Parkinson's and Parkinson's Plus Disorders

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Disclosures

Overview

- **Parkinson's Disease (PD) and Dementia associated with Parkinson's Disease (PDD)**
- **Parkinson's Plus Syndromes**
  - Synucleinopathies
    - Parkinson's Disease
    - Dementia with Lewy Body
    - Multiple System Atrophy
  - Tauopathies
    - Progressive Supranuclear Palsy
    - Corticobasal Degeneration

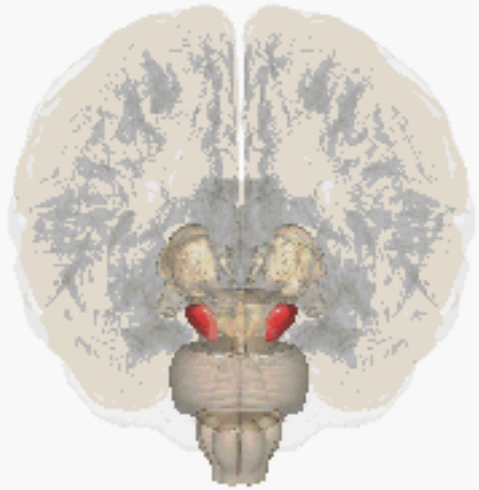
Overview

- Primary characteristics
  - Ages
  - Gender
  - Prevalence
  - Prognosis
- Etiology
  - Suspected causes and underlying neuropathology
- Diagnosis
  - Consensus criteria
  - Risk factors
- Neurobehavioral characteristics
  - Cognitive
  - Psychiatric
- Treatment
  - Pharmacological
  - Surgical
  - Behavioral

Parkinson's Disease

- Progressive neurodegenerative disease characterized by bradykinesia, rigidity, and/or resting tremor
- Prevalence
  - Most common movement disorder
  - 1,000,000 people in USA and 60,000 more each year
  - 3.5% of those over 85
  - Most often develops after age 50, average is 60.
  - Men > Women
- Typical course = 8-10 years
- Mostly idiopathic
  - Only 2-5% of familial PD
  - Risk factors: pesticides, MPTP, trauma, heavy metals

PD - Neuropathology



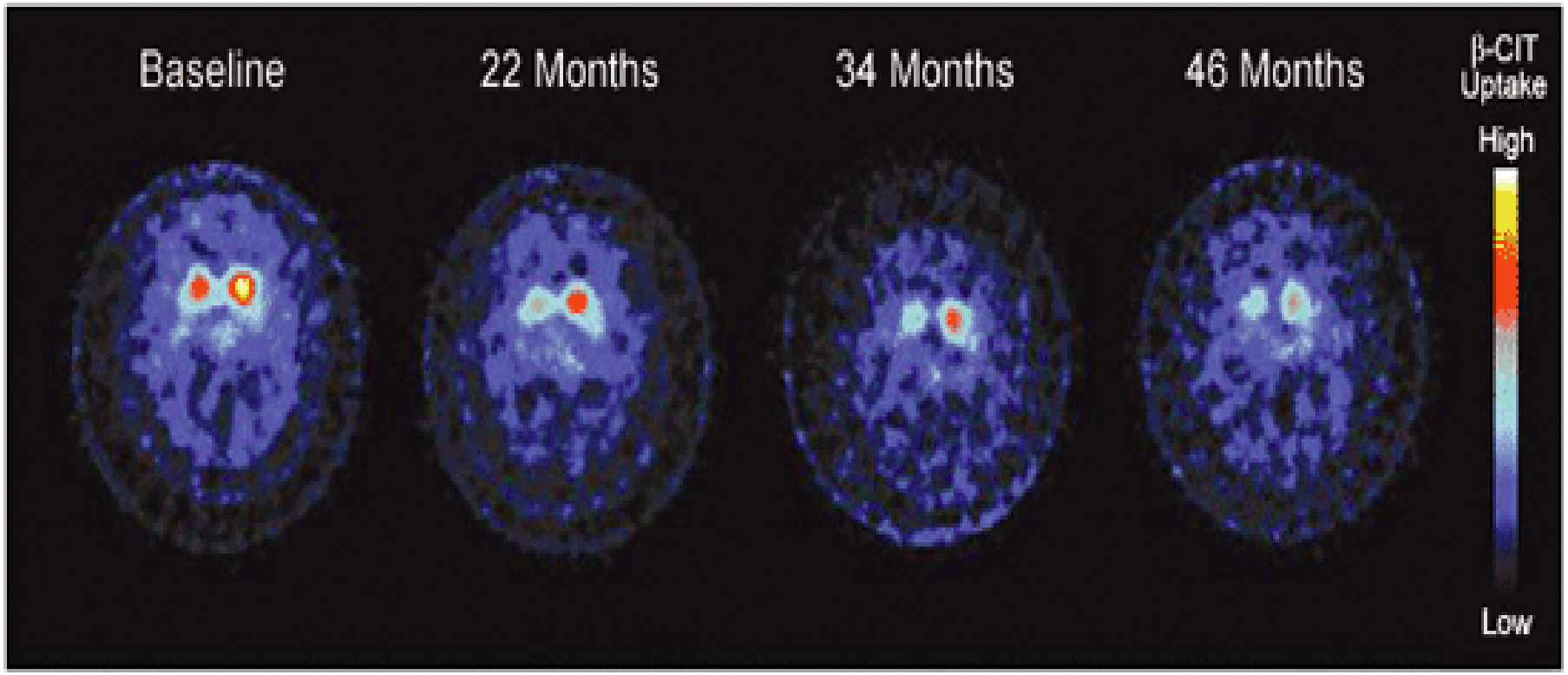


Figure. SPECT images show progressive decline of nigro-striatal DAT function.

PD – Diagnosis (MDS)

Movement Disorder Society (MDS) Clinical Diagnostic Criteria for Parkinson's Disease (2015)

Critical Features

- Parkinsonism: Bradykinesia with Resting Tremor and/or Rigidity

Diagnostic Certainty

- Clinically Established PD
  - Absence of absolute exclusion criteria
  - At least 2 supportive criteria and No Red Flags
- Clinically Probably PD
  - Absence of absolute exclusion criteria
  - Presence of red flags counterbalanced 1:1 by supportive criteria, with no more than 2 red flags

PD – Diagnosis (MDS)

Supportive Criteria

- Clear and dramatic response to DA therapy
- Presence of levodopa-induced dyskinesia
- Rest tremor of limb
- Presence of either olfactory loss or cardiac sympathetic denervation based on MIBG scintigraphy

PD – Diagnosis (MDS)

Absolute Exclusionary Criteria

- Unequivocal cerebellar abnormalities
- Downward vertical gaze palsy
- Diagnosis of FTD-bv or primary progressive aphasia within first 5 years of disease
- Parkinsonism of lower limbs only for >3 years
- Indication of drug-induced parkinsonism
- Absence of response to high dose levodopa
- Unequivocal cortical sensory loss, ideomotor apraxia, or progressive aphasia
- Normal functional neuroimaging of presynaptic DA
- Documentation of other condition known to produce parkinsonism

PD – Diagnosis (MDS)

Red Flags

- Rapid progression of gait impairment requiring regular use of wheelchair within 5 years
- Complete absence of progression of motor symptoms for >5 years unless due to treatment
- Severe dysphonia or dysarthria (speech unintelligible) or severe dysphagia within first 5 years
- Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- Severe autonomic failure in the first 5 years of disease
- Recurrent (>1 time per year) falls because of impaired balance within 3 years of onset
- Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 years
- Absence of any of the common nonmotor features of disease despite 5 years 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
  - psychiatric dysfunction (depression, anxiety, or hallucinations)
- Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia
- Bilateral symmetric parkinsonism.

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PD - Neurobehavioral Symptoms

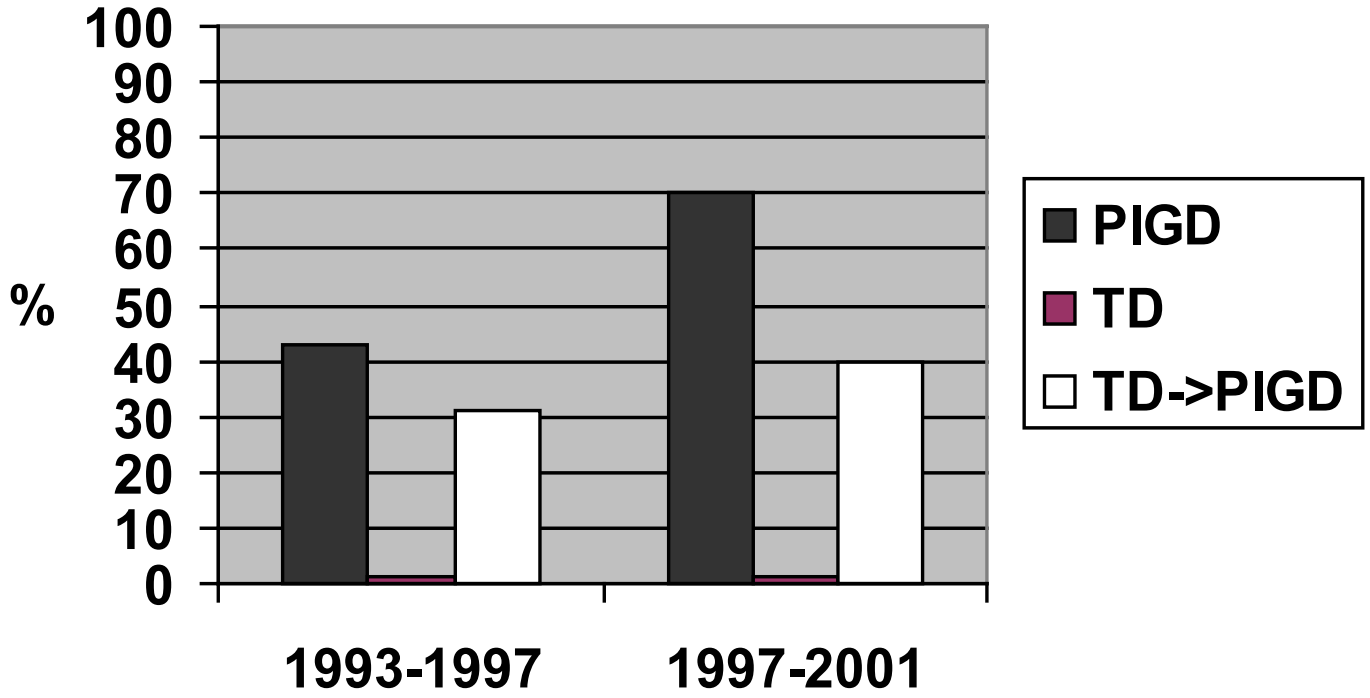
- Depression
  - 4-90% affected (average 40%)
  - Bradykinesia and lack of expression may be mistaken as depression
  - DA boosting medications may exacerbate depression
  - Responds well to antidepressant medication
- Anxiety
  - 50%, and a considerable number with symptoms of OCD
- Apathy
  - 15-42% prevalence rate
  - Less common than depression
- Hallucinations
  - Usually visual, not unpleasant or scary
  - Often iatrogenic (caused by medication)
- Personality changes
  - Shy, cautious, apathy, irritability, DA Dysregulation Syndrome
- Sleep disturbances
  - Fragmented, REM behavioral disorder, daytime drowsiness

Dementia in PD (PDD)

Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease. 2007. *Movement Disorders,* 22 (12), pp. 1689-1707.

- Point prevalence around 30% in all PD patients
- Incidence around 10%/year
- Cumulative prevalence over 8 years – 78%
- Risk Factors: Higher age, MCI at baseline, more severe parkinsonism, rigidity, postural instability and gait disturbance (vs. resting tremor)

Motor subtypes and incident dementia in PD



PIGD: Postural instability & Gait disturbance
TD: Tremor dominant

Alves, Mov Disord 2006

Dementia in PD (PDD) Diagnostic Criteria

Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease. 2007. *Movement Disorders,* 22 (12), pp. 1689-1707.

- **Probable** – Impairment in 2+ cognitive domains severe enough to impair ADLs, and the presence of at least one behavioral symptom in context of PD
- **Possible** - Atypical cognitive profile in one or more domains in context of PD

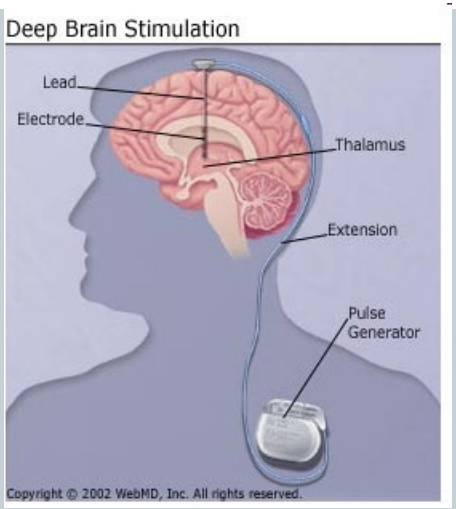
PDD Neuropathology

- The main pathological correlate of PDD seems to be the Lewy Body-type inclusions in neurons of the cerebral cortex and limbic structures.
- Alzheimer's-type pathology frequently co-exists, but it often does not reach a severity to justify pathological diagnosis of AD

PD Treatments - Pharmacologic

- DA Agonists/Enhancers
  - Amantadine
  - Levadopa
- NMDA receptor antagonists
  - Memantine
  - Riluzole
- COMT Inhibitors
  - Tolcapone
- Cholinesterase inhibitors
  - Donepezil
  - Rivastigmine
- MAO-B inhibitors
  - Selegiline

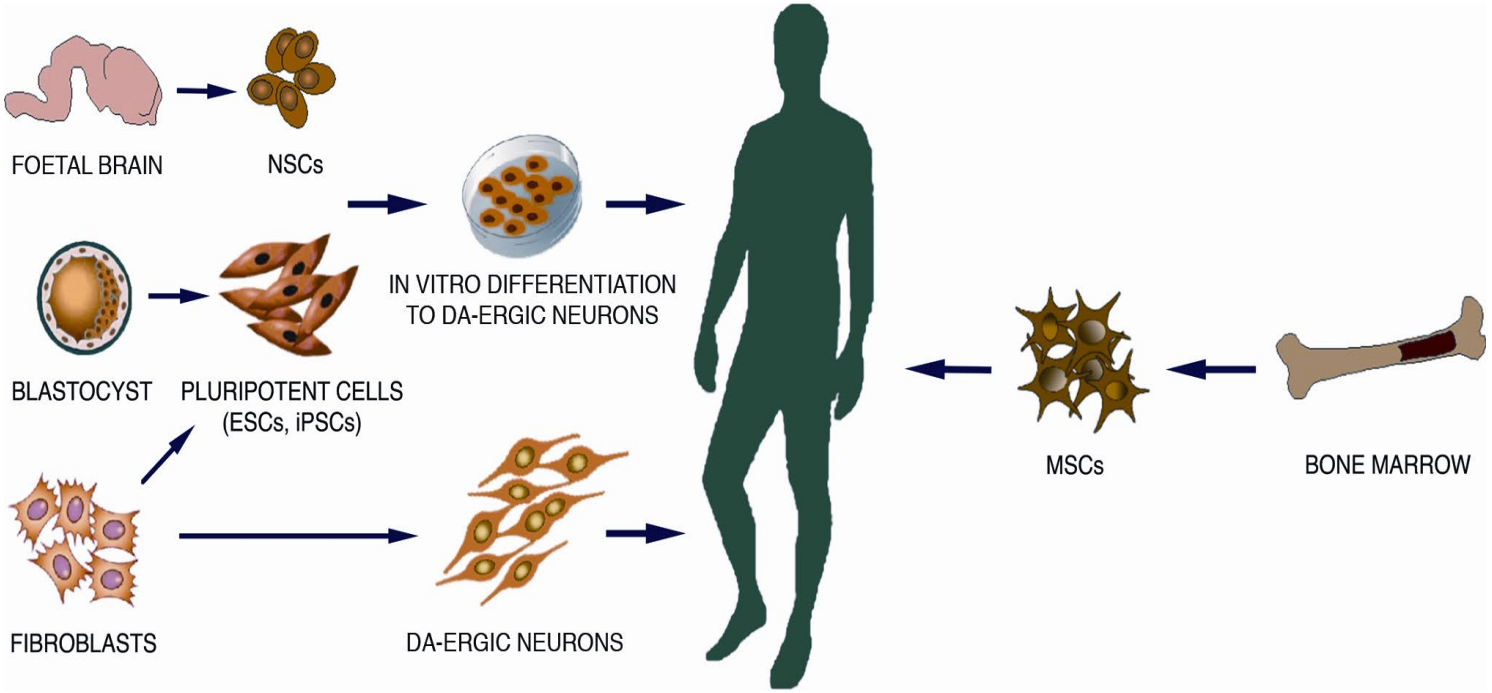
PD Treatments - Surgical



Those ideally suited to DBS for Parkinson's disease have the following characteristics:

- The predominant symptoms are motor and likely to respond to DBS of a particular target:
  - motor fluctuations: STN and GPi
  - tremor: STN and thalamic
  - gait freezing and postural instability—possibly helped by pedunculopontine nucleus
- Low burden of non-motor symptoms
- Low risk of developing dementia in the next 3–5 years
- No psychiatric contraindications (e.g., VH)

PD Treatments - Surgical



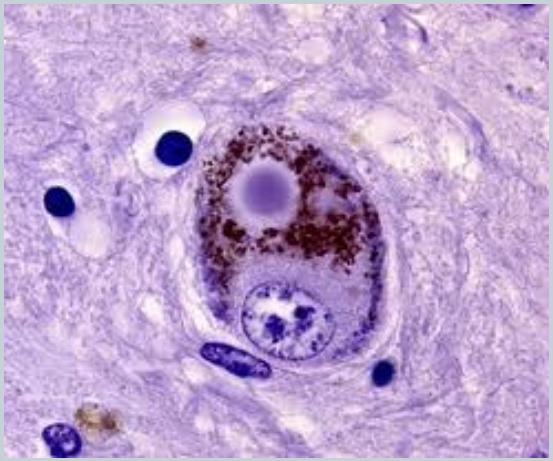
1) Neural stem cells (NSCs) from human fetal brain, expanded and differentiated to DA-ergic neurons;
2) Pluripotent cells generated from blastocysts (ESCs) or fibroblasts (iPSCs), expanded and differentiated to DA-ergic neurons;
3) DA-ergic neurons generated by direct conversion of fibroblasts;
4) Bone marrow-derived mesenchymal stem cells (MSCs).

Dementia with Lewy Bodies

- DLB (alternatively called Lewy Body Dementia) is 2nd most common type of progressive dementia in older (>64) adults
- Estimated as high as 26% of dementia cases in >64
- Symptom triad: VH, fluctuating MS, parkinsonism
- Estimated up to 5% of general population
- 2/3 are Male
- Disease course = 7-8 years

DLB - Neuropathology

- Extensive LB formation, particularly in brainstem (substantia nigra), neocortex, anterior cingulate gyrus, insular cortex, and medial temporal regions.
- Modest loss of DA, corresponding to the reduction of cells in the substantia nigra.
- Some AD pathology as well, particularly neuritic plaques. Neurofibrillary tangles less common.



DLB – Diagnostic Criteria

Diagnosis and management of dementia with Lewy bodies - Fourth consensus report of the DLB consortium. (2017)

- Diagnostic Criteria
  - Central Feature: Dementia
  - Core Features: VH, fluctuations, parkinsonism, RBD
  - Suggestive Features: RBD, Neuroleptic sensitivity
  - Supportive Features: Often present but no specificity
- Certainty
  - Probable
  - Possible

DLB – Diagnosis: Central Feature

(Essential for possible or probable DLB diagnosis)

- Dementia
  - Prominent or persistent memory impairment may not necessarily occur in the early stages
  - Attention, executive function, and visuospatial deficits may be especially prominent

DLB – Diagnosis: Core Features

- Fluctuating cognition with pronounced variations in attention and alertness
  - In some cases = periods of LOC or syncope
- Recurrent VH that are typically well formed and detailed
  - VH present at onset in up to 80% of patients
- Parkinsonism
  - Seen in >85% of patients
  - Less responsive to L-dopa
- REM sleep behavior disorder
  - Recurrent dream enactment. Often begins many years before the diagnosis.

DLB – Diagnosis: Supportive Features

- Severe sensitivity to antipsychotic medication
- Postural instability
- Repeated falls
- Syncope or other transient episodes of unresponsiveness
- Severe autonomic dysfunction
- Hyper- or hyposomnia
- Non-visual hallucinations
- Systematized delusions
- Apathy, anxiety and, or depression

DLB – Diagnosis: Biomarkers

Indicative Biomarkers

- Reduced DA transporter update in basal ganglia (based on SPECT or PET)
- Low uptake of ^{123}iodine-MIBG myocardial scintigraphy
- Polysomnographic confirmation of RBD without atonia

Supportive Biomarkers

- Relatively preserved medial temporal lobe structure (MRI)
- Generalized low uptake on SPECT/PET with reduced occipital activity +/- the cingulate island sign on FDG-PET
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in pre-alpha/theta range

DLB – Diagnosis: Non-unsupportive Features

- Presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
- Presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
- If parkinsonism only appears for the first time at a the stage of severe dementia

DLB - Diagnosis

- Probable DLB
  - 2+ core features
  - 1 core feature + 1 biomarker
- Possible DLB
  - 1 core feature
  - 1 indicative biomarker
- Definite DLB
  - Via autopsy confirmation

DLB - Treatment Considerations

- Nonpharmacologic interventions :
  - Cognitive dysfunction and VHs may be exacerbated by low levels of arousal and attention.
  - Strategies to increase arousal/ attention: increased social interaction and environmental stimuli.
  - Behavioral management of psychiatric symptoms

DLB - Treatment Considerations

- Pharmacologic treatments:
  - Cognitive symptoms:
    - Cholinesterase inhibitors (rivastigmine, donepezil, galantamine)
  - Neuropsychiatric symptoms:
    - VHs, delusions, behavioral disturbance can be treated using cholinesterase inhibitors. Atypical antipsychotics should be used cautiously (quetiapine, clozapine, aripiprazole)
    - Depression: SSRIs and SNRIs are preferred
    - RBD: clonazepam, melatonin, quetiapine
  - Motor symptoms:
    - Levodopa may be introduced at low doses and increased slowly to minimize disability w/out exacerbating psychiatric symptoms.
    - Avoid anticholinergics

Diagnostic Issues

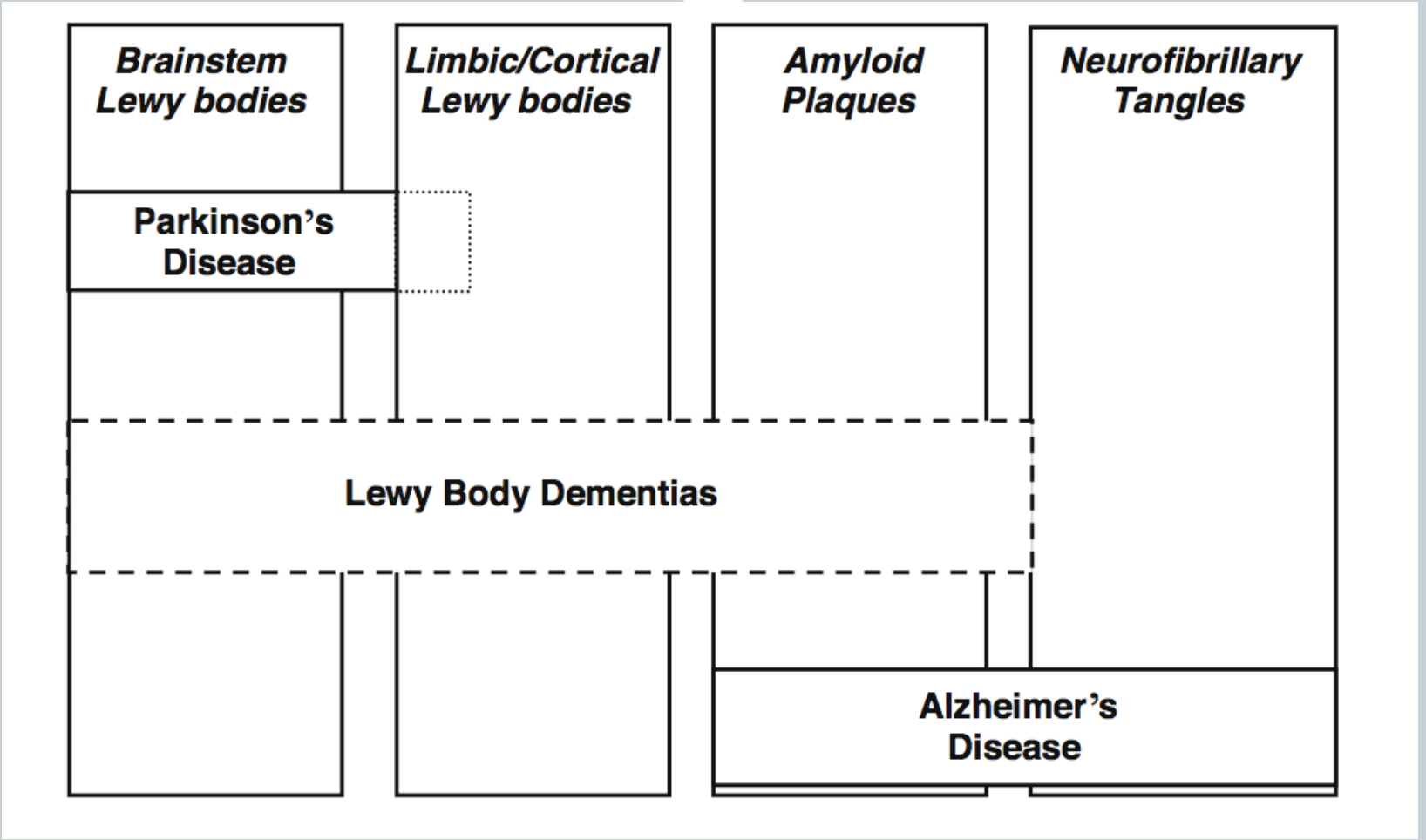
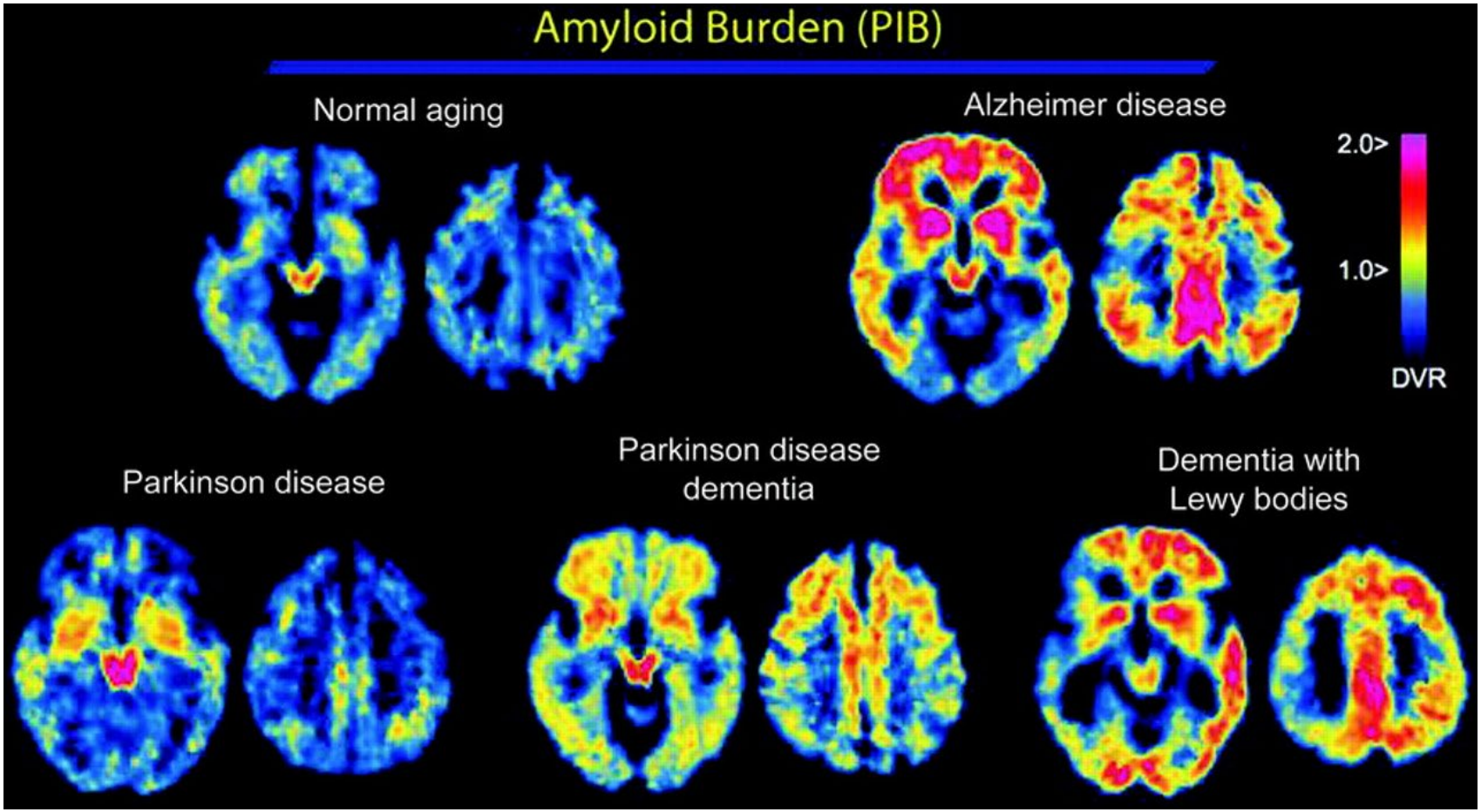


Figure. Clinical-pathologic relations among AD and Lewy body disorders (Kaufer and Tröster 2008)

Amyloid imaging (PIB) in LB disease



Gomperts, SN et al. Neurology 2008;71:903-910

PDD/DLB vs. AD: Neuropsychological

Cognitive domain	PDD/DLB	AD
Frontal-executive	Prominent and early deficits; PD patients without dementia may have impairments in sustained attention and set shifting	Later and less severe than PDD/DLB
Memory	Retrieval memory impaired, but encoding memory less affected	Early memory complaints are common; both encoding and retrieval affected; inability to form new memories is common
Language	Complaint of word finding difficulty common, but language problems are not prominent on formal testing	Language problems including paraphasic errors are common
Visuospatial	Impairments often found on formal testing; may be most common impairment in formal testing	Deficits present but less pronounced than in PDD/DLB
Psychosis/behavioral disturbance	Formed visual hallucinations common and may occur without dopaminergic therapy	Visual hallucinations unusual; suspiciousness and disinhibition more common

(Gross, Siderowf, & Hurtig, 2008)

Differential Diagnosis: DLB vs. PDD

Temporal sequence of symptoms

- DLB: dementia occurs before or concurrently with parkinsonism (if it is present).
- PDD: dementia occurs in the context of well-established Parkinson disease.
- 1-year rule (time of onset of cognitive symptoms after motor symptoms) to distinguish between DLB and PDD is recommended

Multiple Systems Atrophy (MSA)

- A progressive neurodegenerative disease characterized by parkinsonian features, *cerebellar ataxia*, *autonomic dysfunction*, *urogenital dysfunction*, and corticospinal disorders.
- Sporadic, although there are some familial cases
- Prevalence 4.6 cases per 100,000 people
- Slightly more common in men
- Occurs after age 30. Typical age of onset in the 50s
- Rapidly progressive (5-10 years)

MSA - Neuropathology

- The distinguishing feature is accumulation of alpha-synuclein in glial cells, particularly oligodendrocytes.
- The presence of synuclein-based Papp-Lantos bodies in the movement, balance, and automatic-control centers of the brain are the defining histopathologic hallmark of MSA

MSA - Classification

Second consensus statement on the diagnosis of multiple system atrophy (2008)

- MSA with predominant parkinsonism (MSA-P) – 80% of cases
- MSA with predominant cerebellar ataxia (MSA-C) – 20% of cases
- Three levels of certainty:

Possible

1. Parkinsonism (bradykinesia with rigidity, tremor, or postural instability),
   OR
   A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction),
2. **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),
3. **AND**
   At least one of the additional features shown in the following table

MSA - Classification

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 years of motor onset
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
- Dysphagia within 5 years 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 - Classification

Probable

1. Adult (>30 y)–onset
2. Autonomic failure involving urinary incontinence (with erectile dysfunction in males) or an orthostatic hypotension within 3 min of standing,
3. AND EITHER

   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)

Definite: requires autopsy confirmation

MSA – Supporting Features

- Orofacial dystonia
- Disproportionate antecollis
- Camptocormia (severe anterior flexion of the spine) and/or Pisa syndrome (severe lateral flexion of the spine)
- Contractures of hands or feet
- Inspiratory sighs
- Severe dysphonia
- Severe dysarthria
- New or increased snoring
- Cold hands and feet
- Pathologic laughter or crying
- Jerky, myoclonic postural/action tremor

MSA – Non Supporting Features

- Classic pill-rolling rest tremor
- Clinically significant neuropathy
- Hallucinations not induced by drugs
- Onset after age 75
- Family history of ataxia or parkinsonism
- White matter lesions suggesting multiple sclerosis
- Significant cognitive impairment or dementia (at least at onset)

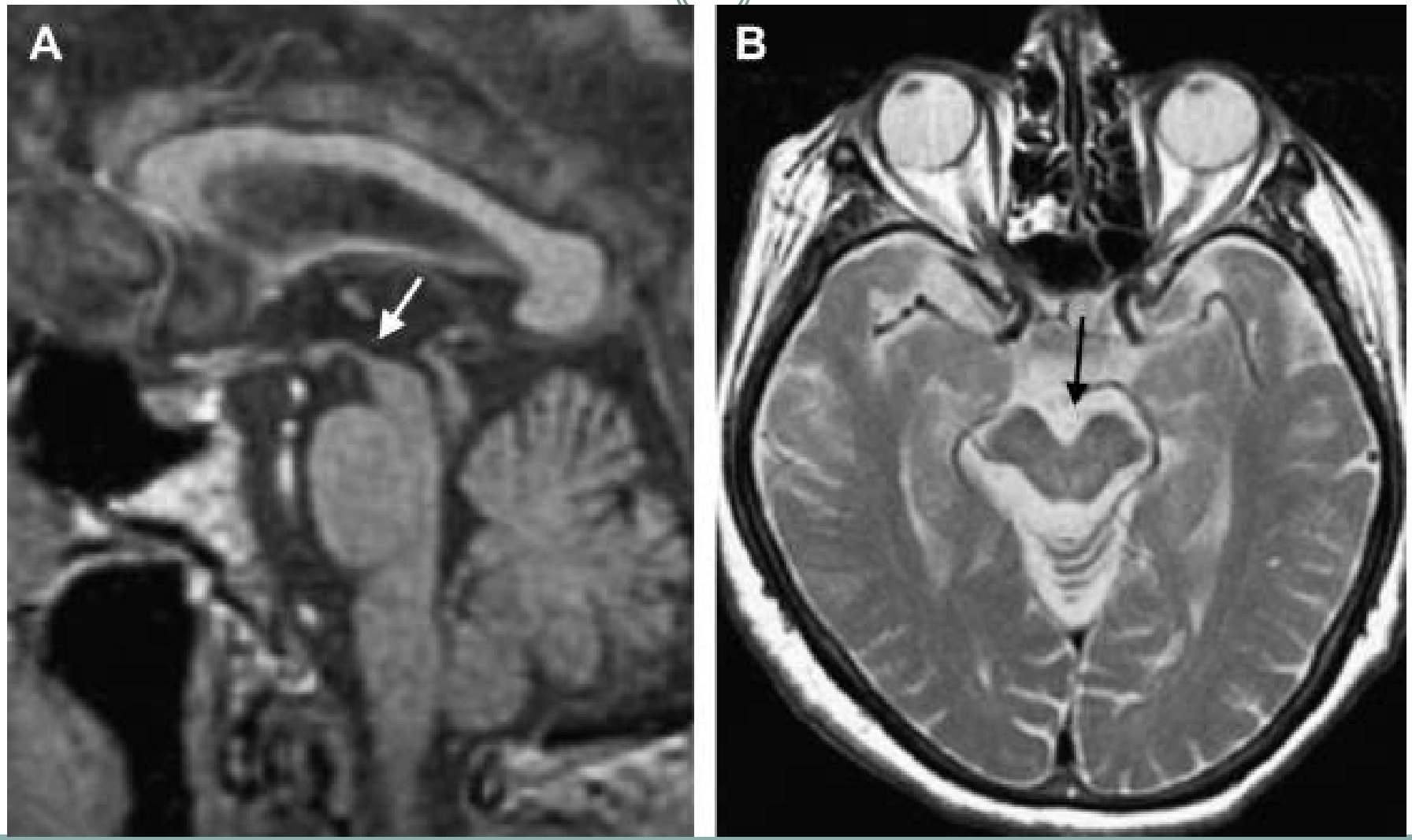
MSA - Treatment

- Treat the symptoms
- Droxidopa to treat orthostatic hypotension
- Anticholinergic drugs to reduce urinary urgency
- L-Dopa fails to improve the parkinsonian symptoms of most MSA patients.
- Install equipment at home to help with ambulation and balance.

Progressive Supranuclear Palsy (PSP)

- A progressive condition with onset over the age of 40 or later
- Primary symptoms are *vertical gaze palsy and postural instability* (e.g., falling)
- 6 people per 100,000
- Sporadic. Rarely caused by mutations in the MAPT gene
- Usually seen in people over 60 (mean = 63)
- Possibly more common in men
- Death in 5-7 years

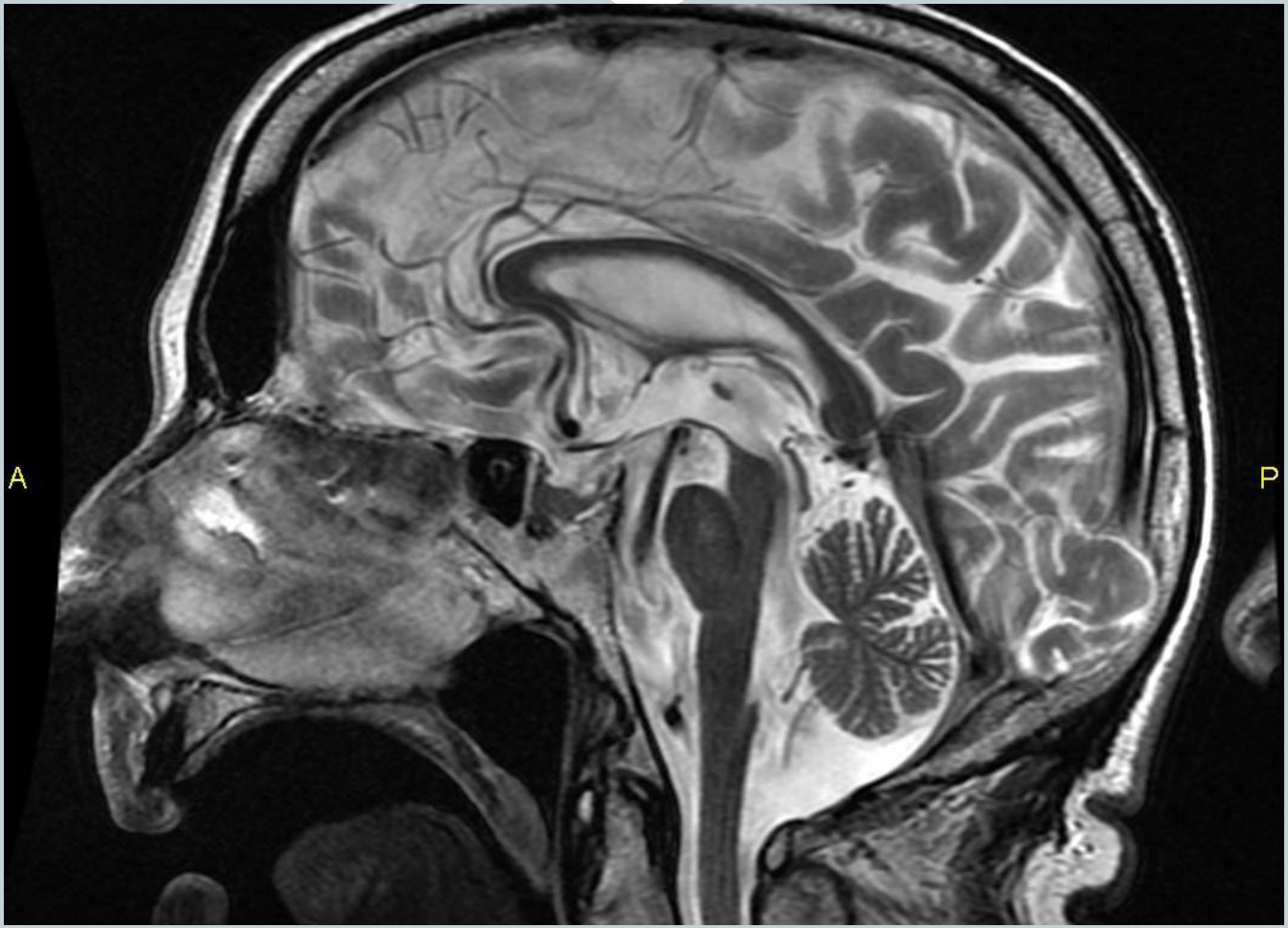
Mesencephalic Atrophy



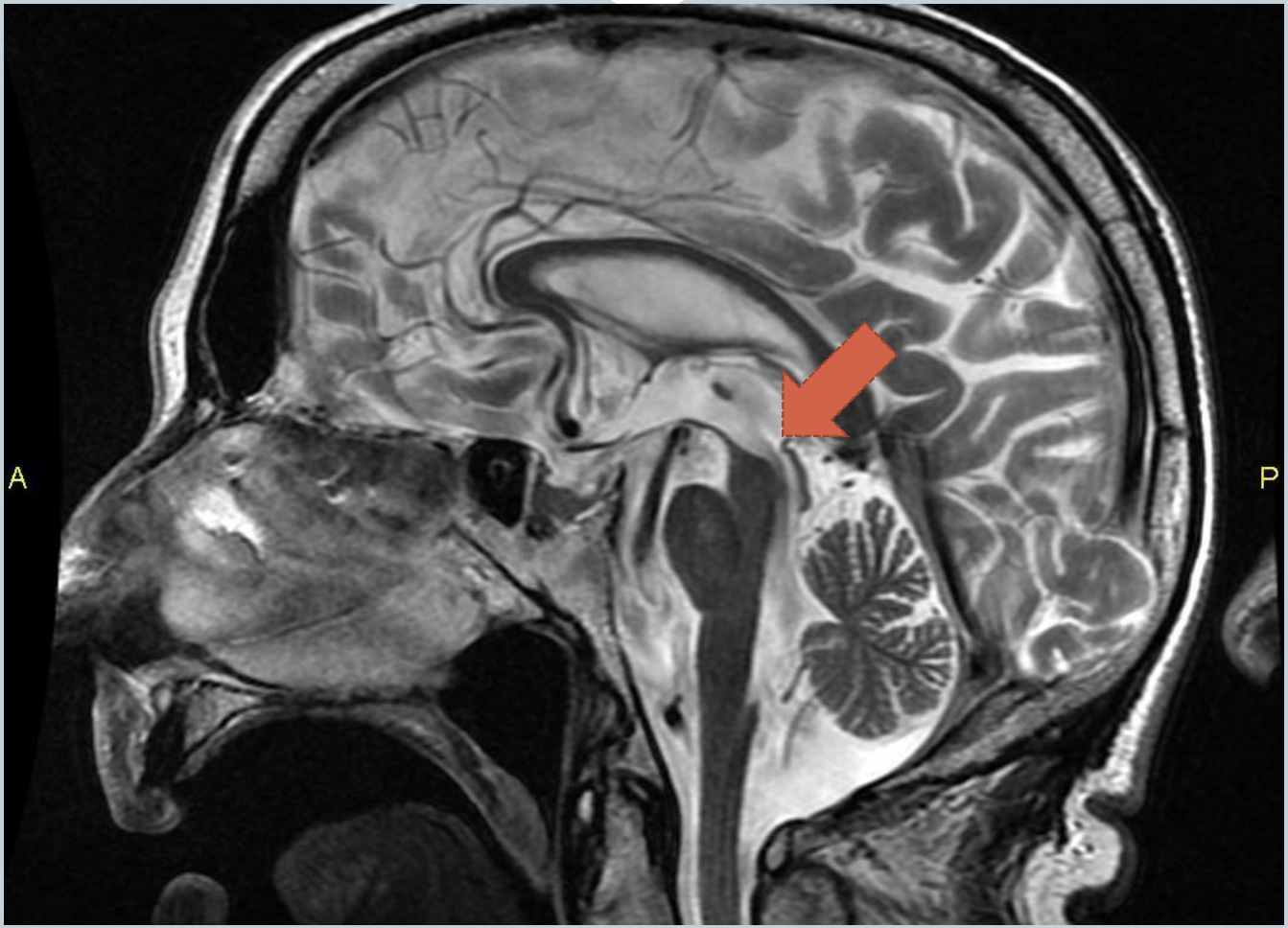
PSP - Neuropathology

- Neurofibrillary tangles and neuropil threads in select basal ganglia and brainstem regions and frontal lobes
- Tauopathy (PD, DLB, MSA are synucleinopathies)
- Loss of neurons and glial cells

Hummingbird or Penguin Sign?



Hummingbird or Penguin Sign?



PSP - Diagnosis

Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson- Olszewski syndrome): report of the NINDS-SPSP international workshop (1996)

- **Possible**: Either vertical supranuclear palsy ***or*** both slowing of vertical saccades & postural instability with falls within first year after disease onset
- **Probable**: Vertical supranuclear palsy ***and*** prominent postural instability with falls within first year of disease onset
- **Definite**: All criteria for possible or probable PSP are met ***and*** histopathologic confirmation at autopsy

PSP – Supportive Findings

- Symmetric akinesia or rigidity, proximal > distal
- Abnormal neck posture, especially retrocollis
- Poor or absent response to levodopa
- Early dysphagia & dysarthria
- Early onset of neurobehavioral changes including:
  - Apathy
  - Depression
  - Impairment in abstract thought, judgment, insight
  - Decreased word-finding and verbal fluency
  - utilization or imitation behavior
  - Personality change
  - Emotional lability

PSP – Exclusionary Criteria

- Recent history of encephalitis;
- Alien limb syndrome
- Cortical sensory deficits
- Focal frontal or temporo-parietal atrophy
- Hallucinations or delusions unrelated to DA therapy
- Alzheimer disease pathology
- Prominent, early cerebellar symptoms or unexplained dysautonomia
- Evidence of other diseases that could explain the clinical features

PSP – Symptoms and Diagnostic Accuracy

- First symptoms in about 66% of cases are loss of balance, lunging forward when mobilizing, fast walking, bumping into objects, and falls.
- Bradykinesia affects nearly half of the patients by the time of diagnosis and up to 95% of patients during the course of their illness
- Frontal lobe deficits develop in the majority of cases (80% of cases in total, 52% in the first year)
- Most often misdiagnosed as PD or Vascular dementia
- A poor response to levodopa along with symmetrical onset can help differentiate this disease from PD

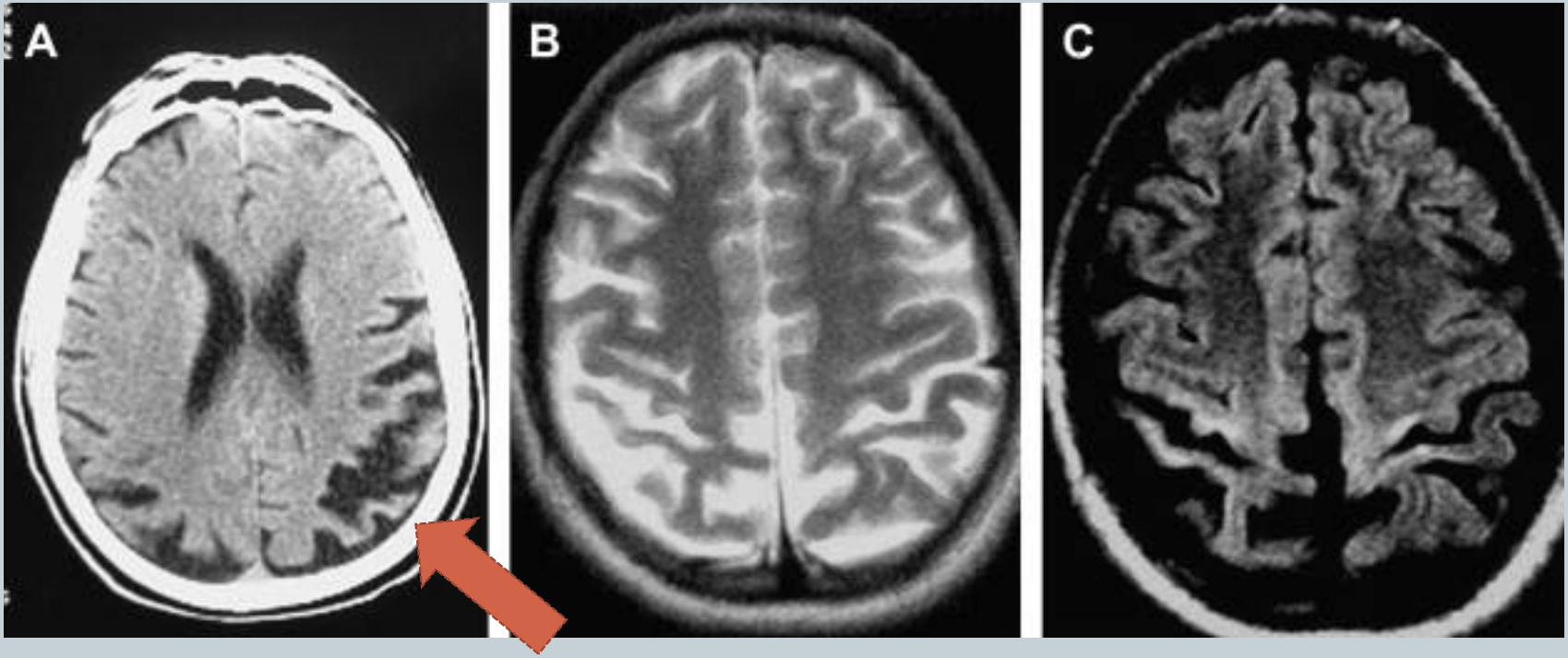
PSP - Treatment

- Levodopa and similar drugs may temporarily reduce some symptoms, such as rigid limbs or slow movements. However, not as effective as they are for Parkinson's disease
- Rivastigmine may help with neurocognitive symptoms

Corticobasal Degeneration (CBD)

- A neurodegenerative condition characterized by alien hand syndrome, asymmetric presentation of bradykinesia, apraxia, and cortical sensory deficits
- Tauopathy
- Typically after age 60
- 4.9 to 7.3 per 100,000 people
- May be more common in women
- Disease course typically 7 years from time of diagnosis

CBD Neuropathology



CBD Neuropathology

- Distribution of focal cortical atrophy is one of the characteristic features of the disease.
- Tau-immunoreactive neuronal and glial lesions
- Ballooned cortical neurons also carry differential diagnostic value *(post-mortem)*

CBD - Diagnosis

- There are diagnostic criteria for CBD, but none of them have been validated in large studies
- Very difficult to differentiate from other PD+ syndromes. Most often misdiagnosed as PSP or PD
- Features supporting diagnosis of CBD:
  - Alien hand syndrome
  - Asymmetric presentation of bradykinesia
  - Severe apraxia (usually ideomotor, less frequently ideational and limb kinetic)
  - Cortical sensory deficits
- May present with motor or cognitive symptoms.
- Horizontal saccadic latencies are significantly increased bilaterally in patients with CBD when compared to PSP patients. In contrast, saccadic velocity is slow (especially vertically) in PSP, and normal in CBD patients.
- Poor response to levodopa useful in differential diagnosis from PD

CBD – Neurobehavioral Symptoms

- Perhaps the most prevalent symptoms are with movement and cortical processing (***cortico***basal). Typically appear asymmetrically and the symptoms are not observed uniformly throughout the body:
  - Parkinsonism
  - Alien Hand Syndrome (about 60% of those diagnosed with CBD)
  - Apraxia (Ideomotor Apraxia and Limb-Kinetic Apraxia)
  - Expressive aphasia may be the only cognitive symptom
- A sudden and detrimental onset.
- Psychiatric and cognitive dysfunctions much less prevalent than in PD and PSP, and lack establishment as common indicators of the presence of the disease.

CBD - Treatment

- Only moderate improvement, if any, with levodopa and the relief from the symptom is not long-lasting.
- Clonazepam may help with myoclonus.
- Palliative therapies, including the implementation of wheelchairs, speech therapy, and feeding techniques, are often used to alleviate many of the symptoms that show no improvement with drug administration

Summary of Key Features - Synucleopathies

- PD
  - Bradykinesia is central with rest tremor and/or rigidity
  - Asymmetric motor problems initially
  - Good response to DA agonists
  - No neurocognitive deficits for at least one year after motor symptoms onset
- DLB
  - Early onset of dementia that usually precedes parkinsonism (1 year rule)
  - Visual hallucinations (non-iatrogenic), variable MS, and parkinsonism
  - Poor response to DA agonists
- MSA
  - Cerebellar ataxia (usually gait or speech)
  - Autonomic dysfunction (incontinence, impotence, orthostatic hypotension)
  - Milder neurocognitive deficits
  - Poor response to DA agonists in most

Summary of Key Features - Tauopathies

- PSP
  - Postural instability, falls, and vertical gaze deficits
  - Early neurobehavioral changes (frontal, psychiatric)
  - Fast course (around 6 years)
  - Mesencephalic (midbrain) atrophy Hummingbird/Penguin sign
- CBD
  - Apraxia
  - Alien hand syndrome
  - Asymmetric motor symptoms
  - Focal and at times asymmetric atrophy in frontal and temporo-parietal cortices. Midbrain atrophy less common than in PSP
  - Poor response to DA agonists

Video – Gait changes in PD

- Https://www.google.com/search?rlz=1C1GCEA_enUS963US974&sxsrf=ALiCzsY9H0Gvlt3TdoYIdsCAgtjJjk6f1A:1669784230637&q=Video+of+Parkinson%27s+patient+walking&sa=X&ved=2ahUKEwjNuKz_jtX7AhVXLEQIHRzOBbIQ1QJ6BAgtEAE&biw=1536&bih=856&dpr=1.25#fpstate=ive&vld=cid:9f78328c,vid:pFLC9C-xH8E

PD – Resting Tremor

- https://www.google.com/search?q=Parkinson%27s+rest+tremor&rlz=1C1GCEA_enUS963US974&sxsrf=ALiCzsZoH-YuQfcA07fXj-y5duDOgJs2iw:1670272286334&source=lnms&tbm=vid&sa=X&ved=2ahUKEwiiiriSqeP7AhU8JkQIHapwBkgQ_AUoAnoECAIQBA&biw=1536&bih=856&dpr=1.25#fpstate=ive&vld=cid:9711ef51,vid:Pkf8GS-Wngc

PD – Bradykinesia, rigidity, masked facies

- https://www.google.com/search?q=Parkinson%27s+bradykinesia&rlz=1C1GCEA_enUS963US974&biw=1536&bih=856&tbm=vid&sxsrf=ALiCzsYWimXt_OIoyRv3MyPjagIS7dYMrQ%3A1670272288189&ei=IFWOY--YC6_gkPIPsbSQ-As&ved=0ahUKEwjvqKmTqeP7AhUvMEQIHTEaBL8Q4dUDCA0&uact=5&oq=Parkinson%27s+bradykinesia&gs_lcp=Cg1nd3Mtd2l6LXZpZGVvEAMyBQgAEIAEMgUIABCABDIFCAAQhgMyBQgAEIYDMgUIABCGAzIFCAAQhgMyBQgAEIYDOgQIIxAnOgUIABCiBDoECCEQClCmBVjyIGCJJmgAcAB4AIABmQGIAd8SkgEFMTIuMTKYAQCgAQHAAQE&sclient=gws-wiz-video#fpstate=ive&vld=cid:ab6175f6,vid:8XPSZmGmko8

PSP – Vertical gaze palsy

- https://collections.lib.utah.edu/ark:/87278/s65x56hg

CBD – Ideomotor apraxia

- https://www.youtube.com/watch?v=EvOYeqM-6CE

CBD – Alien Hand Syndrome

- https://www.google.com/search?rlz=1C1GCEA_enUS963US974&tbm=vid&sxsrf=ALiCzsZEY0NXmKbDJjH80qso T0s3Tm-6Pg:1670273464124&q=Alien+hand+syndrome+real+video&sa=X&ved=2ahUKEwjp1IbEreP7AhUMJTQIHbajBZ4Q1QJ6BAgCEAE&biw=1536&bih=856&dpr=1.25#fpstate=ive&vld=cid:d4f6efe8,vid:e-NfY_DnWNM