Pruritus an important symptom of internal diseases

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SUMMARY

Pruritus is a common unpleasant sensation, accompanied frequently by scratching. This symptom can be caused by numerous cutaneous diseases and by internal disorders. Pruritus is mediated by histamine, proteases, prostaglandins, and substance P. The biochemical, cellular mechanisms and the neuroanatomical pathway which determine the outbreak of pruritus in different internal diseases are described. The exact diagnosis is important for choosing an appropriate treatment.

Introduction

Pruritus is one of the most prominent and disturbing symptoms of skin and other diseases, which was already known to the physicians in the Old Age, including Hippocrates who wrote about it (1).

Despite its common use, the word pruritus is not easy to define. A simple description is that pruritus is an unpleasant cutaneous sensation that provokes a desire to scratch. This desire is the most remarkable characteristic of itch or pruritus in its differentiation from other similar sensations. In the seventeen century Hafenreffer, already described it as "tristis sensatio, desideri scalpendi excitans" (2). Although it seems simple, this attempt to define pruritus can be imprecise; recently Savin noted that the "word unpleasant means different things to different people", and patients suffering from itch do not always want to scratch (3). Pruritus can be a physiological sensation if the consecutive scratching removes a potentially harmful agent, or pathological, if associated with skin and internal diseases, and psychic disorders, or caused by some drugs.

We will use the terms pruritus and itch as synonyms, but some authors use the term itch if there are skin lesions expressed, and pruritus if there are no primary skin alterations "pruritus sine materia" (4,5).

The present article reviews some aspects of itch caused by internal diseases based on new investigations obtained by immunohistochemical, clinical,

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neurophysiological, electrostimulative and molecular studies.

General clinical aspects

Pruritus can be experienced only on the skin, because of the unique neural mechanisms present in it, and they also permit a precise localization.

Pruritus has to be distinguished from pain, burning, tickling, touch and other sensations. It should be stressed that pruritus is a symptom and not a disease. It is a subjective sensation, but sometimes it can be accompanied by excoriations, crusts, hyperpigmentation, lichenification with thickening, increased skin creasing, and burnished nails. It can also lead to pyodermization. Pruritus affects patients of all ages and both sexes. The intensity can be mild, moderate, severe or distressing with sleep disturbances, loss of weight, discomfort, increased irritability, problems in daily activities, and even stress. It may be acute or long lasting, and it can be localized on the scalp, anal and genital area, back, legs or generalized. Chronic itch triggers psychic responses but the psyche can also influence itch. Pruritus may present a diagnostic and therapeutic challenge to the clinician, a dermatologist, family physician, internist, pediatrician or psychiatrist. Some point in the patient's history can be helpful.

Etiopathogenesis and mediators

Pruritus can be provoked by many different exogenous agents (weak mechanical stimuli, electrical, thermal and chemical excitation) or by endogenous causes or stimuli. Although our knowledge of some aspects of the pathogenesis of pruritus is still incomplete, it has greatly increased in recent years. Incomplete data concerning the primary cause of pruritus are in part resulting from the fact that this subjective sensation is, unfortunately, hard to measure, as well as from the lack of a good animal model. Much has been deduced from investigations concerning pain, and from intradermal injection of pruritogenic substances. Recently, the intensity of pruritus was measured by instruments that measured the movement of scratching, or by an infrared video camera that acted also during sleep (6,7).

A number of pathological processes can lead to pruritus: inflammation, hypersensitivity, degenerative changes, malignant tumors, and even psychic abnormalities.

To understand the pathogenesis of pruritus, it is necessary to review briefly the neuroanatomical basis of pruritus, which is relatively well known, and the mediators of the itch. Itch originates in free nerve endings near the dermo-epidermal junction and is conducted centripetally by afferent nerves entering the spinal cord via the dorsal roots. The sensitive nerves for pruritus are small, non-myelinated C fibers with a slow conduction rate. The cell bodies of these nociceptive primary neurons are located in the dorsal root ganglion. After entering into the spinal cord the primary neurons synapse secondary neurons whose axons cross to the opposite side, and then by the tractus spinothalamicus reach the laminar nuclei of the thalamus. Finally, these nuclei relay to the cerebral cortex, i.e. the sensory area in postcentral gyrus. Here we note the location, the nature, the intensity and other quality of this sensation. Recent investigation by positron emission tomography demonstrated the activation of the premotor area and of the inferior parietal lobule, a region, which propose movement, after intracutaneous injections of histamine (8). Probably there are synaptic connections to the motor area of the cortex, which prepare scratching.

For a long time it was thought that itch represents a weak pain, and there was a debate whether the same nerves conduct itch and pain. Now we believe that itch and pain are different and independent sensory modalities, even if local anesthesia or cutting of the sensitive nerves can abolish both. Following observations confirm the opinion that receptors for itch and pain differ:

- itch elicits scratching, while pain a withdrawal response,
- morphine relieves pain but can produce pruritus,
- the heating of the skin to 41°C relieves itch but not pain,
- removal of the epidermis and upper dermis abolishes pruritus, but not pain.

Recent studies suggest the existence of specific C fibers for pruritus (9,10). In a well-designed study, Schmelz and collaborators using a microneurographic and histamine iontophoretic method demonstrated the existence of specific very thin C fibers with low conduction velocity (0,5m /s) which seem to be the receptors for itch in humans (10).

Gradually, investigators established that a number of chemical substances provoke or enhance pruritus. These released substances are mediators, which act peripherally on receptors, on cells or nerves. The most known are histamine, proteinases, prostaglandins, neuropeptides, cytokines and bile salts. Some of the substances can act directly on the free nerve endings, other act indirectly through mastocytes or other cells. Histamine, an imidazolethylamine, was the first and most important recognized pruritogenic substance but it does not account for all the types of pruritus. This biogenic amine is present in the numerous metachromatic granules in mast cells, and when released acts on the H1 receptors, eliciting itch (11,12). Interestingly, histamine applied intraepidermally or at the

basal membrane, causes itch, while when released deeply in the dermis causes pain and edema (angioedema). Itch provoked by histamine is generally associated with flare and wheal. It acts on neurons by elevating the concentration of c AMP. Some experiments demonstrated that serotonine (5-hydroxytryptamine, 5-HT), only scantly present in the skin, and injected intradermally, can also cause pruritus and pain (13). Among prostaglandins, PGE2 does not itself elicit itch, but lowers the threshold and potentiates the itch provoked by histamine (14). PGE is a vasodilatator present in healing wounds. It causes inflammation and itch after solar exposition. Antihistamines can partially alleviate the pruritus induced by this substance.

Substance P (SP), a proinflammatory neuropeptide, consisting of eleven aminoacids, is produced in the dorsal ganglia and then transported to the periphery by nociceptive nerves A and C (15). SP can release histamine from the mast cell granules and so provoke itch. In the skin, SP can also cause erythema, edema and neurogenic inflammation releasing histamine, IL -1, prostaglandins and lysosomal enzymes but is quickly degraded in the dermis (16). The prior oral administration of antihistamines inhibits the pruritus caused by SP. Capsaicin obtained from hot pepper applied locally depletes SP from cutaneous nerves, and so diminishes pruritus.

Among other cytokines, interleukine 2, given intradermally or i.v. causes itch (17). Proteases and peptidases such as papain, trypsin, chymotrypsin, kallikrein injected in the skin also cause pruritus (18). Furthermore, these substances could induce pruritus in histamine depleted skin. It is worthy to say that Shelley and Arthur were the first to demonstrate, in their classic experiments with spicules from the itch producing plant of cowhage (mucuna pruriens), that the itch is caused by an endopeptidase (papain) present in the specules (19).

It is well known that in cases with obstructive jaundice, bile salts and bile acids probably cause pruritus. Recent research has shown that in addition to these substances, opioids such as β-endorphin, met-enkephalin, and leu-enkephalin, can play an important role in causing itch, acting centrally or peripherally (20, 21).

On the other hand, scratching the skin stimulates inhibitory reflexes which break circuits in the spinal cord or centrally and so abolishes or alleviates pruritus. This is in agreement with the "Gate theory" proposed by Melzak and Wall (22).

Studies on volunteers demonstrated that cooling the skin from 32.8°C to 29.7°C or the application of menthol on histamine induced pruritus can reduce its intensity. These findings suggest a central inhibitory effect of cold on activation of A - delta fibers (23).

Table 1. Conditions associated with pruritus

- Chronic renal failure	- Sclerosis multiplex
- Patients on hemodialysis	- Stroke
- Intrahepatic cholestasis	- Psychogenic states
- Posthepatic cholestasis	- Delusion of parasitosis
- Pregnancy	- Lymphoma
- Drug-induced cholestasis	- Mastocytosis
- Polycythemia vera	- Brain tumors
- Iron-deficiency anemia	- AIDS
- Hyperthyroidism	- Systemic parasitosis
- Mixoedema	- Sjögren's syndrome
- Diabetes mellitus	- Drug eruptions
- Hyperparathyroidism	

Classification of pruritus

Huet has classified the causes of pruritus in three groups (24):

- predisposing causes, that include genetic and allergic factors as well as endogenous and exogenous intoxications;
- fortuitous that include environmental factors like temperature, humidity, wind, emotions;
- determining causes, such as physical agents, chemical agents, infections, infestations and others.

It is important to distinguish the localized from the generalized pruritus, which can be divided traditionally into:

1. Pruritus due to a variety of cutaneous diseases in which various mediators act on free nerve endings;
2. Pruritus associated with internal diseases;
3. Idiopathic or "pruritus of undetermined origin" (PUO) (25), if no cause can be identified.

The most frequent internal diseases associated with generalized pruritus are shown in Table 1. Dry skin (asteatosis, xerosis) as well as excessive bathing may provoke pruritus, especially in old individuals. In such cases the itch can be triggered by mechanical or osmotic mechanisms (26,27). Pruritus is a frequent and important symptom of various systemic disorders (28-30). Skin disorders characterized by itching are beyond the scope of this review.

Uremic pruritus

Pruritus uraemicus or renal itch is a common and often intolerable symptom of chronic renal insufficiency (31), being present in about 13 % of the cases; secondary

skin lesions due to scratching can be seen. It is even more common (50-90%) in patients undergoing peritoneal dialysis or hemodialysis (32); it can be localized (about 50 % of the cases), or generalized. Itching is not present in acute renal failure. The pathogenesis of this pruritus is poorly understood. The cause can be asteatosis, iron deficiency, secondary hyperparathyreoidism, hypervitaminosis A, proliferation of mast cells in the skin, release of histamine, allergic reactions to the material used for dialysis, uremic neuropathy affecting motor, sensory and autonomic nerves, changes in the calcium-phosphate product, endogenous opioids and others (33). Probably the cause is multifactorial. Several studies do not indicate that plasma histamine concentration is implicated in renal pruritus (34,35) and antihistamines are rarely beneficial. The treatment of renal pruritus is based on intensive and efficient dialysis to remove pruritogenic substances from the blood, and on the use of non-complement-activating membranes. One can also use UV therapy, emollient ointments, activated charcoal, cholestyramine (4 grams twice a day), phosphate binding agents. Sometimes parathyroidectomy is necessary. Recently, erythropoietin (100 units/kg IV or S.C) demonstrated an antipruritic effect in these patients (36,37). Improvement occurs after transplantation.

Cholestatic pruritus

Pruritus is a well-recognized manifestation among patients with liver diseases and intrahepatic or posthepatic cholestasis. Hepatic diseases leading to pruritus include primary biliary cirrhosis, B and C viral hepatitis, primary sclerosing cholangitis, carcinoma of bile ducts, alcoholic cirrhosis, autoimmune hepatitis and others. The pruritus is generalized and more intense on hands, feet and around tight-fitting clothes, while face, neck and genital area are rarely involved (38). The pathogenesis is still poorly understood, as the precise substance responsible for it is not known. Some authors believe it is caused by the bile acids in the blood (cholemia) or skin (39, 40), but there is a poor correlation between the skin concentration of bile salts and intensity of pruritus. Recently, an elevation of endogenous opioids was found in the blood of these patients (41), and treatment with the opiate antagonist naloxone improved pruritus. The itch in patients with cholemic pruritus can be lessened by treatment with cholestyramine, phototherapy, plasmapheresis which lower or remove the unknown circulating pruritogen; antihistamines can be used as adjuvants. Ursodeoxycholic acid has been used (10-15 mg/kg) with good success. Interestingly, some serotonin subtype-3-receptor antagonists like ondansetron, given intravenously, have been helpful in the treatment of cholestatic pruritus (42). On the other hand, drugs like testosterone, chlorpromazine, oral contraceptive pills, erythromycin, allopurinol, rifampicin can also provoke cholestatic jaundice and pruritus (43, 44).

Pruritus in pregnancy

Generalized pruritus is present in 1-8% of pregnant women (45). This pruritus gravidarum must be differentiated from pruritic dermatoses in pregnancy, such as pemphigoid gestationis (herpes gestationis), papular and pruritic dermatosis of pregnancy and others (46). Pruritus gravidarum was described together with jaundice by Kehrer in 1907 (47). It manifests without any rash mostly in the third trimester of pregnancy, but it may also appear earlier, firstly on the abdomen and then becomes generalized. This symptom usually tends to be worse at night and disappears after delivery (within 1-4 weeks). Probably it is associated with intrahepatic cholestasis, as there is an increase of gamma GT and alkaline phosphatase, and sometimes also of direct bilirubin level in these patients. Pruritus is more frequent in multiple pregnancies and can recur in subsequent pregnancies or during the use of oral contraceptives (48). Severe pruritus can be treated with ursodeoxycholic acid or by induction of delivery at 38 weeks (49).

Pruritus in hematologic disease

Some hematological disorders are known to be associated with pruritus. In polycythemia rubra vera with overproduction of all three hematopoietic cell lines, patients typically experience severe itch located on the trunk, but sparing the face, hands and feet, a few minutes after contact with warm water. Water-induced itching (aquagenic pruritus, or bath itch) can be present in 70% of the patients (50). The itch can last for about 15 minutes to one hour, and be so severe that the patients refuse to bathe. It is caused by release of histamine (51) or other substances from an increased number of basophils in blood; antihistamines do not relieve this symptom, and currently the most effective method to treat it is the use of salicylates, photochemotherapy or interferon alfa (52). In patients with hypochromic anemia, localized or generalized pruritus is also common (53). It seems that iron deficiency is the cause, and treatment with iron abolishes the symptom. In older patients the cause can be a malignant tumour leading to anemia. Interestingly, in patients with hemochromatosis in which the level of iron in blood and tissues is elevated the pruritus may also be present (54). In the last decades pruritus has been described in patients with graft versus host reactions after bone marrow transplantation.

Endocrine pruritus

Pruritus can be a symptom of endocrine disorders. It is present occasionally in diabetic patients. In 1927 Greenwood, studying 500 patients with diabetes, found pruritus in 7% of them (55). The itch can be generalized or more frequently localized in the anogenital area. The pruritus can be linked to neuropathy, candida infections, dry skin, and drug administration. Pruritus vulvae in diabetic women is often associated with poor diabetes control, i. e. elevated glycosylated hemoglobin level in blood. Treatment consists in regulation of diabetes, topical antifungal drugs. In some cases of localized pruritus topical capsaicin can be helpful. Pruritus associated with hyperthyreosis was known from the beginning of the 20th century (56). The mechanism of this pruritus is unclear, perhaps an increase in blood flow and consecutively in skin temperature may be a causative factor. Today, pruritus in patients with mixoedema is rare; if present, it 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. In such cases appropriate treatment is levothyroxin 0.05 mg/day.

Patients with abnormal parathyroid gland activity can also have pruritus. This suggests that secondary increased PTH during renal diseases can have a role in uremic itch, but intradermal injection of this hormone failed to trigger itch (57). Dry skin and cutaneous candidosis probably cause pruritus in patients with primary hypoparathyreoidism (58). Vulvar pruritus can be linked to hormonal deficit in women in the postmenopausal period (59).

Pruritus and malignancy

A number of malignant tumors can cause pruritus (pruritus paraneoplasticus). Carcinoma of the lung, stomach, colon, prostata, breast and pancreatic can rarely be associated with generalized pruritus (60,61). Treatment consists in the surgical removal of the tumor and, in inoperable cases in the use of paroxetine, a serotonin re-uptake inhibitor, or of topisetron, a serotonin antagonist. Lymphomas such as mycosis fungoides and Hodgkin's disease are frequently associated with itch. Goldman and Koh found pruritus in 35% of patients suffering from Hodgkin's disease (62). In Hodgkin lymphoma, pruritus can be for a long time the only symptom before the disease becomes apparent, and it improves after radiation therapy or chemotherapy. In these diseases and in leukemia severe pruritus and excoriations can indicate a poorer prognosis and pruritus may precede recurrences. Pruritus can be the initial symptom of Sézary syndrome, but is rare in leukemia (63,64). It is an important symptom in patients with different form of mastocytosis: solitary mastocytoma, urticaria pigmentosa, teleangiectasia macularis eruptiva perstans, systemic mastocytosis (65). Mast cells (MC) in human's skin are mostly of the MC-tc type, i.e. containing tryptase and chymase, while in the alveoli and gastrointestinal mucosa they are of the MC-c type. This distinction can help to differentiate the skin mastocytoses from the systemic ones (66,67). In carcinoid syndrome pruritus is sometimes associated with flushing. The pruritus is elicited by serotonin, produced in the enterochromaphine cells of the tumor (68). Treatment with antiserotonin drugs alleviates the symptom. Andreev and Petkov have found frequent (17%) associations of pruritus with brain tumors. Interestingly, nasal pruritus was present in about half of the cases (69). The reason of annoying pruritus in patients with tumors is not always understood. It may be triggered by immunological mechanisms, tumor metabolites, iron deficiency, dry skin and other causes. Antihistamines do not relieve it, but it is known that the eradication of the tumor can diminish or abolish itch. In patients with MEN syndrome (Multiple Endocrine Neoplasmas) 2A (Sipple syndrome) a unilateral pruritus over the scapular region, linked to deposition of amyloid can be present (70).

Drugs given for chemotherapy (plant alkaloids, alkylating agents, antimetabolites), and irradiation can also produce pruritus that is generally self-limiting (71-73).

Neurogenic pruritus

In patients with brain diseases (stroke, sclerosis multiplex, brain tumors, abscesses, Creutzfeldt-Jacobi disease and others) severe generalized or localized pruritus sometimes occurs (74-76). Characteristically, the itch occurs in paroxysms and can be unilateral. It is probable that in such cases the pathologic processes provoke an interruption of the descending inhibitory tracts. This is partly confirmed by the treatment with amitriptyline, which is blocking the uptake of serotonin, increases the conduction in the medulla, and alleviates itch (77). Patients with neuropathies complain rather of paresthesias than of pruritus.

Psychogenic pruritus

Psychological factors, such as anxiety, depression, and psychoses, can be the cause of pruritus. In more than 10% of the adults with generalized pruritus is triggered by psychological causes (78,79). A particular form is present in patients with Ebkom syndrome or delusion of parasitosis. In 1937, Ebkom described the

syndrome calling it "Dermatozoenwahn"; it appears typically in elderly people, usually women (80). Zhey often complain about itch and believe that they are infested with some parasites, such as lice, ants, flies, and scratch the skin to eradicate them (81,82). Therapy with pimozide (phenilbutyl piperazine) 2mg/day, an antipsychotic drug, seems to be effective, but psychiatric advise is needed.

Drug-induced pruritus

Finally, the use of some drugs can induce pruritus acting directly on skin structures, or indirectly through iatrogenic hepatotoxicity, or nephrotoxicity. Morphine and opioids were cited above; other known drugs are angiotensine converting enzyme inhibitors, analgetics, vitamin A, contrast media, gold, chloroquine and sulfonamides (83-84). There are a few reports on pruritus caused by infusions of hydroxyethylstarch, used to treat sudden hearing loss. The drug remains for a long time in the dermal macrophages (85). The use of antihistamines is not helpful, so one may assume that histamine does not play a role.

Conclusion

All the anatomical structures involved: the skin, peripheral nerves, central nerve system and various mediators can be influenced by treatment. The therapy can be topical or systemic, symptomatic and causal. In many cases it is necessary to avoid excessive bathing, irritative fabrics, vasodilatation caused by alcoholic beverages, hot liquids or foods, stress, etc.

Internally, one can use antihistamines, sedating or not. The non-sedating include loratadine, astemizole, terfenadine and others. The classic sedating antihistamines are difenhidramin and clorpheniramin, which induce side effects like sedation, slowing the motor skill and somnolence. Phototherapy, cholestyramine, capsaicine and other drugs can be of value, as well as the specific treatment of the internal disease. Useful is also the tricyclic antidepressant doxepin used topically or systemically.

In conclusion, pruritus is a symptom, which should never be underestimated.

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