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REVIEW ARTICLE

Pruritus in certain internal diseases

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Abstract

In the past it was widely believed that pain and itching are transmitted by the same nerve pathway with the low intensity stimulation of unmyelinated polymodal C fibers resulting in sensation of pruritus whereas high intensity stimulation causing pain. In recent experiments however, stimulation of single unmyelinated C fibers led to the identification of two kinds of fibers. Stimulation of most of these fibers induces pain, whereas a small number of fibers provoke the sensation of itching. Pruritus is an unpleasant sensation, often accompanied by scratching. It may present due to a number of cutaneous diseases or internal disorders. Pruritus may be caused by some chemical substances as histamine, prostaglandins, proteases and substance P. This review describes the existence of pruritus in different internal disorders. It is quite important the reason of pruritus to be discovered, for the application of an adequate therapy. *Hippokratia 2007; 11 (2): 67-71*

Key words: *pruritus, unpleasant sensation, itching, internal diseases, antihistamines, cholestasis, uremia, dialysis, malignancy*

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A simple definition of pruritus or itching is "the unpleasant skin sensation that frequently provokes scratching". Of course the word "unpleasant" means different things to different people[1]. Pruritus can be a physiological event as well, if the provoked scratching removes a potentially dangerous agent, or if it is due to some drugs or psychic diseases[2].

Pruritus must be differentiated from tickling, burning, pain and touch. It must be underlined that pruritus is only a symptom of a number of disease and is generally a subjective sensation, sometimes accompanied by crusts, excoriations, hyperpigmentations, lichenification with thickening, pyodermia, increased skin creasing and burnished nails[1,2].

The intensity can be mild, moderate or severe with sleep disorders, discomfort and increased irritability, disturbance of daily activity or general stress. Pruritus may be acute or chronic, localized or generalized[3,4].

It has been a long time since the general belief that itching and pain are transmitted by the same nerve pathway, with low intensity stimulation of unmyelinated polymodal C fiber resulting in sensation of pruritus whereas high intensity stimulation causing pain. Now two kinds of fibers have been identified: most of these fibers produce pain, whereas a small number of them produce the sensation of itching upon stimulation. The following data are in favor of the concept that receptors for itching and pain are different: itching provokes scratching, while pain causes a withdrawal response; morphine relieves pain, but can cause pruritus; removal of the epidermis and upper dermis abolishes itching, but not pain; heating of skin to 41^0 C relieves itching, but not pain[5,6].

Pruritus is provoked or enhanced by a number of chemical substances such as histamine, prostaglandins, proteases, cytokines, neuropeptides, including substance P, and bile salts. Some of the substances act directly on the free nerve ending, while others act indirectly through mastocytes or other cells[7].

The itch impulse is transmitted from peripheral nerves to the dorsal horn of the spinal cord, across the cord via the anterior commissure, and ascending along the spinothalamic tract to the laminar nuclei of the contralateral thalamus. Thalamocortical tracts of tertiary neurons are believed to relay the impulse through the integrating reticular activating system of the thalamus to several areas of the cerebral cortex. Factors that are believed to enhance the sensation of pruritus include dryness of the epidermis and dermis, anoxia of tissues, dilation of the capillaries, irritating stimuli, and psychological responses[5,7].

The motor response of scratching follows the itching. Scratching is modulated at the corticothalamic center as a spinal reflex. After scratching, pruritus may be relieved for 15 to 30 minutes. The mechanism of this relieve by scratching is unknown. Scratching probably generates sensory impulses that disrupt circuits in some areas of the spinal cord. Scratching may enhance the sensation of itching, creating a itching-scratching-itching cycle. Other physical stimuli such as heat, cold, vibration, and ultraviolet radiation diminish itching and increase the release of proteolytic enzymes, blocking the itch-scratch-itch chain[6-8]. It is thought that spinal modulation of afferent

stimuli and central mechanisms may play a role in the relief of itch[5,6] Pathogenesis of pruritus associated with underlying disease states are varied. Malignant, hepatic, and renal diseases, are thought to produce itching by circulating toxic substances. Released from circulating basophils histamine and leukopeptidase - from white blood cells - may trigger pruritus associated with lymphomas and leukemias. Higher kininogen in Hodgkin's lymphoma, release of histamine or bradykinin precursors from solid tumors, and serotonin in carcinoid may all be the agents, causing pruritus. People receiving cytotoxic chemotherapy, irradiation, and/or biologic response modifiers for treatment of malignancy are likely to experience pruritus. This same population is quite likely to be exposed to many of the other etiologic factors relating to pruritus ranging from nutritionally related xerosis (dry skin) to radiation desquamation, chemotherapy and biologic agent–induced side effects, antibiotic reactions, and other drug sensitivities.

Classification of pruritus

Pruritus may be acute or chronic, localized or generalized[8]. Generalized pruritus can be divided into the following types[9]:

1. Pruritus of variety of skin diseases in which the mediators act on free nerve endings.

2. Pruritus in internal diseases.

3. Idiopathic pruritus – when no cause can be identified.

This review points on pruritus, associated with some internal diseases. The most frequent internal diseases and borderline states, causing pruritus are in Table 1.

Table 1: *Causes of pruritus in Internal Medicine*

Intrahepatic cholestasis	Sclerosis multiplex
Posthepatic cholestasis	Stroke
Drug-induced cholestasis	Delusion of parasitosis
Chronic renal failure	Lymphoma
Dialysis treatment	Mastocytosis
Diabetes mellitus	Polycythemia vera
Systemic parasitosis	Iron-deficiency anemia
Sjogren's syndrome	Hyperthyroidism
AIDS	Hyperparathyroidism
Drug eruption	Brain tumors
Pregnancy	Myxoedema
Psychogenic conditions	

It would be impossible to discuss all the pruritus – associated internal diseases in the limits of the present manuscript. However, the most important of them are shortly described.

Cholestatic pruritus

Pruritus is a frequent manifestation in patients with liver diseases and intra- or post- hepatic cholestasis[10]. Primary biliary cirrhosis, primary sclerosing cholangitis, B and C viral hepatitis, autoimmune hepatitis, carcinoma of bile ducts, alcoholic cirrhosis are among the hepatic disorders with pruritus. The pathogenesis of cholestatic pruritus is still poorly understood: the precise substance, causing the pruritus is not known. Some authors suggest that pruritus is caused by the bile acids in the blood (cholemia) or skin[10], but the correlation between the skin concentration of bile salts and intensity of pruritus is quite poor. The itching in patients with cholemic pruritus can be positively influenced by treatment with phototherapy, cholestyramine, plasmapheresis which lower or remove the unknown incriminated circulating substances; antihistamines can be used as adjuvants. Ursodeoxycholic acid has been used with a good therapeutic result; serotonin subtype-3-receptor antagonists ondansetron, given intravenously, have been helpful in the treatment of cholestatic pruritus as well[11].

Pruritus in chronic renal failure and dialysis patients

Pruritus in uremia is a common and often intolerable symptom of chronic renal insufficiency. It presents in about 15 % of the cases[12], mostly with skin lesions due to scratching. Pruritus is even more common in about 50-90% of patients undergoing dialysis and can be localized or generalized[13]. Interestingly, pruritus is not present in acute renal failure.

Similarly to most internal diseases itching, the pathogenesis of uremic pruritus, is poorly understood. The cause is probably multifactorial. Iron deficiency, release of histamine, disturbances of calcium-phosphate metabolism, secondary hyperparathyroidism, proliferation of mast cells in the skin, hypervitaminosis A, allergic reactions to the material used for dialysis, affection of motor, sensory and autonomic nerves, endogenous opioids may be considered as possible causative agents[14]. Treatment of renal pruritus is based on the use of ultraviolet therapy, emollients, activated charcoal, cholestyramine, and phosphate binding agents. Sometimes parathyroidectomy is necessary for reduction of itching. Evidence based medicine and practicing do not indicate that histamine concentration is implicated in uremic pruritus. Consequently, antihistamines are not beneficial for the treatment of renal pruritus[15,16]. A useful recommendation for patients on dialysis is to improve the intensity and efficiency of dialysis by removing from the blood the harmful substances, that may induce itching and by using non-complement-activating membranes for hemodialysis. Pruritus disappears or improves significantly after transplantation[17,18].

Pruritus in hematologic diseases

A number of hematological diseases are associated with pruritus.

In polycythemia vera, where overproduction of all three hematopoietic cell lines occurs, itching may appear following contact with water or after a hot bath. It is of note that aquagenic pruritus may precede the development of polycythemia vera by several years[19].

Itching may be so severe that patients refuse to bathe. It is caused by release of histamine[20] and other substances from an increased number of blood basophils; antihistamines do not relieve from this symptom, and currently the most effective method to treat this kind of pruritus is the use of salicylates, photochemotherapy or interferon-a[21].

Iron deficiency is often regarded as a cause for pruritus, even in the absence of anemia. Iron loading abolishes the symptom.

In older patients the cause of pruritus can be a malignant tumour, that may also lead to anemia.

Pruritus may also be present in patients with hemochromatosis where the levels of iron in blood and tissues are elevated[22].

About 30% of the patients with Hodgkin's disease feel itchy. Pruritus can be an early or presenting complaint. It can be very severe, and this may imply a worse prognosis. Hodgkin's pruritus improves after radiation therapy or chemotherapy.

Pruritus is uncommon presentation of chronic leukemia, myelomatosis and lymphosarcoma. It is more often in lymphatic than in granulocytic forms.

Pruritus has also been described in patients with host reactions after bone marrow transplantation.

Endocrine pruritus

Pruritus is present occasionally in diabetics. Itch may be generalized or more frequently localized on the scalp, the genitalia or the perianal area. It may be attributed to a concomitant candidiasis or, more often, to poor control of diabetes, sometimes expressed as elevated glycosylated hemoglobin blood levels[23]. The pruritus in diabetes mellitus may also be linked to neuropathy, dry skin, and drug administration. Treatment consists in the control of diabetes, and the use of antifungal agents. Topical capsaicin may be helpful in some cases of localized pruritus.

Pruritus-associated hyperthyroidism or hypothyroidism was known from the beginning of the 20th century[24]. Its mechanism is unclear. An increase in blood flow and consequently in skin temperature may be a causative factor in hyperthyroidism. Myxoedema-associated pruritus is rare and may be related to the dry skin. Pruritus and even chronic urticaria may be associated with the presence of thyroid autoimmunity and antibodies against several thyroid components such as are thyreoglobulin, and TSH receptor. Levothyroxin is the appropriate treatment in such cases.

Abnormal parathyroid gland activity may also cause pruritus. Secondary hyperparathyroidism in chronic renal diseases may be an additional provocative factor in uremic itch. Parathyroid hormone however, as intradermal injection, failed to trigger itch[25]. Dry skin and cutaneous candidosis probably cause pruritus in patients with primary hypoparathyreoidism[26].

Hormonal deficit in women in the postmenopausal period may provoke vulvar pruritus[27].

Pruritus and malignancy

Carcinoma of the lung, stomach, colon, prostate, breast and pancreatic rarely have been associated with generalized pruritus[28-29]. Treatment consists in surgical removal of the tumor and, in inoperable cases in the use of serotonin re-uptake inhibitors, or of serotonin antagonists.

Pruritus is an important symptom in patients with different forms of mastocytosis: solitary mastocytoma, urticaria pigmentosa, teleangiectasia macularis eruptiva perstans, systemic mastocytosis[30]. Mast cells in human skin are mostly of the tryptase-containing type, while in the alveoli and gastrointestinal mucosa they are of the chymase-containing type. This distinction can help to differentiate the skin mastocytoses from the systemic ones[31,32]. In carcinoid syndrome pruritus is sometimes associated with flushing. The pruritus is elicited by serotonin, produced in the enterochromaphine cells of the tumor[33]. Treatment with antiserotonin drugs alleviates the symptom.

Some authors have pointed the frequent association of pruritus with brain tumors; nasal pruritus was present in about half of the cases[34]. The association of pruritus with tumors is not always understood. It may be triggered by immunological mechanisms, toxic metabolites, iron deficiency, and dry skin. Eradication of the tumor can diminish or abolish itch; antihistamines do not relieve it.

In patients with MEN syndrome (Multiple Endocrine Neoplasms) a unilateral pruritus over the scapular region, linked to deposition of amyloid can be present[35].

Drugs given for chemotherapy such as antimetabolites, alkaloids, alkylating agents and irradiation can also provoke pruritus[36-38].

Neurogenic pruritus

Brain diseases like stroke, sclerosis multiplex, brain tumors, abscesses, may sometimes induce severe generalized or localized pruritus[38,39]. This itching occurs in paroxysms and may be unilateral. The treatment with amitriptyline, which is blocking the uptake of serotonin, increases the conduction in the medulla, and alleviates itch.

Tabes may give rise to segmental pruritus[40].

Multiple sclerosis is also accompanied by pruritus in some cases.

Patients with neuropathies complain rather of paresthesias than of pruritus.

Psychiatric/Psychogenic pruritus

Emotional stress and psychological trauma, anxiety, depression and psychoses intensify all forms of pruritus. Neurosis may be another cause. In adults with generalized pruritus a 10% is triggered by psychological causes[40].

A particular form is the so called "Ebkom syndrome" or "delusion of parasitosis". It appears typically in elderly people, usually women. They often complain of itch-

ing and believe that they are infested with lice, ants, flies or some other parasites, and scratch the skin to eradicate them[41,42]. Therapy with antipsychotic drugs seems to be effective.

Cutaneous and systemic causes of itching have to be excluded before a diagnosis of psychogenic or psychiatric pruritus be made.

Drug-induced pruritus

Pruritus can be a side effect of a variety of drugs. This may be the result of a direct action on skin structures, or indirect through iatrogenic hepatotoxicity or nephrotoxicity. Subclinical sensitivity to any drug may cause pruritus. Morphine, opioids, angiotensine converting enzyme inhibitors, analgetics, vitamin A, contrast media, gold, chloroquine and sulfonamides are among the drugs that may induce pruritus[43]. The implicated drugs remain for a long time in the dermal macrophages[44]. The use of antihistamines is not helpful.

Conclusion

Pruritus therapy can be topical or systemic, symptomatic and causal. In many cases it is necessary to avoid excessive bathing, irritative fabrics, vasodilatation caused by alcohol, hot liquids or foods and stress[45]. In some cases, patients can use antihistamines and / or sedating drugs[36,45]. Tricyclic antidepressants are also useful. The classic sedating antihistamines diphenhydramin and clorpheniramin induce side effects like sedation, slowing the motor skill and somnolence[11,18]. Phototherapy, cholestyramine, capsaicine can be used successfully in some cases[21,36]. The most important tool for treatment of the pruritus in internal diseases is the specific treatment of the concrete internal disease, which should not be underestimated[9-11; 45].

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