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REVIEW ARTICLE

Psoriasis: Is it in the Mind?

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Abstract

Psoriasis is a chronic, relapsing, multifactorial cutaneous disease which may severely affect quality of life. The worldwide prevalence is about 2%, but varies according to regions. Studies from Indian subcontinent have reported the prevalence range from 0.44 to 2.8%. It usually presents clinically as erythematous, indurated, scaly plaques over the skin. Nails and joints may also be affected. Various pathogenetic mechanisms have been implicated in Psoriasis. Role of stress, cytokine storm and genetics are fundamental aspects which form the basis of targeted therapies. Since stress and stress-related hormones promote serotonin (5-HT) synthesis, the potential involvement of 5-HT in psoriasis is speculated. Role of brain derived neurotrophic factor (BDNF), vascular changes in psoriasis, Substance P and their interplay has given directions for multiple therapeutic regimens.

Key Words

Psoriasis, Serotonin, Brain derived neurotrophic factor, Keratinocyte, Substance P

Introduction

Psoriasis is chronic, relapsing multifactorial cutaneous condition with worldwide prevalence of about 2%, but varies according to regions (1). Asian and some African populations show lower prevalence as compared to 11% in Caucasian and Scandinavian populations (2). Studies from Indian subcontinent have reported the prevalence range of psoriasis from 0.44 to 2.8% (3).

Pathogenesis

Genetic changes, altered immune function and marked keratinocyte proliferation are key features which mark development of psoriatic lesions. Research studies have narrowed down to the key concept that there is intricate interplay between epidermal keratinocytes, T cells and dendritic cells. Immune response (innate and acquired) is activated by keratinocytes. Myeloid dendritic cells in dermis modulate activation of T cells and formation of cytokines that trigger inflammation cascade.

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Psychological Factors in Psoriasis

(a) Role of Stress

Stress is a well-known trigger factor in the appearance or exacerbation of psoriasis. Stress reaction in patients with psoriasis is probably mediated by the hypothalamic-pituitary-adrenal relationship causing release of adrenal hormones. Th1 cells leading to marked IFN gamma synthesis play important role in psychological stress (4). Animal model studies have shown that certain life events leading to stressful mental state are associated with higher levels of Substance P in the central and the peripheral nervous system. It has proinflammatory effects in immune and epithelial cells. Substance P and its receptor substance P-NK-1 receptor (R) pathway may play important role in onset and development of pruritis in Psoriasis (5).

Additionally, there is reduction in effectiveness of various treatment modalities in patients of psoriasis with psychological stress (6). Stress causing factors also

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referred to as *stressors* can be personal, genetic, emotional and social. Every individual's ability to deal with a particular stressful condition is different. These four factors play an intricate role in tolerance and stamina to prevail over stressful situation (7).

The vicious cycle....

Studies have documented that psychological stress may lead to increased formation of proinflammatory cytokines as Interferons and TNF (tumour necrosis factor). This affects metabolism of monoamine neurotransmitters (dopamine, serotonin, norepinephrine) and leads to decrease in availability, synthesis and uptake of serotonin. Due to low serotonin levels again, there will be enhanced proinflammatory mediators and activation of NF-κb (nuclear factor kappa-light-chain-enhancer of activated B cells) which triggers keratinocyte hyperproliferation leading to psoriatic hyperplasia. This psoriatic skin further participates in vicious cycle by producing more mediators of inflammation, which cross blood brain barrier and lead to sickness behavioural changes hence there are continuous and prolonged stress stimuli to brain (8-10) [*Figure 1*].

(b) Role of Anxiety

Anxiety is the feeling of fear that occurs when faced with threatening or stressful situations. This response is considered to be normal when someone is in crisis or threatening circumstances. If this feeling continues to linger on, it can be considered under disorders of anxiety. These disorders include post-traumatic stress disorder and social anxiety disorder. Such disorders are related to chronic and continuous stimuli of depression and anxiety. Identification of cause of these factors are essential to restore the appropriate quality of life in such patients (11).

(c) Role of Depression

Depression is a prolonged medical ailment that can have multiple effects on thought processes, mood, and physical health. Studies on prevalence of depression in patients with psoriasis have reported rate between 20% to 30% (12). Key features include unhappiness, feeling of dejection, low mood and lack of sleep and energy. Sleep interference was likely due to intense pruritis and pain. Role of Substance P has been speculated in sleep disturbance and in interrelating pathogenetic mechanisms between depression and Psoriasis, thereby, forming link

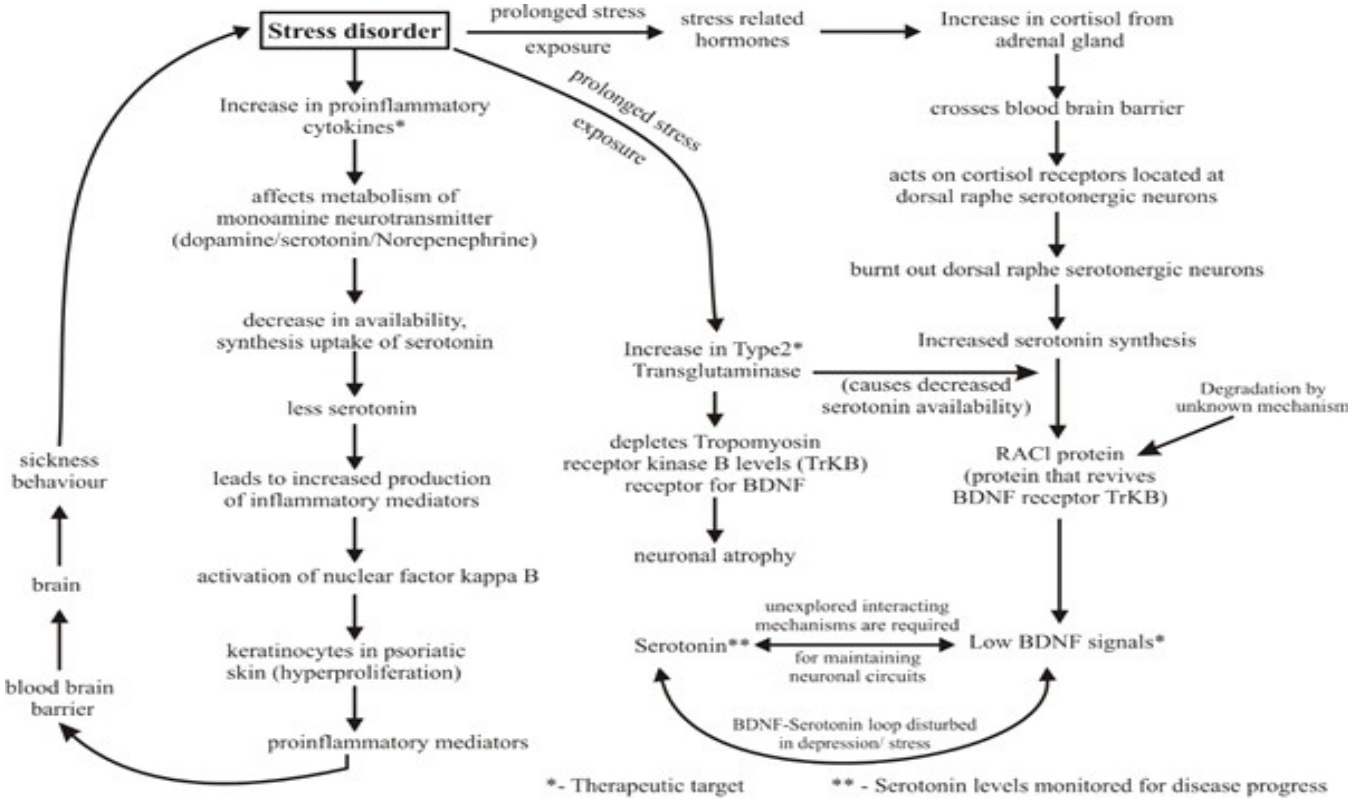

Fig. 1 : Stress and Psoriasis : a crosstalk

between depression, sleep quality and depression (13).

(d) Internalized Stigma

Goffman defined Stigma as an "attribute that is deeply discrediting" and that reduces the bearer "from a whole and usual person to a tainted, discounted one." A person marked by stigma struggles with diminished self-esteem, discrimination, and isolation. When someone adapts negative or pessimistic attitude with certain notions of society regarding a person's ailment, feeling and state of Internalized stigma develops. It causes low self-esteem, increased suicidal tendency, depression and dissatisfaction from life. Psoriatic patients may develop this feeling of internalized stigma. Intensity of this feeling may be associated with severity of the disease (14).

Serotonin -BDNF loop

Serotonin (5-hydroxytryptamine 5-HT) is a neurotransmitter. It is a monoamine neurotransmitter formed from L tryptophan catalysed by tryptophan hydrolases (TPH). TPH1 is in periphery and TPH2 is in brain. Most of human body's serotonin is produced by enterochromaffin cells in gastrointestinal with active uptake by platelets and is stored in dense granules. When platelets are activated, serotonin is released and exerts its functions (15).

Peripheral serotonin monitors cell growth and modulation with help of its seven types of cell surface receptors (5HTR 1-7). Peripheral serotonin affects function of cardiovascular and gastrointestinal motility. Brain derived serotonin regulates behavioural aspect, sleep patterns, blood pressure and thermoregulations. Immunohistochemical studies have shown significantly higher serotonin 5-HT expression was in psoriatic skin as compared to normal skin, with 5-HT expressed in basal and suprabasal skin layers of psoriatic patients. (16). Expression of Serotonin receptors(5HT) is significantly altered in Psoriatic skin (17). There is lower expression for subtype 5-HT1AR and higher expression for 5-HT2AR in psoriatic dermis compared to normal skin, whereas 5-HT3R was detected in the basal epidermis layer of non-involved psoriatic skin. Young *et al.* (18) showed that use of selective serotonin reuptake inhibitor antidepressants may be beneficial in patients of Psoriasis.

Persistent stressful situations cause stress hormones to burn out dorsal raphe serotonergic neurons leading to increased serotonin levels (19-21). Mice model studies have shown that prolonged stress exposure causes significant increase in levels of type 2 transglutaminase in mouse prefrontal cortex (basic activity of this region is implicated in personality expression, decision making, social behaviour and active short-term memory) (22). This enhanced expression of type 2 transglutaminase in mouse cortical neurons depletes Tropomysin receptor kinase B (TrkB) levels and cause neuronal atrophy. TrkB is a receptor for brain-derived neurotrophic factor (BDNF), brain nourishing molecule made by Astrocytes which helps neuronal connectivity maturation and differentiation of new neurons and synapses. It acts on central and peripheral nervous system (23). Cross talks between BDNF and serotonin systems play important regulatory roles in development of neuronal circuits which are changed in depression.

BDNF levels are low in depression and its receptors are also depleted. Although serotonin is considered to be major neurotransmitter having many functions including mood regulation, it can only be useful if it is made available with efficient signalling mechanisms. Increased TG2 levels decreases availability of serotonin causing inadequate levels for neuronal communications. TG2 converts serotonin to RAC1 (a protein that revives BDNF receptor, TrkB). But there are unknown mechanisms causing degradation of RAC1and hence low BDNF signals. Since unexplored interacting mechanisms between serotonin and BDNF appear to be important to maintain proper functioning of neuronal circuits, it is speculated that serotonin levels increase in depressed cases because there is low serotonin signalling process in brain [*Figure 1*]

Drugs targeting lowering of TG2 levels and increased BDNF signalling are newer scope in treatment of depression. Direct measurement of serotonin levels in such treatment regimens can be used for monitoring the disease progress (24).

Histopathology

Elongated and dilated blood vessels in the dermal papillae and abundance of neutrophils in the psoriatic skin lesions represent histological hallmark of psoriatic skin lesions. Neutrophils can cause skin inflammation by producing cytokines as IL-17 and stimulating dendritic cells. The vascular changes in psoriasis during early stages of pathogenesis closely correlate with enhanced cutaneous blood flow even in the neighbouring perilesional, clinically unaffected skin. Electron microscopy shows ultrastructural changes of the capillary loops in the dermal papillae. Local release of angiogenic growth factors is responsible for the uncontrolled endothelial cell

proliferation that takes place during tumour neo-vascularization; in angiogenesis dependent disease such as diabetic retinopathy, psoriasis and rheumatoid arthritis.

Statistically significant differences in the expression of CD34 between lesional and non-lesional skin as well as between non-lesional skin and control group have been documented. Thus "anti-angiogenesis" may eventually become a useful therapeutic approach in psoriasis (25).

Recurrence of Psoriasis in specific areas of the skin shows that molecular imprints of psoriasis remain in clinically cleared skin. It is proposed that these cells are capable of producing certain cytokines as IL17A even after various long term and efficient keratinocyte proliferation modulating therapies (26).

Treatment

Intricate relationship and dialogues between brain–skin, explains grave effects which psychological stress can have on skin leading to occurrence or flare up of Psoriasis, a multifactorial disease with complex pathogenesis. Hence, a Psychodermatologic assessment can be beneficial to modify and improve in planning the effective treatment plan. Family history of psychiatric diseases and comorbidities should be considered in work up of such patients. Effective understanding of biochemical mechanisms of response of anti-psychotic treatment in psoriasis patients is required to know their therapeutic importance (27).

Since mental wellbeing can have impact on ability of patient to take the treatment properly, hence it is very important to plan a complete and meticulous treatment plan. This umbrella approach should include holistic, psycho social and conventional aspects of treatment. Psychological burden of disease may span from pain, disfigurement and psychological distress. Timely intervention of appropriate treatment plan may help the patient.

Studies to analyse the effect of various modalities of chemotherapy on Quality of Life (QOL) reveal that combination chemotherapy (topical + systemic) is more efficacious and associated with significant improvement of QOL as compared to topical therapy alone. Methotrexate and cyclosporine are equally efficacious in treating and improving the QOL in patients suffering from psoriasis (28).

Conclusion

Psoriasis is established by WHO (World Health Organization) as a serious, chronic, disfiguring, disabling, non-communicable disease (29). It seems existing knowledge is just tip of iceberg of actual scenario. Psoriasis is an immune mediated disease with intricate pathogenetic mechanisms involving role of stress, serotonin, cytokine storm, genetics and molecular scar. Various pathogenetic mechanisms which form the basis of targeted and integrated therapeutic regimens, provide new hope for complete cure of Psoriasis.

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Conflicts of Interest
There are no conflicts of interest.

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