AAITO POSITION PAPER.
PRURITUS: CAUSES, DIAGNOSTIC WORKUP AND TREATMENT

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§ AAITO Committee for Chronic Urticaria and Pruritus Guidelines:
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Introduction

Definition: Pruritus (itch) can be defined as an unpleasant sensation which causes the urge to scratch.

Pathophysiology: Although itching represents one of the main symptoms in a number of skin disorders and is frequently associated with systemic diseases, its pathophysiologic mechanisms are still partially unclear. Electrophysiologic studies showed that the itch sensation is transmitted through the activation of a subset of specialized nociceptor fibers in the skin and/or in the central nervous system. The non-myelinic C fibers of the skin are characterized by a very slow conduction rate and do not respond to mechanical or thermal stimuli but are extremely sensitive to histamine (1). Moreover, in the skin, these activated "itch receptors" release neuropeptides that may induce local inflammation. In the spine, C-fibers penetrate in the gray substance where they form synapses with secondary neurons which ascend to the thalamus where tertiary neurons of the cerebral sensory cortex turn the itch sensation into a conscious sensation; in this process the Brodman area no. 24 is involved as well (2). In the so-called "central itching" pruritus is perceived in the skin but the sensation originates in the CNS due to malfunction of the nervous pathways involved in the processing of sensitive information.
However, not all authors agree with this view. Greaves at al. (3) assert that specific itch fibers have never been found and that experimental evidence support the existence of very local groups of small fibers in the skin that are intermittently excited. Small-diameter afferent fibers connect to interneurons and synaptic mechanism which in turn produce long-lasting hyper-excitability. They propose that local excitation of small numbers of fine afferents will produce itch, and that disorders or unusual settings of the central inhibitory mechanisms can produce itch even though there is no input from periphery"

Mediators of pruritus

Histamine

The intradermal injection of histamine causes a pruritic wheal-and-flare reaction. Both H1 and H2 receptors are expressed in human skin, although histamine-induced itching involves the former but not the latter receptors. A role for H4 receptors in mediating itch has been demonstrated in mouse but not yet in man (4). H1 anti-histamines are highly effective in inducing a reduction or the remission of itch (5).

However, not all forms of pruritus, including those secondary to renal or hepatic diseases, are relieved by anti-histamines.

Neuropeptides

Activated skin nociceptors release some neuropeptides, including substance P (SP), the vasoactive intestinal peptide (VIP), the calcitonin gene related peptide (CGRP), somatostatin, and neurotensin that cause neurogenic inflammation and itch (6). Low concentrations of SP are present in normal skin; SP levels are much increased in the inflamed skin. The intradermal injection of SP causes pruritus via histamine release from skin mastcells (7). VIP and CGRP do not by themselves cause itching although they can worse itching due to other triggers.

As yet, no substance P antagonists have been introduced in clinical practice and have been tested on pruritus. Capsaicin (the active principle of red pepper) depletes cutaneous nociceptor nerve endings of substance P and alleviates pruritus after repeated topical applications.

Cytokines

Interleukin-2 (IL-2) is considered a strong pruritogenic agent. When administered at high doses to patients with cancer, IL-2 frequently causes erythema and itching (8). Ciclosporin, a potent inhibitor of IL-2, markedly reduces pruritus (9).

Prostaglandins

PGE2 is able to induce pruritus both indirectly via an increase of skin sensitivity to histamine (10) and directly at the conjunctiva (5).

Other vasoactive peptides

Some mast cell-derived peptides, such as trypsin, chimotrypsin, and papain are reportedly able to induce pruritus through direct stimulation of cutaneous nociceptors. The itch induced by these substances is partially controlled by anti-histamines (5).

Some eosinophil-derived mediators such as platelet activating factor are regarded as possibly able to induce pruritus in view of their histamine-releasing activity either direct or mediated by a neurogenic mechanism (11,12).

Central mediators

© Opioid peptides induce pruritus both centrally as a side effect of their analgesic activity and peripherally through their histamine-releasing activity (13).

© High levels of acetylcholine (Ach) are commonly found in patients with atopic dermatitis (14). The intradermal injection of Ach in atopic subjects induces pruritus (14,15) and this mediator seems to play a role in the pathogenesis of the itch that follows baths and showers in AD patients.

© Serotonin (5HT) may regulate itch by binding to 5HT3 receptors. The HT3 antagonist ondansentron has been shown to reduce pruritus associated with cholestatic disorders (16).

Systemic diseases associated with pruritus:

a) Chronic renal failure

b) Hepatic diseases

c) Polycythemia vera: Pruritus appears characteristically some minutes after contact with water and lasts for 15-60 minutes. Platelet-derived mediators are considered as the possible cause of itch in these patients. Moreover, high levels of circulating histamine and acetylcholine are sometimes found in this disease (17).

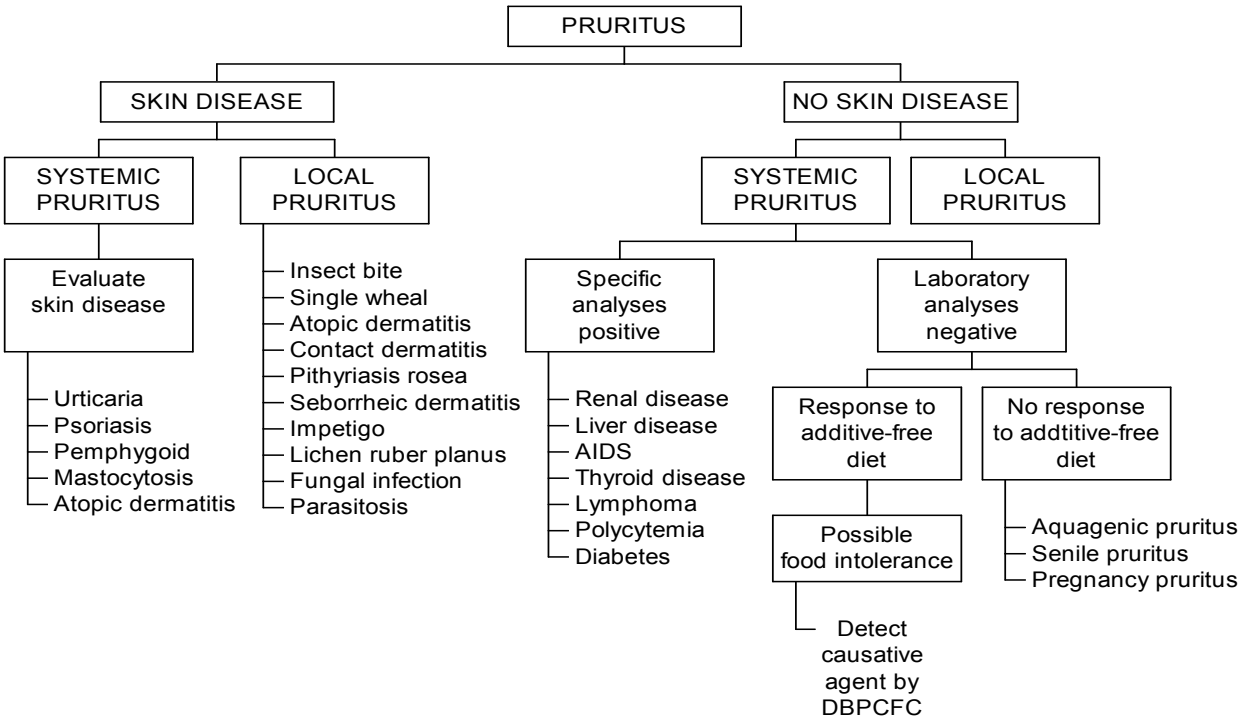
d) Lymphoproliferative disorders, including Hodgkin and non-Hodgkin lymphomas and, in particular Sezary syndrome, may be associated with pruritus (generally nocturnal) (18).

e) Acquired immune deficiency syndrome (AIDS). In HIV-infected subjects pruritus may be idiopathic or be the consequence of skin infections and infestations, cholestasis, seborrheic dermatitis, photodermatitis, drug-induced rashes and lymphoproliferative disorders etc. (19).

f) Thyroid disorders (20).

g) Diabetes mellitus is frequently associated with itching at the anal/genital region (probably due to the presence of yeasts) and at the head (21).
h) Food additives intolerance. Some recent reports show that intolerance to some food additives (particularly nitrates) may present as chronic unremitting pruritus in the absence of any skin eruption (22-24).
Dermatologic diseases associated with pruritus: A number of primary skin disorders are associated with pruritus. The most frequent of them are listed below.
© Atopic eczema.
© Urticaria.
© Psoriasis.
© Skin fungal infections.
© Parasitical diseases.
© Seborrheic dermatitis.
© Pitiriasis rosea.
© Bullous pemphygoid.
© Herpetiform dermatitis.
© Impetigo.
© Mastocytosis.
© Photodermatitis.
© Lichen planus.
© Aquagenic pruritus.
Itching may occur also in normal-looking skin as consequence of reduced water content. This problem is common especially in elderly people and is not associated with systemic diseases.

Diagnostic workup of pruritus
Clinical and laboratory approach to the patient with pruritus.
© Clinical history.
© Accurate physical and dermatological examination.
© Blood investigations: ESR, hemocytometric with differential. BUN, creatinine, glucose, AST, ALT, gammaGT, alkaline phosphatase, LDH, beta 2 microglobulin, TSH, HIV.
© Additive-free diet: 2 weeks are sufficient to establish whether the patient has food intolerance or not. In case of complete response carry out double blind, placebo-controlled challenges with single additives. Additives, timings and doses have been described elsewhere (22-24).
If evidence of skin disorder, appropriate specific investigations.
If evidence of systemic disorder, appropriate specific investigations.



Treatment

In most cases itching is the symptom of a dermatological or a systemic disorder. Therefore, appropriate treatment depends on identification of the etiology. H1 antihistamines represent the mainstay of treatment; older sedating antihistamines may be preferred to obtain maximum relief. Some inflammatory skin disorders may benefit from local or systemic steroids and from immunosuppressive therapy, namely with ciclosporin. The antipruritogenic effect of ciclosporin can be explained by its inhibition of histamine release from mast cells and basophils and of interleukin-2 biosynthesis by T lymphocytes (25). H1 antihistamines provide little or no relief from itching in chronic renal failure and hepatic disorders. Naltrexone, oral activated charcoal, UVB-phototherapy, the 5HT3 antagonist ondansentron and local capsaicin have been used with some benefit in the treatment of renal itch. The definitive treatment in these patients remains however renal transplantation (26). In patients with hepatic disorders, ursodeoxycholic acid, ondansentron and opiate antagonists, such as naloxone, have been shown to relieve pruritus. Liver transplantation again remains the only option to eliminate pruritus in patients with end-stage liver disease (27). In patients with evidence of food additive intolerance, avoidance of foods containing the culprit additive is the only measure to prevent a relapse of pruritus.

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