Sleep Disorders in Neurodegenerative Diseases

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Neurodegenerative Disorders

- AD
- LBD
- PK
- PSP
- MSA

Alpha-synuclein

- Alpha-synuclein modulates DNA repair processes, including repair of double-strand breaks
- Attenuating synaptic vesicle recycling and neurotransmitter release

Synucleinopathy

-Characterised by the abnormal accumulation of aggregates of alpha-synuclein protein

-Targeted cells are: neurons, nerve fibres or glial cell

-Neurodegenerative diseases of this category : PD , LBD, MSA

PD

-**Motor:** tremor, slowness of movement (bradykinesia), rigidity, and postural instability

-**Cognitive:**disorders of cognition, mood, behavior, and thought

-Psychosis: Hallucination and delusions occur in about 50% of people with PD

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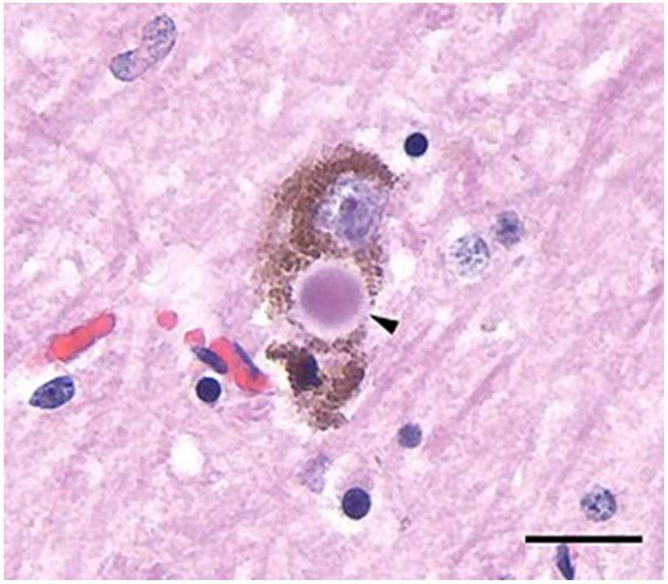
LBD

-Fluctuating cognition and alertness :spontaneous variations of cognitive abilities, alertness, or arousal

-**REM sleep behavior disorder**

-Parkinsonism: 4 cardinal features 85% of the time

-**Visual hallucinations:** 80% of the pts with LBD

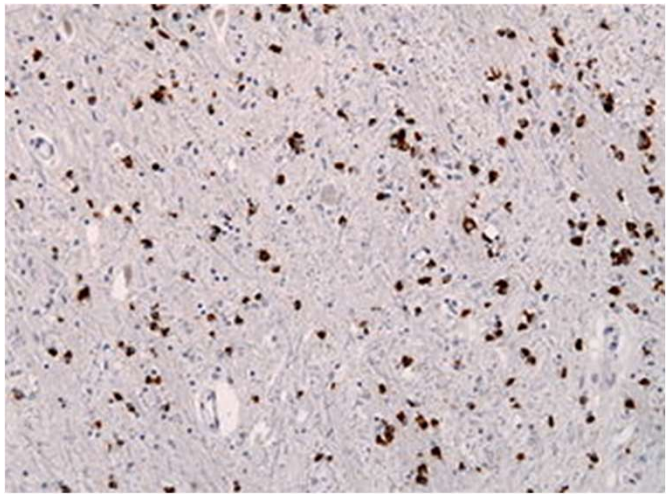


Multisystem Atrophy MSA

-Autonomic dysfunction : orthostasis impotence ,loss of sweating, dry mouth, urinary retention

-**Palsy of vocal cords**

-**Parkinsonism**



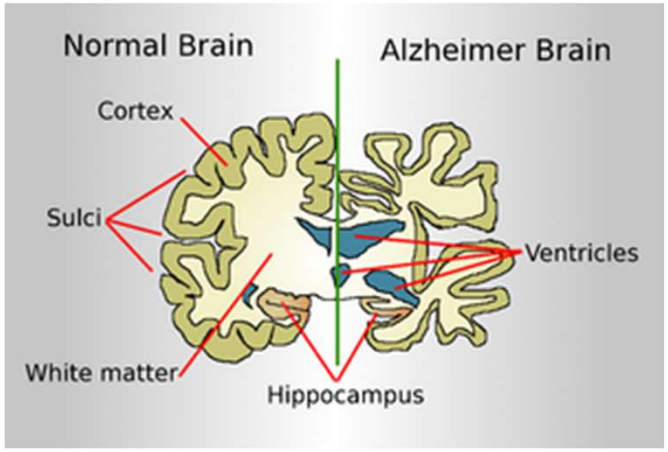
Non Synucleinopathy

AD

- Amyloid plaques, neurofibrillary tangles, and loss of neuronal connections

- Presents with difficulty in remembering recent events

Later language, disorientation (including easily getting lost), mood swings, loss of motivation, self-neglect



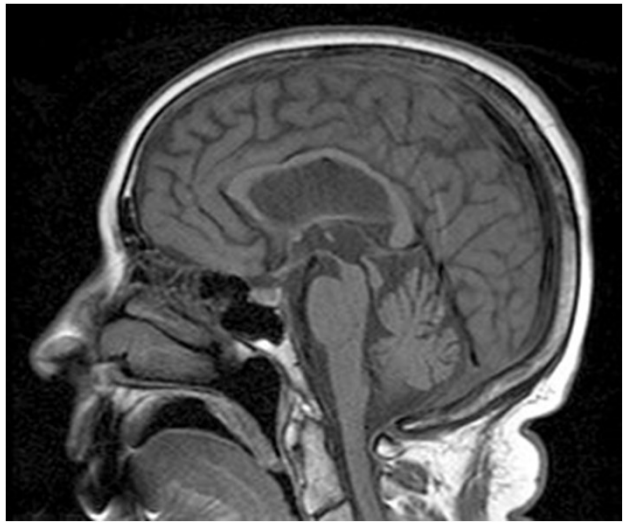
Progressive Supranuclear Palsy

-Accumulation of tau protein within the brain

-Early: Loss of balance, lunging forward when mobilizing, fast walking, bumping into objects or people, and falls

-Later: dementia (typically including loss of inhibition and ability to organize information), slurring of speech, difficulty swallowing, and difficulty moving the eyes, particularly in the vertical direction

-Parkinsonism



Sleep and NDD

-Neurodegenerative dementias report and exhibit more disruptive sleep compared with age-matched controls

- bidirectional relationship between dementia and sleep

-Subjective reductions in total sleep time, increased nighttime wakefulness, reduced sleep efficiency, poor subjective sleep quality, long (>9 hours) and short (<7 hours) sleep times, and disturbed sleep

-Sleep plays a critical role in beta-amyloid regulation, the pathological process involved in Alzheimer disease (AD), and sleep disturbances are linked to amyloid pathology even prior to onset of cognitive impairment

-Alpha-synucleinopathies are characterized by nighttime sleep disturbances that tend to occur early in the course of disease (even preclinically) and remain stable throughout the disease course

-Sleep disturbances in AD are usually more prominent in later stages of the disease

Sleep Architecture

-Patients with AD have more and longer awakenings, with subsequent increases in stage 1 sleep and decreases in slow-wave sleep

-Patients with AD and PD exhibit a decreased percentage of REM sleep as well as reduced REM episodes, latency, and density when compared with healthy older adults

-Electrophysiologic changes associated with specific types of dementia include a decrease in the frequency and amplitude of K complexes in patients with AD

- Increase in the prevalence of REM sleep without atonia in patients with alpha-synucleinopathies

Circadian Rhythm

-Circadian rhythm disturbances are more prominent and more disabling in patients with dementia compared with healthy older adults

-Patients with dementia exhibit reduced rhythm amplitude as well as increased phase-delay in activity rhythms and core body temperature

- Sundowning, where behavioral disturbances peak in the late afternoon or evening, is closely related to circadian rhythm

-Abnormalities a multifactorial phenomenon, caused by the neurodegenerative process itself, pathologic changes in retinal photoreceptors and the SCN, and environmental influences

-Older adults average about 60 minutes of exposure to bright light per day, whereas patients with AD living at home average only 30 minutes

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Clinical Manifestations

Difficulty falling or staying asleep: (PD)

- 32 % difficulty falling asleep
- 39% frequent awakening during the night,
- 23 % early morning awakenings

-**Difficulty Falling or staying asleep in AD** 19 - 44%

-Insomnia disorder 30 to 50%older adults

- Irregular sleep-wake rhythm disorder contributing factor

Abnormal Movements During Sleep and NDD

Restless legs syndrome

Atypical presentation due to inability of dementia patient to describe their feelings

-Restlessness

-Frequent limb movements

-Rubbing or kneading the limbs

-Wandering

-Difficulty falling asleep

PLMD

-PLMD, are increasingly common with age and may increase risk for cognitive impairment

-Patients with PLMD have PLMS that are thought to cause significant sleep disturbance or impairment in mental, physical, social, occupational, educational, or behavioral areas

RBD

-RBD is highly prevalent in patients with neurodegenerative dementias that are due to alpha-synucleinopathy

-Often emerging well before overt signs and symptoms of dementia

-Can result in injuries to both patients and bed partners

-Symptoms of RBD range in severity from brief, nonforceful hand or arm gestures to violent thrashing, punching, or kicking. Sleep-related vocalizations may be loud and laden with expletives.

-Symptoms predominate during the second half of the sleep period, when REM sleep is most prevalent

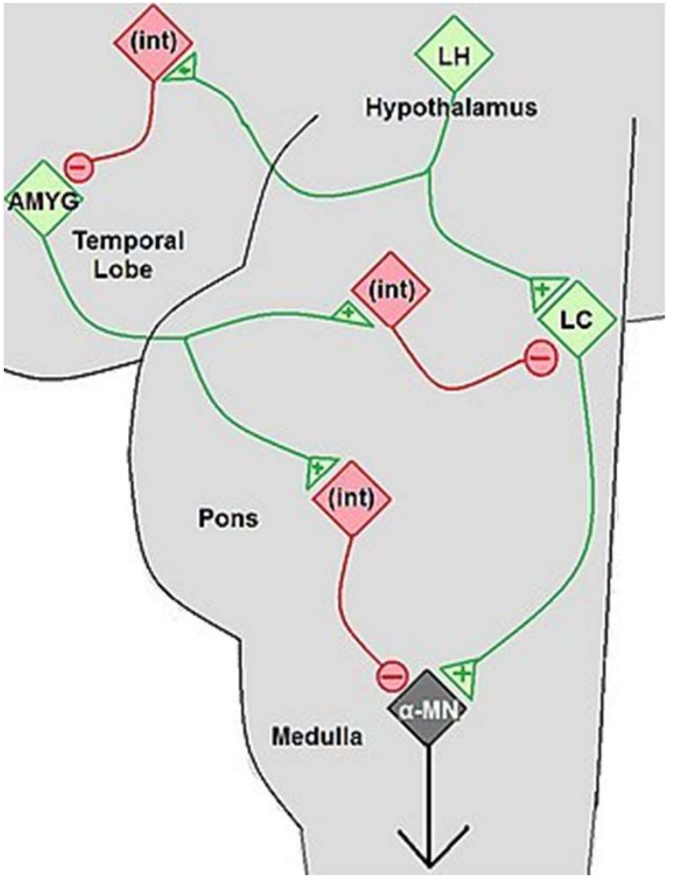
RBD and ASP Association

-The pontine and medullary nuclei that control REM sleep are early targets of synucleinopathies

-RBD confirmed by video polysomnography is among the strongest early predictors of PD

-Nonmotor findings of PD, such as anosmia and constipation, often coincide with RBD and are manifestations of alpha-synuclein pathology in the olfactory bulb and enteric plexus

-Symptoms are typically either dismissed as clinically insignificant or misattributed to some other etiology



RBD and NSP

- Interval between the onset of RBD and the parkinsonian triad of resting tremor, bradykinesia, and cogwheel rigidity may vary from months to decades.

- The annual phenoconversion rate was 6 percent, with 74 percent phenoconverting within 12 years of RBD diagnosis

-Even among the rare cases of apparently persistent isolated RBD, neuroimaging biomarkers have demonstrated impending neurodegeneration and postmortem examinations have revealed diffuse Lewy body pathology typical of alpha-synuclein degeneration

Pre Dementia Changes in RBD

-Neuroimaging studies such as dopamine transporter (DAT) imaging demonstrate coincident and progressive dopaminergic abnormalities in patients with RBD before motor symptoms arise

-Cholinergic denervation has also been reported in the brains of patients with RBD; similar to cholinergic impairment in PD, these findings are correlated with cognitive decline [

- **MRI, functional MRI, and EEG** cortical abnormalities similar to those in PD and DLB

Pathology: Phosphorylated alpha-synuclein deposits can be detected in the autonomic nerve fibers of the submandibular, salivary, and parotid glands in patients with RBD as well as those with PD

Non-synuclein Neurologic Disorders and RBD

-PSP and AD Amyotrophic lateral sclerosis **spinal cerebellar ataxia type 3**, Huntington disease, myotonic dystrophyT2

-Postpartum evidence suggests comorbid alpha-synuclein pathology

- Simple questionnaire distinguish patients who will ultimately go on to develop PD vs AD .

- Compared with DLB from AD, the presence of RBD symptoms is even more specific than tremor or parkinson's

-Other neurologic disorders with RBD: Encephalitis and Williams syndrome

Sleep Breathing Disorders

-The estimated prevalence of OSA ranges from 40 to 70 percent in patients with AD

-20 to 60 percent in patients with PD

-Severe OSA (apnea hypopnea index [AHI] ≥30) may lead to further impairments in neurocognitive function, including deficits in attention, concentration, executive function, immediate and delayed recall, planning and sequential thinking, and manual dexterity

-CSA is also common with aging in general and recognizing its symptoms and consideration of treatment is challenging

Nocturnal Stridor

-Seen in patients with MSA

- Results in partial obstruction of the larynx

- High-pitched wheezing sound during inspiration

- Occur throughout the day but most common during sleep

-Nocturnal stridor can be life threatening

-CPAP has been used effectively to avoid tracheotomy and improve sleep

Excessive Daytime Sleepiness

-More common in patients with DLB and PD than in those with Alzheimer disease (AD)

-One-third and three-quarters of patients with PD

-Unknown etiology.

-Multifactorial ? insufficient sleep, sedating medications (eg, dopamine agonists), the underlying disease process, psychiatric comorbidities, disturbed circadian rhythms, or major sleep disorders such as OSA

Management

-Rarely single intervention is successful and risks and burdens of various interventions must be weighed against expected benefits

-Nonpharmacologic strategies should be fully explored and employed before considering pharmacotherapy

-RLS ,PLMD amd RBD may be an exception

Environmental Restructuring

-Keep the environment dark during the night and bright during the day

-Reduce noise at night

-Eliminate unnecessary nocturnal awakenings for vital signs and medication administration

-When possible, match roommates living in institutions based on their sleep-wake patterns

Addressing Polypharmacy

Medications for chronic medical and/or psychiatric conditions (eg, antipsychotic medications, stimulants, respiratory medications, antihypertensives, and decongestants) may significantly impact sleep and result in sleep disturbances

Multicomponent Behavioral Therapy

Sleep-wake scheduling:

- Setting a consistent wake-up time. Also
- Maintain a consistent bedtime;
- Limitation : napping during the day, exerting more energy on some days
- . Even if a patient goes to sleep at different times, waking up at a consistent time will help stabilize the rhythms.

Light Therapy :

Bright light therapy either natural or synthetic

At least 30 minutes in front of the light box first thing in the morning using a 10,000 lux light box or full spectrum light.

Pharmacologic Treatment for Insomnia Systemic Review

Melatonin – low-certainty evidence that melatonin doses of up to 10 mg nightly have little to no effect on any major sleep outcome over 8 to 10 weeks (five trials, n = 222)

Trazodone – The review found low-certainty evidence that trazodone (50 mg nightly for two weeks) may improve total sleep time in patients with moderate to severe AD (one trial, n = 30). However, other outcomes, including number of awakenings and time awake during the night, were similar between groups

Ramelteon – Ramelteon, an oral melatonin receptor agonist, showed no evidence of benefit in a single trial in 74 patients with mild to moderate AD

Orexin receptor antagonists – The review identified moderate-certainty evidence that orexin receptor antagonists (lemborexant and suvorexant) improve total sleep time and decrease time awake during the night in patients with AD (two trials, n = 323)