Review Article

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Severe Acneiform Facial Eruption: An Updated Prevention, Pathogenesis and Management

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Abstract

Acne scarrings and papulopustular rosacea (PPR) are well documented cutaneous condition associated with major psychosocial morbidity. The burden of disease to the family and society is significant. A positive family history is a predictor. Inflammation involved an interplay of body inmate immunity and pro-inflammatory mediators, cytokines, neuropeptides and defence immune response to microbiomes results acneiform eruption. Modern research in molecular biology, neuroimmunology and clinical science enable the practicing physician to understand more about the pathogenesis of this complex skin disease and hence better therapeutic measures and management of the disease.

Introduction

Acneiform facial eruption is a common and complex skin disease which primarily involve the epidermis and pilosebaceous units with significant co-morbidities of other body systems. In the past, clinicians have mainly focused on pathogenic microbes like Propionoibacterium acnes by using antibiotics in treating acne vulgaris patients. The sole use of systemic and topical antibiotics has added velocity to the worldwide emergence of antibiotics-resistance skin bacteria [1-3]. Recent advances in neurophysiology, immune endocrinology and molecular biology provide new insights that inflammation through its mediators is the key element in this disease [4-6]. The following update will discuss these recent scientific findings and hopefully enable the clinicians a new mind frame in approaching the management of this chronic distressing condition. The article will mainly discuss acne vulgaris, rosacea and drug induced acneiform eruption.

Acne vulgaris is one of the earliest sign of puberty and comedone is the characteristic sign [7]. The exact cause of comedone is unknown. Proliferation of the basal layer of the epidermis and hyperkeratinisation of the acroinfundubulum of the sebaceous glands are the initial triggering factors. The excess keratin with sebum production will then cause skin pore inflammation and blockage. Overgrowth of the normal bacterial flora including P. acnes with secondary colonization of Staphylococcus epidermidis and Staphylococcus aureus attack the body innate and immune defence mechanism resulting in a plethora of acne manifestations like inflammatory comedones, papules, pustules, nodules, cysts, complications like hypertrophic and keloid scars. Results can be quite serious to a teenager without proper management of the disease. Acne in many studies can cause psychiatric morbidities like depression (30%), anxiety disorders (51%), low self- esteem (66%) and rarely suicidal ideation [8-10]. Acne scarring has been documented to significantly affect one's life and career [11]. Acne management need to address both the primary skin condition and psychiatric manifestations. But without knowing details in the underlying pathogenesis of acne vulgaris; it would be difficult to enable the clinicians to counsel their patients and manage the disease.

Rosacea characterised by flushing, centrofacial erythema of face, burning and stinging sensation aggravated by heat, hot food, spices, alcohol, solar exposure and stress share a similar complexity with acne vulgaris. Rosacea sufferers are more seen in their third and fourth decade of life and the female gender [12]. An article published in the Lancet interactive journal studied Rembrandt using his self-portrait drawn in 1645 at the age of 65 arrived the conclusion that the famous Dutch painter may suffer from rosacea and other systemic diseases [13,14]. Although the picture has not given us vivid descriptions of different subtypes of rosacea: erythematous, papulopustular, phymatous, ocular and peri-oral; and the signs of cardiovascular disease in this picture are disputable; it impressed the audiences an unhappy, depressed and helpless life of the artist before his death **(Figure 1) [**13,14**].**

Figure 1: An article published in the Lancet Interactive journal studied Rembrandt using his self-portraits and came to the conclusion that Rembrandt may had had rosacea.

Rosacea has been shown to decrease a person's Quality of Life (QOL) and Dermatology Life Quality Index (DLQI) and affect a patient subjective disease perception [12,15]. The stress associated with a negative self - perception may make the condition worse and prolong its chronic nature [15]. Moreover, there is evidence that rosacea may be associated with many systemic diseases like hypertension, hyperlipidaemia, migraine, airborne and food allergies and inflammatory bowel diseases, therefore, it is important for clinicians to take into consideration the whole person well- being including emotional stress, lifestyle habits and general physical health including the cardiovascular and neurological systems[16-19]. Recently, an increased risk of cancer like liver cancer, non-melanoma skin cancer, breast cancer and glioma has been linked with rosacea [20-22].

While the exact pathogenesis of acne is still not known, inflammation seems to play a pivotal role in severe acne [4-6]. A Gut – Brain –Skin hypothesis has been postulated [23]. Risk factors like positive family history of severe acne may involve expression of Insulin Growth factor -1 genes (IGF-1) and Androgen Receptor genes; high calorie and high glycaemic index diet consisting of dairy products; excessive stress are all shown to cause severe acneiform eruption [24-26]. Psychological stress with an increase consumption of bovine milk products change the normal bio - flora of the lining of the gastrointestinal tract. A lack of high fibre in the diet slows the gut motility and make the membranous lining of the intestine more permeable. Toxins produced are more readily absorbed and the toxaemia cause an increase secretions of Substance P and other stress hormones like IGF, corticosteroids and cytokines mediators especially tumour necrosis factors. Insulin resistance at the cellular level has been demonstrated in these severe acne susceptible individuals and with a decrease Insulin sensitivity of tissues and increase in IGFI expression [27]. This increase sebum secretions in the pilosebaceous gland with an imbalance in the production of saturated and unsaturated fatty acids concentration in the sebum. This scenario magnified in individuals who are genetically susceptible to severe acne. These patients innate immunity produce a high level of IGFI, androgens and growth hormones or growth factors and corticosteroids from the adrenal glands. The latter further stimulate the liver to enhance the IGFI activity on sebaceous glands. This hypothesis has gain support from clinical observation that women suffered from Polycystic Ovarian Syndrome (POS) presented with severe acne vulgaris has generalized high insulin resistance and obesity. In male, the conventionally used hypoglycaemic drug metformin decrease hepatic glucose output and act as an insulin sensitizer by increasing glucose utilization by muscle and adipocytes; hence reducing serum insulin concentration; may have an anti-inflammatory and beneficial effect on severe acne [27].

In the cellular level, IGF and other androgenetic hormone interact with Growth Receptor (GR) and G-Protein Coupled Receptor (GPCR). The former act through the Ras - MEK -1 and ERK 1 and p 38 antigen signalling pathway activate the Peroxisome Proliferative Activated Receptors (PPAR) gamma in the cell nucleus which then influence adipocyte differentiation and glucose metabolism [28,29]. GPCR act through the c AMP activator and Phosphokinase (PKA) in turn act on PPAR alpha in the cellular nucleus affect the hepatic cellular fatty acid metabolism. 29Interestingly, the stress associated cytokines TNF alpha has also been shown to work on a cellular level by stimulating the TNF alpha receptor located on the cell membrane interact with the PPAR beta in the cytoplasm. The PPAR beta in the nucleus is then switched on and translate into proteins that affects fatty acid metabolism, lipid homeostasis and ultimately skin proliferation [29]. Thus, an impairment in neuro – endocrine metabolic pathways may be implicated in the pathogenesis in severe inflammatory acne. (**Figure 2**)

This concept has been in coherence with the satisfactory clinical

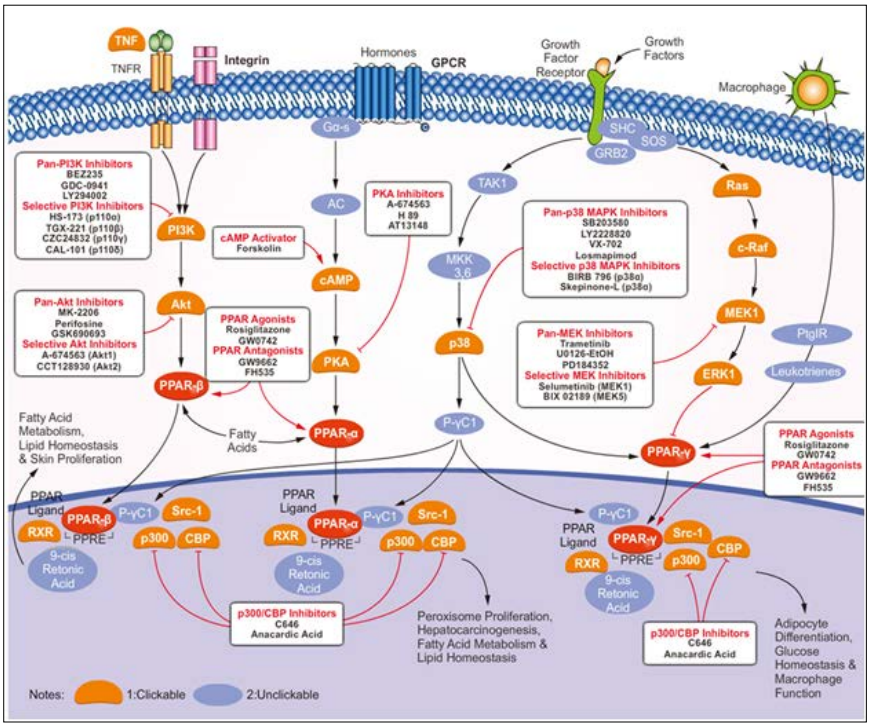

Figure 2: Signalling pathway of Peroxisome Proliferator Activated Receptor (PPAR) in the cytoplasm and nucleus of cell involved in the pathogenesis of Acne vulgaris. (Illustration as kindly permitted by Selleckchem; from Selleckchem.com)

use of retinoids in controlling severe acne and even curing it [30]. Retinoids has been shown to interact with RXR receptors and RAR receptors which are closely associated with PPAR alpha, beta and gamma inside the nucleus of the cell. Retinoids thus exert its effects on severe acne by modulating and normalizing skin proliferation, differentiation and controlling inflammation by influencing fatty acid and lipid homeostasis [21,32]. In recent years, more and more anti-inflammatory agents have been shown to be efficacious in controlling severe acne. For example, Nicotinamide (Vitamin B3) an anti – inflammatory agent and laser delivered gold nano - particles and have been shown to improve acne outcome [33,34].

On the other hand, in Rosacea, there appears a more complicated interaction between the brain, nervous system, cardiovascular system, the gut and the skin[35,36]. A neurovascular coupling appears to occur in the pathogenesis of Rosacea. (**Figure 3**) Known triggering factors of rosacea refer as stressors like species, stress, exercises and heat act through the Transient Receptor Potential Vanilloid -1 (TRPV) and Transient Receptor Potential Ankyrin (TRPA) located on neuronal endings sensitize the autonomic nervous system both the sympathetic and parasympathetic pathways causing vasodilatation like flushing and hyperalgesia like stinging sensation [37,38]. Nerves containing Calcitonin genes related peptide (CGRP) may be linked to flushing through the messenger cAMP. Furthermore, CGRP may also serve to regulate inflammation by modulating chemokine production by the cells lining the blood vessels. TRPV act like a N-methyl-D-aspartate (NMDA) receptor cause calcium influx thus changes transmembrane potential transmits signals to the cardiovascular system via the central nervous system. Excessive solar radiation generates Fibroblast Growth Factor (FGF) and Vascular Epidermal Growth Factor (VEGF) promoting blood vessel proliferation and skin and pilosebaceous gland inflammation resulting in skin papules, pustules. The inflammatory insults also cause a direct vaso - vascular effects on angiogenesis resulting in erythema and telangiectasia respectively [39,40]. Pathogenic microorganisms may invade the defective epidermal barrier of the skin of rosacea and the epidermal keratinocyte in response produce a potent anti-bacterial cytokine called beta defensins [41]. Cathelicidin (LL-37); a potent antibacterial protein by skin keratinocyte in response to antimicrobial invasion; is produced through the Kallikrein 5 pathway involving the Matrix metalloproteinases (MMP). LL-37 also known as defensins activated protein has been demonstrated to be a major pathogenetic factor in causing rosacea through inflammation and angiogenesis of skin [42-45]. Finally, an abnormal skin microflora consisting of an increasing number of Demodex folliculorum in the sebaceous glands and S. epidermidis in the defective epidermal barrier initiate the production of Toll –Like Receptor (TLR) from keratinocytes which also enhance the production of LL-37 [46,47]. Recently, there are study suggests that the bacterium Bacillus oleronius harboured by the Demodex mites are the genuine culprit in causing the release of TLR [48]. Whether the Demodex play a more significant role in the pathogenesis of rosacea than LL-37 is not known; however; this may be important especially when one is considering using an antimicrobial to treat rosacea. Nonetheless, LL-37 and TRPV/TRPA channels are important neurovascular mediators and signalling pathways in causing rosacea. This may have important implications in designing future pharmacological therapy in managing severe rosacea as LL-37 inhibitors and TRPV channels blockers may be found to antagonize the neurovascular coupling that occur in rosacea [49].

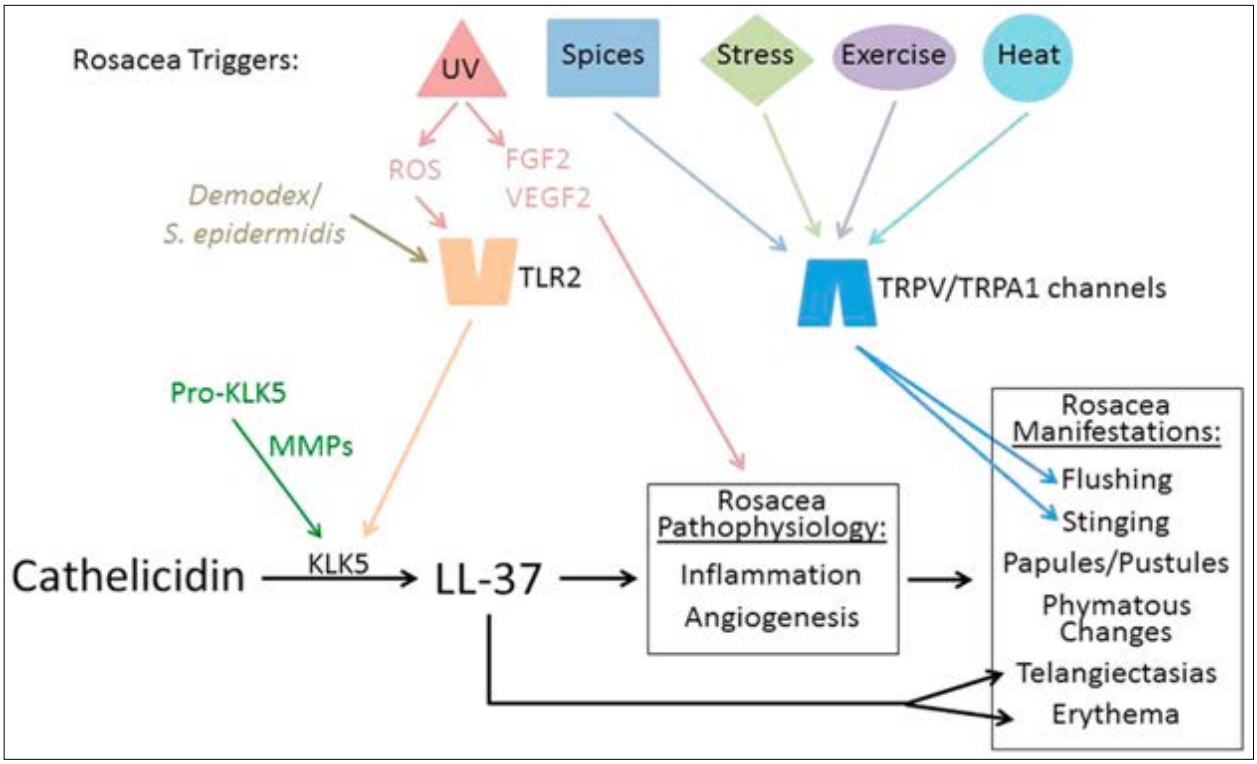

Figure 3: Pathways known to contribute to the pathophysiology and clinical manifestations of Rosacea (From Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. JAAD.2015;72:749-58).

Many drugs have been reported to adversely affected the treated patients with severe acneiform skin eruption [50]. They can be classified as hormonal, anti-depressant, anti-convulsant and anti-cancer drugs. They may result a severe papulopustular skin eruption resembling acne and rosacea. The pathogenesis may also involve an aberrant immune endocrine metabolic signalling pathways in genetically susceptible individuals. Epidermal growth factor receptor (EGRF) inhibitors and tyrosine kinase inhibitors which are widely used biologics targeting specific receptors of the cancer cells have all reported to cause significant skin reactions especially acneiform eruptions (**Table 1**) [51-54].

Table 1: Drugs that are known to induce Acneiform facial eruption

	Drugs that caused acneiform facial eruption
Steroid Hormones	Topical steroids
	Systemic steroids
	Anabolic steroids for muscle building
	Testosterone
Antidepressants	Lithium
Antiepileptic	Phenytoin
Halogens	Iodides
	Bromides
Target therapy for metastatic internal malignancies	Anti EGFR
	Anti BRAF

The recent development in the research of molecular biology reveal a better understanding of the pathogenesis of severe acneiform eruption compatible with clinical observations and findings. This may assist the busy clinicians battling with this distressing disease to have a new, more positive, dualistic mind frame in approaching the management. The conventional use of antibiotic alone in treating severe cases of these patients may not be all satisfactory. It will only further promote the already devastating bacteria antibiotic resistance pandemic without relieving the actual psychological distress of these sufferers. Prevention is better than cure. Counselling the teens suffered from severe acne and a heavy work laden middle-aged women suffered from rosacea required an updated knowledge of what's happening in acne and rosacea [55]. An effective approach in future may involve dietary manipulation by using pro-biotics; anti-inflammatory agents; cytokines inhibitors and genuine receptors antagonist to target the multi- faceted of the pathogenesis of acneiform eruption.

In conclusion, a new mind frame need to be set to understand severe acneiform eruption. The burden of disease of acne and rosacea is more than skin deep; and may neurologically, psychologically and systemically affect an individual. It involves an orchestral interplay between the gut, immune system, vascular system neuro-endocrine and brain organs. Further advancement in understanding the pathogenesis hence management of this complex disease entity required collaboration, communication and inter connectiveness involving the neuro-psychiatrists, neuroscientists, immune endocrinologists and all relevant medical professional partners.

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