scientific update

Mid-Term CME 2016 of
Indian Psychiatric Society, Assam State Branch

PSYCHODERMATOSES

Editors:
Shyamanta Das
Uddip Talukdar
Bornali Dutta (Ray Baruah)

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Scientific Update of Mid-Term CME 2016
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PREFACE

Skin is the biggest organ in the human body, and is the most exposed. Skin is also our window to the environment. Skin sends us important information about the environment, based on which our body makes adapations for proper functioning. Skin sends a massive volume of data to the brain, and brain has to take decisions based on that. So, skin remains in constant ‘touch’ (pun not intended) with the brain.

When brain is involved, there is bound to have relation with the ‘mind’. So, it is possible that wrong signals in the brain might make a person feel problems in the skin. It is not only possible, but it is a fact that there are some skin conditions that have root in the brain functions.

Skin is a very senstitive organ. Both physical and psychological stress can cause the skin to show tantrums.

Studies have verified all that is mentioned above. And, hence, there is group of conditions that is known as ‘psychocutaneous disorders’. All

psychiatrists and dermatologists are aware of psychocutaneous disorders. However, it is very infreuqent when both these specialities share a platform. Meanwhile, new science is being done in both these specialities everyday.

With a view to bring to together psychiatry and dermatology together to exchange knowledge, the topic of the Mid-Term CME of this year was taken 'Skin & Psychiatry.' As a by-product of these CME we are releasing this Scientific Update, which is small but packed with some valuable information.

We hope readers will find this Update useful.

With thanks,

Editors

Stress and Acne

Dr. Bornali Dutta (Ray Baruah)

Acne vulgaris, more commonly known simply as acne, is a milestone which one never misses in their journey to adulthood. It is an integral part of puberty and 80–95% of adolescents aged 12–24 suffer from acne .Fortunately for many, the prevalence declines dramatically after the age of 25. But it is sometimes seen to persist or emerge in later life too and 25% of all adult men and 50% of adult women at some time in their adult lives are seen to suffer from acne. Though it appears to be "a superficial nuisance" only and physically scarring acne accounts for less than 20% , yet, the burden of this condition on adolescent's life and mental status can be considerable; it can not only cause a dent in their present but can also dim the prospects of a bright future.

Adolescence is a complex life-cycle stage characterized by many striking biological, physical, psychologic, and interpersonal changes. This era is usually conceptualized as consisting of 3 phases.

1) Early adolescence, from age 10 to 13 years, coincides with the onset of puberty and many changes in school life. However, during these years the family is still a key context for the changing young boy and girl.

2) In middle adolescence, from age 14 to 16 years, there may be increased evidence of changes in parent adolescent relationships and often increased conflicts in these family relationships, together with the adolescent's growing attention to his or her emerging individual autonomy. It is also in mid adolescence that peer and romantic relationships become more salient. An attractive physical appearance contributes in a big way in building bridges in relationships and earning approval from their peers.

3) In late adolescence, from age 17 to 21 years, adolescents often make important life decisions about life directions—committed enduring relationships, career/work, and further schooling. During this final phase, integration of self-images and overall identity formation are dominant themes as the adolescents move toward young adult years and roles.[1,2]

Stress is a constant in our lives, but for the acne sufferer it can be especially troubling. There seems to be a two-way street with acne and stress; acne can cause stress and negative emotions, and stress and negatives can cause and worsen acne. There is a vicious cycle between stress and acne that keeps the condition flaring up again and again even if one takes good care of their skin. The reasons linking stress and acne are multifactorial. . Arck et. al., have reviewed the recent research offering solid evidence for a local neuroendocrine skin axis that operates as an

important "brain-skin" connection.[3] The skin and its appendages are capable of generating the same mediators that are used during systemic stress responses, and they have established a fully functional peripheral equivalent of the systemic, stres-activated hypothalamic-pituitary-adrenal axis.[4,5] The classical neuroendocrine pathway for response to systemic stress is by hypothalamic release of corticotropin releasing hormone (CRH), subsequent activation of pituitary CRH receptors (CRH-R), and production and release of proopiomelanocortin (POMC) derived peptides. Pro-opiomelanocortin (POMC) is a precursor polypeptide with 241 amino acid which is cleaved to give rise to multiple peptide hormones namely; α MSH, ACTH, β Endorphin and Metenkephelins. When the brain senses stress, the hypothalamus releases corticotrophin releasing hormone. This hormone travels through the bloodstream to the adrenal glands, where it triggers the release of the stress hormone cortisol.

Skin cells produce both CRH and express functional CRH-R1, thereby supporting the existence of a local CRH/CRH-R neuroendocrine pathway that may be activated within the context of a skin stress response system. Thus, when the skin senses stress, it doesn't have to wait on the brain to send a signal to the adrenal glands to release stress hormones. It makes its own CRH to respond to its own stresses which also instructs mast cells in the skin to release inflammatory chemicals like histamine. The skin becomes redder and itchier and swells, all because of heightened sensitivity in its nervous system.

CRH stimulates the sebaceous glands to produce more sebum. The added skin oil makes the skin more flexible—or wrinkled, depending on how

long stimulation goes on. CRH also activates immune and inflammatory pathways responsible for stress induced acne. Keratinocytes are stimulated to release inflammatory chemicals like leukotriene to attack infectious microorganisms. In doing so, they can also attack healthy skin cells. The process of ductal hyperkeratosis is also stimulated which lead to entrapment of both sebum and bacteria within the follicles. The sebum that is trapped in the pore is food for acne bacteria, which multiply rapidly. Acne bacteria do not usually irritate the skin. In fact, one of the byproducts of their digestion of excess sebum in pores is essential fatty acids that reduce inflammation in the skin. Resident bacterial flora in sebaceous follicles like Propionibacterium acnes, Propionibacterium granulosum, Pityrosporum ovale and Staphylococcus epidermidis play an important role in the production of acne. To protect themselves from the immune system, however, acne bacteria secrete chemicals that make surrounding skin cells more sensitive to inflammation. That way, when the skin makes stress chemicals, it is the skin itself that gets bombarded with inflammation, not bacteria. As a lesion eventually opens up, a few acne bacteria escape to go to live in a different pore.

Another part of the answer seems to be that stress interferes with the thyroid's response to thyroid stimulating hormone, and low levels of thyroid hormone leave the skin more vulnerable to inflammation. Vitamin A and its topical derivatives are believed to help raise thyroid hormone levels when they heal the skin. And yet another explanation seems to be that stress increases production of not just testosterone but also two other sex-

related hormones, luteinizing hormone and prolactin. Testosterone can increase sebum production leading to blockage of pores. At the same time, the skin is releasing inflammatory factors, adding to the pathogenesis. . Good sleep is believed to increase the amount of melatonin in the brain which leads to less production of corticotrophin stimulating hormone thereby preventing the pathogenesis of acne.

One of the newest topics in acne research is the relationship between a psychiatric condition known as alexithymia and acne. Alexithymia which literally means "without words for emotions" is a personality trait that causes difficulty in expressing, understanding, or describing emotions. Researchers have recognized for nearly 40 years that the inability to express or understand emotions makes all kinds of illnesses more likely and all kinds of treatments less effective. People who have alexithymia tend to get lower back pain, fibromyalgia, irritable bowel syndrome, allergies, asthma, nausea, and, scientists have recently discovered, acne.Having acne does not mean that one has alexithymia. However, having alexithymia increases the chances of having acne. The relationship between the inability to express emotions and the appearance of acne is explained in terms of the brain-skin connection. However, in a study by Sunay et al (2011), results did not demonstrate a link between the two conditions.[6] But the study was limited by its small sample size, age limitation and single center data. Further multicenter studies with larger study groups and different age ranges may provide definite results. In a later study by Ozuguz et. al. (2016) on evaluation of alexithymia in patients admitted to a dermatology clinic, scores

of 50, 61 were obtained which though similar to the previous study were statistically significantly higher compared with our control group.[7] Although research works on of alexithymia in dermatology are still scarce and reveal conflicting results, preliminary data show that alexithymia seems to be associated with some skin diseases

Acne is the most common problem that presents to dermatologists. It commonly affects young people at a time when they are undergoing maximum psychological, social and physical changes. Smithard et al. studied 317 students between 14-16years of age and found that those with acne were more likely to score in the abnormal/borderline range for emotional or behavioral symptoms. Do et al. reported in their study that adolescents with definite acne had significantly high-score self-perceived severity, stress, and disturbances in interpersonal relationships and daily life. Kubota et al. found that students with acne were significantly more depressed than those without acne. In a cross-sectional study by Magin et al. it was found that 'non-psychiatric diagnosis' psychological morbidity-embarrassment, shame, self-consciousness, impairments of self-image, self-confidence and self-esteem, anger, and stigmatization-were more prominent than symptoms of anxiety and depression in patients with acne, psoriasis and atopic dermatitis.[8-11]

The relationship between the severity of acne and emotional distress is poorly understood. A study of university students showed that patients with acne experienced a worsening of their disease during examinations. Increased acne severity was significantly associated with increased stress

levels. It is considered that there is a linear relationship between the clinical severity of acne and impairment of quality of life (QoL). However, impairment is also dependent upon a person's coping ability and some individuals with little objective evidence of acne may endure severe subjective impairment, greatly affecting their QoL. So acne can have a great impact on patient's lives, often independent of severity.[13,14]

Severe acne is associated with increased depression, anxiety, poor self-image and poor self-esteem. Psychiatric symptoms are more common in more severe acne and in the later stages of puberty. Adolescent girls may be more vulnerable than boys to the negative psychological effects of acne.[15-17] Acne is associated with increased risk of depression, anxiety and suicidal tendencies and there are some important gender differences. In a regression model for body mass index and depressive symptoms, boys suffered from significantly lower self-attitude and girls from poor self-worth.[18]

Acne is one of the commonest conditions encountered in most dermatological out patient departments, after infections and infestations In the private set up also, dermatologists very frequently come across distressed patients and even more harassed parents. The new generation teenager seems much more affected by their physical appearance and its psychosocial impact than their predecessors. The large armamentarium of topical and systemic therapies available fail to bring a smile to expectant patients. It is only few cases of acne excoriee that receive the privilege of a psychiatrist or counselors evaluation and have the benefit of a dual

consultation. Researchers have made it quite clear that acne is not only an expected physiological change influenced by pubertal changes centering around androgens , sebaceous glands and propionobacterium acnes. It goes much beyond to include the stres-activated hypothalamic-pituitary-adrenal axis at both central and peripheral level with profound mental and psychological consequences. This apparently innocuous cosmetic problem in reality runs very deep. Even if acne is not associated with severe morbidity, mortality or physical disability, it can nevertheless have considerable psychological and social consequences. The social, psychological and emotional impairment that can result from acne, especially in its more severe clinical forms has been reported to be similar to that associated with epilepsy, asthma, diabetes, back pain or arthritis. Patients could be more prone to immediate problems like depression, anxiety, social withdrawal and anger, not to mention the more persistent problems like scarring that can lead to lifelong problems with self-esteem.

Acne vulgaris is a common skin disease with potential complications that are more than skin deep. The treatment of acne should involve much more than addressing skin problems. Any treatment plan should include both physical and psychological care. The severe burden of acne is strong justification for effective acne treatment and psychiatric screening for patients with the condition. Most important, improvements in acne after appropriate treatment have been shown to result in enhanced self-esteem, body image and social functioning. A good amount of time needs to be invested not only in the quantitative assessment of the skin condition but also on the qualitative evaluation of its impact on the individual. A

comprehensive approach where the clinical acumen of a dermatologist and the perceptive skills of a psychiatrist come together will unravel the ongoing burden of the condition on the individual. This will help us envisage a suitable management approach which will be patient specific, curtailing not only time and financial loss and but also ensuring the exclusion of distracting factors, which hamper the progress of potentially equipped individuals. Adolescents and young adults will be at peace with their physical state and they will be able to focus on their goals in life .They will be armored by the time tested tools of success; self esteem and self confidence. Experiencing high self-esteem fosters a sense of confidence and positivity and serves as a protective factor in coping with new life changes. Effect of acne on an adolescent's wellbeing is often underappreciated. Increased understanding of the psychiatric comorbidities associated with acne and identifying the high-risk patients with early intervention will ultimately improve the patient's life.

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Is beauty only skin deep? Revisited with a psychotherapeutic approach

Dr. Mythili Hazarika

Treatment for any skin conditions is a common phenomenon, may it be for acne-vulgaris in adolescents and psoriasis or chronic delusiononal parasitosis at any age group because we consider "looking good" as being beautiful. And, it is the beauty of appearance, what we call "looking good." It has little to do with personality, character, wit or morality. But we also are quite aware that for many other salient qualities, how things look may not actually be taken as a guide that is reliable. Still, we shy away, falter and question ourselves about the maxim "beauty is only skin deep" which was originally used by Sir Thomas Overbury in his poem "A Wife" (1613): "All the carnall beauty of my wife is but skin-deep".[1]

Our skin being the largest organ is one of the most important one as it is external and is exposed at all times. Unlike our thoughts which no matter how ugly they are but could be hidden at one's will and choice.

When literature search was carried out it is found that psychodermatology or psychocutaneous medicine is a relatively old domain, which is built on well studied and documented connections between mental / psyche and skin. Numerous studies have highlighted the idea that evolution of a significant percentage of dermatoses is negatively influenced by psychological factors and stress. One's mental state affects not only how the disease is perceived but its intensity as well as its severity.

Thirty to 40% of dermatological patients show a concurrent mental disorder or psychological problems that may be the causative, predisposing or aggravating factor of the cutaneous disease.[2]

Hence, the various psychological conflicts in the domain of self-esteem, social embarrassment, social withdrawal, anxiety, depression and biological dysfunctions which are deeply associated with dermatological problems are difficult to treat with only one approach i.e. either pharmacotherapy or psychotherapy as no approach appears to be the best one according to the review done by the author in pub-med and various other journals from the last decade. Research suggests an eclectic approach of various psychotherapies as well as medicines to address the issues of skin lesions leading to the perception of "looking ugly" and thereby suffering from various psychological ailments. One common question about which the author wonders is, if beauty is only skin-deep then would the psychiatric and psychological concerns associated with skin lesions ever arise?

A study conducted in India on depression and quality of life in patients of lichen planus in comparison to the same in both males and females.

Along with designed semi-structured proforma for necessary information, tools administered include Dermatology Life Quality Index as well as Beck's Depression Inventory. Number of sample fulfilling the criteria was 35. The study found that 25% were depressed and females being more affected than males with impaired quality of life in more than 90% patients. Symptoms as well as illness feelings were associated with maximum impairment along with disturbed daily activities, or work and time consumption in treatment and interestingly, across genders a strong association between depression and impairment in quality of life was noted. Hence, the findings throw important implications about the necessity of early identification of psychological problems in lichen planus patients and in planning their future course of management, which would help in productivity, favorable prognosis and thereby improve the quality of life.[3]

Studies done in India on psychotherapeutic approaches for psycho-cutaneous conditions were not available in the web-search so most of the studies reported here are from western literature. There is a rich literature of non-pharmocologic therapies for psycho-cutaneous conditions in the west which could be due to the adherence of a bio-psycho-social framework of treatment given more prominence in the west in the field of dermatology. The author hypothesize that non-pharmocotherapeutic management for these set of disorders may not be felt by the treating team of skin specialists and other professionals for which research could be minimal in India.

There are a few case studies (unpublished) recorded by the author on psychotherapy on patients from the burn ward of the Guwahati Medical

College and Hospital who had shown significant improvement in anxiety, depressive, self esteem and social embarrassment with supportive and cognitive behavior therapy approaches.

In psychotherapy outcome research, it is important to ascertain about concrete and realistic goals for psychocutaneous interventions. Science is based on facts which are observable and testable so goals such as reduction in scratching activity, decreased redness, reduced plaque or thickness, decreased anxiety and anger, improvement in social relationships, decrease in social embarrassment and improvement of biological symptoms could be set as goals to attain in the intervention programs of chronic skin lesions. Larger global goals could include an improved sense of well-being, sense of control and easily accepting and dealing with a positive approach about some inevitable aspects of a skin disease where cure should never be the goal. Most of the disorders are chronic in nature so goal of complete cure may lead to disappointment and a sense of failure.

From clinical experience as well as literature review the author believes that psychocutaneous medicine had indeed come a long way and is currently being incorporated in the mainstream medical practice. The requirements of patients are changing with time. Knowledge about various therapies had motivated the patients to request for more sophistication in treatment so actively seek for alternative approaches and adjuncts to standard treatments by pharmacotherapy.

Research had emphasized the need of referral to “skin-emotion specialist” who may be a psychiatrist, psychologist, social worker,

biofeedback specialist or any behavior or mental health specialist. The inclusive treatment program would expand therapeutic horizons and improve the quality of life of patients with chronic skin disease. Therapeutic success is difficult in patients with personality disorders and with any active psychotic process but they could profit with combinations of psychotherapy and medicines.[4]

Findings of a review of literature on psychocutaneous disease for the past 80 years reported that therapeutic options were standard psychotropic drugs, alternative drugs and supplements, active suggestion, CBT methods, biofeedback and hypnotic therapies as well. It also mentioned that when the simple measures failed to produce the desired results, combinations of drugs or addition of non-pharmacological therapies was found to produce better results.[5,6] The effectiveness of nonpharmacologic psychocutaneous techniques like hypnosis, biofeedback, psychotherapy, meditation, support groups, guided imagery and progressive muscle relaxation, and psychotherapy to treat dermatological conditions has been reported by numerous other studies. Few studies focused on the non-pharmacological management of psycho-dermatologic conditions which included both structured and unstructured interventions which could ameliorate skin disorders, reduce psychological distress, and improve the functional status of the affected individual and influenced the immune response and endocrine functions of the autonomic nervous system.[7-9] The biofeedback consisting of a variety of progressive relaxation techniques and other relaxation programs used in disorders pathogenically involve the autonomic

nervous system, CBT was found to relieve anxiety and obsessive-compulsive behavior associated with dysfunctional thought patterns and / or leading to skin damage and hypnosis consist in inducing a state of trance in order to obtain long- term analgesia, reduce itching, promote healing after surgery or reduction of self harm behavior and other methods of complementary therapies, herbals and supplements, aromatherapy with lavender oil or passion flower, melatonin were also reported to be beneficial.[10-12]

In a survey, it was found that 35-69% of persons with skin disease have used complementary and alternative medicines (CAM) in their life time so the influence of psychocutaneous interventions cannot be underestimated. Though in-depth studies about their efficacy were felt necessary by the authors but they concluded that acceptable therapies include acupuncture as well as psychocutaneous therapies. Reason may be low-risk profile of these therapies because of them being techniques that are less invasive. Instead of using them independently, combination treatment of these with that of the conventional ones should be the norm.[13] More data in this line that are sound is awaited.

A recent study on the importance of dual dermatologic and psychiatric approach in psychocutaneoous disorders reported that morbid conditions such as psoriasis, atopic dermatitis, alopecia areata, vitiligo, severe acne have a marked negative impact on patients' quality of life through both debilitating and chronic character of the diseases and by their psychosocial consequences which could be decreased self-esteem, embarrassment,

depression, social phobia, social discrimination to employment, difficulties and differences in family and couple relations. Hence, the authors concluded that collaboration with a psychiatrist for optimal management of psycho-cutaneous disorders is essential but difficult to achieve because most patients with such morbidity refuse (do not accept) the referral to psychiatric/psychological consultation due to the age old stigma of psychiatric illness. To fill in this vast gap in treatment and rehabilitation it was suggested that dermatologists need to have knowledge on pharmacological and non-pharmacological means useful in treating these disorders and to reconsider the importance of training in the field of psycho-dermatology.

Moreover the important insight was laid down for the mental health professionals on the cutaneous side effects of psychotropic drugs as they are more frequently encountered than most common psychiatric side effects of drugs used in dermatology.[2]

In conclusion, literature have well documented the interrelationship between skin and mind dualism in the last few decades but the influence of cognition and internal psychic mechanism is still poorly understood. A study reported that only 18% of dermatologists, is familiar with psycho-dermatology and only 39% of them were interested in continuing medical education activities focused on psycho-cutaneous disorders.[14] Hence, an increased knowledge of bio-psychosocial implications of psycho-cutaneous disorders is mandatory for corrective approach and their effective management. Considering the high incidence of comorbid psychological

problems in dermatological patients and their additional negative impact on the quality of life, dual medical approaches with dermatological and psychological / psychiatric methods, appears to be the treatment of choice for these patients. Research throw insight into the challenging nature of adherence to pharmacotherapy in patients with psychiatric disorders and their secondary cutaneous manifestations because they refuse psychiatric evaluation. Hence, a thorough knowledge of the gamut of biological and psychological causations, manifestations and management of psycho-cutaneous disorders by dermatologists as well as mental health professionals may add value to the maxim " beauty is only skin deep" and Yes, Indeed!

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Immunopsychiatry in Systemic Sclerosis

Dr. Puneet Mathur

Introduction

Immune system shares a complex relationship with the central nervous system (CNS). Across the literature, it has been observed that behaviour problems are common consequences of auto-immune diseases. Neuropsychoimmunology has become an exciting field to explore deep in to the interactions among immune state, brain and the behaviour. In face of a medical illness or chronic psychological stressor, complex interactions between immune factors and nervous system promote a constellation of immune induced behaviour changes, referred to as sickness syndrome or sickness behaviour. These include anorexia, altered sleep- wake pattern, fatigue, dysphoria, anhedonia, social withdrawal, hyperalgesia and cognitive dysfunction. [1]

Basics of the Immune System - CNS interaction

Alterations in CNS functions have been shown to influence the immune system as well as the natural history of the disease involving the immune

system. A number of hormonal and neurotransmitter pathways mediating such influences have been elucidated, and are areas of active research. Cytokines derived from immune cells and microglia could have profound effects on pathophysiology of psychiatric disorders.[2] Recently, increased interest has been laid to investigate the role of inflammation in a number of psychiatric illnsses, specially depression.

While stress has been widely reported to be associated with suppression of immune functions, newer findings indicate that the immune system in mammals respond to the environment in much more complex fashion. Stress activates certain aspects of the immune system, specially the innate immune system. Immune changes in response to various psychosocial stressors include increased numbers of white blood cells, CD 8 T lymphocytes and natural killer (NK) cells and decreased numbers of total B lymphocytes. It also includes a decrease in lymphocyte response to several non-specific mitogens. Chronic stress has been found to affect both humoral and cellular immunity. It could result in various kinds of deficits, i.e. Impairment in the suppression of the activity of a latent virus, or failure of antibody development following a vaccination. Life stressors in early developmental phase, including parental loss or child abuse are associated with increased markers of innate immune system, including C-reactive protein (CRP). Production of nitric oxide (NO) by macrophages has been shown to be involved in biochemistry underlying the capacity of stress to reduce lymphocyte proliferation. Stress leads to the production of pro-inflammatory cytokines, specially IL-6 in both peripheral blood and CNS, and activate

inflammatory signalling cascade including NF-kB in peripheral blood mononuclear cells. A pattern of sickness behaviour can be reproduced in humans by administration of innate immune cytokines, such as IFN-α, IL-1, IL-6, IL-2 and TNF-α. In experimental setting, blocking the cytokine activity by means of IL-1 receptor antagonist, insulin like growth factor-1, á-melanocyte-stimulating hormone, or IL-10 diminishes or prevents the development of sickness behaviour in laboratory animals.[1,3,4,5,6]

Hypothalamo-Pituitory-Adrenal (HPA) axis play central role in mammalian stress response. Corticotrophic releasing hormone (CRH) has varied effects on Immune system. In contrast to immunosuppressive properties, it has also been reported to increase the levels of proinflammatory cytokines, i.e. IL-1 and IL-6. In opposite direction, cytokines have also been shown to be capable of activating HPA axis at multiple levels with major final common pathway involving the stimulation of CRH production in the paraventricular nuleus of the hypothalamus.[1]

Proinflammatory cytokines including TNF-α, IL-1, and IL-6 within the CNS have been implicated in neurodegenerative changes found in illnesses such as Alzheimer's disease, multiple sclerosis, and HIV related dementia. It has been reported that Stress suppress hippocampal neurogenesis and reduces brain derived neurotrophic factor (BDNF). Administration of cytokines in laboratory animals produces significant alterations in the metabolism of neurotransmitters, including serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in CNS. Chronic administration of IFN-α may influence mood by diminishing 5HT availability as a result

of an IFN-α induced enhancement of the activity of the enzyme indoleamine 2,3 –dioxygenase (IDO), which breaks down tryptophan, the primary precursor of 5-HT, into kynurenine and quinolinic acid. Independently, quinolinic acid is cytotoxic for brain cells. It is also an agonist at the glutamtergic NMDA (N-methyl-D-aspartate) receptor. In background of chronic IFN-α exposure, it can lead to development of behaviour problems. It has been shown that cytokines can increase the expression and function of synaptic reuptake pumps for serotonin and norepinephrine through stimulation of pathways linked with p38 MAPK. Depression is far more common in the presence of medical illness specially autoimmune diseases than in healthy people. Inflammation may alter CNS and hormonal functioning in ways that biologically predispose a person to develop behavioural problems, including depressive symptoms. [1,7,8,9]

What is Systemic Sclerosis

A rare disorder with unknown aetiology, Systemic Sclerosis (SSc), also known as Scleroderma is a multisystem disorder characterized by vascular abnormalities, connective tissue sclerosis and atrophy, and autoantibodies.[10] As per American Rheumatic Association (ARA), to diagnose a case of SSc, it should fulfil one major criteria which is, scleroderma proximal to the digits and affecting limbs, face, neck or trunk, and two of the three minor criteria, which are sclerodactyly, digital pitted scarring and bilateral basal pulmonary fibrosis.[11,12] On the basis of extent of cutaneous involvement it is classified into two variety, which are Limited cutaneous systemic sclerosis (LcSSc), and Diffuse cutaneous systemic

sclerosis (DcSSc).[13] The word scleroderma means "hardening of skin". Incidence of SSc ranges from 2.3 to 10 per million. It is more common among females, with the female: male ratio of 3-6:1. The peak onset is in the forth decade in females and usually later in males. [10,14]

A clear etiology is not known, though various factors are frequently associated. The primary pathology has been suggested to be in endothelial cell.[15,16] Injury to endothelial cell may trigger release of growth factors from platelets and other inflammatory cells leading to a fibrotic process. Tissue anoxia occurs following the damage to endothelial cells, vascular occlusion due to thrombus formation, and various other abnormalities in blood components. There is increased plasma viscosity, further compromising microvascular blood flow.[17,18,19] Fibromucinous changes occur in vascular endothelium. Increased collagen production in the subcutaneous tissue causes associated fibrosis. Fibroblast in SSc produces more collagen than in normal control.[20]

SSc involve multi-systems. Skin, lungs, heart, gastrointestinal tract (GIT), muscles, and kidney develop changes of endarteritis. Inflammatory cell infiltration, particularly of lymphocytes may occur in the joints, mucosa, and submucosa of GIT, and in striated muscle.[21] In severely involved skin there is loss of rete ridges, atrophic changes, and homogenization of collagen leading to skin induration.[22] In GIT, patchy disappearance of muscle and replacement by the fibrous tissue is common finding.[10] In lung, there is an inflammatory alveolitis which is then followed by progressive diffuse alveolar fibrosis with obliteration of capillaries and

alveolar spaces.[23] In heart, myocardium may develop considerable streaky or focal fibrosis. Occasionally, the mitral and tricuspid valve is involved.[24] Kidney involvement is usually characterized by a triad of intimal proliferation of the small intralobular arteries and arterioles, fibrinoid necrosis of the walls of the afferent arterioles and glomerular loop, together with cortical infarction.[25] Fibrotic changes are also seen in bile ducts, gall bladder, spleen, adrenals, mammary glands, pancreas, uterus, ovaries, thyroid glands, parathyroid glands and muscles. There may be thickening in the vessel wall in white matter and lymphocytic or granulomatous infiltration of meninges.[26]

Raynaud's Phenomena is often the earliest feature in natural history of SSc. Swelling of the hands, face and joints are early symptoms. Ulceration of fingers, gangrene and bone changes including absorption of terminal phalanges occur, often associated with calcinosis.[10,26] As the disease progresses, there occur pestle and mortar deformity due to erosive arthropathy[27], various deformities including facial deformities, pulmonary hypertention[28], dysphagia, abdominal distension and pain, diarrhoea, steatorrhea, malabsorptio[29,30], cardiac dysrhythmia[31], azotaemia,and various neuropathis[32]. Tightness of lids, diminished tear secretion, and keratoconjunctivitis sicca are some of the ophthalmological finding[33].

Immune factors in Systemic Sclerosis

Autoimmune response has been suggested in etiopathology of systemic sclerosis. 80% patients show the presence of antinuclear antibodies. Major

antibodies seen in the circulation are anti-topoisomerase (22%), anticentromere (up to 30%), and antiendothelial cell antibodies (30%).[10,34] Deficiency in circulating T lymphocytes and impairment in functions of cellular immunity is related to severity of disease, visceral involvement and association with HLA-B8 [35]. Presence of antitopoisomerase(Scl-70) and antihistone antibodies are associated with pulmonary fibrosis.[36] Anti RNA polymerase antibodies have been observed in SSc.[37] They were found associated with diffuse disease. Anticollagen antibodies to collagen type-1 and type-4 have been found to be inversely associated with severity of disease.[38] 50% patients show circulating immune complexes.[39] Inhibition of leukocyte migration has been reported in SSc patients.[40] IL-1 has been suggested to increase the synthesis of glycosaminoglycan from fibroblasts in patients of SSc.[41] Excessive response of fibroblasts to connective tissue growth factor (CTGF) and transforming growth factor-α (TGF-α) has been reported in SSc.[42,43] Increment in levels of soluble cytokine receptors and adhesion molecules in SSc have been observed.[44,45] Raised levels of helper-T cells and NK cells, and decrement in suppressor T cells have been shown. Activation of helper-T could be due to raised levels of IL-2.[46,47,48,49] A study observed the delayed cutaneous reaction to autologous leucocytes in some SSc patients.[50] Role of IL-2 and IL-21 has been supported with single nuclear polymorphism studies.[51] It has been concluded that IL-13 is critical in fibrotic inflammation in SSc.[52] A Spanish study on immunological profiling in SSc patients observed low rate of apoptosis and low count of

B-lymphocytes. Patients also had increased count of monocytes, activated B-cells, and NK cells.[53]

Psychiatric morbidities in Systemic Sclerosis

Systemic sclerosis affects multiple systems that along with compromised bodily functions, lead to disability and subsequent state of stress. Cosmetic concerns secondary to disfigurement play a role in low self esteem and perceived mental stress. Decrement in subjective well being and Impairment in social and occupational life badly affect the overall quality of life.

High prevalence of major depression and anxiety is observed in SSc.[54] Prevalence of clinically significant depressive symptoms ranging from 51-67% have been reported in a systemic review.[55] It has been observed that depressive symptoms are related to disease severity. Successfully treating dyspnea, GIT symptoms and joint pain were observed to improve mood.[56] A recent Greek study observed depression, anxiety, somatisation, interpersonal sensitivity and obsessive-compulsiveness to be common among SSc patients. They also observed many patients to have paranoid ideations and psychotic symptoms.[57] SSc patients have been found to have maladaptive defences and low level of sense of coherence, associated with their diminished quality of life.[58] 81% patients of SSc had psychiatric disorders in an Italian study.[59] SSc patients suffer with sexual impairments due to diminished desire, poor lubrication, fatigue, pain and erectile disorder.[60,61] Thombs et al [62] summarized that highly disturbing in SSc were depression, fatigue, pain, pruritis, body image distress, sexual functioning and poor sleep. In a recent Indian study on SSc

patients, 87% patients had depression while 83% patients had significant anxiety.[63] Patients were also observed to have poor quality of life. There was worsening of psychiatric morbidities with increased duration of SSc.

Conclusion

Immune system and brain influence each other. Cytokines are common mediators of such interactions. Both humoral and cellular immunity get involve in stress responses. Immune factors also interact with neuro-endocrine system to bring about changes in brain and behaviour. Systemic Sclerosis is such disorder that could present great opportunity to further exploration of neuropsychoimmunology. A number of cytokines including various interleukins i.e. IL-1, IL-2, IL-6, IL-13 and IL-21 play an important role in pathophysiology of SSc. Other important agents are IFN-γ, and TGF-α. Systemic sclerosis is complicated with a number of behavioural problems including depression and anxiety. A major concern is the poor quality of life that remains strongly associated with severity of disease.

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Trichotillomania: "wind of change"

Dr. Shyamanta Das, Tanushree Sharma

"Welcome to the jungle"

Guns N' Roses welcomed us to the jungle in their album, "Appetite for destruction" while talking about American cities.[1] Similarly, with the changing concepts of disease and their respective nomenclatures, we too sometime feel like being in the mess of a jungle!

Hallopeau first described trichotillomania in 1889; it is a psychiatric disorder that features the incontrollable urge where one pulls out own hair.[2] Characteristic symptoms of the disorder include pulling of hairs resulting in loss of hair; there are attempts to resist. Increasing tension is a common accompaniment before the act or during resistance. The act itself subsequently leads to pleasure, gratification, or even relief.[3] In the daily functioning of the individual, it causes significant impairment. The condition is neither associated with a medical condition nor explainable by other psychiatric disorders. Till very recently, it was considered to be an impulse control disorder.[4,5]

However several experts have opined that trichotillomania required a new scheme of classification, the previous one being too narrow. The said hair loss is often not noticeable in subjects.[3] Approximately 20% of patients with a diagnosis of trichotillomania do not report an urge/ increasing tension to pull hair or a sense of pleasure/ gratification after pulling.[6] Thus, the symptoms of impulse control disorders may not always be present necessarily in trichotillomania patients.

The disease has a lifetime prevalence of 0.6%, but it is more common in females than in males (3.4 : 1.5) as cited by Christenson *et al.*[2] Hair pulling is mainly from the scalp but other areas like eyebrows, eyelashes, face, axillary, and pubic regions is also seen.[2]

Various genetic and neurobiological studies have been undertaken to ascertain the cause of trichotillomania. It has been shown that various neurobiological factors interact in a complex manner to give rise to the disease. Metabolic aberrations in the serotonin and opioid systems have also been implicated.[7] Neuroimaging techniques have revealed a hyperactive cerebellum and right superior parietal lobe, and possible structural anomalies in other parts of the brain.[8] The various neuropsychological abnormalities are problems in spatial processing, divided attention, nonverbal memory, and executive functioning.[8]

Genetic factors also play a role. In 2006, Zuchner *et al.*[9] proposed that a sequence variation in the SLITRK1 gene may play a role in the disease. The other gene implicated is the HOXB8 gene.[10] Variations in

this gene have been believed to have lead to excessive grooming behaviour in mice.

The onset of trichotillomania is often (in more than one fourth of the cases) related to a stressful situation.[7] The disorder can either be focused or automatic. Automatic is when the person pulls hair while doing day to day activities (for example, while watching TV); a more focused style is seen when the individual pulls out each hair one by one in a selective manner. The latter may be in order to avoid undesirable thoughts.[11]

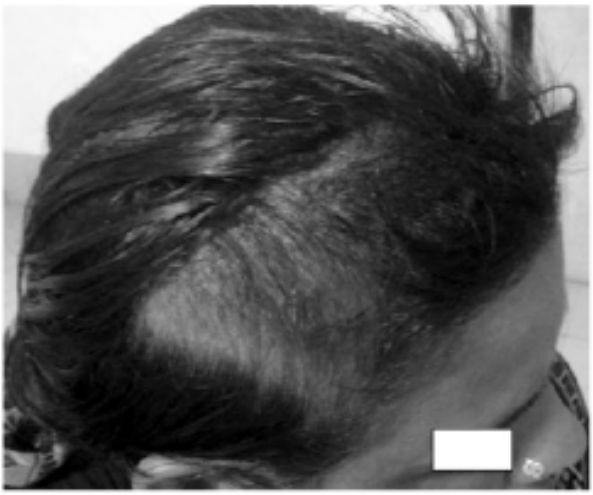
"The heart of the matter"

Like Don Henley saying, "I've been trying to get down to the heart of the matter",[12] we from the Departments of Dermatology and Psychiatry here in the Fakhruddin Ali Ahmed Medical College Hospital, Barpeta, treated many such patients as a consultation-liaison team.[13,14] We enquired during that time in 2012 whether it is the "time to test trichotillomania terminology" and asked "do trichotillomania need reclassification into a new group of disorders?"

Patient 1

A 40 years old woman had creeping sensation of head. It led to pulling of hairs. The urge to pull hairs was irresistible. Following the act, there was immediate gratification. Eight months of these symptoms resulted in hair loss over scalp (Figure 1). Vegetative functions were disturbed in the forms of increased sleep, diminished appetite, frequent micturition, irregular bowels, and weight loss. Stress was present. Similar episode three years

back was reported. Her socioeconomic status was lower middle and background was rural. She was illiterate and homemaker. She married and was a mother. She used smokeless tobacco. Along with depressed and anxious mood, she had helplessness and death wish. Insight was level three.



patient 1

Patient 2

A 35 years old woman was pulling her hairs for ten years. It resulted in hair loss over scalp (Figure 2). There was generalised body itching. Sleep disturbance exacerbated her symptom. There were episodes of apparent unresponsiveness. Stress was present. Occasional fever was also reported. She hailed from lower middle socioeconomic status. Background was rural. She was married and a mother. She was high school educated and was a homemaker. Menstrual bleed was scanty. Her mood was depressed. Insight was level four.

patient 2

Priti Singh and her colleagues [15] reported a rare presentation of trichotillomania with comorbid antisocial personality disorder. They also discussed the difficulty issues in the management of the patient.

Most of the patients were treated successfully with fluoxetine.

"Wind of change"

As the legendary Scorpions' number "wind of change" goes,[16] we in psychiatry also are in such a phase following the introduction of the DSM-5 and ICD-11 Beta Draft.[17,18] Now, a chapter on obsessive-compulsive and related disorders is included. This inclusion is reflective of evidence for relatedness of these disorders to one another. Diagnostic validity and clinical utility bring these disorders to the same group. This chapter includes

trichotillomania or hair-pulling disorder. The characteristic feature here is the recurrent body-focused repetitive behaviours. Another similar disorder, i.e. excoriation or skin-picking is included here.

In DSM-5, the rest of the group is formed by body dysmorphic disorder and hoarding disorder, apart from obsessive-compulsive disorder. Finally, substance/ medication-induced obsessive-compulsive and related disorder, obsessive-compulsive and related disorder due to another medical condition, and other specified obsessive-compulsive and related disorder and unspecified obsessive-compulsive and related disorder are clubbed here. In ICD-11 Beta Draft, along with obsessive-compulsive disorder and body dysmorphic disorder, hypochondriasis and olfactory reference disorder complete the list in this group.

Reasons for classifying trichotillomania under obsessive-compulsive disorder are many. The biology underlying both the conditions has some similarities.[19] Compared to desipramine, clomipramine is more effective in treating these disorders.[20] Involvement of frontostriatal circuitry in obsessive-compulsive disorder as well as trichotillomania revealed by brain imaging is another commonality between them.[21]

Trichotillomania is not diagnosed when the hair pulling or hair loss is attributable to medical conditions like inflammation of the skin or other dermatological conditions. From dermatological point of view, it is important to consider other causes of scarring alopecia or nonscarring alopecia in individuals with hair loss but who deny hair pulling. Alopecia

areata, androgenic alopecia, telogen effluvium are the causes of scarring alopecia. And causes for nonscarring alopecia include conditions like chronic discoid lupus erythematosus, lichen planopilaris, central centrifugal cicatricial alopecia, pseudopelade, foliculitis decalvans, dissecting folliculitis, acne keloidalis nuchae. To differentiate trichotillomania from other causes of alopecia, skin biopsy and dermoscopy or trichoscopy is helpful. Dermoscopy shows decreased hair density, short vellus hair, and broken hairs with different shaft lengths in trichotillomania.

A joint approach by dermatology and psychiatry is required to tackle this disorder. The previous few years have seen significant advances in the study of this much ignored disease.

"Where do we go now?"

We started with Guns N' Roses' welcome and now to conclude let us use another of their number from the same album, i.e. appetite for destruction, "Sweet child o' mine" where they ask, "Where do we go now?"[22] Now, talking about trichotillomania, we need to go beyond this impulse versus obsessive-compulsive classificatory dilemma and look into the brain mechanisms involved in the disorder in order to offer improved treatment and better outcome to the sufferers.[23]

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Adverse Cutaneous Drug Reactions (ACDR) associated with psychiatric medications

Dr. Ashimav Deb Sharma

Psychiatric disorders rank among the highest prevalent disorders among the population. Depression alone is the second highest cause of morbidity in the population. Course of treatment also lasts longer for psychiatric disorders. As a result a high proportion of population is taking medications for psychiatric disorders at any given time and psychiatric medications are among the most widely prescribed medications in the world.

Adverse cutaneous drug reactions (ACDR) are common adverse effects of many medications. Psychiatric medications are also associated with ACDR. Approximately 2- 5% of the individuals prescribed psychiatric medications show ACDR. Most ACDR associated with psychiatric medications are benign in nature. However, these reactions disturb the patients and interrupt therapy leading to non-compliance; rarely, some reactions can be life-threatening. Serious ACDR has been found with mainly with the mood stabilizers.

Withdrawal of suspected drug is the first step for consequent treatment. As some adverse cutaneous reactions are life threatening, the most important action is to discontinue the drug usage promptly, and thus minimizing morbidity. It is very important for physicians and psychiatrists to be aware of the potentially serious adverse skin reactions to psychiatric drugs. Patients must be provided with simple information on these adverse effects, and given proper directions to consult immediately if any of the signs of ACDR appear. Some of the common ACDRs are discussed below:

Pruritus

Pruritus or Itching is defined as an unpleasant sensation of the skin that provokes the urge to scratch. It found in many skin diseases and can also be a symptom associated with some systemic diseases. Pruritus is an annoying physical symptom, frequently related to mental states. Pruritus occurs secondary to most ACDRs and is often primary adverse effect of nearly all anti-psychotic, antidepressant, and mood stabilizing drugs.

The high incidence of itching among psychiatric in patients necessitates awareness of the psychiatrist of this potential discomfort. Examination, diagnosis and treatment when needed can relieve the physical symptoms, which may also have an emotional effect on the patient.

Pruritus can occur with any psychiatric medication, but more frequently reported after using mood stabilizers including carbamazepine, lithium carbonate, valproic acid, lamotrigine, gabapentin, and oxcarbazepine.

Dermatologic treatment commonly includes psychotropic medications along with symptomatic treatment.

Pruritus
All antipsychotics
All antidepressants
All mood stabilizers

Exanthematous eruptions

Exanthematous eruptions, also known as morbilliform or maculopapular eruptions are the most common form of drug eruptions, accounting for approximately 95 percent of skin reactions. Simple exanthemas are erythematous changes in the skin without evidence of blistering or pustulation. The eruption typically starts on the upper trunk and spreads peripherally in a symmetric fashion.

Eruption may generalize and include the entire body including palms, soles, and mucous membranes. Pruritus is almost always present. These eruptions usually occur within 1-2 week of therapy initiation; a re-challenge reaction occurring within days. Resolution occurs with a change in color from bright red to brownish red, which may be followed by scaling or desquamation. This type of reaction is common and can occur to most mood stabilizers, carbamazepine, and lamotrigine. In some cases, the eruption may subside without discontinuation of the drug and will not recur on re-administration of the drug.

Skin rashes are a well known complication of antiepileptic drug (AED) treatment. It has also been recognized that some patients will develop rashes from multiple AEDs (because of cross sensitivity). The cross sensitivity rate for rashes involving carbamazepine and phenytoin is 40%-58%. [ref] If rash develops from either of these AEDs, valproate or clobazam are safe alternatives.

Exanthematous reactions
All phenothiazines
Chlorprothixene, Clozapine, Haloperidol
Loxapine, Olanzapine, Risperidone, Ziprasidone
All antidepressant
Carbamazepine, Gabapentin, Lamotrigine
Lithium carbonate

Urticaria and edema

Urticaria is characterized by pruritic red wheals of various sizes. Individual lesions generally last for less than 24 hours, although new lesions can commonly develop. When deep dermal and sub-cutaneous tissues are also swollen, the reaction is known as angioedema. Angioedema is frequently unilateral and non-pruritic and lasts for 1 to 2 hours, although it may persist for 2 to 5 days.

When associated with drug use, urticaria and angioedema are usually caused by an immunoglobulin E (IgE) mediated immediate hypersensitivity

reaction. Signs and symptoms of IgE-mediated allergic reactions typically include pruritus, urticaria, cutaneous flushing, angioedema, nausea, vomiting, diarrhea, abdominal pain, nasal congestion, rhinorrhea, laryngeal edema, and bronchospasm or hypotension, or both.

Urticaria is the second most common cutaneous adverse effect. Among psychiatric medications urticaria and/or angioedema have been frequently reported after administration of clomipramine, paroxetine, ziprasidone, clozapine, and bupropion.

Urticaria and edema
All phenothiazines
Clozapine, Olanzapine, Risperidone, Ziprasidone
All antidepressant
Carbamazepine, Gabapentin, Lamotrigine
Lithium carbonate

Fixed drug reactions

Fixed drug reactions (FDR) usually appear as solitary, erythematous, bright red or dusky red maculae that may evolve into an edematous plaque. There may be presence of bullous-type lesions. FDRs are most commonly found on the genitalia and in the perianal area, although they can occur anywhere on the skin surface. FDR can develop from 30 minutes to 8-16 hours after ingestion of the medication. After the initial acute phase lasting for days to weeks, residual grayish hyperpigmentation develops.

Some patients may complain of burning or stinging associated with the lesions, and others may develop fever, malaise, and abdominal symptoms. On re-challenge, not only do the lesions recur in the same location, but often new lesions also appear.

FDRs have been reported with any antidepressant, antipsychotic and mood stabilizers and antiepileptic medications. They have been specifically found in patients taking carbamazepine, lithium carbonate, gabapentin, olanzapine, quetiapine, risperidone, haloperidol, and prochlorperazine.

Fixed drug reactions
Haloperidol, Olanzapin, Quetiapine, Risperidone
All antidepressant
Carbamazepine
Lithium carbonate
Gabapentin

Photosensitivity

Photosensitivity induced by exogenous agents can be divided into phototoxicity and photoallergy. Phototoxicity is the result of direct tissue injury caused by the phototoxic agent and radiation. It can occur in all individuals exposed to adequate doses of the agent and activating wavelengths of radiation. In contrast, photoallergy is a type IV delayed hypersensitivity response to a molecule that has been modified by absorption of light energy. Drugs that can cause photosensitivity reactions has been mentioned in the box provided.

Photosensitivity
All phenothiazines
All TCAs
All SSRIs
Carbamazepine, Gabapentin
Oxcarbazepine, Topiramate, Valproic acid

Drug induced pigmentation

Change in the pigmentation of the skin leading to discolouration can be an ACDR associated with many drugs including psychiatric medications. Pigmentation disorders of the skin can be either hypomelanotic or hypermelanotic or may present with a pattern of mixed hypo- and hyper-melanosis. [ref] Cutaneous discoloration is secondary to dermal granules containing melanin bound to the drugs or their metabolites.

Among antipsychotics, phenothiazines are most frequently associated with pigmentary changes, especially chlorpromazine, thioridazine and haloperidol. Chlorpromazine and related phenothiazines can produce bluish-gray pigmentation, especially in sun-exposed areas, and pigmentations of the conjunctivae.

Drug induced pigmentation
All phenothiazines, Clozapine, Haloperidol,
Olanzapine, Quetiapine, Risperidone
All SSRIs
Carbamazepine, Gabapentin, Lamotrigine

Pigmentary changes have also been observed with amitriptyline, imipramine, desipramine and clomipramine. Among mood stabilizers, pigmentary changes have been associated with carbamazepine, topiramate, lamotrigine, and gabapentin.

In most cases, discolouration slowly fades with discontinuation of the offending agent. Treatment options include drug discontinuation or use of cosmetic agents to mask skin discoloration.

Alopecia / hair changes

Alopecia or hair loss is common skin problem and can be adverse effect of a prescribed drug. Drug induced alopecia is characterized as a diffuse, non-scarring alopecia with localized or generalized hair loss, which commonly affects the scalp. Hair loss generally occurs when normal telogen hairs are shed, typically several months after the drug administration or rapidly in anagen efluvium.

The hair loss is reversible upon discontinuation of the offending agent. Drug induced alopecia has been reported with numerous antipsychotics, antidepressants and mood stabilizing drugs. Hirsutism and hypertrichosis have been reported with some antidepressants and rarely with mood stabilizers.

Alopecia/hair changes
Haloperidol
Olanzapine, Risperidone
Divalproex Sodium

Erythema multiforme

The typical eruption of erythema multiforme is acute, polymorphous, and sharply demarcated. The eruptions are red in colour with various forms. The typical lesion can be recognized by the presence of spots that look like small targets, with a dusky red center, a surrounding paler area and a dark ring round the edge. [ef] Cause of erythema multiforme is not fully known, but it is considered to be a hypersensivity reaction triggered by variety of agents. Viral infections (herpes simplex) are most common triggers, and around 10% of these are caused by medication.

Erythema multiforme
Clozapine, Risperidone, Fluoxetine, Paroxetine, Bupropion, Carbamazepine, Gabapentin Lamotrigine, Oxcarbazepine, Valproic acid

Erythema multiforme-like eruptions occur within days of the drug initiation. The reaction is characterized by typical target lesions that are variable in size, configuration and appearance. Mucous membranes can be severely involved in some episodes and spared in others. Erythema multiforme-like eruptions can precede a more severe reaction such as Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (SJS or TEN).

In most cases, erythema multiforme-like eruption involves well under 10 percent of the body surface area. Erythema multiforme-like eruptions do not occur frequently with antidepressants and antipsychotics, but have

been observed with fluoxetine, paroxetine and bupropion; and among antipsychotics with clozapine and risperidone. Erythema multiforme-like eruption occurs more frequently with mood stabilizing drugs such as carbamazepine, valproic acid, lamotrigine, gabapentin, and oxcarbazepine.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and TEN (Lyell's syndrome) are rare and life-threatening, mainly drug induced reactions characterized by confluent purpuric and erythematous maculae evolving to flaccid blisters and epidermal detachment predominating on the trunk and upper limbs and associated with mucous membrane involvement.[ref] Early identification and withdrawal of suspect drugs are essential for good patient out-come. The suspected medication should never be re-administered. Treatments of these conditions are mainly symptomatic.

Antipsychotics are rarely the cause of SJS and TEN, but they have been observed with clozapine, chlorpromazine, and flurazepam. Among antidepressants, bupropion has been observed to cause SJS, while fluoxetine, fluvoxamine, paroxetine and amoxapine were in rare instances associated with TEN.

Mood stabilizers are often the cause of SJS and TEN. Life-threatening reactions are caused by carbamazepine, valproic acid, lamotrigine, gabapentin, phenytoin, Phenobarbital, and oxcarbazepine. Valproic acid in combination with lamotrigine increases the risk of SJS and TEN. .

Patients that undergo therapy with antiepileptic drugs (AEDs), particularly new users of these agents, should be informed of and monitored for possible systemic and cutaneous adverse effects of AEDs. Concomitant use of lamotrigine and aripiprazole possibly increases the risk of SJS.

Recently, the USA Food and Drug Administration (FDA) has made a labeling change to the drug information contained in carbamazepine. Owing to recent data implicating the HLA allele B*1502 as a marker of carbamazepine-induced SJS and TEN in Han Chinese, the FDA recommends genotyping of all Asians for the allele.

Steven-Johnson Syndrome and Toxic Epidermal Necrosis
Clozapine, Chlorpromazine
Flurazepam, Bupropion, Fluoxetine, Fluvoxamine
Paroxetine, Amoxapine
Carbamazepine, Gabapentin, Lamotrigine, Oxcarbazepine
Valproic acid
Phenytoin, Phenobarbitone

Drug hypersensitivity syndrome / reaction

An exanthematous eruption in conjunction with fever and internal organ involvement (e.g., liver, kidney, central nervous system) signifies a more serious reaction, known as the hypersensitivity syndrome reaction (HSR).[ref] HSR occurs most frequently on first exposure to the drug, with initial symptoms starting 1 to 6 weeks after exposure. Fever and malaise

are often the presenting symptoms. Atypical lymphocytosis with subsequent eosinophilia may occur during the initial phase of reaction in some patients.

Although most patients have an exanthematous eruption, more serious cutaneous manifestations may be evident. Internal organ involvement can be asymptomatic. In most individuals, the chemically reactive metabolites that are produced are detoxified by epoxide hydroxylases. If detoxification is defective, however, one of the metabolites may act as a hapten and initiate an immune response, stimulate apoptosis, or cause cell necrosis directly.

Approximately 70 percent to 75 percent of patients that develop anticonvulsant HSR in response to one aromatic anticonvulsant show cross-reactivity to other aromatic anticonvulsants.

Drug hypersensitivity syndrome
Aromatic anticonvulsant
Olanzapine, Perphenazine
Desipramine, Amitriptyline, Imipramine
Carbamazepine, Lamotrigine, Oxcarbazepine
Valproic acid

In addition, in vitro testing shows that there is familial occurrence of HSR induced by anticonvulsants. Mood stabilizing agents that have been associated with HSR are carbamazepine, lamotrigine, oxcarbazepine and valproic acid. Antipsychotics and antidepressants that have been associated

with HRS are listed below. Prompt withdrawal of the offending drug is the first step in the treatment of HRS.

Drug hypersensitivity vasculitis

The clinical hallmark of cutaneous vasculitis is palpable purpura, classically found on lower extremities.[ref] Urticaria can be a manifestation of small vessel vasculitis, with individual lesions remaining fixed in the same location for more than 1 day. Other features include hemorrhagic bullae, ulcers, nodules, Reynaud disease, and digital necrosis. The same vasculitic process may also affect internal organs such as the liver, kidney, gut, and central nervous system and can be potentially life threatening.

Drug induced vasculitis can be dif cult to diagnose and is often a diagnosis of exclusion. Clozapine-induced allergic vasculitis is a rare but serious complication that should be added to the adverse reactions caused by clozapine therapy. Paroxetine, fluoxetine, maprotiline, and trazodone have been reported to cause urticarial vasculitis.

Drug hypersensitivity vasculitis
Clozapine
Paroxetine, Fluoxetine
Maprotiline
Trazodone
Carbamazepine

Exfoliative dermatitis

Exfoliative dermatitis is diffuse erythema and scaling of the skin involving more than 90 percent of total body skin surface area.[ref] Systemic complications include fluid and electrolyte imbalance, thermoregulatory disturbance, fever, tachycardia and high output failure, hypoalbuminemia, and peripheral edema.

It may appear abruptly or may manifest as progression of a benign drug induced skin eruption. Exfoliative dermatitis has been reported with quetiapine, risperidone, ziprasidone, and phenothiazines. It is also been associated with most TCAs and a number of other antidepressants. Among mood stabilizers, exfoliative dermatitis has been reported with carbamazepine, lithium and gabapentine.

Exfoliative dermatitis
All phenothiazines
Risperidone, Quetiapine, Ziprasidone
Most TCAs
Most SSRIs
Carbamazepine, Gabapentin
Lithium carbonate

Psoriasiform reactions

The eruptions are localized, regional or generalized, and are characterized by scaly pink papules and plaques, sharply demarcated by silvery-white scales. The lesions are often bilaterally distributed with a

predilection for elbows, knees and scalp. Psoriasiform reactions have been reported in association with quetiapine, risperidone, fluoxetine, citalopram, venlafaxine, trazodone, carbamazepine, lithium carbonate, valproic acid and oxcarbazepine .

Psoriasiform reactions
Quetiapine, Haloperidol
Fluoxetine, Citalopram
Venlafaxine
Trazodone
Carbamazepine, Gabapentin, Oxcarbazepine
Valproic acid

Acneiform eruptions

Acneiform eruptions are monomorphic, diffuse folliculocentric pustules, usually without comedones; they appear on the face, chest and upper back. Acneiform eruptions have been associated with most TCAs and all SSRIs as well as with other antidepressants. Almost any drug can cause these eruptions.

Seborrheic dermatitis

The affected skin is pink, edematous, and covered with yellow-brown scales and crusts, often associated with increased sebum production (seborrhea) of the scalp and the sebaceous follicle rich areas of the face and trunk.

Psychiatric drugs associated with seborrheic dermatitis are antidepressants (fluoxetine, fluvoxamine, paroxetine, mirtazapine, venlafaxine), mood stabilizers (carbamazepine, lithium carbonate, valproic acid, gabapentin and oxcarbazepine). Atypical antipsychotics (olanzapine, quetiapine, loxapine) have been associated with seborrheic eruptions.

Seborrheiceruptions are very common ACDRs in patients taking phenothiazines for a longer period, Sixty percent of patients with chronic neuroleptic induced parkinsonism also has comorbid seborrheic dermatitis.

Seborrheic eruptions
All phenothiazines
Olanzapine, Loxapine, Quetiapine, Fluoxetine
Fluvoxamine, Paroxetine
Mirtazapine, Venafaxine
Gabapentin, Lamotrigine, Topiramate
Valproic acid

Hyperhidrosis

An increase in perspiration has been noted in patients treated with carbamazepine, topiramate lamotrigine, gabapentin, and oxcarbazepine. Among antipsychotics, hyperhidrosis has been noted in patients treated with olanzapine, quetiapine and pimozide. Clomipramine, nortriptyline, phenelzine, bupropion, and maprotiline have been noted to cause an increase in perspiration. Hyperhidrosis as part of the serotonin syndrome has been reported as a side effect of citalopram use.

Acneiform eruptions
Haloperidol, Quetiapine, Desipramine
Protriptyline, Amitriptyline, Doxepine
Trimipramine, Clomipramine, Imipramine
Maprotiline
All SSRIs
Bupropion, Nefazodone, Venlafaxine
Mirtazapine
Carbamazepine, Gabapentin, Topiramate
Lamotrigine, Oxcarbazepine
Lithium carbonate

Hyperhidrosis
Olanzapine, Pimozide, Quetiapine
Risperidone
Nortriptyline, Clomipramine
Maprotiline
Phenelzine
Bupropion
Carbamazepine, Gabapentin
Lamotrigine, Oxcarbazepine
Topiramate

Diagnoses of Adverse Cutaneous Drug Reactions

First step to diagnose ACDR is taking a good history and to do clinical examination. Information about the prescribed drug, dosage and duration is essential, along with a keen clinical examination, as most of the ACDRs have distinctive lesions. Other measures to confirm the diagnosis include skin biopsy, other laboratory tests, provocation test, prick or scratch test and patch test.

Skin biopsy:

Skin biopsy can differentiate between drug hypersensitivity and its severity. The presence of eosinophils, edema and inflammation all suggest drug hypersensitivity. Vasculitis and necrotic changes may suggest erythema multiforme, Stevens-JohnsonSsyndrome or Toxic Epidermal Necrolysis.

Laboratory tests:

Allergic type of ACDR show high eosinophil count in peripheral blood sphere. Counts of more than 1000 cells/cmm indicate a serious drug-induced cutaneous eruption. For non-allergic type of reactions, estimation of drug level may be valuable diagnostic information. Tryptase level estimation may be helpful in confirming acute IgE mediated reactions

Provocation test:

In selected cases re-exposure may be of value; however, considering the degree of drug reaction and risks, this is usually not advisable.

Prick or scratch test:

Skin testing, including prick and intradermal testing, has been found to be useful for the confirmation of IgE-mediated immediate hypersensitivity reactions. Emergency resuscitation equipment should be available.

Patch test:

May be helpful to confirm allergic contact dermatitis, fixed drug eruptions, exanthematous drug eruptions, drug hypersensitivity syndrome, acute generalized exanthematous pustulosis (AGEP) and other delayed skin eruptions; however, no validated protocol has been established for these tests.

Avoiding ACDR

Best way to avoid ACDR is to identify the patients at risk before starting a particular drug. A thorough personal and family history of any Adverse Drug Reaction (ADR) proves to be immensely helpful.

Patients having history of ACDR to one drug may also be hypersensitive to other drugs in the same class. One common example is anticonvulsant hypersensitivity syndrome. Phenytoin, carbamazepine, and phenobarbital may be cross-reactive. A patient who is hypersensitive to carbamazepine have a e”30% risk of reacting to oxcarbazepine. A major predictor of rash associated with lamotrigine is history of a rash from another antiepileptic. Cross-reactivity also may occur among antidepressants, particularly selective serotonin reuptake inhibitors.

Genetics also play a role in ACDR risk. Inquiry to family history of ACDR is helpful in identifying 'at risk' patients. There are reports of ACDR occuring in several members in one family to a single Psychiatric medicine-Fluoxetine. If a patient reports that a relative had an ACDR, particularly a severe reaction, to a drug being considered, it is prudent to chose an alternate drug or proceeding cautiously by slowly titrating the dosage and monitoring carefully.

In general, ACDRs and dosage are not correlated, but anticonvulsants may be an exception. Lowering the starting dosage of lamotrigine reduces ACDR risk. To reduce ACDR risk, patients should be given the lowest effective anticonvulsant dosage.

Multi drug therapy should be carefully chosen to avoid ACDR. As drug-drug interactions are common causes of ACDR. Inhibition of metabolism leading to higher plasma concentrations of a drug can lead to ACDR. Valproic acid inhibits lamotrigine metabolism, so when prescribing these two medications together one should be careful and monitor for early signs of ACDR.

Identify factor(s) which can aggravate ACDR is an important step to reduce the risk of ACDR. Antipsychotic induced ACDR is related to sun exposure. These patients should be advised to use sunscreen and wear protective clothing. Antioxidant supplementation helps to prevent photosensitive reactions.

Certain populations are at increased risk of developing a drug rash. This includes African-Americans, persons age >70, Female sex, Underlying diseases, such as human immunodeficiency virus.

Early detection of serious ACDR (Danger Signs)

When a patient develops a rash, differentiating the serious from benign reactions can help prevent morbidity, which can range from work loss or hospitalization to disfigurement or death. Danger signs to look for are enumerated in the associated box.

Danger signs for severe cutaneous reactions:

Sudden flush, Severe urticaria

Severe angioedema,patricularly of oropharyngx with difficuly swallowing, horseness

Centrofacial edema, Erythroderma

Painful skin

Nikolsky's sign positive

Epidermolyses

Vesicles, Bullous lesions

Mucosal erosions at multiple sites

Atypical target lesions

Hemorrhagic or necrotic lesions

High fever

Laboratory findings

Eosinophilia, Neutrophilia, Lymphoblast, Blood cytopenia, Elevated LFT and Bilirubin level

Management of ACDR

Discontinuing the offending drug immediately is the first step in the management of ACDR. Immediate consultation with dermatologist and other related specialists is recommended. Patient may need hospitalization if indicated

Adverse cutaneous reactions to psychoactive drugs are common. They disturb and interrupt therapy often leading to non-compliance. The majority of adverse cutaneous reactions are benign if they are promptly recognized. Withdrawal of suspected drug is the first step for consequent treatment. As some adverse cutaneous reactions are life threatening, the most important action is to discontinue the drug promptly, thus minimizing morbidity. It is very important for physicians to be aware of the potentially serious adverse skin reactions to psychoactive drugs. Patients must be provided with simple information on these adverse effects. The good thing about ACDR is that with sincere effort of the treating doctors it is possible to reduce ACDR, and in case ACDR is already established a prompt consultation-liaison effort between dermatologist and psychiatrist can reduce complications of ACDR, thus not only helps the patient to revive from ACDR, but also adds to drug compliance for the primary disorder.

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