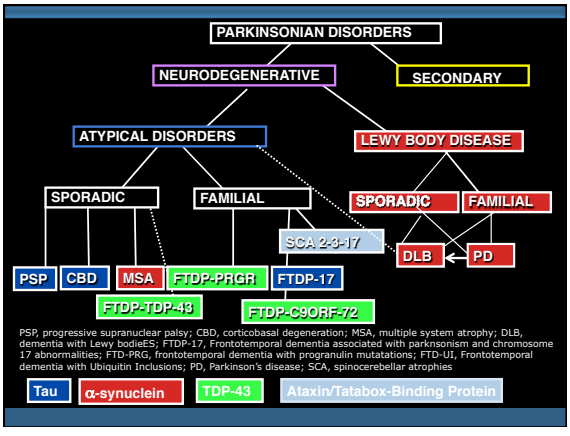
  - –
  - –
- Novel tools:
  - –
  - – Polysomnogram for REM Sleep behavior disorder/Mayo RBD
  - – Structural and Functional Neuroimaging





Typically, PD presents with:

- Unilateral
  - Slowness
  - Pill-rolling resting tremor
  - Stiffness
- Good & maintained Levodopa response
- Lack of atypical features

Need to exclude: Drug Induced Parkinsonism

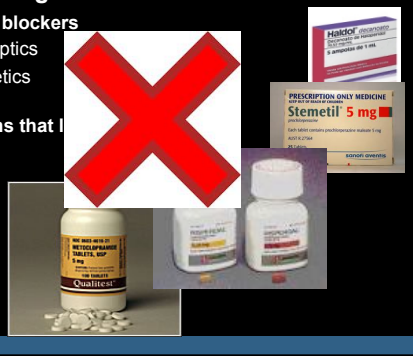
Dopamine blockers

Neuroleptics

Antiemetics

Medications that I

methyldopa)



Symptoms suggestive of Atypical Parkinsonism

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-
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- Oculomotor problems
- Early significant orthostatic hypotension
- Early swallowing disturbances
- Early and severe urinary problems
- Early hallucinations unrelated to medication / cortical dementia
- Ideomotor apraxia

Early PD features

- Anosmia
- REM sleep behavior disorder
- Depression
- Constipation
- Executive dysfunction

Prodromal symptoms

- Unilateral decrease of associated movements
- Tremor at rest
- Micrographia

Olfactory dysfunction in incidental Lewy body disease and Parkinson's disease

Erika Driver-Dunckley [a,*], Charles H. Adler [a], Joseph G. Hentz [b], Brittany N. Dugger [c], Holly A. Shill [c], John N. Caviness [a], Marwan N. Sabbagh [c], Thomas G. Beach [c], the Arizona Parkinson Disease Consortium

[a] Parkinson's Disease and Movement Disorders Center, Department of Neurology, Mayo Clinic, Scottsdale, AZ, USA
[b] Biostatistics Section, Mayo Clinic, Scottsdale, AZ, USA
[c] Banner Sun Health Research Institute, Sun City, AZ, USA

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ABSTRACT

Background: Olfactory dysfunction in Parkinson's disease (PD) is well-established and may represent one of the earliest signs of the disease.
Objective & methods: The objective of this study was to evaluate the relationship of olfactory dysfunction, using the University of Pennsylvania Smell Identification Test (UPSIT), to clinical and pathological parameters of clinicopathologically diagnosed PD ($n = 10$), incidental Lewy body disease (ILBD) ($n = 13$), and identically assessed controls who lacked a neurodegenerative disease ($n = 69$).
Results: Mean UPSIT scores were significantly lower in PD (16.3, $p < 0.001$) and ILBD (22.2, $p = 0.004$) compared to controls (27.7). Using an UPSIT cutoff score of <22 (the 15th percentile) the sensitivity for detecting PD was 9/10 (90%) and ILBD 6/13 (46%), while the specificity was 86% (Controls with score of <22 = 10/69).
Conclusions: These results add to the growing body of evidence suggesting that olfactory testing could be useful as a screening tool for identifying early, pre-motor PD.

UPSIT scores <22 sensitivity to diagnose PD was 90%, spec. 86%

What investigations?

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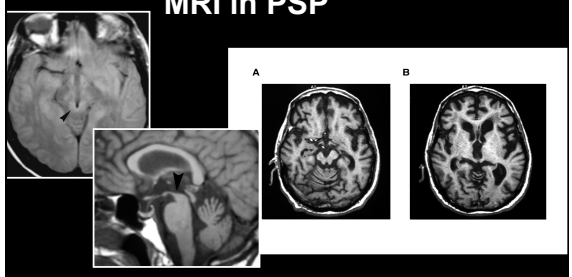
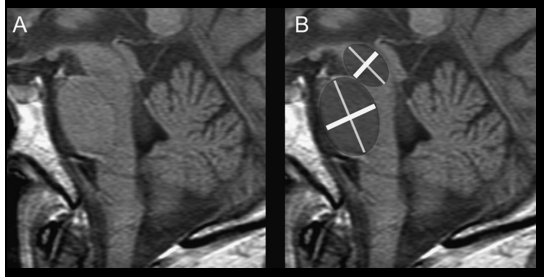
-
- Urofunctional
- Tilt-table Test
- Imaging

MRI in PSP



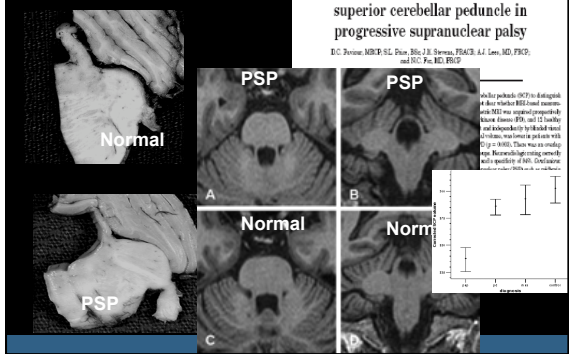
- AP-midbrain atrophy ≤13.4 *or* ≤17mm
  (Schrag et al. 2000
- Dilation of 3rd ventricle

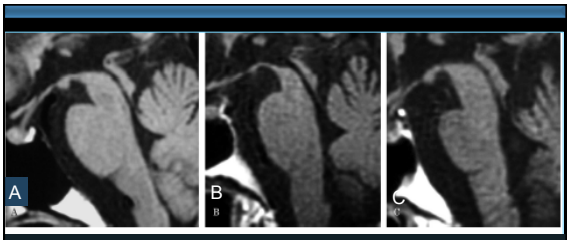
Midbrain/pons ratio < 0.52 in PSP



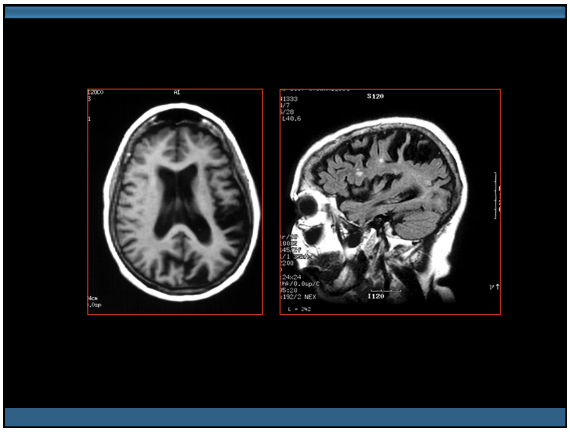
Massey et al. Neurology 2013;80:1856-1861

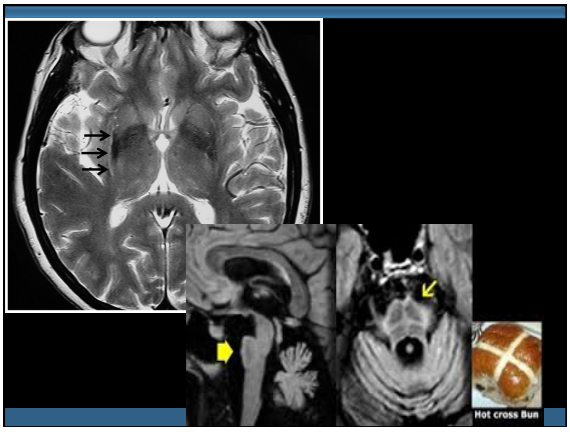
Superior cerebellar peduncle atrophy

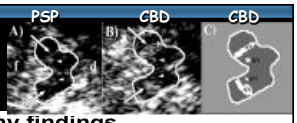




- Tauopathy
- Parkinson disease
- α-synucleinopathy







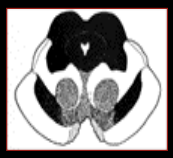
Transcranial sonography findings

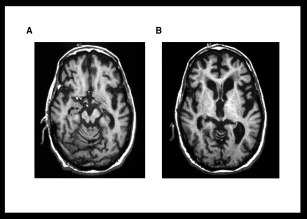
Condition	Substantia Nigra hyperechogenicity	Lenticular Nucleus hyperechogenicity	Caudate Nucleus hyperechogenicity	3rd ventricule dilation	Lateral ventricule dilation
Normal >60 y/o	+	+	+	(+)	+
PD	+++	+	++	(+)	+
MSA	(+)	+++	++	_	(+)
PSP	+	+++	+++	+++	++
CBD	+++	+++	+++	_	+

- not found so far; (+) rarely found; + sparsely found;
- ++ frequently found: +++ almost always found

Walter et al., 2007

The underlying anatomic distribution explains the symptomatology & radiological findings





Neuromelanin 3D sensitive MRI to measure the volume of the SNc

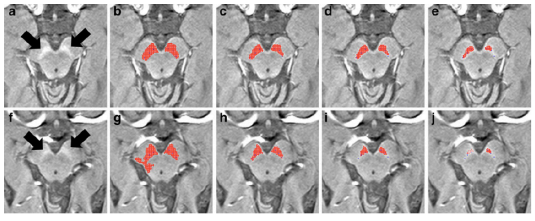


Fig. 1 Neuromelanin-sensitive MRI at the level of the midbrain. The SNc is seen as a high-intensity area (*arrows*) in a control subject (**a**–**e**) and a PD patient (**f**–**j**). The control subject was a 69-year-old male, and the PD patient was a 64-year-old female with a Hoehn–Yahr score of 4. The VOIs at a threshold of 1.8 (**b**, **g**), 1.9 (**c**, **h**), 2.0 (**d**, **i**), and 2.1 (**e**, **j**) are shown as *red pixels* in the control (**b**–**e**) and PD (**g**–**j**) subjects. The size of the VOI decreases with the increase of threshold. Note that the volume of the SNc is smaller in the PD patient than in the control subject. Seed points are also shown as *blue dots*

Ogisu et al, 2013

Increase diffusivity in the striatum in APD

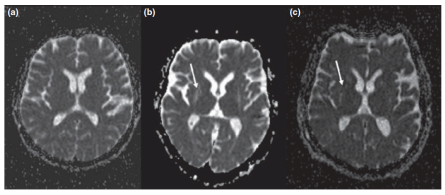
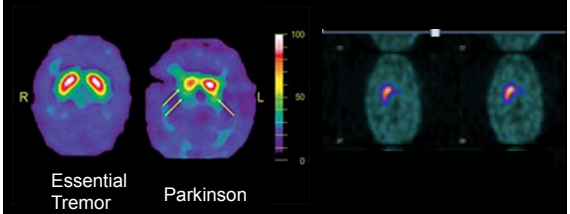


Figure 5 Axial Trace(D) maps at the level of mid-striatum in a patient with Parkinson's disease (PD) (image a), a patient with MSA-P (image b) and a patient with progressive supranuclear palsy (PSP) (image c). Note the diffuse hyperintensity – corresponding to increased diffusivity – in the putamen (arrows) in the patients with MSA-P (image b) and PSP (image c)

DAT Scan



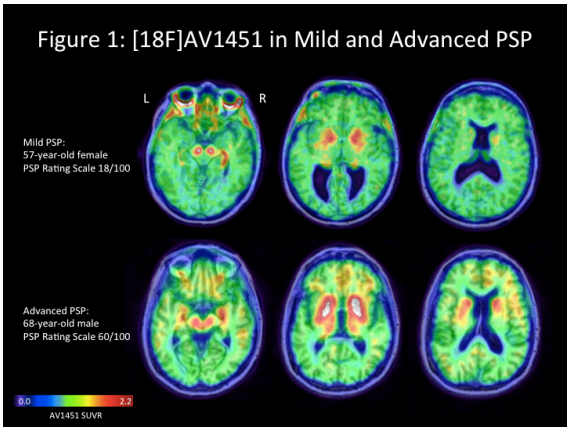
Essential Tremor

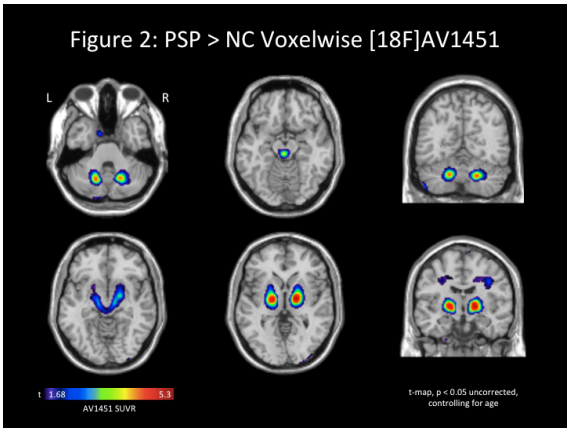
Parkinson

Most Common Imaging Patterns of Idiopathic Parkinson Disease and APS

	Imaging Modality			
Disease Entity	MR Imaging	FDG PET	Amyloid PET	^{123}I Ioflupane SPECT
Parkinson disease	Often normal, occasional diffuse atrophy	Usually normal, preserved putaminal activity, occasional decreased uptake in the parieto-occipital cortex	Normal	Decreased striatal activity (usually asymmetric)
MSA	Putaminal atrophy and marginally increased T2 signal, "hot cross bun sign"	Decreased putaminal or cerebellar uptake, subtype dependent	Normal	Symmetric or asymmetric decreased striatal activity
PSP	"Hummingbird sign," "Mickey Mouse sign"	Decreased uptake in the posterior frontal lobes, midbrain, and basal ganglia	Normal	Symmetric or asymmetric decreased striatal activity
DLB	Diffuse atrophy	Generalized decreased uptake (more prominent in the occipital lobes)	Positive in most cases	Symmetric or asymmetric decreased striatal activity
CBD	Asymmetric parietal and/or frontal cortical atrophy	Asymmetric decreased uptake in the parietal and/or frontal lobes	Normal	Decreased striatal activity (usually asymmetric)

Broski et al., 2014





Submandibular Gland Biopsies: Advanced PD

Methods:

- 15 PD patients
- > 5 yrs dis duration
- outpatient, local anesthetic

Results:

- 3 insufficient gland tissue
- 9/12 were LTS+
- 5/15 swelling and bruising

Adler et al. *Neurology '14*

Colonic mucosal α-synuclein lacks specificity as a biomarker for Parkinson disease

Naomi P. Visanji, PhD
Connie Marras, MD, PhD
Drew S. Kern, MD, MSc
Amaal Al Dakheel, MD
Andrew Gao, MD
Louis W.C. Liu, MD, PhD
Anthony E. Lang, MD
Lili-Naz Hazrati, MD, PhD

Correspondence to Dr. Visanji: naomi.visanji@uhnresearch.ca

ABSTRACT

Objective: To determine the utility of detecting α-synuclein (αSyn) in colonic mucosal biopsy tissue as a potential diagnostic biomarker for Parkinson disease (PD).

Methods: We used the paraffin-embedded tissue (PET) blot, which degrades physiologic nonaggregated αSyn using proteinase K and enhances antigen retrieval allowing sensitive and selective detection of remaining protein aggregates, to detect αSyn in colonic mucosal biopsies from 15 patients with early PD (<3 years), 7 patients with later PD (>5 years), and 11 individuals without PD. αSyn and serine 129-phosphorylated αSyn (Ser129p-αSyn) were assessed by PET blot and conventional immunohistochemistry.

Results: PET blot–resistant aggregated αSyn and Ser129p-αSyn was present in 12 of 15 individuals with early PD, 7 of 7 individuals with later PD, and 11 of 11 control subjects. The number of biopsies positive by PET blot relative to conventional immunohistochemistry was significantly lower in both PD groups compared with the control group for both αSyn and Ser129p-αSyn, whereas routine immunohistochemistry was positive more often in PD, but was positive in as many as 9 of 11 control individuals.

Conclusion: Strong evidence of the presence of aggregated hyperphosphorylated αSyn in individuals with and without PD, using such a sensitive and specific method as the PET blot, suggests that colonic deposition of αSyn is not a useful diagnostic test for PD. The utility of detecting αSyn in the colon as a biomarker in combination with other assessments remains to be determined.

Neurology® 2015;84:609-616

	Idiopathic PD	Atypical parkinsonisms
Parkinsonism	Dopamine responsive	Usually not dopamine response
Progression	Slow, almost similar general population	Fast 5-10 years
Saccades	Normal	Usually abnormal: slow, hypometric, long latency, hypermetric
Praxis	Normal	Normal or ideomotor apraxia (CBS)
Language	Normal	Normal, non-fluent aphasia, speech apraxia
Myoclonus	None	None, lateralized or distal
Dystonia	Usually not present	Axial or lateralized
REM-Sleep Behavior	Frequent	Mostly in MSA and DLB
Orthostatic Hypotension	Late	Early in MSA and DLB Normal in PSP and CBS
MRI	Normal	Atrophy Pons / Cerebellum / Midbrain / Frontal or parietal cortices
PET tau	Negative	Positive

Summary:

Accurate diagnosis depends on:

- High index of suspicion
- Detailed medical history and examination
- Medications & response to dopaminergic agents
- Evaluation of OH, Cognition, Saccades and Motor
- Consider: Neuropsychological / Urofunctional
- Neuroimaging: MRI / PET
- Most novel tools remain experimental