EXPLORING THE LINK BETWEEN SLEEP AND NEURODEGENERATIVE DISEASES

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Abstract- **Sleep disorders are common during the clinical course of the main neurodegenerative diseases. Neurodegenerative diseases can lead to functional changes in the respiratory system that facilitate the emergence of apnea.Many neurodegenerative diseases manifest in an overall aged population, the pathology of which is hallmarked by abnormal protein aggregation. It is known that across aging, sleep quality becomes less efficient and protein homeostatic regulatory mechanisms deteriorate. Sleep disturbance such as RBD may be an early sign of neurodegeneration in these diseases, and also serve as an assessment of cognitive impairments. In an aged population, when sleep is chronically poor, and proteostatic regulatory mechanisms are less efficient, the cell is inundated with misfolded proteins and suffers a collapse in homeostasis. We also present data suggesting that reducing cellular stress and improving proteostasis and sleep quality could serve as potential therapeutic solutions for the prevention or delay in the progression of these diseases. The present study aimed to investigate the sleep disorders associated with various neurological pathologies, including amyotrophic lateral sclerosis (ALS), multiple system atrophy (MSA), hereditary ataxias, Huntington's disease (HD), progressive supranuclear palsy (PSP), and dementia with Lewy bodies(DLB).**

Index Terms- **Sleep, neurodegenerative disease, aging, sleep disturbances, ataxias, insomnia.**

I. INTRODUCTION

Many times One of the basic physiological functions that is essential to preserving general health and well being is sleep.Restorative processes, memory consolidation, and the control of numerous body functions take place during this period.But people with neurodegenerative illnesses interfere[1]. The areas of the brain that control sleep-wake cycles and sleep-related functions may be directly impacted by the neurodegenerative processes themselves. Conversely, sleep disruptions may worsen or hasten neurodegeneration via pathways that include inflammation, oxidative stress, and impaired protein clearance[2].Most of these disorders appear to have a physiopathological process in which cells are unable to fold certain proteins in their native configuration, leading to aberrant accumulation in the form of fibrillar aggregates or inclusion bodies[3].All of the animals that have been researched so far have sleep. It is an essential and universal component of general health. Some advantages of sleep, including as memory consolidation and cellular process control, have been shown, even if research on the precise roles of sleep is still ongoing[4].

Many age-related neurodegenerative disorders, including Alzheimer's disease, are frequently accompanied by poor sleep[5].This raises the question of how much sleep is causally linked to the aging process and neurodegenerative symptoms. Signal transduction mechanisms including the unfolded protein response and quality control systems uphold proteostasis, also known as protein homeostasis[6].Crucially, the cell's protein regulatory systems and the quality of our sleep both decline with age[7]. Sleep and neurodegeneration are related, according to clinical disorders and experimental data. For example, the clinical phenomenology of neurodegenerative diseases (NDGD) has long been known to include sleep-related breathing, excessive daytime drowsiness, insomnia, and motor and behavioral symptoms[8].While insomnia, sleep apnoea syndrome, or hypersomnia may be less commonly impacted, REM-sleep-behavior disorder (RBD) in Parkinson's disease (PD) may be clearly impacted[9].

Lack of sleep during experiments on lab animals or healthy humans may encourage the buildup of harmful proteins in the brain, which might lead to the onset of Parkinson's disease (PD) or Alzheimer's disease (AD)[10].Lastly, sleep problems, regardless of their aetiology, may develop initially in a well-established NDGD, such as Parkinson's disease (PD) or Lewy body dementia (DLB), and they may also play a role in the development of neuropathology and the advancement of

NDGD.When NDGD patients have a sleep issue, the illness typically progresses more quickly and severely[11].

It is therefore still challenging to distinguish the precise association between sleep disturbances and neurodegeneration and determine the cause or effect of the issue, despite the fact that a lot has been learnt. The Bradford Hill criterion must be applied in order to uncover any conclusive evidence of a causal relationship between sleep and NDGD.Numerous epidemiological studies have examined the link between sleep disturbances and neurodegenerative diseases[12]. Twelve of the fourteen included studies are of excellent quality.The maximum follow-up period for 13 studies was at least five years. Sleep duration, sleep quality, napping, parasomnia, a general sleep disturbance, or the presence of daytime sleepiness, insomnia, use of sleep "aids" (hypnotic or alcohol intake), frequent distressing dreams, snoring and OSA, RBD, RLS, and chronotype were all evaluated in the studies for their association with the risk of Parkinson's disease[13].

Sleep, Proteostasis and Anotomical Structures:

The physiological mechanism of sleep is widespread. The two-process model of sleep is currently the accepted explanation for how sleep is physiologically regulated[14]. Light throughout the day and the cycling of proteins like melatonin control the circadian mechanism[15]. According to this theory, the amount of time spent awake correlates with the accumulation of molecules. (Ramírez and Couve, 2011; Berridge,2002)[16]. The ER lumen, which includes molecular chaperones that attach to the freshly produced proteins to help them achieve their proper shape, is where newly synthesised proteins are found. To stop aggregation, proteins that are unable to fold correctly are directed to the proteasome for destruction[17]. In some cases, the ER's protein buildup is too great for chaperone proteins to handle alone. Once attained, this is known as ER stress, which sets off a series of cellular signalling events known as the UPR to deal with the clumped proteins in the ER lumen[18]. Apoptotic pathways are triggered, which eventually results in cell death, when the ER is under prolonged stress and these three UPR mechanisms are insufficient to alleviate that stress[19].

Three ER transmembrane proteins—PKR-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6—act as the cell's "stress detectors[20]. These mechanisms work together to help the cell deal with or control the buildup of misfolded proteins, and we know that sleep deprivation activates these systems. In particular, a number of studies have demonstrated that sleep deprivation causes the PERK pathway of the UPR to be activated and levels of the chaperone protein BiP/GRP78 to rise[21]. Another well-researched proteostasis process that is triggered by the integrated stress response after the UPR is autophagy[22]. Studies on yeast have shown that ER stress triggers the autophagy response and that the production of autophagosomes requires the downstream signalling protein Atg1[23]. Specifically, it has been demonstrated that autophagy activation requires the IRE1-JNK pathway[24].

According to recent research, autophagy is controlled by the circadian rhythm, and the transcription factor CEBPB and Rev-erb play a direct role in tying these two processes together[25]. Poor sleep quality has been linked to issues with verbal knowledge, working memory, long-term memory, and visuospatial thinking, according to other research[26]. Furthermore, enhancing protein homeostasis by the administration of 4-phenyl butyrate (PBA), a tiny chemical chaperone molecule, enhances sleep in older flies[27]. Collectively, these investigations imply that cellular stress is the root cause of several neurodegenerative illnesses and may be a therapeutic target for the management of those who suffer from them. A significant portion of individuals with AD and PD, in particular, report having sleep abnormalities include increased fragmentation of sleep, increased daytime drowsiness, and interruptions of REM sleep[28].

Within the cerebral hemisphere, the hypothalamus is located near the pituitary gland. To control the sleep and arousal cycle, the hypothalamus is made up of several nerve cell bodies called suprachiasmatic nuclei (SCN), which receive sensory information about light exposure. The anatomical recess between the superior colliculi is where the pineal gland is located. The circadian rhythm is mostly controlled by the regulation of melatonin synthesis, a neurohormone that encourages sleep and is impacted by a number of linkages. Rapid eye movement (REM) sleep has been shown to be associated with increased activity in the amygdala, a neuroanatomical area involved in emotion regulation. This finding provides a possible explanation for why mood disorders and sleep difficulties frequently co-occur[29].

Neurophysiology of Sleep:

Numerous neurobehavioral and physiological functions, including the control of body temperature, the manufacture of melatonin, and the 24-hour sleep-wake cycle, are regulated by the circadian timing system[30]. Numerous physiological functions, including blood pressure regulation, thermoregulation, and sleep regulation, depend heavily on melatonin. Because of the decreased or nonexistent exposure to light stimuli, its synthesis is most noticeable at night. Sleep difficulties

might result from any perturbations along this route, which could also induce changes in the circadian cycle[31].

Four phases of non-rapid eye movement (non-REM) sleep and one stage of rapid eye movement (REM) sleep make up typical sleep, and each has distinct electroencephalogram (EEG) features. The brain cycles through these stages in a cyclical fashion, usually repeating four to five times in a single night and happening at intervals of around 90 minutes. The first stage of the sleep cycle, known as stage 1, is defined by the change from awake to sleep. People are in a condition of light slumber at this point and are readily awoken. They might not be aware that they have been asleep. “Sleep spindles” and “K complexes” are two unique electroencephalogram patterns that appear during Stage 2 sleep, which is characterised by a reduced alertness. In addition, there is a decrease in body temperature, heart rate, and respiration rate. A decrease in brain wave activity occurs during Stages 3 and 4 of the sleep cycle, often known as deep sleep, which leads to a reduced ability to arouse. If arousal is experienced, the person may show signs of fatigue and confusion. People have rapid eye movements (REM) when they are in the rapid eye movement (REM) sleep stage increased respiratory and cardiac rates, and often experience spasms in the muscles. One common sign of the ageing process is a decrease in REM sleep during Stages 3 and 4. This decrease in sleep phases might be a factor in the frequency of nocturnal awakenings, difficulty falling back asleep, and daily tiredness that older people commonly complain[32].

Rapid Eye Movement Sleep Behavior Disorder:

Loss Muscle atonia during REM sleep and dream enactment are hallmarks of rapid eye movement (REM) sleep behaviour disorder (RBD). RBD typically affects 0.5% of the general population over 50 and 7% of those over 70. It is often chronic and progressive[33]. Abnormal behaviours and lack of muscular atonia, such as vocalisations, jerks, and motor behaviours during rapid eye movement (REM) sleep, are hallmarks of rapid eye movement sleep behaviour disorder (RBD), a parasomnia that is frequently linked to REM-related dream content[34]. Although RBD is thought to affect 0.5–2% of people, bigger population-based studies of possible dream enactment symptoms indicate that older persons who live in the community are likely to have RBD at higher rates (5–13%)[35]. Males and women under 50 have about the same frequency of RBD, but among older individuals, males seem to be more likely than women to have it. There are two types of RBD: idiopathic and symptomatic[36].

Multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and Parkinson's disease (PD) are synucleinopathies that are thought to be significantly preceded by iRBD[37].Indeed, up to 82% of elderly men with RBD go on to acquire dementia or parkinsonism[38].RBD is present in over half of PD patients, at least 88% of MSA patients, and around 80% of DLB patients[39].Approximately 80% of DLB patients, at least 88% of MSA patients, and more than half of PD patients have RBD[40]. The pontine and medulla oblongata were the focal points of the brain networks that produced REM sleep. During regular REM sleep, the descending glutamatergic fibres from the ventromedia medulla and the spinal cord stimulate the glycinergic or gamma-aminobutyric acid (GABA) ergic premotor neurones. neurones in the sublaterodorsal nucleus (SLD). Muscle atonia results from premotor neurones suppressing the activity of motor neurones[41]. Since it has been shown to be a symptom of early-stage alpha-synuclein-linked NDDs such Parkinson's disease (PD), Lewy body dementia (LBD), and multiple system atrophy (MSA), the label "iRBD" is inappropriate[42].

Clinical features and diagnosis of RBD:

Excessive motor activity, ranging from mild limb twitches to severe, complicated motions, can interrupt sleep and result in harm to the patient and/or their sleeping partners[43].Since REM sleep is more common in the morning, the behaviours may be more prevalent at that time. They may also begin as early as 90 minutes following the initial REM sleep event[44].

According to recent research, cognitive impairment in certain iRBD patients may be a sign of the early stages of neurodegenerative illnesses, and an Epworth sleep scale score of greater than 8 indicates a faster transition to PD and dementia at the time of iRBD diagnosis[45]. The following was the RBD diagnosis: recurring vocalisation and/or motor behaviour episodes linked to sleep. Video polysomnography (vPSG) is used to record these behaviours during REM sleep or in response to a patient's medical history. Extremely high night-to-night stability was demonstrated by the behaviours. More than 80% of RBD patients may be diagnosed with just one vPSG[46]. EMG switching or excessively high submental electromyogram (EMG) activity are signs of REM sleep without atonia (RSWA)[47]. The RBD Screening Questionnaire (RBDSQ), the REM Sleep Behaviour Questionnaires-Hong-Kong (RBD-HK), the Mayo Sleep Questionnaire (MSQ), and the Innsbruck RBD Inventory are among the questionnaires that may also be used to diagnose RBD.The RBD Screening Questionnaire (RBDSQ), the REM Sleep Behaviour Questionnaires-Hong-Kong (RBD-HK), the Mayo Sleep Questionnaire (MSQ), and the Innsbruck RBD Inventory are among the questionnaires that may also be used to diagnose RBD[48]. It may be possible to identify structural alterations in RBD

patients' brains using neuroimaging methods. For instance, it has been observed that individuals with iRBD might have white matter abnormalities detected by diffusion tensor imaging (DTI), a commonly used magnetic resonance imaging (MRI) method[49]. In 11 iRBD patients, a 3.0-T MRI research revealed a decrease in nigral hyperintensity, which is consistent with a 123I-N-3-fluoropropyl-2β-carbomethoxy-3β-4-iodophenyl tropane, a tracer of the striatal pre-synaptic dopamine transporter, had significantly decreased uptake ratios[50].

In general, PSG confirmation is the basis for a definitive diagnosis of RBD. Single screening questions, followed by particular RBD rating scales and a more thorough sleep interview, might be employed for identification or screening in large populations. To monitor the outcome of RB, other clinical symptoms such olfactory loss, autonomic dysfunction, and cognitive impairment, as well as tests like functional MRI, transcranial sonography, and peripheral nerve tissue biopsies, may be useful[51].

Pathogenic mechanisms of RBD:

Neurodegenerative illnesses, antidepressant medications, alcohol, and drug withdrawal can all cause RBD. However, it is still unclear what processes underlie the pathophysiology of RBD. The lateral hypothalamus, dorsal paragigantocellular reticular nucleus, and ventrolateral periaqueductal grey (vlPAG) are the main components of the REM-generating circuit in rodents. To induce REM sleep, these neurones inactivate REM-inhibiting monoaminergic neurones in the tuberomammillary nucleus, locus coeruleus (LC), dorsal raphe, and GABA-ergic neurones in the vlPAG. Muscle twitches during REM sleep are increased when glycine and GABA receptors in the VMM are blocked pharmacologically or genetically[52]. Only a small number of limbic regions, including the retrosplenial cortex, medial entorhinal cortex, anterior cingulate cortex, and dentate gyrus, exhibit cortical activation during REM sleep. These regions generate dreams and trigger the motor cortex, which in turn triggers the activation of spinal motor neurones[53]. According to the hypothesis, both people and animals (cats, rats, and mice) may exhibit RBD-like motor behaviour as a result of injuries in the REM sleep circuits[54]. Through postmortem examination of PD brains, Braak has put forth the theory that the α-syn disease gradually progresses from caudal to rostral; this advancement may be brought on by cell-to-cell communication across related brain areas[55].

Management of RBD:

Withdrawal of medications:

Melatonin and clonazepam are the two primary pharmacological therapies for RBD. While clonazepam does not lessen RSWA, it does alter motor behaviours and dreaming. Even though clonazepam is the first-line treatment, individuals with RBD who also have dementia, gait abnormalities, or OSA should have its use closely monitored over time[56]. Melatonin reduces RSWA by raising REM sleep atonia levels. Melatonin demonstrated good safety, excellent tolerance, and little interactions with other drugs[57]. In small-sample clinical trials, pramipexole, donepezil, ramelteon, and cannabinoids were among the other RBD therapies that demonstrated effectiveness[58].

The pathogenic alterations start in the medulla and pons, which may be connected to the onset of RBD and RSWA in idiopathic RBD, and then progress to more rostral tissues[59]. There is little study on the genetic components of RBD. Research indicates that in individuals with idiopathic RBD The glucose encephalo-glucosidase (GBA) mutation is closely linked to both PD and RBD[60]. RBD is also linked to PD-associated loci, scavenger receptor class B member 2 (SCARB2) rs6812193, and microtubule associated protein tau (MAPT) rs12185268. A faster progression to synucleinopathy is observed in homozygous carriers of the ubiquitin specific peptidase 25 (USP25) rs2823357 single-nucleotide polymorphism (SNP)[61]. PTEN-induced putative kinase 1 (PINK1) SNP rs45478900 carriers may be more likely to develop PD in RBD patients[62]. There is some correlation between RBD and PD and the mutation in leucine rich repeat kinase 2 (LRRK2)[63].

II. THE LINK BETWEEN SLEEP AND NEUROLOGICAL DISORDERS

There are many facets and complexities to the connection between sleep and mental illnesses. Many mental health issues often co-occur with sleep abnormalities, including insomnia, hypersomnia, nightmares, and disruptions of the circadian rhythm. The Diagnostic and Statistical Manual of Mental problems (DSM-5) provides diagnostic criteria that help physicians diagnose sleep problems in the context of mental health assessments. But it's important to understand that this link is reciprocal since untreated sleep issues can make mental health symptoms worse and vice versa[64].

Sleep disorders in Parkinson's disease(PD):

The clinical features of Parkinson's disease (PD), a common and complex neurodegenerative disease in the elderly, include non-motor symptoms like olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue, as well as motor symptoms like bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment[65]. The loss of dopaminergic and other pigment-containing neurones, particularly in the substantia nigra pars

compacta (SNpc), and the development of eosinophilic inclusion bodies, also known as Lewy bodies, in the cytoplasm of remaining neurones are the primary pathological alterations of Parkinson's disease (PD). Between 60 and 70 percent of those with Parkinson's disease have sleep difficulties[66].

Difficulties falling or staying asleep, sleep fragmentation, and daytime tiredness with involuntary naps and RBD are all examples of sleep disruption in Parkinson's disease[67]. RBD and later increases in the incidence of dementia in PD may share a cholinergic mechanism[68]. According to a meta-analysis, approximately 42.3% of people with PD had RBD[69]. Patients with PD with RBD had a somewhat greater burden of cerebrovascular illness than patients without RBD[70]. While it was not substantially linked to a risk of PD in the NPCD and CLSA trials, the presence of insomnia was also significantly connected with a reduced risk of PD in the UKBB study and a greater risk of PD in the WHI and NHIRD studies[71]. A second beneficial substance with less adverse effects is melatonin[72].

Sleep disorders in Parkinsonism plus syndrome:

Parkinsonism plus syndrome is a collection of neurodegenerative illnesses that share the hallmarks of Parkinson's disease (PD), such as tremor, stiffness, akinesia/bradykinesia, and postural instability, but also include characteristics that set them apart from PD, such as MSA, PSP, and CBD. MSA is a rare, adult-onset neurodegenerative illness that manifests clinically as a mix of urogenital dysfunction, autonomic failure, cerebellar ataxia, parkinsonian symptoms, and corticospinal abnormalities[73]. Both MSA subtypes—MSA with predominant cerebellar ataxia (MSA-C) and MSA with predominant parkinsonism (MSA-P) have sleep issues[74]. Supranuclear ophthalmoplegia, pseudobulbar palsy, dysarthria, axial stiffness, frontal lobe dysfunction, and dementia are the hallmarks of PSP, a progressive tauopathy[75]. Neuronal loss, gliosis, and MAPT-positive inclusions in neurones and glial cells, particularly in the brainstem, cerebellum, and basal ganglia, are examples of the common pathology[76]. Pharmacological treatments for RBD include melatonin at night or clonazepam[77]. CBD is an uncommon neurological condition that worsens with time. There are several phenotypes that it can exhibit, but none of them are distinct enough to provide a conclusive diagnosis. It's unknown what causes CBD in the end[78].

Sleep disorders in Alzheimer's disease (Ad):

The loss of cognitive function and behavioural abnormalities are hallmarks of AD, the most prevalent form of dementia among the elderly. According to reports, 24.5–40% of AD patients suffer from sleep disturbances, which mostly show themselves as excessive daytime sleeping, agitated evening behaviour, and frequent nighttime awakenings[79]. Sleep issues are correlated with Alzheimer's disease (AD) in both directions. Because the suprachiasmatic and cholinergic nuclei degenerate, the disorder causes severe sleep disturbances and deprivation. These anomalies have a significant impact on patients and carers ability to remove β-amyloid, which may affect cognition by compromising the brain's capacity to do so. Sleep difficulties are common, impacting around 45% of people[80].

Many medications are used to improve the quality of sleep, even though there is a dearth of convincing scientific evidence. These include of atypical antipsychotics such quetiapine, benzodiazepines, melatonin, and sedative antidepressants[81]. Despite lengthy follow-up periods (8.5–13.07 years), studies evaluating daytime sleepiness [15], chronotype [22], or sleep quality [49, 15] did not find a statistically significant association with AD risk[82]. Despite the widespread belief that RBD is a reliable indicator of neurodegeneration in specific synucleinopathies, research has shown that RBD occurs in a small percentage of AD patients[83].

According to a study of individuals with probable AD, four out of fifteen patients exhibited RSWA, and one of them had every polysomnographic characteristic of RBD[84]. Five AD patients showed signs of RBD, according to a different research that included 105 likely AD patients[85]. However, 18 out of 84 individuals with iRBD acquired neurodegenerative disorders, and three of these patients were diagnosed with AD, according to a longitudinal research with a follow-up of almost 4.2 years[86]. Melatonin has been suggested as a substitute therapy for AD patients with respiratory disorders and RBD[87].

Sleep Disorders in Dementia with Lewy Bodies (DLB):

DLB, FTD, and vascular dementia (VaD) are among the numerous illnesses with distinct pathogeneses that cause cognitive impairment and dementia in addition to AD. Visual hallucinations, Parkinson's syndrome, and cognitive impairment are the hallmarks of DLB. It is characterised pathologically by intracytoplasmic inclusions known as Lewy bodies, which are made up of filamentous protein granules made of ubiquitin and α-syn that are present in the neocortex and brainstem nuclei. Additionally, DLB exhibits some clinical characteristics of AD, including as NFTs and Aβ deposits[88]. After Alzheimer's disease, dementia with Lewy bodies (DLB) is the most common kind of dementia. It is characterised by a variety of symptoms, such as visual hallucinations, parkinsonism, motor abnormalities, and cognitive deterioration. The presence of Lewy bodies in the limbic system, brainstem, and cortical areas is one of the

neuropathological changes. Nearly 80% of people with dementia with Lewy bodies (DLB) experience sleep difficulties, which is more common than in Alzheimer's disease (AD)[89].

Ibrahim and colleagues discovered that the most significant characteristics linked to neurodegenerative diseases, such as mild cognitive impairment, Alzheimer's disease, Alzheimer's and vascular dementia, unspecified dementia, Parkinson's disease, isolated REM sleep behaviour disorder, Parkinson's disease dementia, and vascular dementia, are wake, sleep stage N3, and REM sleep percentages[90]. A significant metabolic decline is shown in the dorsolateral and medial frontal areas, left precuneus, bilateral superior parietal lobule and rolandic operculum, and amygdala of DLB patients with RBD[91]. The majority of frontotemporal degenerations are linked to the fused-in-sarcoma (FUS) protein, TAR DNA-binding protein with molecular weight 43 kDa (TDP-43), and MAPT[92].

Sleep Disorders in Huntington's Disease (HD):

HD is a neurodegenerative disease that progresses over time and often manifests as a variety of signs and symptoms, including mobility, cognitive, and mental health issues[93]. Frequent insomnia, earlier sleep start, decreased sleep efficiency, increased stage 1 sleep, shorter and delayed REM sleep, and increased periodic leg movements are among the sleep abnormalities associated with HD[94].Another common characteristic of sleep difficulties in HD is the disruption of circadian rhythms[95]. Quick eye movements While restless legs syndrome (RLS), obstructive sleep apnoea syndrome (OSAS), and sleep behaviour disorder (RBD) have been observed in patients with Huntington's disease (HD), their prevalence is neither high nor considered concerning. Compared to control individuals, those who have the premutation gene experience more sleep disturbance, as seen by a fragmented sleep pattern[96].

Sleep Disorders in Multiple System Atrophy (MSA):

Multiple system atrophy (MSA) is a neurological condition that can present as a variety of autonomic failure, cerebellar dysfunction, and parkinsonism. The presence of alpha-synuclein-positive cytoplasmic inclusions in the glial cells of various brain regions is the pathogenic characteristic that distinguishes multiple sclerosis[97]. It is unknown how common periodic limb movement syndrome (PLMS) and restless legs syndrome (RLS) are in the general population of a similar age. A small percentage of people who were first diagnosed with idiopathic rapid eye movement sleep behaviour disorder (RBD) go on to develop multiple system atrophy (MSA). Notably, the majority of these people go on to receive diagnoses for Lewy body dementia and Parkinson's disease. When compared to Parkinson's disease and dementia with Lewy bodies, MSA is comparatively less common in the general population, which explains the disparity in diagnostic rates. 80% to 100% of individuals with multiple system atrophy (MSA) will experience rapid eye movement sleep behaviour disorder (RBD)[98].

Central respiratory control and changes with aging:

Fiber-optic laryngoscopy visualisation of the upper airway in MSA patients has revealed bilateral, rhythmic contractions of the arytenoids54,66, as well as "floppy epiglottis" and constriction of the airway at the level of the vocal folds, base of the tongue, and soft palate66. 66: a condition when the glottis and epiglottis are drawn together during inspiration[99].

Sex Differences In Sleep Apnea:

Sleep apnoea is diagnosed in males two to three times more frequently than in women, and its prevalence rises sharply with age in both sexes. This implies that the development of sleep apnoea is influenced by sex hormones[100]. The severity of AHI incidents does not seem to rise as women reach menopause, despite the incidence appearing to do so. Interestingly, obstructive sleep apnoea is more likely to occur in young women with polycystic ovary syndrome (PCOS), which is characterised by elevated testosterone levels. This implies that these sex disparities in the start, course, and severity of sleep apnoea may be caused by sex hormones (such as androgens and oestrogens)[101].

III. DISCUSSION

Zhang et al. at Dalian Medical University conducted a narrative review to assess the link between RBD and neurodegenerative diseases. They found RBD is highly prevalent in synucleinopathies (Parkinson's disease, dementia with Lewy bodies, multiple system atrophy) and also occurs in non-synucleinopathies (Alzheimer's, Huntington's, ALS). They concluded that RBD may be an early biomarker for neurodegeneration and cognitive impairment, and understanding its mechanisms can improve early diagnosis and treatment[102]. Anghel et al. at 'Dunarea de Jos' University, Romania, conducted a review on sleep disorders in neurodegenerative diseases like ALS, MSA, hereditary ataxias, Huntington's, PSP, and DLB. Using literature search and qualitative analysis, they found insomnia, RBD, restless legs syndrome, and sleep-related breathing disorders are common and worsen quality of life and disease progression. They concluded that both pharmacological and non-pharmacological treatments are crucial to manage sleep disturbances, improve care, and potentially slow disease progression[103].

IV. FUTURE PERSPECTIVES

Sleep and Digital Health Interventions:

Digital Sleep Tracking and Feedback:Customised sleep feedback systems may result from developments in artificial intelligence algorithms and digital sleep tracking. AI-powered systems may provide real-time insights and practical suggestions for improving sleep for those with mental illnesses by integrating sleep data from wearable technology and other sources.

Sleep and Artificial Intelligence:

AI-Powered Sleep Disorder Prediction: Algorithms that use artificial intelligence have demonstrated impressive ability to analyse large volumes of data. AI-powered platforms may combine data from wearable technology, electronic medical records, genetic data, and behavioural patterns in the context of sleep and mental health to forecast the risk of mental diseases based on sleep disruptions.

V. CONCLUSION

Although it is also seen in other neurodegenerative disorders, sleep is frequently linked to synucleinopathies. It might be a possible early indicator of neurodegeneration as it could appear years before motor or cognitive problems. Degeneration in the brainstem circuitry that control REM sleep is connected to the syndrome, which frequently mirrors more severe cognitive impairment in conditions like Parkinson's. Depending on the underlying pathophysiology, clonazepam, melatonin, or ramelteon are the major treatments. There is enough proof to conclude that sleep quality and cellular health are related. Numerous studies show a link between impaired memory and cognition and poor sleep quality. Although it is hard to study human neuronal protein levels and homeostasis, data from neurodegenerative illnesses makes it abundantly evident that cellular stress levels are elevated and protein folding is poorly regulated, which results in the aggregations that are frequently observed in these conditions. According to this viewpoint, reducing cellular stress and enhancing sleep quality may be important treatment targets for many debilitating illnesses.

Sleep disturbances are becoming more widely acknowledged as signs of neurodegenerative illnesses as well as possible contributors to their aetiology. REM sleep problems, excessive daytime drowsiness, sleep behaviour disorders, insomnia, and circadian disorders including amyotrophic lateral sclerosis and Alzheimer's disease. Both a result and a potential trigger of neurodegenerative processes are sleep disturbances. Sleep is both a diagnostic sign and a therapeutic target because of the two-way relationship between sleep and neurodegenerative diseases, wherein brain pathology interrupts sleep and inadequate sleep accelerates neuronal destruction. In addition to providing symptomatic relief, treating sleep disturbances in individuals with neurodegenerative diseases may lead to the development of novel disease-modifying treatments. It's unclear exactly how OSA and the neurodegenerative process are related. Nonetheless, data from the literature to date suggests a two-way road or bidirectional link.

Acetylcholine and serotonin, two neurotransmitters crucial for preserving upper airway patency, are deficient in some neurodegenerative disorders. The challenge for the next ten years is to keep expanding our understanding of this relationship by supporting research that more accurately evaluates the mechanisms at play, the significance of interactions with genetic and environmental factors, the factors that determine whether neuronal damage is reversible, and the effects of treating one condition on the development of another. The effects of androgens and oestrogens may be the cause of the reported sex variations in sleep apnoea. In order to cure neurodegeneration, it will be helpful to know how sleep apnoea affects the central nervous system's oxidative stress and inflammation. Additionally, research is required to determine how sex and sex hormones might either protect against or increase the risk of sleep apnoea and associated comorbidities.

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