MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Causes and Differential Diagnosis of Parkinson's disease

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Disclosures

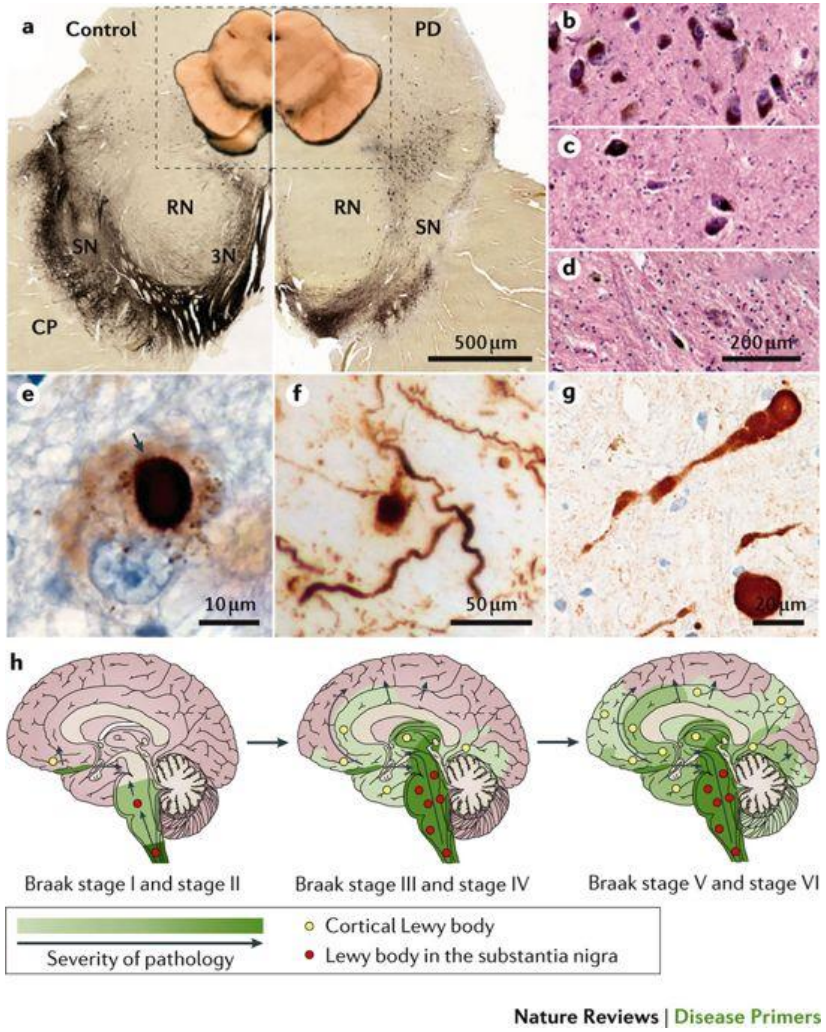
Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Overview

- Aetiology and pathogenesis of Parkinson’s disease
- Differential diagnosis of Parkinsonism
- Video examples of Parkinson’s disease mimics and rare causes

Pathology

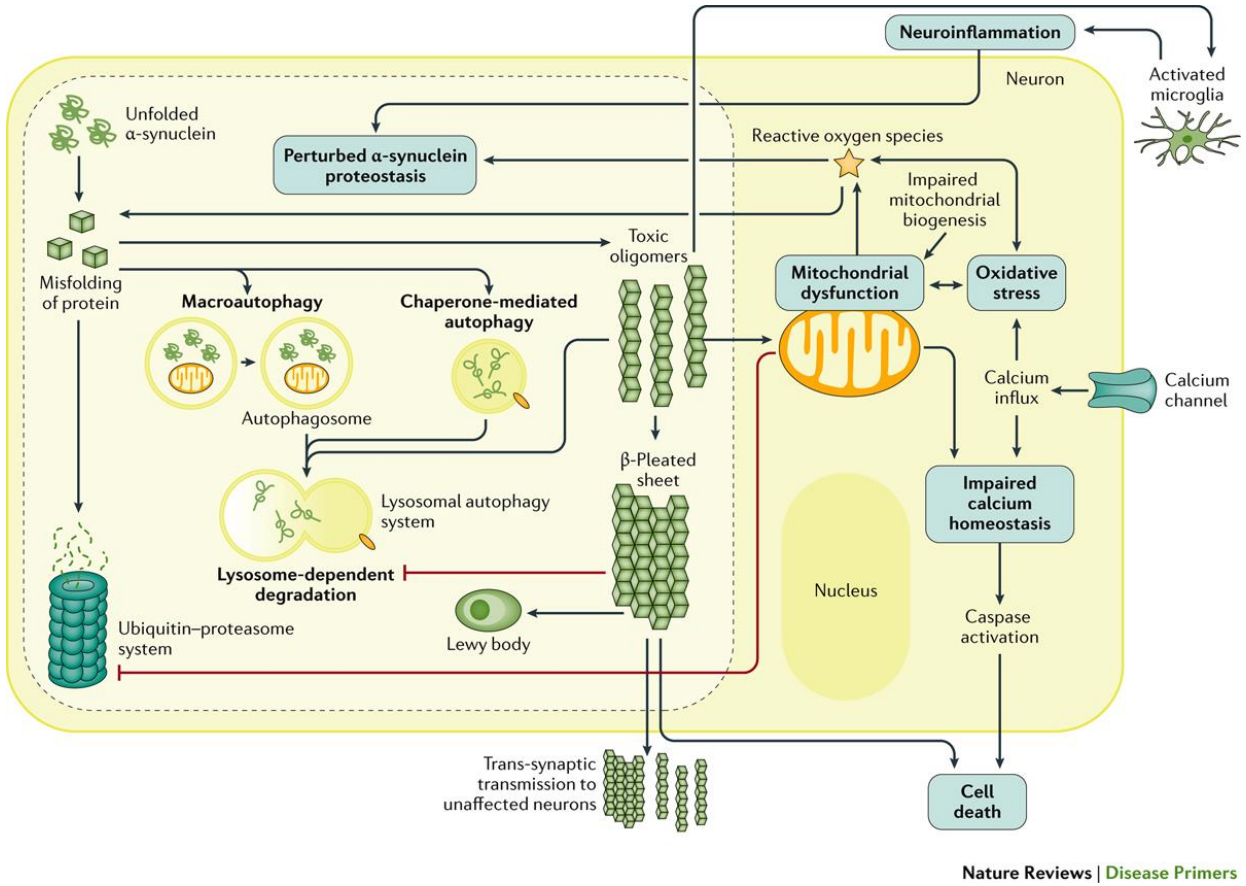
- Neuronal loss in substantia nigra and widespread α-synuclein deposition
- Results in striatal dopamine deficiency
- Dopamine plays an important role in the brain
  - Executive function, motivation, impulse control (addiction behaviour), arousal, reinforcement and reward
  - Motor control
  - Lower-level functions including lactation, sexual gratification, nausea
- Pathological feature - Lewy bodies (aggregated α-synuclein)
- Spread of pathological α-synuclein protein (Braak hypothesis)



Poewe, et al. Nat Rev Dis Primers 2017

Pathophysiology

- Unclear cause
- Some have postulated a prion-like spread (Angot, Lancet Neurol 2010)
  - ? First sites gut enteric nerves and olfactory bulb, resulting in prodromal hyposmia and constipation
- Complex pathophysiology
- Genetic risk genes being investigated include LRRK2 and GBA – potential additional therapeutic avenues



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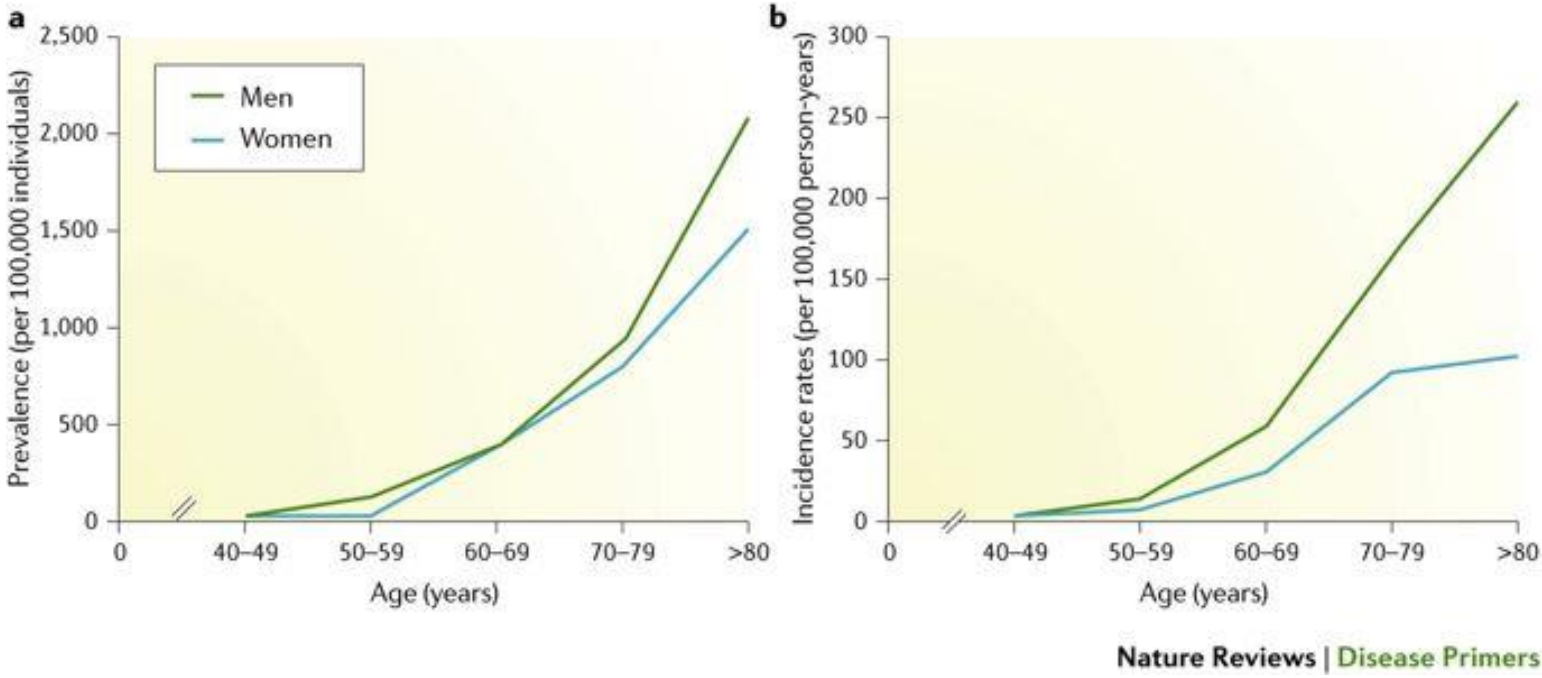
Scope of the problem

- Incidence 5-35 per 100,000
- Incidence greatly increases after 6th decade
- A **big problem** in an ageing population
- Found in all regions



Poewe, et al. Nat Rev Dis Primers 2017

Clinical Definitions

- **Parkinsonism**: Symptoms/signs that can be seen in Parkinson's disease but also in other conditions
- **Rigidity**: Stiffness of movement
- **Tremor**: Oscillatory movement of limb or head
- **Bradykinesia**: Slowness of movement
- **Hypomimia**: Reduced facial expression ("mask-like" face)
- **Hypophonia**: Quiet speech
- **Dysarthria**: Slurred speech
- **Dysphagia**: Swallowing difficulty
- **Aphasia**: Difficulty with speech output or understanding
- **Apraxia**: Difficulty performing a learned task
- **Dystonia**: Abnormal, often twisting posture
- **Ataxia**: Incoordination, which may be related to a cerebellar disorder

Parkinsonism

- Triad of Tremor, Rigidity, **Bradykinesia**, (postural instability)
- Diagnosis is **clinical**
- Requires a complete medical history that includes timeline of symptoms, recognition of important clinical signs and consideration of differential diagnosis
- Clinical diagnosis can change over time due to emerging clinical signs

Parkinson’s disease videos with a musical twist

Differential diagnosis of Parkinsonism – Primary movement disorders

- Essential Tremor
- Primary Parkinsonian disorders
  - Idiopathic Parkinson's disease (PD)
  - Atypical Parkinsonism ("Parkinson's plus" syndrome)
    - Progressive Supranuclear Palsy (PSP)
    - Dementia with Lewy Bodies (DLB)
    - Multiple System Atrophy (MSA)
    - Corticobasal degeneration/syndrome (CBD/CBS)
- Secondary Parkinsonism
  - Normal Pressure Hydrocephalus
  - Vascular parkinsonism
  - Other neurodegenerative diseases (Huntington's disease, DRPLA, SCAs, Wilson's disease, neurodegeneration with brain iron accumulation, neuroacanthocytosis etc)
  - Idiopathic basal ganglia calcification (Fahr's disease)
  - Other secondary causes
- Functional (psychogenic) parkinsonism

Secondary Parkinsonism

- Normal Pressure Hydrocephalus
- Vascular parkinsonism
- Other neurodegenerative diseases (Huntington’s disease, DRPLA, SCAs, Wilson's disease, neurodegeneration with brain iron accumulation, neuroacanthocytosis etc)
- Idiopathic basal ganglia calcification (Fahr’s disease)
- Other secondary causes
- (Functional/psychogenic parkinsonism)

Other secondary Parkinsonism causes

- Drugs (classic and atypical antipsychotic agents, metoclopramide, prochlorperazine etc.)
- Toxins (carbon disulfide, carbon monoxide, cyanide, MPTP, manganese, organic solvents)
- Head trauma, isolated or repeated (dementia pugilistica)
- Structural brain lesions that affect striatonigral circuits (hydrocephalus, chronic subdural haematoma, tumour)
- Metabolic and miscellaneous disorders (hypoparathyroidism, pseudohypoparathyroidism, chronic liver failure, extrapontine myelinolysis)
- Infections (encephalitis lethargica or Economo's encephalitis, HIV/AIDS, neurosyphilis, prion disease, progressive multifocal leukoencephalopathy, toxoplasmosis)

Essential tremor

- Most common cause of a pathological tremor
- Estimated prevalence 5% of the population
- Polygenic with family history common, so-called “familial tremor”
- Onset usually 60s-70s (younger onset rarer)
- Characteristics
  - Bilateral, largely symmetrical postural and kinetic tremor involving the hands and forearms
  - Worse on action
  - Can be associated with jaw (less common) and head tremor
  - Vocal tremor
  - Improves with alcohol

Essential Tremor Video

Bhidayasiri and Tarsy, Movement Disorders: A Video Atlas, Springer 2012

Progressive Supranuclear Palsy (PSP)

- Tauopathy (also found in AD, frontotemporal dementia, CBD)
- Should be considered in all patients presenting with parkinsonism and:
  - Poor response to levodopa therapy
  - Slowing of vertical saccades/ supranuclear vertical gaze palsy
  - Early postural instability with falls, executive dysfunction, dysarthria/dysphagia
  - (Eye-opening apraxia)
- Subtypes
  - Classic form –Steele-Richardson-Olszewski syndrome (PSP-RS)
  - PSP-parkinsonism (PSP-P)
  - PSP-pure akinesia with gait freezing (PSP-PAGF)
  - PSP-corticobasal syndrome (PSP-CBS)
  - PSP-frontal presentation (PSP-PNFA/PSP-bvFTD)
  - PSP-cerebellar features (PSP-C)

Progressive Supranuclear Palsy (PSP)

- Mean age at diagnosis is 65 years
- Progression of disease and accumulation of disability in PSP is more rapid and severe than in PD
- Terminal stages of disease
  - Severe communication difficulties
  - Immobility
  - Severe axial rigidity
  - Severe dysphagia
  - Complete ophthalmoplegia

PSP - Richardson syndrome

- Early difficulties with balance (severe postural instability with tendency to fall) in relation to relatively mild bradykinesia
- Personality changes (apathy)
- Visual disturbances
  - Slowing of vertical saccades
  - Hypometric saccades
  - Square-wave jerks (fixation instability)
  - Supranuclear vertical gaze palsy – test with vertical and horizontal saccades
- Severe autonomic dysfunction and cerebellar ataxia is rare
- MRI - midbrain atrophy
- Prognosis
  - Patients usually dependent on others for care 3-4 years
  - Mean disease duration from onset to death is about 7 years

PSP – Parkinsonism

- Difficult to differentiate from PD in the earliest stages
- Helpful pointers - rapid progression, prominent axial symptomatology, and suboptimal response to levodopa despite typical clinical features of PD
- Bradykinesia and limb rigidity at disease onset, which can be asymmetric and, in some cases, associated with tremor
- Axial rigidity is often a striking early feature, and limb rigidity is more common and severe
- Over time most will develop more typical PSP features - severe postural instability, frontal cognitive decline, and vertical supranuclear gaze palsy
- Disease duration to death is about 3 years longer in PSP-parkinsonism than Richardson syndrome

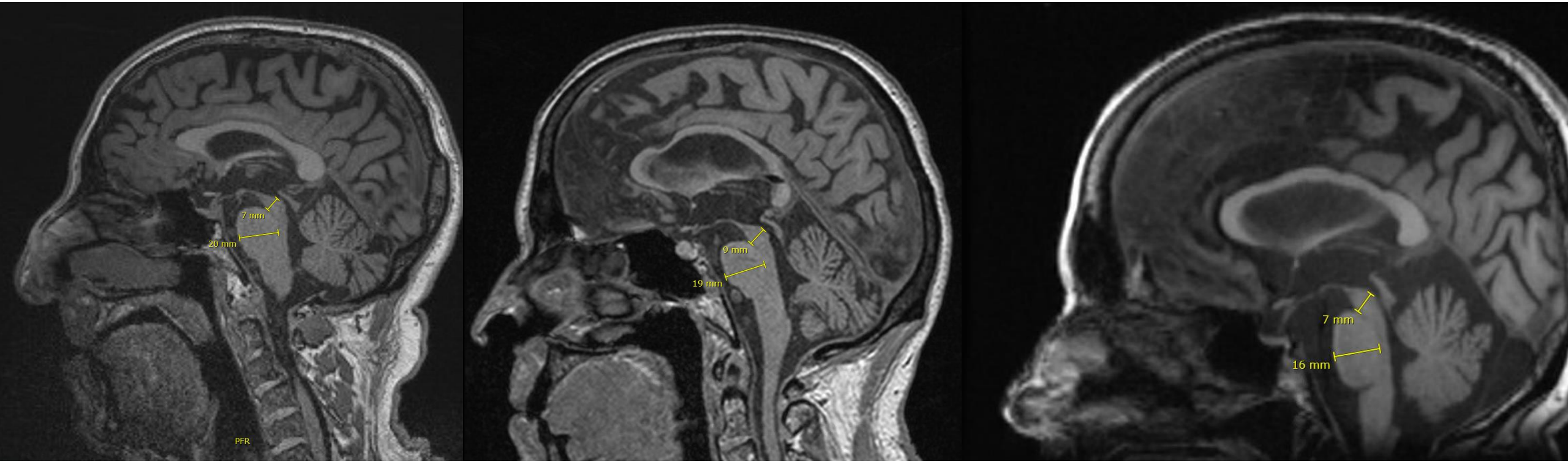
Other PSP variants

- Progressive supranuclear palsy– corticobasal syndrome
- Progressive supranuclear palsy– frontotemporal dementia
- PSP – pure akinesia with gait freezing
- PSP with predominant cerebellar features (PSP-C)

- Comprehensive diagnostic criteria for the various subtypes of PSP are found in the Movement Disorder Society Criteria (Höglinger, Mov Disord. 2017)

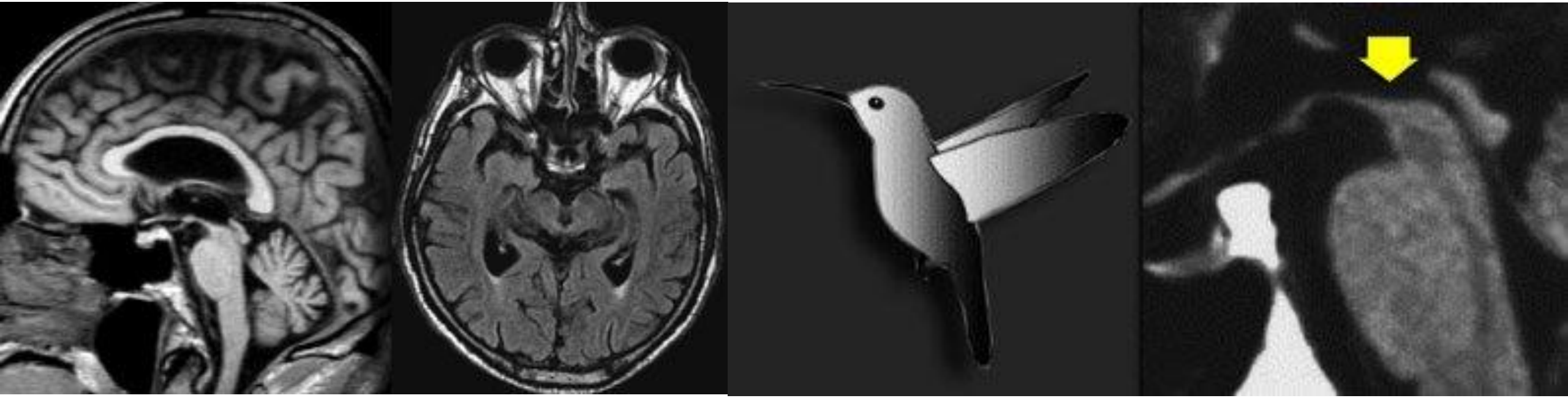
PSP Video

PSP Imaging



Midbrain atrophy and reduced midbrain:pons ratio

“hummingbird sign” of PSP



Frederik Barkhof, et al., Neuroimaging in Dementia

Multiple System Atrophy (MSA)

- Parkinsonism of MSA is usually symmetrical and classically responds poorly to dopaminergic therapies
- Alpha-synucleinopathy
- Bradykinesia and rigidity progress somewhat faster than in PD, and as a consequence, postural instability and falls usually emerge within the first 3 years of disease onset.
- Parkinsonism in the presence of increasing urinary urgency, constipation, postural hypotension, and erectile dysfunction in men
- Early progressive autonomic dysfunction precedes the evolution of motor symptoms by up to several years
- 2 subtypes
  - MSA-P – Predominant Parkinsonian symptoms (80%)
  - MSA-C – cerebellar syndrome with subtle Parkinsonism (20%)

Revised MSA Diagnostic Criteria

Table 1 **Criteria for the diagnosis of probable MSA**

A sporadic, progressive, adult (>30 y)–onset disease characterized by
• Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic *and*
• Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Table 2 **Criteria for possible MSA**

A sporadic, progressive, adult (>30 y)–onset disease characterized by
• Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) *and*
• At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) *and*
• At least one of the additional features shown in table 3

Gilman S, et al. Neurology. 2008

Table 3 **Additional features of possible MSA**

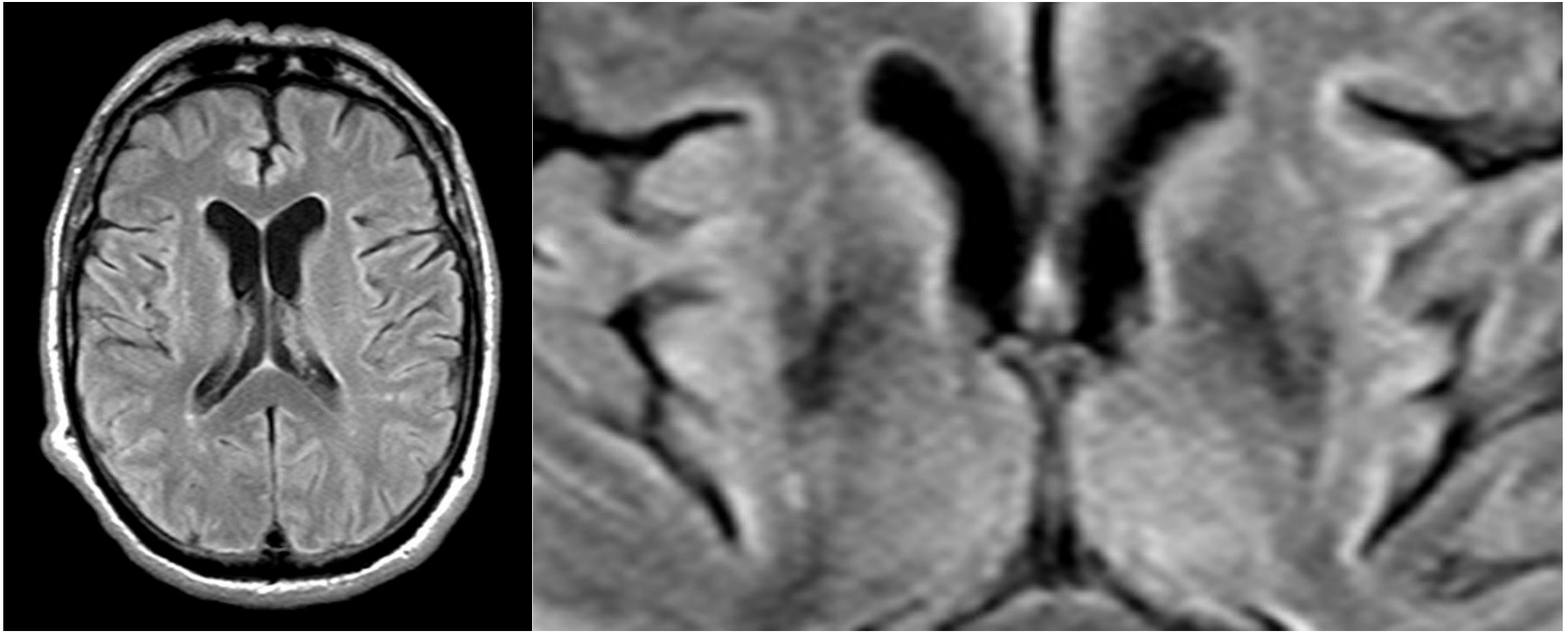
Possible MSA-P or MSA-C
• Babinski sign with hyperreflexia
• Stridor
Possible MSA-P
• Rapidly progressive parkinsonism
• Poor response to levodopa
• Postural instability within 3 y of motor onset
• Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
• Dysphagia within 5 y of motor onset
• Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
• Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-C
• Parkinsonism (bradykinesia and rigidity)
• Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
• Hypometabolism on FDG-PET in putamen
• Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

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

Gilman S, et al. Neurology. 2008

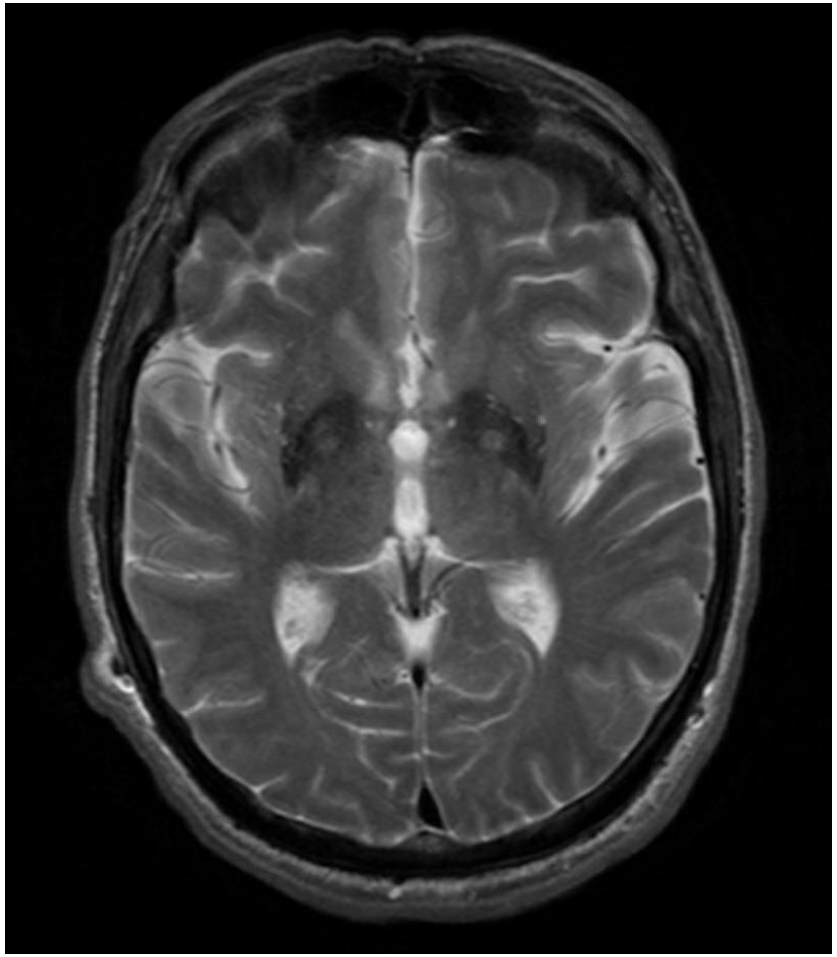
MSA-P Video

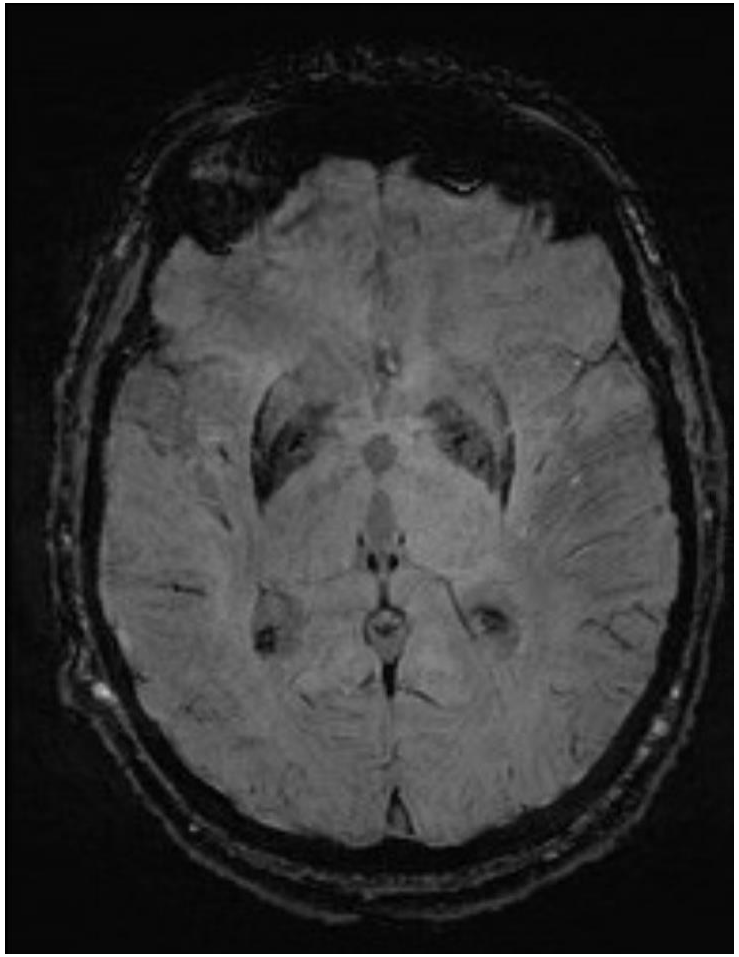
MSA-P Imaging



T2 hyperintense putaminal rim

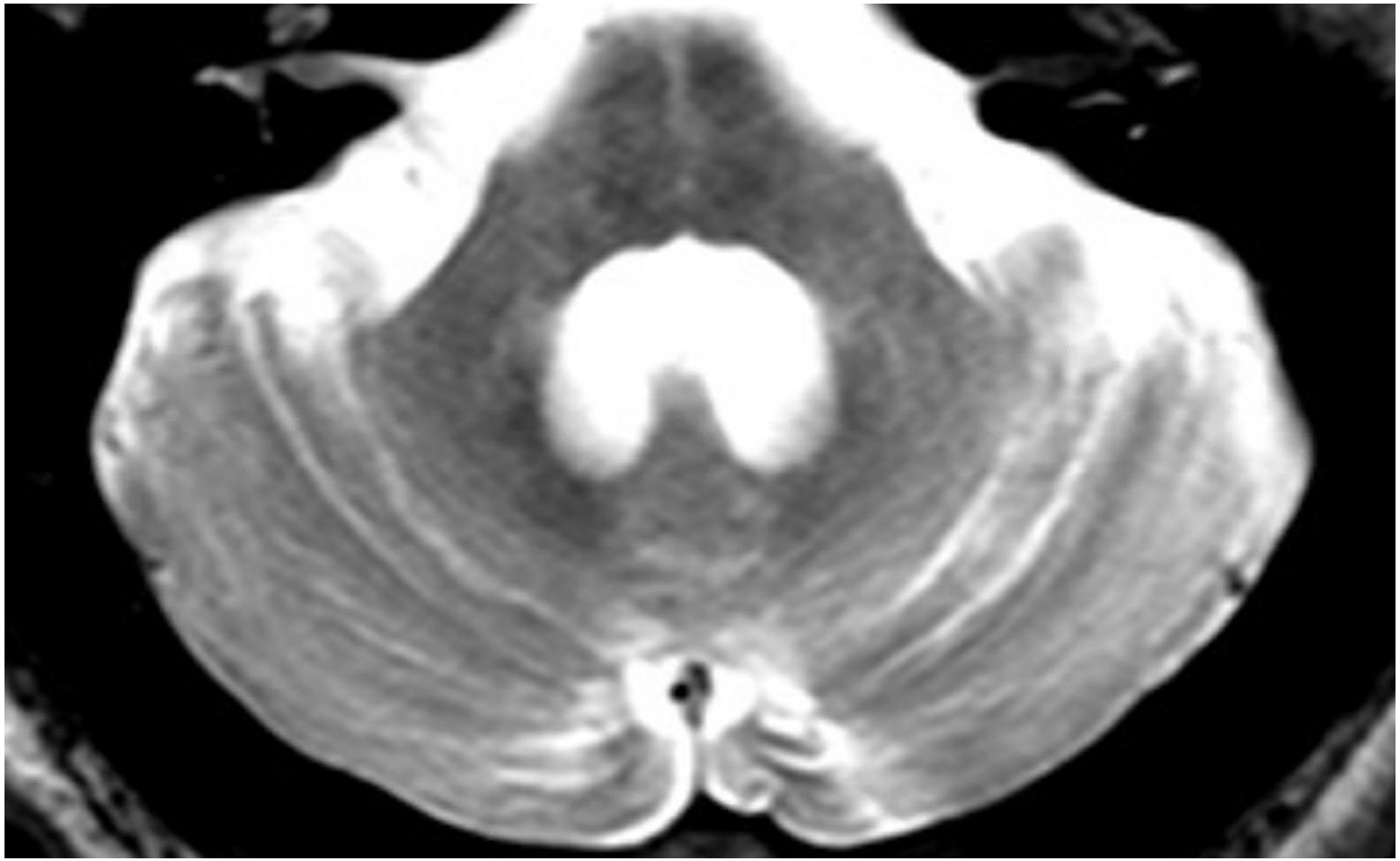
MSA-P Imaging





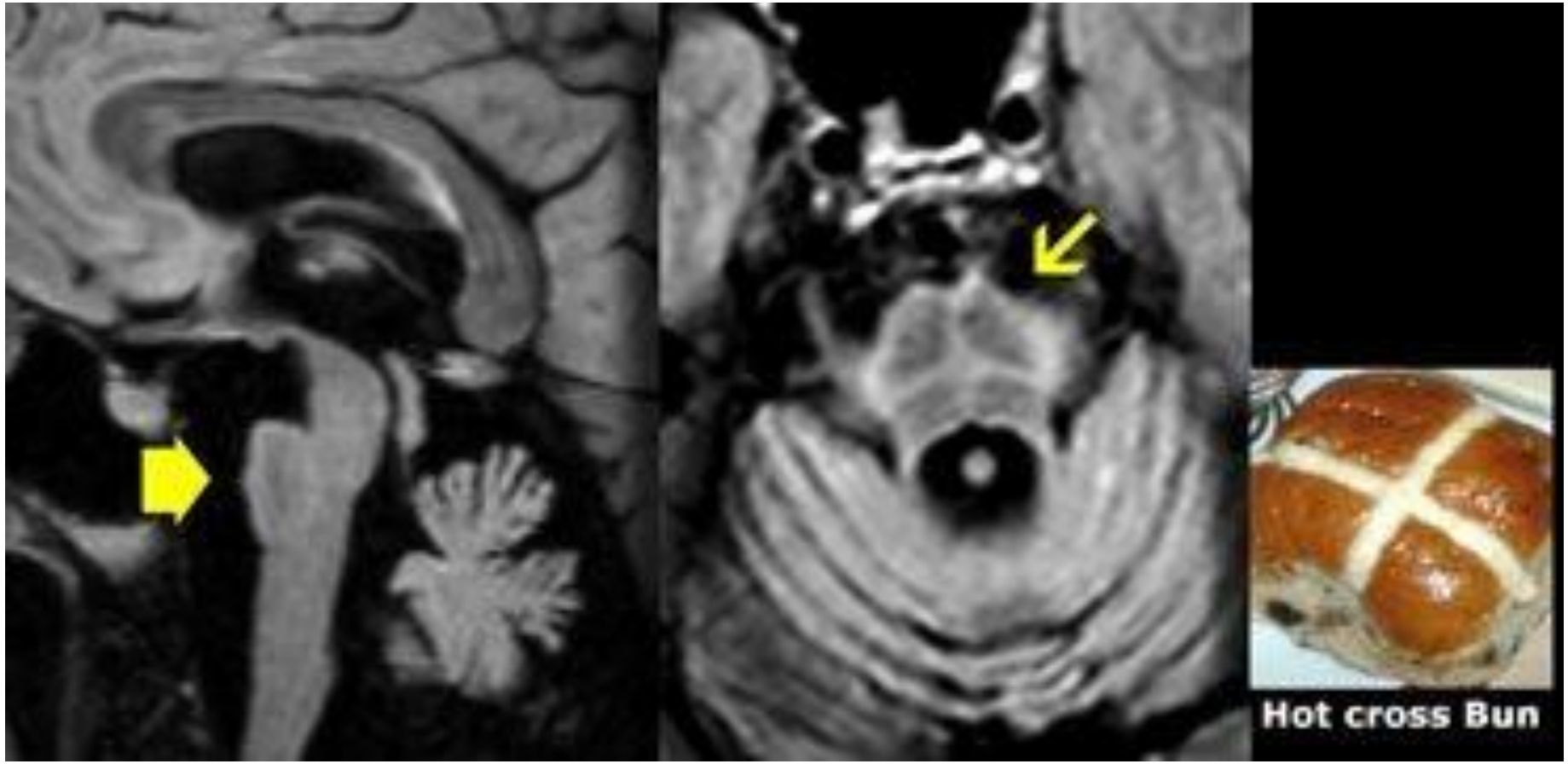
Putaminal hypointensity on T2/T2*

MSA-P Imaging



Cerebellar/MCP atrophy and linear hyperintensity in brainstem

“Hot Cross Bun” Sign



Frederik Barkhof et al, Neuroimaging in Dementia

Corticobasal degeneration (CBD) / Corticobasal syndrome (CBS)

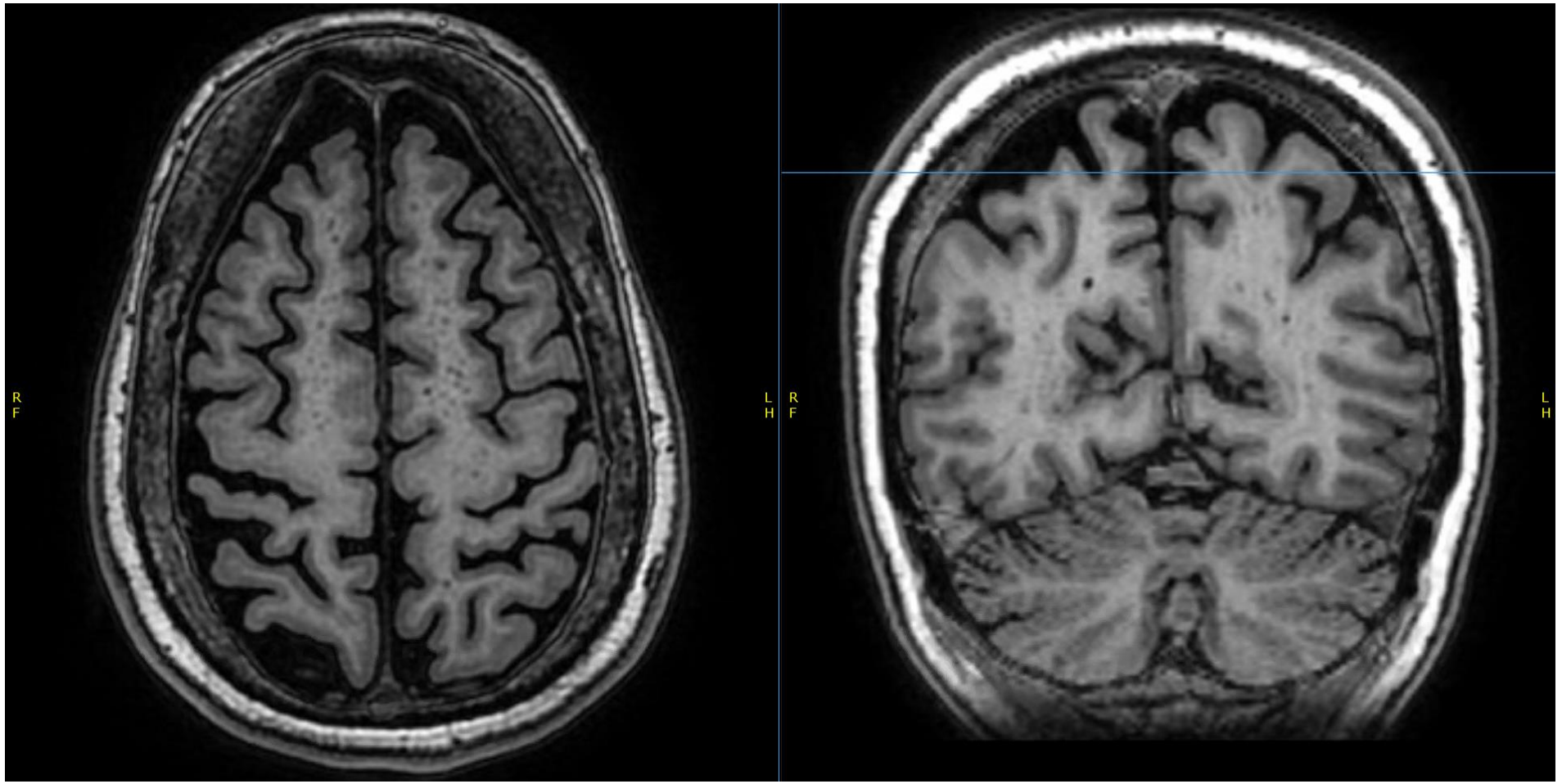
- Usually develops in the fifth to seventh decades of life
- Presents with various phenotypes that include CBS, FTD, progressive nonfluent aphasia
- Definite diagnosis of CBD requires autopsy confirmation.
- Symptoms
  - Asymmetric ideomotor apraxia, associated with rigidity, myoclonus, dystonia
  - Alien-limb phenomenon - involuntary grasping, purposeless movements, or levitation in an apraxic limb
  - When affecting the right extremities, often associated with a non-fluent aphasia
  - When affecting left extremities, often associated with visuospatial and visuoconstructive deficits
  - Oculomotor disturbances
    - Oculomotor apraxia (delayed latency of saccades with normal optokinetic nystagmus) -> supranuclear gaze palsy

Corticobasal degeneration (CBD) / Corticobasal syndrome (CBS)

- Diagnostic criteria for probable corticobasal degeneration (Armstrong, Neurology 2013)
  - Asymmetric presentation of two of
    - Limb rigidity or akinesia
    - Limb dystonia
    - Limb myoclonus
  - plus two of the following:
    - Orobuccal or limb apraxia
    - Cortical sensory deficit
    - Alien limb phenomena
- MRI
  - Asymmetric parietal or frontoparieto-occipital atrophy
- Prognosis
  - Symptoms are relentless and survival is usually 7 to 8 years

CBD Video

CBD Imaging



Focal right posterior parietal atrophy

Dementia with Lewy Bodies (DLB)

- Second most common type of degenerative dementia after Alzheimer disease
- 10-22% of dementia cases
- Pathology – alpha-synuclein, Lewy Bodies
- Can co-exist with Alzheimer's disease
- Differential diagnosis – Parkinson's disease dementia (dementia early in DLB)
- Clinical features
  - Dementia - early impairments in attention and executive and visuospatial function, memory later
  - Fluctuations
  - Visual hallucinations in 2/3; well-formed images of people or animals; illusions
  - Parkinsonism – milder and more symmetric than PD
  - **Neuroleptic sensitivity**

Clinical and radiologic features of dementia with Lewy bodies (DLB)

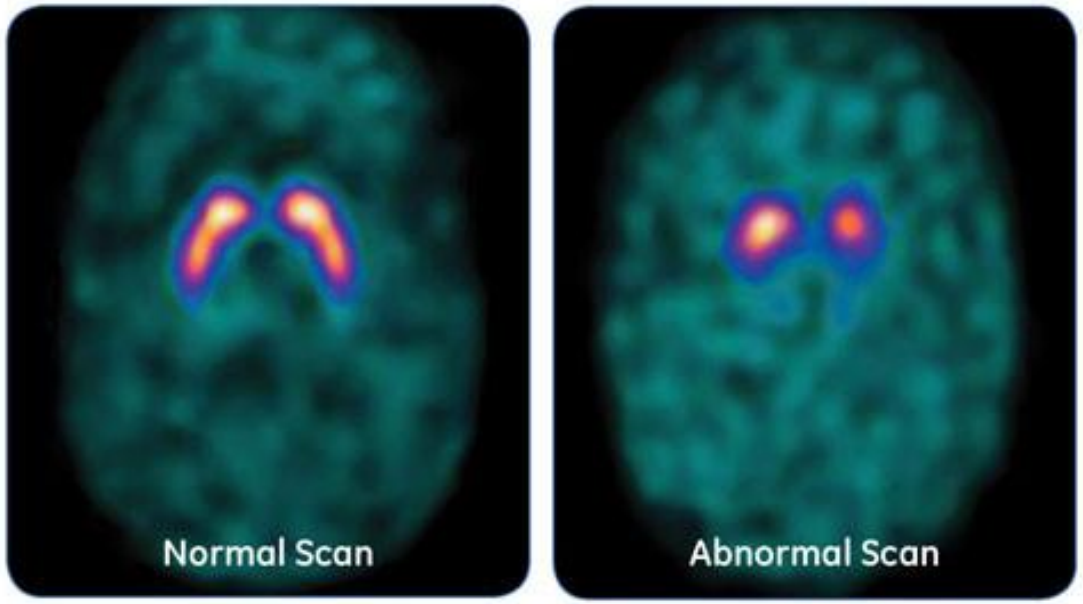
	Frequency in DLB (percent)*
Central feature (essential for the diagnosis)•	
Progressive cognitive decline, dementia	100
Core features (two features essential for diagnosis of probable DLB, one for possible DLB)•	
Fluctuating cognition	60-80
Recurrent well-formed, detailed visual hallucinations	50-75
Spontaneous features of parkinsonism	80-90
Suggestive features (one suggestive feature with one core feature may diagnose probable DLB, one or more suggestive features may diagnose possible DLB)•	
REM sleep disorder	85
Severe neuroleptic sensitivity	30-50
Low dopamine transporter uptake in basal ganglia on SPECT or PET	
Supportive features (common features with undetermined diagnostic specificity)•	
Repeated falls	33
Syncope or transient loss of consciousness	
Severe autonomic dysfunction	
Hallucinations in other modalities	20
Systematized delusions	55-75
Depression	30-40
Relative preservation of medial temporal lobe on MRI or CT	
Generalized low uptake on SPECT or PET perfusion imaging with reduced occipital activity	
Abnormal (low uptake) MIBG myocardial scintigraphy	
Prominent slow wave activity and temporal lobe transient sharp waves on EEG	
Conflicting features (features which make DLB less likely)•	
Cerebrovascular disease evidenced by focal neurologic signs or neuroimaging	
Other physical illness or brain disorder which is consistent with some or all of clinical features	
First appearance of parkinsonism at late stage (severe) dementia	
Temporal sequence (feature which distinguishes DLB from Parkinson disease dementia)•	
Dementia should occur before or concurrently with onset of parkinsonism	

* References for frequency provided in text.
• Consensus criteria of the third report of the DLB consortium. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005; 65:1863.

Select secondary causes of parkinsonism

Drug-induced Parkinsonism

- Features suggestive of DIP
  - Subacute bilateral onset and progression of symptoms temporally associated with medication intake
  - Early postural tremor
  - Oro-buccal dyskinesia
- DIP usually resolves within weeks to months after stopping the offending drug; however, parkinsonism may persist or progress in 10%
- Diagnosis – clinical and DaTscan
- Treat by discontinuation of the offending drug



Alvarez et al, Neurology. 2008

Drug-induced Parkinsonism

Table 1. Common offending drugs of drug-induced parkinsonism

Drug frequently causing parkinsonism		Drug infrequently causing parkinsonism	
Typical antipsychotics	Phenothiazine: chlorpromazine, prochlorperazine, perphenazine, fluphenazine, promethazine	Atypical antipsychotics	Clozapine, quetiapine
	Butyrophenones: haloperidol		
	Diphenylbutylpiperidine: pimozide	Mood stabilizer	Lithium
	Benzamide substitutes: sulpiride		
Atypical antipsychotics	Risperidone, olanzapine, ziprasidone, aripiprazole	Antidepressant	SSRI: citalopram, fluoxetine, praoxetine, sertraline
Dopamine depleters	Reserpine, tetrabenazine	Antiepileptic drugs	Valproic acid, phenytoin
Antiemetics	Metoclopramide, levosulpiride, clebopride	Antiemetics	Domperidone, itopride
Calcium-channel blocker	Flunarizine, cinnarizine		

SSRI: selective serotonin reuptake inhibitor.

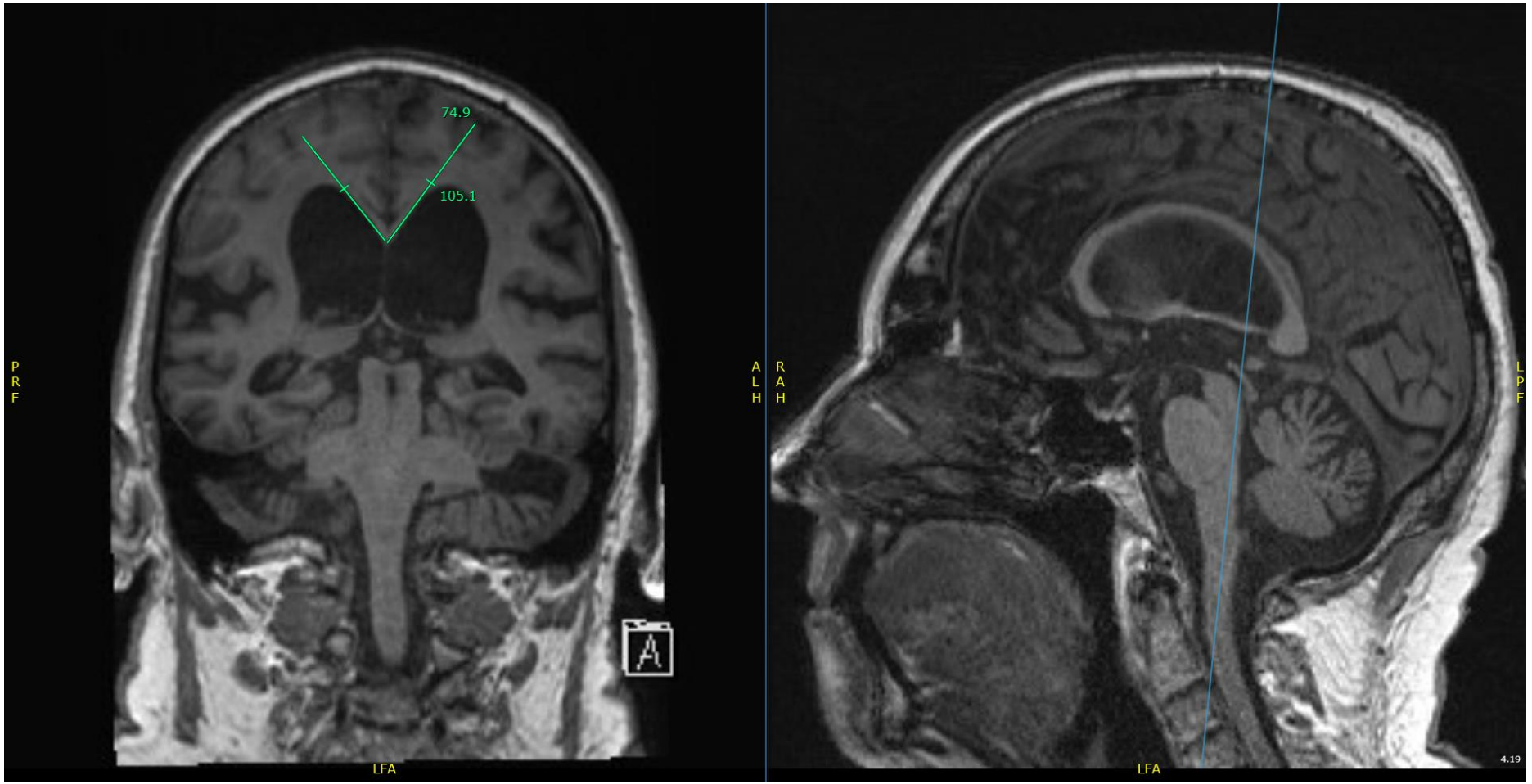
Shin and Chung, J Clin Neurol. 2012

Normal pressure hydrocephalus (NPH)

- Form of communicating hydrocephalus with dilation of ventricles disproportional to cortical atrophy and without evidence of CSF obstruction
- Triad of dementia, gait disturbance (with parkinsonism) and urinary incontinence
- Diagnostic test with large volume lumbar puncture
- May be treated with CSF shunting

NPH Video

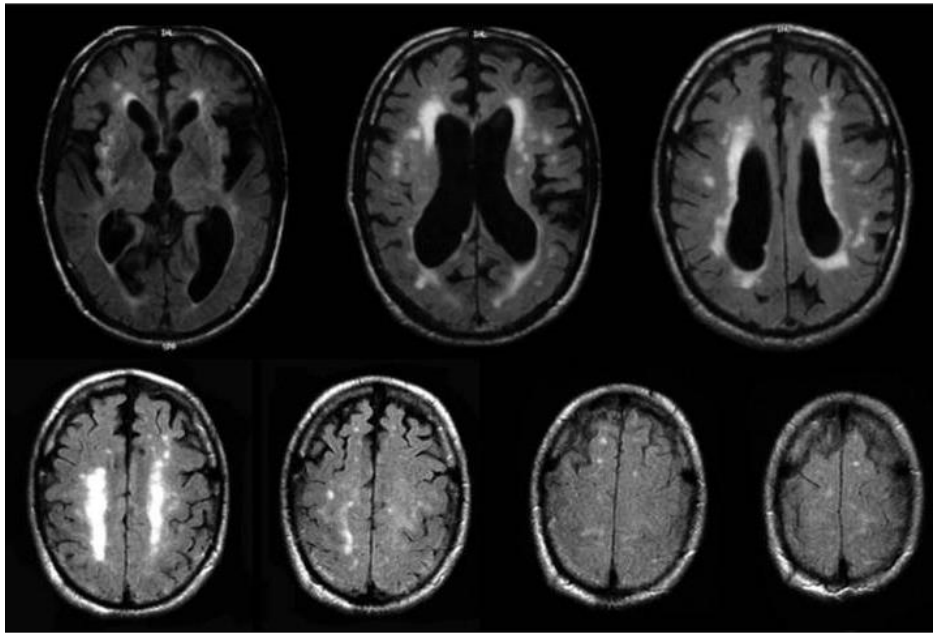
NPH Imaging



Ventriculomegaly and acute callosal angle

Vascular parkinsonism

- 4.4-12% of all parkinsonism (Mehanna, Lancet Neurol 2013)
- “lower body” parkinsonism, with a shuffling “magnetic” gait
- Atypical features
  - No resting tremor
  - Absent or poor response to dopamine replacement
  - Often in individuals with significant vascular disease
- Associated features (Zijlmans, Mov Disord 2004)
  - Diffuse vascular disease
  - Development of parkinsonism within one month of a stroke (rare)
  - Stroke in basal ganglia or diffuse subcortical whit mater disease
  - Vascular disease in 2 or more vascular territories
  - Vascular risk factors (hypertension, smoking, diabetes mellitus, hyperlipidemia, presence of heart disease, family history of stroke, peripheral vascular disease)
  - Stroke in two or more prior stroke or vascular risk factors
- Can co-exist with vascular dementia
- **Levodopa responsive in 30% (Miguel-Puga, Front Neurol 2017)**



Vizcarra, Mov Disord. 2015

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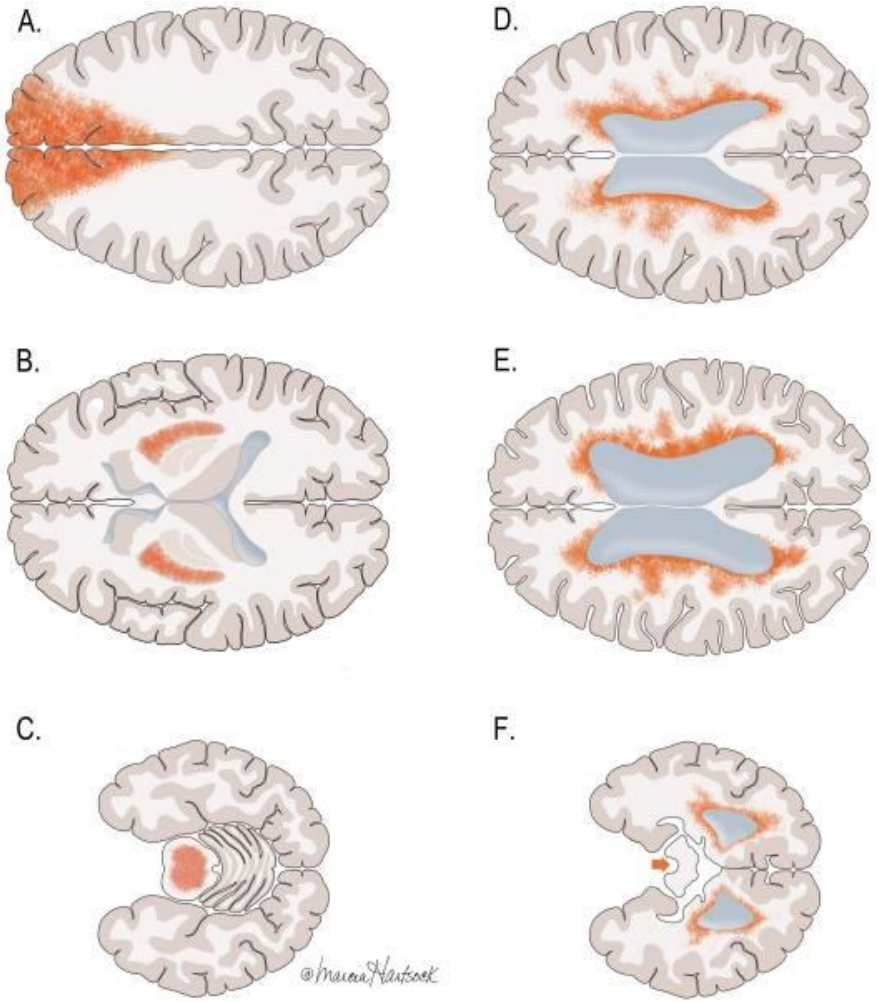


Vizcarra, Mov Disord. 2015

Select rare causes of parkinsonism

Rare case 1

Functional (psychogenic) parkinsonism

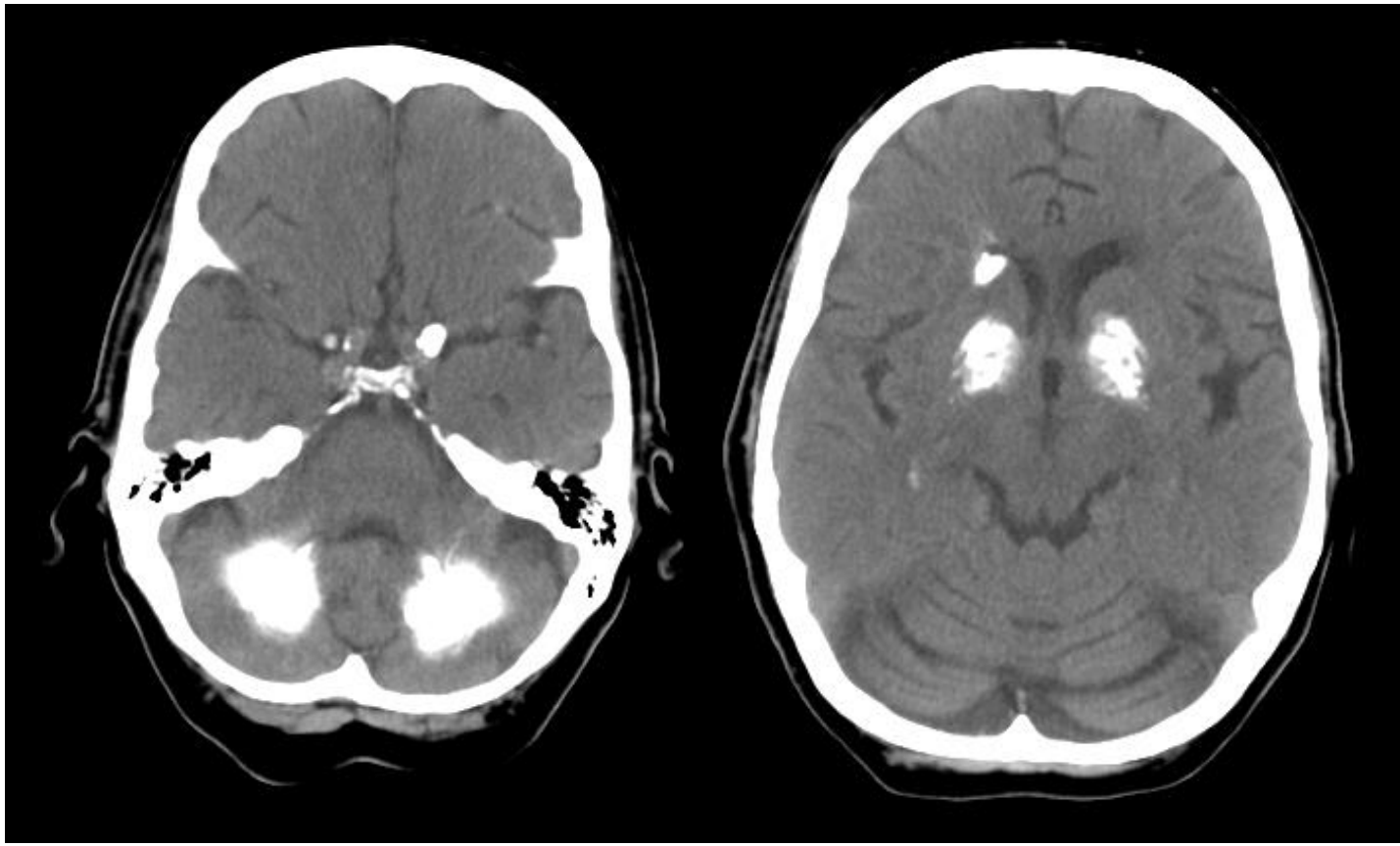
- 10% of Functional (Psychogenic) Movement Disorders (Hallett, J Neurol Sci 2011)
- Difficult to diagnose
- Inconsistent with typical features of parkinsonism
- May have sudden onset
- Can have dramatic “on” or “off” periods inconsistent with those seen in PD
- Functional tremor
- “Rigidity” with gegenhalten and voluntary opposition
- Bradykinesia characterised by ponderous, effortful slowness
- Inconsistent postural instability with even slight perturbations in contrast to better walking and balance than claimed
- Normal DaT scan

Rare case 2

X-linked dystonia parkinsonism (XDP)

- Rare neurogenetic movement disorder, almost exclusively found in individuals with Filipino ancestry.
- Founder effect with origins in the Panay Islands
- Onset in the third to fifth decade (Lee, Medicine 1991)
- Significant phenotypic spectrum ranging from pure parkinsonism to varying combinations of parkinsonism and dystonia and rare development of chorea or myoclonus (Evidente 2018).
- Genetic cause is a hexameric repeat expansion within the SINE-VNTR-Alu (SVA) intronic region of the TAF-1 gene on the X-chromosome(Bragg, Proc Nat Acadm Sci 2017).
- Like other repeat expansion disorders, a larger repeat length correlated with an earlier age at onset

Rare case 3



Gross calcifications in basal ganglia and cerebellum

Rohani, Parkinsonism Relat Disord. 2017

Idiopathic basal ganglia calcification

- Physiologic calcification in the basal ganglia are usually punctate and are located within the globus pallidus, the head of the caudate nucleus, and the putamen
- Especially if age <30., consider metabolic disorders, such as hyper/hypoparathyroidism, congenital disorders such as Fahr's disease,and infections
- Idiopathic basal ganglia calcification (Fahr's disease)
  - Rare, autosomal dominant genetic disorder SCL20A2 most common, PDGFRB and PDGFB (Batla, Parkinsonism Relat Disord. 2017)
  - Characterised by abnormal deposits of calcium in basal ganglia, cerebellum and cortex
  - Presents in third to fifth decade of life but may appear in childhood or later in life
  - Neuropsychiatric disorder with mixed movement disorder (dystonia, chorea, **parkinsonism** in 20-30%)
  - Can be associated with headache, seizures, dementia, mood disorders and psychosis

Questions?