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GAVIN PUBLISHERS

Archives of Epidemiology

Review Article

Mawardi P. Arch Epidemiol: AEPD-109.
DOI: 10.29011/AEPD-109. 000009

The Role of Psychodermatology in Acne Vulgaris Pathophysiology

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Citation: Prasetyadi Mawardi (2018) The Role of Psychodermatology in Acne Vulgaris Pathophysiology. Arch Epidemiol: AEPD-109. DOI: 10.29011/AEPD-109. 000009

Received Date: 29 November, 2017; **Accepted Date:** 14 February, 2018; **Published Date:** 20 February, 2018

Abstract

Acne vulgaris (AV) is a common skin disease, affecting over 90% of male adolescent and about 80% of female adolescent in all ethnic groups. It causes both physical and psychological disorders. Its pathophysiology is multifactorial interplay of hormonal imbalance, increased sebum production, bacterial colonization, and neuropeptides that plays a major role.

Acne vulgaris is a visible skin disease and commonly occurs in adolescent, therefore it is relevant to understand AV correlation with psychosocial and psychoneuroimmunology factors. Due to adolescent is a significant and vulnerable phase of life to the various stressor, it is also transition time from the immaturity of childhood into the maturity and independent of adulthood.

Psychodermatology addresses the interaction between mind and skin. Psychiatry is more focused on the 'internal' non-visible disease, and dermatology refers to the presence of morphological abnormalities appear in the skin, where connecting the two disciplines is a complex interplay described as neuro-immuno-cutaneous system (NICS). Facial skin from AV patients show marked increase of substance P-positive nerve fibers around the sebaceous glands and around acne lesions. Substance P induces gene expression of peroxisome proliferator-activated receptor (PPAR)-γ, which plays a unique role in stimulating sebocyte lipogenesis. It also stimulates various pro-inflammatory cytokines release from sebocytes, including IL-1, IL-6, and TNF-α. The interaction between nervous system, skin and immunity has been explained by discovered of various release of mediators or cytokines from NICS. There is no doubt that AV can lead to anxiety and stress, hence the patients may experience social issue and decreased quality of life.

Keywords: Acne vulgaris; Neuro-immuno-cutaneous system; Psychodermatology; Quality of life

Introduction

Acne Vulgaris (AV) is a common skin disease, affecting over 90% of male adolescent and about 80% of female adolescent in all ethnic groups [1]. It causes both physical and psychological disorders. It has multifactorial pathophysiology, involves some main processes: hormonal imbalance, increased sebum production, and bacterial colonization [2,3]. Acne vulgaris is a visible skin disease and commonly occurs in adolescent, therefore it is relevant to understand AV correlation with psychosocial and psychoneuroimmunology factors. Due to adolescent is a significant and vulnerable phase of life to the various stressor, it is also transition time from the immaturity of childhood into the maturity and independent of adulthood [2]. Acne vulgaris is a common disorder encountered on the face and upper chest, and it affects nearly teenagers each day. Furthermore, it is interesting and substantial to study deeper the contributing factors of etiology of AV [4].

Epidemiology

Acne vulgaris is an epidemic skin disease in developed countries, with its prevalence of 85% in adolescent. In the United States, AV persistent in teenagers and frequently continues into 30s in both men and women. These findings suggest that there are environment factors inducing AV after puberty, and it is found to be an independent factor from hormonal factor during puberty [5]. Acne vulgaris affect more in adolescent, approximately 90% of male adolescent and 80% of female adolescent in all ethnic groups. It significantly causes physical and psychosocial disorders. Its pathophysiology is multifactorial interplay of hormonal, sebum

production, and bacterial colonization that play an important role. Psychological stress may have in AV exacerbations [4]. Green and Sinclair conducted on 215 graduating medical students showed that 67% of students believed that stress plays a role in acne exacerbations [6]. Chiu et al. conclude that patients with acne may experience worsening of the disease during examinations with increasing stress level [7]. Kilkenny et al. showed in their study of 2525 Australian students and conclude that students reporting moderate acne were more likely to report psychiatric symptoms of depression and anxiety [8]. Smithard et al. observed 317 comprehensive school students with range of age 14-16 years old in the Nottingham, and they found that there was correlation between AV severity and emotional or behavioral symptoms [9].

Acne vulgaris is generally recognized as a skin disorder of adolescents, however a significant number of patients experience acne in patients between the ages of 35-44 years [10]. A study of 200 patients with post-adolescent acne revealed that 50% of patients had a first-degree relative suffering acne in family history [11]. Based on gender, AV is increasingly seen in women than men [12]. By recognizing AV as a chronic disease similar to eczema, early and aggressive treatment can be started to avoid the psychological sequela that can result from active AV and acne scars [13].

Clinical Manifestations

The active AV lesions appears similar in various ethnic patients. Acne vulgaris lesions in dark-skinned patients as in African Americans can develop inflammatory papules, pustules, nodules and cysts, and these inflammatory lesions can promote the development of Post Inflammatory Hyperpigmentation (PIH), acne scars and keloids. Inflammatory papules in lighter-skinned patients characteristically have an erythema; however, these lesions can develop an overlying hyperpigmentation and mimicking PIH, but the distinction is made upon palpation. Nodulocystic acne is less common in African Americans than Caucasians based on a study by Wilkins et al. Rates of nodulocystic acne lesions were significantly lower in dark-skinned patients. On the other hand, in Hispanics and Asians have similar prevalence rates of nodulocystic acne as Caucasians, although supporting evidence is lacking [14,15].

Pathophysiology

Conventional View/Theory

The pathophysiology of AV is multifactorial process involving both endogenous and exogenous factors. Acne begins with the retention of desquamated keratinocytes within the pilosebaceous unit leading to follicular plugging (microcomedo), the microcomedo wall eventually ruptures and leading to inflammation process. *Propionibacterium acnes* (*P. acnes*), an anaerobic/microaerophilic, Gram-positive rod, resides within the sebaceous follicle and also incites an inflammatory response by acting on Toll-Like Receptor (TLR)-2, which may stimulate the secretion of cytokines, such as Interleukin (IL)-6 and IL-8 by follicular keratinocytes and IL-8 and IL-12 in macrophages [16,17]. Other contributing factors include hormonal influences from estrogen and androgens, such as De Hydro Epi Androsterone Sulfate (DHEAS), which has been shown to increase sebum production in adolescent leading to AV [18]. Genetic factors may also play a role in the development of AV [19,20]. He et al published a study in 2006 showing a possible association between the CYP17-34T/C polymorphism and the development of severe AV in Chinese patients [21]. However, further studies are required to evaluate the exact roles played by hormones, particularly estrogen, and genetics in the development of AV. Some AV lesions may progress to become visibly inflamed, appearing as papules, pustules, and/or nodules. As each follicle goes through its own independent pathophysiologic “life cycle”, most patients present at any given point in time with a mixture of AV lesions in various stages [22].

Psychodermatology View/Theory

Neuro-Immuno-Cutaneous System (NICS)

Understanding the psychosocial and occupational context of skin disease is critical for the optimal management of psychocutaneous disorders. The correlation between psychiatric and dermatological disorders exists due to more than a fact, that the brain, as the center of psychological functions, and the skin has the same ectodermal origin. Connecting the two disciplines is a complex interplay between neuroendocrine and immune systems that has been described as the Neuro- Immuno-Cutaneous System (NICS) [23].

The concept of NICS means narrow interrelations between nervous system, immunity and skin. Indeed, there are numerous cellular contacts between nerve fibers, cutaneous cells and immune cells; cutaneous cells can synthesize neuromediators and they express receptors to these molecules; neuromediators are able to modulate functions of cutaneous and/or immune cells. Using confocal or electron microscopy, connections between nerve fibers and cutaneous cells have been observed. In the skin, nerve fibers may secrete neuromediators: Substance P (SP), Vaso-Active Intestinal Peptide (VIP), somatostatin, Calcitonin- Gene Related Peptide (CGRP), Gastrin-Releasing Peptide (GRP), Neuropeptide Y, Peptide Histidine-Isoleucine (PHI), neurotensin, neurokinins A et B, bradykinin, acetylcholine, catecholamines, endorphins and enkephalins. Neurohormones such as prolactin, Melano-Stimulating Hormone (MSH) or Adreno-Corticotrophic Hormone (ACTH) are also expressed in the skin [24].

Skin conditions, such as AV, are sometimes thought of as insignificant in comparison with diseases of other organ systems. Physicians’s assumptions about the effects of a skin condition are often inaccurate. The psychological effect of AV is unique for each patient. Patients should be asked how much their acne bothers them, regardless of how severe it appears to physicians.

Acne's effect on psychosocial and emotional problems, however, is comparable to that of arthritis, back pain, diabetes, epilepsy, and disabling asthma [25]. Acne vulgaris often flares with stress and premenstrually. It has been reported that psychological stress perturbs epidermal permeability barrier homeostasis, and it may act as precipitant for inflammatory skin disorders [26]. This enables multidisciplinary approach with the cooperation of psychiatric and dermatologic for diagnostic procedures and treatment of patient with psychodermatologic disorders. In psychophysiologic disorders, psychiatric factors are significant instrumental in the etiology, course and management of skin disease. The skin disease is not caused by stress but appears to be precipitated or exacerbated by stress [27]. The proportion of patients reporting emotional triggers varies with the disease, ranging from approximately 50% in acne to greater that 90% in rosacea, alopecia areata, neurotic excoriations, and lichen simplex [28].

The habitual act of picking at acne lesions, apparently driven by compulsion and psychologic factors independent of acne severity, has been reported in the perpetuation of self-excoriation. Most patients with this disease are females with late onset acne. Psychiatric comorbidity of acne excoriee includes body image disorder, depression, anxiety, Obsessive-Compulsive Disorder (OCD), delusional disorders, personality disorders, and social phobias. Immature coping mechanisms and low self-esteem have also been associated with psychodermatology. Interesting gender differences have been observed in this disease. In men, self-excoriation is exacerbated by a coexisting depression or anxiety, while in women this behavior may be a manifestation of immature personality and serve as an appeal for help [29,30].

Stress signals induce release of hormones, including Corticotropin-Releasing Hormone (CRH) from the Paraventricular Nucleus (PVN) of the hypothalamus; then CRH will target the anterior pituitary to release ACTH [31]. In turn, ACTH regulates glucocorticoids (mainly cortisol in humans) secretion from the adrenal cortex [32]. Cortisol has several functions including negative feedback of the hypothalamus and anterior pituitary and induces epinephrine and norepinephrine secretion from the adrenal medulla [33]. Glucocorticoids, such as cortisol, may enhance cutaneous immune responses at low concentrations and suppress immune responses at high concentrations [34]. Stress signals also stimulate the Locus Coeruleus (LC) norepinephrine cells of the sympathetic nervous system. Neuropeptide products of the sympathetic response (SP, CRGP, and cutaneous Nerve Growth Factor (NGF)) have been shown to be proinflammatory and anti-inflammatory dependent on the immune cell type [31].

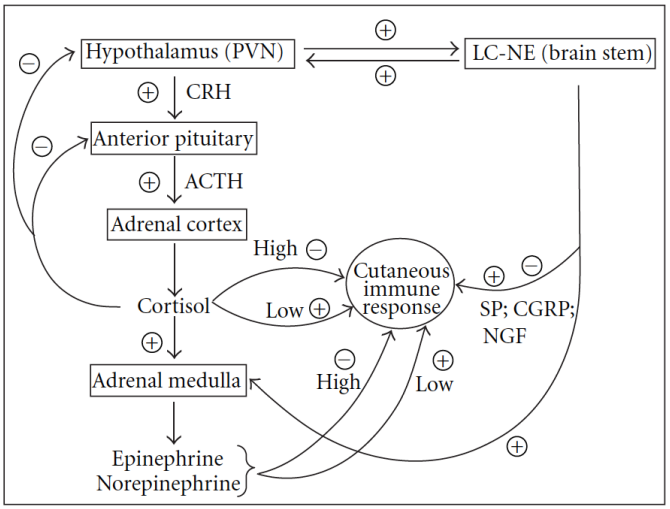

Figure 1: A schematic representation of the hypothalamus, anterior pituitary, adrenal cortex and sympathetic nervous interaction with the cutaneous immune system [31].

Skin Peripheral Hypothalamic-Pituitary-Adrenal (HPA) Axis

The skin also developed a fully functional peripheral Hypothalamic-Pituitary- Adrenal (HPA) system where CRH, ACTH, and their receptors are produced in skin cells. Corticotropin-releasing hormone is produced by epidermal and hair follicle keratinocytes, melanocytes, sebocytes, and mast cells upon stress, Ultra Violet (UV) irradiation, and cutaneous pathology [35,36].

Adrenocorticotropic hormone stimulates IL-18 production in skin keratinocytes, as IL-18 is a pro-inflammatory cytokine that enhances T-cell activity and promotes T helper type 2 (Th2) cytokines production [37]. Since CRH down- regulates IL-18 in keratinocytes, IL-18 may participate in the negative feedback loop to regulate HPA axis activity.38 In sebocytes, ACTH can work through the melanocortin-5 receptor (MC5R) and induce sebocytes differentiation [39].

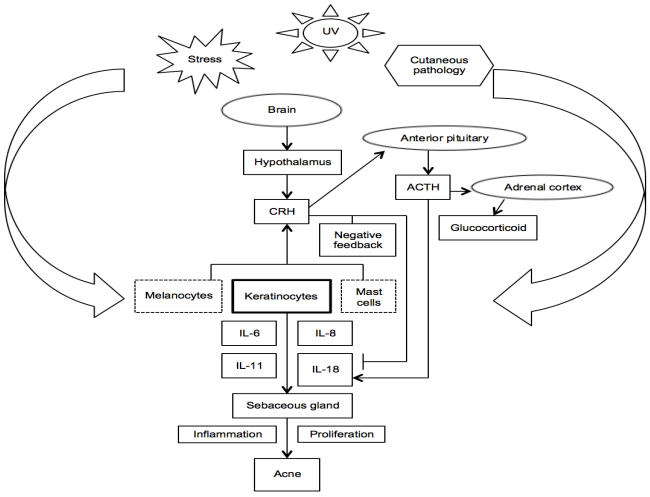

Figure 2: A schematic representation of HPA axis.

The Development in Acne Vulgaris Pathophysiology

Acne vulgaris pathophysiology is characterized by increased colonization of P. Acnes anaerobic bacteria, increased sebum production from the sebaceous glands, inflammation, and hyperkeratinization. The role of stress has long been suspected to induce AV flares by clinical experiences and anecdotal observations [40,41]. During its development, the role of skin peripheral HPA axis has been studied in the pathophysiology of AV. Corticotropin-releasing hormone and its receptors have been detected on sebocytes. It was shown that CRH promotes lipogenesis in sebocytes through up-regulation of a key enzyme [42]. In addition, CRH stimulates keratinocytes production of IL-6 and IL-11, and CRH also may have important activity on keratinocyte function [43]. Adrenocorticotropic hormone and α-MSH also contribute to sebum production and possibly worsen the acne phenotype [44].

The role of neuropeptide, specifically substance P in acne has been studied extensively. Facial skin from AV patients show marked increase of substance P- positive nerve fibers around the sebaceous glands and around acne lesions [45]. Substance P induces gene expression of Peroxisome Proliferator-Activated Receptor (PPAR)-γ, which plays a unique role in stimulating sebocyte lipogenesis. It also stimulates various pro-inflammatory cytokines release from sebocytes, including IL-1, IL-6, and TNF-α [38].

Conclusion

The concept of NICS means narrow interrelations between nervous system, immunity and skin. Indeed, there are numerous cellular contacts between nerve fibers, cutaneous cells and immune cells; cutaneous cells can synthesize neuromediators and they express receptors to these molecules; neuromediators are able to modulate functions of cutaneous and/or immune cells. Psychodermatology describes an interaction between psychiatric or a psychological problems to skin disorders. Therefore, it is suggest that for many skin disorders including AV requires comprehensive management in accordance by understand the development of AV pathophysiology.

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