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SLEEP DISTURBANCES IN NEURODEGENERATIVE DISORDERS.

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ABSTRACT:

Neurodegenerative disorders are those affecting the cognition, behavior and motor function of an individual. According to a report from the World Health Organization, an astounding 30 million people in Europe and United States alone will suffer with Alzheimer's disease- one of the most common neurodegenerative disorders. Though many authors have extensively studied the pathophysiological mechanisms involved in these diseases, reporting neuroinflammation to be the cause with almost certainty; very few have tried to delineate the risk factors responsible for these diseases. Recent advances in polysomnography have indicated that patients with dementia displayed "increased wakefulness" after onset of sleep. Moreover, this increased wakefulness was directly related to the severity of the neurodegenerative disease. Subsequently, there is sleep fragmentation, excessive sleepiness during the day, and Rapid eye movement behavioral disorders in these patients. Motor disorders like the Parkinson's disease are also associated with melatonin changes, thereby disrupting the whole sleep-wake pattern. Actigraphy studies have demonstrated that the risk of developing Alzheimer's disease was 1.5 times higher in people with excessive sleep fragmentation. Apart from neuronal loss in the intermediate nucleus which maintains sleep, there is also a loss of orexin secreting neurons. Orexin is one of the neuropeptide involved in stabilizing the sleep-wake transitions. Several studies conducted in patients with Alzheimer's disease using positron emission tomography have demonstrated that, accumulation of Amyloid Beta protein in brain was directly linked with poor sleep quality. Other studies on subjects with Parkinson's have also linked the severity of motor manifestations with insomnia. Sleep disruption in neurodegenerative diseases is the major cause of institutionalization of the patients and is also a reason for caregiver distress.

KEYWORDS: Neurodegenerative disorders, Alzheimer's, Parkinson's, Huntington's, Sleep disturbances.

INTRODUCTION:

The term "neurodegenerative" literally means "degeneration and death of neuronal cells[1]." The disorders which occur in response to neurodegeneration are termed as

"Neurodegenerative Disorders." Some of the most common disorders include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS)[2,3]. The 21st century has witnessed a spike in these disorders as they are age-dependent and there is a rise in elderly population in recent years[4]. The neurodegenerative disorders, in general, can be classified into two types based on the clinical presentation of the patients. The first category includes diseases with pyramidal and extrapyramidal motor disturbances and the other includes cognitive and behavioral disorders[5]. Due to slow and continual loss of neuronal cells, these disorders are generally progressive[6]. The NINDS, which overlooks medical trials on neuroprotective medications in the US, estimates that there are approximately 600 types of neurological disorders[7,8]. These disorders not only cost billions of dollars for the countries in direct health-care costs[9], but there is also a huge emotional burden on patients and their attenders[10]. It is to be noted that each neurodegenerative disorder typically develop after some neuroanatomical abnormality or accumulation of a specific protein[11]. Apart from these, the neurodegenerative disorders share copious fundamental processes which are ultimately responsible for nerve dysfunction and death[5]. These processes generally include neuroinflammation, apoptosis, oxidative stress, abnormalities in proteosomal and lysosomal systems etc[12,13]. It is to be noted that the protein abnormalities specific to a neurodegenerative disease are evident upon imaging, much before the development of clinical manifestations[14]. Based on the type of protein abnormalities and accumulates the neurodegenerative diseases can further be classified into tauopathies, $\boldsymbol{\alpha}$-synucleinopathies, proteinopathies and amyloidoses[15].

Sleep Disruption in Neurodegenerative Disorders:

The relationship between sleep disturbances and decline in cognizance is complex and bidirectional[16]. Sleep disturbances are a common issue among the elderly[17]. There is a progressive disruption of sleep-wake cycle with escalating sleep latency, deterioration of sleep quality, difficulty maintaining sleep and excessive wakefulness[18]. Sleep influences various domains of cognizance including memory consolidation and attention[19]. Therefore, sleep disturbances are a major risk factor for neurodegenerative disorders in the elderly[20]. Generally, the neurodegenerative disorders have an insidious onset and attain a progressive course in due time[21]. Commonly occurring sleep disorders in neurodegenerative diseases include difficulty falling asleep (insomnia), fragmentation in sleep, excessive sleepiness during daytime, circadian rhythm disturbances, REM behavior disorder (RBD), obstructive sleep apnea, restless leg syndrome etc[22]. While all other disorders are a part of parasomnia's and sleep-wake disorders; OSA occurs in response to degeneration of respiratory control centers in the brain[23]. These disorders can sometimes occur much before the appearance of the cardinal symptoms relating to the neurodegenerative disorders[18]. These finding can help identify the individuals at risk of these disorders.

Alzheimer's disease:

Alzheimer's remains the leading cause of Dementia in the world[24]. Epidemiological studies show that 5.8 million cases of Alzheimer's were reported in the US alone in 2019[25]; of which 2/3rd were women. The reason behind this discrepancy is, statistically, women tend to live longer than men and oldage is one of the risk factor for this disease[26,27]. Ethnically, Hispanics, and African-Americans are more likely to develop this disease compared to Native American's and Caucasians[28–30]. In contrast, the prevalence of Alzheimer's in European and Asian population is similar[31]. One of the reasons for higher prevalence of this disease in minority communities[32] is socio-economic characteristics. Poverty, lower education rates and subjection of these communities to discrimination contributes to the development of this disease[33,34]. In accordance with prevalence, Alzheimer's also leads to significant morbidity

and mortality[35]. In 2017, CDC recorded 121,404 deaths related to Alzheimer's[36]. This disease, per se, doesn't prompt mortality; but the chain of events set in after the development of Alzheimer's can be accounted for high mortality rates. Severe Dementia following Alzheimer's can lead to complications like immobility, malnutrition and swallowing disorders[37]. It has a multifactorial etiology with genetic, environmental and life-style factors implicated in its pathophysiology[38]. Based on genetic factors, Alzheimer'sis broadly classified into Late-Onset and Early-Onset Alzheimer's[39]. Late onset Alzheimer's is associated with a genetic variant of APOE (Apolipoprotein E) gene located on chromosome 19. This variant is abbreviated as APOE ε4[40]. APOE codes for a protein which helps in carrying cholesterol and other fatty acids in the blood[41].The presence of one or two alleles of this variant in a person increases the risk of Alzheimer's. Similarly, Early-Onset Alzheimer's is associated with mutations in single genes on three different chromosomes. The three genes are Presenilin 1 (PSEN1), Presenilin 2 (PSEN 2), and Amyloid Precursor Protein (APP)[42]. So far, nearly 150 different types of mutations have been identified in PSEN1 gene, ranging from simple missense mutation to complex splice mutations[43]. All mutations lead to the development of Familial Alzheimer's disease[44]. PSEN1 codes for Presenilin 1 protein, which is a sub-unit of the Gamma-secretase enzyme complex[45]. This complex is involved in breaking down and eliminating large protein complexes in the form of small peptides[46]. The fact that ***γ***-secretase primarily processes Amyloid precursor protein in the brain, implicates it in the development of the disease. Likewise, PSEN2 codes for Presenilin 2, which helps in processing intracellular proteins that acts as secondary messengers between cell membrane and nucleus[47]. Similar to Presenilin 1, it is involved in the processing of APP; more specifically, smaller peptides of APP like soluble amyloid precursor protein (sAPP) and Amyloid beta protein (Aß)[48]. The exact pathophysiological mechanism involved in the development of Alzheimer's disease is not understood. Nonetheless, six hypotheses have been proposed to better explain the mechanisms involved[49]. The most accepted hypothesis is, "overproduction of Amyloid beta peptide due to mutation in APP gene or its reduced clearance due to mutation in PSEN1/PSEN 2 gene.[50]" The second most accepted mechanism is, "aggregation of hyper-phosphorylated Tau proteins[49]." NMDA receptor excitotoxicity is also linked with this disease[51]. The fact that Memantine, an NMDA receptor antagonist, slows down progression of Alzheimer's is enough clinical evidence for its implication.

Sleep Disturbances in Alzheimer's disease:

In contrast to the conventional understating, that sleep disturbances in Alzheimer's is a consequence of the pathophysiological mechanisms behind the disease; recent epidemiological studies suggests that sleep disturbance can itself acts as a risk factor for the disease[19,52]. Nevertheless, the disrupted sleep pattern in Alzheimer's brings about considerable distress not only to the patient but also their attenders. It is often the reason for patient's attenders to seek institutionalization as there is a need for constant vigilance towards the patient's unpredictable behavior[53]. Subsequently, the same patients display a behavior of day-time sleepiness.

Sleep disturbance as a risk factor for AD:

Multiple cross-sectional observational studies have linked sleep duration with an increased risk of cognitive impairment. Sleep duration <5 hr and >11 hr per night have a significant role in the pathophysiology of AD[54,55]. Other prospective studies conducted over 1 year have associated poor sleep quality, increased wakefulness after sleep and, increased daytime sleep with increased risk of cognitive impairment[56]. Similar findings were reported from animal models[57]. Physiologically, sleep, in humans, is composed of two parts namely REM (Rapid Eye Movement) and non-REM sleep. NREM is further classified as stages N1, N2, and N3

based on the findings from the electroencephalogram[58]. Sleep fragmentation and intermittent arousals from sleep lead to an increase in the duration of N1 and N2[59]. This further leads to the disruption of circadian rhythms and the promotion of AD pathology.

A recent meta-analysis by Bubu et.al revealed that improper sleep duration (short, long), poor sleep quality, and circadian rhythm disturbances, sleep fragmentation, and insomnia contribute to a significant increase in the risk ratio for Preclinical, Clinical, and AD-based diagnoses[60]. Also, PET scan studies on older people with poor sleep quality and sleep fragmentation revealed a significantly greater deposition of Aß in the frontal medial orbital cortex, precuneus, and angular gyrus[61]. Although many epidemiological studies have tried to link impaired sleep with AD pathology, a definite causal relationship between them has not been established yet, probably due to shorter periods of follow-up compared to disease course[19]. AD mouse models, when deprived of sleep, revealed that sleep restriction accelerates AD-associated pathophysiological and biochemical changes such as, increase in $Aß_{40}$, $Aß_{42}$, and phosphorylated Tau protein deposition[62,63].A possible mechanism includes decreased clearance of the deposits from the brain[64]. Studies have shown that there is an increase in the interstitial space of the brain by 60% during sleep. This allows CSF to clear maximum deposits[65]. Aß deposition is strongly correlated with the severity of sleep impairment[66].

Genetics have also been implicated in the pathology of AD. The presence of Apolipoprotein Epsilon 4 allele (APOE E4) in a normal adult with sleep disturbances increases the risk of the development of dementia by 7 times[67].

Sleep disturbance as a consequence of AD:

Once Aß accumulation starts, slow-wave sleep (SWS) and memory consolidation impair[68]. This leads to further accumulation of tau proteins andAß, as noticed in PET scan studies[69], resulting in the continuation of this vicious cycle. Animal studies using transgenic mice, prone to Aß deposition display behavior suggestive of impairment of the sleep-wake cycle[70]. Similarly, when the same mice were immunized to remove those deposited plaques, the sleep-wake cycle normalized[71]. Physiologically, the AD pathology affects the intermediate nucleus of the hypothalamus; specifically, the galaninergic neurons[72]. The intermediate nucleus remains active during the sleep[73], inhibiting the signals to the sleep-awakening areas[74]. Lim, Ellison et.al tried to correlate the number of intactgalaninergic neurons in the autopsied brains of the AD patients and sleep fragmentation behavior in them antemortem. They found a strong positive correlation between them, proving that sleep fragmentation exists in AD patients due to galaninergic neuron loss[72].

The cholinergic neural network is also affected by AD pathology which initiates and maintains REM sleep. The brainstem, cerebral cortex, thalamus, and basal forebrain are the most affected[75]. The Vasopressin and vasoactive intestinal peptide-expressing neurons involved in the regulation of circadian functions of the suprachiasmatic nucleus, also suffer a significant loss[76].

Parkinson's disease:

Parkinson's disease is a motor disorder following dopaminergic neuronal degeneration in the substantianigra of the brain. The hallmark symptoms of this disease include resting tremors, bradykinesia, impaired reflexes, and rigidity of the muscles[77]. Although dopamine deficiency has been implicated in the pathology of Parkinson's disease, most of the symptoms and the pathological course itself also involve cholinergic[78], serotoninergic[79], and noradrenergic pathways[77]. The degeneration of these pathways generally results in non-motor symptoms

like depression, sleep disturbances, autonomic dysfunction, cognitive impairment, etc[80]. The distinctive morphological change in the neuropathology of Parkinson's disease is the degeneration of the dopaminergic- neuromelanin secreting neurons in the substantianigra pars compacta and locus ceruleus[81]. The motor symptoms initiate once the neuronal loss reaches 30%[82,83]. Several other neurotransmitter systems like serotonergic, noradrenergic, glutamatergic, GABAergic,etc, are also affected. Degeneration of these systems accounts for the non-motor symptoms in the disease. Histological studies of brain tissue reveal another hallmark feature of Parkinson's disease i.e., the abnormal deposition oflewy bodies. Lewy bodies are aggregates of neuronal cell bodies and $\boldsymbol{\alpha}$-Synuclein protein[77]. In 2003, Braak et.al postulated that, in Parkinson's disease, the lewy bodies predictably spread throughout the brain. They classified the disease into 6 stages. The lewy bodies, in Braak stage 1 and 2, spread across the dorsal motor nucleus, anterior olfactory nucleus, and the reticular formation. The patient may be asymptomatic or may display "subclinical symptoms," at these stages. These subclinical symptoms generally include non-motor features related to circadian rhythm, autonomic, and olfactory dysfunction. Stages 3 and 4 correspond with clinical motor symptoms as the nigrostriatal pathway gets involved. Severe Parkinson's disease with dementia and significant gait problems generally occur at stages 5 and 6[84]. Although this theory was widely accepted initially, successive postmortem studies proved that a significant proportion of PD brains do not follow this pattern. The theory was also criticized due to its emphasis on lewy body pathology rather than neuronal loss[85]. Other simultaneously occurring pathogenic mechanisms include mitochondrial complex-1 depletion[86], dysfunctional protein clearance systems[87], and Neuroinflammation[88].

Sleep disturbance as a risk factor for Parkinson's disease:

Though there is insufficient evidence linking sleep impairment as a risk factor for the pathology of Parkinson's disease, many small observational studies have tried to link either. A large retrospective cohort study using a national insurance database was performed in Taiwan. A total of 91,273 adult patients, suffering from non-apnea sleep disorders and without any history of Parkinson's disease, were recruited. An age, gender, income, and urbanization matched control group of 91,273 participants was also recruited. At the end of the study, it was statistically proven that non-apnea sleep disorders acted as an independent risk factor for the development of Parkinson's disease[89]. In a subgroup analysis involving patients with chronic insomnia; the risk of them developing the disease was the highest[89]. Another longitudinal study in which, nurses from both day and night shifts were recruited found out that those with night shift jobs had a significant risk of developing Parkinson's disease[90].Parasomnia's like REM sleep behavior disorder has been linked with the development of severe motor PD[91].

Sleep disturbance as a consequence of Parkinson's disease:

As discussed earlier, motor symptoms in PD only begin when there is a degeneration of dopaminergic neurons in the substantianigra pars compacta. The axons projecting from the dopaminergic neurons of substantianigra and hypothalamus extensively form 4 pathways i.e. the mesolimbic, the mesocortical, the nigrostriatal, and the tuberoinfundibular pathways[91]. The mesolimbic and nigrostriatalprojections innervate dorsal and ventral striatum and regulate cognitive functions, motor behavior and sleep-wake cycles[92]. Animal studies have shown that inputs from nigrostriatal neurons activate Globus pallidus and promote sleep in rats[93]. In addition, the serotonergic and nor-adrenergic neurotransmitter systems also get impaired resulting in the degeneration of raphe nuclei and locus ceruleus respectively[84]. These nuclei have a critical role in the regulation of sleep-wake cycles and arousal. As a result, both REM and NREM sleep is impaired, giving rise to symptoms like parasomnias,

insomnia, and hallucinations. REM behavior disorder (RBD) is also quite common among patients with PD[94,95]. During REM sleep, the voluntary muscles of an individual are in atonic condition, lacking the ability to contract. But patients with RBD lose their ability to achieve atonia and display voluntary muscle contractions based on the experiences of their dreams. E.g. A person fleeing the bed if they experience chasing in their dream[96]. Sleep Disordered breathing can also occur either with CNS involvement (Central apnea) or through the obstruction of breathing passages (Obstructive apnea). The incidence of RBD and Apnea in PD patients, based on the severity of the disease, is around 15-50%[97]. Restless Legs Syndrome (RLS), vivid dreaming, Excessive daytime sleepiness, fatigue, and sleep attacks are also quite common in PD patients[98].

Huntington's disease (HD):

It is a genetic disorder caused as a result of an autosomal dominant mutation of the HTT gene located on the 4th chromosome[99]. This leads to the formation of abnormally elongated amino acid strings called Huntingtin's protein. Accumulation of these misfolded proteins causes neuronal death.This mutation leads to neurodegeneration of the CNS tissue in the cortex, cerebellum, thalamus, hypothalamus, and amygdala[100–103].The disease is progressive in nature. Early stages involve patients displaying involuntary muscular movements of the head, limbs, and chorea which progresses to cognitive and psychological impairment in later stages[104]. Cognitive impairment includes the inability to take decisions, failure to execute complex activities, and reduced ability to think and imagine[105,106]. Anxiety, emotional lability, dysphoria, and sometimes[107,108], full-blown psychosis and schizophrenia[109] constitute psychological impairment.

Sleep Disorders as a consequence of Huntington's disease:

Normally, the NREM sleep cycle comprises three stages i.e. N1, N2, and N3, lasting for about 60-90 mins. REM cycle follows NREM lasting around 15-20 mins and is considered as a stage of "deep sleep", where the patients exhibit atonia of the muscles[103]. The pattern of Sleep disorders in Huntington's disease is not homogenous[110]. Any stage of the sleep cycle may be affected and impaired. Patients experience insomnia, decreased sleep time, frequent night arousals[111–113], REM sleep disorders[113], poor sleep quality, and excessive daytime sleepiness[114]. Electroencephalogram studies show that patients with Huntington's disease display reduced duration of the N3 stage due to increased sleep onset time (N1)[111]. Hence, HD patients spend less time in the deep sleep stages and experience frequent arousals. Arnulf et.al proved that REM sleep disorders precede chorea in HD patients. They have theorized that REM sleep disorders in people with the mutation can act as an early marker of disease progression[115]. Their theory was found to be consistent with brain histological studies observing atrophy and degeneration in the brain stem[116,117]. Patients with HD also experience Circadian rhythm Disturbances like Circadian Rhythm Sleep Disorder (CRSD) and Excessive Daytime Sleepiness (EDS)[103]. The suprachiasmatic nucleus of the hypothalamus controls the synthesis of melatonin in the pineal gland and thus, maintains the circadian rhythms in the mammal. Impairment in melatonin secretion has been observed from the early stages of HD[118,119]. The most common circadian rhythm disorder is the EDS, where patients tend to fall asleep anytime in the day and experience difficulty to maintain wakefulness. Sleep Attacks, a severe form of EDS, is characterized by the sudden, involuntary incidence of falling asleep. This usually happens when the patient is performing a monotonous activity like operating machinery or driving[120]. Also, insomnia, reduced sleep time, and frequent night arousals can also be the consequence of psychiatric disorders like depression; common in patients with HD[121].

ABBREVIATIONS:

AD: Alzheimer's disease.

PD: Parkinson's disease.

HD: Huntington's disease.

ALS: Amyotrophic Lateral Sclerosis.

NINDS: National Institute of Neurological Disorders and Stroke.

REM sleep: Rapid Eye Movement sleep.

RBD: Rapid Eye Movement Sleep Behavior Disorder.

OSA: Obstructive Sleep Apnea.

APOE: Apolipoprotein E.

PSEN1: Presenilin 1.

PSEN2: Presenilin 2.

APP: Amyloid Precursor Protein.

sAPP: Soluble Amyloid Precursor Protein.

Aß: Amyloid Beta Protein.

NMDA: N-Methyl D-Aspartate.

NREM: non-Rapid Eye Movement Sleep.

CSF: Cerebro-Spinal Fluid.

SWS: Slow Wave Sleep.

GABA: Gamma Amino Butyric Acid.

HTT gene: Huntingtin Gene.

CRSD: Circadian Rhythm Sleep Disorder.

EDS: Excessive Daytime Sleepiness.

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