Diagnostic Work-up of the Itchy Patient

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KEYWORDS

• Pruritus • Itch • Diagnosis • Evaluation • Pruriceptive • Neuropathic • Systemic

KEY POINTS

- Itch is a symptom of many dermatologic, systemic, neurologic, or psychiatric disorders.
- Chronic or severe itch has a negative impact on the quality of life of affected individuals.
- The most important and fundamental factor in ultimately diagnosing the cause of itch remains a detailed history and physical examination.
- In the absence of primary inflammation, a work-up for other systemic or neurologic causes may be necessary.

INTRODUCTION

Itch, also called pruritus, is defined as a sensation that provokes the urge to scratch. Pruritus arises commonly in the setting of numerous dermatologic, systemic, neurologic, and psychiatric disorders, affecting all age groups, races, and both genders. Pruritus is considered chronic when symptoms arise regularly for more than 6 weeks. At any given time, approximately 25% to 38% of the general population may be affected by pruritus. Rates of moderate to severe itch may be much higher in specific populations, such as those with inflammatory or allergic skin disease, or individuals with chronic medical disorders (eg, chronic renal failure, cholestasis, or malignancy).[1–3]

Chronic pruritus has a significant and negative impact on patient quality of life. Similar to chronic pain, patients with chronic or severe itch experience reduction in time and quality of sleep, impaired memory and attention, physician-diagnosed depression and anxiety, and social isolation and withdrawal.[4–12]

Because itch is a symptom that may arise in the setting of many conditions and is not itself a singular disease, identifying the cause of a patient's pruritus is often challenging. It is thus important to have a framework for how to approach the diagnostic evaluation of the chronically itchy patient. This article reviews basic pathophysiology of itch signaling, discusses the broad differential diagnosis for chronic pruritic disorders, and outlines an approach to the clinical assessment of patients with chronic itch in the presence or absence of primary skin findings.

ANATOMIC ITCH CLASSIFICATION

Chronic itch is often classified into several subtypes typically reflecting anatomic basis of disease activity. In one scheme proposed by Twycross and colleagues,[13] pruritus subgroups include pruriceptive or dermatologic itch (arising in the skin), neuropathic itch (arising along the neural pathways caused by injury or damage), neurogenic itch (arising from abnormal activation of undamaged nerves because of endogenous or exogenous agents), and psychogenic itch (arising in the context of psychiatric disease). Building on this scheme, the International Forum for the Study of

Disclosure Statement: The author has nothing to disclose.
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Dermatol Clin ■ (2018) ■–■
https://doi.org/10.1016/j.det.2018.02.002

Itch (IFSI) designed a two-tiered classification system that allows a physician to categorize itch based on clinical features alone (in the absence of a known or definitive anatomic target) or once diagnostic data have been obtained that suggest the underlying cause.[14] In the first tier, the IFSI scheme divides itch into three major types based on patient history and physical examination including Group I (pruritus on diseased skin including autoimmune or allergic disorders, drug rashes), Group II (pruritus on nondiseased or noninflamed skin including itch caused by systemic, neurologic, or psychiatric disorders, diseases of pregnancy, and drug-induced itch without a rash), or Group III (pruritus presenting with secondary scratch lesions, such as prurigo nodularis, lichen simplex chronicus, or hyperpigmentation). If clinical evaluation and diagnostic tests suggest a cause for the patient's pruritus, further categorization into one of the following six groups may be possible: (1) dermatologic diseases; (2) systemic diseases including diseases of pregnancy and drug-induced pruritus; (3) neurologic; (4) psychiatric/psychosomatic diseases; (5) mixed, when more than one underlying disease may contribute to itch; and (6) other, when no cause is identified.[14]

DIFFERENTIAL DIAGNOSIS OF ITCH

Itch in dermatologic disease or pruritoceptive itch results from the elaboration of inflammatory mediators in the skin in the setting of allergic diseases, infections, autoimmune or connective tissue diseases, cutaneous neoplasms, and genodermatoses. Commonly encountered primary inflammatory dermatoses that are associated with itch include atopic dermatitis, psoriasis, allergic or irritant contact dermatitis, urticaria, bullous pemphigoid, dermatophytosis, scabies and other infestations, xerosis, and many other conditions. Itch may be localized (as in the case of allergic contact dermatitis) or widespread (as in the case of scabies, atopic dermatitis). In many of the previously mentioned conditions, the presence of primary inflammatory lesions allows for immediate diagnosis by the trained clinician. In some cases, however, secondary changes of the skin may obscure primary lesions and further evaluation may be required.

Generalized pruritus may manifest in the context of numerous systemic diseases, including malignancy, renal and hepatic dysfunction, metabolic and endocrine disorders, infectious syndromes, and as a side effect of systemic medications (**Table 1**). In the IFSI classification, pruritic disorders of pregnancy are also included in this category. The exact mechanism by which such disorders provoke itch is unknown. In general, it is believed that damage, dysfunction, or neoplasia of specific organs results in the production of one or more byproducts that function as pruritogens that directly activate peripheral or central nerves. In some scenarios, acquired dysfunction of the nerves or neuropathy may lead to abnormal sensations of itch, similar to pain. Because of the highly variable nature of how pruritus arises in systemic disease, itch may manifest early in disease and can precede other systemic symptoms (eg, paraneoplastic itch in Hodgkin lymphoma), or may arise late in disease (eg, in chronic kidney disease). When chronic pruritus arises in the setting of systemic disease, only secondary lesions, such as excoriations, lichenification, prurigo nodules, and hyperpigmentation are observed on examination. Occasionally, other cutaneous stigmata of disease may be present and help the clinician hone in on a possible diagnosis (eg, jaundice, palmar erythema, and periumbilical varicosities in the setting of liver failure; acanthosis nigracans in diabetes or metabolic disorders; diffuse petechiae or purpura in the setting of various hematologic malignancies; nail changes in liver or kidney disease).

Itch that results from injury, degeneration, or acquired dysfunction of the afferent pruritoceptive pathways is considered neuropathic in origin (**Table 2**). Examples of neuropathic pruritus include localized pruritus syndromes, such as brachioradialis pruritus, notalgia or meralgia paresthetica, and postherpetic itch. Widespread or generalized neuropathic itch may develop in the context of neurodegenerative disorders, such as multiple sclerosis or because of small fiber neuropathies. Similar to what is observed in systemic itch, clinical findings in patients with neuropathic itch conditions consist of secondary lesions including excoriations, hyperpigmentation, and lichenification. Some systemic diseases may compromise neural pathways resulting in itch and may thus reflect a neuropathic cause. However, because neural compromise in these situations is secondary to another underlying disorder, such itches are currently classified under the systemic rubric.

Individuals with psychiatric or psychosomatic diseases may experience itch, formication and other tactile hallucinations, self-injurious or picking behaviors, and neurotic excoriations. One study estimated that approximately 40% of individuals admitted for inpatient psychiatric care experienced generalized itch.[15] Although skin picking is common in the general population, it frequently accompanies affective and anxiety