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Mini Review

Exploring the Relationship between Psychoneuroimmunology and Oral Diseases: A Comprehensive Review and Analysis

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The relationship between psychoneuroimmunology (PNI) and oral health has recently garnered increasing attention due to the intricate interaction among psychological factors, the nervous system, immune responses, and oral diseases. This comprehensive review aims to elucidate the multifaceted connections between PNI and various oral conditions and conduct an in-depth analysis. Psychological factors, such as stress, anxiety, and depression, have been linked to oral microbiome alterations and immune function and the development and progression of oral diseases, such as periodontal disorders, oral ulcers, and temporomandibular disorders. Conversely, oral health conditions, particularly chronic periodontitis, have been associated with systemic inflammation, affecting mental health and overall well-being through neuroendocrine–immune pathways. Moreover, neural mechanisms, including the brain–gut axis and the autonomic nervous system, significantly influenced oral health through immune modulation and inflammatory responses. Understanding these complex interactions has implications for therapeutic interventions that target both psychological well-being and oral health outcomes. This review synthesizes current research findings from various disciplines, including immunology, neuroscience, dentistry, and psychology, to offer a comprehensive understanding of the bidirectional relationship between PNI and oral diseases. The implications of these interactions on treatment strategies, preventive measures, and interdisciplinary approaches underscore the need for integrated healthcare models that address psychological and oral health aspects to improve outcomes and quality of life in patients.

Keywords: Immune system concepts, Oral diagnoses, Psychology, Psychoneuroimmunology, Stress disorders

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INTRODUCTION

Psychoneuroimmunology (PNI) serves as the tangible embodiment of the biopsychosocial paradigm in medicine. In the interdisciplinary exploration, PNI delves into the interactions among psychological, neuronal, endocrine, and immunologic processes and connects with various physiological systems. The nervous, immune, and endocrine systems share signalling pathways collaboratively, thereby producing an integrated response. Acknowledging these interactions is pivotal in PNI, offering a deeper understanding of the intricate connection between mental and physical health [1]. The concept of the intricate relationship between psychological factors and physical well-being is not a recent revelation and was first reported by Galen in ancient history, around 200 AD, who reported melancholic women have higher susceptibility to breast cancer compared to their sanguine counterparts [2]. This body of research reinforces the notion that psychological factors can alter the course of various diseases through mechanisms such as stress-induced immunosuppression, stress-induced inflammation, and subtle regulatory changes in the endocrine and immune systems. Stress entails the mental and physical responses triggered by particular stimuli (stressors) in order to manage specific demands within subjectively challenging circumstances. The term stress refers specifically to distress—characterizing situations that surpass individuals' resources in a maladaptive manner, leading to negative emotions and associated physical reactions [3].

Stress experiences vary widely among individuals, shaped by their current and past encounters. When a stressor is subjectively assessed, stress axes kick into action, involving brain areas like the prefrontal cortex, hippocampus, and amygdala. The two prominent stress axes are the sympathetic nervous system or sympatho-adrenomedullary axis, releasing catecholamines, and the hypothalamic-pituitary-adrenal (HPA) axis, triggering cortisol release. Both axes impact target organs and induce diverse stress-related peripheral effects [4]. The inflammatory activity in response to acute stress is controlled by catecholamines, which protects the body against potential harm or infection. However, prolonged stress prompts the HPA axis, releasing cortisol to counteract excessive inflammation. This involves pro-inflammatory cytokines forming a self-regulatory feedback loop on various HPA axis levels [5]. In relation to the immune system, acute stress typically triggers an initial surge in inflammatory activity under the control of catecholamines. This serves as a likely protective mechanism, swiftly mobilizing immunological responses to counteract potential injury or infection. However, to prevent harm from an exaggerated inflammatory reaction, the stress response further engages the HPA axis, prompting the release of cortisol [6]. This stimulation primarily occurs through the release of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α). These cytokines establish a self-regulatory feedback loop by influencing various levels of the HPA axis, such as the paraventricular nucleus, the pituitary, and the adrenal gland. As a result of persistent (intermittent) stress, the HPA axis may experience dysregulation, marked by prolonged elevated cortisol levels, potentially lasting for years termed hypercortisolism, indicating an over reactive HPA axis or hypercortisolemia. Within the immune system, hypercortisolism can lead to compromised cytokine production, the depletion of lymphoid, thymic, and splenic tissue, and a systemic suppression of cellular immunity [7].

In a long run the stress related hypercortisolism is managed by compensatory inhibition of the immunoregulatory cortisol effect leading to decrease in the cortisol levels. In addition action of cortisol in target tissues can be altered because of glucocorticoid receptor (GR) activity and cortisol-induced HPA axis downregulation. Hypocortisolism and resistance to GR, in a reciprocal manner, are connected to heightened inflammatory activity and consequential tissue damage [8].

PSYCHOLOGICAL FACTORS, IMMUNE FUNCTION AND EFFECTS ON ORAL HEALTH

Numerous research studies have established connections between psychosocial factors, the immune system, and oral health [9,10]. Specifically, psychosocial stress has been correlated with diminished oral health, although the precise psychophysiological pathways remain largely ambiguous. The direct immuno-neuro-endocrine impact was underscored by changes in various biomarkers found in the saliva of healthy individuals (e.g., α-amylase, TNF-α, IL-6, IL-1b) following specific psychological influences. This suggests a direct biochemical influence of psychosocial events on the oral environment [11]. The various diseases discussed below includes oral lichen planus (OLP), periodontitis, recurrent aphthous stomatitis (RAS), pain associated with temporomandibular joint (TMJ) disorders, herpes labialis, burning mouth syndrome, eating disorders and atypical odontalgia (Fig. 1).

PERIODONTITIS

Periodontitis is an inflammatory condition that progressively damages the tissues supporting teeth, ultimately resulting in tooth loss. While certain microbial species are associated with periodontitis, it differs from traditional

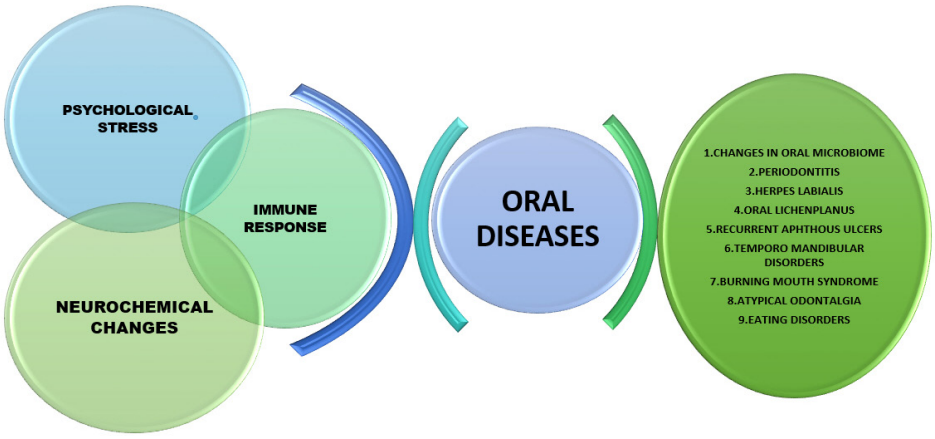

Fig. 1. The interplay between psychoneuroimmunology and oral diseases.

infectious diseases as tissue damage arises from an inappropriate inflammatory response rather than the direct action of microbes. The development of periodontal issues is intricately linked to the dynamic interplay between microbial challenges and the host's immune response. Individual susceptibility to periodontal destruction is further shaped by genetic factors, adding a layer of complexity to the underlying pathophysiological processes. The link between periodontitis and systemic health has been extensively explored, revealing associations with cardiovascular disease, diabetes mellitus, obstetric complications, respiratory diseases, chronic kidney disease, and cancer. Two major systemic mechanisms involve the invasion of bacteria from periodontal pockets, causing bacteremia, and the excessive production of pro-inflammatory cytokines, leading to elevated systemic levels [12]. The psychosocial aspects of periodontitis have been well-documented, with stress, depression, and inadequate coping behaviours identified as contributors to its onset and progression. Short-term stress may suppress cellular immunity, while chronic stress leads to comprehensive immune system dysregulation. Salivary levels of cortisol and β-endorphin, as well as psychological factors like depression and anxiety, correlate with periodontal outcomes.

A potential psychoneuroimmunological connection between psychosocial stress and periodontitis could be attributed to heightened activation of the HPA axis, leading to a suppression of cellular immune activity through increased cortisol release. This inhibition adversely affects the healing of soft tissues, including the periodontium, resulting in slower wound healing in individuals with elevated cortisol or epinephrine levels. This delayed healing process heightens the susceptibility to infection or further damage. Stress-induced immunosuppression may also create an environment conducive to bacterial infections, contributing to the development of destructive periodontitis [13]. The correlation between psychosocial stress, salivary cortisol concentrations, and the severity of periodontitis has been established in human studies. Experimental evidence suggests a psychoneuroimmunological mechanism, stressful life events, depression, and cortisol levels correlate with the extent and severity of periodontitis in humans [14]. These findings underscore the potential benefits of incorporating stress management and addressing depression in routine periodontal treatments to enhance immunologic and behavioural aspects conducive to periodontal healing.

HERPES LABIALIS

Herpes labialis, commonly known as "cold sores," results from an infection with the herpes simplex virus type 1 (HSV-1), characterized by the formation of blisters on the lips and perioral area. In some instances, the condition may be accompanied by fever and constitutional symptoms such as headache, myalgia, and malaise. Following the primary infection, the virus remains dormant in the trigeminal ganglion and can be reactivated when cellular immune activity diminishes. Various studies have consistently indicated that psychosocial stress, along with other factors like sunlight and physical exertion, constitutes a significant risk factor for recurrent symptomatic HSV-1 outbreaks [15]. The intricate relationship between psychological stress and herpes recurrence involves stress hormones such as glucocorticoids and catecholamines. These hormones likely act as mediators, influencing the activity of specific memory T cells, dendritic cells, and natural killer cells. Yan et al. [16] employing a research approach with weekly measurements spanning 32 weeks, observed a decrease in CD4+ T cells during the initial phase of HSV-1 relapse. The inhibition of cellular immunity can lead to viral reactivation, compensated by an upsurge in specific antibodies against newly formed viral proteins.

Studies on adolescents exposed to adverse early-life experiences, such as physical violence or growing up in an orphanage, demonstrated significantly elevated levels of HSV-

1-specific antibodies in saliva compared to those from more favourable family environments [17]. Additionally, research indicated that women who experienced both physical and psychological abuse in intimate relationships had a lower ability to neutralize HSV-1 in their saliva compared to those who did not face violence. However, a follow-up study three years later revealed that women who ceased exposure to violence exhibited no detectable difference in neutralizing activity, emphasizing the potential for stress-induced immune dysregulation to return to normal under favourable conditions, such as the cessation of abuse. The well-documented relationship between psychological stress and the exacerbation of herpes virus infections encompasses various factors, including short-term stress, stressful life events, dysphoria, anxiety, anger, and negative mood. Exacerbation manifests when stress-induced imbalances disrupt the cellular immune response, notably affecting the secretion of catecholamines, glucocorticoids, and pro-inflammatory cytokines (IL-1, IL-6, and TNF) [18]. While the psychoneuroimmunological interaction in recurrent herpes infections is well-established, quantifying psychological stress and determining its etiological significance in the onset of the disease remains challenging.

ORAL LICHEN PLANUS

OLP is a chronic inflammatory condition affecting the skin and oral mucosa, resulting from a dysregulated T-cell immune response [19]. Psychological stress is one of the important etiological factor associated with OLP, potentially playing a role in its pathophysiology. Studies show elevated stress, anxiety, and depression levels in patients, suggesting a link between psychological disturbances and autoimmune reactions [20]. Psychiatric assessments reveal mental disturbances in a significant percentage of patients, indicating a higher sensitivity to stress and increased cortisol levels suggesting alteration in the HPA axis [21].

The primary treatment involves corticosteroids and other immunosuppressive agents. Addressing the psychological aspect as adjunctive therapy is mandatory but there are not enough studies to prove the same. A multidisciplinary approach is recommended due to the profound impact of the disease on psychological well-being. The oral microbiome in OLP patients differs from healthy controls, but its causative role remains unclear—whether influencing immune response or resulting from the changed oral environment. Prior studies have indicated the pathogenic relevance of psychobiological factors in the progression and prognosis of OLP. Controlled investigations demonstrated that OLP patients exhibit heightened levels of psychosocial stress, depression, and anxiety, alongside less effective coping mechanisms and an increased occurrence of stressful life events. Furthermore, individuals with OLP tend to score high in specific personality traits, such as being norm-conscious, conservative, emotionally reserved, and highly self-controlled (16 Personality Factor Questionnaire). They also exhibit elevated levels of depression and a tendency to somatize, manifesting physical symptoms in response to psychological stress (Minnesota Multiphasic Personality Inventory) [22-24]. Despite establishing a psychosomatic connection, the underlying mechanisms that mediate the relationship between psychosocial stress and OLP remain poorly understood. A review of immuno-neuro-endocrine interactions in OLP yielded inconsistent findings regarding the involvement of the HPA axis: 55.55% of studies reported higher salivary cortisol concentrations in OLP patients compared to healthy controls, and 33.33% and 11.11% showing no difference and lower cortisol concentrations respectively in OLP patients [25]. Similarly, another study detected elevated serum cortisol only in patients with erosive lesions, and not in those with reticular lesions suggesting that cortisol levels may be predictive of the severity of the disease [26]. Clearly, further research is imperative to elucidate the nature and interplay of psychobiological components in the development and chronicity of OLP.

RECURRENT APTHOUS ULCERS

RAS is a chronic condition with an unclear origin, marked by the repeated occurrence of painful ulcers and erosions primarily on unattached oral mucosa. The disease is believed to stem from a hyper-reactive immune response influenced by genetic predisposition and various factors, including viral and bacterial infections, nutritional deficiencies, food allergies, psychological stress, mechanical trauma, and hormonal imbalances. Psychological stress plays a significant role in exacerbating RAS, with higher anxiety levels and elevated cortisol in plasma and saliva linked to the condition. The onset of RAS appears more closely tied to exposure to stressful situations than to personality profiles or stable psychological traits, although some evidence suggests trait anxiety as a predisposing factor. Surveys conducted over a year revealed a notable association between stressful life events, particularly psychological stressors, and RAS exacerbations [27].

Despite the complex and multifactorial nature of RAS, reports vary on the association of the condition with cortisol levels and psychological factors like stress and depression. Frequent flare-ups of painful RAS lesions disrupt daily activities, negatively impacting the quality of life. The psychological consequences of RAS may further contribute to the disease's progression, creating a cyclic pattern similar to

OLP. As conventional treatment for RAS is symptomatic and lacks long-term efficacy, supportive psychotherapy emerges as a potentially beneficial approach to alleviate patient discomfort [28].

TEMPOROMANDIBULAR DISORDERS

Temporomandibular disorders (TMD) involve chronic pain in the TMJ and associated muscles, impacting mandibular movement and causing sounds during motion. Despite causing significant distress, TMD is self-limiting and generally doesn't lead to progressive structural or functional deterioration. Psychological stress and pain are intricately linked, sharing biological pathways in the HPA axis, serotoninergic, and opioid systems. Research suggests elevated levels of anxiety, depression, and somatization in individuals with TMD. The experience of pain in TMD patients is influenced by emotional distress, muscular tension, and parafunctional habits. Maladaptive coping strategies and stress are linked to TMD pain, and the presence of sleep disorders may worsen symptoms by heightening pain sensitivity and contributing to muscular parafunctions [29]. Symptomatic treatment typically involves orthopaedic appliances, aiming to improve TMJ biomechanics and raise awareness of parafunctional habits. A multidisciplinary approach, including physiotherapy, biofeedback, and cognitive-behavioural therapy, is recommended due to TMD's multifactorial nature. While treatments targeting psychological factors may reduce symptoms and functional limitations, their effectiveness is currently supported by low evidence. Combined modalities, including antidepressants, may offer more effective and enduring results compared to the conventional use of orthopaedic appliances alone in managing TMD pain, irrespective of potential comorbidities with depressive disorders [30].

BURNING MOUTH SYNDROME

Burning mouth syndrome is a chronic pain condition with an unknown origin, typically characterized by a persistent burning or stinging sensation, along with a subjective feeling of dryness and altered taste. Clinically, there are no identifiable oral lesions or objective signs [31]. Heightened levels of neuroticism, anxiety, and depression along with psychological factors, with exposure to stressful life events, have been linked to the syndrome. Certain hypotheses propose the potential involvement of specific personality disorders and dysregulation of cortisol. Treatment for burning mouth syndrome should focus on identifying and addressing underlying psychological disturbances.

ATYPICAL ODONTALGIA

Atypical odontalgia is persistent dental pain without an identifiable cause, often leading to unnecessary tooth extractions. It mimics toothache, occurring in healed sites or healthy teeth with no pathology. Its etiopathogenesis involves unclear psychogenic and neuropathic factors. Managing symptoms is challenging, with no definitive treatment. Psychological counseling is essential to prevent irreversible damage, highlighting the need for cautious intervention [32].

EATING DISORDERS

Psychiatric conditions characterized by restricted food intake (anorexia nervosa) or purging behaviours such as induced vomiting or laxative use (bulimia nervosa) are known as eating disorders. The precise causes of these disorders are unclear, but there is a possibility of involvement of serotoninergic dysregulation in the brain. Regular exposure of dental hard tissues to gastric acid from vomiting can lead to cumulative demineralization and extensive erosions on both enamel and dentin, requiring thorough restorative or prosthodontic interventions. These disorders are linked to elevated pro-inflammatory cytokine levels, indicating a psychoneuroimmune interplay [33]. Psychological stress and inadequate coping behaviours are associated with eating disorders, often co-occurring with other psychiatric disturbances like anxiety and depression, suggesting a probable bidirectional interaction. In the acute phase of anorexia nervosa, increased levels of salivary cortisol, secretory immunoglobulin-A, and alpha-amylase indicate dysregulation of the HPA axis. Changes in enzymatic activity of proteases, collagenase, and pepsin in resting and simulated saliva, contributing to dental erosions are reported in patients with bulimia nervosa [34].

CHANGES IN ORAL MICROBIOME

The oral microbiome provides local benefits by preventing pathogenic colonization, known as colonization resistance, impacting both local and systemic health. Psychoneuroimmunological factors affect oral microorganism adhesion, with stress enhancing certain strains while decreasing coadherence. Stress-induced alterations in salivary composition may heighten susceptibility to diseases linked with oral microbiome changes [35]. Despite well-established connections between psychoneuroimmunological factors and the gut microbiome, their impact on the oral microbiome remains understudied. Understanding this interplay could

allow for oral microbiome modification using probiotics, potentially mitigating periodontal destruction by inhibiting microbial processes and altering inflammatory responses.

CLINICAL IMPORTANCE OF PSYCHONEUROIMMUNOLOGICAL ORAL DISEASES

Stress, anxiety, and depression have been identified as significant contributors to the development and progression of oral diseases. The intricate network of communication between the brain, nervous system, and immune system plays a crucial role in oral health. Chronic psychological stress can weaken the immune system, making individuals more susceptible to oral infections and periodontal diseases. Moreover, stress-induced behaviours such as poor oral hygiene and unhealthy dietary choices further exacerbate the risk of dental issues. Conversely, oral diseases can also impact mental health. Chronic oral conditions, such as periodontitis, have been linked to systemic inflammation, which can have implications for mental well-being. The clinical importance of understanding the psychoneuroimmunological aspects of oral diseases lies in the development of holistic treatment approaches. Integrating psychological interventions, stress management techniques, and mental health support into dental care can enhance treatment outcomes [36]. Patients with chronic oral diseases may benefit from a multidisciplinary approach that addresses both the physical and psychological aspects of their condition. Furthermore, recognizing the bidirectional relationship between PNI and oral health underscores the importance of preventive measures. Oral health education programs should include information on stress management and mental well-being to empower individuals in maintaining a healthy balance between their psychological state and oral hygiene.

CONCLUSION

In conclusion, exploring psychoneuroimmunological aspects in oral diseases unveils intricate connections between mental health, the nervous system, and the immune system. The bidirectional relationship between psychological factors and oral health emphasizes the need for a holistic dental care approach. Recognizing the impact of stress, anxiety, and depression on oral health, and vice versa, underscores the importance of integrated interventions. Future research in psychoneuroimmunological oral diseases promises to advance preventive strategies and treatments. Understanding molecular and cellular mechanisms mediating the nervous system, immune system, and oral health interaction can lead to targeted therapies. Incorporating PNI into dental education equips professionals for comprehensive care. Collaborative efforts among dental professionals, psychologists, and immunologists are essential in managing complexities. This multidisciplinary approach holds potential to revolutionize dental care by deepening the understanding of mind-body interrelation in oral health.

NOTES

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