Consequences of Circadian Disruption on Neurologic Health

Aleksandar Videnovic, MD, MSc[a,*], Phyllis C. Zee, MD, PhD[b]

KEYWORDS

• Circadian • Sleep • Clock genes • Cerebrovascular • Stroke • Alzheimer • Parkinson • Huntington

KEY POINTS

- Numerous brain diseases show a clear rhythmicity of symptoms and its outcomes seem to be influenced by the time of day.
- Circadian rhythm dysfunction is common in neurodegenerative disorders such as Alzheimer, Parkinson, and Huntington diseases.
- Circadian disruption may be a significant risk factor for cerebrovascular and neurodegenerative disorders.
- The circadian system may be a novel diagnosis and therapeutic target for neurologic diseases.

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. Twenty-four-hour diurnal fluctuations in symptom intensity, responsiveness to treatment modalities, and survival have been well documented. Important advances in circadian biology over the past several decades provide an opportunity to systematically investigate relationships between diseases, endogenous circadian rhythms, and exogenous influences. Many neurologic disorders show fluctuating rhythms of symptoms and responsiveness to therapies. This article outlines the available literature pertinent to circadian function in common neurologic disorders with an emphasis on cerebrovascular and neurodegenerative disorders.

CIRCADIAN DISRUPTION IN CEREBROVASCULAR DISEASE

Stroke is the third leading cause of death in the United States. Sleep disorders are common in people who have had strokes. Sleep dysfunction has also been repeatedly linked with cardiovascular and cerebrovascular insults and implicated in poststroke recovery. Although well recognized, the relationship between sleep, circadian disruption, and stroke is not fully understood. Sleep and circadian dysfunction may lead to vascular events through direct or indirect mechanisms. Sleep loss, sleep disordered breathing, and sleep-related movement disorders, such as restless legs syndrome and periodic limb movements disorder, may increase the risk of stroke, hypertension, and cardiovascular disorders.[1] Sleep loss itself seems to be an independent risk factor for cerebrovascular events, likely because of alterations in the autonomic nervous system and immune homeostasis.[2]

Emerging evidence suggests important effects that circadian homeostasis has on cerebrovascular health. Major cardiovascular parameters such as heart rate (HR), blood pressure (BP), and endothelial function, known to affect a wide range of cerebrovascular disorders, have intrinsic circadian properties. The onset of major cerebrovascular disorders frequently shows a unique diurnal

[a] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, 165 Cambridge Street, Suite 600, Boston, MA 02114, USA; [b] Northwestern University Feinberg School of Medicine, Abbott Hall 11th Floor, 710 North Lake Shore Drive, Chicago, IL 60611, USA
* Corresponding author.
E-mail address: avidenovic@mgh.harvard.edu

Sleep Med Clin 10 (2015) 469–480
http://dx.doi.org/10.1016/j.jsmc.2015.08.004
1556-407X/15/$ – see front matter

pattern. Both epidemiologic data and animal model data strongly point to circadian disruption as a risk factor for cerebrovascular disease.

Circadian Cardiovascular Rhythms

BP, HR, and baroreceptor sensitivity show robust physiologic oscillations over a 24-hour period.[3] Normally BP dips overnight, increases shortly before awakening, and reaches its maximum during midmorning hours. Individuals with nondipping BP pattern have less than 10% decline/increase in systolic BP and/or diastolic BP during sleep relative to their mean daytime BP levels. Nondipping BP rhythm is associated with cardiac ventricular hypertrophy, renal dysfunction, and alterations in the cerebral vasculature.[4] Individuals lacking the normal circadian rhythm of BP are therefore at increased risk for cerebrovascular events, which tend to occur in the early morning hours. Factors contributing to cerebrovascular insult, in particular ischemic events, follow a circadian pattern.

Circadian Variation in Stroke Onset

Diurnal variation in stroke onset has been reported in numerous studies, with higher frequency of stroke occurring in the morning.[5] Approximately 55% of all ischemic strokes, 34% of all hemorrhagic strokes, and 50% of all transient ischemic attacks occur between 06:00 and 12:00 hours.[6] Mortality from stroke remains high in strokes occurring in the morning hours.[7] Although stroke shows this clustering in the morning, some studies reported a bimodal distribution of stroke onset in hemorrhagic strokes with the second peak being in the afternoon.[8–12] The effects of recombinant tissue plasminogen activator treatment on outcomes have been independent of time of day of stroke onset.[13] Most investigations related to 24-hour patterns in stroke are centered on the time of day when stroke occurred, lacking relevant determinants of exogenous influences such as the rest/activity rhythm and other known risk factors.

Pathophysiologic factors that may explain a diurnal pattern of stroke onset include early morning increase in BP (so-called morning surge), increased platelet aggregation, and prothrombotic factors, as well as blunting of endothelial function in the morning hours. The peak level of circadian sympathetic activity also occurs in the morning, which along with the simultaneous increased activity of the renin-angiotensin-aldosterone activity influences the morning increase in BP and HR. Further, the propensity for rapid eye movement (REM) sleep increases in the early morning hours. This stage of sleep is associated with reduced coronary blood flow and increased occurrence of coronary spasm, which contributes to heightened sympathetic activity and increases in BP and HR. Primary sleep disorders, such as sleep disordered breathing, are additional causes, through repetitive intermittent overnight hypoxemia and sympathetic activation. Most of the available studies failed to show significant demographic and clinical differences between wake-up strokes and those occurring while awake.[5] Available studies have numerous methodological limitations, and better controlled prospective investigations are needed to distinguish between stoke present on awakening and those while awake. This distinction is important because these differences have potential implications for treatment.

Other circadian rhythms implicated in the pathophysiology of cerebrovascular disease include rhythms of plasma viscosity, blood flow volume, hematocrit, peripheral resistance, and platelet levels. Platelet numbers and aggregation both have rhythmicity, with peak number of platelets being in the afternoon. Platelet aggregation response to various stimuli tends to peak during the late night or early morning hours. Several factors within the coagulation pathways have their own circadian rhythms. For example, the peak activity of factor II remains in close correlation with the peak incidence of thromboembolic events.

Aside from circadian rhythms, cerebrovascular events are also linked with periodicities longer than circadian. For example, fibrinolysis has circaseptan (approximately 7-day) rhythm with the lowest amplitude of the rhythm on Monday and the peak between Tuesday and Thursday. This pattern mirrors that of thromoembolic events during the week. Similarly, circannual variations in cardiovascular parameters may affect the pathophysiology of vascular events.[14] Numerous studies reported 7-day and annual patterns in stroke onset. It is important to emphasize that many exogenous stressors affect the occurrence of cerebrovascular events, likely through complex interactions with endogenous circadian rhythms. These factors may include emotional stress, napping, physical activity, and medication schedules.

Clock Genes and Cardiovascular Function

Circadian transcription rhythms have been shown in 4% to 6% of protein coding genes in mouse heart and aorta.[15–17] Similar oscillations persist in endothelial and vascular smooth muscle cells as well as in human cardiomyocites.[18–20] Recent investigations suggest a role of the nuclear receptor PPARγ in BP rhythm regulation, likely through its interactions with Bmal1, a major circadian clock gene. Cry1/2 genes have also been implicated in the