Innovations

Oral lichen planus and stress-a review

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Abstract

Oral lichen planus is a chronic inflammatory condition that affects the mucous membranes inside the mouth. It is characterized by bilateral white striations or plaques on the buccal mucosa, tongue or gingiva. the last few years, significant advances have been made in understanding the mechanisms involved in the pathogenesis of the disease. One prominent and commonly accepted aspect of OLP relates to its potential relationship with several psychological diseases, primarily anxiety, depression, and stress. In this review we assess the role of stress in the pathogenesis and progression of lichen planus.

Keywords*: OLP, Stress*

Introduction

Lichen planus is a common dermatological disorder, which may affect the skin and oral mucosa. The condition was described for the first time by Erasmus Wilson in 1869 who characterized the patients as anxious, high strung, and sensitive with a tendency to worry excessively and with periods of undue emotional stress [1].

Oral lichen planus (OLP) is a chronic inflammatory disease that affects the mucus membrane of the oral cavity. In the general population, the prevalence of OLP ranges from 0.9 to 2.2 percent [2],[3]. Females suffer from lichen planus more frequently than men do, and it is recognized as an adult disease.[4],[5]. Although its etiopathology is yet unknown, there is a wealth of evidence that suggests immunological systems play a critical role in the development of lichen planus [6],[7]. Oral lichen planus is a chronic inflammatory disease characterized by bilateral white striations or plaques on the buccal mucosa, tongue or gingiva. OLP has a variety of clinical manifestations, the most prevalent of which are reticular, erosive, and atrophic forms.[8] Significant progress has been made in recent years in understanding the mechanisms involved in the pathophysiology of the condition. Although research to date suggests a psychosomatic component in the etiology and progression of OLP and the ailment is frequently referred to as stress-associated ulcerations of the oral mucosa, very little evidence has been published to support this widely held belief. In the majority of investigations, an association between psychological stress and OLP was observed. [9],[10],[11],[12],[13],[14]. In this review, we assess the possible role of psychological stress in the etiopathogenesis of OLP.

Etiology

Although the exact etiology of this disease is still unknown, but some factors are associated with it.

These are as follows:

Genetic factors. [15],[16],[17]

Drugs NSAIDs, beta blockers, sulfonylureas, some angiotensin-converting enzyme (ACE) inhibitors, and some antimalarials, contact allergens including toothpaste flavorings, especially cinnamates.[18],[19]
Dental materials like amalgam [20]
Infectious agents -Gram-negative anaerobic bacillus and spirochetes -not been confirmed.[21] Recently, it has been found in some literature that few periodontopathogenic microorganisms are also associated with the patients of OLP.[22]
Candida species -Several studies have shown an increased prevalence of candida species.[19]
Viral agents -human papilloma virus (HPV), Epstein Barr virus (EBV),human herpes virus 6 (HHV-6) and human immunodeficiency virus (HIV)hepatitis C virus (HCV)[23];[24];[25],[26],[27]
Autoimmunity OLP may occasionally be associated with autoimmune disorders such as primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis, myasthenia gravis, and thymoma.[27]
Bowel disease-Bowel diseases occasionally described concomitant with OLP include coeliac disease, ulcerative colitis and Crohn's disease.[28],[29]
Stress [3],[30]
Habits like smoking, betel nut chewing[31],[32]
Trauma -may be the mechanism by which other etiological factors exert their effects.[8]
Diabetes and hypertension Studies have revealed that both diabetes mellitus (DM) and high blood pressure are associated with OLP[33]
Malignant neoplasms LP has been observed on the skin and/or mucosae of patients affected by a range of different neoplasms such as with breast cancer and metastatic adenocarcinoma.[8]
Miscellaneous associations OLP has occasionally been associated with other conditions, including psoriasis, lichen sclerosis, urolithiasis, agents used to treat gall stones, Turner's syndrome, etc. [8]

Pathogenesis

OLP is a T-cell mediated autoimmune disease in which the auto-cytotoxic CD8 + T cells trigger apoptosis of the basal cells of the oral epithelium.

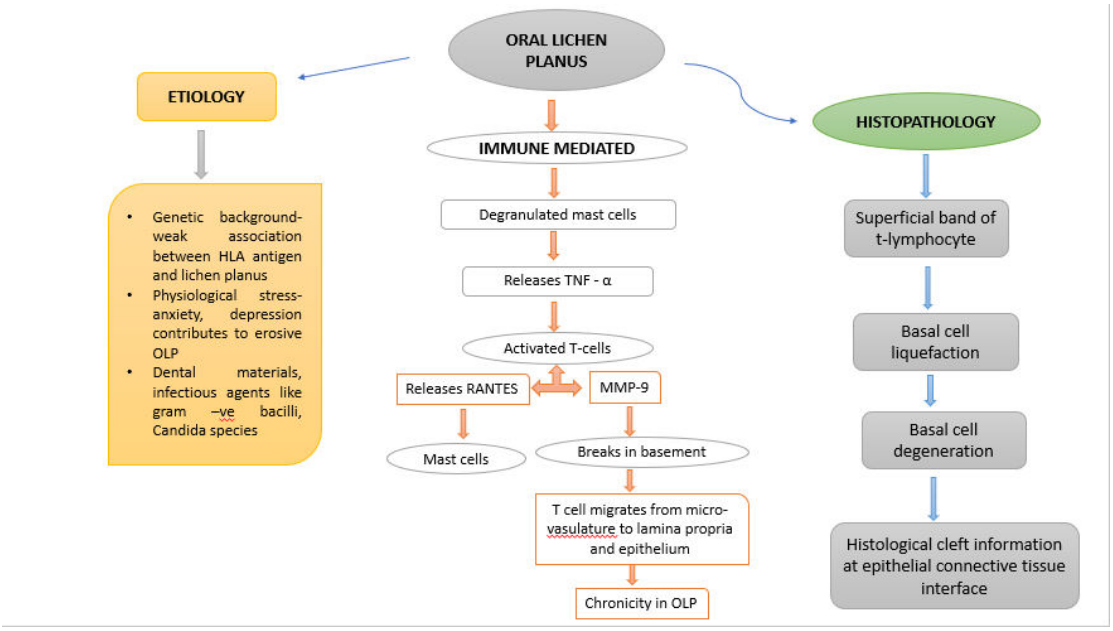

Figure 1

Clinical presentation

OLP has got varied clinical presentations such as reticular, erosive, and atrophic, which are the most commonly reported. Bullous type oral lichen planus is also seen, but it is a very rare entity.(figure 2)

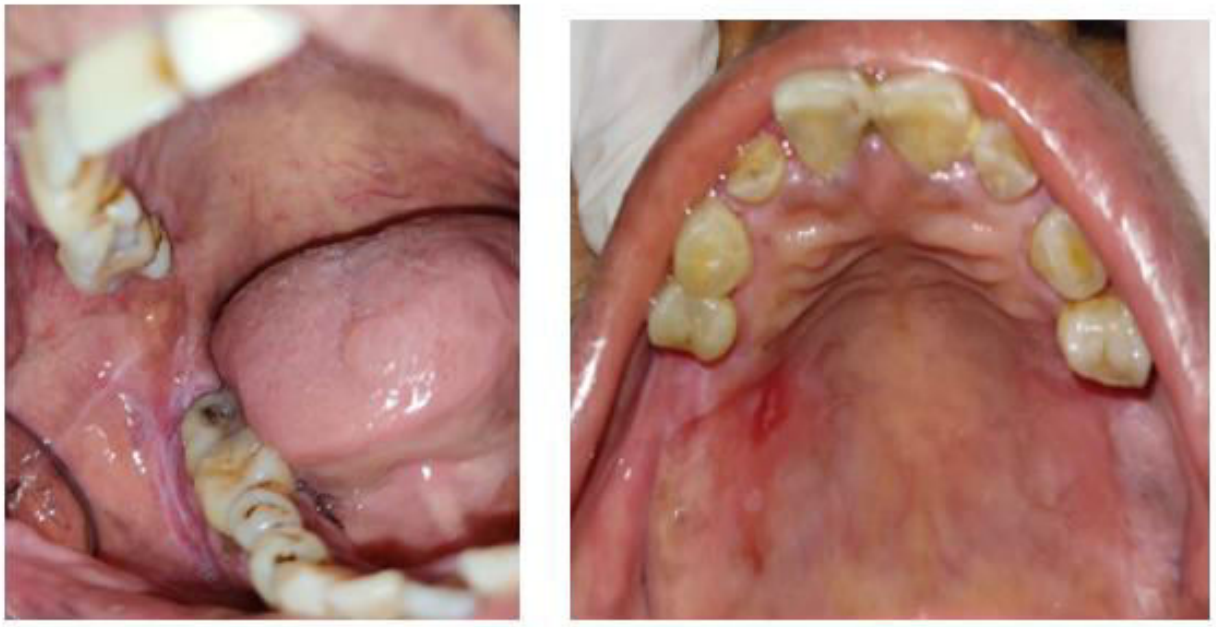

Figure 2

Histopathology

The classic histopathologic features of OLP include liquefactive degeneration of the basal cell accompanied by apoptosis of the keratinocytes, a dense band-like lymphocytic infiltrate at the interface between the epithelium and the connective tissue, focal areas of hyper keratinized epithelium and saw tooth rete pegs). Eosinophilic colloid bodies (Civatte bodies), which represent degenerating keratinocytes, are often visible in the lower half of the surface epithelium. Histologic clefts (Max–Joseph spaces) may form by Degeneration of the basal keratinocytes and disruption of the anchoring elements of the epithelial BM and basal keratinocyte

Role of stress in the etiopathogenesis of oral lichen planus

Psychological stress has the capability to activate the immune and endocrine response systems which can in turn lead to lichen planus.

1. Effect of Stress on Immune System

Even little temporary stress can result in immunological dysregulation and a decline in lymphocyte function. The influence of stress on the immune system and inflammatory process has the ability to influence depression, infection, autoimmune, diseases. Current studies indicate that psychological stress is an important factor in the etiopathogenesis of OLP.[34] It has been shown that in up to 80% of patients with the autoimmune disease had an onset emotional stress before their illness has been reported.

Stress hormones, acting on antigen-presenting immune cells, may affect the differentiation of helper T-cells away from a Th1 and towards a Th2. It leads to suppression of cellular immunity and activation of humoral immunity. Additionally, most investigations have proposed the possible role of humoral immunity in the pathogenesis of OLP.In most of the studies the concentration of cortisol was shown to have an increased in OLP patients.It might be presumed that this elevation may be caused by the compensatory mechanism of the adrenal glands to counter disease.[34]

Repeated instances of acute or chronic stress may trigger an acute phase response, which in turn causes a chronic inflammatory process, such as an autoimmune illness. Many studies have suggested that the imbalance between Th1/Th2 has a critical role in the pathogenesis of several autoimmune disorders.[35] T lymphocytes promote their function through cytokine release. T lymphocytes promote their function through cytokine release. Generally, Th1 cytokines include IL-2, IL-12, IFN-Ɣ, and TNF-α, and Th2 cytokines consist of IL-4, IL-5, IL-6, IL-10, and IL-13.It has been postulated that repeated episodes of acute or chronic stress can induce an acute phase response that results in a chronic inflammatory process such as autoimmune disorder.[36]

One of the most common cytokines in this process is IL-6 which is a part of the innate immune system IL-6 has a key role in acute phase response, differentiation and stimulation of B cells, and growth and differentiation of T cells, that lead to chronic phase and autoimmune disease like OLP.

Some studies have indicated that levels of IL-6 are increased in OLP patients while others believe that levels of IL-6 are decreased. It has been hypothesized that the decreased levels of IL-6 in OLP patients may suppress an immune response that eventually leads to induction of the inflammatory process in OLP.

Effect of Stress on Hormonal System

To maintain homeostasis, activation of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system during stress leads to an increased secretion of glucocorticoids and catecholamines. Several studies on the circadian rhythm have identified a negative correlation between numbers of circulating T-cells and amounts of blood cortisol. Stress hormones, acting on antigen-presenting immune cells, may affect the differentiation of helper T-cells away from a Th1 and towards a Th2. It means suppression of cellular immunity and activation of humoral immunity[35],[36]

During the stress, neuroendocrine hormones cause a change or amplification of cytokine production result in immune dysregulation, atopic autoimmune diseases, and/or diminished host defense. Catecholamines induce an increase in CD8+ and NK cell in peripheral blood Band-like infiltration of lymphocytes in lamina propria and keratinocyte apoptosis are two major criteria for the diagnosis of OLP. Existing data has established an increase of CD8+ T-cells in the intraepithelial layer which are involved in antigen presentation, lymphocyte activation, proliferation, and migration as well as keratinocyte apoptosis [35],[36]

Role of serum and salivary biomarkers of stress in Oral lichen planus

Saliva is the principal fluid responsible for protection of the oral cavity from ROS(Reactive oxygen species). The salivary antioxidant system includes uric acid and glutathione peroxidase (GPx). There are few reports concerning the use of saliva, serum reactive oxygen species and collagen degradation markers in OLP patients for clinical application. The literature contains several reports concerning the effects of oxidative stress on OLP. The significant decrease in important salivary antioxidants, such as uric acid and glutathione peroxidase, and the significant increase of salivary OS(oxidative stress) biomarkers and MDA(malondialdehyde), observed in OLP could provide a starting point for using these characteristics as oral biomarkers for monitoring or avoiding malignant transformation. [37],[38]

In recent decades, investigations aimed at finding biomarkers involved in OLP pathogenesis have been conducted employing various tissues and fluids. Among the biomarkers for OLP, measuring salivary cytokines could be a useful tool for diagnosis, prognosis, and treatment. The most studied cytokines in the saliva of OLP patients were interleukins IL-4, IL-6, IL-8, IFN-γ, and TNF-α, which were higher in OLP patients than in healthy controls. Moreover, three studies found an association between salivary cytokine concentration and the clinical form of OLP, with higher levels of IL-4, IL-6, and TNF-α in erosive/ulcerative lesions than in reticular lesions.[39]The higher salivary IL-6 levels in patients with erosive OLP seem to reflect local production by keratinocytes, monocytes, activated T lymphocytes, endothelial cells, macrophages, and fibroblasts. [40] Additionally, the levels of this cytokine are also used to monitor the use of glucocorticoids, disease activity, and prognosis since it is correlated with a malignant transformation of OLP. Psychological alterations can modify and cause dysregulation of immune functions,

such as changing the balance of Th1/ Th2 cytokines and increasing the Th2 response, which, in turn, is associated with the development of autoimmune diseases. In a research involving a psychoneuroimmune approach to OLP, Prolo and coworkers showed that peripheral blood T cells obtained from subjects with OLP revealed blunted responses to T-cell–specific mitogenic stimulation and decreased expression of IL-2 and IFN-γ. Additionally, these authors showed high levels of morning plasma cortisol and low CD3+ T cells in OLP patients, especially those with erosive lesions, suggesting a neuro-immune-endocrine relationship in OLP.[41]

Additionally, the determination of serum and/or salivary hormones, including cortisol, a well-known biomarker of chronic stress and anxiety, and nitric oxide (NO), one of the most important cytotoxic mediators of activated immune cells, may help to clarify the relationship between psychological disorders and OLP development. measurement of the salivary cortisol and anxiety which reflect response to stress seems a promising parameter in the investigation of OLP. Therefore, it can be a useful aid in not just understanding the pathogenesis of OLP but also determining the progression of these lesions. The rate of salivary cortisol can be an indicator of higher level of stress. Salivary cortisol and its correlation to OLP have been evaluated. A study by Koray et al. showed the salivary cortisol and state and trait anxiety levels in OLP group were significantly higher than healthy group that concluded that oral lichen planus is closely related with stress.[42].Shah et al. also showed that salivary cortisol, anxiety, depression, and stress levels in OLP patients were higher than healthy group suggesting a positive correlation between psychiatric disorders and salivary cortisol levels in OLP patients. [43]

Study done by Lakshmi Kavitha et al in 2014 has shown a significant raise in salivary cortisol and anxiety levels in OLP patients compared to healthy controls. It also showed a positive correlation between salivary cortisol levels and anxiety levels in OLP patients suggesting that stress may play a role in etiopathogenesis of OLP.[44]

A role of NO as a mediator in the etiopathogenesis of OLP has been suggested by only a few studies. it is a cytotoxic molecule that influences the ability of cells to kill bacteria, viruses, and protozoans as well as tumor cells, raising the possibility of its participation in OLP pathogenesis. In the immune system, NO seems to have proinflammatory and/or antiinflammatory effects, as previously demonstrated in studies related to periodontal disease, diabetes. All included studies reported an increase of salivary NO in OLP patients, which hypothetically results from increased levels of IL-6, TNF-α or IL1-ß produced by T lymphocytes and macrophages. [40]

TLRs or toll like receptors are proteins that play an important role in innate immune system. It is expressed by white blood cells like macrophages, natural killer cells and dendritic cells. It performs function in identifying pathogenic antigens. It also plays an essential role in the mode of action of tumor associated macrophages.Srinivasan et al conducted a study comparing CD14 and Toll like receptors in OLP and BMS and found that CD 14 levels were increased and Toll like receptors were decreased in OLP and BMS. Ghallab et al, conducted a study evaluating the levels of INF- gamma, TNF- alpha and TNF receptor-2 and concluded that their levels are detectable in erosive lichen planus and are reduced significantly following treatment with corticosteroids, thereby showing potential as a prognostic and therapeutic marker for LP[45], [46]

Consequences of Stress

Normal development and preservation of life and species depend on a normally functioning stress system. Maladaptive neuroendocrine responses, i.e., dysregulation of the stress system, may lead to disturbances in growth and development, and cause psychiatric, endocrine/metabolic, and/or autoimmune diseases or vulnerability to such diseases. Stress has been shown to be responsible for the depletion of several free radical detoxifying enzymes such as glutathione peroxidase, catalase, and superoxide dismutase. This results in oxidative burden, which has been implicated in stress as well as in the pathogenesis of several disease states.[47]

In order to assess the true relationship between stress and OLP, a longitudinal study must be designed because OLP is an autoimmune disease and has exacerbation and remission phases with different levels of cytokines and pathogenesis. (Figure 3)

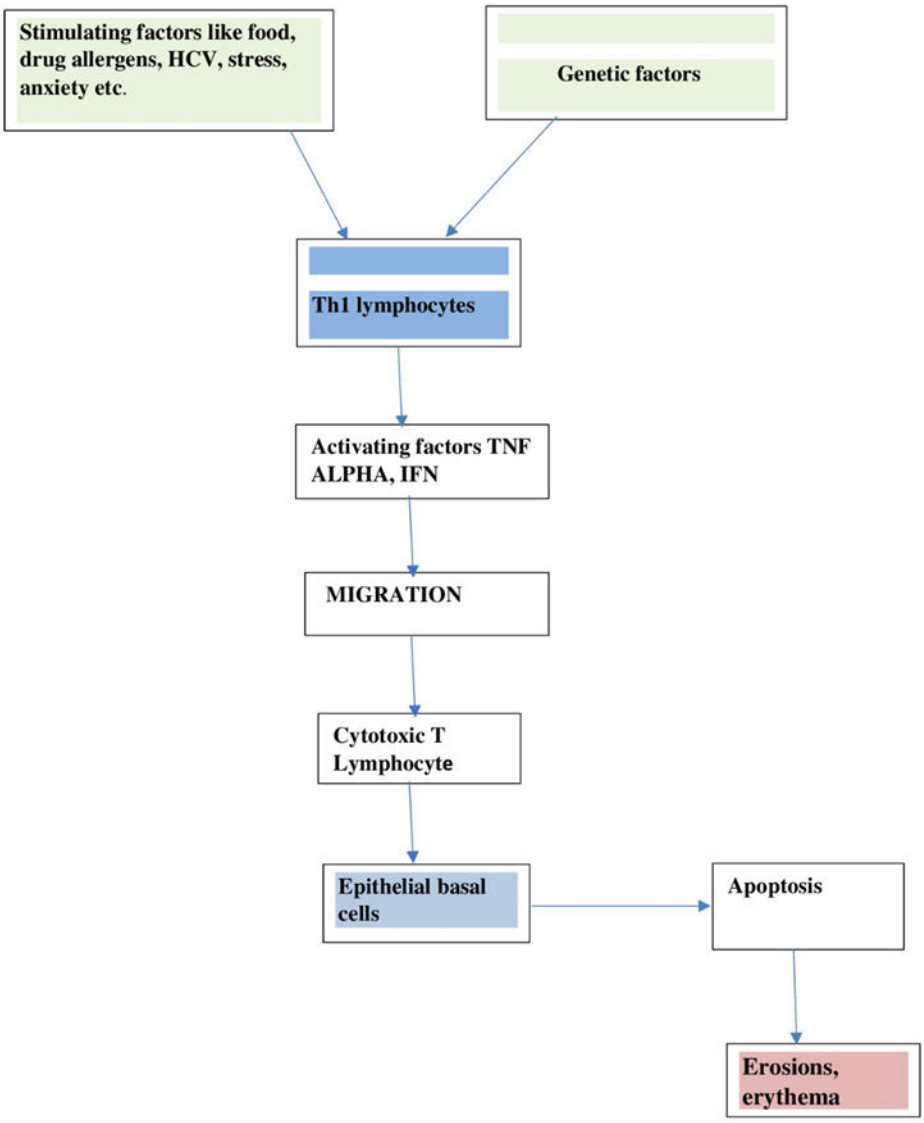

Figure 3

Diagnosis

The diagnostic criteria of OLP were introduced by WHO in 1978, and modified by van der Meij and van der Waal in 2003. In 2016, the American Academy of Oral and Maxillofacial Pathology proposed new clinical and histopathologic criteria. The histopathologic examination indicates band like or patchy, mostly lymphocytic infiltrate in the lamina propria limited to the epithelium lamina propria interface, basal cell liquefactive (hydropic) degeneration, lymphocytic exocytosis, without any epithelial dysplasia, or verrucous epithelial architectural change.

To a clear and precise final diagnosis, a thorough history and clinical features of lesions should be correlated with complex testing histopathologic examination, DIF, IIF, cutaneous patch testing. Also, it is

important to mention that the diagnostic process of OLP and OLL demands continuous follow up and if necessary additional biopsies for histopathological evaluation and immunofluorescence tests.[36]

Management of oral lichen planus

A stepwise approach should be adopted. The first step is establishment of diagnosis, based on history, clinical examination, and complex testing - histopathology examination, direct immunofluorescence (DIF), indirect immunofluorescence (IIF), cutaneous patch testing.

Therapeutic attitude depends on associated symptoms and clinical presentation. In asymptomatic, non-ulcerative lesions of OLP no pharmacologic intervention is required and follow up is indicated. For symptomatic, non-ulcerative LP a topical anestheticbenzydamine hydrochloride (0.15%) is indicated. Tantum, liquid/spray for topical application or oral rinse can also be used. The usual dose for an adult is at least 15 ml (1 table spoon) for mouth rinsing, 3 or 4 times a day, according to the severity of the lesions.For lesions that are not dysplastic and do not show malignant transformations, topical steroids should be taken into consideration. These were recommended as first line treatment in consensus guidelines published in 2005.[48]

Limited lesions located on the fixed oral mucosa (gingiva and palate) can be treated using ointments, creams and adherent paste; this technique has the advantage in controling the contact time and the extension of the surface exposed to the drugs. The systemic administration of prednisolone is indicated in case of the severest multifocal lesions with large areas of ulceration. The usual adult dose is 40 mg of prednisolone per day for the first 5 days and then the dose is reduced to 10 20 mg of prednisolone daily for the next 7 10 days. This treatment protocol can significantly improve the healing rate of the lesions.[48]

Laser therapy seems to be more effective in treatment of painful erosive OLP, compared with topical super potent corticosteroids. Their effect is the destruction of the superficial epithelium (containing the target keratinocytes by protein denaturation); in addition, the diode laser also destroys the underlying connective tissue with the inflammatory component along the epithelium.

Management of stress

Pharmacological approaches for the management of stress

One of the important consequences of stress is anxiety. Benzodiazepines (e.g., flurazepam, diazepam, chlordiazepoxide) are effective in the rapid treatment of anxiety disorder. Buspirone is a non-benzodiazepine anxiolytic agent and tandospirone, is an azapirone derivative similar to buspirone and has anxiolytic effects. Diazepam is also a widely used anxiolytic and inhibits various stress-induced changes such as activation of the HPA(hypothalamic pituitary axis) axis. Naproxen (non-selective cyclooxygenase (COX) inhibitor) and rofecoxib (selective COX-2 inhibitor) are known to attenuate oxidative stress by inhibiting COX and thereby prostaglandin release.

Non-pharmacological approaches for management of stress

These strategies include exercises, relaxation techniques, and physical exercise programs including laughter and motivation. Exercising is the most effective way to becoming stress-free. Walking, light aerobics, jogging, and riding a cycle or bike are some of the simplest ways out of de-stressing. Playing games is also effective in releasing stress .Relaxation techniques can help relieve stress and put the mind at ease. Soft music can be therapeutic for a stressful mind. Yoga and meditation can also be used as relaxation techniques to relive stress. Deep breathing can help relax and relieve stress. Laughter releases the anger and frustration bottled up inside from being stressed .S tress can be used as a motivator to change the way of thinking in life. motivated in life and make things better.[47]

Management of stress induced Oral lichen planus

Treatment of OLP lesions is a complex treatment. Corticosteroid therapy, both topical and systemic, is the most appropriate therapy and the role of a psychologist or psychiatrist is needed in managing patient stress to increase the percentage of patient recovery.

Many studies reveal that, high levels of stress and anxiety can increase the risk of OLP. In stress-induced OLP, the ability to express and process awareness of the problem at hand and the awareness that there are people who care to listen can often lift the patient's burden, tension, anxiety and stress. Operators can improve the quality of care for patients such as through this approach and refer patients with psychological risk factors to psychologists or psychiatrists to evaluate and treat these patients. The reason for the need for referral should be conveyed to the patient carefully to avoid defensiveness from the patient and increase patient cooperation.

Corticosteroids can be given either orally or topically. Corticosteroids might be gradually lowered depending on the severity of the lesion. Corticosteroids have long been utilised as anti-inflammatory medications for autoimmune illnesses. Corticosteroids influence fat, carbohydrate, protein, calcium, and electrolytes. Glucocorticoids reduce all types of inflammation and allergy reactions by suppressing plasminogen activity and decreasing inflammatory mediators such as prostaglandins and leukotrienes. The production of glucocorticoid molecules would raise corticotrophin-releasing hormone (CRH) and arginine vasopressin levels (AVP). Both hormones stimulate the sympathetic nervous system as well as the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, glucocorticoid receptors are found in the hippocampus and amygdala, which govern specialised stress responses. The presence of glucocorticoid receptors and the translocation of steroid receptor complexes to the nucleus can influence gene transcription. These alterations will result in the production of neurotransmitters such as dopamine, serotonin, and neuropeptides such as somatostatin and beta-endorphins. Endogenous glucocorticoids can indirectly control psychological stress reactions such as depression and anxiety.

Antioxidants have boundless importance in oral disease pathology because of their possible action against free radicals. Dietary macronutrients contribute to the antioxidant defense system. These include β-carotene, vitamin C, and vitamin E.Micronutrients, like antioxidants, modify the role of the immune system and are perceived appealing substitutes of negligible side effects while handling OLP..Oral lichen planus being hypothesized to be an autoimmune disease, several researches have been carried out to treat lichen planus by micronutrients including antioxidants that modify the immune system function. Such studies involve the impact of vitamins A, D, E.Topical retinoids like tretinoin, isotretinoine or fenretinide have been reported to induce transient reversal of white striae in OLP. However, relative to topical corticosteroids, topical retinoids are usually less effective since they are associated with side effects such as cheilitis and elevated serum triglyceride and liver enzyme levels, One study showed that subjects who took vitamin D supplements in addition to the routine treatment improved the clinical appearance of the lesion in the 1st week and completely disappeared on a period of 4 weeks. In another study of OLP treatment, 3 groups of patients were put on psychiatric counseling and vitamin D along with topical corticosteroid. The result of this study showed that patients receiving vitamin D supplements with or without the psychiatric counseling, improved their symptoms.In another clinical trial, adjunctive systemic use of vitamin E with topical triamcinolone acetonide adhesive paste has demonstrated positive results without any side effects.[49]

Some studies postulate that certain herbal drugs are useful in the treatment of stress induced Oral lichen planus by acting as stress relievers and to help combat anxiety and stress. Adaptogens are of particular interest because they are also immunomodulating, and thus may help alleviate immunopathologies. [50]

Glycyrrhiza glabra (licorice) root is an example of an herb that embodies almost all the actions such as: adaptogenic; immunomodulating; inflammation-modulating; and demulcent. In a study, the triterpenoid saponin glycyrrhizin, which imparts the sweet taste to licorice root, has been given intravenously (IV) for 4 weeks to treat OLP successfully in patients with Chronic hepatitis C, compared with just giving oral cleanings to control patients. A typical dose of fluid extract would be 1–2 mL diluted in water, and for tea, the dose would be 1–2 g per cup of water simmered for 15–20 minutes, with three cups taken per day.[50]

Topical administration of timolol along with triamcinolone acetonide has also been reported to show significant improvement in lesions both in terms of pain, lesion size and patient quality of life. Timolol is a non-selective propranolol beta-blocker that has an inhibitory effect that can reduce lymphocyte infiltration in cases of OLP. This is related to the role of catecholamines as non-traditional cytokines that can activate immune cells through b-adrenergic receptors on immune cell.[51]
There are some alternative non-pharmacological treatments available such as PRP, PDT, laser, and ozone therapy recently emerged as a new and futuristic therapeutic modality, specially in severe cases and patients who are not reacting to conventional treatments.

Conclusion

Available literature has shown that OLP patients experience higher levels of stress. The psychological tension that exists behind the OLP is a significant contributing factor. According to some sources, psychological stress may not be what triggers the development of OLP, but rather, OLP might increase psychological stress by affecting the patient's perception of themselves and their interactions with others in public. Therefore, psychological health is a crucial component that should be considered.

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