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Stress and Allergic Diseases

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Summary

Allergy describes a constellation of clinical diseases that affect up to 30% of the world's population. It is characterized by production of allergen specific IgE which bind to mast cells and initiate a cascade of molecular and cellular events that affect the respiratory tract (rhinitis and asthma) skin (dermatitis, urticaria) and multi systems (anaphylaxis) to a variety of allergens including pollens, mold spores, animal danders, insect stings, foods and drugs. The underlying pathophysiology involves immunoregulatory dysfunctions similar to those noted in highly stressed populations. The relationships in terms of potentials for intervention are discussed.

STRESS = ↑ Allergic Response

Keywords

allergy; asthma; stress; immunoregulation

Introduction

Allergic diseases such as asthma, allergic rhinitis, food allergies, and insect sting allergies have been described since early in recorded history. A clinical condition with asthma-like symptoms was described 3500 years ago in an Egyptian manuscript dubbed the Ebers Papyrus[1]. In 1906, Austrian pediatrician Clemens Von Pirquet first used the word *allergy* to describe the strange, non-disease-related symptoms that some diphtheria patients developed when treated with a horse serum antitoxins[2]. Subequently the field of clinical allergy developed, based upon multiple discoveries: the clinical effectiveness of allergen immunotherapy[3], mast cell granules as the major source of histamine in humans [4], identification of IgE as the allergen-specific initiator of allergic reactions[5] and the lipoxygenase- based leukotriene cascade as the clinically described slow reacting substance of anaphylaxis[6] . These and other discoveries have ushered in the modern day practice of allergy and clinical immunology that cares for up to 30% of people in western societies who suffer with various allergic diseases including hay fever (allergic rhinitis), asthma , atopic dermatitis, food allergy, drug allergy and the life threatening systemic mast cell-mediated reaction known as anaphylaxis.

Allergy has been defined as the result of immune reaction to specific types of mostly protein antigens known as allergens. Atopy, genetically mediated predisposition to produce specific IgE following exposure to allergens, is clinically defined as having evidence of allergic sensitization to at least one environmental allergen. Atopy is a fundamental component of the pathogenesis of allergic disorders. Although the clinical manifestations can be distinct between affected organs in a patient and even the same organ among different patients, allergic diseases share a common pathophysiology resulting from immune dysregulation and subsequent potentially harmful inflammation (so called hypersensitivity disease).

In recent decades, many studies have shown multiple links between nervous, endocrine and immune systems. The field of psychoneuroimmunology (PNI) has and continues to describe various links between behavior, neuroendocrine functions, immune responses and health. Excessive psychological stress and allergic disorder have been linked together in clinical practice for centuries. Many allergic conditions have long been considered psychosomatic disorders which had worsened outcomes in patienst with high levels of psychosocial stress. For example, asthma was commonly referred to in most early medical texts as "asthma nervosa" based upon the belief that , in many children, it was the result of a conversion reaction from living with a histrionic mother[8]. Early descriptions of atopic dermatitis used the term "neurodermatitis" due to belief that the itch and scratch cycle which results in a rash, was related primarily to "nerves" and emotion.

Thus it is not surprising that allergy, one of the most prevalent of all human disease categories and psychological stress are related. This chapter will explore the relationships between allergic diseases and stress and suggest future mechanism-based research directions to develop therapeutic and even prophylactic approaches to disease management with stress-based interventions.

Stress

Stress can be thought of as a psychophysiological process that is a product of both the appraisal of a given situation to assess potential adversity and the ability (either perceived or actual) to cope with that potentially adverse situation[8]. The events/situations posing the potential threat are called stressors. Situations can be experiences in daily life, including daily hassles (ordinary stressors from interactions with family, neighborhood and/or school/ in the work place) as well as major life events, which may be either positive or negative such as a large promotion that requires significantly increased physical and mental effort or losing one's job resulting in financial crisis. Based on their duration, stressors are often considered acute (minutes to hours), subacute (less than one month duration) or chronic (months to years). Intensity of the stress, even when acute, may have longer lasting effects that can ovelap with a less intense stressor lasting for a longer period of time. Further, repetitive acute stressors (the same ones or even different ones) may, with time and intensity, have similar effects to that of a single long term stressor.

PNI research focuses primarily on the understanding of the relationships between psychological stress perception (both conscious and subconscious) and downstream behavior, endocrine and immune changes occurring in response to that stress perception. The brain perceives and responds to stressors and determines both the behavioral and physiological responses. The typical host response to isolated episodes of acute stress is adaptive for the protection of the host whereas chronic stress can lead to dysregulation of the mediators and exacerbate underlying inflammatory disease pathophysiology. There are multiple reported factors that can impact this cause-and-effect relationship including genetic background (which may include gender and racial differences) , previous life experiences

and past/present environmental exposures. Of note, the same factors have been reported to impact the incidence and severity of allergic diseases as well.

Adverse Impact of Stress on Health

A common clinical observation is the often adverse relationship between stress and human diseases[10]. Various sources have estimated that up to 75% of all visits to physician's offices are stress-related. This appears to be particularly true in relationship to other immune-based dysfunction such as increased susceptibility to infections and various autoimmune diseases. Stress is also implicated in morbidity and mortality of other inflammatory based diseases such as cancer, HIV/AIDS, inflammatory bowel disease and even immune senescence associated with aging. Stress may also cause persistent increases in sympathetic nervous system activity, including increase blood pressure, heart rate and catecholamine secretion as well as platelet aggregation which may explain, at least in part, the known association between stress, immune alteration and cardiovascular disease. In addition, altered sleep can modulate stress-health relationship. Sleep disturbance have been associated with adverse physical health outcomes including increase morbidity and mortality compared to population with adequate pattern and duration of sleep. Other pathologies associated with allostatic overload from chronic stress include depression[11], tendencies towards unhealthy behavior[12], diabetes[13], dyslipidemia[13]; irritable bowel syndrome[14] and cerebrovascular accidents[15].

Stress and Allergic Disease

Stress-induced exacerbation of existing allergic disease

Clinical observations implicating the adverse effects of psychological stress on disease activity in allergic patients is supported by studies that have demonstrated that allergic responses can be modulated by mood and psychological stressors. Gauci et al found a correlation between the Minnesota Multiphasic Personality Inventory distress related scales and skin reactivity in response to allergen challenge [16]. In addition, different studies have shown that the impact of life event, negative support and current mood disorder were associated with increased rate of asthma hospital admission[17] and negative life event and negative rumination were associated with asthma morbidity[18]. Further, behavior problems and family conflicts preceded the development of asthma in multiple pediatric populations[19, 20].

Another study showed enhancement of allergic inflammatory responses with natural stress exposure[21]. Sputum eosinophils levels in 20 otherwise healthy college students with asthma were evaluated before and after an allergen challenge. Although there were no baseline differences before antigen challenge at low (mid semester) and high (during final examinations) stress exposures, sputum eosinophils counts rose higher and persisted longer in response to allergen challenge during final examinations. Additionally blood eosinophils levels were significantly higher both before and after challenge during final examinations compared to mid semester samples.

Stress and incidence of allergic disease

The potential for adverse impact of maternal stress on immunity in a developing fetus and possible postnatal disease occurrence is concerning. Psychological maternal stress is increasingly considered a possible perinatal programming agent. Perinatal programming occurs when characteristics of the *in utero* environment, independent of genetic susceptibility, influence fetal development to permanently organize or imprint physiological systems. Intrauterine stress hormone levels (both maternal and fetal) are thought to rise with prenatal maternal stress. Since fetal immunity initially is involved primarily in self-nonself

programming to prevent future autoimmunity, such prenatal stress hormone exposure may alter natural immunoregulatory mechanisms such that the child has increased risk for developing various inflammatory diseases including allergy and asthma. Various animal and human studies have shown linkage between maternal stress and immune dysregulation in children. Wright *et al* reported that increased stress in early childhood was associated with an atopic immune profile in children predisposed to atopy-asthma (i.e. positive family history for atopy) [22]. They have also shown that caregiver stress can increase the incidence of early childhood wheeze independent of caregiver smoking, breast-feeding behaviors, allergen exposure, birth weight or lower respiratory tract infections[22, 23]. These findings indicate a significant potential impact of psychological stress on childhood wheeze and subsequent development of clinical allergy and asthma. These studies and others support a strong role for stress in exacerbation and possible etiology of allergic diseases.

Immunopathophysiology of allergic disease

IgE-mediated allergic disorders may manifest clinically as any combination of conjunctivitis, rhinitis, asthma, atopic dermatitis, food and/or drug intolerance and/or anaphylaxis. It has been well recognized that atopic dermatitis and food allergies are often the earliest manifestation of atopic predisposition in a young child. Nearly 50% of children with atopic dermatitis develop asthma and 75% develop allergic rhinitis. The *allergic march* is a sequential or sometimes simultaneous expression of two or three of the above mentioned allergic disorders in an individual progresses from infancy to adolescence and adulthood[24].

The prevalence of allergy and asthma has increased in nearly all countries worldwide and is more common in Westernized and economically developed countries. As many as 1 in 3 individual suffer from some form of allergic disorder[25]. Development of allergic disorders involves multiple factors including genetic components (family history) , both indoor (dust mite, molds, animal danders) and outdoor (pollens, ozone and diesel exhaust) environmental exposure – as well as other life style factors including maternal diet, reproductive physiology and birth outcomes, breast feeding, child nutrition and vitamin D level, obesity, physical activity and psychological stress.

Atopic Dermatitis (AD)

AD is a chronic relapsing inflammatory skin disease commonly associated with respiratory allergy[26]. It is the most common chronic skin disease of young children, with lifetime prevalence in US schoolchildren up to 17%. Itching and scratching are the hallmark of this disease. Itching is often worse at night leading to chronic sleep disturbance in patient and immediate family members and is a source of significant psychological and physiological stress. When patients with AD become upset, they tend to itch even more, probably secondary to flushing of the skin due to vasodilatation induced by neurogenic peptides, followed by increased histamine and prostaglandin E2 release [27]. Distribution of the rash on the face and extensor aspects in infant and young children, changing to more flexural surface involvement in older agesis a classical finding of AD. . About ninety-five percent of patients with AD become colonized by a ubiquitous pathogen, *Staphylococcus aureus* which releases toxins that can act as superantigens and stimulate marked inflammatory responses as well as specific IgE production. Patients with AD are prone to recurrent bacterial (impetigo), fungal (tinea) and viral (Herpes Simplex molluscum contagiosum) skin infections. Allergens, irritants (wool, soap, detergents, heat and humidity with sweating), infections and certain foods can worsen eczema[28, 29]. The impact on self esteem and social interactions of both children and adults with this condition cannot be underestimated and may account for some of the chronicity commonly seen in these patients[30].

ADD PSORIASIS & ECZEMA

Allergic Rhinitis—Allergic rhinitis (AR) is a debilitating disease that currently affects up to 30% of the world population . Classical symptoms of AR include profuse watery rhinorrhea, sneezing, itchy nose, and congestion. Post nasal drip might be present and cause cough or persistent throat clearing. Sometimes AR patients can also experience itchy conjunctiva, ears and throat. . AR is generally classified as seasonal (SAR) and perennial (PAR), based on presence or absence of seasonality and the source of allergens triggering the symptoms.but more recently has been classified based on duration and severity of symptoms as mild intermittent, mild persistent, moderate or severe intermittent, and moderate or severe persistent to aid with choice of therapy.

Non-allergic triggers like strong odors, tobacco smoke, and temperature changes can stimulate symptoms in AR patients similar to those induced by allergens., suggesting hyper responsiveness which is more commonly reported in lower airways. Neural reflex arcs in the upper airways, when challenged with allergens, can incite lower airway bronchospasm. These observations gave rise to the concept of "one linked airway" which addresses the observed connection between nasal and pulmonary symptoms in allergic individuals."[31]. Patient with allergic rhinitis can often have sleep impairment due to nasal obstruction which typically worsens at night. Fatigue, malaise, and impairment of work and school performance are common when AR symptoms are severe[32]. Patients with AR are more prone to upper respiratory infections during periods of high psychological stress[33].

Asthma—Asthma is defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment[34]. Based on 2005 NHIS results, an estimated 32.6 million Americans have received an asthma diagnosis during their lifetimes, an increase in prevalence by 16% from 1997[35]. Atopy, particularly to house dust mites and cockroaches and family history of allergy or asthma are known risk factors for asthma. Common symptoms described by patients include cough, wheezing, chest tightness, dyspnea and occasionally chest pain. In up to 15% of asthma patients, dry cough may be the only presenting respiratory symptom.. Exercise induced bronchospasm is present in almost 90% of all asthmatics which results from rapid change of airway temperatures with increased tidal volumes and mouth breathing. Any and all of these symptoms have been reported to be worsened in asthma patients experiencing high stress levels.

Acute exacerbation of asthma can be triggered by upper and lower respiratory tract infections (specially viruses such as rhinovirus, influenza, parainfluenza, respiratory syncital viruses), changes in weather, significant allergen exposure in sensitized individuals, cold air, exercise, various stressful situations and hormonal changes related to menses in some women. Approximately five thousands deaths occur in the United States from asthma annually.

B. Altered Immunity in Allergic Diseases

For purposes of this discussion, allergy or immediate hypersensitivity describes a series of immune based reactions occurring as a result of the induction of allergen specific IgE that binds to mast cells via high affinity FcεR1 receptors. Subsequent re-exposure to the inciting allergen causes a cross-linking of the mast cells-bound IgE with activation and release of the mast cell contents such as histamine, leukotrines, tryptase, chymase, kininogenase, and heparin within 5–60 minutes of exposure. These mediators can induce vasodilatation and vascular leaks, causing mucosal edema, increased mucus gland secretions, nasal and/or

bronchial congestion and occlusion resulting in various clinical signs and symptoms. . Late phase allergic reactions can occur six to twenty-four hours after initial exposure following the recruitment and migration of inflammatory cells like eosinophils, basophils, neutrophils, T lymphocytes, and macrophages to the target tissues (skin, nose, lung, gastrointestinal tract, and/or blood vessels). These result in more persistent symptoms. TH2 cytokines play a critical role in orchestrating ongoing inflammation.

Chronic changes seen in airways of asthmatics include smooth muscle hypertrophy and hyperplasia, goblet cell hyperplasia, submucosal gland hypertrophy, neovascularization, thickening of reticular basement membrane, and fibrotic changes with collagen deposition[49]. Airway smooth muscle hyper responsiveness is another hallmark of asthma which might precede, accompany and sometimes be independent of airway inflammation, suggesting heterogeneity of asthma phenotypes. While, increase transepithelial water losses, defective skin barrier function, allergen-and-infection-induced inflammation, and abnormal regeneration of damaged skin are the characteristics of atopic dermatitis[29].

As already discussed, the production of the IgE is under the direct control of type 2 cytokine production with IL-4 and IL-13 being responsible for isotype switch from IgM to IgE. IL-4 is also a mast cell growth factor and IL-5 is a major chemotactic, growth and activation factor for eosinophils, which are a central component of allergic inflammation[50]. Thus, clinical allergic diseases can be viewed as immunoregulatory imbalances where Th2 cytokines predominates[51].

Dysregulation of Th1 and Th2 cytokine balance play a central role in the immunopathology of allergic diseases. . Allergen-specific T- cell clones from atopic patients have a much higher percentage of TH2 or TH0 type compared with healthy individuals, which tend to have more TH1[40, 52]. Finally, treatment of allergic rhinitis with allergen immunotherapy has been demonstrated to result in a shifting of overall Th1 and Th2 cytokine levels toward a more balanced Th1/Th2 response, which correlates with decreases in clinical disease activity [53]. These mechanism studies would support the theory that physiological states associated with type II cytokine environment could exacerbates asthmatic and allergic diseases.

Since we and others have shown that chronic psychosocial stress is associated with an altered Th1/Th2 balance toward a Th2 predominance, it is not surprising from an immune standpoint that stress can exacerbate allergic diseases such as AR, AD and asthma. Such observations lead to interventions for these diseases that are based upon the notion of managing (if not reducing) stress as a means to control symptoms and, perhaps in the future, prevent the appearance of allergic diseases in the most susceptible individuals. (Fig 1)

Management of Allergic Disease

Clinical principles for managing allergic diseases include of

1. Avoidance of exposure to known allergic and non-allergic triggers
2. Controlled exposure to allergens that cannot be totally avoided (i.e. airborn pollens, mold spores, dust mite proteins)
3. Pharmacotherapy to treat mast cell mediated symptoms and reduce allergic inflammation
4. Allergen Immunotherapy for upper and lower airway disease in selected individuals

Identification of allergens to which an individual is sensitive is typically accomplished by *in vitro* (ImmunoCAP-RAST) or *in vivo* (skin prick or intradermal skin testing) assays when feasible, which is correlated with the clinical history of symptoms. Environmental control,

which includes improve symptoms of susceptible patients with allergic diseases[54]. The general goal of pharmacotherapy for any disease is to minimize the impact of the disease on patient's life with minimal adverse side effects of the medications. There are many different types of medications used to treat allergy and asthmabut corticosteroids are the most effective anti-inflammatory medications. C exert their anti-inflammatory effects by suppressing the expression of a host of inflammatory mediators (growth factors, cytokines, chemokines) and inflammatory enzymes involved in metabolism of arachidonic acid and nitric oxide (NO). Topical forms of corticosteroids (i.e. inhaled steroids for asthma, intranasal steroid sprays for allergic rhinitis and topical steroid crèmes and ointments for allergic dermatitis) represent first line therapy in everyday management of allergic diseases. In addition, short courses of systemic corticosteroids are typically used for acute exacerbations of allergic diseases . Inhaled bronchodilators (β2-agonist) and anticholinergic are also used in management of acute asthma exacerbations . Antihistamines in oral, intranasal and ocular forms as well as leukotriene receptor antagonists are also used in management of various allergic diseases.

Immunotherapy for inhaled allergens induces regulatory T cells that dampen the allergic responses to allergens. Two forms of immunotherapy, Subcutaneous Immunotherapy (SCIT) and Sublingual Immunotherapy (SCIT) are in use currently. SCIT is the conventional immunotherapy which involves injecting gradually increasing doses of an allergen that a given patient is sensitized to and has history of problems on exposure followed by a maintenance therapy with the same. Studies showed that the global assessment of improvement with SLIT was significantly better than placebo although only half the difference recorded in the SCIT study[55, 56] . Use of recombinant technology in immunotherapy is under development and in experimental phase.

Immunomodulatory therapy with anti-IgE is a major advancement in the field of allergy and immunology. It reduces the rate of clinically significant asthma exacerbations irrespective of baseline oral corticosteroid use, concomitant treatment with other controller medications and patient characteristics.

Impact of Stress on Immune system

The link between the brain and immune system involves two main pathways: the autonomic nervous system (ANS) and the-hyphophyseal-pituitary - adrenal (HPA) axis. Perception of stress leads to activation of HPA system which begins with the secretion of corticotrophin releasing hormone (CRH) which in turn induces the secretion of adrenocortictrophic hormone (ACTH) by the anterior lobe of the pituitary lobe. ACTH activates the secretion of corticoids by the adrenal cortex and catecholamines (adrenalin and noradrenalin) by the adrenal medulla. The catecholamines and corticoids suppress the production of IL-12 by the antigen-presenting cells which is a primary TH1 cytokine-inducing inducing stimulus[57]. Corticoids can also exert a direct effect upon TH2 cells thus increasing the production of IL-4, IL-10 and IL-13[58]. The end result is the predominance of a TH2 cell mediated response which would favor an "allergic" inflammatory response in a susceptible individual.

The ANS is composed of sympathetic (adrenergic, noradrenergic) and the parasympathetic (cholinergic) systems in the CNS with noradrenalin and acetyl choline as neurotransmitters, respectively and the non-adrenergic, non-cholinergic (peptidergic) system primarily located in the gastrointestinal tract. The main peptides of this system are vasoactive intestinal peptides (VIP), substance P (SP) and calcitonin gene-related peptide (CGRP). The innervation of important organs and systems related to the immune system such as the liver, spleen, thymus gland, bone marrow, lymph nodes, skin, digestive tract, and respiratory

apparatus is by postsynaptic ANS[59]. Most immune system cells have surface membrane receptors for varying combinations of neurotransmitters, neuropeptides and hormones[60].

The CNS modulates immune system through neurotransmitters (acetyle choline, noradrenalin, serotonin, histamine, γ-aminobutyric acid (GABA), glutamic acid), neuropeptides (ACTH, prolactin, vasopressin, bradykinin, somatostatin, VIP, SP, neuropeptide Y, encephalin, endorphin), neurological growth factors (neuron growth factor (NGF)), and hormones (adrenalin and corticoids) whereas the immune system can also modulate CNS function via various molecules including cytokines (tumor necrosis factor alpha – TNFα and TGFβ), chemokines (interferons) and nitric oxide (NO)[61]. Perception of acute stress stimulates the locus ceruleus which secretes noradrenalin. Noradrenalin activates the sympathetic nervous system leading to decrease production of IL-12 as described earlier.

Neuropeptides including SP, CGRP and VIP are potent vasodilators and also increases vascular permeability. SP increases the production of TNFα and IL-12 by monocytes and macrophages. SP and CRH can degranulate mast cells within inflammatory foci. All of the above processes lead to inflammatory changes[62].

SP and CGRP have been identified in bronchial mucosa as neurogenic inflammatory agents[63]. In addition, Neurokinin-1, receptor for SP, is located on bronchial vessels, bronchial smooth muscle, epithelial cells, submucosal glands and immune cells. Stress likely exerts its effect on bronchial mucosa of asthmatics by varying combinations of impacting number and function of various immune/inflammatory cells as well as direct action on bronchial mucosa[64].

Increased tissue levels of neurotrophins, acting as nerve growth factors, have been described in different respiratory and dermatologic allergic disorders. They act on immune cells, structural cells (keratinocytes, epithelial cells) and can increase angiogenesis[65]. Eosinophils and submucosal glands of the nasal mucosa are a major source of neurotrophins[66] which have been shown to regulate eosinophil survival in the lungs, increase production of specific IgE and change the cytokines profile towards TH2 predominance.

These findings and others demonstrate that interactions between the CNS and immune systems are complex and bidirectional.

Addressing stress in comprehensive allergic disease management

Similar to allergic diseases, progression of the other immune-based diseases such as cardiovascular disease, diabetes mellitus, development of AIDS in HIV+ patients and certain malignancies has been suggested for high-stress population. Thus it follows that managing stress in these patients could be expected to have salutatory effects on their underlying disease course.

Strategies for stress management as part of a comprehensive treatment plan should involve identification of high-risk population or , ideally, individuals. Current efforts are underway in our group and others to identify biomarkers that would categorize individuals into risk categories for adverse effects of psychological stress on their immune system which, in turn, would effect risk for or activity of underlying immune-based diseases. The categorization would be followed by (ideally) individualized prophylactic interventions in the highest at-risk individuals to prevent immune based diseases or therapeutic intervention in the diseased individuals with the intent to minimize the immunoregulatory imbalance that characterizes chronic stress –induced immune changes.

Stress reduction/elimination would be the most desirable intervention but is often difficult to achieve in our fast paced, high pressure societies. Accordingly, , methods (psychological, physiological, pharmacological or some combination) to improve individual coping abilities to stressful situations are more likely to be clinically valuable as a core of the interventional strategies for stress management[67].

Many studies have shown the encouraging effects of psychological interventions on clinical outcome in allergic diseases. Smyth et al showed that expressive writing about stressful events was associated with symptom reduction in asthma patients. Biofeedback as well as mental imagery has a positive role in asthma management[68–70]. In a systematic review, Huntley et al. described that relaxation therapy had a positive effect on asthma outcomes[71]. While Psychotherapy can reduce the number of asthma exacerbations and ER visits in depressed asthma patients[72]. Although evidence suggests that these interventions result in restoring a more normal Th1/Th2 balance , further research is warranted to prove a direct link between clinical improvement and immune changes following psychological interventions in allergic diseases.

Physiological interventions for allergic diseases include various forms of exercise programs as well as complementary and alternative medicine techniques such as acupuncture, chiropractic and applied kinesiology all of which may work, at least in part, by their impact on the underlying stress of the individual.. So far, well designed studies have not shown a clear benefit of complementary and alternative medicine interventions, perhaps secondary to the robust placebo effect with subsequent psychophysiological impact on immunity[73, 74] and thus likely on allergic diseases[75]. Based upon the severity of the underlying dysfunction, exercise had varied effects on immune function. Exercise training program are well tolerated in children with mild-to-moderate asthma and improves both aerobic and anaerobic fitness[76]. Exercise rehabilitation programs improve aerobic conditioning, ventilatory capacity as well as decrease hyperpnea of exercise occurred in patients with mild asthma[77]. But, as a caution, excessive exercise can lead to an exacerbation of disease in poorly controlled asthmatic patients.

Reported pharmacological interventions for stress have mainly included psychoactive agents . Both tricyclic and SSRI antidepressants may have a therapeutic role in asthma by suppressing production of proinflammatory cytokines, inducing production of anti-inflammatory molecules and/or preventing the effects of these inflammatory molecules on the brain[78]. Both adult and child/adolescent populations with asthma appear to have a high prevalence of anxiety disorders[79]. In addition, anxiolytic drugs may have beneficial in increasing the quality of asthma therapy in asthmatics with anxiety disorder[80].

Psychological stress increases superoxide release[81]. This finding suggests a potential prophylactic role of anti-oxidant agents like Vitamin C and E against stress-induced immune changes. Studies have shown vitamin C and vitamin E can reduce immunoregulatory imbalances noted in stressed individuals[82].

Thus, many different approaches with proven or likely beneficial effects are available to modulate stress and thus immune function to have positive effects in allergic patients.

Future directions

Although the adverse role of psychological stress in allergic disease activity has long been suspected by clinicians, recent research has found more direct mechanistic links between stress and immunity. Future research should include developing ways to identify high-risk individuals as well as more accurate assessment of the specific impact of stress on various regulatory and effector components of the immune system and resulting allergic diseases.

Concluding remarks

Based upon the available evidence, it seems apparent that chronic stress in susceptible individual can favor the manifestation of allergic disease and exacerbate as well as complicate control of the existing allergic diseases. Current research has delivered anatomical as well as physiological evidence of intense communication between neuroendocrine mediators, nerve fibers and immune cells in allergic diseases. There is a bi-directional relationship between psychosocial factors and allergic disorders. This suggests that optimal management of allergic disorders must involve a multipronged approach including psychological interventions as well as conventional physical and pharmacological therapies.

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References

1. Ebers, G. Das hermetische buch uber die arzneimittel der slten aegypter. Leipzig: Henrichs; 1875.
2. Bukantz SC. Clemens von Pirquet and the concept of allergie. J Allergy Clin Immunol. Apr; 2002 109(4):724–726. [PubMed: 11980437]
3. Noon L. Prophylactic inoculation against hay fever. Int Arch Allergy Appl Immunol. 1953; 4(4): 285–288. [PubMed: 13096152]
4. Riley JF, West GB. The presence of histamine in tissue mast cells. J Physiol. Jun 29; 1953 120(4): 528–537. [PubMed: 13070225]
5. Kirkpatrick CH. The Ishizakas and the search for reaginic antibodies. J Allergy Clin Immunol. Mar; 2005 115(3):642–644. [PubMed: 15753922]
6. Dahlen SE, Hedqvist P, Hammarstrom S, Samuelsson B. Leukotrienes are potent constrictors of human bronchi. Nature. Dec 4; 1980 288(5790):484–486. [PubMed: 6108512]
7. Marshall GD. Neuroendocrine mechanisms of immune dysregulation: applications to allergy and asthma. Ann Allergy Asthma Immunol. Aug; 2004 93(2 Suppl 1):S11–17. [PubMed: 15330008]
8. Osler, W. The principles and practice of medicine. Edinburgh: YJ Pentland; 1892.
9. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol. Apr 7; 2008 583(2–3):174–185. [PubMed: 18282566]
10. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med. Sep 27; 1993 153(18):2093–2101. [PubMed: 8379800]
11. Clays E, De Bacquer D, Leynen F, Kornitzer M, Kittel F, De Backer G. Job stress and depression symptoms in middle-aged workers--prospective results from the Belstress study. Scand J Work Environ Health. Aug; 2007 33(4):252–259. [PubMed: 17717616]
12. Muller N, Ackenheil M. Psychoneuroimmunology and the cytokine action in the CNS: implications for psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. Jan; 1998 22(1):1–33. [PubMed: 9533165]
13. Golden SH. A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. Curr Diabetes Rev. Nov; 2007 3(4):252–259. [PubMed: 18220683]
14. Blanchard EB, Lackner JM, Jaccard J, et al. The role of stress in symptom exacerbation among IBS patients. J Psychosom Res. Feb; 2008 64(2):119–128. [PubMed: 18222125]
15. Harmsen P, Lappas G, Rosengren A, Wilhelmsen L. Long-term risk factors for stroke: twenty-eight years of follow-up of 7457 middle-aged men in Goteborg, Sweden. Stroke. Jul; 2006 37(7): 1663–1667. [PubMed: 16728686]
16. Gauci M, King MG, Saxarra H, Tulloch BJ, Husband AJ. A Minnesota Multiphasic Personality Inventory profile of women with allergic rhinitis. Psychosom Med. Nov–Dec; 1993 55(6):533–540. [PubMed: 8310114]