Circadian Rhythms in Aging and Neurodegeneration

Aleksandar Videnovic, MD, MSc, FAAN, FAASM
Massachusetts General Hospital
Harvard Medical School
Boston, MA

Introduction

The relevance of circadian rhythms and timekeeping for human health has been increasingly recognized not only by sleep medicine but also by many other medical specialties. 24 hour diurnal fluctuations in symptom intensity, responsiveness to treatment modalities and survival have been well documented. Tremendous advances in the field of circadian biology over the past several decades provide an opportunity to systematically investigate relationships between diseases, endogenous circadian rhythms, and exogenous influences.

Circadian Rhythms and Sleep in Aging

Aging is associated with numerous changes in sleep and circadian rhythmicity. Nighttime sleep in elderly is frequently interrupted by awakenings and daytime naps occur increasingly.[1] While sleep latency does not seem to be affected significantly by age, the amount of slow wave sleep decreases. These changes are frequently accompanied by increases in primary sleep disorders such as sleep disordered breathing and restless legs syndrome.[2] Some of these changes in sleep associated with healthy aging stem from alteration within the circadian system. Circdian phase has been shown to move earlier, or advance, with age.[3] Numerous reports demonstrated reduced circadian amplitude if rhythms with aging. In contrast to changes in phase and amplitude, it seems that circadian period remains stable throughout the aging process. Light is the main synchronized of human circadian system to the rotation of Earth. Available evidence suggests that light transmission through lens becomes altered with age, which may have significant implication for circadian homeostasis.[4] The suprachiasmatic nucles (SCN), the main circadian pacemaker, remains relatively resistant to age at the molecular level, but undergoes significant age-related changes at the network level.[5] This encompasses changes in SCN neuronal firing properties that has downstream effects leading to desynchronization and decreased circadian amplitude.

Circadian Rhythms in Neurodegenerative Disorders

Disrupted rest/activity cycles are common in neurodegenerative disorders. Pathophysiological mechanisms that underlie disruption of circadian rhythmicity in Alzheimer's disease (AD) have been well established. Circadian biology of other neurodegenerative conditions such as Parkinson's (PD) and Huntington disease (HD) has not been systematically studied.

Circadian rhythms in Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Both motor and non-motor manifestations of PD demonstrate strong diurnal oscillations. Examples of profound diurnal fluctuations in PD are oscillations in daily motor activity[6-9], autonomic function[10-15], rest-activity behaviors, visual performance, as well as fluctuating responsiveness to dopaminergic treatments for PD. It is plausible to suggest that these fluctuations may be reflective of modifications in circadian system in PD.

Actigraphy studies in PD patients demonstrate lower peak activity levels and lower amplitude of the rest-activity cycle compared to healthy older adults.[8,9,16] Increased levels of physical activity and shorter periods of immobility during the night, result in an almost flat diurnal pattern of motor activity in PD.[17,18] The circadian pattern of motor symptoms in PD is characterized by worsening of motor functioning in the afternoon and evening, present in both stable and patients with motor fluctuations.[6,19] Furthermore, responsiveness of PD motor symptoms to dopaminergic treatments declines throughout the day, despite the absence of significant changes in levodopa pharmacokinetics.[6,20] Alterations in the circadian regulation of the autonomic system in have been reported in PD. Blood pressure monitoring in PD demonstrates reversal of circadian rhythm of blood pressure, increased diurnal blood pressure variability, postprandial hypotension, and a high nocturnal blood pressure load. [12,21-23] This is associated with a decrease of daily sympathetic activity with a loss of the circadian heart rate variability and a disappearance of the symphatetic morning peak. [11] Although these abnormalities are more prominent in advanced PD, suppressed 24-hour heart rate variability remains present in untreated patients with early PD as well [24] Impairments of several sensory systems, such as olfaction and visual functions, are also reported in PD. Similarly to motor performance, circadian fluctuations of visual performance, measured by contrast sensitivity, have been reported in PD. [25]

Several studies examined markers of circadian system in the PD population. Initial studies that focused on the secretion of melatonin reported phase advance of melatonin rhythm. [26,27,28] Plasma

cortisol rhythms in these studies did not differ between the PD group and controls. These studies did not control for exogenous factors that are known to influence endogenous circadian rhythms such as light exposure, timing of meals, ambient temperature and physical activity, and co-existent depression. Recent circadian investigations eliminated these methodological limitations. Using salivary dim light melatonin onset (DLMO) in 29 PD patients and 27 healthy controls, Bolitho et al. demonstrated a prolongation of the phase angle of melatonin rhythm in the medicated PD patients compared to the un-medicated PD group and controls.[29] Two other recent studies did not show alterations in the circadian phase of melatonin secretion.[30,31] Both studies, however reported decreased amplitudes of melatonin secretion. Further, compared with PD patients without excessive daytime sleepiness, patients with excessive sleepiness had significantly lower amplitudes and 24-hour melatonin area under the curve (AUC). Temperature, perhaps the most valid marker of endogenous circadian system, was also examined in the PD population. While 24-hour rhythms of core body temperature remain similar in PD relative to healthy controls [32], basal body temperature is significantly lower in parkinsonian patients. [33] PD patients with coexistent depression have altered circadian rhythms of rectal temperature and lower amplitudes of core body temperature. [34]

Circadian rhythms in Huntington's Disease

Huntington's disease (HD) is a neurodegenerative movement disorder characterized by abnormal involuntary movements, cognitive decline and behavioral/psychiatric dysfunction. Aside from these cardinal manifestations of the disease, impaired sleep and alertness are also common in the HD population. Up to 90% of patients with HD endorse sleep problems.[35] Despite these high numbers of HD patients affected by poor sleep, there is relatively small number of studies dedicated to sleep in HD. Available literature points to insomnia and excessive daytime somnolence. Few polysomnography studies reported reduced REM and slow wave sleep, prolonged sleep onset latency, sleep fragmentation, reduced sleep efficiency, and reduced total sleep time. Parasominas and sleep related movement disorders are rarely present in HD.

Circadian disruption in HD has neuroanatomical correlates, as postmortem studies documented reduced expression of vasoactive intestinal peptide (VIP) and arginine vasopressin (AVP), characteristic peptides in the SCN.[36] Actigraphy studies in HD patients reveal decreased level of daytime activity and increased overnight activity, leading to abnormal night-day activity ratios. Delayed sleep phase and increased REM latency have been reported in HD patients.[37] Phase delay seems to be present in both premanifest HD mutation carriers and HD patients.[35] Later wakeup times correlate with more prominent depressive symptoms, lower functional scores and cognitive performance. Changes in melatonin secretion were also reported.[37] Dim light melatonin onset is quite variable in HD

patients compared with controls. Moreover, concentrations of melatonin in serum are significantly decreased in HD patients, with manifest patients showing more significant reductions compared with premanifest HD mutation carriers.[38] Alterations in cortisol and adrenocorticotropic hormone have been found in HD.

Circadian rhythms in Alzheimer's disease

Alzheimer's disease (AD) is the most common form of neurodegenerative dementia and affects one in nine people aged ≥65 years.[39] Sleep and circadian disruption are very common in AD, affecting up to 40% of patients with mild to moderate dementia.[40] Disruption of the rest-activity cycles may be predictive of cognitive impairment / dementia. A large epidemiological study demonstrated increased risk of developing AD in the setting of fragmented sleep and others reported associations between impaired cognition and poor sleep quality, low sleep efficiency, and frequent daytime napping. [41-44]

Circadian dysregulation has a major impact on quality of life and represents a major reason for the institutionalization among the AD population.[45] Pathophysiological mechanisms which underlie disruption of circadian rhythmicity in AD have been well established and include neuronal cell loss within the SCN, loss of pineal gland function.[46,47] These changes within the SCN become more prominent with the progression of AD. Lack of zeitgebers necessary for the entrainment of the circadian system and co-existance of primary sleep disorders such as sleep disordered breathing are additional cause of circadian and sleep disruption in PD.

While the changes in circadian markers in AD mimic those observed in aging, the magnitude of these changes is enhanced in AD. Circadian rhythm of temperature shows phase delayed and dampened amplitude. The age related decline of melatonin is more pronounced in AD relative to healthy peers.[48,49] CSF melatonin levels are reduced in preclinical stages, and they continue to decrease with the progression of AD.[46,50,51] Alterations in amplitude and timing of cortisol and core body temperature are altered in AD as well.[52,53] There is a positive correlation between circadian rhythm disturbances and the degree of dementia in AD. [54-56] The amplitude of the rest-activity cycle is low in AD patient and circadian phase becomes progressively delayed throughout the course of the disease.[57] Further, sleep duration is reduced, fragmented and daytime becomes interspersed with frequent napping. Sleep interruption and naps during the daytime alter rest-activity rhythms leading to a reversal of the normal pattern of rest-activity, well documented in actigraphy studies conducted in the AD population.[56,58] Most prominent disruptions in the rest-activity cycles are evident in institutionalized patients with AD.

Emerging literature points to likely bi-directional relationship between AD and circadian dysregulation.[59] Studies that employed animal models of AD including transgenic APP/PS1 mouse model and the PLB1 triple knock-in model have shed additional light onto these associations.[60-62] The sleep-wake states influence amyloid dynamics, and there is well-establish Aβ rhythmicity in CSF.[60,63] Sleep deprivation promotes Aβ deposition into insoluble amyloid plaques, and therefore likely has a negative impact on cognitive decline.[64] Further, poor sleep quality and specifically, reduced slow wave sleep results in neuronal hyperexcitability during sleep, which is yet another mechanism that promotes greater release of Aβ.[65] Similarly, sleep deprivation leads to increased Aβ levels in healthy individuals and to markedly increased Aβ accumulation in AD.[66] Cognitively intact individuals who have evidence of amyloid plaques have worse quality of sleep, sleep efficiency and overnight awakenings compared with healthy controls.[67]

Several circadian-based interventions have been attempted to improve sleep-wake cycles and circadian function in AD. Melatonin seems not be effective at restoring rest-activity cycles in AD, as measured by actigraphy.[62,68] Light therapy may be effective in restoring circadian rest-activity behaviors but also in improving sleep quality in the AD population.[69-71]

Conclusions

Numerous studies have demonstrated the importance of healthy circadian rhythmicity in maintaining neurological homeostasis. Future research on chronobiology of neurodegenerative diseases will involve greater understanding of the role that circadian phenomena play at the cellular and molecular level in the pathogenesis of brain disorders. This will form the foundation for the development of new circadian-based interventions to improve clinical management of brain disorders. For example, with increasing understanding of the importance of circadian rhythmicity for brain health, one important direction will be to focus on the importance of chronopharmacology in neurological disorders. Already considered in other medical disciplines, time of day needs to be accounted for when considering side effects but also efficacy of pharmacological therapies for neurological disorders. Circadian system has therefore become a novel diagnostics and therapeutic target for neurological disorders.

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