Early Detection of Sleep Disturbance May Act As Potent Biomarker for Alzheimer’s Diagnosis

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ABSTRACT

Alzheimer disease is an insidious heterogeneous neurodegenerative disorder that cause excessive undesirable production of certain proteins including Beta-amyloid and tau protein that ultimately results in the neuronal deterioration mostly in the hippocampus area of the brain which lead to the decline in the several brain activities specifically associated with memory impairment, problems related to reasoning, thinking, planning etc. After USA and China, India has the more cases of Alzheimer approximately 1.5 million Indians are suffered from this disease yet. Currently, according to the different research studies, the co-relation between sleep disturbance and Alzheimer has been found. A good quality of sleep enhances the brain health by maintaining metabolic homoeostasis. In this review, the study is focused on the topic that “how quality of sleep affects the Alzheimer disease”. Through the analysis of samples containing cerebrospinal fluid of different individuals specifically those who are feeling problems in sleeping or sleep deprivation, higher concentration of beta amyloid and tau proteins have been found as compared to normal individuals. In addition, certain studies on the mice also has been carried out which have been shown that the mice when undergoes sleep deprivation results in the twice the concentration of beta amyloid and tau proteins both are the main causes of pathology of Alzheimer disease. In fact, in AD patients sleep deprivation also varies on the basis of stages like in case of early onset of disease, individual sleeps more than normally and with the disease progression, it leads to more worsen state as the patient start sleeping the whole day and remain awaken throughout the whole night. However, there is a high risk of developing Alzheimer I case of insomnia. Currently, the different work has been done by various researchers shows that quality of sleep controls the generation of amyloid and tau protein. By controlling the problems associated with sleeping or proper sleep wake cycle may lower or reduce the risk of Alzheimer’s.

Keywords: Alzheimer disease, neurodegenerative disorder, sleep deprivation

How to cite this article: Manhas S, Khan ZA (2020): Early detection of sleep disturbance may act as potent biomarker for Alzheimer’s diagnosis, Ann Trop Med & Public Health; 23(S15): SP231531. DOI: http://doi.org/10.36295/ASRO.2020.231531

INTRODUCTION

Neurodegeneration is a Distarous mechanism that leads to the destruction of neurons results in the strongly decline in the brain activities by hindering the cell signaling pathways. Among the number of neurodegenerative diseases, Alzheimer is also affecting the today society at a very worst level with no proper cure. In addition to that, people who are exposed to this incurable disease feel lots of problems in their daily based activities due to worst reduction in cognitive functions (memory Impairment, difficulty in language and so on) that usually occurs due to neuronal loss in the hippocampus regions that controlled the memory processing, storage and many other functions. In spite...
of all these things, AD patient also feel problems in their sleeping patterns too that means start sleeping whole day and awaken during nocturnal sleeping. From different research studies, it has been concluded that a normal sleep deprivation also results in the increase uncontrolled abnormal production of beta-amyloid protein whose presence in brain highlighted the development of AD.

**Disturbance in Normal Sleep Wake Cycles during AD**

Disruption in sleep wake cycles is frequently examined and observed as a foremost symptom reported at the earliest stage during neurodegenerative disease that somehow shows an effective way to disclose the pathophysiology related to AD because circadian rhythm also controlled under the action of the neurons or neurotransmitters. Being a symptom of AD, Sleep wake cycle consists of two different mechanism that are controlled by different neurons and varied specific regions of brain that includes the neurons that particularly controlled the phenomenon of wakefulness are cholinergic neurons that are found in the basal region of forebrain and locus coeruleus of nor-epinephrine, laterodorsal and nuclei of pedunculopontine tegmental and potent role is displayed by the presence of orexin which is the neuronal peptide that causes wakefulness. Although neurons especially those that contain gamma –aminobutyric acid (GABA) promotes sleep that are located in the ventrolateral pre-optic nucleus. Sleep can be categorised into different categories that are Rapid eye movement sleep (REM) and Non-rapid eye movement Sleep (NREM). Ventrolateral pre-optic nucleus is promoted the NREM sleep to inhibit the pathways associate to ascending arousal. In other hand, Cholinergic neurons of latero-dorsal tegmental nuclei gets activated to mediate REM. Disruption in pattern of sleep like increase sleeping timing in different time varied fragments thus cause irregularity in sleeping patterns (sleep-wake cycles) that represent the high chances of developing REM sleep behaviour disorder (RBD) in many neurodegenerative related disorder [1].

**Disruption in Normal Sleeping Patterns may be recognized as an Early Symptom Associated with AD**

From different research studies, it has been recognized that during progression of Alzheimer Disease, sleeping problems also increase that causes the disturbance in normal sleep wake cycles by causing fragmentation in sleeping patterns thus results in the sleeping time increase throughout the whole day and keep awakening during night thus leads to increase in nocturnal awakenings and also REM and slow wave sleep gets disrupted or decreased. Although sleep disorder often develop in certain individuals in which sleep gets fragmented into three different bouts in the time period of 24 hours that results in the sundowning by which confusion get worst during the end of the day. The AD mouse model Tg2576 that has beta amyloid deposition in the brain showed the significantly increase in the circadian period and lacked in the delta power increase subsequent sleep deprivation as compared to normal mice that kept as a control model. On the basis of objective actigraphy data where the in case of AD, patterns associated with rest activity were measured which showed that fragmentation in sleeping patterns and reduction in the amplitude of rhythm associated with rest activity which correlated with the reduction in the cognitive activities and dementia. Interestingly, according to various reports it has been estimated that the disturbance in circadian rhythm and sleep disruption may appear earlier to the symptoms develop due to AD. On the basis of actigraphy study that had been conducted on 1,200 women with healthy status, it had been found that the reduction in the amplitude of...
circadian rhythm associated with rest activity at baseline that was correlated with increase the chances of developing dementia and destruction in the cognitive activities over the upcoming five years, these sleeping problems may be either the early symptom of disease or the risk factor associated with pathophysiology related to AD. In addition, for the cure of sleeping problems hypnotics is used but it may enhance or increase the risk of dementia but the exact mechanism that is associated with this is not clear yet. Furthermore, insomnia patients particularly those who are taken hypnotics for treating insomnia that increase the risk of development of dementia as compared to either normal individuals or individual with insomnia being evident. In addition, the frequently used of various neuroplectic medications as a source of treating sleeping disturbance that occur during dementia, these medications also increase the risk of morbidity and mortality in case of dementia patients. All these studies demonstrate that continuous use of these medications in order to treat sleeping problems will not help in the cure of disease but convert it into more worsen state.

**How Sleep Wake Cycle Affects the Regulation of Interstitial Fluid tau in case of Mice and Cerebrospinal Fluid Tau in Humans**

The research study was conducted to check that could sleep deprivation increase the level of tau protein which the hallmark of AD in which mouse ISF (interstitial fluid) was analyzed to check the level of tau protein in normal conditions or under normal wakefulness or in case of sleep deprivation. On the basis of this experimental approach, it was concluded that the ISF tau level increased about 90% in case of normal wakefulness in mice and it gets increased about 100% under sleep deprivation. In addition, the level of protein tau in the CSF (cerebrospinal fluid) also increased upto 50% in SD condition. Furthermore, it has been found that wakefulness in mice that is driven chemo genetically results in the significantly increase in the concentration of protein beta amyloid and tau protein [2].

**Sleep Deprivation induces the Progression of Alzheimer’s disease**

Sleep disorders somehow connected with the neurodegeneration as a risk factor contributing to the pathology of various neurodegenerative diseases including Alzheimer disease. Sleep deprivation in mice results in the increase level of β-amyloid and tau protein. Therefore, a experimental study was performed on mice to clarify the aggregation of β-amyloid in case of sleep deprivation in which Sprague Dawley rats (250-300g) were divided randomly into five groups: two groups related with SD condition, other two kept as a platform control group and the last one kept as home cage control group. In case of SD group, SD was induced by using the modified multiple platform method (MMPM). On the basis of this experimental study, it was found that Sleep deprivation leads to the aggregation of beta amyloid and strong decline in the cognitive activities or memory impairment that increase the risk of developing AD. The results of this study suggested that SD accelerates the AD progression through the modulation of the metabolism associated with β-amyloid [3].

**Monitoring Different Sleep Stages by Electroencephalography**

When the studies were conducted to check the variations in different stages of sleep by using electroencephalography and EEG also associated with two AD pathology causing proteins including β-amyloid and tau protein. For Instance, it has been found that the deposition of β-amyloid in APPswe/ PS1βE9 results in the sleep...
wake cycle disruption whereas taupathy increase in case of P301S tau transgenic mice was related with the reduced time in NREM (non-rapid eye movement) sleep and rapid eye movement sleep (REM) thus induce wakefulness and NREM slow wave activity decreased. In this research study, sleep wake activity was monitored in 119 participants at Knight Alzheimer’s Disease Research Centre at Washington University where EEG (Advanced Brain Monitoring, Sleep profiler) that was worn on the forehead was used to monitor the slow wave activity over six nights. In addition, participants who undertaken apolipoprotein E genotyping, cognitive testing, AD biomarker assessment in CSF[Aß42, tau or phosphorylated tau] or PET scans with \[^{18}\text{F}\] and traces of tau also analyzed. In this study, it was hypothesized that reduction in the non-rapid eye movement and slow wave activity may lead to the increase in tau pathology. On the basis of CSF biomarkers and PET imaging, it has been found that there is an inverse relationship between AD pathology and NREM SWA. Accumulation or aggregation of beta amyloid and tau in brain cause decrease in the NREM SWA [4].

**How Sleep Deprivation leads to Tau Pathology?**
Disturbance in circadian rhythm and sleep in older age is associated with the impairment in the cognitive activities [5]. In addition, numerous studies have been conducted to link the relationship between disturbance in sleep and circadian rhythms with the abnormal production of beta-amyloid that is one of the recognized hallmarks of AD neurodegeneration. Recent experimental studies suggested that disruption in sleep wake cycle leads to the significantly increase the abnormal concentration of tau protein as compared to Aß-amyloid that cause AD progression and impairment in the brain activities [5]. Several different studies have implied that restricted sleep enhance the β-amyloid deposition in different area of brain thus leads to the development of neuro-fibrillary tangles that is the micro-structure observed during AD pathogenesis [6]. In addition, it has been estimated that the involvement of various risk factors like reactive oxygen species, Apolipoprotein E, damages in endoplasmic reticulum, inefficacy of orexinergic system, phosphatase and kinase dysregulation and due to dysfunctioning in glymphatic system all these act as a mediator in between these conditions [6].

**Relationship between Obstructive Sleep Apnea, Slow Wave Activity and Aß-Clearance:**
Obstructive sleep apnea halts the mechanism of beta-amyloid clearance from brain that ultimately cause problems in sleeping patterns specifically in slow wave cycle and increase in the beta-amyloid concentration in a abnormal way [7]. A study was conducted in which OSA (obstructive sleep apnea) treatment was given continuously upto 4 months, and then examined the beta-amyloid concentration in the cerebrospinal fluid and slow wave cycle. The results showed increase in the slow wave cycle that was correlated with the reduction in the beta-amyloid concentration. The research model showed that greater reduction in the OSA led to the greater reduction in the beta-amyloid concentration [7].

**Role of Orexin A and Adenosine A (1) Receptor in Sleep Disorder and AD:**
An experimental research study was conducted on cell and animal models to evaluate the correlation between amlyoid-ß and sleep disruption. Through observation, it was found that Aß25-35 administration remarkable reduced the NREM (non-rapid eye movement) while in other way, it also induced wakefulness in mice. In addition, on the
basis of reverse transcription-quantitative polymerase chain reaction with western blot analysis disclosed the upregulated expression of various different potent factors like tau, phosphorylated tau and neurons of orexin A express A(1) receptor when it was compared to the samples obtained from the mice that kept as a control [8]. Furthermore, when human neuroblastoma SH-SY5Y were treated with Aβ25-35, the results revealed the increase in the expression level of orexin A, Adenosine A (1) receptor, phosphorylated tau and the tau when it was compared with cells kept as control. Inspite of Tau and β-amyloid, orexin A may act as a potent biomarker. Further, more research is needed.

**Relation of Dysfunctional Hypothalamus with Impairment in Sleep and CSF Biomarkers**

All the homeostatic functions are controlled by the brain hypothalamus region including circadian rhythms. The regions of the brain that control the sleep wake cycle get affected due to AD pathology. The post-mortem studies revealed the association between AD and Sleep wake rhythms. In this experimental study, 2-deoxy-2-(18F) fluoro-D-glucose ([18 F] FDG) positron emission tomography was used to induce in vivo alterations in hypothalamus and then detected its co-relation with CSF biomarkers and sleep impairment in which sleep was measured by using polysomnography [9]. It was documented that there was remarkable reduction in the hypothalamic ([18F] FDG) PET uptake in case of AD patients (n=18) compared to controls (n=18) (p<0.01). Moreover, it has been found that increase level of orexin A in the CSF cause alteration in the nocturnal sleep in case of people who suffered from AD. According to vivo report, due to hypothalamus dysfunctioning in Alzheimer’s get destroyed the connections with limbic system that is associated with nocturnal sleep disruption and CSF AD biomarkers [9].

**Orexin A levels in the CSF Fluid and AD Pathology:**
An experimental study was performed on 82 patients in which 41 AD patients, 41 suffered from mild cognitive impairment, 24 affected with other neurological disorder and rest of 24 kept as control. The various different proteins levels were checked including orexin that revealed that orexin A was associated with amyloid β42. The concentration of orexin A was found high in MCI and AD patients as compared to OND (other neurological disorder) than in controls. In addition, it revealed that increase in sleep duration during nighttime was negatively affected the beta amyloid [10]. At the very early stage of AD, sleep wake cycle disruption get started that should be detected. For this, further investigations are required to properly and deeply describe the mechanism inter-related with AD and sleep wake cycle.

**Co-relation between β-amyloid Diurnal pattern and β-amyloid kinetics**
To evaluate the relation between beta-amyloid kinetics, amyloid concentration and Aβ diurnal patterns in humans, experiment was performed on 77 individuals under the age of 60 to 87 years with and without amyloid beta deposition by using mass spectrophotometer. The findings that obtained were compared by two orthogonal methods; those were mass spectrometry and enzyme-linked immunosorbant assay. Out of 77 adult participants, 46 (59.7%) were male, and 72.6 (60.4-87.7) years was the mean range. In addition, mass spectrophotometer method was more useful to define the diurnal patterns in the concentration of beta-amyloid as compared to enzyme assay (mean difference found in SD residuals: Aβ-42, -3.72 pM; P<0.001; Aβ-40, -7.42pM; P<.001). Deposition of beta-
Amyloid decreased day/night amplitude and linear rise of Aβ42 not the Aβ-40. Day/night amplitude age reduction increased in both Aβ-42 and Aβ40. After controlling for amyloid deposition, Aβ-40 amplitude was related positively to the production rates (r = 0.42; P < .001), while the linear increase was related with turnover rates (r = 0.28; P < .05). The amplitude and linear increase of Aβ-42 were both connected with turnover (r = -0.38; P < .001) and production (r = 0.238; P < .05) rates [11].

**CONCLUSION**

In AD patients, sleep disruption is very common but on the basis of certain evidences and experimental studies, it has been found that a normal wakefulness results in the increase production of protein beta-amyloid and tau also. But yet it is not clear that sleep may be the symptom of AD, or primary cause of AD. By analyzing those proteins that control the normal wakefulness or sleeping patterns and comparing their concentration or presence in case of AD, better approach to check the effect of sleep disruption in AD. More experimental studies should be conducted in this field by analyzing the different protein concentration or involvement of certain receptors or transcriptional factors or specified enzymes and evaluate them in both the cases (Insomnia and Alzheimer’s disease).

**REFERENCES**
