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Review Paper

Beyond Biology: The Role of Psychosocial Factors in Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis (ALS) are characterised by progressive neuronal loss, with no current effective treatments. Emerging research emphasises the role of psychosocial factors—specifically stress, chronic pain, and mental health—in exacerbating neurodegeneration through mechanisms like neuroinflammation and oxidative stress. Chronic stress disrupts the hypothalamic-pituitary-adrenal (HPA) axis, contributing to excessive neuroinflammation and oxidative stress, which in turn accelerate neuronal damage. Chronic pain, often comorbid with both chronic stress as well as neurodegenerative diseases, perpetuates neuroinflammation via pain-induced activation of microglia, while mental health conditions such as depression and anxiety are both risk factors and common comorbidities in neurodegeneration. This review highlights the intricate interplay between these psychosocial factors and neurobiological processes that drive disease progression. It argues for a multidisciplinary approach to neurodegenerative disease management, integrating psychosocial interventions like cognitive-behavioural therapy (CBT), mindfulness, and physical activity-based therapies. Such treatments can modulate neuroinflammation, alleviate pain, improve mental health, and potentially slow disease progression, enhancing patient outcomes and quality of life.

Keywords: *Neurodegeneration, neuroinflammation, oxidative stress, chronic stress, chronic pain, mental health, psychosocial factors, Alzheimer's Disease, Parkinson's Disease, cognitive-behavioural therapy, mindfulness, multidisciplinary care*

Neurodegeneration refers to the progressive loss of neurons in both the central nervous system (CNS) and peripheral nervous system (PNS). Neurodegeneration is a hallmark of several neurodegenerative diseases, such as Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis (ALS) to name a few (Lamptey et al., 2022). Despite substantial research efforts being made to find a cure for such conditions, as it currently stands, there are no effective treatments available. Consequently, researchers have turned their focus on finding ways to slow down the progression of neurodegenerative diseases. The role of various factors such as lifestyle, stress, brain injury, and genetics have been analysed to identify potential risk and protective factors that can contribute to disease progression (Hrelia et al., 2020; Nag & Jelinek, 2019).

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Although neurodegenerative diseases have distinct pathological features such as differing genetic variants, protein aggregates as well as varying symptoms, one commonality seen is the presence of chronic neuroinflammation (Zhang et al., 2023). Neuroinflammation is a key risk factor in neurodegenerative diseases as studies have found that it further exacerbates protein aggregation and speeds up disease progression. Neuroinflammation refers to an inflammatory response in the nervous system triggered by disease or injury. This response is mediated by the production of cytokines, chemokines, reactive oxygen species and secondary messengers which can have an immunological and biochemical impact on the nervous system (DiSabato et al., 2017).

Stress is another important risk factor for neurodegeneration, as it plays a crucial role, both with respect to pathogenesis as well as disease progression (Knezevic et al., 2023; Peña-Bautista et al., 2020). Stress refers to an organism's response to certain challenging or threatening stimuli in their environment. It's a natural response that can have a psychological and a physical component: the psychological impact of the pressure faced in a challenging situation and the body's response to this pressure or stress that is mediated by changes in the autonomic nervous system and specifically in the HPA axis (Bomholt et al., 2004). When it comes to stress and neuroinflammation, studies have found that chronic stress results in excessive inflammation due to a dysregulated stress response system (Song et al., 2020). In addition to this, chronic stress also exacerbates oxidative stress, another crucial process that can speed up disease progression. Oxidative stress is an imbalance between free radicals and antioxidants with the latter being in larger concentration than the former. Both oxidative stress and neuroinflammation are linked and can enhance the workings of each other having a collaborative role in aggregating neurodegeneration (Fischer and Maier., 2015; He et al., 2020).

While chronic stress can significantly contribute to neuroinflammation, it also closely interacts with another major player in neurodegeneration: chronic pain. The International Association for the Study of Pain defines chronic pain as pain that persists for more than 3 months (Trouvin and Perrot, 2019). Chronic pain is a widespread condition, affecting approximately 20% of the global population (Abdullah and Geha, 2017; Wyns et al., 2023). When it comes to inflammation, chronic pain can contribute to neuroinflammation through pain signals that perpetuate an inflammatory response in the nervous system (Sadlon et al., 2023). The persistent physical discomfort individuals with chronic pain experience can also act as a potent stressor itself. In patients with chronic pain, the additional impact of stress can worsen the perception of pain. Conversely, individuals with PTSD or those who have experienced adverse life events are more likely to develop chronic pain conditions such as chronic musculoskeletal pain (Wyns et al., 2023). Ageing is a risk factor for most neurodegenerative diseases (Hou et al., 2019). Older adults with neurodegenerative diseases are particularly vulnerable to chronic pain not only because of their age but also due to the presence of comorbid conditions such as an altered perception of pain all of which may further influence the progression of neurodegenerative diseases (Tommaso et al., 2016). Understanding the relationship between these various processes and how they affect each other at the neurobiological level can provide an understanding about their collective impact on disease progression. A multidisciplinary approach that addresses both the biological and psychological dimensions of these diseases will be crucial in improving the lives of affected individuals.

Neurodegenerative diseases

Neurons are the fundamental units of the brain and nervous system, the cells through which information is carried out all over the body. In humans, there is limited potential for neural regeneration in the event of injury or disease of the nervous system. Neurodegenerative diseases are characterised by various pathological changes at the molecular level, including synaptic and mitochondrial dysfunction, protein misfolding and aggregation, oxidative stress, and other such changes at the molecular level (Farooqui, 2020). Certain genes can increase the risk of developing a neurodegenerative disease such as the APOE gene in Alzheimer's disease, the LRRK2 gene in Parkinson's disease, and genes such as C9orf72, TARDBP, and SOD1 in ALS (Wang et al., 2021). However, beyond genetic predisposition, epigenetic factors play a crucial role in the development and progression of neurodegenerative diseases. Epigenetics refers to a process that alters gene activity without any changes in the DNA sequence. Such epigenetic changes can occur in utero as well and environment and lifestyle are one of the largest influences on the epigenome (Al Aboud et al., 2023). When it comes to neurodegenerative diseases, there is evidence for the role of chronic stress, poor diet, and exercise that can contribute to neuroinflammation, oxidative stress, and protein misfolding - hallmarks of neurodegenerative disease (Angelopoulou et al., 2022: Modgil et al., 2014). Conversely, environment and lifestyle can also be protective factors, delaying the onset or progression of neurodegeneration and cognitive decline. The Nun Study by Snowdon (1997), a longitudinal study examining the risk factors in the expression of Alzheimer's traits demonstrated how a healthy lifestyle can slow cognitive decline, even if the individual does have pathological signs of Alzheimer's such as amyloid beta plaque or neurofibrillary tangles.

Neuroinflammation and Oxidative Stress

Neuroinflammation is the basic immune response of the brain and is responsible for protecting the neurons from any damage. While such a system typically protects the brain, excessive or chronic neuroinflammation can accelerate the progression of neurodegenerative diseases (He et al., 2020). The microglia are the immune system cells in the CNS and are responsible for maintaining tissue homeostasis, removal of pathogens, and injury recovery. In neurodegenerative diseases such as Alzheimer's and Parkinson's, neuroinflammation is often dysregulated and these microglia become overactivated. As a result, they release pro-inflammatory cytokines such as TNF-alpha, IL-1beta, and reactive oxygen species. These molecules contribute to a chronic inflammatory environment and disrupt the blood-brain barrier which can speed up neuronal death (Muzio et al., 2021; Zhang et al., 2023). This creates a vicious cycle where the release of inflammatory mediators thereby further damages neurons and activates the microglia. In this manner, neuroinflammation accelerates disease progression. When homeostasis is affected ROS (reactive oxygen species) are excessively produced which then leads to oxidative stress. Oxidative stress can induce cell damage and also promote inflammation, indicating an interplay between the two can accelerate neurodegeneration (Fischer and Maier, 2015; He et al., 2020).

Chronic Stress

Stress, particularly chronic psychological stress, is a significant contributor to neurodegeneration by exacerbating both neuroinflammation and oxidative stress. The hypothalamic-pituitary-adrenal axis (HPA axis) is an important response system to stress and when stressed, the hypothalamus activates the pituitary gland which in turn signals the adrenal gland to release the hormone cortisol which is an essential hormone for the body's response to stress or the 'fight-or-flight' response. Cortisol influences several changes in the body such as affecting blood sugar levels, and changes in the immune system as well as

resulting in changes to autonomic functions such as heart rate, oxygen distribution, and functions such as digestion, reproduction, and growth (Stephens et al., 2012). While such a stress response system is crucial for survival, chronic or prolonged activation of the HPA axis and the subsequent long-term exposure to cortisol can lead to dysregulation of the HPA axis (Knezevic et al., 2023). Glucocorticoids generally play a role in regulating inflammation, however, sustained stress promotes glucocorticoid resistance which further aggravates inflammation. Chronic stress can also disrupt the blood-brain barrier, resulting in neuroinflammation as additional cytokines and inflammatory cells from the periphery are given passage into the brain. Thus, inflammation is implicated as a potential mediating mechanism in the role of stress as a damaging factor in neurodegeneration progression (Garcia-Bueno et al., 2008; Peña-Bautista et al., 2020: Picard et al., 2021). The sustained release of cortisol during chronic stress also leads to an overproduction of reactive oxygen species (ROS) in the brain. Elevated ROS levels overwhelm the brain's antioxidant defences, resulting in oxidative damage to neurons. This oxidative stress, combined with the neuroinflammation triggered by the disrupted blood-brain barrier creates a toxic environment that accelerates neuronal injury and death. The interplay between chronic stress-induced neuroinflammation and oxidative stress thus acts as an indirect driver of the neurodegeneration process, suggesting that managing stress might be an important component of disease progression and management in diseases like Alzheimer's and Parkinson's.

Chronic Pain

Age is an important risk factor when it comes to both pain and neurodegenerative diseases (Lawn et al., 2021). Many individuals with neurodegenerative diseases complain about pain, however, their symptomatology is vague and variable, and thus, their presence is not considered in standard guidelines for treatment (de Tommaso et al., 2016). In addition to this, patients with dementia are often unable to effectively self-report their pain, resulting in this being an overlooked symptom (de Tomasso et al., 2016). Several subjective factors involving cognition, psychological function, and socioeconomic condition can influence the pathogenesis and perception of pain. Stress is one such factor that plays a major role in how we experience pain. Chronic pain and stress are two distinct, but interrelated conditions that have a bidirectional influence on each other (Abdallah, C. G., & Geha, P., 2017). Pain can be a stressor that triggers the body's stress response system. In patients with chronic pain, the additional impact of stress can worsen the perception of pain. At the neurobiological level, the hypothalamic-pituitary-adrenal axis (HPA axis) is an important response system to stress. In patients with chronic pain, dysfunction of the HPA axis is indicated by heightened or flattened basal levels of cortisol or excessive/reduced behavioural response and cortisol levels following a common stressful situation (Timmers et al., 2019). On the other hand, individuals dealing with chronic pain are more vulnerable to stress-related mental health conditions such as depression and anxiety (Wyns et al., 2023). When it comes to neurodegenerative diseases, the origin of pain is multifactorial and therefore cannot be attributed to a singular process (de Tomasso et al., 2016). However, chronic pain can impact neurodegeneration and cognitive decline via microglial activation and neuroinflammation (Cao et al., 2019). As discussed previously, microglia are the immune cells in the CNS, and activation of these cells as seen in the case of chronic pain results in promoting the release of pro-inflammatory molecules. Chronic pain can therefore induce neuroinflammation as well. Additionally, research has shown that chronic pain not only affects disease progression but is also a risk factor for the development of Alzheimer's disease and other related conditions (Bornier et al., 2023). Addressing chronic pain in individuals with neurodegenerative disease

is crucial to improving their overall quality of life and potentially preventing disease onset or slowing its progression.

Mental Health

Mental health disorders are an often overlooked part of neurological conditions. It's only in recent times that we have begun to take mental health into account when considering physical health. However, depression and other psychological disorders are common comorbidities in neurodegenerative diseases and often impact the quality of life and disease outcomes while increasing the disease burden (Galts et al., 2019; Pagonabarraga et al., 2022). Although mental health issues can develop at any time in a person's life, there are certain periods when an individual is more vulnerable to developing a mental health issue such as depression. As reported by Paulsen et al. (2019), the period after reporting a neurodegenerative disease including predictive genetic testing can negatively impact an individual's mental health with depression and anxiety being reported following the results. When it comes to mental health issues as comorbidities to neurological diseases, the heterogeneous nature of the symptoms seen in common psychological disorders such as depression and anxiety as well as the shared pathophysiological processes in psychological and neurological disorders make diagnosis difficult (Pagonabarraga et al., 2022). Similar to chronic pain here as well, pathogenesis is likely multifactorial with altered neurotransmitter signalling, structural and functional changes in the brain as well as neuroinflammation being implicated (Dunn et al., 2021; Lorenzetti et al., 2009). Not only are mental health conditions a comorbidity in neurodegenerative diseases but also are considered to be a risk factor for developing neurodegenerative diseases as well. A meta-analysis by Santabárbara et al. (2020) that looked at longitudinal studies of depression and dementia found that there was a significant association between depression and dementia risk. In addition to this, treatment of depression is also not a protective factor here as another meta-analysis of longitudinal studies to investigate whether antidepressant usage can be a potential protective factor for the development of dementia and mild cognitive impairment noted that individuals using antidepressants have a significantly higher risk of dementia compared to non-users (Chan et al., 2019). Drugs with anticholinergic properties, such as the ones used to treat depression have been found to enhance Alzheimer's disease pathology and neurodegeneration (Yoshiyama et al., 2012). Mental health conditions can also be a comorbidity of other psychosocial conditions such as chronic stress and pain. For instance, chronic stress and depression can induce neuroinflammatory responses and oxidative stress, both of which, as discussed above, contribute to neurodegeneration (Correia et al., 2023; Young et al., 2014). Mental health can also indirectly contribute to an increased risk of neurodegenerative diseases via lifestyle factors such as a poor diet, sedentary behaviour, and social isolation (Livingston et al., 2020). These findings underscore the importance of mental health as a central component of neurodegenerative disease risk and progression, not just a peripheral concern.

DISCUSSION

This review paper underscores the importance of considering psychosocial factors such as stress, chronic pain, and mental health in the context of neurodegenerative diseases with special emphasis on the neurobiological roles of neuroinflammation and oxidative stress as drivers of neurodegeneration. While traditionally, these factors have been overlooked in the clinical management of neurodegenerative diseases, emerging evidence suggests that they do play a more central role in both the onset and progression of these conditions (Burke et al., 2018; Pinto et al., 2023). Chronic stress, chronic pain and mental health conditions such as depression and anxiety are not only common comorbidities but are also increasingly

recognized as contributing risk factors that can exacerbate the neurodegenerative process. Consequently, the integration of psychosocial treatments and developing a multidisciplinary disease management plan for potentially slowing disease progression and improving the quality of life of patients is essential.

Psychosocial treatments that target chronic stress have gained prominence due to their capacity to modulate the body's stress response and reduce neuroinflammation. A meta-analysis by Shields et al., (2020) found that psychosocial interventions were associated with a reduction of systemic inflammatory activity. Cognitive-behavioural therapy (CBT), mindfulness-based stress reduction (MBSR) and relaxation techniques like yoga and meditation have been shown to lower cortisol levels and reduce stress-induced neuroinflammation (Chiesa & Serretti, 2009; Knezevic et al., 2023). These interventions work by promoting psychological resilience, reducing anxiety, and fostering adaptive coping mechanisms, which are particularly helpful for patients dealing with the chronic stress associated with neurodegenerative diseases. For instance, mindfulness and relaxation practices can help regulate the hypothalamic-pituitary-adrenal (HPA) axis, thereby reducing the prolonged activation that contributes to neuronal damage and cognitive decline (Pascoe et al., 2021).

Addressing chronic pain through psychosocial means is also vital, as pain significantly contributes to the neuroinflammatory environment that accelerates neurodegeneration. Techniques such as CBT for pain management, biofeedback, and mindfulness have been effective in helping patients reinterpret pain, reducing its intensity, and improving the patients coping strategies. By focusing on altering the psychological perception of pain, these treatments attempt to reduce the persistent pain signals that trigger inflammatory responses in the nervous system (Davis et al., 2016; Fournié et al., 2021; Zeidan & Vago, 2017). Moreover, such interventions can alleviate the compounded effects of pain and stress which often coexist in individuals with neurodegenerative conditions.

Mental health disorders, such as depression and anxiety which are prevalent among individuals with neurodegenerative diseases, can be managed through psychosocial interventions. Psychotherapy and CBT along with supportive group therapies can significantly improve mental health outcomes by addressing the cognitive and emotional aspects of living with a neurodegenerative disorder (González-Martín et al., 2023). Physical activity-based therapies such as dance therapy interventions are also very effective having a positive effect on both mental and physical health. They can alleviate the symptoms of depression and improve overall physical well-being (Pagonabarraga et al., 2023). Additionally, such interventions that enhance social support and reduce isolation can help mitigate the adverse effects of depression and anxiety (Livingston et al., 2020).

CONCLUSION

Psychosocial factors such as stress, chronic pain, and mental health conditions play an important role in contributing to disease onset and progression. Interventions targeting these factors would be beneficial in mitigating the biological processes that underlie neurodegeneration. By incorporating such treatments into standard care practices, it is possible to improve patient outcomes, enhance quality of life, and potentially slow the progression of such diseases.

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Conflict of Interest

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