

# Itch

Tabi Anika Leslie

## Abstract

Itching (pruritus) is a distressing symptom of many skin diseases, as well as systemic, neurological or psychosomatic disorders. Itching is the sensation defined as the reflex or desire to scratch the skin. Chronic itching has a similar impact on the quality of life as chronic pain. The pathophysiology of itch is implicated in the mechanisms and pathways that are described for pain. Itch is caused by a number of inflammatory chemical mediators in the skin and blood, with involvement of peripheral, as well as central neural mechanisms. Some dermatoses, such as atopic dermatitis, urticaria and lichen planus, are characterized by itch. Itching can be associated with systemic diseases, including renal failure, hepatic disorders, thyroid dysfunction, infections, haematological malignancy and solid tumours. The treatment should be directed at the underlying cause, guided by the history, clinical examination and laboratory findings. Treatments include topical corticosteroids, oral antihistamines, opioid antagonists and phototherapy. The management can be complex and no single therapy is consistently effective. This article summarizes the common causes of itching, including those associated with a rash, with normal skin or skin that has the signs of scratching. Common systemic causes of itch are also discussed with possible treatment options.

**Keywords** antihistamine; atopic; dermatoses; haematological; hepatic; itch; pruritus; renal; thyroid; urticaria

## Introduction

Itching (pruritus) is a frequent symptom of many dermatoses and systemic diseases, as well as some neurological and psychological disorders. Itch is the sensation that leads to reflex scratching of the skin to relieve it, just as pain elicits the withdrawal reflex to remove the cause. It may be acute or chronic (lasting more than 6 weeks) and is an extremely distressing symptom that can be disabling and can impair quality of life.<sup>1</sup> Each patient with itch has to be considered individually as the origins of the symptom are numerous. A recent study showed a high burden of chronic pruritus in the general population.<sup>2</sup>

## Pathophysiology of itch

The pathophysiology of itch is complicated and multifactorial. Itching is caused by a number of complex factors including chemical mediators in the skin and blood. Involvement of peripheral and central neural mechanisms is similar to the pathways described for pain.<sup>3,4</sup> Unmyelinated nerve fibres for itch

## What's new?

- Recent studies show a high incidence and burden of itch in the general population
- Recent data from the International Forum on the Study of Itch suggest that structural questionnaires in addition to visual analogue scales are useful in the assessment of itch
- New mediators have been implicated in itch; therefore combination therapies are important
- New guidelines on management of urticaria recommend up to four times the usual daily dosage of non-sedative H<sub>1</sub> antihistamines
- New European guidelines recommended gabapentin for the treatment of pruritus associated with chronic renal disease and neuropathic chronic pruritus
- Antidepressants may be helpful in treatment due to their sedative properties, although precise mechanisms are still unclear

and pain both originate in the skin with information being conveyed centrally by two distinct systems. However, both use the same peripheral nerve bundle and spinothalamic tract.<sup>5</sup> A number of different types of stimuli can induce itch. Histamine is still the most well-known mediator but other factors include prostaglandins, proteinases, opiates, neuropeptides (substance P), neurotrophins (nerve growth factor) and cytokines (interleukin (IL)-2, IL-31). This explains why not every itch is relieved by antihistamines and why no single therapy is consistently effective.<sup>6,7</sup>

## Classification of itching

A useful clinical approach for patients with chronic pruritus is the clinical classification of itch by the International Forum on the Study of Itch (IFSI).<sup>8</sup> The IFSI classification draws a clinical distinction between patients with itch, depending on whether their skin is normal, primarily inflamed (dermatoses) or associated with lesions secondary to scratching. The underlying disease process can be masked due to excoriations. Chronic itching can result from dermatological and systemic diseases. Itching is present in all patients with certain dermatoses, such as atopic dermatitis, urticaria and lichen planus. Patients with systemic diseases, such as primary biliary cirrhosis, chronic renal failure and Hodgkin's disease, can also present with itch. In patients where no identified underlying disease is detected, the term pruritus of unknown origin is used. The IFSI has recently provided invaluable data on the use of visual analogue scales (VAS) as an assessment tool in routine examinations, although more disease- and population-specific questionnaire validation is recommended for future studies.<sup>9</sup>

Other clinical classifications have been proposed in the past, based on the understanding of peripheral and central origins of itch. The four categories proposed were pruritoceptive itch (due to inflammation), neuropathic itch (post-herpes zoster), neurogenic itch (itch of cholestasis) and psychogenic itch (delusional parasitophobia). This classification is also clinically relevant and informative as to the pathomechanisms of pruritus.

**Tabi Anika Leslie BSc MBBS FRCP** is Consultant Dermatologist at Barnet Hospital and Honorary Consultant at St John's Institute of Dermatology, Guy's & St Thomas' Hospital, London, UK. Competing interests: none declared.

## Causes of itch

### Common dermatoses characterized by itch

The commonest inflammatory dermatoses causing itch include eczema, urticaria, lichen planus, scabies and immunobullous disorders (e.g. dermatitis herpetiformis). Psoriasis can also be associated with itch. To establish the diagnosis, a skin biopsy may be necessary, with histology, and in some cases direct immunofluorescence (as in immunobullous disorders or autoimmune disease) (Table 1).

Dry skin (xerosis) can be itchy, especially in the elderly (senile pruritus, asteatotic eczema), and can result from decreased function of the stratum corneum, polypharmacy or underlying disease (e.g. hypothyroidism).

Urticaria is an example of a cutaneous disease characterized by or associated with itch. It may be spontaneous, inducible and intermittent (Table 2). The history and assessment of the patient is very important as there may be no rash when the patient is seen. Urticaria is managed according to the assessment of the patient by history, clinical examination, and physical or laboratory tests. It can be acute (less than 6 weeks) or chronic (more than 6 weeks). Non-sedating H<sub>1</sub> antihistamines are the preferred treatment for symptomatic relief and current European guidelines suggest increasing the dosage by up to four times the recommended dosage.<sup>10</sup> H<sub>2</sub> receptor antagonists (ranitidine, cimetidine) can be used as well. Montelukast may be used off licence in some individuals with urticaria. Further treatments include immunomodulatory agents such as prednisolone, ciclosporin, methotrexate, mycophenolate mofetil or dapsone. The latest treatment for urticaria unresponsive to second-line treatment is the biologic immunoglobulin E (IgE) receptor antagonist, omalizumab, anti-IgE.

### Classification and common causes of pruritus

#### Dermatological

Most inflammatory dermatoses — *Atopic dermatitis, lichen simplex, lichen planus, urticaria, drug hypersensitivity, scabies, xerosis, mycosis fungoides*

#### Systemic

Hepatic — *primary biliary cirrhosis, biliary obstruction, cholestasis during pregnancy, hepatitis B and C*

Renal — *chronic renal failure, dialysis*

Endocrine — *hypothyroidism*

Malignancies — *lymphoma, myeloma, central nervous system tumours*

Haematological — *polycythaemia rubra vera, paraproteinaemia, iron deficiency*

#### Neurological

*Multiple sclerosis, brachioradial pruritus, notalgia paraesthetica, post-herpetic neuralgia*

#### Psychogenic/psychosomatic

*Parasitophobia*

#### Mixed

*Co-existence of several diseases*

#### Other

*Pruritus of undetermined origin*

Table 1

### Classification of urticaria

#### Spontaneous urticaria

Acute urticaria — *Spontaneous weals <6 weeks*

Chronic urticaria — *Spontaneous weals >6 weeks*

#### Inducible urticaria

Physical Urticaria:

Acquired cold urticaria — *Cold air, water, wind*

Delayed pressure urticaria — *Vertical pressure, weals arising 3–8 hours later*

Heat urticaria — *Localized heat*

Solar urticaria — *ultraviolet or visible light*

Dermographic urticaria, urticaria factitia — *Mechanical shearing forces, weals arising after 1–5 minutes*

Vibratory urticaria, angioedema

#### Other types of urticaria

Cholinergic urticaria — *Increase of core body temperature*

Exercise-induced anaphylaxis, urticaria — *Physical exercise*

Contact urticaria

Aquagenic urticaria — *Water*

Table 2

### Itch and systemic disease

Systemic diseases are frequently associated with itching which can precede the diagnosis of the underlying disease.<sup>11</sup>

#### Pruritus in liver disease

Itching can be a feature of primary biliary cirrhosis, cholestasis (induced by drugs, mechanical obstruction, amyloidosis<sup>12</sup>), hepatitis B, hepatitis C and alcoholic liver disease.<sup>13</sup> Successful treatments include opiate antagonists, bile salt-binding agents, hepatic enzyme inducers and ultraviolet B (UVB) phototherapy.

#### Pruritus in renal disease

Itch is commonly seen in patients with chronic renal disease, especially those undergoing dialysis. The pathogenesis of itch due to uraemia is unknown, but metabolic factors have been implicated (calcium, magnesium, parathyroid hormone, histamine, and tryptase), as well as dysfunction of peripheral or central nerves involved with opioid receptors.<sup>14</sup> Dry skin is also associated with chronic renal failure. Chronic renal failure patients may be treated with erythropoietin, opioid antagonists, thalidomide, parathyroidectomy or UVB phototherapy.<sup>15</sup>

#### Itching in metabolic/endocrine disease

A significant number of patients with endocrine disorders (e.g. thyroid disease, diabetes mellitus) report itching. In hypothyroidism the itch is often associated with dry skin. In diabetes there can be localized anogenital pruritus, which may be caused or exacerbated by mucocutaneous candidiasis. But it is unclear whether diabetes is responsible for generalized pruritus without a rash.

#### Pregnancy

Itching in pregnancy can be due to polymorphic eruption of pregnancy, pemphigoid gestationis, intrahepatic cholestasis or

atopic eruption of pregnancy.<sup>16</sup> These are treated with topical or systemic glucocorticoids and antihistamines. Delivery may alleviate symptoms, but in some cases the itching can persist after childbirth.

### Haematological disorders

Iron deficiency or iron overload (haemochromatosis) can present with pruritus, as can haematological disorders. Polycythaemia rubra vera can be associated with aquagenic pruritus. Other myeloproliferative disorders may also cause itching.

### Itching in malignancy

A number of different malignancies can present with pruritus.<sup>17</sup> Lymphoproliferative disorders are often associated with itch, which may be secondary to toxic by-products or allergic reactions that can directly affect neurones or the brain. Hodgkin's lymphoma leads to itching without a rash, which could be secondary to peptidases, bradykinin, histamine release or increased IgE concentration. Carcinoid syndrome may lead to flushing, diarrhoea, cardiac symptoms and itching.

### Infectious diseases

Infections such as hepatitis can cause itch. HIV disease can result in itch with purpuric, papular and folliculitic lesions.<sup>18</sup> Some infestations, such as scabies or lice, cause generalized itching with widespread evidence of scratching (excoriations). Scalp, finger webs and clothing seams should be closely examined.

### Drug-induced itching

In most cases of drug reactions the itch is associated with a rash, such as urticarial lesions, morbilliform lesions, dryness or phototoxicity. In some cases, only scratch marks are seen, as in cholestasis due to the oral contraceptive pill and phenothiazines. Opiates appear to act centrally and on mast cells, inducing histamine release and itch.

### Neuropathic and psychogenic itching

Multiple sclerosis, cerebral infarctions and brain tumours can all lead to itching. Neurological itch may also be secondary to compression of nerves or spinal damage, as in brachioradialis pruritus and localized chronic itching (following herpes zoster infection). Somatoform pruritus is defined as itching where psychiatric and psychosomatic factors play a critical role in the inflammation, intensity, aggravation or persistence of itching.<sup>19</sup>

## Assessment and investigations

### History

A detailed history of the itch is important, including its duration, onset, frequency, time-course and whether it is localized or generalized. Factors that alleviate or exacerbate itch should be documented, as well as any previous skin disorders or history of atopy. The presence of a rash, the severity and effect on quality of life should be assessed. A full medical, drug and social history is essential.

### Investigation

**Dermatoses with rash:** examination of the skin in generalized pruritus should include the finger webs, nails, scalp and mucosae. Dermographism should be elicited, as well as signs of scratching,

such as excoriations, purpura or bruising. Evidence of chronic scratching may present as lichenification or pigmentary changes.<sup>20</sup> Dermatoses causing itch can be localized or generalized (Table 3).

**Generalized itching without rash:** this can be extremely challenging. A wide variety of disorders are associated with itch, although in many cases no single cause may be identified. Underlying causes should be looked for in the history, examination and tests of these patients to detect a treatable systemic disease. Often the itch can predate evidence or diagnosis of the underlying cause. If no cause for itch can be found (pruritus of unknown origin), psychological disorders, such as anxiety, neuroses and parasitophobia, should be considered.

## Management of itching

While the diagnosis can be difficult to establish, investigation of the underlying cause is important so that the most appropriate and successful therapeutic intervention may be given. Several topical, systemic and physical treatments are available.<sup>21,22</sup> General measures can be beneficial in both primary dermatoses and where the itch is secondary to an underlying cause. These include avoiding heat, allergens and certain drugs, as well as use of emollients and cooling menthol preparations. Soap substitutes and moisturizers prevent loss of water from the skin and form a barrier to irritants. Systemic treatments include oral

## Investigation of common causes of itching

### History

*Establish history of pruritus or rash, identify associated systemic disorders, past medical history including psychiatric disorders, drug history, allergies, family history. Itch may occur without a rash.*

### Examination

*There may be evidence of skin disease or signs of systemic disorders should be looked for, examine all areas - finger webs (scabies), scalp (lice, fungal infection) and mucosae. Look for evidence of urticaria (wheals) symptomatic dermatographism, cholinergic urticaria (small inducible papules) and cold urticaria (ice cube test), should be tested for when suspected from the history.*

### Baseline investigations

*Full blood count, erythrocyte sedimentation rate, iron, serum ferritin, renal function, liver function, thyroid function, blood glucose, chest X-ray*

### Other investigations where appropriate

*Calcium, serum electrophoresis and urine test, stool for ova, cysts and parasites, HIV testing, hepatitis B, hepatitis C, cancer screening, serum C-reactive protein, autoantibodies, antinuclear factor*

### Diagnostic investigation

*Skin biopsy, histopathology and consider direct immunofluorescence*

### Questionnaire assessment

*Visual analogue scales, quality of life measurements*

Table 3

antihistamines (urticaria), and are effective in breaking the itch–scratch cycle (atopic dermatitis) due to their sedative properties.

If topical treatments and antihistamines are not successful, further treatment options include immunosuppressants, such as prednisolone and ciclosporin for inflammatory diseases. Tricyclic (doxepin) and other antidepressants may be useful, but the precise mechanism is not known and they may act through an antidepressant or antineuralgic effect. Paroxetine and other selective serotonin re-uptake inhibitors (SSRIs) may also be helpful. Other neuromodulatory agents, such as gabapentin and pregabalin, have recently been found to be safe and effective in treating itch associated with chronic renal disease and neuropathic chronic pruritus. Phototherapy is useful in itching associated with malignancy and pruritus of unknown origin (Table 4).<sup>23</sup>

## Treatment of itch

### Common topical treatments

#### Emollients

Reduce trans-epidermal water loss by improving barrier function.  
*Aqueous cream, emulsifying ointment, white soft paraffin, hydrous wool fat*

#### Other topical lotions

*Calamine, menthol, capsaicin*

#### Topical corticosteroids

Use in corticosteroid-sensitive inflammatory conditions such as eczema

*1% hydrocortisone (mild), clobetasone butyrate (Eumovate®) (moderate), betamethasone valerate (Betnovate®) (potent), clobetasol propionate (Dermovate®) (very potent)*

### Systemic treatments

#### Antihistamines

Reduce itch in some conditions associated with histamine release or can act as sedative agents to reduce the itch–scratch cycle; H<sub>1</sub> antihistamine and H<sub>2</sub> receptor blockers can be helpful in some conditions, such as urticaria

*Chlorphenamine, loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine*

#### Immunosuppressants

Consider in inflammatory disorders

*Prednisolone, ciclosporin*

#### Antidepressants

May be effective by antihistaminic, antidepressant or antineuralgic effect.

*Tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs)*

#### Other neuromodulatory agents

In chronic renal failure and liver disease

*Gabapentin*

*Opiate ( $\mu$  receptor) antagonist — naltrexone*

### Physical treatments

#### Phototherapy

Used in itching associated with malignancy. Useful in patients with pruritus of unknown origin

*Ultraviolet (UV) A, psoralen UVA*

## Conclusion

Itch is often extremely distressing, affecting the patient's quality of life. Successful management of the itching patient relies on a thorough clinical history, examination, investigation and diagnosis. This allows treatment to be directed towards the underlying cause, resulting in symptomatic relief.<sup>24</sup> Itch can be due to an underlying skin disease or systemic disorder, but in some cases its origin remains unknown. Even when a diagnosis has been established it can be a difficult symptom to treat. No single therapeutic agent is consistently successful in treating itch. Recent advances in mechanisms underlying this common symptom may identify novel targets for future therapy.<sup>25</sup> ◆

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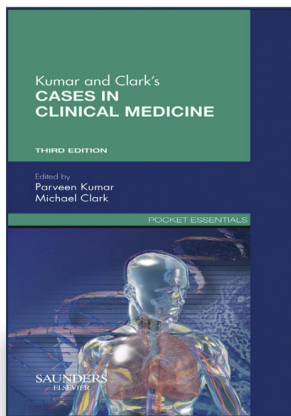
Table 4



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