

Generalised Pruritus: An Etiological Breakup of 700 Patients Presenting to Dermatology OPD of a Local Hospital, Peshawar

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Abstract

Objective: To identify the underlying cause of generalised pruritus in patients presenting to dermatology outdoor excluding pruritic dermatological diseases.

Methodology: This is a cross-sectional observational study conducted on 700 patients from January 2018 to October 2021, in Fauji Foundation hospital Rawalpindi. Patients between the ages of 15 to 69 years visiting the dermatology OPD of the department with complaints of generalised pruritus were recruited for the study after filling the consent form. Clinical investigations (Blood Cp, LFTS, RFTs, TFTs) and past medical history were taken to identify the underlying cause of pruritus was conducted and diagnoses were documented Only the patients who had non dermatological causes were included in the study, and the diagnoses were further categorized as idiopathic, systemic, endocrinological, neurogenic, psychogenic, and drug induced. Results were compiled and analyzed using SPSS version 22.

Results: The results of this study show that 700 participants with a mean age of 47.39, of which 110 were males and 590 were females had generalized pruritus. Out of them, 126 (19%) had pruritus due to chronic renal disease, 119(17%) had chronic liver disease, 63 (9%) had diabetes mellitus, 42 (6%) had paraneoplastic, 126(18%) senile pruritis, 35(5%) had cholinergic pruritus, 21 (3%) iron deficiency anemia. 14(2%) had atopic dermatitis of elderly. Drug induced pruritus 56(8%).

Conclusion: Pruritus without known pruritic dermatoses is a common presenting complaint in patients presenting to outdoors having one of the underlying systemic disease. Further work is needed to evaluate impact of pruritus on quality of life in these already diseased patients.

Keywords: pruritus, systemic disease, generalize, etiology

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Introduction

Pruritus is an itching sensation over the skin that may be localized in response to a local stimulus or generalized due to an underlying condition. Pruritus is a constant urge to itch with or without the presence of the causative agent. It can be caused by dermatological or systemic conditions, iatrogenic or as a normal response to external substances such as parasites generalized pruritus may not be necessarily due to dermatological cause. Various systemic, neurologic, endocrinologic, and psychogenic conditions may have pruritus as a cutaneous manifestation.

Pruritus is defined as an itching sensation or a constant urge to itch over the skin that may be localized in response to a local stimulus or generalized due to an underlying systemic condition. It can be caused by dermatological or systemic conditions, iatrogenic, or as a normal response to external substances such as parasites.¹ Pruritus occurs in response to spinal reflex modulated by the brain and studies show that free nerve endings in the dermis are not only activated by nociceptive stimulus but scratching as well; although both stimuli reach higher centers through separate pathways.

These stimuli activate C fibers that transmit the sensation to

Authorship Contribution: ¹Substantial contributions to the conception or design of the work; or the acquisition, Final approval of the version to be published, ²Data analysis, ^{4,6}Literature review, ^{3,5}Drafting the work or revising it critically for important intellectual content, literature review and drafted the article,

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the spinal cord from where signal is then transmitted to higher cortical centers through the spinothalamic pathway Figure 1.²

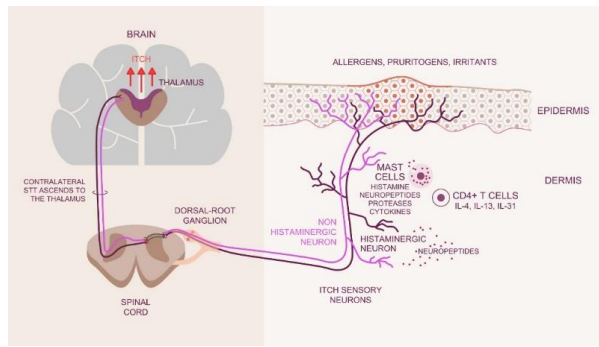


Figure 1. Pathway of Pruritus.

The presence of cytokines like histamine in peripheral circulation and central nervous system enhance the perception of itch. It is seen that some neuropeptides release histamine from mast cells while acting independently. Along with histamine, opioids are also centrally acting pruritic agents increasing itchiness caused by histamine.³ Studies show that long-term pruritus cause lichenification and excoriations that decrease the overall efficacy of skin as a protective barrier. A wide range of the population is affected by pruritus at some stage of life.⁴

Results of a systemic review designed to investigate the epidemiology of pruritus showed that 8.4% population of Oslo had acute pruritus. Another French study show prevalence of pruritus to be 42% in their population whereas another German cross-sectional study confirms pruritus to be prevalent in 17% of the population. This study also showed that prevalence increases with age; from 12.3% in 16-30 years to 20.3% in 61-70 years population.⁵ There are various etiological factors responsible for causing pruritus, however exact pathogenesis of each of their occurrence need further research based on duration of the underlying condition. Pruritus is classified as acute or chronic pruritus but mostly in literature, classification of pruritus depends on the location of the itch i.e. local or generalized.⁴ It is seen in literature and clinical settings that generalized pruritus may not be necessarily due to a dermatological cause. Various systemic, neurologic, endocrinologic, and psychogenic conditions may have pruritus as a cutaneous manifestation. A classification of generalized pruritus proposed by the international forum for the study of itch (IFSI) considering clinical and differential diagnosis with presence of skin changes, categorizes generalized pruritus as figure 2.⁶

- I. Group 1: pruritus on primary diseased inflamed skin; due to inflammatory conditions like infections, autoimmune disease, lymphomas, or drug reaction.
- II. Group 2: pruritus on primary non-diseased, non-inflamed skin; neurologic or psychiatric origin.

III. Group 3: secondary scratch lesions; patients with excoriations, crusts, papules causing a vicious cycle between mechanical stimulus and pruritus, however, this does not determine the origin.

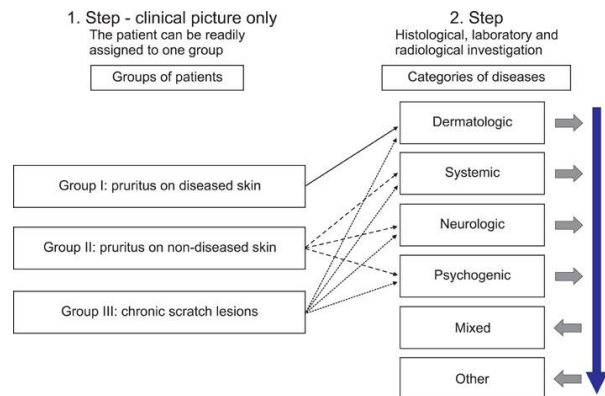


Figure 2. Categories of diseases causing pruritus based on IFSI classification.⁶

In the case of inflammatory skin diseases, pro-inflammatory chemical mediators; histamine, neuropeptide, and eicosanoid are considered as causative agents. A research conducted over 149 populations show that 38.9% had inflammatory eczema, 12.1% had lichen simplex chronicus, 11.4% had a skin infection, 6.7% had psoriasis Vulgaris, 4.7% had urticaria, 2% had drug rash 0.7% had insect bite.⁷ Various systemic diseases also cause pruritus. Pathogenesis of pruritus associated with systemic diseases varies according to the underlying condition. Toxins released from circulating basophils are responsible for pruritus in renal, hepatic and malignant diseases. Whereas, pruritus in lymphomas and leukemias is due to histamine and leukopeptidase released from white blood cells. Release of histamine or bradykinin precursors from solid tumors and serotonin in carcinoid syndrome leads to intractable pruritus. The following figure elaborates on systemic conditions resulting in chronic pruritus as a cutaneous manifestation, Figure 3.⁸

Metabolic and endocrine diseases	<ul style="list-style-type: none"> • Chronic renal insufficiency • Liver diseases with or without cholestasis • Hyperparathyroidism • Hyper- and hypothyroidism • Iron deficiency
Infective diseases	<ul style="list-style-type: none"> • HIV and AIDS • Parasitoses including Helminthosis
Haematological disorders	<ul style="list-style-type: none"> • Polycythaemia vera, myelodysplastic syndrome • Lymphoma e.g. Hodgkin lymphoma
Neurological diseases	<ul style="list-style-type: none"> • Multiple sclerosis • Brain tumors (e.g., gliomas) • Notalgia paresthetica • Brachioradial pruritus
Psychiatric or psychosomatic diseases	<ul style="list-style-type: none"> • Depression • Affective disorders • Hallucinoses • Obsessive and compulsory disorders • Schizophrenia • Eating disorders

Figure 3. Systemic causes of pruritus.

Patients with Hepatobiliary disorders including intra or posthepatic cholestasis, primary biliary cirrhosis, primary sclerosing cholangitis, viral, autoimmune, Hepatitis B and C, bile duct carcinoma, and alcoholic cirrhosis often present with generalized pruritus. Although the precise etiology is still not clear, it is assumed to be caused by regurgitation of bile acids in the blood due to obstruction in biliary channels ie cholemia.

It is relieved by phototherapy, cholestyramine, plasmapheresis, and adjuvant antihistamine.⁹ About 15% of patients with chronic renal insufficiency have intolerable pruritus, reported in generalized or localized form among 50% - 90% of patients undergoing dialysis. Although the exact pathogenesis of uremic pruritus is not known, it is assumed to be caused by multiple factors including iron deficiency, release of histamine, calcium-phosphate metabolism disturbance, secondary hyperparathyroidism, mast cell proliferation, or allergic reaction to products used in dialysis.

Renal pruritus is successfully treated by ultraviolet therapy, emollients, oral activated charcoal, cholestyramine, and phosphate binding agents and in some cases by parathyroidectomy.¹⁰ Iron deficiency is often regarded as a cause of pruritus, even in the absence of anemia as iron loading abolishes this symptom.¹¹ Pruritus is also a prominent manifestation of various endocrine disorders like diabetic mellitus where patients often have generalized or localized pruritus associated with candidiasis or uncontrolled diabetes; expressed as elevated glycosylated hemoglobin blood level. The underlying cause can be neuropathy, dry skin, and drug administration whereas good glycemic control and oral antifungals can reduce generalized pruritus.¹¹

However, topical capsaicin relieves localized pruritus.¹² In the case of thyroid disorders, raised basal body temperature and increased blood flow may cause pruritus in hyperthyroidism, however, pruritus associated with myxedema is rare but is due to dry skin. Autoimmune Thyroiditis and presence of anti-thyroglobulin antibodies also cause pruritus which is treated by levothyroxine. Dry skin and cutaneous candidiasis in primary hyperparathyroidism can cause pruritus although Secondary hyperparathyroidism due to chronic renal failure also trigger intractable pruritus.¹³ Neurological conditions like stroke, multiple sclerosis, brain tumor, and brain abscess may induce severe pruritus which can be generalized occurring in paroxysms and can be unilateral. The treatment with amitriptyline blocks serotonin uptake increasing medullary conduction thus relieving pruritus.¹⁴ Nearly all type of pruritus intensifies in presence of emotional stress, psychological trauma, anxiety, depression, and psychoses whereas 10% of pruritus in adults is triggered by psychological causes.¹⁴

Pruritus can be a side effect of a variety of drugs either due to direct action on skin structures or indirect action through iatrogenic hepatotoxicity or nephrotoxicity.¹² Management of pruritus is a stepwise process based on treating the

underlying cause and application of topical treatment modalities that include symptomatic antipruritic treatment, ultraviolet phototherapy and systemic treatment management guidelines (S2K) for pruritus contain the following steps based on the severity of the condition Table I.¹⁵

Table I; S2K treatment guidelines for pruritus.¹⁵

Step 1	General therapeutic measures, basic moisturizer therapy Initial symptomatic therapy: systemic H1 antihistamines*, topical corticosteroids
Step 2	Symptomatic causative-adapted therapy if the origin is unknown
Step 3	In pruritus of unknown origin or therapy refractory cases in step 2: symptomatic topical therapy, especially in localized forms with, e. g. calcineurin inhibitors, cannabinoid agonists, capsaicin and/or systemic therapy with gabapentin or pregabalin, antidepressants (doxepin, mirtazapine, paroxetine), UV phototherapy, naltrexone, immunosuppressants (cyclosporine)
Concomitant treatment in every Step	Diagnostics and treatment of underlying disease General therapeutic measures In sleep disorders: sedative H1-antihistaminics, tranquilizers, tricyclic antidepressants, or neuroleptics Psychosomatic care, behavioral therapy for scratch behavior In erosive scratch lesions: topical antiseptics, topical corticosteroids

Since pruritus can be due to various reasons, with each having different pathogenesis. It is crucial to identify the underlying cause of pruritus. Although various studies have identified causes of generalized pruritus, they are either based on a certain targeted population or the sample size was not enough to generalize results. Therefore, the purpose of this study is to identify the underlying cause of generalized pruritus in a larger population excluding the established pruritic skin diseases.

Material and Methods

This is a cross-sectional observational study conducted on 700 patients from January 2018 to October 2021, in Fauji foundation hospital Rawalpindi. Patients between the ages of 15 to 69 coming to the OPD of the dermatology department with complaints of generalized pruritus were asked to participate in the study. Those who signed the consent form were included in the study. Clinical investigations (Blood Cp, LFTS, RFTs, TFTs, Chest X Ray) and past medical history were taken to identify the underlying cause of pruritus was conducted and diagnoses were documented. The diagnoses were further categorized as idiopathic, dermatological, systemic, endocrinological, neurogenic, and psychogenic. Results were compiled and analyzed using SPSS version 26.

The number of participants in each category is shown as a cross-tabulation. And demographics are documented in tabular form.

Results

The results of this study show that 700 participants with mean age of 47.39, out of which 110 were males and 590 were females had generalized pruritus and these demographic details are shown in the Table II.

Variable	Participants
Age (year)	
Range	15-69
Mean	47.31
Sex %	
Male	110(15.3%)
Female	590(82.2%)

Out of them, 126 (19%) had pruritus due to chronic renal disease, 119(17%) had chronic liver disease, 63 (9%) had diabetes mellitus, 42 (6%) had paraneoplastic, 126(18%) senile pruritus, 35(5%) had cholinergic pruritus, 21 (3%) iron deficiency anemia. 14(2%) had atopic dermatitis of elderly and drug induced pruritus 56(8%). (Table III)

Cause of pruritus	N(%)
Chronic renal disease	126 (19%)
Chronic liver disease	119 (17%)
Diabetes mellitus	63 (9%)
Hypothyroidism	42 (6%)
Psychogenic P	49 (7%)
Paraneoplastic P	42 (6%)
Senile P	126 (18%)
Cholinergic P	35 (5%)
Iron deficiency anemia	21 (3%)
Atopic dermatitis of elderly	14 (2%)
Drug induced P	56 (8%)

Discussion

The results of our study show that there are various systemic diseases responsible for generalised pruritus: important major systemic causes being diabetes mellitus, chronic renal disease, chronic liver disease, hypothyroidism and senile pruritus. There is less than significant occurrence of pruritus in neurologic and psychogenic conditions. A three-year retrospective study conducted by Franz Sommer, who identified characteristics of underlying disease-causing pruritus, revealed that 41.8% of their 223 participants had some form of dermatosis, 13.3% had systemic disease, including undiagnosed neoplasms, 0.4% had a neurological disorder, and 44.5% did not have any disease.¹⁶

Another study conducted by Muhterem Polat et al to determine the etiology of generalised pruritus by conducting a

prospective controlled study through comparison of clinical data and laboratory parameters showed that of patients having pruritus, 21% had a systemic cause. The underlying diseases included hypothyroidism, chronic lymphocytic leukemia, hepatitis C, hepatitis B, diabetes mellitus, lung cancer, uremia, and iron deficiency anemia. Of these, iron deficiency anemia was the most common cause.¹⁷

Depending on the severity and location of pruritus. There is a significant impact of pruritus on patient's quality of life. A study conducted by Tomasz Hawro et al to identify burden of pruritus on chronic dermatoses patients showed that significant sleep disturbance and lack of productivity at work was reported by patients having moderate to severe psoriasis and suicidal tendency were prevalent in chronic pruritus and atopic dermatitis patients.¹⁸ Numerous medications may cause pruritus as a side effect. This may happen as a direct result of an effect on skin structures or indirectly as a result of iatrogenic nephrotoxicity or liver toxicity.^{12,18} We noted an increase incidence of pruritus in patients taking ACE inhibitors¹⁶ for hypertension, NSAIDs¹⁴ for arthritides, Statins¹⁰ for hypercholesterolemia or ischemic heart disease, calcium channel blockers⁸, chemotherapy⁵ Tramadol³ during previous admission to hospital 3 to 4 months back but intractable pruritus was persistent even after discharge. Szepletowski describes in detail the various mechanisms underlying each class of drugs that cause pruritus.¹⁹

Conclusion

Pruritus without known pruritic dermatoses is a common presenting complaint in patients presenting to outdoors having one of the underlying systemic disease. Further work is needed to evaluate impact of pruritus on quality of life in these already diseased patients.

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