

Pruritus in selected dermatoses

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Abstract. – Pruritus is a natural defence mechanism of the body and creates the scratch reflex as a defensive reaction to potentially dangerous environmental factors. Together with pain, pruritus is a type of superficial sensory experience. Pruritus is a symptom often experienced both in healthy subjects and in those who have symptoms of a disease. In dermatology, pruritus is a frequent symptom associated with a number of dermatoses and is sometimes an auxiliary factor in the diagnostic process. Apart from histamine, the most popular pruritus mediators include tryptase, endothelins, substance P, bradykinin, prostaglandins and acetylcholine. The group of atopic diseases is characterized by the presence of very persistent pruritus. It is found in almost all patients with atopic dermatitis or urticaria. Cutaneous T-cell lymphoma is another group of pruritic diseases where the symptom of pruritus develops at an early stage and becomes intensified as the disease progresses. Other dermatoses include psoriasis, parasitic diseases and also systemic diseases in which pruritus is often the first and the only symptom suggesting an internal health problem. Cases of pruritus in healthy subjects, possibly associated with skin dryness or pregnancy in women, have also been reported. This paper presents mechanisms responsible for pruritus and the most important dermatoses in which this symptom is found. Treatment of pruritic dermatoses is difficult and always requires an interdisciplinary approach. Not all dermatoses can be successfully treated with antihistamine drugs, particularly if patients suffer from cutaneous T-cell lymphoma, liver or kidney diseases. For this reason, the problem of pruritus is the focus of attention of many scientists, and the subject of interdisciplinary studies.

Key Words:

Atopic dermatitis, Cutaneous T-cell lymphoma, Itch, Parasitic diseases, Pruritus, Pruritic dermatoses, Psoriasis.

Introduction

Pruritus is defined as an unpleasant sensation that provokes the desire to scratch. It is a physio-

logical self-defence mechanism similar to other skin sensations, such as touch, pain, vibration, cold or heat, enabling the protection of the skin from external factors. Pruritus is a frequent symptom associated with dermatoses and various systemic diseases¹. Acute pruritus often develops simultaneously with urticarial symptoms or as an acute undesirable reaction to drugs. The treatment of this form of pruritus is much easier.

The chronic pruritus that often develops in patients with cholestasis, kidney diseases or skin diseases (e.g. atopic dermatitis) is often more difficult to treat^{2,3}. Persistent rubbing, scratching or pinching leads to the formation of secondary skin lesions such as excoriations, erosions, eschars, hyperpigmentation or patches of discolouration, impetiginisations or even scars, which results in the creation of the itch-scratch cycle and self-stimulation of the pruritic mechanism and scratching. Very often traditional methods for the treatment of chronic pruritus provide no success, and therefore better understanding of the neurophysiological aspects of pruritus can contribute to the development of new therapeutic methods.

Pruritus can be induced by chemical, physical or thermal agents. In addition, pruritus can develop in peripheral nerves that have pathological changes and also in the central nervous system.

The skin has the structure of a dense network of highly specialized sensory fibres of afferent and efferent autonomic nerve branches. The autonomic system consists of a small number of fibres and is responsible for the innervation of eccrine, apocrine, and sebaceous glands, hair follicles and blood vessels. The activation is followed by the secretion of acetylcholine (ACh) or epinephrine, which activate target cells, muscarinic or catecholamine receptors. The sensation of burning pain, heat or pruritus are transmitted via nociceptive non-myelinated C-type neurons with a speed of 0.5-2.0 m/s and via A- δ fibres. Non-myelinated C-type nerve fibres are responsible for the transmission of information about itching

in an unspecified location, while the second type of fibres (A- δ) transmit precise information on the location and time of the itch's onset. Itch receptors, which are non-myelinated nerve endings, are located in the papillary layer of the epidermis, with the highest number in the epidermis/dermis transition layer. When itch receptors are stimulated, the elicited neural impulse is transmitted to the dorsal roots of the spinal cord. The impulse is transmitted further via the spinal cord and in the central nervous system. Interestingly, rubbing or scratching offers temporary relief from the itch. This phenomenon has not yet been fully investigated.

Mediators of Pruritus

Pruritus can be evoked directly by mechanical stimuli, or by thermal or chemical agents. However, it can arise directly through the stimulated degranulation of mastocytes and intensified histamine release⁴. Most mediators and receptor sys-

tems involved in the pathogenesis of pruritus are also involved in the neurotransmission of pain (Table I)⁵. Histamine is the most frequently listed and important mediator. It is released from mastocytes or keratinocytes and plays an important role in many dermatoses, mainly in those caused by allergic factors. Histamine is one of the most important mediators of pruritus but not the only one with a significant role. Many histamine receptors have been identified in pruritus, such as H₁, H₂ and H₃, and the recently discovered H₄ receptor. About 70 years ago, Lewis et al demonstrated that the intradermal administration of histamine caused erythema and oedema. Acetylcholine is another mediator and is the major neurotransmitter between the autonomous nervous system and muscarinic or nicotinic receptors. Intradermal administration of ACh causes pain rather than pruritus. Bradykinin is another mediator of pruritus. It belongs to the class of kinines and binds to bradykinin recep-

Table I. Mediators of pruritus and pain⁸.

Mediator	Receptor	Pruritus	Pain
Histamine	H1, (H2), H4	Direct activation of receptors	After intradermal administration of higher doses or deeper (subcutaneous) injection
Tryptase	PAR2	Direct activation of receptors	
Endothelin	Endothelin A-receptors	Direct activation of endothelin receptors	Direct activation of endothelin receptors
IL-2, IL4, IL-6, IL-31	IL-2R and IL-6R receptors on nerve fibre endings	Direct activation of specific receptors on nerve fibre endings	Sensitization of nerve fibres
Substance P	NKR1-3 neurokinin receptors	Direct activation of receptors on nerve fibre endings and mast cells (release of histamine and proteases)	Central sensitization, neurogenic inflammation
Capsaicin, heat, low pH	TRPV1 on nerve fibre endings	Direct activation	Direct activation
Bradykinin	B1 and B2 bradykinin receptors	Sensitization of nerve fibres	Activation of receptors, sensitization
Prostaglandins	Prostaglandin receptors	Sensitization, aggravation of histamine-induced pruritus	Sensitization
NGF	TrkA on mast cells and nerve fibre endings	Sensitization, stimulation of histamine and protease release	Peripheral and central sensitization
Opioids	μ -, κ -receptors	μ -agonists induce pruritus, antagonists inhibit it, κ -agonists inhibit pruritus	μ -agonists inhibit pain
Cannabinoids	Cannabinoid receptors (CB1, CB2)	Inhibition of pruritus	Peripheral and central analgesic effect
Acetylcholine	Muscarinic receptors (M1-M5)	Intradermal administration to patients with AD causes pruritus	Intradermal administration to healthy people causes pain

tors (B₁-B₂ type). Intradermal administration of bradykinin more often causes pain than pruritus, which is mediated by B₂ receptors⁶. Apart from that, bradykinin sensitizes nerve fibres to other chemical stimuli. Bradykinin-mediated stimulation significantly increases the release of substance P (SP), a calcitonin gene-related peptide (CGRP), and prostaglandin E₂, while serotonin and prostaglandin E₂ have no effect on the release of neuropeptides⁷. Serotonin has been known for years for its stimulating effect on nociceptive C-type nerve fibres. Intradermal administration of serotonin or the application of iontophoresis during the intervention evokes pruritic reaction but it is less intensive than that induced by histamine⁸. Serotonin type 3 receptors are widely distributed within the central and peripheral nervous system, and for this reason, they can play a role in various pruritic diseases. Endothelin is another mediator of pruritus. It belongs to the group of peptides, has a number of biological properties and is synthesized by endothelial cells. Endothelin 1, 2 and 3 stimulate neurogenic inflammation associated with burning itch. Neuropeptides deserve special attention as mediators of pruritus. They are important factors in the pathogenesis of many dermatoses, including atopic dermatitis, psoriasis, eczema, acne rosacea and nodular prurigo. In intact skin, most nerve fibres containing neuropeptides are located in the papillary layer, around skin appendages and blood vessels. The most important neuropeptides include SP, CGRP, somatostatin, neuropeptide Y, bradykinin and vasoactive intestinal peptide (VIP). For example, the intradermal administration of SP is followed by the development of oedema and pruritus at the injection site. The mechanism of this reaction depends on the release of histamine and tumor necrosis factor alpha (TNF α) following the stimulation of mastocytes by SP⁹. In our continuous studies on the pathogenesis of pruritus, we discovered that proteases can mediate the onset of pruritus. Proteases cause the degradation of many mediators of pruritus but also take part in its induction. Tryptases and bacterial proteases are released from the mastocytes and induce neurogenic inflammatory condition after PAR receptors are stimulated. The expression and function of PAR differ depending on the location of these receptors. PAR1 receptors are involved in homeostatic processes and induce peripheral or central anaesthesia in chronic inflammation^{10,11}. PAR2 is found in many cells, such as keratinocytes, en-

dothelial cells, hair follicles and the endings of thin sensory fibres in the skin. When PAR2 receptors are stimulated their structure becomes permanently modified, and this fact can open the way to studies on chronic pruritus in many pruritic dermatoses¹². Mast cell degradation results in the release of tryptase, which stimulates PAR2 receptors and this leads to an increase in intracellular calcium level and the activation of the protein kinase C. These reactions lead to the release of neuropeptides, mainly SP, neurokinin A (NKA) and CGRP¹³. Prostaglandins and leukotrienes also play a role in the induction of pruritus. Leukotriene injected intradermally into mice was shown to induce the scratching reflex. The inhibition of leukotriene receptors is correlated with a less intensive scratch reflex, particularly in patients with atopic dermatitis, while prostaglandins, mainly PGE₂, cause the dilation of blood vessels and induce pruritus.

Primary Cutaneous Lymphomas

Pruritus is a common symptom in patients with hematological diseases. In patients with cutaneous T-cell lymphoma, it is often found before the onset of other clinical symptoms of the disease. The problem of pruritus in this group of dermatoses is not fully understood and has not been fully investigated. Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of lymphoproliferative disorders characterized by varying degrees of malignancy. Lymphomas are defined as primary if no abnormalities are found in the lymph nodes, the bone marrow or visceral organs at the time of diagnosis. Mycosis fungoides (MF) is the most common type of T-cell lymphoma. Sézary syndrome, characterized by three dominant symptoms: erythroderma, lymphadenopathy and the presence of Sézary cells in the peripheral blood, lymph nodes or the skin, is much less common. For a long time the disease has very few and mild symptoms, and lesions on the skin are limited to patches without infiltrates. Along with the progression of the disease, patients present with intensified skin manifestations and a distinct increase in the pruritus, which do not respond well to the applied treatment (mainly antihistamine drugs, emollients or topical corticosteroids)¹⁴. There are single reports published across the world dealing with this problem.

The recently identified histamine H₄ receptor seems to be important in the development of pruritus in CTCL. The receptor is expressed in hemopoietic cells, mainly in dendritic cells, masto-

cytes and eosinophils. It plays a role in regulating the functions of immune system cells such as chemotaxis, cytokines and chemokines expression. Some *in vivo* studies demonstrated the role of H4R in natural and acquired cellular immune response¹⁵. It was found in particular that the H4R receptor stimulated the Th 2 response under *in vivo* and *in vitro* conditions, and the use of H4R antagonists reduced lung inflammation in mice. These and other studies allow us to expect that H4R will be helpful in the successful treatment of allergies and autoimmune or inflammatory diseases. Apart from the effects listed above, the H4 receptor was also found to be directly responsible for pruritus in studies carried out in mice¹⁶. It has been shown that histamine-induced pruritus in Balic BALB/c mice through the stimulation of the H4 receptor, and the use of the H4R antagonist provided better outcomes in suppressing pruritus in mice than H1 receptor antagonists. The protease-activated receptor 2 (PAR2) is another receptor important for the development of pruritus. It has been shown that proteases not only suppress pruritus and an inflammatory condition in the skin, but can also cause pruritus through the activation of specific PAR2 receptors. Trypsases and bacterial proteases released from the mastocytes can cause pruritus by inducing a neurogenic inflammatory condition after PAR2 receptors are stimulated. These receptors are also found in nerve endings, and it seems that they can also induce pruritus directly by stimulating sensory nerves. After stimulation, the PAR2 is permanently modified and, therefore, its role in chronic pruritus has been claimed¹⁷.

The role of interleukins as mediators of pruritus in CTCL should also be mentioned. In Sézary syndrome T-cells synthesize IL-3, IL-4, IL-5, IL-6 and IL-10, enhancing the secretion of Th2 cytokines¹⁸. IL-2 and IL-6 have been described as histamine-dependent mediators of pruritus.

There are reports on the role of histamine and mast cells as mediators of pruritus in MF, particularly in more advanced stages of the disease. Histamine, secreted by mast cells, has been known for a long time as a factor responsible for pruritus. Other mediators secreted by mast cells, such as serotonin, are neuromediators causing pruritus in certain diseases, including lymphomas¹⁹. In 1996, Vermeer and Willemze²⁰ reported in their paper a case of two patients with MF who suffered an exacerbation of skin symptoms after the administration of fluoxetine, an antidepressant acting as a selective serotonin reuptake inhibitor.

Pruritus is a very common symptom in patients with cutaneous T-cell lymphoma, and it may trigger the onset of pathological lesions or present in patients at advanced stages of the disease. In patients with MF stages IIB to IV pruritus is frequently described as a burning pain resistant to treatment with topical drugs and emollients. A published study carried out in the United States by Demierre et al²¹ qualified 309 patients with CTCL to complete a survey. The majority of patients (88%) reported pruritus, with 41% also reporting some pain. In primary cutaneous T-cell lymphoma pruritus can occur without any skin lesions, making the diagnostic process even more difficult. It can often take years before the correct diagnosis is made based on clinical symptoms, histopathological evaluation of skin biopsy taken from the lesion, and a number of molecular tests. A detailed understanding of the mechanisms responsible for pruritus in this group of diseases will help us to develop better methods for the treatment of CTCL²².

Atopic Dermatitis

Pruritus is very common in patients with atopic dermatitis (AD). It is considered one of the major diagnostic criteria for AD according to Hanifin and Rajka²³, but is also a part of a scoring system used in scientific studies for the comparison of groups of patients, or assessment of disease course in individual patients at various time intervals, both a few days long and a several years long²⁴. The severity of pruritus is also a feature considered in the severity scoring of clinical disease symptoms using SCORAD and EASI indices^{25,26}. The pathomechanism of pruritus in AD has not been fully explained. AD was found to be associated with disorders within the dermis/epidermis barrier, which result in the onset of characteristic skin lesions in the locations typical for this dermatosis^{27,28}. Different forms are considered, including neurogenic pruritus, psychogenic pruritus and neuropathic pruritus. Neurogenic pruritus is induced centrally without any damage to the nervous system, while neuropathic pruritus is induced as a result of damage to the afferent impulse transmission pathway²⁹. Psychogenic pruritus can also accompany many diseases in which the nervous system plays an important role. Patients with AD often find pruritus unbearable. In AD pruritus is not caused by histamine alone, because the administration of drugs inhibiting histamine receptors does not offer full relief and elimination of this persistent symptom. Scratching is a natural re-

response, and it leads to the formation of excoriations, erosions and erythema, also contributing to skin damage and the creation of the itch-scratch cycle. Emotional and mental factors are also important in AD. Ständer et al³⁰ carried out a valuable study on the pathophysiology of pruritus in AD. The researchers presented the results of studies supporting a certain role of the central nervous system in the mediation of pruritus in AD. Raised plasma levels of beta-endorphin and skin levels of ACh were found in patients with AD. ACh is a neurotransmitter in sensory nerves surrounding eccrine sweat glands, and is released and synthesized *in vitro* by keratinocytes. Intradermal administration of ACh to patients with AD into the lesion and apparently intact skin results in slightly different skin reactions. In the first case pruritus and burning pain is provoked, but in the second case pruritus only. Does this mean that pruritus is caused by different mechanisms in the same patient with AD? We can only speculate that in skin lesions more intense pruritus is associated with excessive perspiration caused by the effect of ACh. One certain fact is that neuropeptides play a very important role in the pathomechanism of pruritus in AD. Abnormalities in the innervation of skin with lesions in patients with AD include an increased number of sensory nerve fibres, an increased expression of SP and CGRP, as well as a higher number of neurofilaments. The increased secretion of the nerve growth factor (NGF) by the epithelial cells in the basal skin layer results in the hypertrophy of nerve endings³¹.

The role of histamine in the pathomechanism of pruritus in patients with AD continues to be the subject of many studies and debates. Initially, histamine was considered the major mediator of pruritus in atopic diseases, but further studies do not fully support this standpoint. Another reason for this is the fact that the administration of H1 receptor antagonists to patients with AD does not offer relief from the persistent scratching³¹. Perhaps this problem can be attributed to the role of interleukins, including IL-2 or IL-31, because the intradermal administration of IL-2 provokes pruritus in patients with AD with more severity than in healthy people³².

Other Allergic Diseases

Urticaria

Urticaria is a disease manifested by skin eruption in the form of wheals. Acute urticaria is the most common skin disease, characterized by rapid

onset and sometimes accompanied by angioedema. Urticaria is more often seen in women than in men (3:2). About 20-30% of the total population may experience a single episode of acute urticaria in life. Statistics for chronic urticaria persisting for longer than 6 weeks from the onset of the first episode are slightly different, as it occurs in about 1-4% of the total population. Wheals (raised areas surrounded by a base) from urticaria have porcelain or light pink colour and result from the limited oedema of the dermis. Oedema results from the dilation of blood vessels and increased permeability of their walls. Regardless of the type of urticaria the common feature of these disorders is the activation and release of mediators from mast cells in the skin. Released mastocytes are accumulated directly near blood vessels and contain characteristic metachromatic granules. Different stimuli trigger the release of preformed mediators (histamine, heparin, various enzymes) and mediators synthesized directly after activation (TNF-alpha, IL-8). In urticaria, there is a direct correlation between the nervous system and mast cells. Neurotransmitters, including substance P, cause the release of histamine, which can affect sensory nerve fibres and provoke pruritus in this dermatosis. In cold-induced, pressure-induced and solar urticaria there are also other factors responsible for the degradation of mast cells. Important mediators, apart from histamine, in these types of urticaria include serotonin, bradykinin, leukotrienes C₄, D₄ and E₄, prostaglandins and proteolytic enzymes. The causes of acute urticaria are often unknown, while 25% of cases of chronic urticaria are caused by infections, allergic or pseudoallergic reactions and autoimmune disorders. Physical urticaria accounts for another 25% of cases, and idiopathic urticaria, in which no causative factor can be identified despite full diagnostic process, account for 50%³³. Severe pruritus, apart from urticarial wheal, is a very characteristic symptom of this disorder. Pruritus is most severe in the phase of wheal formation and is rare in children. No excoriations are found on the skin, as patients rub lesions rather than scratch them. Exacerbation of symptoms in the evening can be attributed to the reaction of the parasympathetic system³⁴.

Contact Dermatitis

Contact dermatitis results from the skin's reaction to external factors triggering inflammation. Two types of this dermatosis have been described and, depending on the provoking factor, these are irritant contact dermatitis and allergic

contact dermatitis. Irritant contact dermatitis results most often from cutaneous reaction to toxic substance acting directly on the skin. Allergic contact dermatitis results from hypersensitivity to toxic substances, usually mediated by T lymphocytes. Skin lesions occur after repeated exposure of the skin to an irritant. In this type of reaction the dose of the provoking factor plays no significant role, but it is important that the reaction spreads beyond the site exposed to the allergen, in contrast to irritant contact dermatitis, in which skin lesions occur only at the site of exposure.

Irritant Contact Dermatitis

There are two types of this dermatitis – acute and chronic. Acute irritant contact dermatitis is found in people who are exposed to an irritant for a sufficiently long time. The corneous layer creates a direct protection against harmful substances. The protective potential depends on its thickness and the presence of skin appendages. The face, genital organs and intertriginous areas are most susceptible to this dermatitis. Major factors provoking acute reaction include alkali, acids, organic solvents, detergents, UV radiation, ionizing radiation, phototoxic factors, certain foods (asparagus, mustard), plants and animals (agave, sea anemone), and military gases. Clinical manifestation is variable and depends on the provoking factor, but various severity erythema with blisters, bleeding, urticarial wheals and erosions are always observed, and these lesions are accompanied by pruritus. In chronic contact dermatitis the major aetiological factor is repetitive exposure to gentle irritants. This results in disorders within the lipid skin layer, leading to the development of symptoms such as lichenification, cracking and exfoliation. More acute reactions can also develop, with the formation of eruptions, oedema and eschars. These reactions are most often caused by detergents, chemicals, physical factors and secretions, including sweat and saliva. Pruritus is a frequent symptom associated with these dermatoses. Continuous scratching leads to the exacerbation of clinical symptoms and secondary infections or lichenification. The introduction of relevant topical and oral treatment reduces inflammatory symptoms and the severity of pruritus. Avoiding contact with the irritant is very important³³.

Allergic Contact Dermatitis

This dermatosis occurs in about 15% of the population. Lesions form in the reaction induced by an allergen, and the acute type is the most

common, although chronic reactions have also been reported. Certain predispositions include allergic diseases, but also skin injury leading to the development of allergic reactions. The immune mechanism of contact reaction has been investigated in detail. At the first stage (induction phase), the antigen is presented to T lymphocytes in regional lymphatic nodes, and Langerhans cells are involved in this process. Sensitized cells return to the skin. Repeated exposure to the minimum dose of the allergen results in the onset of a hypersensitivity reaction. Receptors of T helper cells identify the specific antigen, then cytokines are released, mainly IL-2, IL-4, IL-6 and IL-8, which activate other inflammatory cells. The list of allergens is very long and continues to grow. Depending on the needs, standard and extended allergen test kits can be used. The clinical manifestation of contact dermatitis varies and depends on the type of allergen provoking the reaction, exposure time, and the surface on which skin lesions develop. The most common symptoms develop within 24-48 hours and include lesions of erythematous and exfoliating nature, excoriations, lichenification, persistent pruritus and inflammation. Finding the causative factor for this reaction and elimination of responsible allergen are very important, otherwise treatment will not be successful. Pruritus in these dermatoses is a very common symptom, is persistent, and does not respond to available treatment methods. Because of the continuous scratching skin lesions do not subside and chronic inflammation develops. Skin patch tests offer very valuable information, and in some cases, a diagnostic biopsy of the skin lesions might be recommended.

There is only scarce literature data on the prevalence of contact allergy in children with atopic dermatitis. In one of the papers, the authors research assess the prevalence of contact allergy among children with atopic dermatitis, seborrhoeic dermatitis and in a population of healthy children. The statistically significant positive results in the highest proportion of patch tests in the youngest age subpopulation of children with atopic dermatitis, and detection of contact allergy most commonly in the youngest subgroup of healthy children, may suggest nonspecifically positive results associated with the immaturity of the epidermal barrier during the first years of life³⁵.

Drug Eruptions

Drug eruptions are frequent disorders, and it should be kept in mind that any drug can cause

an adverse reaction. Acquiring a detailed patient history, covering not only days before the onset of skin lesions but also the ten or more past days, plays an important role. It should be remembered that adverse drug reactions can, depending on the active substance of the drug, lead to skin lesions caused by all four immune mechanisms. The administration route also plays an important role. At topical administration hypersensitivity response at the drug application site can be expected, oral or nasal administration stimulates the synthesis of immunoglobulins A and E, while intravenous administration can lead to anaphylactic shock. The drugs most often responsible for adverse reactions include antibiotics, non-steroid anti-inflammatory drugs, diuretics, certain cardiovascular drugs and drugs acting on the CNS. Because there is a possibility of an immune allergic reaction, and also a non-immune reaction, various skin lesions can be observed. Symptoms of urticaria or angioedema are the most common. Other common disorders include lesions resembling lichen planus, acne, psoriatic-like lesions, eczema, blisters and pigmentary changes. Lesions are often associated with pruritus of various severity. The treatment method involves the elimination of the provoking factor and the use of topical medications plus antihistamines.

Prurigo

This is a group of disorders of various aetiologies, manifested by the formation of usually small urticarial exudative nodules. The small nodules are swollen and red at their base, sometimes with a minor blister filled with serous fluid. In contrast to urticaria, these lesions do not subside completely within a few hours.

Acute prurigo (*prurigo simplex acuta*, *strophulus infantum*) usually occurs in children aged 2 to 8 years. It may be associated with insect bites, because acute prurigo tends to occur during summer, and tests with insect allergens carried out in patients often provide a positive response. The disease is manifested by clinical symptoms similar to urticaria, and in healthy children very itchy papules develop rapidly on the skin, with pale pink infiltration on the margin. Lesions most often occur on the trunk and extremities. A barely perceptible papule that increases its size to a clearly visible form (*strophulus bullosa*) may develop within the nodular lesions. Usually, the exudative papule grows and forms a hard nodule. These lesions are accompanied by intense itching that leads to the formation of excoriations cov-

ered with eschar. Lesions heal leaving no marks, although hyper- or hypopigmentation may sometimes occur on the affected skin. The administration of antihistamine drugs is recommended because of the severe pruritus, and insect bites, varicella and scabies should mainly be considered in differential diagnosis³³.

Subacute prurigo (*prurigo simplex subacuta*, *strophulus adultorum*) is another type of disease. It usually affects women aged 30-40 years and women during menopause. Subacute prurigo affects men aged over 50 years. The etiology has not been fully understood. There may be many causes but major listed agents include concurrent diseases, such as renal and liver disorders, diabetes, *prurigo gestationis* and *prurigo dermatographica*. The major characteristic symptom of this disease is very intense itching subsiding after scratching which results in bleeding of the lesion. Excoriations perceptible on the skin almost never affects the adjacent intact skin. The disease is manifested by an eruption in the form of a pink exudative nodule with a characteristic papule on the top. Lesions usually occur on the extensor surface of the trunk or shoulder girdle. Characteristically, the areas between skin eruptions remain intact, which helps to differentiate this disease from atopic dermatitis or other disorders. Skin lesions do not occur on mucous membranes, hands or feet³³.

Prurigo nodularis occurs in patients with chronic pruritus. It is often found in patients with atopic dermatitis or other atopic diseases. It may occur in women during menopause due to the development of depression symptoms and psychosocial disorders. Prurigo may also develop because of underlying self-injury disorders. Scratching results in local proliferation of skin nerves and an increase in the levels of neuropeptides. This process leads to increased secretion of proinflammatory cytokines, and stimulation of keratinocytes and fibroblasts, which can explain epidermal fibrosis and hypertrophy. Papules observed clinically tend to form solid nodules most often located on distal parts of lower extremities, buttocks and, rarely, on the trunk. Skin lesions may accompany atopic diseases, but also lichen planus, chronic contact dermatitis, crural eczema and scabies. Because of the coexisting chronic pruritus lesions are often scratched and covered with crust.

Psoriasis

Psoriasis is one of the most common chronic and recurrent skin diseases and its cause is not

fully understood. It has been estimated that in highly developed countries psoriasis affects about 1-2% of people. There are many factors that may influence the onset of psoriasis and exacerbate symptoms. These include genetic but also environmental factors, mainly stress, tobacco smoking, and certain drugs or alcoholic beverages³⁶. Stress may trigger exacerbation of psoriasis in a number of ways. It can activate the hypothalamus-pituitary-adrenal axis and stimulate the secretion of corticotrophin (CRH), which has a proinflammatory effect and can activate mastocytes, stimulate angiogenesis and modulate immune cells. Increased levels of CRH and its receptors were found in the skin of patients with psoriasis. Stress can also be responsible for the aggravation of disease by stimulating the release of many proinflammatory neuropeptides such as SP, CGRP, VIP or somatostatin from nerve endings in the skin³⁷. In psoriasis, however, the connection between histamine and pruritic symptoms is not completely clear. No correlation was found between the severity of pruritus and histamine plasma levels in patients with pruritic psoriasis versus a group of patients without pruritus³⁸. In addition, treatment with antihistamine drugs rarely offers improvement, and any improvement which does occur is most likely associated with the sedative effect of these drugs³⁹. Reich et al⁴⁰ found no significant difference in plasma levels of SP, CGRP or VIP between patients with pruritic psoriasis and patients with psoriasis who did not report pruritus. A negative correlation was found between the plasma levels of SP and VIP and severity of pruritus in patients with psoriasis. This most likely results from the increased activity of enzymes degrading neuropeptides and, therefore, reduced plasma level of these neuropeptides. Nakamura et al⁴¹ carried out a study focused on pruritus in patients with psoriasis, and they demonstrated an increased number of nerve fibres containing SP near blood vessels, and reduced the activity of enzymes degrading SP. The researchers also found that patients with pruritic psoriasis had an increased expression of NGF and TrkA receptors on keratinocytes in the basal layer and in nerve fibres within inflammatory infiltrates in comparison to patients who had non-pruritic psoriasis. Chang et al analyzed the expression of receptors for selected neuropeptides (SP, NGF, VIP and CGRP) on keratinocytes from the psoriatic skin and found the expression considerably increased. Despite many studies on the role of IL, mainly IL-2, no

statistically significant differences were found between patients with pruritic psoriasis and patients with non-pruritic psoriasis.

Pruritus in Systemic Diseases

Pruritus can also be a symptom of systemic conditions in the human body. It is most common in patients with cholestasis, liver dysfunctions, uraemia and renal diseases.

Pruritus in Renal Diseases

Uraemic pruritus affects about 40 to 70% of patients on dialysis. It often has a generalized manifestation and is exacerbated during the night. The cause of uraemic pruritus has not been fully understood, but a significant role is attributed to skin dryness in these patients. The term uraemic pruritus is not correct, as there is no correlation between the level of urea and the severity of pruritic symptoms. In addition, pruritus may occur in patients with normal renal parameters. Increased levels of IL-6 were found in patients with uraemia in comparison to patients without renal disorders^[42]. The role of histamine or serotonin is arguable, and carried out studies have not provided conclusive evidence supporting these assumptions. Attempts to treat this condition with antihistamines or selective serotonin receptor inhibitors 5-HT₃ offered no success. This may be attributed to disordered clearance of medium molecular weight proteins leading to peripheral neuropathy, or to the effect of parathormone or calcium and phosphorus ions^[43]. In some studies increased mastocyte count and histamine levels were reported in patients with uraemic pruritus. The accumulation of endogenous opioids and other compounds not removed during dialysis may be a causative factor for pruritus in these patients. Because of the multifactorial pathogenesis of uraemic pruritus, researchers continue their studies to identify agents causing this persistent symptom in patients.

Pruritus in Liver Diseases

Patients with liver conditions and cholestasis are often affected by pruritus. All the causes of cholestatic pruritus have not yet been identified. However, the role of bile salts, progesterone metabolites and histamine have been considered. Beyond any doubt, many studies demonstrated that mediators of cholestatic pruritus are secreted with bile and reabsorbed from the intestines into the bloodstream. Cholestatic pruritus is more common in women, particularly during menstru-

al bleeding or those on hormone replacement therapy⁴⁴. This may be associated with sterolic metabolites acting as mediators of cholestatic pruritus. Fatty acids can cause degradation of mast cells and the release of histamine. Therefore, histamine plays a certain role in this condition, and its increased plasma levels were found in patients with cholestasis⁴⁵.

Pruritus in Endocrine and Metabolic Disorders

Pruritus may also be associated with thyroid disorders, both hypothyroidism and hyperthyroidism, as well as with diabetes mellitus. Control of hormonal parameters is most important in endocrine disorders and can contribute to improved clinical skin state and reduce itching. Pruritus occurs in 4-11% of patients with hyperthyroidism and may be associated with increased blood flow to the skin. In hypothyroidism pruritus accompanies the dryness of the skin which is very typical of this condition. Diabetes mellitus is another endocrine disorder, and generalized pruritus may be its first and only symptom. It may be a symptom associated with disorders secondary to diabetes, such as candidiasis or dryness of the skin⁴⁶. Diabetic patients may present with skin lesions caused by atherosclerosis, such as ischemia and ulcerations. Neuropathy leads to trophic lesions, cracking and dryness of the skin on the lower extremities. Patients taking drugs reducing blood sugar level may develop urticarial skin lesions or eruptions. Phototoxic reactions are sometimes observed.

During pregnancy, women experience many hormonal changes. Pruritus is one symptom of this process, particularly in the second and third trimester of gestation. It may be associated with pregnancy-related complications and dermatoses characteristic for this period, but may also be due to skin dryness and stretching in certain body parts as a response to enlargement in areas of the abdomen, thighs and buttocks. In the latter case, pregnant women can achieve fast relief from pruritus by using vitamin A-free emollients with a moisturizing effect. However, if pruritus persists in a pregnant woman despite using moisturizers, diagnostic tests have to be carried out to rule out cholestasis, renal disorders or gestosis.

Neurological Disorders

Many disorders of the central nervous system can cause pruritus. According to the current classification the category of neurological pruritus in-

cludes neurogenic pruritus and neuropathic pruritus. Neurogenic pruritus develops after inducing the pathway transmitting the itch sensation but with no neural damage. Neuropathic pruritus is chronic in most cases and responds poorly to treatment. Here we can list tumours of the CNS, mainly cavernous angioma and ependymoma, abscesses of this area and ischaemic diseases. Pruritus in these diseases is unilateral, located opposite to the injured hemisphere, and is associated with other perceptive disorders. Patients with multiple sclerosis (MS) may suffer paroxysmal attacks of itching located symmetrically and lasting from several seconds to several minutes. Paroxysmal pruritus in patients with MS can cause sleep disruption at night and may be an early, and the only, symptom of MS. Brachioradial pruritus is another type of neuropathic pruritus. Lesions occur on the dorso-lateral side of the arm. The affected skin is intact, but post-inflammatory discolourations can sometimes develop. Interestingly, symptoms become aggravated after exposure to sunlight. The pathogenesis of this disease is not fully understood. One certain fact is that an important role is attributed to the compression of nerve roots at the C5-C8 level, or other pathology of the spinal cord at this level⁴⁷. Notalgia parasthetica is a pruritic disease localized unilaterally in the interscapular area (Th2-Th6 dermatomes) with coexisting increased sensitivity of the skin to sensory stimuli. Skin patches affected by pruritus often show abnormal pigmentation caused by persistent scratching of this area. The primary role in this disease is attributed to injury of the posterior rami of spinal nerves arising in T2 through T6 corresponding with degenerative changes in the thoracic section. This problem is rather rare in young people, but if diagnosed it may be one of the symptoms of multiple endocrine neoplasia type 2A (MEN 2A). Treatment of pruritus in these nervous system disorders is difficult and requires a multidisciplinary approach⁴⁸.

Psychiatric Disorders

The diagnostic process focused on pruritus in psychiatric disorders often requires consultation with a psychiatrist. Pruritus occurs most often in patients suffering from stress, fatigue or anxiety, and is apparently reported more frequently by women. Patients may be affected by pruritus without developing any skin lesions, but there are also cases of patients with excoriations and injuries from scratching. It is noteworthy that pruritus and the skin lesions associated with it may give rise to symptoms of depression and breakdown⁴⁹. Gener-

ally, psychogenic pruritus is diagnosed after ruling out other causes. Precise criteria for diagnosing psychogenic pruritus have been proposed by the French Psychodermatology Group.

Parasitic diseases and skin lesions Induced by contact with insects

Diseases Caused by Arthropods

There are many dermatoses in which pruritus is a significant and persistent symptom. The most important that have to be mentioned are scabies, invasion by intestinal parasites, larva migrans, pediculosis, human flea and skin lesions induced by insects. Arthropods are the largest group within the animal kingdom. From the medical point of view insects and arachnids are the largest group. Arthropods can have a negative effect on their host through bites (lice, mosquitoes, flies, fleas, centipedes and spiders) or stings (bees, hornets and wasps).

Pediculosis

There are three lice species important for human pathologies: head louse (*Pediculus humanus capitis*), body louse (*Pediculus humanus corporis*) and pubic louse (*Phthirus pubis*). The head louse is most common in children of preschool and school age. It is transmitted from human to human by direct contact and on combs, hair brushes or other hair accessories. Lesions are generally found on the scalp, and less commonly on the eyebrows, eyelashes and beard. Lice are usually located in the retroauricular area, and after biting induce the formation of intensely pruritic nodules. Severe itch and scratching leads to the inflammatory condition defined as louse eczema. In skin areas affected by lesions secondary bacterial infection and contagious impetigo may develop. Pediculosis corporis is a disease associated with poor personal hygiene and is most common in homeless people. The irritant effect of lice saliva results in the development of erythema, urticarial lesions and itchy nodules and pustules. Persistent pruritus leads to excoriations with secondary infection and reactive lymphadenopathy. Because of the skin's appearance, this condition is also called vagabond's disease. The pubic louse, the smallest of all lice species, is transmitted sexually and infests the genital and axillary areas due to the presence of apocrine glands. In this condition pruritus is the least intense of all types of pediculosis. Blue spots that appear at the feeding site caused by pubic lice are a characteristic sign of infestation.

Bed bug (Cimex lecularius)

Bed bugs are active at night, and during the day they lodge in furniture crevices, floors or paintings. Skin lesions appear as groups of several erythematous nodules or urticarial changes. Lesions are located on the extremities and face. Urticarial lesions transform into hard nodules that persist for several days with accompanying severe pruritus. Treatment involves the control of pruritus with topical antipruritic medications.

Human flea (Pulex Irritans)

Human fleas are a considerable problem; they can jump and also fly. They tend to live in crevices, carpets and furniture. The human flea is small (2-4 mm) but can jump up to 50 cm into the air and 60 cm in distance. Bites by human fleas cause the development of numerous wheals and nodules arranged irregularly. Diascopic examination reveals the presence of purpura pulicosa. In rare cases reactions to a bite can have a bullous appearance or resemble bullous pemphigoid. Lesions are associated with severe itch and, therefore, acute urticaria, lichen urticatus, prurigo or bites by other insects should be considered at a differential diagnosis.

Nematodes

Cutaneous Larva Migrans

Cutaneous larva migrans, also called the 'plumber's itch' is a disease known worldwide, but is more common in countries of the tropical and subtropical regions. Infection is caused by the contact with soil contaminated by animal faeces. This usually occurs at the beach, to people working in the mining industry, in tunnels, and to plumbers. The disease is caused by various species of nematodes, which penetrate the skin, but are not able to mature there, or move to deeper layers to infest body organs. Shortly after a larva penetrates the skin intense itch, oedema, small nodules and eruptions develop. Larvae create the typical red wormlike burrows visible underneath the skin accompanied by severe pruritus. Larvae may be removed sometimes as a result of scratching. This condition is usually confined to the skin of the feet.

Enterobiasis

This condition has no association with any socioeconomic level, race or culture and is commonly transmitted via the faecal-oral route. Parasites live in the colon, duodenum and rectum. Female

pinworms, after leaving the small intestine, emerge from the anus and deposit eggs in the perianal area and genitals (in women). Then eggs are then ingested and reach the human gastrointestinal tract, where larvae hatch already in the duodenum. Patients feel well and the disease is often asymptomatic. The major clinical symptom is perianal pruritus, intensifying during the night. Scratching can result in self-infection as patients transfer pinworms on dirty hands to the mouth. Erosions and excoriations develop on the scratched skin. Enterobiasis should be considered when making a differential diagnosis in patients with perianal pruritus. Treatment is uncomplicated and requires personal hygiene and oral medication.

Ascariasis

This is the most common human disease caused by intestinal parasites, and infection occurs usually by ingestion of unwashed fruit and vegetables or through contact with soil contaminated by faeces containing eggs of the parasite. The parasite lives in the small intestine, where newly ingested eggs hatch, and then larvae burrow through the gut wall to the blood system, and migrate via veins to the lungs. In the lungs, the parasites can cause Löffler's syndrome (eosinophilic pneumonia). After 10 days the parasites migrate along the trachea to the larynx and are reingested to reach the small intestine, which starts the life cycle again. Most infections are asymptomatic, but some patients present with symptoms of intestinal obstruction or pains resembling appendicitis.

Skin Lesions Induced by Contact with Insects

Mosquitoes (Culicidae)

Mosquitoes can transmit infectious diseases. Their life cycle takes place in water bodies, either large, or small like a paddle or dumped tyres. Mosquitoes have a role in spreading diseases such as malaria, filariasis, yellow fever, dengue fever, and encephalitis of various etiology. Skin lesions after mosquito bites are numerous and itchy. Secondary bacterial infection can occur due to scratching. Children often present with a bullous form of the disease. Treatment involves control of the scratching reflex by the use of topical antihistamine medications.

Bees and Wasps (Hymenoptera)

This group of Hymenoptera includes insects such as wasps, honey bees, bumble bees, hornets

and ants. Each of these insects can cause a painful bite and provoke a very dangerous allergic response, including anaphylactic shock. Honey bees, unlike wasps or hornets, can sting their victim only once in their lifetime. The venom of Hymenoptera has a complex structure and can cause various reactions when introduced into the human body. Desensitization to Hymenoptera venom is very difficult and requires extensive knowledge and experience. A honey bee sting causes redness, itch, pain and a burning sensation. Swelling often develops after the sting and it may persist for a few days. Stings to the face or mouth may cause immediate and acute anaphylactic reaction.

Arachnids – Scabies

The itch mite is a human parasite, and is transmitted by direct human-to-human contact, particularly in pre-schools, nurseries and schools, but also among adults at workplaces. Scabies is typically manifested by an intense itch, becoming more severe after an increase in body temperature, retiring for bed, and at night. Skin lesions are typically located between fingers, on the skin of wrists, soles, and around nipples and genital organs. Secondary papules develop in reaction to mite faeces, located on lateral parts of the trunk, on extremities, in the gluteal cleft, and on the waist. In children skin lesions may occur on the scalp, hands, soles and face. Lesions are eczematous and lichenoid in nature and transform into nodules, eruptions and pustules. Itchy red nodules contribute to the onset of urticarial allergic reactions. Intense pruritus causes the formation of lichenoid patches^{50,51}. Treatment has to cover all family members, and requires the laundering and ironing of all the clothing used by the people occupying a dwelling. Parasites can also be successfully controlled by topical preparations.

Other Dermatoses Accompanied with Pruritus

There are many dermatoses accompanied by pruritus. These include infectious diseases such as zoster, seborrhoeic disorders, e.g. simple acne, acne rosacea, and also other dermatoses, like seborrhoeic dermatitis and pemphigus, particularly Dühring's disease. Other diseases that should be mentioned are ichthyosis and keratosis follicularis. Lichen planus is a distinct type of disease, in which pruritus is very intense and is used as a diagnostic criterion. Pruritus can be caused by a reaction to drugs or be associated with hepatic

Table II. Other selected pruritic dermatoses.

Lichen planus	Macular amyloidosis
Lichen sclerosus et atrophicus	Nodular amyloidosis
Dermatitis herpetiformis	Seborrhoeic dermatitis
Pemphigoid	Pityriasis rosea Gibert
Herpes	Pityriasis pilaris
Zoster	Xerosis (skin dryness)
Varicella	Ichthyosis
Tinea glabrosa	Keratosis pilaris
Cutaneous mastocytosis	Darier's disease
Lichen amyloidosus	Grover's disease

diseases, and both these causes are considered to be factors intensifying pruritus. Lichen sclerosus et atrophicus is a specific type of connective tissue disorder, and skin lesions are located mainly in the genital area and are accompanied by unpleasant and persistent pruritus, resistant to topical treatment, including phototherapy.

Cutaneous mastocytosis can also be associated with pruritus. Mast cells become accumulated only in the skin. The disease affects mainly children, the prognosis is good and lesions often subside spontaneously. Urticaria pigmentosa occurs in infants and children. It is clinically manifested by nodules and patches of abnormal pigmentation which after rubbing transform into urticarial wheals (Darier's symptom). Lesions are most often located on the trunk, and rarely occur on soles, hands and face. Major symptoms include fever and pruritus, but other symptoms may occur, such as diarrhoea, vomiting, tachycardia and less often respiratory symptoms. All symptoms are mainly caused by mediators released from activated mast cells in the skin. Selected diseases accompanied by pruritus are listed in Table II.

Conclusions

Because of the complex nature of the mechanisms involved in the induction of pruritus this problem requires more comprehensive and detailed analysis. Focus on the life quality of patients with pruritic disorders is vital. In many cases pruritus is also a significant psychological problem³⁸. Therefore, it is very important to understand the mechanisms responsible for the development of this symptom. In many dermatoses, the mediators of pruritus have not been clearly defined, which prevents the introduction of targeted and effective treatment. We hope that multiple studies carried out on this difficult subject

will help us to better understand the pathomechanism of pruritus and will contribute to advances in this important domain of medical science.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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