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PSYCHODERMATOLOGY – FOCUS ON PSYCHIATRIC OUTCOMES OF THERMAL SKIN INJURIES

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PSIHODERMATOLOGIJA – FOKUS NA PSIHIJATRIJSKE ISHODE TERMIČKIH POVREDA KOŽE

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ABSTRACT

Psychodermatology represents the discipline that explores the complex interaction between the central nervous system and the skin and offers a lot of confirmations for bidirectional interconnection between the pathological alterations that affect both the skin and nervous system. Psychodermatological disorders can be classified into three principal groups: Psychophysiological disorders, Psychiatric disorders with dermatological symptoms, and Dermatological disorders with psychiatric symptoms, while other entities that appear in clinical practice are classified as Miscellaneous. Thermal skin injuries are classified in the category of dermatitis artefacta. It has been confirmed that burns do not only affect somatic health components, but also have a deep impact on the patient's mental health and overall quality of life. Severe thermal skin injuries have also been shown to exert a significant systemic response that is finally accompanied by a visible impact on mental health. Oxidative stress and inflammation markers, neurotransmitters, and neurotrophin system elements, are the major groups of markers that show the common type of alterations that connect cutaneous events (typical for thermal injury) and mental outcomes accompanied by burns. The aim of this literature overview was to summarize some specific clinical entities for psychiatric/dermatological disorders that share the same underlying pathophysiological mechanisms, especially from the rarely evaluated direction ("skin to brain") – psychiatric outcomes of thermal skin injuries.

Key words: *psychiatry; dermatology; wounds and injuries.*

SAŽETAK

Psihodermatologija predstavlja disciplinu koja se bavi ispitivanjem složene interakcije između centralnog nervnog sistema i kože koja omogućava brojne potvrde za bidirekcionu povezanost između patoloških promena koje afektiraju kožu i nervni sistem. Psihodermatološki poremećaji mogu se klasifikovati u tri osnovne grupe: psihofiziološki poremećaji, psihijatrijski poremećaji s dermatološkim simptomima i dermatološki poremećaji sa psihijatrijskim simptomima, dok se ostali oblici koji se pojavljuju u kliničkoj praksi klasifikuju kao mešoviti. Termičke povrede kože ubrajuju se u kategoriju dermatitis artefacta. Potvrđeno je da opekotine ne afektiraju samo somatsku komponentu zdravlja nego imaju i značajan uticaj na mentalno zdravlje pacijenata i ukupni kvalitet života. Za teške termičke povrede kože pokazalo se da izazivaju značajan sistemski odgovor, koji je konačno udružen s vidljivim uticajem na mentalno zdravlje. Glavne grupe markera koji pokazuju zajednički tip odgovora koji povezuje događaj u koži (tipičan za termičku povredu) i mentalni ishod povezan sa opekotinama jesu markeri oksidativnog stresa i inflamacije, neurotransmiteri i elementi neurotrofinskog sistema. Cilj ovog pregleda literature je bio objedinjavanje pojedinih specifičnih kliničkih pojava psihijatrijskih/dermatoloških poremećaja koji imaju iste patofiziološke mehanizme u osnovi, naročito u ređe ispitivanom smeru („od kože prema mozgu") – psihijatrijski ishodi termičkih povreda kože.

Ključne reči: *psihijatrija; dermatologija; rane i povrede.*

INTRODUCTION

The causal relationship between dermal lesions and psychiatric disorders cannot be considered as a field of new medical evidence. Psychodermatology (i.e. psychodermal medicine) has a huge historical background, since the ancient times. Even in the fifth centuryBC, Hippocrates reported the relationship between the stress of the psychological origin and skin lesions, while Aristotle believed that mind and body (including skin) are complementary and inseparable. Despite that enormous timeframe as a medical science issue, psychodermatology has been recognized as an authentic and specific discipline in the last two decades (1). Although there are evident differences between the origin of dermatological and psychiatric disorders, the complex interaction between the central nervous system and skin offers a lot of confirmations for bidirectional interconnection between the pathological alterations that affect both skin and the nervous system. The fundamental attestation for this statement can be found in the fact that more than a third of dermatological patients' protocols require psychiatric observation, while on the other hand psychiatric outcome is significantly accompanied by severe dermatological diseases, such as eczema and psoriasis (2, 3).

A described psychodermatological link has its specific and confirmed pathophysiological background that includes the negative effects of psychological stressors on the epidermal barrier integrity, which has been considered

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as an underlying mechanism involved in dermal inflammatory processes, described for psoriasis and atopic dermatitis (4). The skin-CNS communication has been also verified by data that confirm skin cells' production of neurotransmitters and hormones, responsible for impact on the nervous and immune system, making the evidence to declare skin as a peripheral neuroendocrine organ (5). Most of the evidence that connects the skin and nervous system may be supported by the fundamental keystone explanation that the whole body surface and brain tissue share the same embryological origin (ectoderm, 6).

The aim of this literature overview was to summarize some specific clinical entities for psychiatric/dermatological disorders that share the same underlying pathophysiological mechanisms, especially from the rarely evaluated direction ("skin to brain") – psychiatric outcomes of thermal skin injuries.

Classification of psychodermatological disorders

Although the literature data offer several classifications of psychodermatological disorders, to date, none of them has resulted from a consensus established by psychodermatology experts. Most classifications are based on two to four main disorder category groups, mainly depending on the criteria of whether psychodermatosis appears as a primary mental health disorder or primary skin disorder. One of the most frequently used classifications was proposed by Koo and Lee (7). According to their expert opinion, psycho-dermatological disorders can be classified into three principal groups: Psychophysiological disorders, Psychiatric disorders with dermatological symptoms, and Dermatological disorders with psychiatric symptoms, while other entities that appear in clinical practice are classified as Miscellaneous (Table 1). Obviously, some patients with psychodermatological disorders initially address dermatologists, while others are asking for psychiatric intervention, although their pathology requires a bidirectional approach. Interestingly, some patients are focused only on one side of those complex clinical entities (usually denying their counterpart). Aside from a very heterogeneous miscellaneous group of psychodermatological disorders, there is growing evidence for the adverse and toxic effects of applied therapy for either psychiatric or dermatologic diseases with manifestations on the other side.

Psychophysiologic disorders

A broad spectrum of physical disorders with symptoms that can be newly brought and/or worsened by stress and emotional factors are classified as psychophysiological disorders (8). The clinical entities of this class of psychodermatologic disorders may appear in different organs and tissues, which is accompanied by specific symptomatology (Table 2).

As presented in Table 2, numerous skin lesions can be causally connected to physical disorders. More often, skin disorders are not caused by stress but appear to be precipitated or exacerbated by stress. Therefore, it is not surprising that stress management, relaxation techniques, benzodiazepines, and selective serotonin reuptake inhibitors have been found useful in these disorders (9).

Psychiatric disorders with dermatological symptoms

This class of psychodermatological disorders does not deserve adequate attention in clinical practice, although some clinical forms are associated with high suicidal risk (10). Although skin lesions and mental disorders go hand in hand, the clear order (meaning that the initial disease is of psychiatric origin) is (more or less) confirmed in this class of psychodermatological disorders. As shown in Table 3, the number of dermatological manifestations, and their severity, implies the necessity for including dermatologists in the therapeutic protocols for those primary psychiatric patients (11).

Dermatological disorders with psychiatric symptoms

A significant incidence (at least 30%) of psychiatric and psychological comorbidity was reported in dermatologic patients (12). Even more, psychiatric comorbidity shows an enormous impact on the overall disability associated with this cutaneous pathology (13). As shown in Table 4, anxiety and depressive disorders are the most common psychiatric features accompanied by primary dermatological disorders.

Miscellaneous group of psychodermatological disorders

Probably the best definition for this class of psychodermatological disorders is that it resembles the variety of disorders that fulfill the definition for joined two-compartment (skin and nervous system) pathology but cannot be classified into three previously described groups. Namely, according to literature data, the primarily encompassing cutaneous reactions to psychotropic drugs and skin signs of substance use disorders represent the clinical entity with the prevalence of 2-5% in the population with adverse reactions to psychiatric medications (14). Some disorders from this class are not connected to drug protocols. For example, psychogenic purpura (an extremely rare condition typically noted in women with psychiatric comorbidity) belongs to the group of autoimmune vasculopathy. Severe stress and emotional trauma always precede the skin lesions manifested by the development of painful edematous skin lesions progressing to ecchymosis over the next 24 hours (15). The borderless characteristic of a miscellaneous class of

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Table 1. Principal classification of psychodermatological disorders.

Psychophysiologic disorders	Psychiatric disorders with dermatological symptoms
Dermatological disorders with psychiatric symptoms	Miscellaneous

Table 2. Types of psychophysiological disorders.

Psychophysiological disorder	Signs and symptoms
Cardiovascular	hypertension, coronary heart disease
Gastrointestinal	irritable bowel syndrome
Respiratory	asthma, allergy
Musculoskeletal	low back pain, tension headaches
Skin	acne, eczema, psoriasis, atopic dermatitis, urticaria, rosacea, pruritus, seborrheic dermatitis, aphthosis, hyperhidrosis

Table 3. Primary psychiatric disorders with dermatological symptoms (adapted from Tohid et al. 2019).

Primary psychiatric disorder	Dermatological signs and symptoms
Stress and anxiety	blushing, hair-rising, growing pale, itching, hyperhidrosis
Phobia	repeated hand washing, cleaning hands and self-mutilation of skin, irritant dermatitis
Dysmorphophobia	feelings of excessive redness, scarring, large pores, blushing, facial hair and protruding or sunken parts of face, hair loss, red scrotum, and herpes
Psychosis	burning, tingling or itchy sensation or feelings of being touched
Delusional disorder	delusion of parasitosis, sensation of insect crawling over or under the skin
Depression	self-harm to the skin – scratching, picking, digging, bumping, cutting, pulling, tearing or harming skin, trichotillomania, neurotic excoriations
Somatic symptoms and related disorders	itching, cutaneous dyestheisas (trichodynia or glossodynia), hyperhidrosis
Impulse control disorder	picking acne, neurodermatitis, dermatophagia, trichotillomania
Obsessive compulsive disorder	acne excoriee, trichotillomania, onychotillomania, neurodermatitis, compulsive pulling of scalp, eyebrow, or eyelash hair, biting of the nails and lips, tongue, and cheeks, excessive hand washing
Eating disorder	acrocyanosis, gingivitis, lanugo-like body hair, hard calluses, onychophagia, generalized pruritus, hyperpigmentation, poor wound healing, cheilitis, seborrheic dermatitis, acquired pili torti, alopecia, Russell's sign, carotenoderma, Sjögren syndrome like changes, brittle nails and hair, periungal erythema, melasma, steatotic skin, hypertrichosis, striae distensae, and dry scalp hair
Factitious disorder	dermatitis artefacta (burn scars blisters, ulcers and purpura, rubbing, picking, scratching, cutting, punching, sucking, biting)
Psychogenic pruritus	itching, scratching

Table 4. Primary dermatological disorders with psychiatric comorbidity (based on the classification by Gupta and Gupta, 2003).

Dermatological disorder	Psychiatric comorbidity
Acne	depression and suicidal ideation, anxiety, anger, eating disorders (including bulimia nervosa), dysmorphophobia
Psoriasis	depression and suicidal ideation, anxiety, obsessive compulsive disorder, difficulties with verbal expression of emotions, alcohol abuse
Atopic dermatitis	anxiety, depression
Urticaria	anxiety, depression

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psychodermatological disorders is also confirmed by cutaneous sensory syndromes. Thus, this disorder represents a heterogenous group of unpleasant and uncomfortable sensations (such as itching, stinging, burning, crawling, or pain-related symptoms) and considered equivalent to chronic pain syndrome (16).

Thermal skin injury – impact on mental health

Looking for the common mechanisms underlying pathophysiological background that shows the same type of response at the site of initial action (skin) and in specific brain regions (that may be involved in these behavioral alterations), we have listed the evidence from the literature sources. The way that clinical practice may benefit from this methodological approach is based on the attempt to immediately attenuate the initial cutaneous damage (with cascade reactions afterwards), to prevent the same response in CNS, and therefore to prevent long-lasting behavioral consequences. To allow better insight into the way of communication between skin and brain, characteristic for psychodermatological disorders, we chose to analyze the pathophysiological events accompanying thermal skin injuries, using bidirectional analysis of common markers in which alterations appear simultaneously, and can make the reasonable explanation for the connection between the skin injury and its impact on mental health.

Thermal skin injuries are classified in the category of dermatitis artefacta. They usually appear as the consequence of unwilling exposure of the skin to heat, hot liquids (scalds), hot solids (contact burns), flames (flame burns), and electrical injury (17). The criteria for choosing the burns for representative analysis that can be applied to psychodermatological models of disease were defined based on the fact that they represent physically and psychologically challenging injuries with the intensity sufficient to initiate numerous responses in both targeted organ systems. Also, they are accompanied by a high incidence of disability, usually require long-term treatment in specialized medical institutions, and are declared as a significant health, economic, and social burden (18).

It has been confirmed that burns do not only affect somatic health components, but also have a deep impact on the patient's mental health and overall quality of life (19). The recent progress in the therapeutic protocols for severe thermal skin injury treatment unintentionally revealed the observations considering (sometimes even more serious) psychological/psychiatric aspects of this kind of trauma (20). Thus, we are now able to frame the broad spectrum (timewise) of psychopathological effects accompanying the burns – starting from the acute stress response (within the first month), followed by post-traumatic stress disorder (may last longer than 30 days), which may finally result in the form of major depressive disorder (21-23).

Aside from characteristic local (cutaneous) reactions, severe thermal skin injuries have been shown to also exert a significant systemic response that is finally accompanied by a visible impact on mental health. This allows quantification of the indicators of systemic response in different compartments, but preferably in the skin and specific brain regions, as well as their alterations in the systemic blood (to follow this compartment also, as the way of communication between the distanced target organs). The major groups of markers that show the common type of alterations that connect cutaneous events (typical for thermal injury) and mental outcomes accompanied by burns, can be listed as: oxidative stress and inflammation markers, neurotransmitters, and neurotrophin system elements.

Cutaneous oxidative damage in burns is initiated with the deformation of cell membrane phospholipids by oxidizing radicals (24). It is worth noticing that the degree of skin injury positively correlates with the lipid peroxidation indicators (25). The burns-induced destruction of oxidative equilibrium is further augmented by the diminishing of cellular antioxidant defense system activity. This was manifested by decreased activity of enzymatic (26) or non-enzymatic antioxidant mechanisms (27). The described pro-oxidative impact of thermal skin injury was accompanied by cognitive decline and decreased synaptic plasticity (28), as well as with clear anxiogenic response (20).

Immediately after the contact of superficial skin layers with the source of high temperature, the local inflammatory response is generated. This is initiated by injured/necrotic for the purpose of devitalized tissue regeneration (29). The most often manifested reaction is the enormous release of cytokines, chemokines, and numerous growth factors originating from both local tissue (keratinocytes and fibroblasts), along with chemotaxically attracted and activated leukocytes (30), in the process that may be localized, as well as generalized (31). Although the blood-brain barrier is not permeable for the majority of released mediators under physiological conditions, systemic reaction results in increased permeability that allows the penetration of pro-inflammatory molecules to brain tissue (32). Aside from standard pro-inflammatory markers with low blood-brain barrier permeability, some other easy penetrating molecules play a significant role in the inflammatory response to thermal injuries. Namely, some authors suggest the crucial role of nitric oxide in the connection between cutaneous inflammatory reactions and behavioral outcomes. It has been reported that NO, with anti-inflammatory abilities under physiological conditions, becomes a pro-inflammatory agent during inflammation

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due to increased production (33). On the other hand, NO has a beneficial role for cognition, behavior, and synaptic plasticity (34-36), especially in short-term memory (37). However, despite the systemic increase, the decline of cerebral NO during inflammatory response may accountfor mood alterations in rats (38) as well as for the cognitive impairment accompanied by delayed cognitive functions recovery following the thermal skin injury (39), although with no direct confirmation (40).

Unlike the pro-oxidative and pro-inflammatory response to burns that significantly affect the skin-brain axis, significant alterations are simultaneously observed for the molecules that initially originate from the nervous system but have an impact on both the brain and skin. It has been reported that neurotransmitting (serotonergic, dopaminergic, glutamatergic) systems are activated on the brain immediately after the cutaneous lesion, but also produce a significant effect on the skin by stimulating regeneration and reintegration of the damaged tissue (41). More specifically, serotonin has a significant role in wound healing by promoting cell proliferation and vitality, so the administration of serotonin and/or 5-HTR agonists may be beneficial in burn healing (42). However, although transmitters' roles in the skin after tissue damage are beneficial, their overall effect under these conditions is very controversial due to significant alterations in the nervous system that lead to aberrant transmission. So, it has been presented that increased serotonergic transmission, decreased dopamine metabolism, and increased norepinephrine levels in the brain regions responsible for food intake regulation may be considered a trigger for anorexia nervosa, as a late response to burns (43). At the same time, increased MAO-A levels following the thermal skin injury have been identified as a potential trigger of depressive behavior, which has been confirmed by the antidepressant action of MAO-A inhibitors in mice after the burns (44). Many behavioral alterations accompanied by thermal skin lesions may involve actions that include alterations in opioid/nociceptive receptors (45).

The neurotrophin system which includes different neurotrophic factors and their receptors has a crucial role in the maintenance of neuroplasticity, which is the intrinsic ability of brain tissue to adapt to environmental and physiological alterations (46). Brain tissue response to thermal skin injury, manifested also by hippocampal astrocyte and microglia activation, results in a significant increase in brain-derived neurotrophic factor (BDNF) levels (47). It has been postulated that overexpression of this trophic factor is responsible for compensatory mechanisms for maladaptive plasticity (47), since this brain growth factor is addressed for transfer of actual stimuli to persistent morphological change (48). The described mechanism was observed in clinical trials in patients who suffered burns (49). The investigation performed on the rodent experimental model with the thick burns showed that the anxiogenic response to the cutaneous lesion was accompanied by hippocampal BDNF level decline (20). The role of other neurotrophins, like nerve growth factor and neurotrophic factors 3 and 4, in brain response to thermal skin injury is less documented (50). The insufficiently documented roles of BDNF in the physiology of skin and surrounding tissues disables the attempt to analyze its alterations during the thermal injury, indicating that further focused investigations are required to reveal the potential bidirectional connection.

Not surprisingly, while the literature sources offer information about the evaluated markers from the skin in both clinical trials and animal experimental models, this cannot be achieved for the brain tissue samples. This confirms the necessity for the employment of animal experimental models for a better understanding of these psychodermatological entities. The animal experimental protocols have remarkable advantages that allow the possibility to:

- Obtain simultaneously the samples from two compartments of specific interest (affected skin portions and specific brain regions), which cannot be achieved in clinical trials. Data obtained from blood samples, like uniformly observed in clinical trials, does not necessarily reflect actual alterations of analyzed markers in target tissues.
- Analyze behavioral changes in a real-time manner, which allows evaluation of the continual relationship between estimated markers and behavioral outcomes.
- Create and, if well designed, evaluate potential therapeutic protocols, or even estimate comparatively the dynamics of desired responses.
- Bring a sufficient quantity of information that is necessary for a reliable translational approach.

However, there is an obvious necessity for establishing and validating new animal experimental models that can successfully mimic psychodermatological disorders in a representative manner.

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