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Current review of conections between lichen planus and mental disorders

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Abstract
The major aim of this article was to examine causal connection or temporal relation between mental disorders and lichen planus (LP).
LP is a chronic, inflammatory skin condition affecting less than 1% of the adult population. It is observed in many different clinical forms, some affecting more psychical state than others. Indeed, connection exist between LP and mental state. LP as an autoimmune disease can also be aggravated by psychosocial stressors. Etiopatogenesis of LP is idiopathic and involves immunologic components. Main pathogenetic mechanism of LP include increased apoptosis of keratinocytes and decreased apoptosis of T-cells. Many authors report relationship LP between mental illness like depression and anxiety disorder or lack of emotional stability. One of the main symptoms of LP is is severe itch (present in 74 from 78 patients), which can be induced by stress.

Key words: lichen planus, mental disorders, etiopatogenesis, stress.

CHARACTERISTICS

The cutaneous form of lichen planus(LP) manifests as a primary eruption in the form of a polygonal, purple flat-topped papule with a diameter from a millimeter to over a centimeter. On its surface there is a characteristic Wickham striae visible as a delicate lines resembling a meshwork. Efflorescence occurs in grouped form or in the form of rash.[1] The most common locations for skin lesions are the upper and lower limbs, with particular emphasis on the wrists on the flexor side, the front surface of the lower leg and the inner surface of the thighs. Torso skin and lumbar sacrum may also be involved. Skin changes may be accompanied by severe itching.[3] Koebner's symptom is present in the cutaneous form of lichen planus manifested by linear changes appearing as a result of irritation, most often as a result of a scratch. During the year, the changes disappear spontaneously leaving brown discoloration. Nevertheless, LP is a chronic skin condition and disease symptoms may recur. [3]

NAIL LICHEN PLANUS

In LP, nail plates may also become involved. These changes may occur together or precede skin eruptions or mucous membranes involvement, but may also be present as the only manifestation of the disease.[1,3] The characteristic changes include thinning of the plate, pterygium and a rough surface with longitudinal grooves and ridges. In some cases, they may result with anonychia [1,3,4,5]

MUCOSAL LICHEN PLANUS

As much as 50% of cutaneous LP will probably also appear on mucous membranes. This form is more common in the female sex. Among the characteristic locations, special attention is paid to the oral cavity. According to research, lesions are most often located on the buccal mucosae, gums and tongue.[6,7] It occurs in six clinical variants as reticular, papular, plaque-like, erosive, atrophic and bullous.[8] Reticular lesions appear symmetrically and bilaterally mainly on buccal mucosae, resembling a lace pattern. Burning pain is present in the erosive and atrophic subtype. LP is considered as a premalignant condition.[9] Women are at an increased risk of cancer transformation. It has also been noticed that transformation occurs more frequently on changes on the tongue.[10, 11]

GENITAL LICHEN PLANUS

LP can also affect the genitals. For women, lesions are located within the labia minora, labia majora and vagina. In men, genital involvement by LP occurs in 20% of cases, mainly in the glans area. Ring formation lesions are most commonly observed here.[3,1] In the clinical picture these changes cause burning, itching and pain. We can observe mucosal changes at the same time in the mouth and genitals. It was noted that in these cases the dominant type of LP is atrophic-erosive form. In women, the simultaneous occurrence of eruptions in the mouth and genitals is called vulvo-vaginal-gingival syndrome. Atrophic erosive form in the mouth predisposes to the occurrence of adhesions, scarring. As a consequence, women experience sticking of the labia minora and narrowing of the vagina. [2,12,13]

CLINICAL VARIANTS OF LICHEN PLANUS

Several clinical varieties of LP are classified due to the morphology and pattern of the changes. A common form is the annular form affecting the skin and mucous membranes. It arises as an effect of the absorption of the central part of the plaques[1,14]

Hypertrophic LP is usually located on the front surface of the lower limb. It manifests itself as inflammation and coherent hyperkeratotic lesions.

In the course of ulcerative type, patients are accompanied by pain and difficulty walking, because this form of LP takes the soles of the feet.

Pigmented lichen planus may resemble herpes zoster and form along the Blaschko line and along the course of the affected veins.

The dominant figure in children and young people is a linear form of LP.[1]

Lichen planopilaris is located on the scalp, affects axillas, groin areas and the sacral zone. Papules around the hair follicles disappear leaving discolored atrophic scars and lead to permanent alopecia.[3,8] Frontal scarring alopecia can occur in postmenopausal women, which, according to some authors, is a different type of scarring baldness. Other clinical variants are atrophicans, bullosus, pemphigoid and erythrodermic forms of LP.[3,1]

EPIDEMIOLOGY

Epidemiological data are limited, but most studies estimate that cutaneous lichen planus occurs at a similar frequency in both female and male sexes.[1] However, women are slightly more vulnerable to this disease than men. The frequency ratio is 1: 2.[2] It was noted that mucosal LP was found more frequently in patients treated with dentistry or gynecology.[1] The disease rarely affects children.[2] The adult population between 30 and 60 years of age is most at risk of developing lichen planus. Occurrence is heterogeneous in different geographical areas. It was noted that people of Indian origin more often suffer from LP. The childhood form of lichen planus affects more African-Americans and units with darker skin color.[1,3,4] This disease can only affect the skin, in 50% of cases it occurs together with changes in the mucous membranes, mainly in the oral cavity, and in about 10% of the cases it also manifests in the subungual location with nail involvement.[3]

Etiopathogenesis

Etiopatogenesis of LP is unknown. The potential causes of the disease are: viral infections, stress, autoimmune processes, oxidative stress, autoimmune diseases such as diabetes mellitus or thyroid disease.

One of the main pathogenetic mechanisms of LP is increased apoptosis of keratinocytes and decreased apoptosis of T-cells. Activated cytotoxic T-cells can upregulate the Fas ligand and induce keratinocyte apoptosis in the suprabasal cell layer by binding to Fas on the surface of keratinocytes. [21]. In the early stages, T-cellsare mainly found in the deeper layers of the epidermis and at the dermal-epidermal junction. CCR5 related chemokines as well as CXCR3-targeting chemokines are significantly overexpressed in LP lesions in combination with the increased trafficking of mononuclear cells to the interface region. This correlation or coincidence suggests that both keratinocyte induced- and self-recruiting mechanisms are involved in T-cell migration within LP lesions. [21]The role in pathogenesis is also played by T cells with alpha-beta T-cell receptors, including CD4+ ("helper"), that produce Th1 and CD8+ ("cytotoxic") T cells. These two cell types may be involved in the immune response type 1. CD4+ produces Th1 factors while CD8+ kills host cells and may contribute type 1 soluble factors. In OLP Th17 has also been identified and is responsible for production of interleukin-17 rather than IFN-γ. Th17 T cells are important contributors to the defense against many bacterial and fungal pathogens and to autoimmune conditions.[20]

NK cells can also migrate to lesions in the LP more often than to healthy skin. They may contribute to the pathogenesis of LP due to their cytotoxic activity and their ability to produce proinflammatory cytokines. In the early stages of the disease, the number of Langerhans cells in the epidermis also increases. These cells function in such a way that before T cells are activated they present autoantigens or foreign antigens to T cells. Langerhans cells are therefore more common in OLP lesions than in healthy oral mucosa [21].

There is a connection between the lichen planus and autoimmune processes. GVHD disease (Graft-versus-host disease), which is a complication after transplantation of host stem cells, is likely to be associated with a lichen planus (LP) - like GVHD. Skin barrier disruption could induce thymic stromal lymphopoietin (TSLP) expression, and the expression of TSLP was increased in lesions of lichen planus (LP)-like GVHD. The cutaneous form of GVHD gives similar histopathological symptoms to lichen planus such as hyperkeratosis, focal increase in the granular cell layer, vacuolar changes of basal layer, scattered keratinocyte necrosis in the epidermis and melanophages, and increased lymphocytic infiltration in the dermis. The studies showed that permeability and antimicrobial barriers are impaired in LP-like GVHD. The immunoreactions, but not the congenital defect, are considered to be the primary cause of skin barrier impairment in LP-like GVHD.[15]

A lot of studies indicate the relationship between the lichen planus and viral infections, including HCV infection. According to them, patients with chronic hepatitis C show extrahepatic symptoms, including LP. The mechanisms involved in the development of skin symptoms in patients with HCV infection are controversial. Virus molecules have been identified in various cells (keratinocytes, lymphocytes), which raised the hypothesis that HCV has a direct cytopathic effect. The theory of autoimmunity is being considered. This theory is supported by the detection of multiple circulating autoantibodies in patients with HCV and by the tropism of the lymphocyte virus, which promotes proliferation of B cells. Another theory,

however, is that the virus works at the level of different organs, and that the skin symptoms are actually the result of a functional impairment of these organs. No histopathological differences of LP lesions were observed in HCV positive patients compared to HCV negative patients. [16]
Another example is the coexistence of lichen planus in diabetic patients. [17] This association may result from endocrine disorder in diabetes, which may be associated with an immune defect. There are also reports of a link between LP and thyroid disease. Additionally, in the case of people with diabetes mellitus, antidiabetic drugs and some antidiabetic drugs may cause the manifestation of allergies to induce a lichenoid reaction.[17]
LP as an autoimmune disease can also be aggravated by psychosocial stressors. During stress, the adrenal cortex secretes, which is responsible for autoimmune inflammatory disorders. Stress modifies the immune response in autoimmune conditions that can be assessed using serum, saliva, and urine cortisol levels. According to studies, the increase in cortisol levels equalled the exacerbation of lichen planus. [18] Furthermore, studies show that acute and chronic psychological stress may cause significant changes in the immune response induced by neuroendocrine mediators from the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal axis. [20]
Recently, several studies have revealed that oxidative stress, which is the result of an oxidant/antioxidant imbalance in favour of oxidants, is also responsible for the pathogenesis of LP. MDA which is the result of oxidation of membrane-associated polyunsaturated fatty acids of phospholipids has been considered as a fundamental representative of oxidative stress. According to the results, MDA levels in subjects with oral LP were higher than in the control group, which may be responsible for its role in pathogenesis.[19].

Connection with mental diseases

There is the connection between mental state and prevalence of dermatological illnesses. From one point of view psychiatric disorders can have impact on exacerbation or acceleration of dermatological disease, and in other hand disorders, which are connected with the skin can be the reason of psychiatric illnesses [22]. Because of this and lack of well-known knowledge about etiopathogenesis of LP, it is consider to be psychosomatic illness [23].
Stress has impact on nervous system, both sympathetic and parasympathetic parts. In consequence it alters the regulation of hypothalamic, pituitary and adrenal axis, what can lead to disorders in immunological system, associated with activity, distribution and proliferation of inflammatory cells, production and phagocytosis of cytokines [24]. These changes, prevalence of autoimmunological diseases and disabilities in activity of endocrine system can be connected with prevalence of LP [24]. Furthermore catch a LP can predispose to reveal symptoms like: tiredness, anxiety, stress and phobias [23]. In big majority of patients with LP is affirmed obvious type C behavior characteristic, which is characterized by: fear, anger, depressive state and pessimism [25]. Related to this is loads of factors like: how long lasts illness, what are the effects of the treatment, and level of the pain, which feels patient.
On development of feelings of pain have impact emotional factors, but they are more important in acute than in chronic one [24]. After six months since distress has shown up, limbic system has been dominating [24]. In consequence it is difficult to localize and isolate source of pain.

With progress of the disease perception of the pain also increases [24].
Simultaneously showing up of new, extra distress sensations correlates with development of skills related to coping with stress, like ignoring pain [23]. However a significant correlation between psychological factors and psychopathological symptoms related to severity, exacerbation and activity of skin lesions wasn't observed [23]. More than half of examined patients can associated time of showing up trigger of stress and exacerbation of symptoms of the illness [24].
In other hand somatic pain provoked by dermatological illness can have impact on emotional and social general sensation [26].
During conducting the research associated with impact of premalignant changes in oral cavity, including LP, on daily exercises, there were identified four main problems, which were reported by patients. They are: difficulties with diagnosis and establishing current state of health, physical disorders and functional limitation, psychological problems and effects of treatment on daily life [26]. The most important from them turned out physical disorders [26].
Time before set out the diagnose was connected to high level of stress and frustration in 41% patients [26].
Patients reported that feeling frustrated was exacerbated by lack of effects of treatment, long-term treatment and no possibilities to relieve pain [26].
Significant factors which may have impact on aggravation of psychological state of patient are side effects of treatment and lack of long-term improvement [23]. Furthermore it was observed that the longer the patient was struggling with the disease, and first of all with its symptoms, there was higher risk that he or she will lose self-control and will develop depression [23]. It may lead to acquired feeling of hopelessness, with which is connected avoiding of undergo treatment [23].
In scientific literature well-labeled is correlation between lichen planus of oral cavity and prevalence of mental disorders. Patients with lichen planus of oral cavity in most cases were complaining about hypersensitivity during eating spicy food [26]. They also reported that they don't feel pleasure with eating their favorite dishes [26]. Patients also mentioned that they have difficulties with daily exercises like brushing teeth, cause it involves feeling pain [26].
In patients, who are diagnosed with premalignant changes in oral cavity like: oral lichen planus, erythroplakia, actinic keratosis, oral leukoplakia or oral submucous fibrosis was observed fear of malignant transformation, what was the reason of psychological distress [26].
One of the main symptoms of the disease is itching (presented in 74 from 78 patients), which can be induced by stress [27]. It has impact not only on aggravation of quality of life, but also on higher risk of koebnerization [27].
Itching is connected with higher desire to scratching, which can result in damage of the skin. In case of Koebner effect, which is observed in lichen planus, new lesions can develop in damaged fragments of the skin, what can result in chronic character of the illness. Stress can be also effect of itching, which patients describe as irritating and awkward [27].
It was demonstrated that there is the connection between age of the patients, who are struggling with this illness and quality of their lives. Among examined people worse quality of life was observed in older ones [23]. There was also checked correlation between quality of life of sick people, level of perceived stress and techniques of coping with stress and sex. Some authors didn't demonstrate this connection [23], however others confirmed that

disorders connected with depression more often includes women (77,7 %, 7 from 9 people, who are affected with lichen planus with depression are women) [22]. The cause of it is that women have higher vulnerability to stress, more often they are not satisfied with their appearance, and lower self-esteem than men [22]. These differences between sexes were observed in the school and work, not in other environments [22]. There was also obserwed that people who are suffering from lichen planus have higher tendency than healthy ones to feel anger which is repressed. In situation when they vent their anger in most episodes they show it in very aggressive way without using words [28].

Exposured on activity of psychological factors, which can induce lichen planus, are the same adults and children [29].

Early direction patients with diagnosed lichen planus to clinic of mental health may result in well-being of the patient and what is more in positive effects of treatment of dermatological disease [22]. That is why very important is looking after awareness of dermatologists about correlation between lichen planus and mental diseases.

Discussion:

In light of current research it is difficult to claim that causal connection between depression, anxiety and LP doesn't exist.[30] Many authors report relationship LP in mental illness like depression and anxiety disorder or the lack of emotional stability. [31]

Moreover, emotional stress was the most frequent cause of recurrence and exacerbation of the skin lesions of LP.[12]

Most of the studies use standardized questionnaires to examine the state of mind, which provide reliable information about mental state of the patients.[10] Discrepancies between studies may result from difference between questionnaires which were used and kind of mental illness examined.[30] Indeed, different studies have used over 20 different assessment methods, such as Beck Anxiety Inventory and Beck Depression Inventory, and in some cases more than one method was used at the same time. Skin lesions were examined by pathologist, which reduced the risk of mistake. [29]

However, it is important to notice that existing researches focused on psychological state of patient, but not on biochemical condition of the brain. Only this kind of studies may prove the relationship between affective and skin disorders.[30] That is the reason why such connection should not be eliminated. Also, the worry about losing good health caused by illness is thought to be the reason of psychopathology. Nevertheless, patients with serious skin lesions could feel better after many visits in doctor's office or by the other methods of pain or anxiety management. [29]

However, no improvement was not observed in people with positive profile of handling the problems.[31]

In recent years the immunological aspect of skin lesions and mental disorders is being widely explored. The results are promising and gives us new information, which researchers try to implement into clinical practice. As example, in psychiatry the pathogenesis of some kind of depression the immune system is involved, with interleukins Il-1, Il-10 and microglia. So it is reasonable to focus the explorations on systemic changes, not on isolated body organs, like skin or brain. [31] Additionally, it can narrow the research to the specific kind of lesions and concrete psychopathology. For example papular and reticulated LP and anxiety disorders or

depression. Of course it is important what psychological profile and kind of handle of problems is represented by the investigated subject. An important argument for exploring biochemical relationships is the fact that more than half of the studies report the coexistence of depression with LP.[10] Given the inflammatory theory of depression, this may be the way to be taken to find potential links between disorders.

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