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Literature Review

The Relationship of Cortisol Levels and Sleep Quality in Acute Ischemic Stroke Patients: A Literature Review

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Abstract

Hormonal factors are one of several elements that contribute to the process by which patients with acute ischemic stroke experience poor sleep quality. The hypothalamic-pituitary-adrenal (HPA) axis is responsible for producing the hormone cortisol. When the hypothalamus is activated, it releases vasopressin and Corticotropin Releasing Hormone (CRH), both of which influence Adrenocorticotropic Hormone (ACTH). This hormone triggers release of cortisol and other glucocorticoids by the adrenal glands. The HPA axis becomes engaged during an acute disease. Cortisol levels will rise as a result of HPA axis activation. Specifically, injury to the frontal or medial temporal lobes of the brain, as well as inflammation, or a lack of regulation of the HPA axis, can lead to this medical condition. Cortisol levels might remain elevated for up to seven days following the start of a stroke. An increase in cortisol levels is connected to an highly risk of stroke severity, length of hospital stay, and mortality in stroke patients. It is also an early warning sign of deteriorating sleep quality in patients with acute ischemic stroke.

Keywords: acute ischemic stroke, cortisol, clinical outcome, quality of sleep

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I. Introduction

Stroke can negatively impact sleep quality by disrupting the brain's ability to regulate the sleep cycle. Abnormal brain tissue may contribute to these problems.[1,2] Deterioration in sleep quality is reported in between 21–77% of stroke patients. There are 129 acute ischemic stroke patients, 65% of patients experienced sleep disordered breathing (SDB), 24% of patients experienced insomnia, 22% experienced hypersomnia, 13% experienced excessive daytime sleepiness. Acute ischemic stroke patients may experience a variety of sleep disorders, including hypersomnia, insomnia, sleep disruptions (SDB), and others. Sleep quality disorders can be diagnosed using a questionnaire and the gold standard is using polysomnography (PSG).[3]

According to a study that used the Pittsburgh Sleep Quality Index (PSQI) questionnaires and PSG. there were a total of 77% patients who suffered from acute ischemic stroke and reported to have decline in sleep quality. Research has shown that the PSQI is a relevant and reliable tool for evaluating patients with acute neurological conditions who have problems with their sleep quality. PSQI has also been used extensively by researchers to detect sleep disturbances in stroke patients.[4] Tests of validity and realibility have been done to PSQI in assessing sleep quality disorders in patient who have had acute brain lesions. Many researchers have widely used PSQI to identify sleep quality disorder in stroke patients.[5,6] PSQI has 86.5% specificity and 89.6% sensitivity. Hormonal variables are one of the components that contribute to poor sleep quality in individuals who have experienced an acute ischemic stroke. The HPA axis is responsible for producing the main hormone

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cortisol. Adrenocorticotropic hormone (ACTH) is influenced by vasopressin and Corticotropin Releasing Hormone (CRH), which are released when the hypothalamus is activated.[7] As a result of this hormone, adrenal glands will secrete cortisol and other glucocorticoids.

In studies conducted by Bradley Bush in 2010 and Julia Ross in 2014, the results showed that elevated cortisol levels were the main cause for poor sleep quality. A 2014 Danish study by Hanna Christense et al. found that cortisol levels rose in the first day after the start of stroke in 162 patients with acute ischemic stroke. cortisol levels elevated in the first day following the initiation of stroke in 162 patients with acute ischemic stroke.[8,9] Cortisol's negative feedback mechanism inhibits the pituitary and raphe nuclei from releasing ACTH and serotonin while also changing melatonin, resulting in poor sleep quality in acute ischemic stroke patients.

Sleep Disturbances in Acute Ischemic Stroke

Impaired sleep quality in acute ischemic stroke is one of the most frequent symptoms in 21–77% of patients and has an effect on outcomes and the stroke recovery process, with poor sleep quality associated with daytime sleepiness, decreased cognitive function and functional status. Previous research reported that poor sleep quality occurred in 32.8% of research subjects assessed by the Pittsburgh Sleep Quality Index (PSQI) questionnaire with a score of >5.8 Poor quality sleep may either increase the likelihood of having a stroke or becomes a direct result of one. Stroke survivors may experience several sleep problems such as Sleep Disordered Breathing (SDB), insomnia, hypersomnia, parasomnia, circadian rhythm sleep disturbance, and sleep-related movement disorder. A clinical study found the three most common sleep quality disorders in stroke patients, namely sleep apnea, excessive daytime sleepiness (EDS) and insomnia.. Breathing and ventilation problems during sleep are two things included in SDB These two things of breathing and ventilation are possibly include habitual snoring, obstructive sleep apnea (OSA) and centra; sleep apnea (CSA)[10,11] Insomnia is a disease characterized by difficulty falling asleep, difficulty staying asleep, waking up early in the morning, and not having restorative sleep even though you have plenty of time to sleep. Insomnia can be diagnosed using ESS, sleep diaries, polysomnograms and actigraphy. When a person has a stroke, neurochemical changes can occur in the brain, such as changes in biomarkers.

Changes in biomarkers that can contribute to disturbed sleep quality are changes in signaling of neurotransmitters such as hypocretin, changes in transcription and translation of the 23 Bmal1 & Cry1 genes, and decreased excretion of melatonin. There are also other factors that contribute to disturbed sleep quality in stroke,

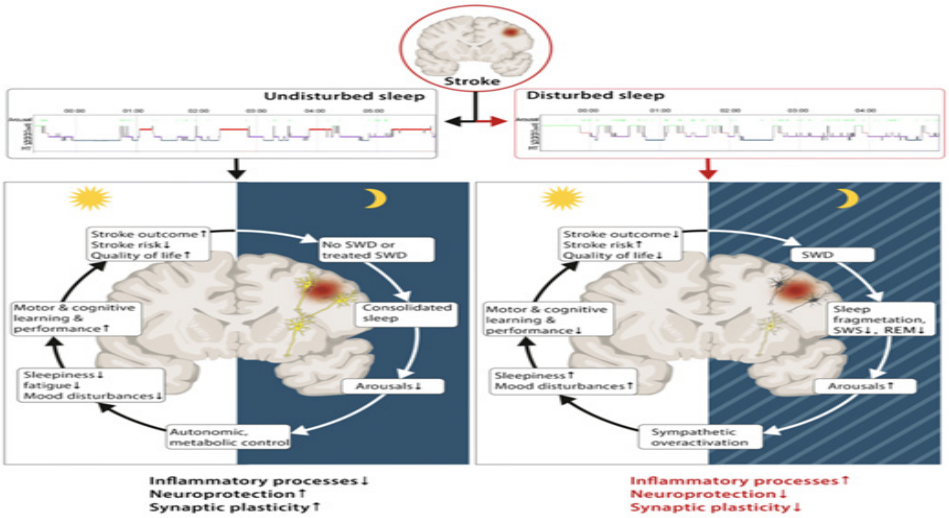

Figure 1. Sleep Disturbances in Acute Stroke.[3]

namely depression, pain, anxiety, and the hospital environment.[3,12]

Cortisol and Sleep Disturbances in Acute Ischemic Stroke

Cortisol is the main hormonal product from hypothalamic pituitary adrenal (HPA) axis. Hypothalamus activation will release corticotropin releasing hormone (CRH) and vasopressin which affect the anterior pituitary gland in secreting ACTH. This hormone will stimulate the adrenal glands to release glucocorticoids (cortisol).[13] Cortisol production is highest in the morning.

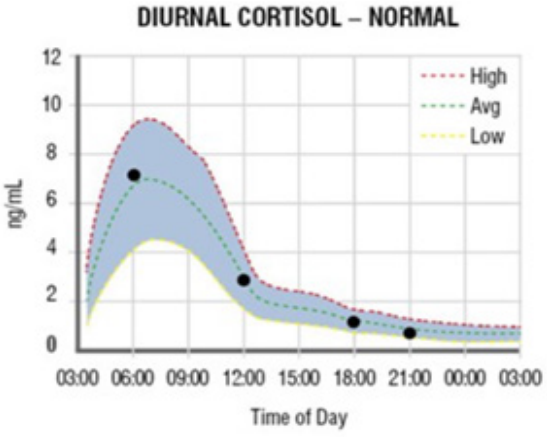

Figure 2. Cortisol Production.[14]

This cortisol pattern can be seen in normal adults. Normal conditions in adults reach a peak at 08.00 –09.00, namely 4.5–7.0 ng/ml with an average of 5.24 ng/ml and decrease starting at 12.00, namely <4 ng/ml.[7,14] The primary manner in which cortisol affects the central nervous system (CNS) is by causing changes in adrenal insufficiency, which manifest as slower rhythms on the electroencephalogram (EEG). Cortisol in the circadian rhythm plays a role in secretion and regulation. In addition, cortisol plays a role in providing a negative feedback effect on cytokines so as not to stimulate the pituitary to produce glucocorticoids. Negative feedback is also on serotonin so that if glucocorticoids are in large quantities, serotonin will decrease, while serotonin is related to melatonin production resulting in disruption of sleep initiation.[7,15]

In cases of severe and acute illness, the HPA axis is activated, leading to increased cortisol levels.

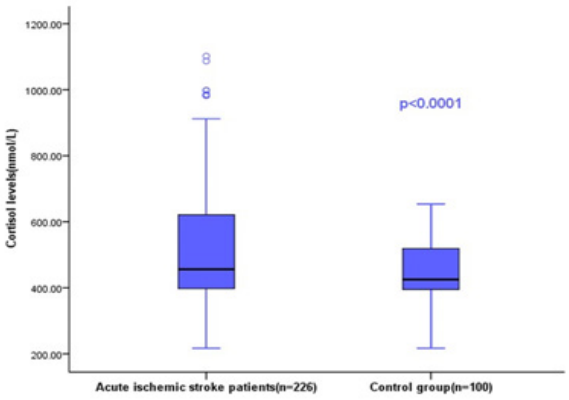

Figure 3. Production of Cortisol in Stroke Patients.[18]

Diurnal variation is observed in the HPA axis, which is coupled to the circadian cycle. Typically, cortisol production peaks in the morning and troughs in the afternoon.[16,17] There are several mechanisms that explain elevation in cortisol levels in acute ischemic stroke, namely activation of HPA axis pathway which secretes CRH. CRH together with vasopressin play a role in secreting ACTH into the systemic circulation. Initiation of cortisol synthesis is facilitated by ACTH in the adrenal cortex's fasciculate zone. It is believed that the HPA axis becomes active in acute ischemic stroke within a few hours of ischemia beginning. In these situations, elevated cortisol levels were generated by the release of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, according to studies conducted on rats that were made to undergo cerebral ischemia. The disorder is characterized by elevated blood cortisol levels. Patients with acute ischemic stroke experience a distinct cortisol elevation compared to healthy individuals.[18]

Typically, cortisol levels reach their lowest point about midnight, then gradually rise over the first two or three hours of sleep and stay high until waking up. Disruption of the sleep cycle can occur when there are elevated cortisol levels during minimum stress situations. Patients experiencing an ischemic stroke often exhibit this symptom, particularly in the initial stages following the

commencement of the stroke. After controlling for other variables, cortisol remains a distinct short-term predictor of functional outcome and mortality in Chinese patients suffering from acute ischemic stroke. The NIHSS clinical score can benefit greatly from the additional predictive information provided by the combined model. It is believed that this process leads to poor quality sleep in those who have experienced a post-ischemic stroke.[18] In addition, cortisol affects melatonin levels. Melatonin is known as a hormone produced by pineal gland. In humans, secretion of hormone melatonin is regulated by the suprachiasmatic nucleus (SCN) based on the light-dark time received by the intrinsic retinal photosensitive ganglion. Melatonin is produced when it is dark at night, and its production is inhibited by light during the day (photoinhibition mechanism). Melatonin synthesis is carried out based on timing by the SCN which is obtained through projections to the paraventricular nucleus of the hypothalamus which receives input from postsynaptic sympathetic fibers, which produce norepinephrine with a trigger in the form of dark conditions.[15,19]

Increased cortisol also affects serotonin. Serotonin is a neurotransmitter produced by nerve cells, especially in the substantia nigra, locus coeruleus, and subcoeruleus. Serotonin plays a role in the process of emotional regulation, hunger, sleep cycles, pain perception, as well as digestive tract secretions and motility. The telencephalon and diencephalon components of the brain are extensively innervated by serotonin (5HT) cell bodies, including the paraventricular nucleus of the hypothalamus which produces CRH. The innervation of the serotonergic system in the hypothalamus which produces CRH has led to the theory that serotonin 5HT can influence the HPA axis.[15] Serotonin precursors, namely 5HTP and tryptophan, are known to stimulate the hormone ACTH, which then increases the secretion of cortisol by the adrenals. Serotonin is produced from the metabolism of the amino acid L-tryptophan (Trp).[20] L-tryptophan itself is a substrate for serotonin and melatonin. In conditions of acute stress, the release of catecholamines will produce the effect of increasing cortisol, thereby suppressing the metabolism of Trp,. A drop in Trp can cause a decrease in melatonin, resulting in poor sleep quality.[20] A stroke in the ponto-mesencephalic region can cause loss of sleep dynamics and a stroke in the thalamus region causes disturbances in brain waves. In addition, lesions in the supratentorial or paramedian thalamus can reduce the duration of non-rapid eye movement (NREM) sleep and lesions in the right hemisphere cause a decrease in the duration of rapid eye movement (REM).[17] An overabundance of glutamate is released during an ischemic stroke. The protease, nuclease, and capcase enzymes are responsible for the cell death that occurs in neurons when glutamate levels are too high. Furthermore, an increase in glutamate has the additional impact of raising cortisol through the hormones CRH and ACTH, leading to disruption of the HPA axis. With patients with acute ischemic stroke, this results in serotonin and melatonin decreasing and impacts the quality of the patient's sleep. During the initial stages of a stroke, impairment in day-night perception could be caused by a disruption of peak melatonin release. Ischemia shortens the length of melatonin secretion and delays the peak of blood melatonin levels after therapy, according to research used rat models of ischemic stroke. Additional research is required to determine the mechanisms that cause melatonin levels and sleep quality to fluctuate after an ischemic stroke in individuals.[20]

Relationship between Cortisol and Impaired Sleep Quality in Acute Ischemic Stroke Patients

Hormone cortisol generally has property of increasing the production of various bone marrow products which can play a role in the adaptation process. Cortisol increases the production of erythrocytes, leukocytes, and platelets. Although it has an effect on increasing the number of blood cells including leukocytes, cortisol has the effect of increasing sequestration and apoptosis in several types of leukocytes, namely lymphocytes, esinophils, and basophils. Cortisol tends to reduce the functions of leukocytes, except neutrophils.[13] Apart from playing a role in regulating the body's metabolism, cortisol can affect the body's immune system. This effect is achieved by inhibiting the

production of T cells or T lymphocytes from the thymus. In addition, cortisol has the effect of downregulating histamine receptors, thereby reducing the chemotaxis of leukocytes.[17] The HPA axis is engaged in situations where disease develops suddenly. Cortisol levels will rise as a result of HPA axis activation. Specifically, damage to the frontal or medial temporal lobes of the brain, as well as inflammation, or a lack of regulation of the HPA axis, can lead to this illness. Even seven days following the start of a stroke, elevated cortisol levels are possible. Cortisol secretion will not return to its normal diurnal pattern until 7–14 days following the start of stroke. Stroke severity, length of hospital stay, and fatality rate are all positively correlated with cortisol levels.[18]

Plasma cortisol levels are negatively associated with neurological clinical symptoms, cognitive function, and emotional mental state in individuals with acute ischemic stroke. Furthermore, in ischemic stroke cases, the level of cortisol hormone release can be used to predict clinical outcome. Results showed a favorable correlation between the degree of hemiparesis and plasma cortisol levels measured between 7 am and 7 pm. are more likely to experience fatal outcomes if their serum cortisol levels are high. The specifics of this mechanism, nevertheless, remain unclear.[19] The relationship between cortisol and inflammation is complex. Cortisol plays a role in anti-inflammatory effects through cellular and transcriptional mechanisms. At the cellular level, cortisol triggers the induction of apoptosis of T lymphocytes, neutrophils, basophils, and eosinophils thereby reducing the inflammatory response. At the transcriptional level, cortisol has an anti-inflammatory effect through the mechanism of decreasing transcription of interleukin-1β (IL-1β), monocyte chemoattractant protein-1, macrophage inflammatory protein-2, and interferon-γ, thus producing effects in the form of reducing fever, inflammation, and cell proliferation, and lymphocyte activation. In addition, cortisol can reduce the inflammatory response by inhibiting MAPK and NF-κβ signaling pathways.[19] However, based on further research, it is known that cortisol has a bidirectional relationship with the immune system. Normal diurnal cortisol levels result in increased immune responses, including inflammation, whereas sudden increases in cortisol levels triggered by stressful conditions are associated with suppressed inflammatory responses and are able to produce protective effects against tissue damage due to prolonged inflammatory responses. Both effects are mediated by the signaling action of glucocorticoid receptors.[20]

Pro-inflammatory effects occur when there is acute exposure or hormone cortisol increase in a short time. There are 3 signaling pathways involved in the pro-inflammatory process by the hormone cortisol, namely Toll-like receptor-2 (TLR-2), NOD-like receptor-3 (RNLP3), and P2Y2R. In the TLR-2 signaling pathway, cortisol can increase the expression of TLR-2 in the cell membrane. This pathway plays a role in the mechanism of inflammation in response to components of the bacterial cell wall, in the form of peptidoglycan. In the RNLP3 and P2Y2R signaling pathways, the proinflammatory mechanism is not known with certainty. Both signaling pathways recognize ATP as a trigger. Cortisol will increase the sensitivity of macrophage cells to extracellular ATP thereby inducing the production of the pro-inflammatory cytokines IL-1β and IL-6 through both pathways.[20]

The proinflammatory effects of IL-1, IL-6, and TNF-a release produce cell dysfunction in the form of elevated glutamate.. Excess glutamate release activates the the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor AMPA and N-methyl-D-aspartate receptor NMDA, allowing calcium ions to enter the cell. Ca entering intracellularly causes cell death. In addition, glutamate increase is possibly cause dysregulation of the HPA axis by quicken CRH release in the hypothalamusCRH plays a role secreting ACTH into systemic circulation. Initiation of cortisol synthesis is facilitated by ACTH in the adrenal cortex's fasciculate zone. When cortisol levels are high, it has a detrimental effect on tryptophan bioavailability in brain tissue, which in turn lowers serotonin and melatonin levels, which disrupts sleep quality.

Furthermore, reduced serotonin has been linked to diseases such as anxiety disorders, depression, and gastrointestinal, all of which can be connected with sleep quality.[19,20] Elevated cortisol levels are associated with worse neurological outcomes and can be used as an early warning sign of worse sleep quality in acute ischemic stroke patients.[19]

Conclusion

An abrupt onset of disease triggers the HPA axis. Hormone cortisol levels rise in response to activation of HPA axis. An increase in cortisol levels is associated with worse neurological outcomes including more severe strokes, longer hospital stays, and higher mortality rates among stroke patients. It can also be used as an early warning sign of deteriorating sleep quality in patients with acute ischemic stroke. On the other hand, there is a negative correlation among cortisol plasma levels and neurological clinical conditions, cognitive function, and emotional state. Consequently, in cases of acute ischemic stroke, the level of cortisol hormone release can be used as a predictor of clinical outcomes

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