



Contents lists available at ScienceDirect



Perspective

Stress and allergic skin diseases—what have we learned?

Maria Luz Lara-Marquez, MD, PhD, FAAAAI^{*}; Keith W. Kelley, PhD[†]^{*} Allergy and Immunology Clinic, San Diego, California[†] Department of Pathology, College of Medicine and Department of Animal Sciences, College of Agricultural, Consumer and Environmental Sciences, University of Illinois at Urbana-Champaign, Champaign, Illinois

ARTICLE INFO

Article history:

Received for publication May 5, 2020.

Received in revised form July 7, 2020.

Accepted for publication July 24, 2020.

The cumulative burden of chronic, ongoing, psychological stress increases health costs in the United States. Globally, psychological stress is considered an important public health threat.¹ Stress is an adaptive response to an internal and/or external disruptive stimulus that may be conscious or unconscious and is considered protective for the host. It is the subjective perception of excessive stress that causes its negative biological impact.² Natural physiological response to a stressor is an adaptive response and may include excitement and challenge that is recognized as good stress. However, when intensity, frequency, and/or duration exceed the physiological capability of the host, the stress response becomes maladaptive. This increases the allostatic load that can be perceived as extreme emotional burden, increased fatigue, excessive frustration, and/or an inability to cope with various life situations. The term allostatic load was coined by McEwen and Stellar in 1993 and refers to the physical wear and tear from excessive bad stress (ie, being stressed-out). In other words, it is the cost of long-term exposure to changing or increased neural or neuroendocrine responses evoked by repeated short-term or long-term environmental (psychological or physical) challenges that an individual perceives as being predominantly threatening and stressful.² The predominance of high stress levels in our current environment and the increasing prevalence of various allergic skin diseases (ASDs) raise the possibility of cause-and-effect relationships—that is, does excessive stress cause or worsen ASD and does ASD increase the allostatic load and thus result in maladaptive excessive stress? Various studies have found that, in general, allergic diseases, including ASD, are adversely affected by stress.¹

The skin is the largest sensory organ and is richly innervated by the somatic, autonomic, and sensory nervous systems. It is not merely a

passive barrier but is organized in distinct layers that contain specialized structures and is rich in blood vessels and immune cells. One of the ASDs that is a hallmark of how stress may affect its presentation and severity of clinical course is atopic dermatitis (AD). There is increasing evidence for the role of psychological stress as both an inflammatory trigger and exacerbating factor in AD.³

Perceived stress and allostatic overload can lead to an increase in proinflammatory cytokines, such as interleukin-1 β , tumor necrosis factor alpha, and interleukin-6 arising from inflammatory sites in the periphery, can lead to activation of the hypothalamic–pituitary–adrenal (HPA) axis that induces increased adrenocorticotropin hormone and increased cortisol secretion from the adrenal cortex. The systemic stress response also includes activation of the autonomic nervous system resulting in the production of various neurotransmitters responsible for the fight or flight response that releases adrenaline from the adrenal medulla, norepinephrine from sympathetic branches, and acetylcholine from cholinergic branches of the autonomic nervous system that innervate multiple parts of the body, including the skin.²

There is a parallel peripheral local HPA axis in the skin that regulates skin responses after exposure to environmental stressors. It is found in different cell structures in the skin, including the epidermis, in which it plays major role in skin barrier function.³ The HPA axis in the skin functions as an autocrine and paracrine hormonal system that responds to cutaneous stress. It is a hormonal and peptide network that is tightly regulated and interacts with proinflammatory cytokines and other stressors, forming a built-in self-defense in the skin barrier. As such, exogenous topical steroids can be detrimental because they may inhibit endogenous glucocorticoids from exerting anti-inflammatory functions. In addition to the components of the HPA axis, there are mediators of the cholinergic, sympathetic, and sensory nervous system terminals that release their neurotransmitters and act on local receptors of cells in the skin.³

The following are the 3 aspects of AD that are most affected by stress hormones: skin barrier function, skin immune response, and

Reprints: Maria Luz Lara-Marquez, MD, PhD, FAAAAI, Allergy and Immunology Clinic, 3675 Ruffin Rd, Suite 120, San Diego, CA, 92123; E-mail: marialuz.laramarquez@gmail.com.

Disclosures: The authors have no conflicts of interest to report.

Funding: The authors have no funding sources to report.

<https://doi.org/10.1016/j.anai.2020.07.025>

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Table 1
Selected Key Targets of Psychological Stress in the Skin of Patients With Atopic Dermatitis^{3–5}

Skin barrier	Immune dysregulation	Pruritus
The epidermis is a key target of the stress response. FLG is one of the main proteins of the skin barrier and is directly involved in the pathogenesis of AD.	In a milieu of high stress and high cortisol, there is a significant increase in the T _H 2 cytokines IL-4, IL-13, and IL-5.	High levels of stress in AD exacerbates the pruritus-itch cycle. Although the mechanism is not fully understood, there are both central and peripheral mediators.
T _H 2 cytokines down-regulate gene and protein expression of FLG and other skin barrier genes, such as loricrin and involucrin.	Predominant T _H 2 cytokines are drivers of both AD and allergic skin diseases. IL-12 is suppressed by GC favoring expansion of T _H 2 cells.	Histamine, certain proteases, IL-2, IL-4, IL-13, IL-31, TSLP, and endothelin-1 among others are local mediators of pruritus.
Cortisol derived from local (skin), systemic stress, or inflammatory cytokines acting on the HPA axis up-regulates T _H 2 cytokines. This leads to decreased FLG and skin barrier protein expression and AD exacerbation.	TSLP, IL-25, IL-33, and GM-CSF are increased by keratinocyte injury caused by barrier disruption. This leads to ILC2 activation and release of T _H 2 chemokines CCL5, CCL17, and CCL22.	One of the major peripheral mediators is SP, released by sensory nerves, that innervate all layers of the skin. SP release can be exacerbated by psychological stress.
Down-regulation of FLG by endogenous or exogenous cortisol leads to barrier disruption, an increase in pH, allergen penetration and microbial colonization. This barrier disruption results in a cascade of events that provokes or exacerbates immune dysregulation in patients with AD.	Resident cells from the epidermis (LCs) and dermis, including DDCs and mast cells, and recruited leukocytes and lymphocytes increase production of T _H 2 cytokines. Inflammasome activation occurs through IL-1 and activates cortisol synthesis in the skin.	Central sensitization is found in adult patients with AD. fMRI studies indicate activation of the ACC and DLPFC during induced pruritus vs controls that activate other areas of the brain.

Abbreviations: ACC, anterior cingulate cortex; AD, atopic dermatitis; CCL5, chemokine (C-C motif) ligand 5; CCL17, chemokine (C-C motif) ligand 17; CCL22, chemokine (C-C motif) ligand 22; DDCs, dermis dendritic cells; DLPFC, dorsolateral prefrontal cortex; FLG, filaggrin; fMRI, functional magnetic resonance imaging; GC, glucocorticoid; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; ILC2, type 2 innate lymphoid cell; LCs, Langerhans cells; RANTES, regulated upon activation, normal T cell expressed and secreted; SP, substance P; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin.

pruritus (Table 1). The epidermis has a major role in the barrier function of the skin.^{4,5} It is susceptible to the adverse effects of excessive stress hormones through T_H2 cytokine-mediated mechanisms. Immune dysregulation observed in AD is another key aspect in the pathogenesis of the disease, which can be modulated by stress hormones. T_H2 cytokines are increased by stress hormones that down-regulate gene expression of filaggrin further affecting disruption of the barrier function of the skin.^{3,4} Pruritus is another manifestation of AD that can be affected by excessive psychological stress. It often worsens at night, thereby potentially disrupting sleep patterns and circadian rhythm with proinflammatory consequences. Controlling the manifestations of all the 3 targets of psychological stress represents an important clinical challenge in maintaining symptom control and minimizing exacerbation potentials.

If we accept that psychological stress can trigger and exacerbate the key drivers of AD which leads to worsening of disease severity and challenges the possibility of optimal control, then it becomes very relevant to assess and address the management of stress in the these patients' therapeutic plans. There are known stress response modifiers, such as gender, race, ethnicity, and cultural background, along with lifestyle, socioeconomic factors, and comorbidities that may affect the perceived stress and its impact on disease.¹ Many of these cannot be changed or readily modified. Yet, there are several measures that can be taken by practicing clinicians to modify or mitigate stress effects that will optimize the therapeutic management of these patients. Examples of these measures are as follows: (1) using tools that involve accurate assessment of stress levels in individual patients. There are multiple validated clinical and research tests for measuring perceived stress, such as the Perceived Stress Scale for teens and adults, the Depression, Anxiety and Stress

Scale (DASS21),^{1,2} and other psychometric scales that can be found for children as well. These assessment instruments can potentially be combined with general allergy intake forms that can give clinicians useful tools to evaluate the patient and decide if an intervention is needed; (2) recommending stress management modalities, such as exercise, and use of integrative medicine therapies, such as mindfulness-based meditations,¹ yoga, and tai chi, among other interventions; (3) referring when needed for psychological and/or spiritual counseling if more severe emotional components are identified through the clinical assessment.

Taken together, the role of psychological stress has been underscored as part of the pathogenesis of AD, which is regulated by major neuroendocrine-immune pathways that mediate the stress response and affect the clinical course and management strategies. A more integrated therapeutic approach for patient care that recognizes and addresses the role of excessive stress is needed to optimize the management of patients with ASD.

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