IMPLICATION OF IL-6 NEUROINFLAMMATION IN THE CONTEXT OF INSOMNIA AS A RISK FACTOR FOR NEURODEGENERATION

by

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Abstract

Sleep is a complex and required physiological process that is important for the health and function of a person. Disturbances in sleep have been linked to neurodegenerative diseases, yet it is unknown through what mechanism insomnia may be playing a role in this pathology. Recently, there has been emphasis in the field implicating disrupted metabolite clearance during slow wave sleep (SWS) in neurodegenerative diseases. However, the context of inflammation, specifically the pro-inflammatory cytokine IL-6, a known mediator of sleepiness, may provide important insight into sleep's role in neurodegenerative diseases.

I. Introduction

Sleep disturbances have long been associated with neurodegenerative diseases, with Alzheimer's being the most common neurodegenerative disorder, affecting approximately 50 million persons worldwide ("Dementia" 2020, "Neurodegenerative Diseases" 2021). The term insomnia can encompass many of these sleep disturbance symptoms, including difficulty falling asleep and maintaining sleep (Schutte-Rodin S. et al. 2008). A 2011 study found that the presence of insomnia was significantly associated with Alzheimer's disease and that insomnia as a comorbidity was also associated with a faster progression of neurodegeneration (Osorio, R. et al. 2011). These findings were further supported in a 2019 meta-analysis, where insomnia was found to be a significant risk factor of neurodegenerative diseases as a whole (Shamim, S.A. et al. 2019). Recent research within the field continues to support insomnia and sleep fragmentation, a subset of insomnia, as a risk factor for neurodegenerative diseases, yet it is unknown through what mechanism insomnia may be contributing to this pathology.

Currently, one of the most popular theories within the field implicates the disruption of metabolite clearance during slow wave sleep (SWS), when metabolite clearance is known to be high, in the development of neurodegenerative diseases (Xie, L. et al. 2013). However, inflammation provides important context to metabolic clearance that has not yet been explored. Importantly, the removal of toxic waste products involves the glymphatic system, which includes the cerebrospinal fluid (CSF), where cytokines circulate. Cytokines are an integral part of innate immunity that work to prevent the spread of foreign bodies in a non-specific fashion, or in response to tissue injury. Cytokines have the ability to influence the central nervous system sleep processes and vice versa, as the presence and release of cytokines is not limited to the peripheral

blood mononuclear cells, but also includes the peripheral nerves and the brain, where neuronal and glial sources for various cytokines and their soluble receptors are expressed (Marshall, L. and Born, J. 2002). In particular, the pro-inflammatory cytokine IL-6 has been heavily implicated in both insomnia and neurodegenerative disease. In this thesis, I will summarize the data from previous studies to provide evidence that insomnia is a driving factor for inflammation through IL-6 signaling and subsequent neurodegeneration. The general overview of this information is provided in Figure 1. Currently, there are no published data on this potential mechanism of disease, although there are multiple studies that investigate IL-6 in the context of sleep, as well as unrelated studies that investigate neurodegenerative diseases in the context of inflammation.

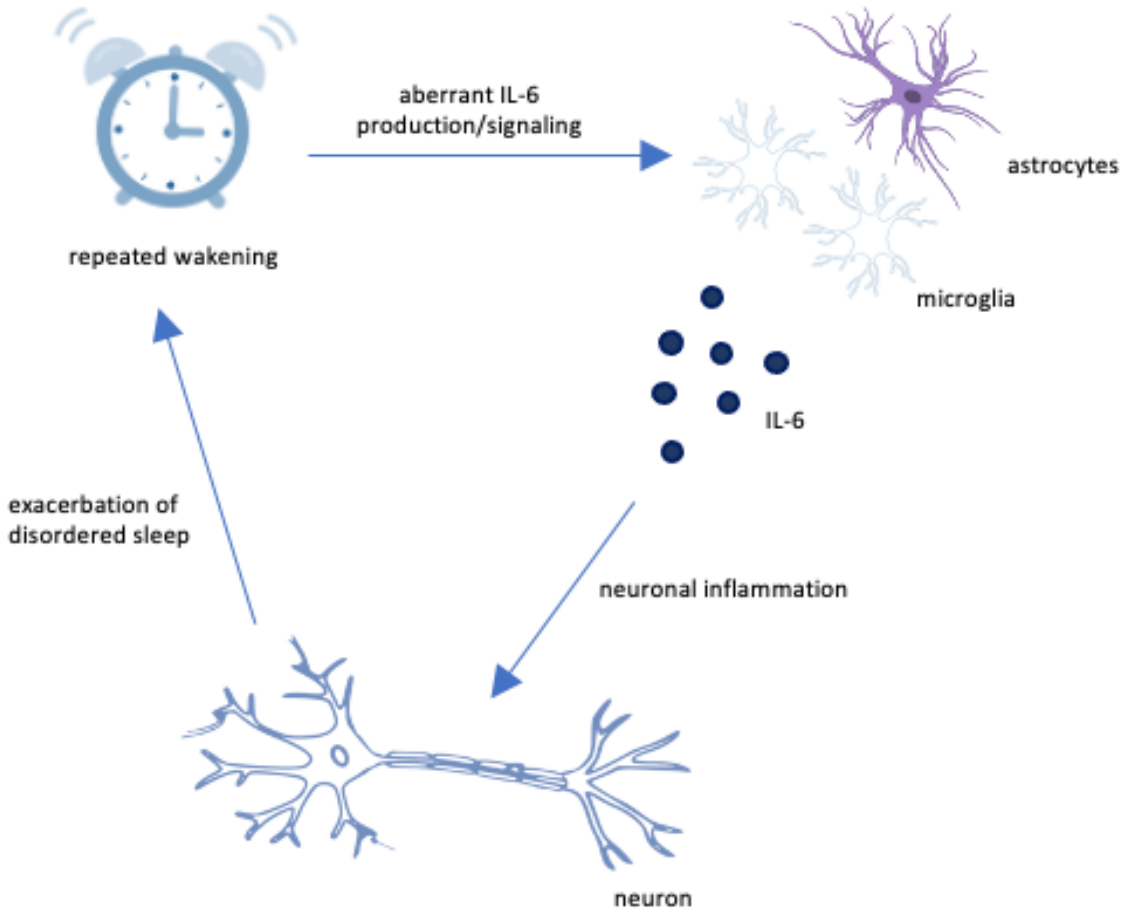

Figure 1. *Overview of the contribution of IL-6 neuroinflammation in the context of insomnia as a risk factor for neurodegeneration*. Repeated wakening during SWS of deep non-REM sleep leads to the aberrant signaling and increased production of the pro-inflammatory cytokine, IL-6, by microglia and astrocytes. These changes in IL-6 production and signaling, separate from its natural circadian rhythm, interfere with blood brain barrier function. The extent and location of the ensuing local damage might facilitate disease processes. These dynamics might be compounded (still further) by sleep fragmentation SWS when metabolite clearance is high. The resulting neurodegeneration then exacerbates the disordered sleep symptoms.

II. Methods

Study Selection

A search strategy was implemented to identify studies that either examined sleep in the context of neurodegeneration and/or sleep disturbances in the context of IL-6. Research papers and reviews were found primarily through Mendeley, a free resource manager, as well as reference lists of included articles. The following search terms were used: “sleep fragmentation and neurodegeneration”, “sleep and Alzheimer’s”, “sleep and Parkinson’s”, “sleep and dementia”, “sleep and IL-6”, “neurodegeneration and IL-6”, “IL-6 and Alzheimer’s”, “IL-6 and Parkinson’s”, “IL-6 and dementia”. Limits were imposed based on the English language and any publication year prior to 1990.

III. Background on Sleep

A. Overview of Sleep and Its Circadian Rhythm

Sleep is a complex and required physiological process that is important for the health and function of a person. According to Cirelli and Tononi, sleep can be defined as a “reversible condition of reduced responsiveness usually associated with immobility” that can be further

distinguished both from quiet wakefulness and coma (Cirelli, C. et al. 2008). Yet the process of sleep is not unique to humans, with the criteria for sleep or a sleep-like state having been studied and met in birds, fishes, reptiles, and as well as invertebrates, like flies, honeybees, and cockroaches. In particular, *Drosophila melanogaster* mimic a sleep-state that is similar to mammals, including behavioral, genetic and electrophysical changes between sleep and wakefulness (Cirelli, C. et al. 2008). The dynamic process of sleep in humans is coordinated through many structures and systems within the brain. The brain stem, thalamus, cerebral cortex, basal forebrain, midbrain, and amygdala all play important roles in the sleep/wake cycle, as well as contribute to important bodily functions during sleep. Importantly, the suprachiasmatic nucleus (SCN), a cluster of thousands of cells within the hypothalamus, is the master or central clock of the circadian pacemaker system, with normal circadian rhythm being crucial to the timing and alignment of sleep with the biological night (Ralph, M.R. et al 1990).

Sleep can be further defined by its stages. Rapid eye movement (REM) is a characteristic of the time during sleep when a person has a waking-like EEG pattern coupled with active suppression of skeletal muscle activity. The skeletal motor atonia prevents the enactment of the vivid dreams that can occur during this stage of sleep. During REM sleep, there is an elevated arousal threshold, as well as autonomic and respiratory activation and fluctuations in brain/body temperature (Peever, J., and Fuller, P.M. 2017). REM sleep occurs more frequently as sleep progresses through the night, and alternates with the stages of non-REM sleep, as seen in Figure 2 (Peever, J., and Fuller, P.M. 2017, Wagner, U. et al. 2001). Non-REM sleep is separated into four stages, 1-4, with stages 3 and 4 compromising deep sleep. Deep sleep dominates the first half of the sleep period, and is characterized by slow wave activity, comprised of high oscillations and slow oscillations (Plihal, W. and Born, J. 1999, Scammell, T.E. et al. 2017).

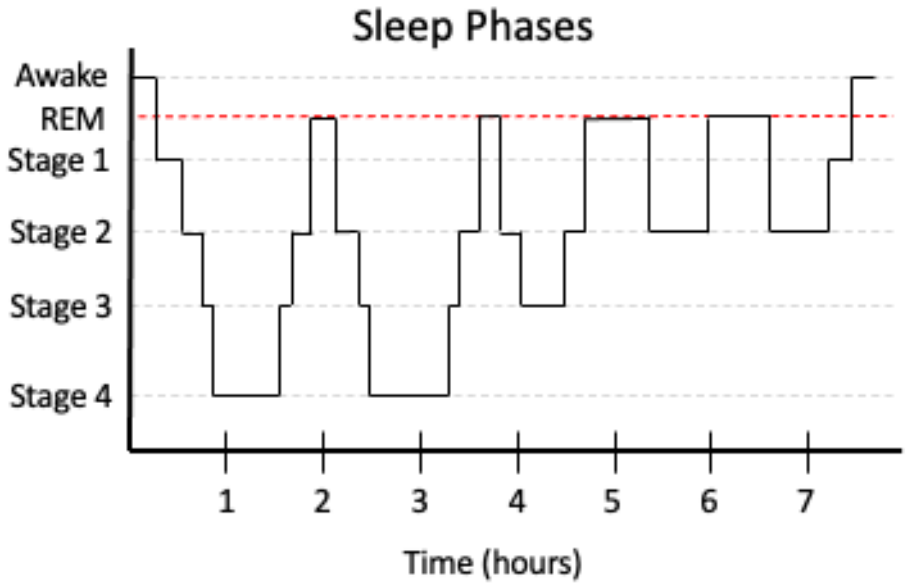

Figure 2. *Typical human sleep phases through an average night.*

B. Sleep and Memory

Sleep is a major contributor to learning and memory consolidation (Gais, S. et al. 2006, Benedict, C. et al. 2009, Marshall, L. and Born, J. 2007). Hippocampus-dependent declarative memory is enhanced when sleep follows within a few hours of learning, independent of time of day. In particular, slow-wave sleep, which is characterized by high voltage and slow oscillations, is supportive of memory consolidation (Gais, S. et al. 2006, Born, J. et al. 2006). Investigation into splitting sleep between a nocturnal period (5-h sleep opportunity) and a short daytime nap (1.5-h sleep opportunity) in sleep-restricted school children resulted in better recall of learned material compared to a purely nocturnal schedule with the same total sleep (6.5-h). This improvement was specifically seen for declarative information learned after the nap in the

afternoon, but did not negatively impact morning learning (Cousins, J.N. et al. 2019).

Importantly, SWS, which dominates the first half of the sleep period, contributes to the consolidation of hippocampus-dependent declarative memories (Plihal, W. and Born, J. 1999, Marshall, L. and Born, J. 2007). During SWS, memory representations are strengthened within neocortical networks through the neuronal reactivation of recent episodic memories. Here, slow wave oscillations synchronize hippocampal-to-neocortical dialogue as to link disparate components of a memory into a unitized cortical representation (Marshall, L. and Born, J. 2007). The emotional aspects of memory, which are amygdala-dependent, as well as procedural memory, which is striatum-dependent, are proposed to benefit preferentially from the second half of the sleep period, i.e., rich in rapid eye movement (REM) sleep (Plihal, W. et al. 1999, Wagner, U. et al. 2001).

IV. IL-6 Signaling

Microglia are the principal immune cells of the brain, acting to survey the microenvironment. When stimulated, they undergo morphological and functional changes, one of which is the release of pro-inflammatory cytokines (Lynch, M.A. et al. 2010). IL-6 is secreted upon microglia activation, as well as astrocyte activation, and plays a critical role in the generation of inflammation (Tanaka, T. et al. 2014). Importantly, IL-6 activity can only occur in the presence of the IL-6 receptor (IL-6Rα) and gp130, a ubiquitously expressed receptor, on the surface of the cell membrane (Murakami, M. et al. 2019). IL-6 signaling through a membrane bound IL-6Rα and gp130 receptor is defined as classic signaling, represented in Figure 2. However, in addition to the membrane bound form of IL-6Rα, there exists a soluble form of this receptor (sIL-Rα),

expressed as two distinct isoforms (McLoughlin, R.M. et al. 2004). IL-6 complexed with the soluble form of IL-6Rα (sIL-6Rα) can act on cells expressing only gp130, a process referred to as trans-signaling, as demonstrated in Figure 3. Furthermore, it has been demonstrated in certain cell types, such as dendrites, that IL-6 bound to cell surface IL-6Rα can act on a separate cell that expresses gp130 in a manner consistent with the IL-6–sIL-6Rα complex (Heink, S. et al. 2017).

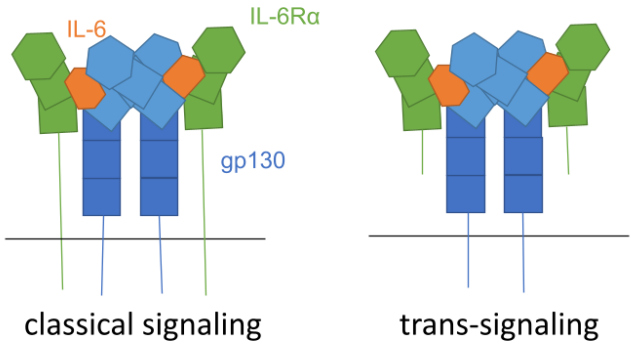

Figure 3. *IL-6 receptor and signaling*. Reproduced from Hirano, T. 2020.

The robust (and sometimes contradictory) role of IL-6 is likely stemming from the multiple soluble receptor isoforms of IL-6, as well as the diverse ways in which IL-6 signaling can occur. This can further be explained by the distinct and separate circadian rhythms of IL-6 plasma and cerebrospinal fluid (CSF) levels in humans. Plasma IL-6 levels follow a biphasic, 12-h, rhythm with peaks at 4pm and 4am, while CSF IL-6 levels follow a dominant, 24-h, rhythm that peaks at approximately 7pm. These differences in human plasma and CSF IL-6 levels suggest local sources of IL-6 production within the CNS (Agorastos, A. et al. 2014).

V. Implication of Insomnia in Neurodegenerative Disease

Sleep disturbances are associated with neurodegenerative disease, but it has yet to be elucidated if these sleep disturbances are secondary to neurodegeneration or causal. Evidence continues to support insomnia as a risk factor for neurodegeneration, although this analysis is most often focused on insomnia as a risk factor for dementia. In a recently published longitudinal study, with >8000 participants, it was found that short sleep duration in midlife was associated with a higher risk of dementia later in life, with short sleep being defined as ≤6 hours (Sabia, S. et al. 2021). However, sleep fragmentation was not investigated within this study, and conclusions from this correlative study could only be made about sleep duration as a whole. This evidence is consistent with subjective complaints of insomnia, where men with sleep disturbance complaints had a 33% increased risk of dementia overall and a 51% increased risk of Alzheimer's disease as compared to people without insomnia (Benedict, C. et al. 2015). Furthermore, in a recent meta-analysis, people with insomnia and other sleep problems, were found to have a 1.68-fold higher risk of developing Alzheimer's or cognitive impairment (Bubu, O.M. et al. 2017). In addition, it has been demonstrated in humans that sleep deprivation - even for a single night - leads to increased deposition of beta amyloid proteins within the interstitial space between brain cells (Shokri-Kojori, E. et al. 2018). Beta-amyloid plaques, together with neurofibrillary tangles, comprise the hallmarks of Alzheimer's disease neurohistopatholgy. Amyloid deposition after sleep loss appears to be a generalized phenomenon across animal models that have been tested, including murine and drosophila models (Kang, J.E. et al. 2009, Tabuchi, M. 2015).

Yet, sleep deprivation does not comprise the entirety of insomnia disorder. Sleep fragmentation, in the context of insomnia, has been implicated in people with neurodegenerative diseases. Over

a six-year period, patients with severe sleep fragmentation (90th percentile) demonstrated a 1.5-fold higher risk of developing Alzheimer's disease as compared to patients with low sleep fragmentation (10th percentile) (Lim, A.S. et al. 2013). In addition, disruption to slow wave activity, which typically occurs during non-REM sleep stage 3 sleep, is positively correlated with the amount of soluble beta amyloid found in the cerebrospinal fluid (CSF) (Ju, Y.E.S. et al. 2017). Slow wave sleep (SWS) decreases appear to begin as early as midlife and this natural aging phenomenon may be exacerbated by sleep disturbances, resulting in high risk of dementia seen in persons who have chronic insomnia during midlife (Ancoli-Israel, S. et al. 2008, Schutte-Rodin, S.L. et al. 2008). However, contrary to the emphasis of slow wave sleep in neurodegeneration, lower REM sleep percentage and longer REM sleep latency, i.e., delayed onset of REM sleep, have also been connected to a higher risk of newly diagnosed cases of dementia. Each percentage reduction in REM was associated with a ~9% increase in risk (Pase, M.P. et al. 2017). It has been hypothesized that significantly prolonged REM sleep latency may be a reflection of early and subtle REM sleep fragmentation (Gupta, M.A. et al., 2018). These data run against the theory of dysregulated metabolic clearance during SWS as playing a causal in neurodegenerative diseases. However, it cannot be ruled out that the metabolic clearance of CNS waste was inappropriate during these 'normal' times of SWS, and either might have contributed to irregularities in REM sleep or compounded them. Yet, these studies provide clarity that the fragmentation of the sleep itself is linked to neurodegenerative disease.

In persons with Parkinson's disease the presence of insomnia was found to be an important and independent predictor of poor health related quality of life (Forsaa, E.B. et al. 2008). People with chronic insomnia were at the highest risk among other non-apnea sleep disorders for developing

Parkinson's disease in the future (Hsiao, Y.H. et al. 2017). Additionally, REM Sleep Behavior Disorder (RBD), where muscle inhibition is lost during the dream state, is a prominent and early feature that affects approximately half of all people who will be diagnosed with Parkinson's disease (Plihal, W. and Born, J. 1999). Patients with Parkinson's and concomitant RBD showed significantly poorer clinical performance compared to both patients with Parkinson's without RBD and control subjects (Vendette, M. et al. 2007). In addition, neurodegenerative diseases, like Parkinson's disease, often include a motor component, independent of RBD, and the amount of stage 2 non-REM sleep, particularly late at night, is predictive of motor skill performance in healthy individuals (Walker, M.P. et al. 2002). Importantly, stage 2 non-REM sleep does not involve slow wave activity.

VI. Implication of IL-6 in Sleep Disorders

A. Insomnia

Regarding insomnia, a meta-analysis of sleep cohort studies showed that symptom reporting of sleep disturbances was associated with higher levels of plasma IL-6. Within this same meta-analysis, short sleep duration was also associated with higher levels of IL-6 (Irwin, M.R. et al. 2016). In a 2013 study investigating the blood transcriptome after short-term sleep deprivation, plasma IL-6 expression was significantly up-regulated in sleep-deprived participants in comparison to their baseline 'normal' sleep state (Möller-Levet et al. 2013). Pharmacological administration of low dose recombinant IL-6 in healthy adult men has been shown to lead to a reduction in the percentage of time spent in REM sleep while also increasing the latency of REM sleep. In addition, with the administration of low dose recombinant IL-6, SWS shifted, from dominating during the first part of the night, to the second part of the night. Subjects also

reported fatigue, difficulty concentrating and felt overall more lethargic after IL-6 administration in comparison to placebo (Späth-Schwalbe, E. et al. 1998). This evidence may also support an IL-6 link to sleep disturbances in patients with frontotemporal dementia (FTD), who rarely have REM sleep disorders, but do exhibit delayed sleep phasing (McCarter, S.J. et al. 2016; Anderson, K.N. et al. 2009). However, this information of acute or chronic plasma IL-6 levels is important to discuss in the context of the circadian rhythm of IL-6 production and its receptor, as well as the circadian rhythms within the immune system. Most infectious processes, particularly during the acute phase of the immune response, alter sleep patterns, prolonging the duration of SWS. In addition, secretions of IL-1β, IL-10, IL-12 and TNFα by monocytes and dendritic cells peak during sleep, independent of circadian rhythms. Importantly, IL-1β, TNFα and IFNα increase the duration of non-REM sleep. In addition, the levels of plasma IL-6 may not be reflective of the IL-6 levels in the CSF that recirculates around the brain.

IL-6 is a known mediator of sleepiness, whose plasma levels increase with age (Tanaka, T. et al. 2014). In a study conducted in mouse models, high IL-6 levels in the brain, blood and adipose tissue correlated with times predominantly occupied by sleep (Guan, Z. et al. 2005). It has also been shown that sleep enhances the effects of IL-6 on cells expressing membrane gp130, in a pro-inflammatory trans-signaling manner. Soluble IL-6 receptors (sIL-6Rα) are also distinctly up-regulated during the late night of human sleep (Dimitrov, S. et al. 2006). This allows for cells that do not express membrane-bound IL-6 receptors to have the ability to respond to IL-6, integrating actions between the immune system and central nervous system that are not usually present during wakefulness. The immune response, including production of cytokines, is also regulated in a circadian manner, as previously discussed in the context of IL-6 production. For

example, isolated macrophages exhibit rhythms in clock gene expression, phagocytic activity, and response to the bacterial endotoxin lipopolysaccharide (LPS). Importantly, LPS induces macrophage release of IL-6. In experiments using an environmental circadian disruption (ECD) model, where the light:dark cycle was advanced 6 hours 4 times weekly, LPS-induced inflammatory responses in mice in vivo and in isolated macrophages ex vivo were elevated. ECD increased the overall level of LPS-induced IL-6 release by increasing immune cell responsiveness and not by affecting immune cell number or the circadian regulation of this rhythm (Adams, K.L. et al. 2013).

B. Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder. It is characterized by episodes of interrupted breathing (apnea) or reductions in airflow (hypopnea). The severity of OSA is classified using the Apnea-Hypopnea Index (AHI). Repeated apneic and/or hypopnea events throughout the night lead to sleep fragmentation as well as hypoxia (Kimoff, R.J. et al. 1996). OSA is associated with neurodegenerative diseases, including Alzheimer's, Parkinson’s, and Multiple Sclerosis (MS) (Abrams, B. et al. 2005, Sheu, J.J. et al. 2015, Dias, R.A. et al. 2012). Women with OSA over a 5-year study were at a greater risk of developing Parkinson’s disease relative to women without OSA (Sheu, J.J. et al. 2015). In addition, levels of tau, a hallmark of Alzheimer’s, are elevated in young adults with moderate to severe sleep apnea (Motamedi, V. et al. 2018).

IL-6 levels are positively correlated with AHI severity in people with OSA and the expression of IL-6 is enriched in the upper airway of OSA patients (Sharma, D. et al. 2020, Kimoff, R.J. et al.

2011). In addition, the IL-6 gene polymorphism -174 G/C is associated with adult risk for OSA, and sIL-6R levels increase after just one night of sleep-disordered breathing (Zhong, A. et al. 2016). Continuous positive airway pressure (CPAP) therapy is an effective treatment for obstructive sleep apnea and is the current "golden-standard" (Parish, J.M. et al. 2007). Use of a CPAP machine does not significantly suppress IL-6 in adults with OSA (Zhong, A. et al. 2016). However, adherence to positive airway pressure (PAP) treatment has been shown to prevent further increases in IL-6 levels, and significantly decreases the odds of incident diagnoses of Alzheimer's and dementia otherwise not specified in persons with OSA over a 3-year period (Arnardottir, E.S. et al. 2015, Dunietz, G.L. et al. 2021).

The role of hypoxia cannot be excluded as a contributing driving factor to the greater risk of neurodegeneration associated with OSA. For example, hypoxia triggers cerebral amyloidogenesis and tau phosphorylation, two hallmarks of Alzheimer's (Daulatzai, M.A. et al. 2013.). Yet, sleep fragmentation is a known clinical consequence of OSA, and may work in isolation or in concert with hypoxia to promote neurodegeneration. Importantly, a sleep study conducted with Parkinson's patients concluded that symptoms related to daytime sleepiness, nocturia and cognitive impairment are mostly caused by other, non-apneic mechanisms and not OSA (Cochen De Cock, V. et al. 2010). This suggests that IL-6 neuroinflammation in the context of insomnia is a potential link between sleep apnea and neurodegeneration (not hypoxia, a mechanism that has been previously emphasized in the literature).

VII. Implication of IL-6 in Neurodegenerative Diseases

Research continues to support the immune system and inflammation as important players within

the development and progression of neurodegeneration. For example, long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to delay the onset of Alzheimer's, and asymptomatic elderly individuals treated with naproxen evinced a lower incidence of Alzheimer's after 2-3 years of continual intake (Breitner, J.C. et al. 2011). IL-6 has been implicated as a key player in the physiology contributing to neurodegenerative diseases, as it can be consistently detected in the brains of Alzheimer's patients but not in the brains of non-demented elderly people. Importantly, the presence of IL-6 could be detected within plaques of Alzheimer's patients prior to the onset of neuritic degeneration (Hüll, M. et al. 1996). In addition, increased IL-6 levels in serum have been shown to differentiate dementia from normal aging (Helmy, A.A. et al. 2012).

In a small phase II trial conducted in 2010, 42 patients with neurodegenerative diseases were administered apigenin. Apigenin is a constituent of chamomile and inhibits lipopolysaccharide (LPS) induced IL-6 production (Smolinski, A.T. and Pestka, J.J. 2003). Today, chamomile is a popular sleep aid, and a common ingredient in many calming and 'sleepy-time' teas. Over a 3-24 month follow-up all of the patients in the trial were clinically stable, with no adverse side effects reported. Of the 12 patients with Alzheimer's disease, 9 had improvement in their Mini-Mental State Exam (De Font-Réaulx Rojas, E. and Dorazco-Barragán, G. 2010). In addition, IL-6 has also been implicated in multiple neurodegenerative disease models. Chronic oral pathogen administration (Pg/gingipain) in a murine model led to an Alzheimer's phenotype, including neurodegeneration and the formation of beta amyloid plaques. Significantly greater IL-6 expressions were also present within the hippocampus of these mice (Ilievski, V. et al. 2018). Furthermore, the GFAP-IL6 murine model, replicates the structural and functional

neuropathology of multiple human neuro-degenerative diseases including Alzheimer's disease and HIV-associated dementia. The GFAP-IL6 murine model uses a fusion gene constructs, where the DNA coding region of the IL-6 gene is placed under the transcriptional control of the GFAP promoter, thereby directing expression of the cytokine to astrocytes (Campbell, I.L. et al. 1998).

VIII. Discussion

Research continues to support both insomnia and inflammation individually with risk and progression of neurodegenerative diseases, yet there are scant data available about how the two might interact in the pathogenesis of these diseases, or in the context of metabolite clearance during SWS. It has been hypothesized that damage arising from the breakdown of the blood-brain barrier may be a starting point for some neurodegenerative diseases (Stolp, H.B. and Dziegielewska, K.M. 2009). Interestingly, in GFAP-IL6 mice, the blood brain barrier never fully develops, and extensive breakdown is observed in both high and low expressing IL-6 models (Brett, F.M. et al. 1995). Disturbances in sleep, such as sleep fragmentation, might lead to an increase in neural inflammation, including abnormal production of IL-6, its membrane bound receptor, and its soluble receptors, thus interfering with blood brain barrier function. The extent and location of the ensuing local damage might facilitate disease processes. These dynamics might be compounded (still further) by sleep fragmentation SWS when metabolite clearance is high. In addition, an age-related decrease in concentration of anti-inflammatory cytokines cannot be ruled out as a primary contributing factor in driving the age-related inflammatory phenotype (Lynch, M.A. et al. 2010).

Although anti-inflammatory administration to asymptomatic patients has proven to reduce incidence of Alzheimer's, it has been shown that NSAIDs have adverse effects on later stages of Alzheimer's pathogenesis (Breitner, J.C. et al. 2011), suggesting that the role of inflammation may change throughout neurodegenerative disease progression. MN9D cells are a line of murine dopaminergic (mDA) neurons that are commonly used in Parkinson's models in conjunction with the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). When applied systemically, MPTP selectively kills murine dopaminergic neurons. MN9D cells release high levels of IL-6, which is downregulated after treatment with MPP^+, the active neurodegenerative metabolite of MPTP taken up by mDA neurons. Neutralization of endogenous IL6 results in the degeneration of MN9D cells but is rescued with the administration of recombinant IL-6 (Spittau, B. et al. 2012). In addition, genetic variants of IL-6 have also been connected to hippocampal volume when analyzed using voxel-based morphometry, implicating a possible neuroprotective role (Baune, B.T. et al. 2012). This evidence highlights the importance of the IL-6 production in the context of acute or chronic elevations of IL-6, as well as the isoform of IL-6 receptors that are being produced, affecting downstream targets that may differentiated between neurodegenerative or neural protective behavior.

Regardless of whether insomnia is secondary or causal to neurodegenerative disease, IL-6 remains an exciting potential link between the two that needs to be investigated further. Currently, there is no published data examining IL-6 in the context of insomnia and neurodegenerative diseases. However, there is an IL-6 blocker on the market under the name Tocilizumab. Tocilizumab has been approved for multiple diseases and is currently in clinical trials for diabetes and obesity, both of which are significant risk factors for dementia (Tanaka, T.

et al. 2014, Shamim, S.A 2019). A longitudinal study of patients taking Tocilizumab and their cognitive function as well as their sleep patterns, may be an invaluable source of knowledge for elucidating the role of inflammation in both insomnia and neurodegeneration. Importantly, IL-6 levels should be followed throughout the progression of neurodegenerative diseases.

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