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Literature Review

Immune System and Its Relation to Depression

Wati Evilia[1], Anak Ayu Sri Wahyuni[2], Luh Nyoman Alit Aryani[2]
[1]Department of Psychiatry , Faculty of Medicine, Universitas Udayana/ Sanglah Public Hospital, Denpasar, Bali
[2]Department of Psychiatry , Faculty of Medicine, Universitas Udayana/ Sanglah Public Hospital, Denpasar, Bali

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*) Corresponding author:
E-mail:
watievilia22@gmail.com

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Abstract

It has been shown that the immune system and mental status are interrelated. Psychoneuroimmunology is a field that studies these two relationships, one of the most studied is the relationship between the immune system and depression. Psychological stress can substantially increase inflammatory activity and increase risk for various health problems. Social environmental conditions trigger biological responses that can lead to an increase in the proinflammatory phenotype, which then plays a role in the emergence and recurrence of depression and is associated with several somatic conditions. The immune system and depression have a bidirectional link that influences each other. Exposure to chronic stressful situations can cause a maladaptive response by the immune system, which will be involved in the pathophysiology of depression. There have been many studies in the field of psychoneuroimmunology that have focused on depression in its diagnosis and management. The immunological markers that have been widely used show promise in their role in this field. Further research is needed on an integrated system in the management of patients with depression associated with immune system function

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INTRODUCTION

It is proven that a compromised immune system is associated with mental health, one of the most studied of which is depression. [1] Psychoneuroimmunology is the study of these two relationships. It is known that psychosocial factors contribute to the development of many diseases, and that the immune system plays an important role in this relationship. Likewise, immune system signals in the brain affect mood, cognitive function, and behavior. This bidirectional link is the focus of psychoneuroimmunology. [2] From psychoneuroimmunology, we know that not only viruses and bacteria play a role in inflammation, but also by events occurring in the social environment. Currently, it is widely recognized that social environmental factors are part of psychological stress, and can substantially increase inflammatory activity and increase risk for various health problems associated with poor prognosis. Approximately 80% of first-onset major depressive episodes occur because of stress in life, so stress is a significant risk factor for depression. [3]

DISCUSSION

Many studies have shown a link between a compromised immune system and mental problems, especially depression. [1] Psychoneuroimmunology provides an understanding of the relationship between immune dysfunction and mental illness. The brain and the immune system communicate bidirectional, the hypothalamus-pituitary-adrenal (HPA) axis being the link between them. Peripheral cytokines affect the central nervous system by affecting neurotransmitters or precursors of neurotransmitters. [4] Stress is a threat to psychological or physiological integrity. Cortisol is secreted when there is stress, this physiological response is important for maintaining the integrity of the organism in the short term, but if stress is prolonged, it will harm the organism. To maintain homeostasis, the body will carry out an adaptive response called allostasis, and the HPA axis will be involved in this process. [5]

Cortisol is a hormone secreted by the HPA axis, which is an anti-inflammatory agent produced during acute stress. When there is long-term stress, the stress response becomes chaotic and then causes a low-level inflammatory response that in the end, this condition can contribute to systemic inflammation and immune system dysfunction. [4] The immune system keeps the body safe from pathogens. Humoral and cellular immunity work together to provide protection in humans against pathogens both in the short and long term. [6]

Cytokines are key mediators of the inflammatory response that coordinate cellular and humoral systems to act against pathogens. Currently, cytokines are assessed in research on the relationship between stress and mental health. [6] Cytokines are divided into those involved in humoral and cellular immunity, also categorized into those that increase inflammatory activity and decrease inflammatory activity (downregulation). [7] Only a few cytokines have been consistently studied in psychoneuroimmunology studies, although hundreds of cytokines have been studied. [8] Cytokines can induce sickness behavior by communicating with the central nervous system by protecting organisms from potential injury. This behavior can range from anhedonia to socially withdrawn behavior. [4,6]

The inflammatory response can be rapidly mobilized by the immune system in acute infection, but rolonged inflammatory activity can later lead to various diseases. So, what saves us in the short term, can also be a killer when the inflammatory process becomes ongoing. Oxidative stress that occurs due to this can increase free radicals derived from reactive oxygen intermediates (ROIs), which can directly oxidize and also interfere with DNA repair mechanisms and ultimately increase the risk of various diseases that have an inflammatory component. Therefore, it was once mentioned to be involved only in certain disorders, such as cardiovascular disease, now it is known that chronic stress is also involved in several mental illnesses, one of which is depression. [9]

The inflammatory response that is supposed to occur is to work quickly in response to a real threat, both physical and psychological, which then disappears after the threat has also disappeared. Psychological stress can alter the immune system response and prolong the inflammatory process. [5] Systemic inflammatory activity resulted not only from the influence of physiological events, but also from the brain's representation of social problems. The body can mobilize immune cells when individuals are threatened by the same pathogen, so the role of neuroinflammation is not only to maintain life during infection. [7]

The production of proinflammatory cytokines can be influenced by the sympathetic nervous system by sending norepinephrine to peripheral tissues, which then stimulates α-adrenergic receptors. This adrenergic signaling cascade suppresses the transcription of the antiviral gene interferon type I and increases the transcription of proinflammatory immune genes, leading to increased systemic inflammatory activity. Therefore, ultimately, the sympathetic nervous system plays a central role in coordinating the conserved

transcriptional response to adversity, which directs the humoral immune system response between proinflammatory and antiviral phenotypes. [1, 5]

The hypothalamic-pituitary-adrenal (HPA) axis regulates proinflammatory cytokines in the periphery of the body. Cortisol is secreted when the HPA axis is activated. [5] Cortisol can also increase inflammation. Increased cortisol levels in the long term can cause glucocorticoid insensitivity in which immune cells become less sensitive and even cause HPA axis activity to increase, the opposite condition when inflammation occurs. [7, 10] High cortisol levels were found in the population aged 40-60 years who had mood disorders and depression. [5] Salivary cortisol levels and CRP levels were found to be high in infected individuals. [11]

Cortisol levels that increase chronically will decrease the volume of hippocampus, which results in degeneration of neurons and the finding of memory impairment. The decrease in hippocampus volume occurs due to decreased levels of Brain-Derived Neurotrophic Factor (BDNF) which is a protein for the growth of neurons in the nervous system, whose levels are most commonly found in the hippocampus and frontal cortex of the brain. [7] A study of the relationship between chronic stress and BNDF levels found that sows that were tethered for long periods of time experienced increased levels of BDNF which resulted in the degeneration of neurons in the brain, particularly in the hippocampus and frontal cortex. [1]

If exposure to social stress occurs chronically, the brain will create subjective perception to a threat, and the parts of the brain that process this are the Anterior Insula (AI) and Dorsal Anterior Cingulate Cortex (dACC). This area will send a signal to activate the HPA axis. Epinephrine and norepinephrine can be increased by activating intracellular transcription of nuclear factor kappa-B (NF-κB) and Activator Protein-1 (AP-1). Expression of this gene causes the production of proinflammatory cytokines that cause depressive symptoms, such as anhedonia to cognitive symptoms. [7] Social environmental conditions trigger biological responses that can lead to an increase in the proinflammatory phenotype which is the key driving pathophysiology and relapse of depression, as well as several somatic conditions such as rheumatoid arthritis. [1]

A causal role for inflammation in depression was first demonstrated by the observation that treatment of proinflammatory cytokines (eg, interferon-alpha (IFN-α)) for Hepatitis C induces depressive episodes in up to half of patients. Several disease studies have shown that cytokines (eg, IL-6 and IL-1β) and other inflammatory biomarkers (eg, C-Reactive Protein (CRP)) are elevated in physically depressed patients. [6, 8]

Clinicians can form a more integrated health concept through psychoneuroimmunology as an approach in preventing mental and physical health problems in society. [4] Immunological markers currently available can be used to assist interventions in the field of psychoneuroimmunology, which can help improve patients' quality of life. [12] There have been many studies linking depression to gut health, exercise, and the role of anti-inflammatory therapy. Diet and depression have a close relationship. Gut health can affect mental health, and vice versa. Stress can alter the balance of composition in the gut, and an unhealthy gut can play a role in the onset of depression. These two pathways are connected via the gut-brain axis, so probiotic administration may be considered. [13] A shows the effectiveness of plant-based molecules that have the same effect as antidepressants, but further research is needed on significant anti-inflammatory effects. [14,15] Omega 3-polyunsaturated fatty acids (PUFAs) have been shown to help improve the complications that arise in depression and bipolar patients. [16] Tryptophan breakdown is also the focus of studies related to its role in inflammation. Food rich in antioxidants can improve the balance of tryptophan levels in the brain, which affect mood and cognitive function. [17] This can be seen in the improvement of intestinal pain which is treated through a psychoneuroimmunology approach. [18] In addition, regular exercise has been shown to increase the positive relationship between the central nervous system and the immune system. [19] Cyclooxygenase-2 (COX-2) inhibitors have been shown to be effective in the early stages of schizophrenia and depression, but more research is needed regarding their side effects and whether they can replace the current psychiatric medications we currently use. [20]

CONCLUSION

The immune system and depression have a bidirectional link that influences each other, inflammation can cause depression, and vice versa. The immune system is an important component in maintaining the homeostasis of organisms. Alterations of the immune system, dysregulation of the inflammatory response—have been associated with mental illness. Exposure to chronic stressful situations can cause a maladaptive response by the immune system, which will be involved in the pathophysiology of depression. Immunological biomarkers may be helpful in the diagnosis and future management of depression. Management in the field of nutrition is important to note and its application must be through an individual approach because not everyone has the

same metabolism, the type and amount cannot be generalized. Anti-inflammatory therapy that is proven to be effective in its role in the field of psychoneuroimmonology still needs to be investigated further regarding side effects and individual variations.

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