Dementias Associated with parkinsonism: diagnosis and management

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Topics for discussion

- Define dementia associated with parkinsonism, and review frequency
- Discuss the diagnosis of different causes of dementia with parkinsonism
- Compare the clinical and pathological features of these dementias
- Discuss management of these conditions including cognitive and behavioral symptoms
- Discuss the effects of these conditions on caregivers

Parkinsonian dementias

- **More common disorders:**
  - Parkinson's disease with dementia
  - Dementia with Lewy bodies
- **Atypical parkinsonism and less common:**
  - Progressive supranuclear palsy
  - Multiple Systems atrophy
  - Cortico-basal degeneration
  - Vascular parkinsonism with dementia

Dementia:

- acquired impairment in memory and at least one other cognitive domain including
  - language,
  - visuospatial ability
  - problem solving ability
  - Mood, personality or judgment
- Severe enough to interfere with social and / or occupational functioning.

parkinsonian syndrome:

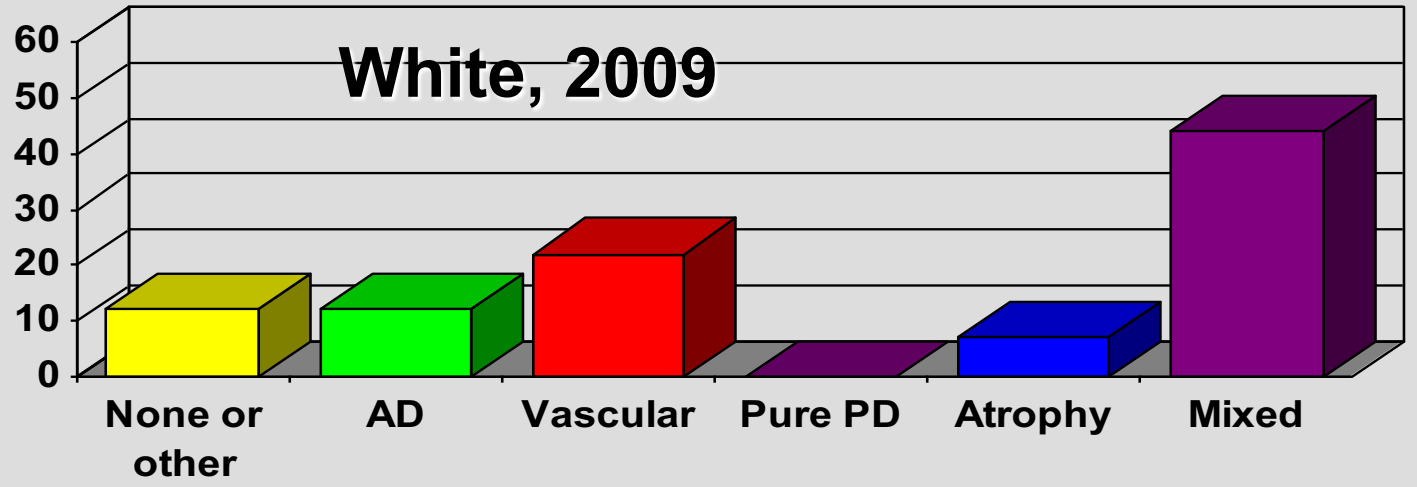
Any 2 of :

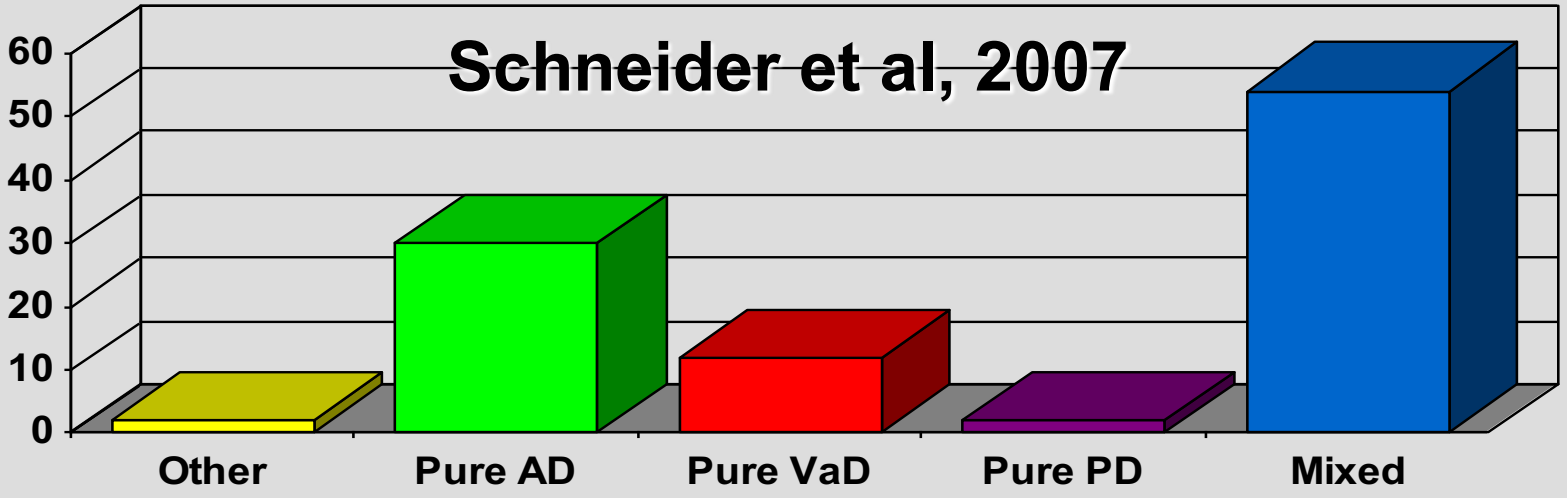
- Rest tremor
- Rigidity or joint stiffness
- Bradykinesia or slow movement
- Postural instability or imbalance

Frequency of parkinsonian dementias

- Parkinson's disease is present in approximately 1% US population over the age of 65
  - 30 to 40 % of these have dementia
- Dementia with Lewy bodies may account for 25% of all cases in dementia specialty clinic. Prevalence (total number of cases at any given time) is estimated to be 5% over the age of 65 years.
- Atypical parkinsonism prevalence:
  - Multiple system atrophy: between 4 and 5 per 100,000
  - Progressive supranuclear palsy: about 6 per 100,000
  - Corticobasal degeneration: 4 - 5 per 100,000

Neuropathology in Elderly Decedents with Dementia HAAS vs Rush Aging





Risk factors:
PD dementia and dementia with Lewy bodies

- Frequency of both increases with age with average age at onset of 70 to 75 years.
- Both disorders more common in men
- Onset of dementia
  - PD dementia: dementia occurs at least one year and often more than 10 years after onset of the movement disorder
  - Dementia with Lewy bodies: dementia is usually the presenting feature occurring prior to or at the same time as the movement disorder symptoms
- Rapid eye movement sleep behavior disorder may precede both conditions by several years.

Risk factors:
REM sleep behavior disorder

- A sleep disorder occurring during the stage of sleep known as rapid eye movement sleep.
- REM sleep is when dreams occur and normally the body is paralyzed during this sleep phase.
- In REM sleep behavior disorder, the normal paralysis is absent and people act out their dreams.
- Dreams may be violent in character and the person may injure their bed partner or themselves.

- REM sleep behavior disorder is present in 40% of PD dementia patients and 90% of DLB patients

Classic motor features of Parkinson's disease

Cardinal Features

- Bradykinesia – slow movements
- Rigidity – joint stiffness
- Rest tremor
- Postural instability

Associated motor Features

- Shuffling gait
- Soft Speech
- Small handwriting
- Masked face

Gowers, 1886

Parkinson's disease: Non-motor features

- Impaired olfaction
- Constipation
- Heart rate abnormalities
- Excessive daytime sleepiness
- **Rapid Eye Movement sleep behavior disorder**
- Sexual dysfunction
- Fatigue

- Seborrhea
- Dry skin and dry eyes
- Drooling and trouble swallowing
- Bladder dysfunction
- Major depression
- **Dementia**
- **Psychosis**

PD dementia clinical features

- Movement disorder precedes dementia by at least a year
- Earliest signs of cognitive impairment are in the area of executive function
  - Impaired planning and initiation of complex behaviors such as following directions
  - Trouble switching between tasks or multi-tasking.
  - Impulsive behaviors and lack of ability to monitor self behavior, poor judgement.
- Impaired naming ability, word finding difficulty
- Memory problems: Impaired ability to recall recently learned information

PD dementia behavioral features

- Hallucinations occur in 45-65% of PD-dementia patients – usually visual
  - Complex and well formed
  - Animals and people
- Depression occurs in about 15% of PD-D
- Apathy or loss of interest is very prominent, occurring in over 50% of PD-D patients.

Dementia with Lewy bodies: Clinical criteria

- Dementia: acquired and progressive cognitive decline severe enough to interfere with social or occupational functioning.
- Core features (2 required)
  - Fluctuating cognition
  - Recurrent visual hallucinations
  - Parkinsonism

McKeith at al, Neurology, 1996

Dementia with Lewy bodies: Fluctuating cognition

- Marked fluctuating level of consciousness and cognitive abilities that may range from near normal to severe confusion
  - Fluctuations may occur over minutes to weeks
  - Fluctuations are independent of the normal daily schedule – (not sundowning)
  - Person may have episodes of severely reduced levels of arousal ("going blank") with increased sleepiness
  - Attention span very short

Dementia with Lewy bodies: Visual Hallucinations

- Recurrent visual hallucinations
  - may be detailed and well formed
  - Frequently of people and animals in the home
  - Response may be indifference, fear, or amusement.
  - Insight may or may not be preserved
  - Worse in cases of visual impairment

Dementia with Lewy bodies: parkinsonism

- Parkinsonism may occur at the time as dementia or develop later in the course of the condition.
  - bradykinesia and rigidity usually present but milder than Parkinson's Disease.
  - rest tremor usually absent
  - Motor features not necessarily responsive to levodopa

Dementia with Lewy bodies:
Clinical features of cognitive impairment

- Short attention span
- Prominent executive function deficits
  - Impaired planning and initiation of complex behaviors like following directions or multi-tasking.
  - Impulsive behaviors and lack of ability to monitor self behavior.
- Prominent visuospatial difficulties or impaired ability to use vision to analyze where objects are in space.
  - Getting lost while walking or driving
- Forgetfulness

Comparison of early neuropsychological profile

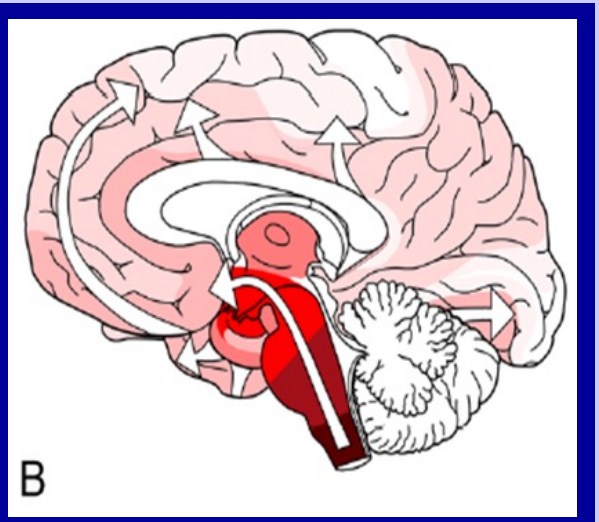
	PD-D	AD	DLB	FTD
Level of consciousness	alert	alert	fluctuates	alert
attention	May be impaired	normal	Severely impaired / fluctuates	normal
Language	Impaired naming	Impaired language early	Variable	Impaired early
memory	forgetfulness	Impaired early	Mild early	Mild early
Visuospatial function	Impaired	impaired	Severely impaired early	Impaired late
Executive function	Severely impaired early	impaired	Severely impaired early	Severely impaired early

Early clinical profile

	PD-D	AD	DLB	FTD
behavioral symptoms	Visual hallucinations more common	Delusions more common	Visual hallucinations more common	Common, often presenting
rigidity and slow movement	Precede dementia onset	Usually late if at all	May occur with dementia onset	Parkinsonism may occur
rest tremor	May be present	absent	rare	absent

Pathological features of PD dementia and dementia with Lewy bodies

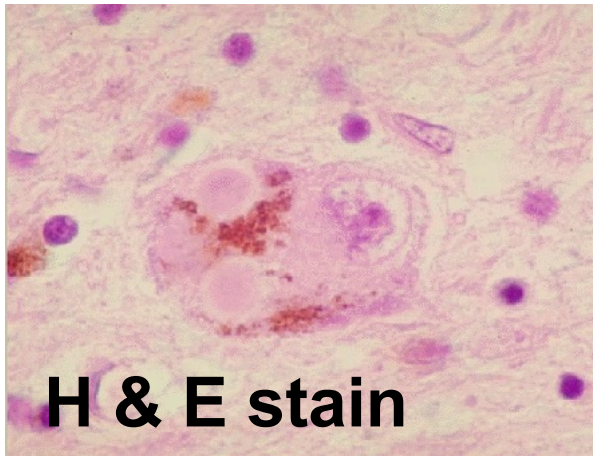
- Both conditions have Lewy bodies
  - in nerve cells in the brainstem that produce dopamine
  - in the brain cortex
- Both conditions have loss of nerve cells that produce dopamine

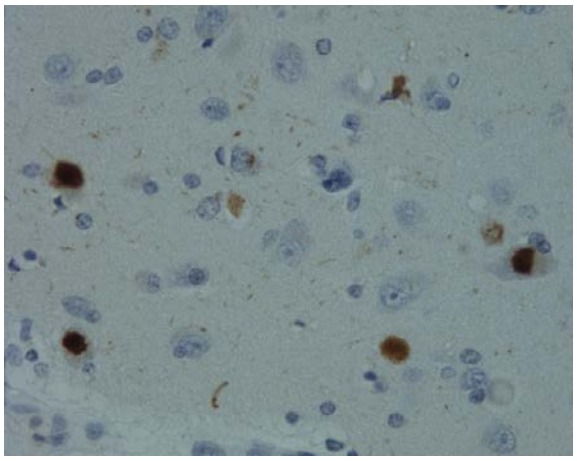


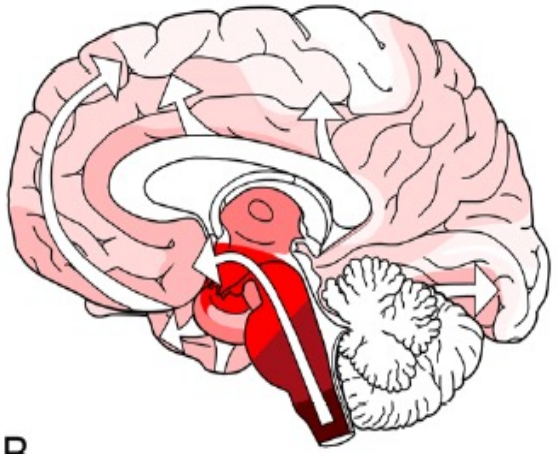
- Both may have changes associated with Alzheimer's disease including neuritic plaques and neurofibrillary tangles as well as deficits in the nerve chemical acetylcholine that is involved in memory
- Bottom line: these conditions may not be distinguishable when just looking at the brain.

Lewy body: target shaped collection of proteins including alpha synuclein within nerve cells that have been injured

- **Classic**
  - Spherical with halo
  - Located in brainstem nerve cells that have melanin pigment
- **Cortical**
  - Irregular shape, less discrete without halo
  - Found in cortical brain regions



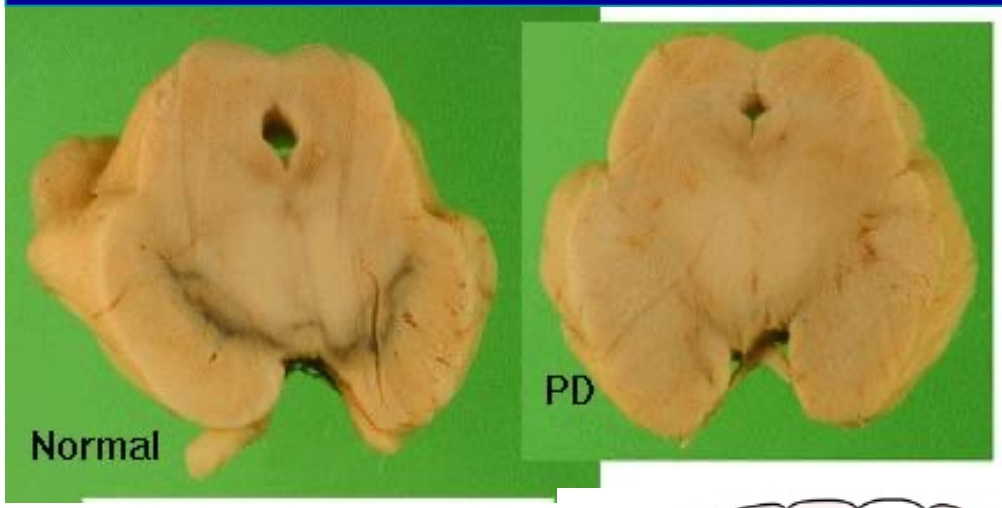


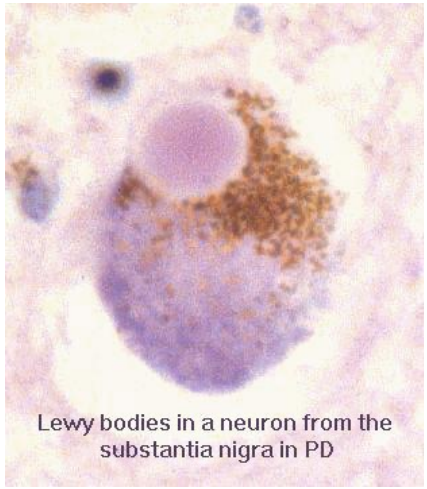


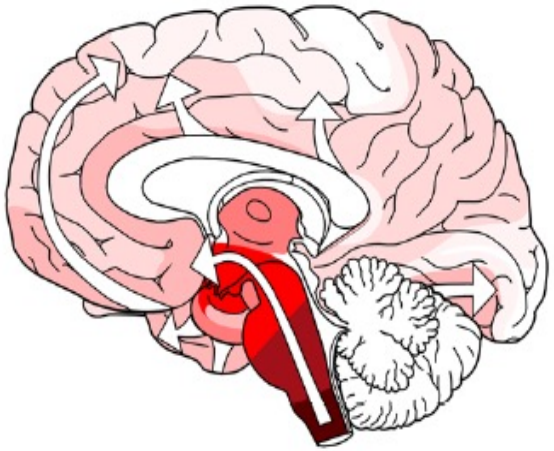
Temporal lobe, Synuclein stain, 40X

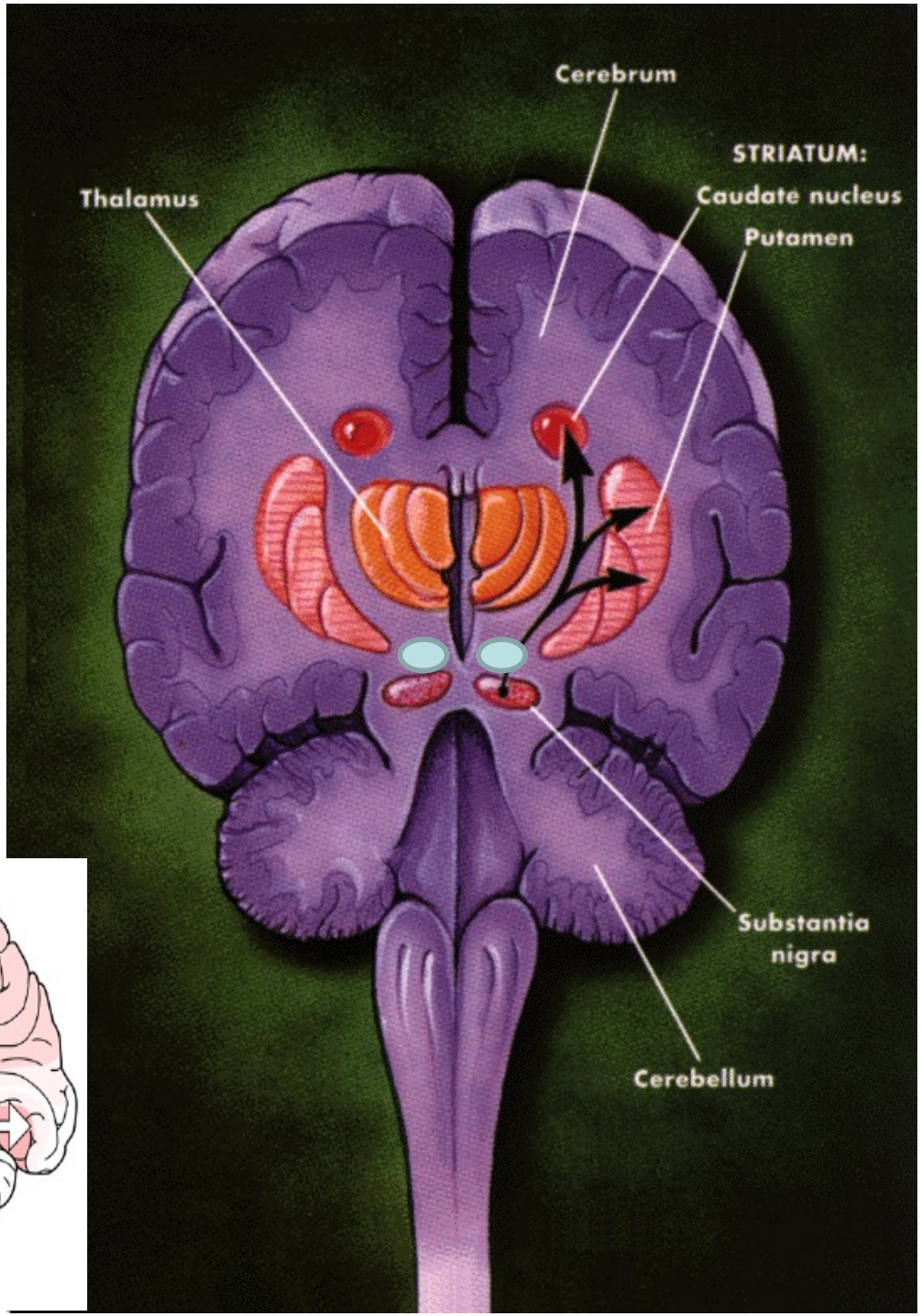
Neuropathology:

- Loss of melanin pigment
- Loss of dopamine producing cells in the substantia nigra
- Lewy bodies
- Low striatal dopamine levels




Lewy bodies in a neuron from the substantia nigra in PD





Treatment of Dementia with Lewy bodies and PD dementia

- There is no cure and no treatment to slow progression.
- Symptomatic management of dementia includes:
  - Medications
  - Occupational therapy (OT)
  - Physical therapy (PT)
  - Speech and Language therapy (SLP)
  - Exercise
  - Management of behavioral complications

Medications to treat memory problems in people with PD dementia and dementia with Lewy bodies

- Cholinesterase inhibitors – block breakdown of acetylcholine in the brain to help memory
  - Rivastigmine and donepezil associated with modest improvement in cognition
  - May help with anxiety and hallucinations
- Memantine associated with marginal improvement in cognition and behavioral symptoms, but no improvement in activities of daily living

Physical, Occupational, and speech / language therapy to assist with management of PD dementia and dementia with Lewy bodies

- PT, OT and SLP may help with motor symptoms of these conditions
  - Exercises to maintain range of motion and balance
  - Home modifications to prevent falls and ease daily tasks
- Use of devices such and canes and walkers may help balance problems and prevent falling
- Use of shower chairs and hand rails in the shower and on the commode prevent falls and ease caregiving
- Speech therapy:
  - To assist with maintaining good communication with speech exercises
  - To assist with prevention of aspiration when swallowing

management of hallucinations in people with PD dementia and dementia with Lewy bodies

- Review medications carefully for meds that can cause hallucinations and decrease dose or discontinue to the extent possible
  - Dopamine medications that are used to treat the movement disorder such as levodopa, amantadine, pramipexole, ropinirole
  - antidepressants
  - Diphenhydramine
- Maximize visual acuity
  - Corrective lenses or cataract surgery
  - Good lighting in hallways and bedrooms including a nightlight
- Reassurance, comfort, distraction, and safety

Medications to manage hallucinations in people with PD dementia and dementia with Lewy bodies

- Work closely with the health care provider, preferably one having expertise in managing hallucinations to
  - Determine if medical therapy is needed
    - Are the hallucinations bothering the patient?
    - Is the patient acting on the hallucinations?
    - Does the patient also have delusions or firmly held ideas that are almost certainly not true?
  - Set goals for therapy
  - Set limits on duration of therapy
- Low doses of atypical antipsychotic medications may be helpful
  - Clozapine
  - Quetiapine
  - Pimavanserin

Exercise

- Physical exercise improves motor function and balance for people with PD.
- Aerobic exercise (walking, swimming) is better than resistance (weight) training for balance, gait, and overall motor function.
- Tai chi and dance improve balance and tai chi reduces falls up to 6 months after training
- <u>Choose exercise that the person is capable of performing</u>

Barriers to exercising for persons with PD

- Low expectation for positive benefit.
  - Nearly every form of exercise has been found to be beneficial for PD symptoms and quality of life.
- Concern regarding the amount of time needed per day to exercise
  - 30 minutes of exercise a day is beneficial
- The fall risk associated with exercise
  - There are many forms of exercise that are safe and that can be performed with a partner

Parkinsonian dementias

- **Atypical parkinsonism and less common:**
  - Progressive supranuclear palsy
  - Multiple Systems atrophy
  - Cortico-basal degeneration
  - Vascular parkinsonism with dementia

Atypical parkinsonism

- Bradykinesia, rigidity, postural instability are core features
- Presence of other clinical features that are not typically seen in PD dementia or dementia with Lewy bodies
- Distinct neuropathological abnormalities
- Treatment and prognosis of atypical parkinsonism syndromes are different than that of PD
- Often misdiagnosed as PD

Atypical parkinsonism dementia features

- Mental slowness, apathy, social withdrawal, and fatigue that progresses to dementia with prominent executive function deficits
- Behavioral problems including disinhibition, anxiety
- Depression

Multiple System Atrophy

- Uncommon, neurodegenerative disease associated with parkinsonism without rest tremor
- Onset age is younger than Parkinson's disease (mean = 53 years)
- Balance problems and falls occur early

Multiple System Atrophy autonomic features (97%)

- Postural dizziness and recurrent fainting
- Urinary incontinence early in the disease course
- Male impotence may be the presenting feature and is very common
- Abnormal sweating (diminished or excessive)
- Cold, dusky hands (Raynaud phenomenon)

Multiple System Atrophy non-motor features

- REM sleep behavior disorder in 2/3
- Sleep disordered breathing including obstructive sleep apnea, central sleep apnea, and stridor
- Inspiratory laryngeal stridor

Multiple System Atrophy Treatment

- Levodopa and dopamine agonists helpful in about 1/3 at least early in the course for the parkinsonism
- Physical, occupational, and speech therapy

Multiple System Atrophy Treatment

- For postural dizziness:
  - increase salt and water intake
  - elastic leg stockings
  - elevate head of bed at night
  - Frequent small meals
  - caution after meals or exercise
  - Medications
    - Fludrocortisone
    - Midodrine 10 mg tid
    - droxidopa

Progressive supranuclear palsy

- Underdiagnosed: 1 of 5 are diagnosed in the U.S.
- Mean onset age 65 years
- Survival is 6 to 10 years after diagnosis

PSP: Early symptoms

- Falling may be presenting feature in 2/3
- Difficulty walking and imbalance
- Slow movement
- double and blurred vision
- difficulty with speech and swallowing.

PSP: Clinical features

- Eye involvement:
  - Slow eye movements
  - Limited ability to look up or down at first then left and right
  - Blepharospasm or forced eyelid closure
- Dysphagia or difficulty swallowing
- Insomnia

PSP: Treatment

- Some respond to dopaminergic medication but good response is short-lived
- Amantadine is helpful in some
- Botulinum toxin injection for blepharospasm
- Physical, occupational therapy
- speech therapy for dysarthria and dysphagia

Corticobasal degeneration

- Uncommon
- Onset usually after age 60
- Men and women equally affected
- Survival is 7.9 years after diagnosis

Corticobasal degeneration Clinical features

- parkinsonian syndrome
- Cortical sensory loss – inability to correctly interpret sensory information
- Action / postural tremor that is jerking
- Prominent dysarthria or speech slurring and apraxia of speech (effortful and halting speech)
- Slow eye movements
- Alien limb

Corticobasal degeneration Treatment

- Levodopa usually ineffective
- Physical, occupation and speech therapy are helpful
- Clonazepam helps the action tremor and myoclonus

Vascular parkinsonism: Clinical features

- Vascular risk factors
  - High blood pressure
  - Diabetes
  - Smoking
  - High cholesterol
- Lower body parkinsonism:
  - lower extremity rigidity
  - shuffling gait with start hesitation
  - postural instability
- Tremor is rare

Neuropathological features

- Alpha synucleinopathies (Lewy bodies)
  - Parkinson's disease
  - Dementia with Lewy bodies
  - Multiple System Atrophy
- Tauopathies (neurofibrillary tangles)
  - Progressive supranuclear palsy
  - Corticobasal degeneration
- Cerebrovascular lesions (strokes)
  - Vascular parkinsonism

Features of parkinsonism dementia most likely to contribute to care provider distress

- Psychosis - Hallucinations, delusions and agitation
- Affective disturbances: Anxiety, depression, and apathy
- Impaired ability to perform activities of daily living such as managing finances, shopping, transportation, and housekeeping; as well as feeding, grooming, dressing, bathing and toileting

Caregiver burden for parkinsonism dementia is as severe or perhaps more severe than that for Alzheimer's disease

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