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Review

Approach to the Patient with Itching

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Abstract

Pruritus is an unpleasant sensation which is found in various dermatologic and systemic diseases. Dermatological investigation is mandatory in conditions with dermal lesions. Severe systemic disorders may be found in patients with pruritus without dermal lesions. For this reason, after a through medical history and examination, laboratory and radiological examinations may be required.

Keywords: Pruritus, itching, systemic disorders, dermatologic disorders

Introduction

Pruritus is an unpleasant feeling that causes an intense desire to scratch the skin. It can be local or general, and acute or chronic. Mechanical effects such as contact, pressure, vibration, wool, and thermal or electrical stimuli may cause itching. Itching is a common symptom, and in addition to the fact that it can be a symptom of many skin diseases, it can also accompany systemic, neurological, or psychiatric diseases (1-3).

Acute pruritus indicates an itching that lasts less than 6 weeks. Longer chronic itching may be tiresome for both the patient and the physician. No etiology can be found in 8%-15% of cases (4).

Generally, chronic itching can be divided into three groups:
Group 1: Itching of the diseased, inflamed skin
Group 2: Itching of intact skin
Group 3: Pruritus in which skin lesions develop due to severe itching

If the cause of itching is known, it can be classified as:

a) Dermatologic diseases-Itching due to a primary skin disease: xerosis, atopic dermatitis, psoriasis, skin infections, cutaneous T-cell lymphoma, etc.
b) Systemic diseases-Chronic kidney, liver, and blood diseases (anemia of iron deficiency, leukemia, lymphomas, Multipl Miyelom, polycythemia vera, lymphoproliferative diseases), malabsorption, malignancies (carcinoid, solid tumors), endocrine diseases (diabetes mellitus, thyroid diseases), menopause
c) Drug reactions (allopurinol, amiodarone, angiotensin-converting-enzyme inhibitors, estrogen, hydrochlorothiazide, hydroxyethylcellulose, opioids, simvastatin)
d) Pregnancy
e) Infection (parasitosis, HIV)
f) Neurological (notalgia paresthetica, brachioradial pruritus, postherpetic neuralgia, multiple sclerosis, abscess, infarct, or tumors)
g) Psychogenic (depression, anxiety, psychogenic excoriation, delusional parasitosis)
h) Mixed-Type of itching (1, 2) in which multiple mechanisms play a role.

According to the European Guideline on Chronic Pruritus, pruritus has been classified as (4)

1) Dermatologic diseases
2) Systemic diseases
3) Neurological
4) Somatoform
5) Mixed
6) Other

Nonspecific skin lesions arise as a result of itching, regardless of the reason that caused it.

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Patient Evaluation

First, it should be investigated whether there is a skin lesion in the patient suffering itching. Systemic, neurological, or psychogenic itching should be considered in the absence of lesions on the skin or in the presence of secondary lesions such as excoriations, hyperpigmentation, or lichenification. Further, it should be investigated whether itching is local or general and whether it is temporary or not. Stimulant factors should be also investigated. It is necessary to question whether the itching appeared before the skin lesion. Scratching the skin due to serious itching can result in excoriations, lichenification, dryness, eczematization, and infections. Bathing excessively and topical treatments can cause dermatitis through contact allergy. These findings should not be interpreted as primary skin lesions. In this respect, the examination of the back region is useful. Here, the presence and quality of lesion may be useful in distinguishing the primary and secondary lesions. Neuropathic or psychogenic itching should be considered in the presence of localized itching without skin lesions. Burning sensation, pain, and loss of sensation can be observed in these patients (2, 4, 5).

While a widespread itching without a sudden onset suggests a systemic disease, a neuropathic origin is considered in localized itching. Complaints related to the thyroid disease, hot or cold intolerance, and systemic complaints such as fever, fatigue, and weight loss may suggest lymphoma, malignancy, paroxysmal pruritus, and multiple sclerosis. Feeling of bugs under the skin may be caused by depression. The itching which is thought to be due to a local, fixed parasite is called delusional parasitosis (2). While evaluating itching in elderly people; especially a relaxation after bath or shower and resumption after a while suggests xerosis. Frequent bathing and rubbing exacerbates itching. Xerosis increases especially in winter and in dry climates. The limbs, torso, hips, armpits, face, and scalp are affected (6).

Using the Itch Severity Index when assessing itching, which is a subjective symptom, may be useful for the patient and treatment evaluation. For this reason, it is useful to question the hours when itching occurs, the patient perception whether it is described as "stinging," "burning," "worrying," or "unbearable," whether it affects work, sleep, sexual function, and finally, whether it causes depression, anxiety, or agitation (7). Table 1 shows the causes of itching, except for dermatological diseases.

Anamnesis

In the history of a patient suffering from itching, the following characteristics should be observed:

- Extent: Widespread, localized, acral involvement
- Characteristics: Burning, pain, numbness, foreign body sensations
- Periodicity: Paroxysmal, continuous, diurnal, nocturnal
- Duration: The number of days, weeks, months, years
- Severity: Mild, moderate, severe, its effect on sleep and daily activity
- Exacerbating factors: Environmental, exercise, occupational factors, bath
- Medical history: History of atopy, known systemic diseases
- Systemic complaints: Fever, weight loss, sweating, jaundice, weakness
- Drugs used: Prescribed, non-prescribed, herbal products, illegal substances
- Social background: Occupation, travel, gender, home and workplace environment
- Whether or not the other people at home and around are suffering from itching
- Whether or not it changes over time
- Which treatments were used and the responses

Whether there was an encounter with a new or different factor (drug, personal care product, animal contact, occupational or hobby-related exposures) should be examined (1, 2, 8, 9)

The presence of itching in people in the same environment suggests scabies and parasitosis. Cholinergic itching related to physical activity that develops after bathing suggests polycythemia vera, myelodysplastic syndrome, metastatic cancer, and hypereosinophilic syndrome; it should point to lymphoma particularly if fever, malaise, and sweating are present; pruritus occurring in the elderly especially in winter should suggest xerosis; itching not affecting sleep at night should suggest somatoform pruritus (4, 10, 11).

The skin temperature, humidity, ecchymosis, petechiae, organomegaly, lymphadenomegaly, and liver disease findings should be investigated in the examination. The skin, mucous membranes, scalp, nails, and anogenital area should be examined. Pigmentation, humidity, fat distribution, yellowness, paleness, color changes in the nails, onycholysis, and skin folds should be especially investigated

Table 1. Causes of itching

Kidney diseases	
Liver diseases	**Neurological diseases**
Primary biliary cirrhosis	Brachioradial pruritus
Hepatitis	Notalgia paresthetica
Cholestasis	Postherpetic neuralgia
	Multiple sclerosis
	Cerebrovascular events
Hematopoietic diseases	**Psychogenic causes**
Polisitemia vera	Depression
Iron deficiency anemia	Psychogenic excoriation
Mastocytosis	Delusional parasitosis
Lymphoma	Anorexia nervosa
Multiple myeloma	
Endocrine and metabolic diseases	**Of infectious and parasitic origin**
Hyperthyroidism	Superficial mycoses
Hypothyroidism	Scabies
Diabetes mellitus	HIV
Carcinoid syndrome	Varicella
	Onchocerciasis
Autoimmune diseases	
Dermatomyositis	
Scleroderma	
Sjogren's syndrome	

upon a skin examination. The eyes should be carefully examined in terms of exophthalmos, paleness, the presence of jaundice, and in terms of any findings that may suggest a systemic disease (1-4). Xerosis is a condition caused by abnormal keratin production and is characterized by a profound reduction of fatty acids, especially in the elderly. It causes itching and subsequently inflammatory skin lesions. The skin is thin and dry. Xerosis may accompany some skin diseases or systemic diseases, but it can also be psychogenic. The skin is observed to be dry, cracked, and peeled. As a result of rubbing and scratching of the skin; irritation and the penetration of peripheral allergens and irritants into the skin; and infection may cause dermatitis. Xerosis is more prominent in cold and dry weather. Frequent bathing and previous illnesses (radiation, kidney, thyroid disease; deficiencies of zinc and essential fatty acids; neurogenic diseases that reduce sweating; antiandrogen drugs and diuretics; HIV; malignancies) create predisposition to xerosis in the elderly (12).

Laboratory examinations should include the following:

- Whole blood count and peripheral spread
- Bilirubin, transaminases, and alkaline phosphatase
- FBS, HbA1c, BUN, and creatinine
- Erythrocyte sedimentation rate
- Calcium and phosphorus
- TS and T4
- Iron and ferritin
- Serum histamine and tryptase levels
- Lung teleradiogram
- Anti-HIV
- Total IgE
- Prick and patch tests

In addition to the tests listed above, hepatitis B and C serologies, protein electrophoresis, serum and urine immunoelectrophoresis, tissue transglutaminase antibodies, parasitological examinations of feces, ANA, and AMA can be requested. Gastrointestinal endoscopies and thoracic and abdominal computed tomography examinations can be performed. An early stage pemphigoid or mycosis fungoides can be identified through the biopsy of the intact tissue and immunofluorescence examination in some cases with diffuse itching without lesions (1-3).

Systemic Diseases that Clinically Cause Widespread Itching

Uremic pruritus

Itching in uremic patients mainly develops due to atrophy of the sweat glands in the skin, liquid shifts in dialysis sessions, and changes in the vitamin A metabolism. Itching is a tiresome complaint that is seen in about 60% of cases. The histamine released from the skin is responsible for the pathogenesis of itching. The allergens against which the patient is sensitized during hemodialysis possibly have an effect on it. Secondary hyperparathyroidism correlates with dry skin due to atrophy of sweat glands, high phosphate levels, dialysis deficiency, elevated magnesium and aluminum, beta-2-microglobulin levels, low albumin levels, anemia and erythropoietin levels, and with the severity of immune dysfunctional itching. Male gender, hypervitaminosis A, neurological diseases, heart failure, and acid presence have also been found to be associated with itching. The hypothesis that uremic itching develops as a consequence of systemic inflammation, rather than a local skin disease, has been suggested. The imbalance in the expression of opioid mu and kappa receptors, increased mu receptor activation, and decreased kappa receptor activity may also play a role. In addition, various pruritogens and histamine release from the mast cells also contribute to itching along with xerosis (13, 14).

Table 2. Drugs that can cause itching

Drug Group	Sample	Mechanism	Frequency
Antiarrhythmics	Amiodarone	Cholestatic	Rare
Antibiotics	Mostly, penicillin and trimethoprim-sulfamethoxazole	Secondary skin lesion/ cholestasis	2%-20%
Anticoagulant	Ticlopidine/heparin	Cholestasis/urticaria	Rare
Antidiabetics	Biguanide/sulfonylurea	Cholestasis /unknown	Rare
Antiepileptic	Carbamazepine, phenytoin	Secondary skin lesion/allergic	Rare
Antihypertensives	Angiotensin-converting-enzyme inhibitors /BB/CCB/methyldopa	Bradykinin increase/ cholestasis /secondary skin lesion	1%-15%/rare
BRAF inhibitors	Vemurafenib	Unknown	19%
Cytokines, growth factors, monoclonal antibodies	GMCSF/Interleukin 2 /matuzumab /lapatinib	Unknown/direct effect/ urticaria	Fairly frequent in GCSF and IL2
Cytostatics	Chlorambucil/paclitaxel/tamoxifen	Secondary to skin lesions/xerosis	Rare/10%/4%
Epidermal growth factor inhibitors	Cetuximab/erlotinib/panitumumab	Unknown	22%/18%/ 58%
Antilipemics	Statins	Unknown/secondary to skin lesions	16%
Monoclonal antibody to CTLA4	Ipilimumab	Unknown	31%
Plasma expanders	Hydroxyethyl starch (HES)	Storage of the HES particles in the nerves	12%-54%
Psychotropics	Tricyclic antidepressants/selective serotonin reuptake inhibitors/neuroleptics	Cholestasis, serotonin receptor activation/ secondary skin lesions	Rare
Others	Antithyroids/nonsteroidal anti-inflammatory drugs /corticosteroids/sex hormones/opioids	Cholestasis/increase in the synthesis of leukotrienes/μ-opioid receptors	Rare/2%-100% in opioids

Uremic itching is especially seen on the back. It can also occur extensively in the arms, head, and neck (14, 15). Its duration is variable. It increases at nights and may disrupt sleeping. While heat and stress increase itching, physical activity, shower, and warm air decrease it. Physical findings are limited, except for the secondary changes created by itching. As a result of repeated scratching, excoriations, lichen simplex, pruritus nodularis, keratotic papules, and follicular hyperkeratosis develop. If there are no cracks or peelings, dry skin may not be noticed. The most common laboratory findings associated with itching are phosphorus, calcium, BUN, and PTH. Kidney disease should primarily be considered as the cause of itching in uremic patients. However, in case of nonresponsiveness to treatment, other causes of itching should be considered. In particular, the associated lymphoma, cholestasis, and hypersensitivity reactions should not be forgotten (14).

Cholestatic pruritus

Cholestasis associated with any reason is accompanied by itching. Itching is expected at a rate of 100% in intrahepatic cholestasis in pregnancy, 80% in primary biliary cirrhosis, between 20% and 40% in primary sclerosing cholangitis (PSC), 45% in malignant biliary obstruction, 20% in chronic viral hepatitis, 17% in benign biliary obstruction, and 7% in liver cirrhosis. Causes such as benign recurrent intrahepatic cholestasis, which is more rarely found, progressive familial intrahepatic cholestasis, Alagille syndrome, biliary atresia, sepsis, cholestasis due to drugs and total parenteral nutrition should also be remembered in patients with cholestasis (2, 16, 17). Although cholestasis-induced itching is explained with increased bile acids, endogenous opioids and with the pruritogenic effect of lysophosphatidic acids on the skin, the mechanism is not fully known (16). In recent studies, the levels of serum autotaxin have been found to be associated with itching severity in cholestatic pruritus, and they decreased along with the response to treatment. Since the positive predictive value of this level is around 70% in the diagnosis of cholestatic itching, it has been reported that it could be the first indicator of itching (18). Bile acids have a stimulating effect on mast cells. Itching may be widespread or local, especially in the palms and soles (4, 15). Its severity is variable and may disappear spontaneously. The severity of itching does not correlate with the underlying disease. It increases at night and with stress. Itching that leads to suicide and affects the quality of life at an advanced level can be seen in some patients. It partially improves in cool weather. Complaints can be overwhelming, especially in premenstrual women. After a long period of itching, secondary lesions are added. Pregnancy cholestasis increases as pregnancy progresses and disappears a few days after delivery. It is seen more frequently in multiparous women, in people who have a history of cholestasis and who have taken oral contraceptives, in those with advanced maternal age, and in winter months. It may show fluctuation in other cholestases. It may require transplantation in some cases due to advanced symptoms and due to the symptoms refractory to treatment (16).

Internal malignancies

The skin sign that accompanies any malignant disease is called paraneoplastic dermatosis. Infiltration of the circulating tumor cells to the skin may be seen. According to the Curth's hypothesis, skin symptoms and malignancy occur simultaneously. The skin also recovers along with the treatment of malignant disease. According to the type of malignancy, a special dermatosis is observed. There is a genetic relationship between the two and the relationship is statistically significant (19). Pruritus can accompany an existing malignancy. It may also have an indirect relationship with the malignant disease (such as a liver malignancy causing cholestasis or a gynecological cancer-causing uremia due to obstruction). It can also be caused by drugs (20). Survival was found to be shorter in malignant cases with severe itching (21).

Metastasis of malignancies into the skin is rare, and unlike paraneoplastic syndromes, it is rare to detect metastatic skin lesions before the primary lesion. However, in the paraneoplastic syndromes, there may be skin symptoms before the detection of internal malignancy (22). Although widespread itching occurs in general, localized itching may also occur. Itching may be seen in testicles in prostate tumors, in nose in brain tumors, in vulva in cervical cancers, and perianal itching may be seen in rectal cancers. Local itching is a sign of worse prognosis in patients with malignancy. Acanthosis nigricans is a velvety-looking picture characterized by hyperpigmentation and hyperkeratosis especially in folded regions, and it has types associated with benign, malignant, and metabolic syndrome. The malignant type is associated with particularly gastrointestinal, lung, and gynecological cancers and with Hodgkin's disease. In acute-onset itching, especially in the presence of multiple seborrheic keratosis, the lesions grow rapidly, and they should be investigated if they increase in number (22). Despite the classic non-itching flushing in intestinal carcinoid, itching is seen in gastric carcinoids (2). Itching is most commonly seen in hematological malignancies. In Hodgkin's lymphoma, an itching that increases especially at night is seen in the lower extremities. It may be the first symptom of the disease and can be observed many years before the development of the disease. Severe itching may also develop in other myeloproliferative diseases and T-cell lymphomas, in mycosis fungoides and Sezary syndrome. Polycythemia vera is characterized by itching related to water. It is more frequently seen in those with the JAK2 mutation (4). Severe itching, burning, and stinging sensation can be seen in the chest, back, neck, and extremities after bathing. In these patients, erythrocytosis-induced skin color may also be noticeable and diagnostic. There is pain along with burning sensation in the distals of extremities. CLL and mastocytosis may also progress along with itching (2). Although the mechanism of itching is not known, it is frequently the iron deficiency regardless of the presence of anemia; in addition, cholestasis-related itching can be observed in hemochromatosis (4, 21).

In hyperthyroidism, one of the endocrinological diseases, while itching is observed due to the activation of vasodilatation and kinin pathways in the skin, pruritus is caused by the dryness of the skin in hypothyroidism. Dermatophyte infections, xerosis, and diabetic neuropathy can cause itching in diabetes mellitus. The first diagnosis of diabetes can be made in an investigation performed because of persistent anogenital itching. Itching may occur due to the mechanisms that are not clear in hyperparathyroidism, which is also one of the endocrinological diseases (2, 4).

Itching is a common symptom in dermatomyositis, one of the connective tissue diseases, and in scleroderma. Usually, itching does not occur in lupus (2).

Itching is a common symptom in HIV infection; it has been reported in 31% of 303 HIV (+) patients. Itching can result from xe-

rosis, seborrheic dermatitis, and dermatophytitis, as well as from lymphoma, liver, and kidney diseases. Eosinophilic folliculitides, which are frequently observed in advanced HIV cases, are itchy lesions (2).

Medicines can cause itching by causing dryness of the skin, as seen in retinoid treatments, or through drug-induced phototoxicity, as observed with doxycycline. Many drugs cause itching without accompanying skin lesions. In Table 2, drugs that can cause itching are presented (2).

Neuropathic itching

Widespread or local itching are seen in most neurological disorders. Neurological itching is accompanied by neuropathic pain and hypersensitivity to stimuli (2, 23).

Brachioradial pruritus, is an itch in the dorsolateral region of the forearm that can spread intermittently or continuously, unilaterally or bilaterally, and can be seen in the arm, neck, and shoulder. A decrease with ice application is helpful in diagnosis. It can occur through the stimulation of C5-C8 nerve roots with the factors such as solar radiation, degenerative diseases of cervical vertebrae, or tumors. In the summer, it is seen more frequently in light-skinned and middle-aged people who participate in outdoor activities.

Notalgia paresthetica is an entrapment neuropathy of the thoracic spinal nerves at the T2-T6 levels. It is caused by the degenerative diseases of the vertebrate. It is a picture accompanied by hyperpigmentation due to unilateral itching in the medial scapula. Sometimes, amyloid deposits can be detected in the skin. Itching may be intermittent and paroxysmal with variable severity. It often creates a stinging, burning, or cold sensation, as if there is a foreign body. It can be unilateral or bilateral (2, 24).

Postherpetic neuralgia

Itching is seen at the lesion site in 30-58% of those who had herpes zoster. It is observed more frequently in the head, face, and neck regions. Itching can occur in acute diseases, as well.

Itching may be seen in multiple sclerosis, cerebrovascular events, and Creutzfeldt-Jakob disease (2).

Psychogenic itching may also be local or diffuse. Itching was found at a rate of 42% in 100 hospitalized psychiatric patients. Excoriation is observed in these cases as a result of intense scratching of the skin. There are scattered, linear, crusted lesions that appear as a result of itching in the regions where the patient is able to reach. Symptoms are associated with stress, conflict, psychiatric illness, and anxiety. Delusional parasitosis is the situation in which the person believes that there is a parasite that actually does not exist (2). It should not be forgotten that there may be symptoms that can emerge with the "nocebo effect," in other words, with placebo effect in drug-provocation tests; thus, itching can be observed frequently (25). Without psychiatric evaluation, the diagnosis of somatoform itching should not be made. The lack of secondary skin lesions in the areas that are not accessible to these patients, in other words, the butterfly sign, also helps the diagnosis (2,4,11). After the severe burns and surgical scars, itching may last for years (26). Psychogenic itching, often diagnosed on the basis of exclusion, is more prevalent in depressive patients and has a negative impact on the quality of life (27).

Local itching

Infectious diseases, allergies, kidney and liver diseases, irritation, aging and dryness of the skin, iron deficiency anemia, contact dermatitis that cause common itching may also cause regional itching (10). Among the local itching types, those related to the anogenital region are especially annoying for the patient.

Anal complaints were reported at a frequency of 20% after telephone conversations in a random community sample. The itch is in this case often attributed to hemorrhoids by the patient. While anal fissures, hemorrhoids, polyps, and cancers were found at varying rates in the etiology of anal itching lasting for more than 6 weeks, no cause was found in 25% of cases. Long-term symptoms are more likely to be malignant. There may be an underlying disease such as psoriasis. In addition, excessive cleaning and the use of local products can increase pruritus. Fecal contamination, dietary factors (tea, coffee, cola, tomato, chocolate, citrus fruits), abscesses, fistulas, fissures, and malignancies of the anorectal region, skin diseases in this region (psoriasis, atopic dermatitis, contact dermatitis, anal squamous cell carcinoma), sexually transmitted infections (condyloma, herpes, syphilis, gonorrhea), candida infections, and enterobius vermicularis can be considered as the reason. Psychogenic anal pruritus, in which no causes can be detected, can also be seen. Changes especially in bowel habits should be examined in patients, and a careful anorectal examination and endoscopic examinations in risky patients should be performed (28). Allergic reactions related to substances used for cleansing of the anal area such as toilet paper, soap, cream, gel, rectal medications, and condoms should be examined. Improper clothing and obesity can also be a factor causing itching (29).

Vulvovaginal pruritus

It is the result of the infection caused by vaginal bacteria, fungi, and trichomonas emerging along with the complaints such as discharge, burning sensation, dysuria, and dyspareunia in women. The causative agent is detected through the medical history and gynecological examination. However, apart from the infections, menopausal and other hypoestrogenic conditions, systemic and local medicines that are used, hygienic products, irritants and allergens, past surgical interventions, relationship, condoms, and chemical preservatives may be the cause of itching. Although they are rarely the cause of itching, localized neoplasms in this region should also be considered (30). A gynecologic examination, and biopsy when necessary, in a patient admitted to the hospital with pruritus of the vulva should be performed (31). Magnetic resonance imaging may also be required if urological examination, patch testing, and neuropathic reasons are considered (32). Allergies caused by seminal fluid are also rare, but they can be seen with clinical pictures ranging from local itching to anaphylaxis (33).

It should not be forgotten that nasal itching along with itching in the throat and eyes is the symptom of allergic rhinitis; however, it can be seen in the central nervous system tumors, and paroxysmal itching may occur in the face in the case of gliomas. In these cases, itching is thought to be due to the increase of xerosis and serotonin (10). Localized itching in the throat may be due to dehydration, drugs, and an excessive use of voice, allergies, and infection.

Itching in Special Patient Groups

Elderly people

The incidence of itching was 11.5% in the elderly in a study conducted in our country, 29% in an American study, 41% in Taiwan, and 48% in Singapore. Pruritus, which causes sleep difficulties and impair the quality of life, has been observed to be less common in independent elderly people. It has been suggested that the most common causes may be dryness of the skin, comorbidities, and drugs (4, 34).

Pregnancy

It should be remembered that approximatey 18% of pregnant women suffer from chronic itching, and in addition to the various pregnancy dermatoses (polymorphic eruption, pemphigoid gestationis, atopic eruptions, etc.), systemic causes such as intrahepatic cholestasis should be taken into consideration. Here, the lesions that are not primary skin lesions, but are caused by scratching, are observed (4, 35).

Postmenopausal period

General and local itching is usually due to atrophic vaginitis, skin dryness, and mucocutaneous candidiasis caused by estrogen deficiency (10).

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