Sleep in the human aging process and circadian sleep rhythm disruptions

Sono no processo de envelhecimento humano e interrupções do ritmo circadiano do sono

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ABSTRACT

The aging process is often related to sleeping difficulties, often due to changes in circadian rhythms. The circadian timing system is centered in the suprachiasmatic nucleus - the master biological clock - which synchronizes the rhythm of oscillators throughout the body, including the sleep-wake cycle. This affects the time, duration and quality of sleep according to the development and aging process, under external and internal influences. This review addresses the human circadian timing system, including endogenous and exogenous influences on circadian rhythms, their age-related particularities, as well as the repercussions of circadian misalignment in neurodegenerative diseases. Circadian rhythms naturally weaken with aging, but there are particularities according to age. Throughout life, sleep and circadian rhythm disorders are strongly bidirectionally related to the pathophysiology of some psychiatric and neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. This knowledge could potentially create valuable opportunities to improve the health of the world's population that is under circadian misalignment and aging.

Keywords: sleep, circadian rhythm, aging, neurodegenerative disease

RESUMO

O processo de envelhecimento está freqüentemente relacionado a dificuldades de dormir, muitas vezes decorrentes de alterações nos ritmos circadianos. O sistema de cronometragem circadiana está centrada no núcleo supraquiasmático - o relógio biológico mestre - o qual sincroniza o ritmo dos osciladores em todo o corpo, incluindo o ciclo sono-vigília. Isso afeta o tempo, a duração e a qualidade do sono de acordo com o processo de desenvolvimento e envelhecimento, sob influências externas e internas. Esta revisão aborda o sistema de temporização circadiana humana, incluindo as influências endógenas e exógenas nos ritmos circadianos, suas particularidades relacionadas à idade, bem como as repercussões do desalinhamento circadiano nas doenças neurodegenerativas. Os ritmos circadianos enfraquecem naturalmente com o envelhecimento, mas há particularidades de acordo com a idade. Ao longo da vida, os transtornos do sono e do ritmo circadiano estão fortemente relacionados bidirecionalmente à fisiopatologia de algumas doenças psiquiátricas e neurodegenerativas, como as doenças de Alzheimer e Parkinson. Esse conhecimento pode potencialmente criar oportunidades valiosas para melhorar a saúde da população mundial que está sob desalinhamento circadiano e envelhecimento.

Palavras-chave: sono, ritmo circadiano, envelhecimento, doença neurodegenerativa

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Fundingt: The authors did not receive funding for this work.
Declaration of competing interests: The authors declare no competing interests.

INTRODUCTION

Aging is linked to several health concerns including the one about sleep difficulties that may occur due to circadian rhythm disruptions defined as the desynchronizations between internal sleep-wake rhythms and the light-darkness cycle. Besides, these disruptions are relevant in age-related neurodegenerative diseases and may occur before the onset of typical clinical symptoms of the disorders such as Alzheimer's disease and related dementias, and Parkinson's disease [1,2,3] . However, the causal link between circadian rhythms and neurodegeneration is still not fully understood, but there is a growing understanding of the neurobiology of sleep that has been steadily increasing over the past hundred years. In the beginning, the framework of the wake and sleep centers was established, but over the past decades, this was more meticulously refined [4].

Another issue of immense interest has been about the circadian regulation of the sleep-wake cycle, originating from suprachiasmatic nuclei (SCN), the master circadian, about 24 h/day, that control mammalian physiology, as the control of sleep, metabolism, and the immune system [1,5,6,7] . The related subject will be unfolded in the next section.

This narrative review approach questions regarding the sleep-wake cycle basics, circadian rhythm through life, circadian rhythms outputs, and their disruption.

SLEEP-WAKE CYCLE

The timing of the circadian system has a complex architecture that is synchronized with geophysical time, mainly through light tracks perceived by the retina that are transmitted to the central pacemaker in the SCN and subsidiary clocks in almost all cells of the body (Figure 1) [3,5,7] . Consequently, environmental stimuli can modify or redefine the time or phase of circadian rhythms [1,6] .

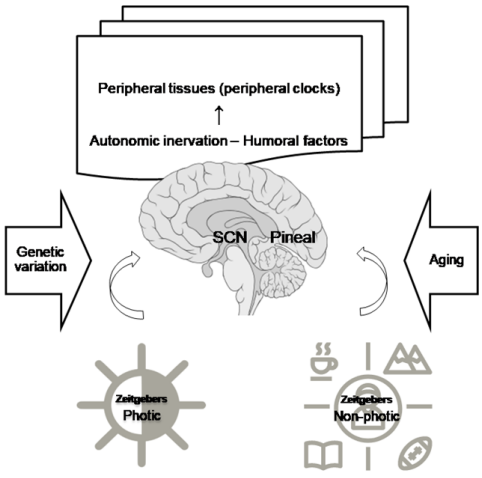

Figure 1. Circadian rhythms are endogenously created although they can be modulated by external cues called zeitgebers ("time giver"), under the influence of genetics and the aging process, and mediated by autonomic innervation and humoral facts

The SCN is anatomic and functionally subdivide into ventrolateral and dorsomedial regions. The generation of circadian rhythmicity is associated with the dorsomedial region and rhythm entrainment is associated with the ventrolateral region[3].

The ventrolateral region of SCN has a high number of cells that produce vasoactive intestinal peptide (VIP), important to circadian rhythm generation (regulating the SCN neural firing rhythm), synchronization of SCN neurons, mediate photic entrainment and output signaling. The dorsolateral region has many cells that synthesize vasopressin, important to circadian rhythm regulation [1,3] .

Discoveries in recent decades have clarified the physiological and molecular-genetic correlates of sleep rhythms and their circadian sleep disorders [1,4,5,7] . Rijo-Ferreira and Takahashi didactically presented the evolution of these timing circadian events determinants, and the corresponding summary is shown in Figure 2. The CLOCK (Circadian Locomotor Output Cycles Kaput) gene is critical to the generation of the circadian rhythm and there are significant remarks regarding circadian timing and human diseases, mainly identification of the SCN as a master regulator, identification of the first mammalian clock gene. This was first identified by using forward mutagenesis screening of mice treated with N-ethyl-N-nitrosourea, a highly potent mutagen, to create and identify mutations in critical genes that broadly affect circadian activity[4].

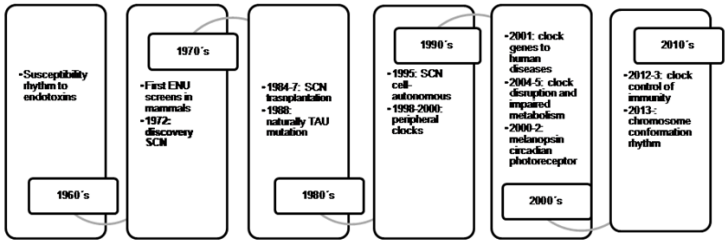

Figure 2. Main mammalian circadian clock research findings. These findings were preceded by the first long-term recordings of locomotor rhythms in rats (the 1920s). Based on Filipa Rijo-Ferreira and Joseph S. Takahashi [4].
SCN:suprachiasmatic nucleus; ENU: N-ethyl-N-nitrosourea.

Besides, other influential findings were the first descriptions of circadian clocks in the periphery, melanopsin was recognized as the circadian photoreceptor in the retina, the first mutation in a clock gene associated with human disease, the association of mutations in clock genes with impaired metabolism, and significant advances in the understanding of the clock control of immunity [4], although proposed underlying pathways include alterations of protein homeostasis and immune and inflammatory function [2].

Now, it is known that the sleep-wake cycle is typically programmed to occur at a specific stage concerning the external cycles, especially the light-dark one, in addition to internal exposure cycles, such as the pineal melatonin rhythm [4,5] .

Circadian time is permeated by humoral and neural signals that synchronize the rhythm of the peripheral oscillators subordinate to the central clock [1,8] . Endogenous rhythm acts even in the absence of external cyclical changes, such as light, temperature, and/or food intake. Thus, each cell in the body is equipped with its circadian oscillator, which is controlled by the central clock and gives rhythm to individual cells and organs[1]. These fundamentals gave rise to the so-called model of two processes for regulating the sleep-wake cycle, called Process S - Homeostatic (restorative) and Process C - Clock (timing, circadian biological clock) [8].

The circadian rhythm in mammals is cell-autonomous regulated and has autoregulatory feedback loops governed by transcription-translation mechanisms involving several genes[3,4,6]. In the positive loop, the genes involved are Brain and Muscle ARNT-like protein 1(BMAL1), CLOCK, and Neuronal PAS Domain Protein 2 (NPAS2) and the negative loop has Period (PER) and Cryptochrome (CRY) genes. The positive loop acts when heterodimers of Bmal1 protein with Clock or Npas2 protein activate transcription of PER 1, 2 & 3 and CRY 1 & 2 genes. The negative loop acts when the proteins produced by the PER and CRY genes inhibit the transcription activity of the Bmal1 with Clock or Npas2 heterodimers in the nucleus[3] .

Human beings, like all mammals, divide their daily behavior into phases of activity (wakefulness) and rest (sleep) that differ widely in their metabolic needs[5]. The circadian clock has evolved as an autonomous timing system by aligning behavior patterns with the solar day, and it supports the body's functions, anticipating, and coordinating the necessary body programs[4,7] .

Sleep plays a critical role in the process of memory consolidation that occurs in sleep without rapid eye movement (NREM), involved in the process of transferring and consolidating long-term information from the hippocampus to the neocortex [9].

SOME CIRCADIAN RHYTHMS ACROSS THE LIFESPAN

The homeostatic and circadian processes shape the time and structure of the sleep-wake cycle, which are changeable throughout the life of their duration, patterns, and cycles[5,7,8]. The interaction between these two processes seems to be sensitive to misalignment, with sleep being affected by changes in the homeostatic process related to aging[7]. Circadian rhythms begin during early infancy and change through the lifespan and with aging, which affects morphological, neurochemical, and circadian rhythmic functions coordinated by the main circadian pacemakers [1,7]. Consequently, there are parallel circadian disorders according to various brain disorders that are expressed throughout human life[5,7] .

Regarding sleep cycles, it is known that exists sleep with rapid eye movement (REM) and without rapid eye movement (NREM), the latter divided into three distinct stages - N1, N2, and N3. In particular, infant and child cycles have a relatively large amount of deep sleep (N3); in adults, N3, REM sleep and latency, total sleep time, and efficiency all decrease with aging as the N1, N2 and sleep awakening increases with age. The elderly generally have relatively short periods of deep sleep and REM sleep, but children and adolescents have practically unchanged sleep stages, despite the shift in the time of sleep[10].

Particular changes also occur, as newborns spend more than 50% in REM sleep which slowly decreases to 25% in the next two years, remaining at this level throughout life[11]. During infancy, sleep-wake rhythms consolidate during the first year of development and are ultradian[5]. There is a change in sleep chronotype from childhood to adolescence, from morning to evening, later it becomes earlier during adulthood, with shorter periods of sleep afterwards, leading the elderly to the tendency to lie down and wake up earlier[5,7] .

Regarding circadian rhythms, they suffer a gradual loss of amplitude during aging [5,6,7,10] , which impacts several aspects such as hormone secretion, body temperature, metabolism, and inflammatory processes. Despite the decrease in the amplitude of the circadian rhythm with aging, the body temperature oscillation pattern remains stable in the elderly, with the maximum increase in temperature in childhood. Also, melatonin secretion rhythms, which are important for promoting sleep onset, in addition to regulating body temperature, are delayed during adolescence and decrease considerably during aging[7]. Cortisol secretion rhythm peaks early in the morning during childhood, but gradually decrease the overall amplitude[5]. The rhythmic release of cortisol is also important because it regulates the rhythmic expression of clock genes. Besides, the amplitude of rhythmic gene expression in the brain and other tissues is reduced during aging[7].

Taking a look at figure 3 in association to sleep epidemiological data, it can be presumed that late childhood may be a good sleep time in comparison to all lifetime. With the onset of puberty, circadian rhythms change later (phase delay), and behaviors such as staying awake and exposing themselves to light then also later change the clock time. Thus, these people are more likely to have a Delayed sleep phase disorder [5,7,10] . As a result of these circadian incompatibilities, adolescents and young adults are the most sleep-deprived in society, which contributes to the emergence of many psychiatric illnesses at this stage of human life[5]. Another problem is related to irregular sleep time, which has been recognized as a subtle but chronic form of circadian disturbance.

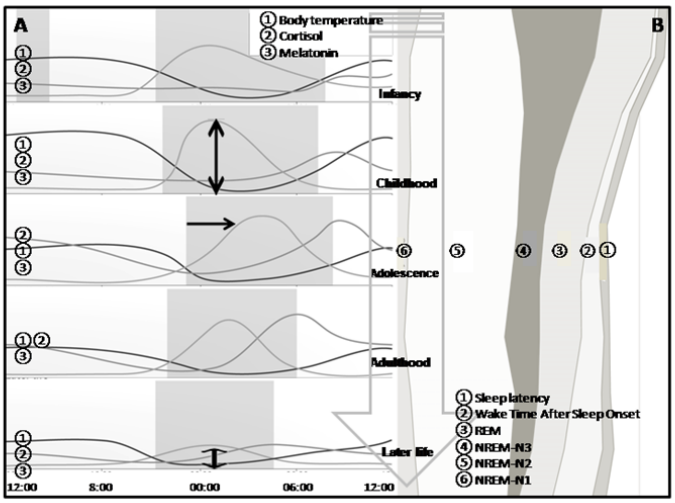

Figure 3. Sleep profile according to age, circadian hormonal variation (A), and sleep phases (B). Adapted from Logan & McClung[5] and Ohayon et al.[10] regarding changes in macrostructure from 5 years old. Notably, there are dramatic changes in early life, such as decreased sleep duration, percentage of NREM-N3 sleep and REM sleep to 20-25% of sleep time compared to 50% in the newborn, while NREM-N2 increases.

The elderly have lower levels of circadian rhythms, in addition to being more prone to less exposure to light, as they spend less time outdoors, and indoor lighting can be reduced[5]. Besides, light transmission through the eyes changes with aging. One study showed that increasing age was associated with a gradual decrease in light transmission at all visible wavelengths, most prominently at shorter wavelengths, which is the wavelength most absorbed by photosensitive retinal ganglion cells[7]. These are some of the reasons why they tend to fall asleep and wake up too early, so they may have an advanced sleep-wake phase disorder, more common in aging [5,7] .

There is an aging process that begins with subclinical molecular changes, affecting molecular pathways and neural mechanisms that control SCN function, thus reducing the strength of its rhythm and output signals[3]. Besides, sleep fragmentation may be accompanied by accelerated aging and microglial activation, which may be associated with cognitive impairment. A study has shown that greater sleep fragmentation was associated with higher expression of genes characteristic of aged microglia, independent of chronological age, and the greater expression of those genes was associated with worse cognition. This finding could potentially relate aging and activation of microglia as a consequence of sleep fragmentation[12].

Neural terminals with gamma-aminobutyric acid (GABA) are important to circadian rhythm, as it interconnects the SCN neurons and plays a role in the environmental lighting cycle and other signals. The quantity of presynaptic GABAergic terminals in the SCN decreases with aging, potentially affecting the coordination of circadian oscillators[3]. Attenuation of SCN VIP that occurs with aging could mediate the age-related changes in circadian rhythm [3,7] .

In conclusion, the biological clock that regulates circadian rhythms is dynamic throughout life, and rhythmic activities, such as sleep-wake patterns, change markedly with aging, and in many cases, become increasingly fragmented[1,5,7] .

DISRUPTED CIRCADIAN RHYTHMS

Under normal circumstances, the central circadian clock in the SCN, under the influence of light, regulates peripherals clocks, but when interrupted, they gradually become more misaligned (Figure 4)[4,7] .

Also, there are age-related changes in the neurochemical composition of the SCN, with a consequent decrease in the overall amplitude of its firing rate. However, perhaps the aging of stem cells will retain a functional clock but be redirected to new circadian functions, and this reprogramming would be related to the differential methylation of DNA that occurs with aging[3,13]. A study demonstrated the relationship between sleep patterns, even in a short period, with molecular aging, through the analysis of DNA methylation corresponding to epigenetic age. The DNA was analyzed in two periods and the results showed accelerated epigenetic aging (positive dissociation between chronological and epigenetic age) in the group with poor sleep (shorter sleep and less regulated) and deceleration of epigenetic aging in the group of good sleep (longer sleepers and more regulated). And as it has already been demonstrated, epigenetic aging has been linked to several causes of mortality[13].

Endogenous circadian clocks govern many changes in physical, mental, and behavioral states. Thus, misalignments between the environment and the internal clocks or desynchrony of clocks within an organism can have abnormal consequences[4,7].

It is also important to note that there is a circadian-metabolic interference, since the output function of the circadian system also sends signals back to cell clocks, to reinforce circadian rhythmicity to adapt physiology to the specific needs of temporal tissues. Also, there are several causes of misalignment between the central circadian clock dragged by light and the peripheral circadian clock dragged, for example, by food in the case of unscheduled meals[1,4] .

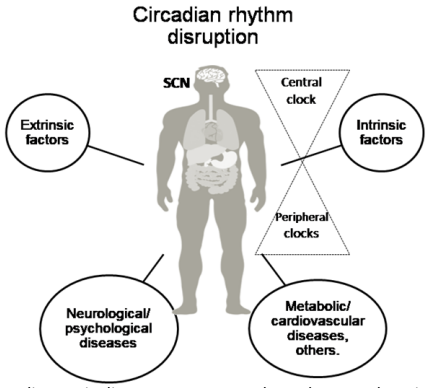

Figure 4. Circadian misalignment means that the synchronization between endogenous systems with the 24-hour day is disrupted, and in consequence, it is a risk factor for several medical disorders.

The quality and duration of sleep play an important role in cognitive and behavioral development with sleep disturbances and circadian disorders being associated with several neurodevelopmental disorders. It was observed that in children under three years old, shorter sleep duration and poor quality are predictive of cognitive impairment, hyperactivity, and impulsivity at six years of age, as well as an inconsistent sleep-wake cycle during early development, which can contribute to emotional and behavioral problems in early childhood. Disorders such as attention-deficit hyperactivity disorder, autism spectrum disorder, and Prader-Willi syndrome also were related to sleep disturbances[5].

Regarding adolescents, evidence from studies suggests that sleep and circadian rhythm disorders during adolescence are implicated in brain development disturbance and might be involved in the vulnerability to substance use and mood disorders. The increased vulnerability to substance use is a consequence of circadian disorders, but also the cause, leading to lasting changes in circadian and sleep networks[5]. Mood disorders, such as depression, are strongly related to circadian and sleep disruptions, such as delayed circadian rhythm, during adolescence, as well as the precipitation and severity of mood disorder symptoms[5,8].

Respecting the prevalence of poor sleep quality in adults is very high, but it affects differently according to age and sex. Shift work is associated with an increased risk of obesity, diabetes, heart disease, cancer, mood, and sleep disorders[5]. Women have more sleep problems during menstrual periods, pregnancy, and menopause[14]. Also, insomnia and interrupted sleep in the elderly are common problems often related to sleep comorbidities or other health problems, and may be secondary to side effects of medications[5,15]. Unfortunately, sleep problems in the elderly are usually not diagnosed. They are not treated simply because many people believe that sleep troubles are a normal component of becoming older or that nothing can be done for them to better sleep[14].

In general, the elderly are less able than younger adults to maintain sleep and thus may suffer chronic sleep deprivation. Also, several factors can contribute to circadian rupture[5,7]. Consequently, the treatment of any underlying medical disorder can improve sleep, and, possibly, disruption of the circadian rhythm may contribute to the development and progression of the vicious neural cycle.

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are strongly related to sleep and circadian disruptions[5,9], with increased risk associated with gene modifications. Studies have shown that polymorphisms in the CLOCK and BMAL1 genes are associated with an increased risk of developing AD[1,3,5]. The same correlation was made with increased risk of PD, but with single nucleotide polymorphisms in BMAL1 and PER1[1,5].

Other circadian clock-regulated processes can also contribute to neurodegeneration, such as inflammation, regulation of oxidative stress, dopamine synthesis, and cellular metabolism[5]. Oxidative stress may collaborate with protein misfolding and aggregation, and accumulation of oxidative damage that occurs with aging may aid in sleep-wake cycle disruption[1].

Metabolic changes can interfere with neurodegenerative disorders by mediating the effects of sleep and circadian rhythm disruption. Insulin resistance is correlated with an increased risk of AD. Studies have shown evidence of the correlation of apolipoprotein E (APOE) with insulin resistance, since the APOE E4 allele impairs mitochondrial function, potentially contributing to insulin resistance and other metabolic disorders[1]. Also, the E4 allele of the APOE gene is an important risk factor for sporadic AD[16,17].

A study found that amyloid-β (Aβ) protein, a pathological marker in the brain with AD, accumulates with sleep deprivation[5,16]. There is a diurnal variation of Aβ levels in the brain and its concentration is inversely proportional to the sleep duration, suggesting a clearance from the brain during sleep[1,4,17]. Recent work demonstrates that the glymphatic system has improved efficiency with sleep[1]. Therefore, during sleep, there would be an exchange of cerebrospinal fluid with interstitial fluid and clearance of Aβ. When sleep deprivation occurs, Aβ would accumulate and increase amyloid plaque formation. However, plaque formation leads to reduced and fragmented sleep, which results in reduced Aβ clearance, leading to a vicious cycle between sleep disturbance and amyloid deposition[1,3,4,17].

Also, in AD occur alterations in the number of VIP and vasopressin neurons in the SCN. Studies show that male AD patients exhibit neurodegeneration of SCN and reduced vasopressin and neurotensin neurons, which are associated with changes in the circadian rhythm. This association was not seen with female AD patients, as the reduced number of VIP neurons was exhibited in middle age but not old age[3].

AD patients have sleep-wake cycle dysfunction with increased sleep fragmentation and irregular sleep-wake patterns, as well as rest-activity dysfunction with increased daytime sleepiness. Also appears to have circadian body temperature cycling disruption. These changes are likely to result from disruption within clock circuits, deficits in outputs, and neuronal loss in the SCN[1,3].

REM sleep behavioral disorder (RBD) is a risk factor for the development of synucleinopathies, including PD, Multiple System Atrophy (MSA), and Lewy Body Dementia (LBD). Circadian dysregulation and insomnia are early manifestations of HD[1]. In individuals with AD sleep disruption often precede the onset of cognitive symptoms and worse as the disease progresses[3] as well as in patients

with PD, which develop sleep disorder years before the motor and cognitive symptoms[5].

In PD patients, sleep disturbances are one of the most important and prevalent non-motor symptoms of a disease, markedly by RBD (the most specific), excessive daytime sleepiness, restless legs syndrome, and insomnia[1,5]. Hallucinations correlate with sleep architecture destruction. These patients also have changes in the regulation of sleep hormones, with disruption of melatonin and cortisol, which suggests generalized circadian dysfunction[1].

Patients with HD show loss of hypocretin neurons (located in the lateral hypothalamus) and vasopressin neurons (located in the dorsolateral region of SCN), which are important to circadian rhythm regulation. Sleep disturbances are present even in the early stages of the disease, with abnormalities in sleep architecture in asymptomatic. As the disease progresses, sleep disorders become more evident with reduced sleep duration and efficiency and can manifest with RBD, insomnia, reduced REM sleep, and advanced sleep phase[1].

In the extreme case of dementia, *zeitgebers* may not be appreciated, and there may also be potentially disintegrated SCN, which provides a less competent circadian rhythm. This can result in multiple episodes of sleep during the day and waking periods at night [17].

In conclusion, interrupted circadian rhythms compromise health and increase the risk of disease [3,4,7], so it is worth compensating for the old circadian system by providing other zeitgebers that act on the circadian system via extra-SCN routes.

CONCLUSION

Overall, circadian rhythms weaken with growing older, but there are particularities according to age group. Thus, the treatment of circadian rhythm misalignments should consider this to even improve sleep quality. However, it is not fully established whether circadian interventions prevent or delay the onset of neurodegenerative diseases.

This approach attenuates the natural fragility of the circadian timing system in the aging process, in addition to avoiding restrictions to it in those with an intact system. Treatments include exposure to light and other appropriate external stimuli at the right time, which is extremely important for their success.

Throughout the lifespan, sleep and circadian rhythm disorders are strongly related to the pathophysiology of some psychiatric and neurodegenerative diseases. It is not yet clear whether neurodegenerative disorders are primarily caused by sleep and circadian rhythm disruptions, but it seems to worsen the progression of these diseases. Therefore, the treatment of circadian sleep disorders should also be considered as a means to mitigate the symptoms of neurodegenerative diseases.

Authors' contribution: conception and design of the study, MMG; AKB wrote the manuscript; Both authors reviewed the final version of the manuscript.

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