

# STRESS: DYSREGULATING OUR IMMUNITY!!!

Ipsa Singh,<sup>1</sup> Parvathi Devi M,<sup>2</sup> Ravindra SV,<sup>3</sup> Dharamveer Singh,<sup>4</sup> Gurez Singh<sup>5</sup>

Post Graduate Student,<sup>1</sup> Professor & Head,<sup>2</sup> Reader,<sup>3</sup> Senior Lecturer,<sup>4</sup> Senior Lecturer,<sup>5</sup>

Department of Oral Medicine & Radiology, Teerthanker Mahaveer Dental College & Research Center, Moradabad.

## Abstract

It is a well-known fact that stressful events take a toll on health. Stress, including both psychological as well as physiological, have been demonstrated to influence the immune response. Several retrospective and prospective studies, have demonstrated effect of psychological and physiological stress on immune-based diseases such as inflammation, asthma, viral infections, auto immune disorders. It is presumed that the stress-triggered neuro-endocrine hormones that lead to immune dysregulation, which ultimately results in these diseases by altering or amplifying cytokine production. In this review we focus on immune dysregulation by stress and the health consequences of these changes.

**Key Words:** - Stress, Psycho-neuro-immunology (PNI), Immune dysfunction.

## Introduction

The central nervous system (CNS), the endocrine system and the immune system are complex systems that interact with each other.<sup>1</sup> Stress, including both psychological as well as physiological, have been demonstrated to influence the immune response, presumably through activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system.<sup>2</sup> Alterations in immune function, in particular the type-1/type-2 cytokine balance, secondary to increased psychological stress, are thought to mediate these changes in health. The field of psycho-neuro-immunology seeks to establish the link between behaviour, neuro-endocrine functions, immune responses and health. The current review focuses on immune dysregulation by stress and the health consequences of this changes.<sup>1</sup>

## Stress & Stress Response

Stress is a psycho-physiological process, usually experienced as a negative emotional state. It can be defined as body's reaction to a change that requires a physical, mental or emotional adjustment or response. The term stress was coined by Walter Cannon in year 1952.<sup>2</sup> Psychological stress occurs when events or environmental demands exceed an individual's perceived ability to cope up with these demands.<sup>1</sup> Stress is caused by an existing stress causing factor or "stressor". 'Stressor' is defined as events posing threat, are judged in the context of dispositional and environmental factors.<sup>3</sup> stressor is a stimulus that activates the hypothalamic-pituitary-adrenal (HPA) axis and/or the sympathetic nervous system (SNS) to help an organism to adapt physiologically to deal with a threat.<sup>4</sup> Stressors may be physical (i.e. infection, chemical exposure), cognitive (death of a loved one, perception of imminent danger), or a combination of both physical and cognitive (fire-fighter on a 24-h shift). Stressors can be further categorised into acute (minutes to hours), sub-chronic (less than 1 month), and chronic (months to years). Different types of stressors as well as duration of stress may elicit different neuroendocrine responses and immune alterations.<sup>2</sup> Various types of Stressors are enumerated in table 1.

**TABLE 1: TYPES OF STRESSORS**

Physical	Cognitive	Chemical
Trauma/Injury	Anxiety	Environmental toxins
Exercise/Exhaustion	Depression	Diet
Pain	Anger	Medication
infection	Major life events	Recreational Drugs
Hyper/hypothermia	Daily 'hassles'	Occupational Exposures

Selye conceptualized the physiology of stress as having two components: the negative, which he called distress, and the positive, which he called eustress. He documented that stress differs from other physical responses in that stress is stressful irrespective of whether the body is receiving good or bad news, that is, of whether the impulse is positive or negative.<sup>4</sup>

## Pathogenesis of a stress induced Immune dysregulation

The immune system communicates bi-directionally with the central nervous and endocrine systems and have an impact on health.<sup>5</sup> The activation of the stress-response system influences the close relationship between the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, and the immune system. Stressors can activate the sympathetic-adrenal-medullary (SAM) axis, as well as the HPA axis, and thereby provoke the release of pituitary and adrenal hormones i.e. catecholamines (adrenaline and noradrenaline), adreno-corticotrophic hormone (ACTH), cortisol, growth hormone and prolactin. Each of these hormones can induce quantitative and qualitative changes in immune function.<sup>1</sup> Neuro-endocrine hormones triggered during stress leads to immune dysregulation either via over-production of neuropeptides and cytokines or via amplified cytokine production.<sup>3</sup> Furthermore, depression can substantially boost cortisol levels, and increases in cortisol levels can provoke multiple adverse immunological changes causing immune dysregulation or altered or amplified cytokine production, resulting in atopic autoimmune disease or decreased host defense.<sup>4</sup> Moreover, stressed individuals may develop unhealthy habits including poorer sleep patterns, poorer

nutrition, less exercising and a greater propensity for abuse of alcohol, cigarettes and other drugs which have adverse immune and endocrine consequences.<sup>1</sup> Chronic stress or depression causes increased circulation of T-cell lymphocytes and lower cortisol levels, placing these patients at risk for developing autoimmune disease and is also associated with a suppression of NK cell cytotoxicity, lymphocyte proliferation and production of IL-2 and IFN-g.<sup>3</sup> Stress could lead to decreased host defenses, decreased response to vaccines, viral susceptibility, or malignancy.<sup>2</sup>

### **Stress and inflammation**

Stress induces immune dysregulation partly through alterations in the production of proinflammatory cytokines. Both physical and psychological stressors can provoke transient increases in pro-inflammatory cytokines, particularly in IL-6. Increased levels of these proinflammatory cytokines, such as IL-6, have been linked to various age-related diseases and conditions including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, frailty and functional decline and to certain cancers e.g.: chronic lymphocytic leukaemia.<sup>1</sup>

### **Stress and asthma**

In comparison to healthy individuals asthmatics have higher levels of life stress and negative emotions, such as panic, fear and irritability. Studies have shown that the increased psychological symptoms are a result of asthma exacerbations and extreme emotional manifestations can worsen asthma symptoms. These studies demonstrated that mild to moderate asthmatic subjects have immunological changes (decreased NK cell cytotoxicity and cytokine alterations) in response to stress. These immune alterations are consistent with a cytokine milieu that could potentially worsen asthma.<sup>2</sup>

### **Stress and viral infections**

Psychological stress has been associated with increased susceptibility and/or risk of infectious diseases, including upper respiratory infections (URI), herpes reactivation and HIV. Cohen *et al* reported & demonstrated that persistent stressors and anxiety causes recurrence of genital herpes in women. Graham and colleagues prospectively followed 235 adults, and found that higher levels of stress were associated with confirmed URIs.<sup>2</sup> Herpes simplex virus (HSV) is a natural human pathogen that is characterized by its ability to cause an acute infection at a peripheral site and to establish a latent infection in the local sensory ganglia, and stress can exacerbate HSV lytic infection. Several studies that have been carried out have provided compelling experimental evidence that stress not only increases the development and severity of HSV infection, in both the peripheral nervous system and the CNS, but also suppresses cytotoxic T lymphocyte (CTL) responses to HSV infection.<sup>1</sup> The incidence of Herpes zoster (also known as shingles), which is caused by the reactivation of latent varicella-zoster virus (VZV), increases with age, presumably owing to a decline in cell mediated immunity to VZV.<sup>2</sup> Schmader *et al* indicated in his study that

psychological stress in healthy community-dwelling older adults was associated with the occurrence of herpes zoster.<sup>1</sup> Kiecolt-Glaser *et al* conducted influenza-virus vaccine studies with human participants showing that stress can influence infectious-disease risk. In the study men and women who were chronically stressed by caring for a spouse with dementia showed clear deficits in both their cellular and humoral immune responses to an influenza-virus vaccine compared with well-matched control individuals who were not carers. Humoral as well as cell-mediated immune responses were poorer in the stressed carers compared with control individuals.<sup>2</sup> Studies of HIV-infected men have also indicated that stress increases the rate of disease progression. Leserman *et al* conducted a study on HIV-positive men who were asymptomatic at entry to the study but those showed faster progression to AIDS who faced more stressful life events and less social or interpersonal support.<sup>2</sup> Epstein-Barr virus (EBV) — the aetiological agent of infectious mononucleosis — is another herpes virus that establishes latent infection and can be modulated by psychological stressors. In a study conducted in West Point Military Academy (New York, United States) cadets who were seronegative for EBV on entry into the academy were followed for 4 years. Men with particular psychosocial risk factors (high motivation for a military career in the face of poorer academic performance) were more likely to develop infectious mononucleosis and were likely to be hospitalized for longer periods.<sup>1</sup> Thus, stress can modulate the steady-state expression of latent HSV, EBV and CMV, down-regulating the specific T-cell response to the virus to an extent that is sufficient to result in viral reactivation.<sup>3</sup> Although the mechanisms behind stress-associated reactivation of latent herpes viruses are not fully understood but, *in vitro* studies have shown that glucocorticoid hormones can reactivate these virus.<sup>4</sup>

### **Stress & Autoimmunity**

Physical and psychological stresses have also been implicated in the development of autoimmune diseases.<sup>4</sup> The aetiology of the loss of normal self-tolerance in autoimmune diseases is multi-factorial. Genetic, hormonal Immunological and environmental factors are all considered important in the development of these disorders.<sup>3</sup> A recent theory combines all these factors together with stress into a mosaic to describe the pathogenesis of autoimmune disorders. Various autoimmune diseases where stress is implicated as a causative factor are: Recurrent Aphthous Stomatitis, Oral Lichen Planus, Rheumatoid Arthritis, Hashimoto's Thyroiditis, Graves disease, Insulin Dependent Diabetes, Multiple sclerosis etc.<sup>6</sup> Autoimmunity may occur in all endocrine tissues, with a particular prevalence in thyroid and pancreatic islets. The most demonstrative clinical expressions of this autoimmunity are Graves' disease and insulin-dependent diabetes.<sup>3</sup> Mitsonis *et al* summarized the psychological and biological mechanisms by which stress may impact the progression of Multiple Sclerosis. Their findings indicate the impact of a number of factors, including duration, frequency, severity and the type of

stress, as well as the patient's optimism, perceived social support, and coping strategies. Applied implications are discussed, concentrating on the need for multidisciplinary care interventions that target the patient's primary disease symptoms.<sup>4</sup> Stojanovich conducted a study in which patients with systemic lupus erythematosus (SLE), RA, and primary antiphospholipid syndrome (PAPS) were asked to complete a questionnaire about different stressors that preceded the onset or exacerbation of their disease. Patients stated that sickness or death in the family, financial problems, loss of a job, and the unstable political situation (e.g., the Serbia bombings and economic sanctions) caused them considerable prolonged anxiety. One or several factors outside of a person's control, many of them persisting for long periods of time, were reported to cause stress. The study included 120 SLE patients, 141 patients with PAPS, and 94 RA patients. SLE patients selected stress in 75.8% of the cases, far more often than other known triggers such as smoking (46.8%) and family history (21.3%). A significant percentage of PAPS patients (44.8%) considered prolonged stress to be the lead cause of their disease, as did a similar number of RA patients (42.5%).<sup>3</sup> Most evidence of stress contributing to autoimmune disease remains circumstantial mechanism by which stress affects autoimmune disease is not fully understood. Unlike hereditary and genetic etiological factors that cannot be changed, many lifestyle & environmental factors can be modified in order to better manage autoimmune disease.<sup>4</sup>

### **Stress management and behavioural intervention**

Han Seyle stated that "Adopting the right attitude can convert negative stress into positive stress".<sup>4</sup> The treatment of immune dysfunction based diseases should also include stress management and behavioural intervention to prevent stress-related immune imbalances. Interventions such as weight management, stress reduction, appropriate diet, and a healthy home environment may be very important in the prevention of flares and in slowing the progression of these diseases. Various Stress reduction methods are: Stop negative thought process, practice breathing exercises, regularly exercising, maintain proper nutritious diet, practice Self-hypnosis, relax in a quiet environment & in comfortable position, join group support, practice yoga, meditation & time management.<sup>8</sup> Given the potential link between Stress and systemic health problems occurring secondary to immune dysfunction, prevention of stress may be an important step in maintaining overall health. It's necessary to spend time planning, breaking task into small parts, evaluating ones goals & objectives to avoid work related Stress. Techniques like Yoga, Meditation, Breathing exercises improves the overall well-being of such individuals by targeting stressors & decreasing pro-inflammatory cytokines, particularly in IL-6 decreased levels of these pro-inflammatory cytokines decreases risk of various immune dysfunction related diseases.<sup>7</sup> Individuals at risk of immune dysregulation should avoid pessimism, perfectionism, smoking, alcoholism, procrastination. These unhealthy habits including poorer

sleep patterns, poorer nutrition, less exercising and a greater propensity for abuse of alcohol, cigarettes and other drugs which have adverse immune and endocrine consequences ultimately amounting to more stress to body & mind.<sup>2</sup> Cognitive behavioural therapy is a well-established treatment for depression & also reduces inflammation. This treatment may be particularly beneficial to those experiencing chronic stress.

### **Conclusion**

It is clearly evident that stress negatively effects immunity in humans.<sup>2</sup> Currently, it is hypothesized that through activation of H-P-A axis and S-A-M axis, stress induces a dysregulation of the type-1/type-2 cytokine and that these type-1/type-2 cytokine alterations either increases susceptibility or severity of immune-based diseases.<sup>1</sup> However, further studies are required to clearly define the role of psychological stress on immune-based diseases, the mechanisms of the stress-associated immune alterations, the specific nature of the stressors and the clinical course of stress mediated alterations in disease.<sup>2</sup> All this will aid in development of pharmacological and behavioural interventions to prevent and also treat the clinical sequelae of stress-associated immune dysregulation.

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### **Corresponding Address:**

Dr.Parvathi Devi M.

Professor & Head,

Department of Oral Medicinie & Radiology,

Teerthanker Mahaveer Dental College & Research Center,

Moradabad – 244001.

Email Id.:- drparvathidevi@gmail.com