Study of Psychoneuroimmunology in Atopic Dermatitis

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Abstract: Psychoneuroimmunology is an inter disciplinary field that specifically examines the biochemical cross talk between brain, behavior and the immune system and between allergy immunology concept and psychosocial factors. The increase of allergic manifestation may be associated with environmental factors such as stress. A growing number of studies have suggested an altered hypothalamus-pituitary- adrenal (HPA) axis function to stress in allergy. It is speculated that a dysfunctional HPA axis in response to stress may facilitate and/or consolidate immunological aberrations and thus, may increase the risk for allergic sensitization and exacerbation especially under stressful conditions. It has been established via clinical and physiological means that psychological stress is a significant contributor to allergy course through its direct and indirect effects on immune response, cutaneous neuropeptide expression, and skin barrier function.

1 INTRODUCTION

Psychoneuroimmunology is an interdisciplinary field of study which focuses in the biochemical interactions between the brain, social behavior and the immune system (Suarez et al., 2012), especially the correlation between immunologic disorders and psychosocial factors (Chida et al., 2008; Nordlind, 2008). Hypersensitivity reactions are identified by overabundant production of immunoglobulin E (IgE), one of which is atopic dermatitis (AD) (Buske-Kirschbaum, 2009).

Allergen presentation by dendritic cells initiates the late phase response via activation of T-helper (Th) cells which in turn secretes large amounts of interleukin (IL)-4, IL-5 and IL-13. This reflects a Th-2 dominant response which plays a big role in allergic inflammations. IL-4 and IL-13 stimulates the synthesis of IgE and also induces B cells to switch from other Ig isotypes into IgE. This is followed with an increase of Vascular Cells Adhesion Molecule 1 (VCAM-1) expressions, and the recruitment and invasion of eosinophils to inflamed sites. IL-5 induces eosinophils to secrete Eosinophyl Cationic Protein (ECO) which contributes to the degradation of cells. The role of immunologic dysfunction in the pathomechanism of allergic diseases including AD has been proven in several previous studies, however most of them remained not well understood (Buske-Kirschbaum, 2009; Dave et al., 2011).

One popular hypothesis which potentially explains the increased prevalence of AD is that its immunopathology is affected by several factors i.e.: lifestyle, nutritional status and intake, pollution and also psychosocial stress.

This study aimed to discuss the role psychoneuroimmunlogy in the pathogenesis of allergy, including the potential impact of hyper or hypo responsiveness of hypothalamus-pituitary-adrenal (HPA) axis towards the onset and chronicity of allergic diseases in dermatology, in this case, atopic dermatitis. Other factors which contributes to the dysfunction of HPA axis in allergy, including stress management therapy which targets neuro-immune systems for comprehensive allergic management is also discussed in this study.

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2 CASE

A 11-year-old female came to the dermatology and venerology outpatient clinic in Dr. Soetomo teaching hospital with clinically severe eczema along with allergic history towards house dust mites, animal fur and certain food. Laboratory results show a total IgE value of 937 (Normal value: <100), with specific IgE positivity towards eggs, poultry, shrimp, crabs, house dust mites, and bird feather as well as cat and dog fur. After a series of thorough anamnesis and examinations, this patient was diagnosed with severe atopic eczema, allergic rhinitis and chronic intermittent cough. Comprehensive patient management was done including skin care and topical as well as oral corticosteroid for eczema, symptomatic medication for allergic rhinitis, and immunotherapy.

Patient went through these regiment for a year. For the first few months, food elimination program almost always fails where the patient fails to avoid food which causes allergic reactions. The impact could be directly seen along with worsening of eczema. Clinical improvement of eczema eventually was seen after 9 months of treatment due to the patient's gradually increased compliance towards the food elimination program.

Patient went through a series of immunotherapy every week for the first 14 appointments, followed by every 3 weeks for the next. Respiratory tract conditions including sneezing, nose itching, show clinical improvement after the 10th administration. Another positive impact was that oral corticosteroid was needed less frequently after 4th immunotherapy. This researcher found an interesting fact that all the clinical improvements regarding eczema and respiratory tract complaints are somehow related to the patients father's presence.

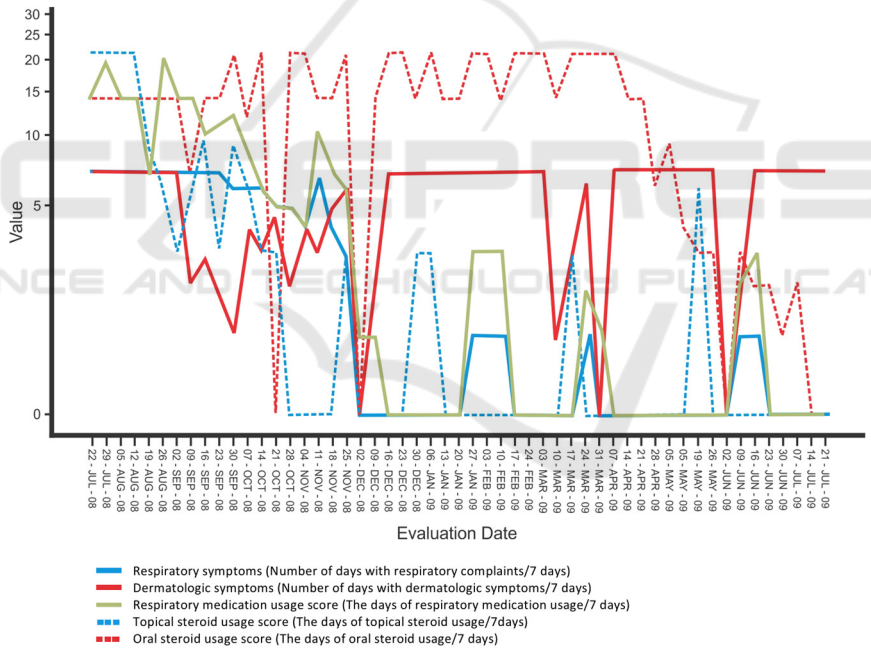

Figure 1: Graph demonstrating evaluated aspects of this patient's disease progression throughout the year, illustrated by different lines. (Endaryanto, 2015).

3 DISCUSSION

In the earlier decades of life, atopy is characterised by hyperresponsiveness of HPA axis to stress (Buske-Kirschbaum, 2009; Ball et al., 2006). The dysfunction of HPA axis mechanism in newborns which eventually leads to allergy is yet well understood. However, some studies have shown that it is influenced by genetic factors and the prosess of fetal programming. (De Weerth et al., 2005; Wüst et al., 2006). During stress psychological, the increase of endogenous cortisol which triggers dominant response from th2 will further increase the risk of allergic sensitisation and (accelerate) the onset of

allergies. Cortisole stimulates IL-4 which will later induce the production of IgE and B-cells. (Barnes, 2001). During the course of time, hyperresponsive HPA axis will switch to hyporesponsiveness. The factors which causes this phenomenon is not fully understood, but it is thought to be affected by chronic inflammation which induces continuous secretion of proinflammatory cytokines or by (chronic/prolonged) stress due to the allergy itself or due to social problems. In chronic allergy in children, lack of cortisol adequate secretion response in stressful conditions causes lack of inflammatory response control such as the regulation of pro-inflammatory cytokines, the adhesion of leucocytes and the activation of eosinophils. Hence, in children, stress also can be a risk factor of exacerbation and chronic progression of allergies due to its impact which causes HPA axis dysfunction.

The central nervous system response to phychologic stress (Suarez et al., 2012). The HPA axis responses to phsychologic stress by increasing the secretion of corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) (Glaser, 2005). which then triggers the secretion of pituitary prolactin (PRL) which inhibits lymphocyte proliferation induced by stress (Foitzik et al., 2009). CRH and ATCH also stimulates norepinephrine (NE) and the release of cortisol from adrenal cortex which in turn stimulates and regulates other immune responses while sending a negative feedback to the hypothalamus and hypophysis. This is followed by an increased release of serotonin (5HT) in the brain stem as well as P-Substance (SP), gastrin-releasing peptide (GRP) and calcitonin gene related peptide (CGRP) in the dorsal ganglia (Norlind et al., 2008; Roosterman et al., 2006; Slominski et al., 2005).

In the dermis, immune cells release cytokines, chemokines and neuropeptides which modulates the inflammatory responses, triggers the sensation of pain and itchiness and also transmits sensory stimuli through dorsal ganglia and spinal tract to spesific areas in the central nervous system. Cutaneous mast cells are known to be well related to SP, CGRP, pituitary adenylate cyclase activating protein (PACAP) and opioid releasing neurons; and is responsive towards said neuromediators. As a response to stress, cutaneous mast cells stimulate several inflammatory mediators, hence inducing local production of neurohormones and neuropeptides (Suarez et al., 2007).

Prolonged psychological stress may damage the natural barrier of the skin and increase levels of endogenous glucocorticoid which will also attribute to the alteration of homeostasis and integrity, also microbial defense of the skin itself. These are mainly caused by the inhibition of epidermal lipid synthesis which is mediated by glucocorticoid. Therefore, replacement of this epidermal lipid is a promising therapy for people who has stress related allergic skin disorder. However, no randomised trial study comparing the efficacy of topical therapy for patients with stress related atopic dermatitis and patients with non-stress related atopic dermatitis (Walker & Papadopuolos, 2005; Suarez et al., 2007; Steinhoff & Steinhoff, 2009).

There's a continuous pattern where psychologic stress causes itch in atopic dermatitis, and the itch will in turn further cause psychologic stress and this will continue on. Hence, psychopharmacology will be useful in breaking this chain. The correlation which was found between anxiety score in AD patients who experiences pruritus and NPY and NGF explains that anxiety causes pruritus via increase of expression of these neuropeptides. Therefore stress management and reduction is an necessary approach in treating pruritus in AD patients.

Patient with stress related AD also experiences an increase in serotonin-sensitive mast cells. Serotonin agonists and SSRIs improves the skin condition and reliefs the patient from pruritus through a poorly understood mechanism. Anti-pruritic effect of SSRI is thought to be due to a certain mechanism in the central nervous system. Tandosiprone Citrate (TC), an anxiolitic serotonin agonist, may be used in stress managements which are related to worsening AD conditions supported by other studies using mice models. The administration of bupropion may show clinical improvements through its role as anti-inflammatory agents which lowers TNF and as inhibitor of neurotransmitter reuptake (Steinhoff & Steinhoff, 2009; Suarez et al., 2012).

Itchiness caused by psychologic stress is also thought to be related to substance P (SP). The increase of psychological stress condition causes elevated levels of plasma SP which is then related to the worsening of AD. Adding oral olopatadine to the regular topical regiment helps relief itchiness and SP plasma levels. Therefore it is thought that olopatadine has a potential use of controlling or reducing the level of SP caused by stress, which is beneficial towards reducing pruritus in AD. Mice model studies show clinical improvement after administration of NK1R antagonists. NK1 receptors is known to be affiliated to SP, which makes it a

possible approach for pharmacological inverventions.

SP levels tend to remain the same, even after remission of AD, which suggests that SP-ergic mechanisms does not play a big role in acute clinical changes in AD (Suarez et al., 2012; Steinhoff & Steinhoff, 2009). The central or peripheral mechanisms related to pruritus management is still poorly understood. Therefore further researches regarding these matter, including the roles of neuropeptides as pruritogenic substances in AD should be done. The decision for psychoneuroalergologic management approaches in dermatology for cases such as AD should be supported by enough clinical evidence. A meta-analytic review regarding psychologic stress and atopic dermatitis proves that there is a two way relation. These findings should receive comprehensive efforts involving psychologic interventions in AD management standards.

4 CONCLUSION

The mechanism underlying psychoneuroalergology in dermatology i.e. the correlation of allergy and psychologic stress is not fully understood. However, new perspectives and concepts have been unveiled from the Psychoneuroimmunology point of view. Clinically and physiologically, psychologic stress is shown to have direct and indirect influence towards immune response, expression of skin neuropeptide and skin barrier function. Several researches have shown huge potentials in identifying new therapeutic approaches by modulating neuroimmune systems. Hopefully this will further improve AD management hence reducing chronicity and recurrence rates, lowering the burden of the disease and improving the patient's life quality.

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