

Editorial

PSYCHO-NEURO-IMMUNO-ENDOCRINOLOGY: STUDY OF THE KEY FACTORS OF DISEASE CREATION

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ABSTRACT: Psychological stressors can show their negative effects on an individual's mental and physical states. Following the psycho-neuro-immuno-endocrine axis, they can influence different internal organs and systems of the body. Such influence can affect the hypothalamus-pituitary-adrenal axis and modify the secretion of different neuroendocrine mediators. Altered secretions of neurotransmitters, neuropeptides, and other cytokines and chemokines (including pro-inflammatory cytokines); corticosteroids, catecholamines, etc. can initiate or potentiate health problems of different types and magnitudes. Psychological stressors can affect feeding, social behavior, pain sensation, learning, memory, reproduction, etc. They may act as the root for the development of conditions like epilepsy, hysteria, dementia, melancholia, psychosis, movement disorders, etc. Anxiety, confusion, depression, memory issues, problems in decision-making, attraction to negative thoughts, difficulty in focusing, lack of self-confidence, emotional disturbances, sudden changes of mood, increased irritability, unhappiness, hopelessness, inability to relax, etc. are some common effects of stress. Physiological conditions like headache, migraine, increased heart rate, sleep disturbances, high blood pressure, muscle tension, decreased libido, early fatigue, different gastrointestinal disorders, obesity, diabetes, idiopathic diseases, atopic skin diseases (eczema, acne, etc.), psoriasis, delayed wound healing, menstruation problems of ladies, etc. are developed due to stress. Developments of various immunity-related, allergic, rheumatic, autoimmune, endocrine, neoplastic, and cardiovascular diseases are connected to different psychological stress components. Development of a self-care attitude, changing the surrounding environment to a favorable one, modification of lifestyle, practicing mind-controlling exercises like yoga and meditation, as well as taking assistance from any mental health professionals can be considered to counter or overcome psychological stress and staying away from different physical and mental health problems.

Keywords: Psychological stressors, Mental health, Physiology, Nervous system, Endocrine system, Immunity, Psoriasis, Cancers.

Human civilization proceeded along with the development of the brain, both in size and activities. The development of a very strong power of thinking is also associated with the development of high ambitions and frustrations. Failure to tackle the adversities of life can affect the power of thinking, and it creates a stressful condition in the mind, termed psychological stressors [1, 2, 3].

The term Psycho-Neuro-Immuno-Endocrinology (PNIE) was first described in 1936, though such effects of psychology on health have been noticed since ancient times and documented in different cultures. It covers the study of interactions between different psychological factors with physiological processes like neuronal, endocrine, and immune responses [1, 4, 5]. Thus, the

subject deals with all four clinical areas together- psychology, nervous system, immunology, and endocrinology at various combinations and might be able to explore the root cause and developmental phenomenon of many disease conditions thought to be of unknown etiology so far [2, 4, 6].

Psychology is the study of mind and behavior and their interactions, nature of expression, etc. The altered functioning of the nervous system, either central or peripheral nervous systems or both, affects both the physical body and mind [2, 3, 7].

Immunology studies the development and functioning of the body's defense mechanisms against invaders. While hypo-functioning of one or a few body systems can make a person over-susceptible to

infective agents, uncontrolled or over-activity of the system/s can also cause several serious disease conditions [2, 7]. The term Psychoneuroimmunology (PNI) describes the interactions between the emotional states, functions of the nervous system, and the immune system of an individual and the outcomes of such interactions [1, 7].

The subject 'endocrinology' deals with coordinated actions of different hormones on metabolism, energy production, growth, reproduction, stress, mood, etc., and various clinical conditions can arise due to altered secretion or functioning of the hormones [1, 3, 7].

The subject psycho-neuro-immuno-endocrinology deals with the identification of mechanisms of mind-body interactions [1, 2, 8] and the effects of one's mental states on physical health, but the reverse effects (effect of physical status on mental health) also happen equally [9]. The outcomes of different interactions of these four systems are studied part-by-part in the name of Neuropsychiatry (NP), Psycho-Neuro-Immunology (PNI), Immuno-Psychiatry (IP), etc. [1, 8, 10].

PSYCHOLOGICAL STRESSORS AND THE CREATION OF DISEASES

Role of different psychological and allied emotional factors on health

The physical and social environments surrounding a person can challenge one's ability to adapt and recover from different challenging situations. For adaptation to undesired circumstances, a balance between mental and emotional equilibrium is necessary; but the power or ability to do so differs between individuals based on factors like personal experiences, coping capabilities, flexibility level of the mind, power of adaptation, etc. Stressors may be of different natures - may be short-term or long-term. The long-term stressors like conflicts in the family, personal life, or workplace; the surrounding environment of an individual, health problems, discrimination feeling, social isolation, continued economic problems, etc. impact more on health than the acute stressors faced for a comparatively shorter period by any individual [11, 12].

Among the easily identifiable expressions of psychological stressors, anxiety feeling, confusion, depression, memory issues, problems in decision-making, attraction to negative thoughts, difficulty in focusing, lack of self-confidence, emotional disturbances, sudden change of mood, increased irritability, unhappiness, hopelessness, inability to relax, etc. are important [12, 13, 14].

The common physiological expressions of the effects of stress are headache, migraine, increased heart rate, sleep disturbances, high blood pressure, muscle tension, decreased libido, early fatigue, etc. [12, 15]. Development of different heart diseases, obesity, diabetes, idiopathic diseases, atopic skin diseases (eczema, acne, etc.), delayed wound healing, menstruation problems of ladies, cancers, etc. is commonly noticed in physical expressions of chronic stress [12, 13, 14]. Psychological stressors can induce or potentiate the symptoms of different gastrointestinal disorders, from simple indigestion to serious diseases like irritable bowel syndrome or inflammatory bowel disease [14, 15].

The PNIE provides an integrative framework to study complex interactions amongst neural, endocrine, and immune systems, as well as behavioral and psychosocial factors on the maintenance of healthy functioning, as well as the development and/or progression of illness. PNI has helped in the investigation of the pathophysiology of many diseases [8]. In addition, the level of different hormones in the body can influence other cells of the immune system, their secretions, as well as expression of the receptors of the hormones and also by creating resistance among them towards the hormones [16, 17].

People have their different psychological makeup and also have their own choices of different lifestyle-related factors. These include the food type, sleeping schedule, working schedule and style, physical exercise, use of narcotics, tobacco, alcohol, chemical drinks, processed foods, etc.; attachment to smartphones, having a nature-loving or nature detachment attitude, etc. All these factors act together and the ultimate mental and physical expressions are observed at the individual level. In another way, it can be said that by the overall outcome of the differences in the chain reactions of effects of all such factors, the psycho - neuro - immune - endocrine functions of the body are influenced and decide a large section of the physical and mental well-being of an individual [6, 18, 19].

The immunity system of the body can be influenced in different ways by psychological stressors. Effects of psychological stress on health following the interactions between the immune system and the brain are generally expressed slowly and so can be identified after a long time [13, 20]. Even the psychological stressors faced during childhood can affect the immune system in such a way that it can influence the development of the brain and its functioning in adulthood [13, 17, 21].

It is assumed from the experimental evidence that the actual root of many immunity-related, allergic, rheumatic, autoimmune, endocrine, neoplastic, and cardiovascular diseases are connected to different psychological components [1, 6, 13]. Neuropsychiatry (NP) is also related to diseases like epilepsy, hysteria, dementia, melancholia, psychosis, movement disorders, etc. [8, 10]. It is also assumed that even behind the development of severe mental disorders, environmental factors affecting psychology also play a role along with genetic predisposition [1, 10, 14].

A. Influence of psychological stressors on the nervous system and subsequent effects on health

The emotional state, mental condition, and attitude together play a very significant role in the functioning of different systems of the body including the nervous and immune systems [1, 13]. The main biological systems studied in PNI are the central and autonomic nervous system, neuro-endocrine systems, and immune system and their interactions. The central nervous system can recognize different experiences and can record them. The autonomic nervous system and the neuroendocrine systems are engaged in performing bodily functions and the immune system is involved in identifying and fighting against all the invaders in the body as well as eliminating the tumor cells. Normal functioning of all these systems by proper coordination with each other is necessary for the maintenance of good health, and any compromise at any of these steps can invite different diseases [8, 13].

B. Impact of psychological stressors on the immune system

Several pathways of interactions between the psychological state and immune system are already identified, but many such activities are still not clear. The strength and magnitude of the immunity system of the body is influenced by different psychological stressors. The psychological stress of a brief period can influence the Hypothalamic-Pituitary-Adrenal (HPA) axis and can influence the cellular immunity of the individuals negatively without showing any major impact on the humoral immunity, but chronic stress can influence both arms of the immunity system of the body [14, 22, 23].

Different studies have identified the mechanisms involved in these interactions involving human or animal models, from which the following conclusions may be drawn.

i) Psychological stressors can influence stressor-specific and time-dependent pattern of secretions from the cells of the central nervous system.

ii) Depending upon the individual, mutual, and antagonistic interactions between different hormone receptors (such as glucocorticoid and estrogen receptors), the inflammation-related genes can show expression profiles unique to the genders.

iii) Repeated social defeats can incur adverse experiences which can lead to the initiation of a few major neuro-immune actions after the migration of immune cells from the bone marrow to the brain.

iv) Exposure to any inflammatory stimulus or stress in early life affects the nervous, endocrine, and immunity systems of the body and their effects can be observed even in the later part of life [24, 25].

vi) The immune system is influenced by stressors through the PNIE pathway and the HPA axis via secretion of cortisol, catecholamine (epinephrine and norepinephrine), gamma interferon (from T lymphocytes), etc. [1, 6].

vi) Due to various activities of the pro-inflammatory cytokines (such as Tumor Necrosis Factors, Interleukin 1, 6, 8, etc.) and the tissue-damaging response of the cells involved in the cellular immunity of the body, systemic damage is performed.

vii) Decreased production of Tumor Necrosis Factor α (TNF- α) by the antigen-presenting cells (macrophages, dendritic cells, some B cells, etc.) and promotion of the T helper 2 (Th2) immune response (via secretion of some cytokines like Interleukin 4, 5, 10, 13, etc.) by the hormones like cortisol or catecholamine try to halt acute immune response but favor development of the allergic diseases.

viii) Some epigenetic factors working on the PNIE axis do not favor any acute response to the stressors and open the way for chronic stress response [1,6,17].

ix) Many psychological stressors can increase the activity of the microglial cells of the brain [3, 6, 26].

x) Psychological stressors can show many important impacts related to susceptibility to many diseases. They can influence the response of the body to vaccines (impaired immunity development), reactivation of some latent infections (such as Herpesvirus), increasing susceptibility to some diseases (such as the suffering of the common cold), cancers, autoimmune diseases, etc. [6, 16, 25].

xi) The effects of food, lifestyle, and their impacts on different internal body parts and cellular organelles (like the gut, brain, mitochondria of the cells, etc.) are

possibly involved in the determination of the immunity status of the body as well as mood and behavior of any individual [25].

C. Influence of stressors on aging and susceptibility to diseases

The major body parameters influenced by the psycho-somatic and environmental conditions (internal and external to the body) are disease susceptibility and aging. Stress is a strong risk for the health and proper functioning of all the systems of the body. Above a limit exercised at the individual level, stress can cause serious harm both in the long term and short term. It has a direct relationship with the development of early aging and more susceptibility to different diseases [6, 25]. Easy vulnerability to microbial or parasitic infections or suffering of other health problems due to lower or improper immunity status of the body are two main important aspects in this regard [13, 14].

Stress can lead to the development of serious mental conditions like depression and anxiety of different levels, and can also lead to some unhealthy lifestyles, etc. It can also lead to many secondary physical conditions like excessive weight gain, development of obesity, etc., and such conditions can invite further health problems like atopic diseases [6, 17].

D. Epigenetic influence of the psychological stressors on expression of genetic predisposition

Epigenetics is the study of the effect of all non-genetic factors influencing one or more genetic traits of an individual. The epigenetic factors are generally involved in the regulation of expression of the genes through methylation, phosphorylation, or acetylation of the DNA molecules, but not by altering the sequence of the nucleotides [6, 9, 27]. Psychological stressors can invite inflammation and different epigenetic activities like oxidative stress (non or improper removal of free radicals), mitochondrial dysfunctions, etc. [28, 29]. Effects of stressors on DNA methylation pattern, DNA wrapping protein histones, functioning of the non-coding R.N.A. during synthesis of proteins, shortening of the length of telomere, gene silencing leading to the development of abnormal cells, status of the epigenetic clock, etc. are some important aspects which can influence the immunity, disease susceptibility as well as the overall health of the individuals [13, 28, 29].

E. Principal agents involved in the physical expression of psychological stresses

Many physiological agents are involved in the physical expression of psychological stresses. The neuro-

endocrine mediators (adrenalin, noradrenalin, glucocorticoids, etc.), neurotransmitters and neuropeptides, different types of cytokines, etc. are the principal agents working in the process [7, 13, 30].

a) The stress hormones - adrenalin and noradrenalin

During responding to psychological stress, stress hormones like adrenalin and noradrenalin are released by the adrenal gland of the body. In response to these hormones, an instant rise in blood pressure, heart rate, and blood sugar level is observed. But for long-lasting or regular repetition of such conditions, serious impacts are observed on different body systems [1, 7].

b) Cytokines and chemokines

Cytokines, a specific type of small-sized proteins secreted by some cells of the immune system of the body, act as agents of communication. The chemokines are a subgroup of the cytokines that mainly engage in control of the movement of different immune cells. Both of these also perform different other vital functions of the body [7, 12]. The cytokines produced in response to the stressors are usually some pro-inflammatory cytokines. Generally, the body secretes such pro-inflammatory cytokines in response to some infections or some injury. These cytokines assist the body system in fighting against the invading microorganisms and also repairing the tissue damage caused by any injury. Hormones like adrenalin can bind with specific receptors of some cells and stimulate the production of such pro-inflammatory cytokines. The increased level of corticosteroids, catecholamine, and pro-inflammatory cytokines can lead to a state of immune suppression in the body that can affect the HPA axis and the Sympathetic-Adrenal-Medullary (SAM) axis and can influence the functioning of leukocytes, involution of the thymus and suppression of lymphopoiesis [1, 7, 8].

The effect of abnormal release of cytokines may be observed after a long time. It is found that even the experience of stressful events in childhood may cause the release of specific cytokines in adulthood leading to mental illness [7, 8]. In animal models, it was observed that the production of the type of cytokines is dependent on the type and nature of the stress [6, 7, 8].

c) Neurotransmitters

The neurotransmitters are some active messengers engaged in the work of transmission of signals from the nerve cells to the target cells (of muscle, glands, etc.) in the body. Acetylcholine, γ -aminobutyric acid

(GABA), glutamate, endorphins, dopamine, histamine, serotonin, etc. are the main neurotransmitters performing versatile functions like breathing, controlling mood, concentration, appetite, digestion, heart rate, sleep cycles, muscle movement, etc. in the body [7, 32].

d) Neuropeptides

The neuropeptides are short-chain amino acids released by the neurons and act as neurotransmitters. Their actions are comparatively long-lasting in comparison with the neurotransmitters. Over one hundred neuropeptides are identified in the human brain. They can modulate the activities of the co-released neurotransmitters in the strength of synaptic signaling. Acting as some peptide hormones, these can also influence physiological and psychological processes like feeding, sensation of pain, social behavior, reproduction, learning, memory, etc. They can also influence other different important bodily functions. Vasopressin, oxytocin, calcitonin, amylin, angiotensin, neurotensin, bradykinin, etc. are some well-known neuropeptides [14, 31, 33].

IMPORTANT PSYCHO-NEURO-IMMUNO-ENDOCRINOLOGICAL DISEASES

A. Psoriasis

Due to abnormal activity of a part of the immune system of the body, skin cells may multiply very quickly and can make patches of different types. The patches of the skin of different organs of the body become scaly and may cause inflammation or other problems in the organs like the nails or hair root of the scalp. In this chronic health problem, the central nervous system, psychological stressors, mental health, and the immune systems are intertwined. Release of some cytokines from the cells of the immunity system of the body is triggered by psychological stressors. The hypothalamus signals to the pituitary to produce more cortisol production. Then cortisol triggers the production of pro-inflammatory cytokines from the immune system of the body and all these work together with the specific genes of the body to stimulate the multiplication of the skin cells at some abnormally high rate. Along with psychological stressors, some other agents may act as epigenetic stimulants to cause psoriasis. It is noticed that some infections (like HIV infection, Streptococcal infection, etc.), some chemical medicines used to treat some heart diseases, mental health problems, malaria, etc.; vices like smoking, physical conditions like obesity, etc. can potentiate the disease. In reverse, psychological conditions like low self-

esteem, anxiety, depression, feelings of increased stress, suicidal thoughts, etc. are observed among people having psoriasis [7, 34].

B. Systemic inflammation

Systemic inflammation may develop as an outcome of psychological stresses in different ways. Continued physiological effects like sleep disturbance, increased sleep duration, production of pro-inflammatory cytokines, etc. can lead to systemic inflammation and the creation or potentiation of different diseases [17, 35]. Chronic release of different chemo-mediators due to long-term stress can cause many serious health problems. Resistance among the receptors of some cells of the immune system against glucocorticoids develops due to such continuous, high-level exposure to glucocorticoids at the cellular level [17, 21, 35]. Evidence suggests that continuous exposure to stressors results in increased phagocytic activity among the microglial cells present in different regions of the brain including the hippocampus. All such effects become a base of development for many serious health problems [3, 26, 35].

C. Cardiovascular diseases

Psychological stressors can impact the cardiovascular system in different ways. They can change the function of the endothelial cells of the blood vessels and also can influence the chemotactic pattern of the cells. The acute stressors can lead to increased Natural Killer (NK) cell-mediated cytotoxicity, leukocytosis, and decreased response to mitogens [25]. Acute and chronic psychological stressors keep the body under an elevated level of pro-inflammatory cytokines, acute phase proteins, and many hemostatic factors. The pro-inflammatory cytokines can increase blood pressure and heart rate along with several other effects. The acute phase proteins and the hemostatic factors can assist in thrombus formation that may result in the development of myocardial infarction. So, all these factors have some crucial roles in the development of Coronary Artery Disease (CAD) and many other cardiac problems [7, 25].

D. Cancers

The effect of different psychological stressors in the initiation or progression of different types of cancers is studied as a part of a thorough search of etiologies acting behind that dangerous disease. However, in spite of extensive studies, many areas of the subject are still not clear [6, 36, 37]. Some important outcomes of the related research can be listed as the following:

a) Social isolation, fatigue, well-being, etc. are studied for probable links between psychological stressors and the development of cancers. It is postulated that the psychological factors can influence cancer progression [36, 37].

b) The relation between stress and the development of cancers is measured by the detection of the level of cancer biomarkers in many cases (as in chronic lymphocytic leukemia). Diagnosis of cancers at an early stage by detection of biomarkers is given much importance nowadays [8, 36, 43].

c) Psychological stressors can lead to cancer through the activities of the pro-inflammatory cytokines or via immunosuppression, generally identified by the biomarkers [36, 37].

d) It is believed that the psychological stress and the oxidative stress are correlated [38, 39, 40]. Increased levels of reactive oxygen species (like hydrogen peroxide, superoxide anions, etc.) were detected in many cancer cells and it is assumed to be related to cancer development and progression [39, 40].

e) Natural Killer (NK) cells have a significant role in the surveillance and elimination of cancer cells from the body. It is observed that stress can lead to a lowering of the NK cell activity and their response to interferon as well as diminish the proliferation of the lymphocytes [6, 41].

f) A telomere is a structure made of nucleic acids and proteins that stay at the end part of the chromosomes and protect the DNA of the chromosomes. Normally, the size of the telomere is reduced with age. Due to some epigenetic influences like chronic psychological stress, the length of the telomere is reduced abnormally. The shorter length of telomere is linked with the development of cancers [36, 42].

g) It was noted that women having a genetic risk factor for the development of cancer show abnormalities in their immune system in response to psychological stresses [7, 8].

h) A link between psychological stress and abnormality in the immune system was identified among women with cervical, ovarian, and breast cancer [6, 7].

i) Depression and stress may influence the progression of cancers, as a poorer survival rate was noticed among cancer patients having such feelings [7, 44].

j) The breast cancer patients who received stress management interference showed improvement in their immune function. That observation can be read reversely to understand the effect of removal of stress can improve the immunity status and possibility of cancer development [6, 14, 36].

MANAGEMENT OF PSYCHOLOGICAL STRESSES

Stresses of all nature and magnitude do not have only some negative impacts on health. Many people may develop higher levels of determination after feeling stress from some failure. But above a certain level, stress may influence life negatively, both physiologically and psychologically. Such levels vary between individuals and are dependent on many variables faced at the individual level [6, 8]. To get relief from the stress and its detrimental effects, some principles may be followed:

a) Identification of the strategies to cope with the situation and development of a self-care attitude are the primary steps to follow to overcome psychological stresses [12, 14].

b) Recognition of erroneous behavior and attitude of the self and then approaching their modification can change the surrounding environment to a favorable one [45].

c) Mind-controlling practices like yoga and meditation can assist in overcoming stress [45].

d) Modification of lifestyle by correcting biological clock, increasing sleeping time, allowing time to self to engage in the favorite activities of entertainment, incurring more socialization attitude, passing time with friends and pets, staying in a natural environment away from electronic gazettes occasionally, lone walking in the morning and/or afternoon, etc. can improve the situation [12, 18, 19].

e) Taking assistance from any mental health professionals and intake of medicines to remove stress can be considered as the next option [12, 46, 47].

REQUIREMENT OF INTENSE STUDY OF THE SUBJECT

The effects of psychological stressors on the initiation and progression of diseases is a vast topic for research, which is, however, at the initial stages and many areas are not clearly understood till now.

The bearing of psychology directly on the development of a few diseases, called psychosomatic diseases, was known to the medical community. The effect of psychological stressors on the creation of a few more diseases is identified at the present time. However, there are ample possibilities to find a strong link between psychological stress felling and disease creation among individuals for many other diseases also.

There may be some indirect relation between stress and disease creation. A person, feeling separated from society, may have a strong chance of tobacco, alcohol,

or narcotic addiction. Such addictions may induce many other vices and ultimately can lead to many serious health or mental problems.

Further importance is warranted to identify the possible epigenetic influences of different lifestyle parameters (causing or assisting psychological stresses) on the initiation or progression of important diseases, specifically. The study of the positive influence of following a designed lifestyle with reduced chance of feeling stress on suppression of the genetic predisposition to the disease/s is another important area waiting for intense study.

As psychological stress can affect many systems of the body through the psycho-neuro-immuno-endocrine axis followed by the hypothalamus-pituitary-adrenal axis and by involving different receptors of cells of different organs, there are ample chances of the effect of it on creation, stimulation of genetic predisposition or potentiation of many other diseases, if not all.

CONCLUSION

Psychological stressors have enormous impacts on maintaining mental and physical equilibrium. They can affect the nervous, endocrine, and immune systems of the body to initiate or potentiate many mental and physical health problems and may lead to many diseases of a very serious nature. Identification of the effect of different individual types of psychological stresses on the individual genotype and their link with specific mental or physical health problems are to be exposed properly. Understanding the link between psychological stressors and the creation of different diseases can lead to finding some easy prevention and remedial strategies to combat different types of diseases.

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