Int J Med Rev 2024 October;11(3): 775-785

doi 10.30491/IJMR.2024.468527.1288

INTERNATIONAL JOURNAL OF MEDICAL REVIEWS

Narrative Review

Relationship between Stress and the Immune System-related Disorders

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Received July 19, 2024; **Accepted** September 4, 2024; **Online Published** October 1, 2024

Abstract

The immune system is vital for the health and proper functioning of living beings. This system plays an important role in coordinating the body's responses to physical injuries and infections, and if it does not function properly, illness and death are its consequences. Researchers in psychoneuroimmunology concentrate on fundamental and applied research to explore the effects of stressors and negative emotions on physiological well-being. Clinical research indicates a reciprocal interaction between the central nervous system, endocrine system, and immune system. Stress-induced immune system dysregulation involves both cellular and humoral responses. Moreover, chronic stress can trigger the release of pro-inflammatory cytokines like interleukin-6, contributing to the development of several chronic illnesses. Vertebrates activate a stress response to manage harmful stimuli, involving physiological, hormonal, and behavioral changes. While adaptive in the short term, chronic stress becomes harmful, leading to conditions like depression, anxiety, and heart disease. Chronic stress increases pro-inflammatory cytokines, disrupts immune balance, and aggravates autoimmune diseases. It also contributes to conditions such as Alzheimer's, asthma, cancer, coronary artery disease, and etc. Given the potential health impacts of stress, enhancing our understanding of the intricate mechanisms through which stress affects immune function, along with identifying psychological factors that can either hinder or enhance the effects of stress on immune responses, appears crucial. This review examines the detrimental impact of stress on immune system-related disorders.

Keywords: Immune System, Stress, Depression, Disorders, Autoimmune Diseases

Introduction

Vertebrates manage unforeseen and harmful stimuli through the activation of a Stress Response, which encompasses a set of physiological, hormonal, and behavioral reactions that have evolved and are consistently observed across various vertebrate species.[1] Disturbances to homeostasis caused by physical or psychological factors initiate a stress response. Initially, this response is beneficial, helping the body to address internal or external challenges. However, when a stressor is perceived or experienced as intense, recurrent (acute stress), or long-lasting (chronic stress), the stress response can turn maladaptive, causing harm to the body's physiology. For example, chronic exposure to stress can lead to negative effects such as depression, anxiety, cognitive deficits, and cardiovascular disease.[2] During brief periods of stress, various physiological systems are mobilized to ensure survival. Research on both humans and non-human species has demonstrated that short-term stress coinciding with immune activation significantly boosts the subsequent immune response.[3] Acute stress raises blood levels of pro-inflammatory cytokines. Similarly, chronic stress, which can persist from days to years, is linked to elevated levels of pro-inflammatory cytokines, though it may result in different health outcomes. Another effect of chronic stress is the activation of latent viruses, indicating a loss of immunological control over these viruses. Frequent activation can lead to wear and tear on the immune system.[4] During the stress response, the locus coeruleus and adrenal gland release catecholamines and glucocorticoids (GCs). These biomolecules regulate various immune cells within

both the innate and adaptive immune systems, consequently modifying the cytokine profile. An increase in interleukin (IL)-4 encourages the differentiation of T-helper 2 (Th2) cells, while a reduction in IL-12 and a rise in IL-10 production decrease the quantity of T-helper 1 (Th1) cells. Stress has been associated with the beginning and deterioration of illnesses like rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, Graves' disease, and other autoimmune conditions. Furthermore, in specific situations such as psoriasis, stress has been linked to delayed healing of lesions after undergoing standard treatment protocols.[5] Increasing evidence indicates that stress negatively impacts a wide range of diseases, including aging, allergies, Alzheimer's disease, asthma, autism spectrum disorder, cancer, coronary artery disease, multiple sclerosis, and myalgic encephalomyelitis/ chronic fatigue syndrome.[6] Ultimately, the impact of stress on the regulation of immune and inflammatory processes can potentially affect depression, infectious and autoimmune diseases, coronary artery disease, and certain types of cancer, such as those mediated by viruses.[7] Many studies have shown the effect of stress on the immune system. The purpose of this review is to investigate the role of stress in some disorders related to the immune system.

Effect of Stress on the Immune System

Stress can influence the immune system through multiple pathways (Table 1). The first pathway involves the sympathetic nervous system (SNS) and adrenergic activation, while the second pathway involves the hypothalamic-pituitary-adrenal (HPA) axis.[8] Research on stressors experienced early in life (i.e., during childhood and adolescence) and later in life (i.e., during aging) suggests that individuals exposed to chronic stressors (such as abuse or caregiving) can suffer from persistent and severe immune dysregulation.[4] Stress encompasses a series of events starting with a stimulus (stressor), which triggers a reaction in the brain (stress perception) and subsequently activates the body's physiological fight-or-flight systems (stress response). It is crucial to recognize that a stressor can influence the brain or body solely through the biological stress response. Despite the involvement of numerous factors, the primary mediators of stress effects are norepinephrine (NE) and epinephrine (EPI) released by the SNS, along with corticotropin-releasing hormone, adrenocorticotropin, and cortisol, which are produced following the activation of the HPA axis. Since nearly every cell in the body has receptors for one or more of these mediators, stress hormones can induce changes in almost all cells and tissues, alerting them to the presence of a stressor.[3]

Table 1. Influence of Stress on the Immune System

Pathway	Mechanism	Effect on Immune System	Examples
Sympathetic Nervous System (SNS)	Adrenergic activation	Release of norepinephrine (NE) and epinephrine (EPI)	Induces changes in almost all cells and tissues
Hypothalamic-Pituitary-Adrenal (HPA) Axis	Release of cortisol and other hormones	Induces changes in cellular trafficking, cytokine secretion, and immune cell functions	Suppression of IL-12, increase in IL-10 production
Central Nervous System (CNS) Interaction	Modulation of immune responses through HPA and SNS	Bidirectional communication among nervous, endocrine, and immune systems	Shift in $CD4^+$ T-helper cells from Th1 to Th2 profile
Psychological Stress	Impact on cytokine balance	Reduced synthesis of Th1 cytokines, increased Th2 cytokines	Stress-induced immune dysregulation during exams
Chronic Stress	Long-term immune dysregulation	Sensitization or desensitization depending on stress intensity, frequency, duration	Delayed wound healing, altered autoimmune responses
Endocrine Effects	Release of glucocorticoids (GCs)	Immunosuppressive properties of catecholamines and opiates	Inverse correlation between epinephrine levels and immune functions

Research on immune dysregulation due to stress has drawn the attention of experts in psychoneuroimmunology, a field that examines the complex interactions between the central nervous system (CNS), the endocrine system, and the immune system, and their combined effects on health. The CNS modulates immune responses through an intricate network of signals that enable two-way communication among these systems. The HPA axis and the sympathetic-adrenal medullary (SAM) axis are the main pathways through which the

immune function is regulated. Immune cells, including lymphocytes, monocytes or macrophages, and granulocytes, have receptors for neuroendocrine products of the HPA and SAM axes, such as cortisol and catecholamines. These substances can alter cellular trafficking, proliferation, cytokine secretion, antibody production, and cytolytic activity. For example, in vitro exposure of peripheral blood leukocytes to catecholamines results in reduced IL-12 synthesis and increased IL-10 production. This can trigger a shift in the phenotype of $CD4^+$ T-helper cells from a Th1 profile, which is involved in cell-mediated immune activities, to a Th2 profile, which plays a role in antibody production. In a study involving medical students undergoing exams, psychological stress was found to induce a shift in the cytokine balance towards a Th2 profile. The findings indicated a reduced synthesis of Th1 cytokines, such as interferon (IFN)-γ, and an increased production of Th2 cytokines, including IL-10. It is hypothesized that this stress-induced reduction in Th1 cytokines leads to dysregulation of cell-mediated immune responses. Aligning with findings in human studies, research utilizing animal models has demonstrated that stress weakens vaccine efficacy, worsens viral and bacterial infections, hinders wound healing, and affects autoimmune diseases. These investigations have shown that stress hormones impede the movement of neutrophils, macrophages, antigen-presenting cells, natural killer (NK) cells, as well as T and B lymphocytes. Furthermore, they inhibit the production of proinflammatory cytokines and chemokines, reduce the synthesis of cytokines necessary for adaptive immune responses, and impair the functional effectiveness of macrophages, NK cells, and lymphocytes.[9] Animal studies have demonstrated that the effects of chronic stressors can vary depending on factors such as the intensity, frequency, and duration of stress. These effects may manifest as either sensitization or desensitization responses. The distinct impacts of trait factors and chronic stress on reactivity under high and low effort conditions may be linked to the balance between the acute release of catecholamines and long-lasting changes in the density and/or sensitivity of β-adrenergic receptors (ADRs) found on T- and NK-cells.[10] As mentioned earlier, the activation of the primary neural pathways triggered by stressors, namely the HPA axis and the SNS. Neurosensory signals undergo processing within two critical regions, namely the paraventricular nucleus of the hypothalamus and the locus coeruleus-noradrenergic center. As a result, the hypothalamus releases corticotropin-releasing factor (CRF) and arginine vasopressin, thereby stimulating the HPA axis. This stimulation leads to the release of pituitary peptides, including adrenocorticotrophic hormone, enkephalins, and endorphins, which are generated through differential cleavage of pro opiomelanocortin. The release of GCs from the adrenal cortex is induced by adrenocorticotrophic hormone. The impact of CRF on the SNS occurs through direct innervation of the locus coeruleus within the brainstem. This innervation subsequently results in the widespread release of NE throughout both the brain and peripheral tissues. The activation of the SNS prompts the hypothalamic paraventricular nuclei to release CRF. This results in the stress-response system functioning as a positive, bidirectional feedback loop, where the activation of one element triggers the stimulation of others. Research on stress suggests that the plasma concentration of EPI is inversely related to the immune functions of lymphocytes and monocytes. It has been observed that catecholamines and opiates have immunosuppressive effects. Furthermore, numerous studies suggest that corticosteroids, which are elevated during stress, significantly suppress the functions of lymphocytes and macrophages, potentially affecting their circulation patterns.[11] The research has demonstrated that adrenalectomy noticeably diminishes the extent of stress-induced reductions in blood leukocytes. Collectively, these studies indicate that the primary stress hormones, namely NE, EPI, and corticosterone, which contribute to the extensive physiological impacts observed during acute stress responses, are also the primary endocrine mediators responsible for distinct phases and redistribution patterns of psychological and physical (exercise) stressors on specific subpopulations of leukocytes.[12] As previously stated, the immune system receives signals from both the CNS and the endocrine system in order to react and adjust to stimuli, such as stress. When stress is manageable, it can potentially facilitate adaptation. However, when stress becomes chronic and challenging to cope with, it can lead over time to wear and tear on the body and brain, ultimately leading to various physiological dysfunctions known as allostatic load. Psychosocial job-related stresses often contribute to the development of allostatic load, increasing the risk of

irreversible or incurable health conditions if effective stress management measures are not implemented.[13]

Relationship between Neuroendocrine Factors and Stress

During exposure to stressors, the release of pituitary hormones, including prolactin and growth hormone, along with neuropeptides such as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), neuropeptide Y (NPY), and opioids, can occur. These bioactive substances have the potential to influence both cellular and humoral immune responses.[14] The stress system is essential in orchestrating the body's and brain's physiological and behavioral reactions to environmental stimuli. This coordination is facilitated by stress system mediators functioning in two separate modes. The immediate-response mode, regulated by CRH, synchronizes behavioral, sympathetic, and HPA responses to stressors through CRH-1 receptors. In contrast, the slower-response mode, which aids in behavioral adaptation, is driven by urocortin's interacting with CRH-2 receptors. Corticosteroid hormones, produced by the adrenal cortex, play a role in both modes of the stress system. Their effects are mediated by two types of receptors: high-affinity type 1 mineralocorticoid receptors and lower-affinity type 2 glucocorticoid receptors (GRs), which are co-localized within limbic neural circuitry. Current evidence indicates that mineralocorticoid receptors play a role in regulating the threshold or sensitivity of the rapid stress response system driven by CRH-1 in specific neural pathways. This function preventing disruption of homeostasis. On the other hand, GRs aid in restoring homeostasis by modulating stress responses and mobilizing energy resources.[15] The immune system can be influenced by the autonomic nervous system, which exerts its effects through nervous innervation of lymphoid tissue. This influence can occur in two ways: firstly, by modulating vascular tone and regulating blood flow into lymphoid organs, and secondly, by directly impacting immune cell function through the local release of neurotransmitters, particularly catechol-amines (norepinephrine), as well as neuropeptides such as NPY, substance P (SP), vasoactive intestinal peptide, and calcitonin gene-related peptide. These neurotransmitters and neuropeptides interact with specific receptors present on adjacent immune cells, thereby influencing their activity.[16] Sensory peptides like SP possess the capability to interact with the immune system, potentially linking stress and inflammatory mechanisms. Within the peripheral system, SP primarily acts to trigger inflammation, acting as a defense mechanism against irritants and pathogens. Many types of immune cells express receptors for SP, and nerve fibers containing SP innervate immune organs. When SP binds to its receptor, it prompts the increased production of pro-inflammatory cytokines and influences other immune processes that enhance inflammation. Moreover, SP plays a role in regulating stress pathways, including the HPA axis.[14] Variations in GC levels, seen during exercise and in accordance with circadian rhythms, correlate with changes in cytokine levels and production by leukocytes. This correlation suggests that physiological changes in GC levels, within the range observed during circadian fluctuations or stress, can influence immune function. However, the strongest evidence supporting the role of endogenous GCs as crucial regulators of the immune response and inflammatory/autoimmune diseases comes from studies using animal models. These models have provided substantial evidence demonstrating the involvement of endogenous GCs in regulating immune function and contributing to the development of inflammatory/ autoimmune conditions.[17] Indeed, GCs can induce a persistent sensitization of microglia, which maintains a pro-inflammatory state even after the resolution of the initial stressful challenge, thereby priming neuroimmune responses to subsequent events.[18] Furthermore, GCs participate in a feedback mechanism that attenuates the central autonomic response by inhibiting the expression of tyrosine hydroxylase, the rate-limiting enzyme in NE synthesis, within neurons of the locus coeruleus. This results in reduced central NE release during stressful periods. Both catecholamines and GCs serve as principal neuroendocrine mediators in response to stress, acting as alarm signals across the body to aid an organism in reacting to and surviving threats.[19] Immune cells have the ability to produce hormones and also possess receptors for specific neuroendocrine peptides, allowing for bidirectional communication between the immune and neuroendocrine systems. Lymphocytes, for instance, express receptors with high affinity for hormones like ACTH, endorphins, and opiate receptors with both high and low affinity. This dual capability implies that immune cells may

influence their own functionality in a manner akin to autocrine regulation. An illustrative example is the presence of both ACTH and its receptor on a B-lymphocytic cell line, suggesting a potential autocrine role for this neuroendocrine hormone.[20]

Psychosocial Stress and Immune-related Diseases

Stress and Rheumatoid Arthritis

The role of stress as a notable risk factor in the development of autoimmune rheumatic diseases, including rheumatoid arthritis (RA), is now widely acknowledged.[21] Within the realm of RA research, it has been widely acknowledged for some time that a multifaceted and reciprocal association exists between psychological factors and the influence of the disease. Recent study findings have revealed that individuals diagnosed with RA commonly encounter elevated levels of work-related stress and interpersonal stressors compared to the general population. Risk factors contributing to stress development encompass heightened levels of pain, functional disability, increased disease activity, younger age, lower socioeconomic status, specific psychological characteristics, as well as inadequate social support.[22] Recent studies have indicated that events such as divorce, bereavement, and job loss are linked to the onset of RA. Research has shown a direct relationship between emotional stress and the activity of RA. Both B cells and T cells contribute to the immune response in individuals affected by RA. Specifically, RA patients exhibit an altered ratio of T cells to B cells, disrupting the normal 1:4 ratio and resulting in fewer T cells than usual. This condition is believed to be caused by an autoantibody specifically targeting the T5/T8 suppressor cells. As a consequence of reduced suppressor cells, B cells produce excessive amounts of antibody (specifically IgM and IgG), which are erroneously recognized by the body as immunogenic in the case of RA. This process is particularly detrimental as it leads to the production of rheumatoid factor in the serum and synovial fluid. Subsequently, a cascade of events initiated which results in the formation of IgG/anti-IgG immune complexes within the synovial fluid.[23] Studies have shown that the immune response to acute stress, including circulating IL-1β and IL-2 levels, may be altered in various chronic inflammatory conditions. It is suggested that acute stress enhances innate immunity by increasing NK cell and neutrophil counts, and also by stimulating the production of cytokines related to acute inflammation, such as IL-1β. In the context of IL-2, a component of the adaptive immune system that activates T cells, its levels were found to be specifically elevated in response to stress in patients with RA. Notably, a study demonstrated that the cytokines IL-1β and IL-2 exhibited greater increases in RA patients compared to patients with psoriasis and healthy controls. These findings suggest that stress might specifically have altered effects on immune function in RA patients, possibly exacerbating disease severity.[24] Research in RA indicates that interpersonal stressors experienced shortly before clinical visits are associated with elevated levels of circulating $CD3^+$ T cells and increased serum levels of soluble IL-2 receptors. Furthermore, RA patients exhibit higher numbers of IL-8-producing monocytes in peripheral circulation following adrenaline infusion. The frequent occurrence of significant stress events preceding RA onset and the presence of personality disorders highlight the involvement of altered stress response systems, such as the HPA and SNS axes, as significant pathogenic factors in the disease.[25]

Stress and Multiple Sclerosis

The etiology of multiple sclerosis (MS), an autoimmune demyelinating disease of the CNS, remains unknown.[26] Various studies have suggested a correlation between stress and increased MS relapse rates. Artemiadis et al. conducted a recent meta-analysis that encompassed studies conducted between 1980 and 2010, focusing on this particular aspect. In their review, Artemiadis et al. identified a total of 17 studies focusing on the association between stress and MS, with 15 of these studies reporting a significant correlation. Buljevac et al., for instance, conducted a prospective study and discovered that stress was linked to a twofold increase in the risk of MS exacerbations. Another meticulous longitudinal study was carried out by Ackerman et al., involving 50 female MS patients who were monitored for a duration of one year. This study meticulously evaluated cardiovascular reactivity at baseline, with exposed patients to a standardized stressor, namely the performance of the Stroop Test. Ackerman et al. discovered that occurrences of MS exacerbations were 3.4 times more probable during the subsequent 6-week period following a stressor event. Moreover, each stressor event was linked to an average

of 0.5 weeks of sick time due to MS exacerbations.[27] The relationship between stress and MS has yielded conflicting results, leading to a significant level of controversy. While some studies have reported an association between stress and MS, others have failed to find such a relationship or have observed only a quasi-significant correlation. These divergent findings can be attributed to variations in study design as well as the indirect nature through which stress influences MS by affecting other variables. Several factors have been proposed as potential moderators and mediators in the stress-MS relationship, including properties of the stressors themselves, environmental factors, and the biological, social, and psychological characteristics of patients. Among these potential moderators and mediators, certain factors have consistently demonstrated an impact on the stress-MS relationship. These factors include the duration, severity, and frequency of stressors; levels of anxiety, cardiovascular reactivity, and heart rate; as well as social support and the use of escitalopram.[28]

Stress and Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic progressive autoimmune disease that can affect various organs, including the skin, kidneys, lungs, brain, heart, and joints. It is more prevalent among women, accounting for around 90% of diagnosed cases.[29] Studies by Pawlak et al. and Jacobs et al. have investigated the immune responses of SLE patients to acute psychological stress compared to healthy controls. Their findings suggest that SLE patients exhibit distinct immune responses when exposed to stress, such as a lack of increase in NK cell activity. The authors propose that in patients with SLE or RA, the reduced activity of NK cells may be due to their persistent activation resulting from the underlying inflammatory disease.[30] Forty-one individuals diagnosed with SLE were recruited from various locations in the United States for a study. The findings indicated that stress, depression, anxiety, and anger are correlated with, and may worsen, self-reported symptoms among patients with SLE.[31] In a study conducted by Dobkin et al., it was found that decreased stress was one of the factors associated with better mental health outcomes. Stress was identified as one of several factors that influenced self-reported clinical symptomatology in a sample of 41 SLE patients.[32] In individuals without health issues, the production of antibodies is controlled by a complex network of immune cells predominantly coordinated by cytokines. As a result, numerous studies have examined the cytokine patterns of SLE and RA patients both in vivo and in vitro. Although findings on the levels of interleukins (IL-2, IL-4, IL-6, IL-10) and IFN-γ in these patients compared to healthy controls have shown variability, research has indicated that individuals with SLE and RA display an altered cytokine profile. In healthy individuals, acute psychological stress prompts a transient rise in lymphocytes in the bloodstream, notably affecting NK cell counts. These stress-induced alterations are largely facilitated by the sympathetic activation of β-adrenoceptors on lymphocytes. Investigations in individuals with SLE and RA have suggested an altered number of β-adrenoceptors on peripheral blood mononuclear cells.[33]

Stress and Type 1 Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by dysregulation in glucose balance due to changes in insulin secretion or function, the hormone crucial for glucose uptake in the body. The World Health Organization identifies two primary types of diabetes. Type 1 DM (T1DM) is an autoimmune condition typically diagnosed in childhood or adolescence. It involves the immune-mediated destruction of insulin-producing β-cells, leading to impaired glucose regulation, inadequate insulin production, and other complications. T1DM may also linked with other autoimmune diseases. The expansion of antibodies targeting pancreatic islet cells and autoantibodies against insulin are hallmark features of T1DM. However, the relationship between stress and T1DM (as well as stress and autoimmunity in general) cannot be simplified to a simple cause-and-effect scenario. Instead, it relies on multiple factors, including the nature of the stressor, the physical and mental attributes of the patient, their resilience, and the presence of a supportive familial environment. Moreover, it remains unclear whether psychological events implicated in disease development occur immediately preceding its onset. Conversely, such events may occur at any point in a patient's life, notably during childhood. Psychological stress experienced by children can influence their immune functions, potentially causing changes in the activity of antigens GAD65, HSP60, and IA-2, which are linked to autoimmunity related to diabetes.[34] As

previously mentioned, type 1 diabetes (T1D) is the result of an autoimmune destruction of pancreatic β-cells in individuals genetically susceptible to the condition. Various environmental factors are believed to trigger the autoimmune process, including viral infections or their reduced frequency during early childhood (the hygiene hypothesis), rapid somatic growth (the accelerator hypothesis), and β-cell stress. The β-cell stress hypothesis, an extension of the accelerator hypothesis, proposes that multiple factors, such as psychological stress or rapid weight gain, can lead to an increased demand for insulin, resulting in stress on β-cells. This, in turn, may trigger an autoimmune reaction in genetically susceptible individuals. A study examined the occurrence of specific stressful conditions in children recently diagnosed with T1D compared to a control group of non-diabetic children matched for age and gender. The study's primary finding revealed a higher frequency of stressful events or adverse psychosocial conditions in children with T1D, particularly those from lower social classes, compared to the control group. These events were predominantly observed during the two years leading up to the diagnosis of T1D.[35] Sipetic et al. conducted a case-control study involving 105 children diagnosed with T1D and 210 control participants matched in terms of age (±1 year), sex, and place of residence. The aim of the study was to examine the hypothesis that psychological dysfunction and stressful life events could contribute to an elevated risk of developing T1D. The researchers investigated various categories of stressors, including health-related stressful events (such as participant hospitalization or accidents), significant family events (such as the loss of a close relative or parental divorce), changes in family structure (such as a relative leaving home or the addition of a new sibling), job-related issues for parents (such as changing or losing a job), school-related issues (such as starting elementary school or changing schools), other major life events (such as severe accidents, hospitalization, or death of a close friend, parental conflicts), and minor life events (such as conflicts with parents, teachers, or neighbors, physical attacks, getting lost in town, separation from parents, or school examinations). The results of the study indicated that all of these stressors were significantly associated with an increased risk of developing T1D.[36]

Stress and Pemphigus

Pemphigus refers to a group of autoimmune disorders marked by blister formation. It is characterized by the deposition of IgG antibodies on the keratinocyte membranes within the epidermis, leading to acantholysis and blister formation. Two primary clinical forms of pemphigus are recognized in the literature. Pemphigus foliaceus (PF), endemic in specific regions, exclusively affects the skin. In PF, autoantibodies predominantly target desmoglein 1, a cadherin-type protein found in desmosomes that plays a crucial role in keratinocyte adhesion. On the other hand, pemphigus vulgaris (PV) affects both the skin and mucous membranes. In PV, autoantibodies are directed against both desmoglein 1 and desmoglein 3. Desmoglein 3 is predominantly found in the lower layers of the epidermis and in the mucosae.[38] Stress has been identified as a potential triggering factor for pemphigus in susceptible individuals. Research involving patients over a 5-year period found that significant life events with a negative impact from 3 to 5 (important, very important, or disastrous) in impact occurring in the months prior to the onset or worsening of pemphigus were prevalent.[38] The primary treatment approach for pemphigus vulgaris typically includes systemic GCs and adjunctive immunosuppressive medications. Emotional stress is recognized as playing a significant role in the onset or exacerbation of pemphigus, especially among individuals with a familial predisposition and specific HLA typing. Mazzotti explored the relationship between psychological stress, dysfunctional investments on appearance, and anxiety and nosocomial depression among 78 patients diagnosed with Pemphigus vulgaris and PF. The study utilized interviews and self-applicable questionnaires to assess dysfunctional investments on appearance. The findings demonstrated that patients experiencing psychological stress also exhibited higher levels of dysfunctional investments in their appearance.[39]

Stress and Infectious Disease

Human Immunodeficiency Virus

Research has demonstrated that stress can impact the progression of virally initiated illnesses, particularly affecting individuals with human immunodeficiency virus (HIV) who are especially vulnerable. Experimental studies with animals have provided supporting evidence, showing that exposure to social stressors leads to reduced survival rates.[7] Several authors have

highlighted the detrimental impact of stress on various clinical outcomes related to HIV disease progression, such as AIDS stage, decline in CD4 cell count, increased viral load, AIDS diagnosis, and mortality due to AIDS. In human studies, the effects of stress on HIV progression are most evident when stress is defined as exposure to traumatic life events or assessed through interview-based methods. For instance, in a longitudinal study spanning one year involving children and adolescents living with HIV (n=618), researchers measured the CD4 percentage and recorded negative stressful life events. These events, ranked by frequency, included hospitalization of a family member, illness of a family member, loss of housing or change in housing, departure of a family member, death of a family member, parent losing a job, death of a parent, and death of a sibling. The study revealed a threefold increase in the risk of CD4 percentage decline among those who experienced two or more stressful life events compared to those who did not.[40] Several studies have reached the consensus that individuals living with HIV who experience elevated levels of perceived stress often exhibit subpar abilities in managing stress and adopting appropriate coping strategies. Moreover, lower scores in perceived stress have been linked to prolonged survival rates among HIV-infected individuals. The presence of depression significantly affects those with HIV, as it is connected to immune system suppression, heightened frequency of symptoms, and expedited advancement to AIDS.[41]

Upper Respiratory Infection

Upper respiratory infections (URIs), which are frequently attributed to rhinoviruses, coronaviruses, or influenza viruses, pose a significant public health challenge. The findings of a research have provided evidence supporting the association between psychological stress and an elevated vulnerability to subsequent URIs. Further analyses indicated that the effect sizes concerning the association with stress did not vary significantly based on the methods used to evaluate URIs, the type of stress assessed, or whether the studies involved natural exposure to pathogens or experimental exposure to a virus with control for preexposure antibody levels.[42] Another research investigated the relationship between psychosocial stress and susceptibility to upper respiratory tract infections in 45 children with a history of recurrent colds and flu, comparing them to 45 healthy children of similar age and gender distribution. Moreover, the study investigated mucosal immune protection against upper respiratory tract infections (URTI) by assessing the concentration of secretory immunoglobulin A (sIgA) in saliva and its ratio to albumin. Children with a history of frequent colds and flu showed increased levels of various psychosocial stress factors, including exposure to stressful events, personality traits associated with stress, and indications of emotional disorder. Additionally, these children exhibited lower sIgA/albumin ratios, indicating a deficiency in local mucosal immunity. These findings support the idea that psychosocial stress reduces the efficacy of local immune defenses against viral invasion or bacterial colonization in the upper respiratory tract. This depletion of immune defense may contribute to an increased susceptibility to colds and flu.[43] When individuals become infected with a URTI-causing pathogen, there is an increase in the production of sIgA, which is a crucial protective marker against URTIs. The peak production of sIgA typically occurs on the fourth day of symptom onset and plays a significant role in preventing viral adherence to the nasal and oral mucosa. On the other hand, chronic deficiency of sIgA have been associated with recurrent URTI, likely stemming from the absence of this crucial protective mechanism. Research findings have suggested that employing stress management strategies can shorten the duration of illness, regardless of negative affect and the rate of sIgA secretion. While the exact element of the intervention responsible for this outcome remains unidentified, psychological interventions could potentially mitigate symptoms linked to URTIs.[44]

Herpes Simplex Virus

Herpes simplex virus (HSV) is a double-stranded DNA virus with an icosahedral structure, classified within the Herpesviridae family. It consists of two antigenically distinct serotypes: herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). While HSV-1 is commonly associated with orofacial infections and HSV-2 with genital infections, both serotypes can affect various regions of the body.[45] In a study, it was found that individuals experiencing frequent recurrences of HSV-1 had significantly higher levels of stress and

negative mood compared to those who experienced occasional or no recurrences. Moreover, there was a longitudinal association observed between high levels of perceived stress and the recurrence of HSV-1. Generally, individuals prone to frequent HSV-1 reactivation might be more susceptible to the impact of stress on immune function. Additionally, higher levels of psychological stress were linked to subsequent reactivation of HSV-1.[46] Numerous investigations have established the connection between stress and the increased likelihood of reactivation from latency in neurons for human alpha-HSV-1, regardless of its form (acute, episodic acute, or chronic). Furthermore, factors such as stress (acute, episodic acute, or chronic), fever, UV light, and heat stress also contribute to the probability of reactivation from latency in humans. It is noteworthy that these diverse stimuli possess the ability to activate the GRs, which is surprising in itself. For example, stress induces an elevation in cortisol levels, subsequently activating the GR through a liganded mechanism. This GR activation triggered by stress expedites the process of reactivation from latency, while the presence of a specific corticosteroid antagonist impedes viral replication and reactivation from latency. Additionally, both the GR and specific stress-induced cellular transcription factors stimulate viral promoters responsible for driving the expression of crucial viral transcriptional regulators, specifically infected cell protein 0 (ICP0), ICP4, ICP27, and viral tegument protein (VP16). Consequently, it is predicted that the GR initially stimulates the expression of viral genes. Furthermore, the immune-inhibitory functions mediated by the GR are anticipated to enhance viral replication and facilitate the spread of the virus.[47] According to research findings, mice exposed to stress during intranasal HSV infection exhibited higher levels of infectious virus in their nasal cavity compared to control mice that were not subjected to stress. Similarly, mice subjected to psychological stress during vaginal HSV infection demonstrated higher vaginal viral titers and increased associated pathology. These effects were linked to compromised innate and HSV-specific adaptive immune responses. Specifically, restraint-stressed mice showed a significant reduction in NK cell numbers at 2 days post-infection. Further investigation into the adaptive immune response revealed a decrease in HSV-specific $CD8^+$ T cells not only in the vaginal tissue but also in the draining iliac lymph nodes (ILN). Moreover, stressed mice demonstrated decrease functionality of these cells, as evidenced by reduced degranulation and IFN-γ production in the ILN, when compared to non-stressed counterparts.[48]

Stress and Cancer

Multiple investigations have identified a correlation between psychological stress and the growth and metastasis of cancer in both animal models and case studies involving cancer patients. Stress triggers the release of stress-related mediators, including catecholamine, cortisol, and oxytocin, through the activation of the HPA axis or the SNS. These stress-related hormones and neurotransmitters have adversely effects on stress-induced tumor progression and cancer treatment outcomes. Notably, catecholamine plays a prominent role in influencing tumor progression by modulating various cellular signaling pathways through ADRs, which are expressed by different types of cancer cells. The activation of ADRs enhances the proliferation and invasive properties of cancer cells, influences cellular activities within the tumor microenvironment, and regulates the interaction between cancer cells and their microenvironment to facilitate tumor progression. Furthermore, other stress mediators such as GCs and oxytocin, along with their respective receptors, are involved in stress-induced cancer growth and metastasis.[49] The impact of stress on immune function in cancer patients, particularly within the tumor microenvironment, has been investigated. It was observed that breast cancer patients experiencing social disruption exhibited decreased levels of TNF-α. Furthermore, individuals with psychiatric illnesses displayed reduced DNA repair capabilities. Stressful life events, depression, and other psychiatric disorders were shown to disrupt the circadian rhythms of the HPA axis. These stress-induced disruptions in hormonal and immunological circadian rhythms were also proposed to contribute to cancer progression. While most carcinogens are expected to cause cellular DNA damage, the body possesses defense mechanisms that activate enzyme systems to eliminate chemical carcinogens and processes to identify and repair damaged DNA. Additionally, the immune system plays a role in eliminating mutant or unrepaired DNA. However, when these defense mechanisms fail to function

properly, faulty DNA may be associated with an increased risk of cancer.[50] The exposure of a mouse fibroblast cell line to serum obtained from stressed mice, or adrenaline, noradrenaline, and cortisol (individually or in combination), resulted in an elevation of DNA damage and a reduction in DNA repair following exposure to UV irradiation. In non-cancerous cell lines derived from both mice and humans, the activation of β-adrenergic receptors led to the production of reactive oxygen species and the degradation of p53 through the β-arrestin–MDM2 pathway, resulting in increased DNA damage and hindered DNA repair. However, it should be emphasized that DNA damage alone is inadequate to initiate the formation of tumors. The process of tumorigenesis requires the accumulation and maintenance of mutations over successive cell divisions, accompanied by the acquisition of specific characteristics such as apoptosis resistance and enhanced proliferation.[51] Chronic stress triggers the release of CRH from the hypothalamus and ACTH from the pituitary gland, which, in turn, ACTH stimulates the release of cortisol from the adrenal cortex into the bloodstream. Catecholamine (epinephrine, norepinephrine and dopamine) is produced from both the adrenal gland medulla and nerve fiber endings. These stress-related hormones exert their biological effects by binding to specific receptors present on the surface of various cell types. Previous studies have demonstrated that catecholamines and GCs contribute to tumor initiation and metastasis, which have been associated with poor survival outcomes.[52]

Conclusion

Chronic stress, particularly in early life, significantly impacts immune function through the release of hormones like NE, EPI, and cortisol, leading to immune dysregulation. This dysregulation includes altered cytokine balance, suppressed immunity, and increased vulnerability to diseases. Effective stress management is crucial to mitigate these effects. Stress hormones, via receptors like mineralocorticoid and GRs, modulate stress responses and immune function. Stress is a significant risk factor in autoimmune diseases like RA and MS, exacerbating symptoms and increasing relapse rates. Psychological stress is associated with worsened symptoms and altered cytokine profiles in diseases like SLE and RA. Stress also impacts autoimmune diseases like T1DM and pemphigus, potentially triggering their onset or worsening. In viral infections, stress weakens immune protection and enhances viral replication, increasing susceptibility and severity. Stress also influences cancer progression through hormonal and immunological pathways, promoting tumor growth and metastasis. Understanding and managing stress are crucial in preventing and managing various diseases.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgement

The authors would like to thank the Clinical Research Development Unit of Baqiyatallah Hospital, for all their support and guidance during carrying out this study.

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