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Etiology of chronic pruritus

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Abstract
Pruritus is considered a very frequent symptom and defined as chronic when its duration is longer than 6 weeks. The prevalence and the etiology of chronic pruritus (CP) are associated with various factors such as, age, atopy, underlying diseases, ethnicity, climate and humidity, as well as access to local healthcare system. The CP significantly affects the patients' quality of life. Over time, patients often report sleep and mood disorders, with a negative psycho-social impact. From skin to brain, pruritus transmission occurs via multiple pathways, which are regulated by numerous cells, mediators, and receptors. A complete history and careful clinical examination are the keys to the diagnostic approach and determining treatment steps. Dermatological examination is essential and sometimes, an extensive laboratory testing must be carried out. The complexity in the presentation of this symptom, its obscure pathophysiology and multifactorial etiology, and the absence of clearly defined therapeutic goals, make CP a diagnostic and therapeutic challenge.

KEYWORDS
chronic pruritus, itch, pruritus, etiology

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1. INTRODUCTION

The definition of pruritus (itch) is: "the unpleasant sensation that causes the desire to scratch" [1]. It is a primary sensory response, through which the Central Nervous System reacts, with complex mechanisms of inflammatory processes and activation of different nerve endings, to internal and external stimuli [2].

Pruritus is a subjective symptom that cannot be "measured" objectively. It is the result of a variety of cutaneous and/or systemic diseases. In terms of its duration, IFSI (International Forum for the Study of Itch), classified pruritus into, acute or chronic (duration more than 6 weeks) [3].

2. EPIDEMIOLOGY

Pruritus is considered a very frequent symptom. It is responsible for approximately 7,000,000 pa-

tients' visits to physicians per year in United States [4].

The prevalence as well as the etiology of chronic pruritus (CP) are associated with various factors such as, age, atopy, underlying diseases, ethnicity, climate and humidity, and the possibility of easy access to the local healthcare system. Different living conditions and migration may play a role in the occurrence of acute and/or chronic itch [5]. However, no cause of pruritus is found in 20% of cases (unknown or undetermined etiology). Pruritus is classified into the 50 most common medical conditions worldwide [6].

The lifetime prevalence of pruritus is estimated at 8-25%. In the elderly and especially in those > 85 years of age, it occurs at a rate of 11.5-25%. CP may also affect the patients' quality of life like chronic pain. Over time, patients often report sleep and mood disorders, with a negative psychosocial impact [7,8]. CP occurs in 100% of patients with urticaria, in 100% with atopic dermatitis, in 80% with psoriasis, in 80-100% with primary biliary cirrhosis and 25-70% of patients with chronic kidney disease [9]. Pruritus also presents in more of 30% of patients with Hodgkin lymphoma [10].

Prolonged and intense pruritus was attributed to underlying systemic diseases and pruritus of unknown etiology, in 132 patients [7]. In the same study, pruritus of the face and scalp was a precursor symptom of psychiatric diseases [7,11]. In general, the frequency of pruritus varies worldwide [12].

3. PATHOPHYSIOLOGY

Over the past few years, the knowledge and perception of the mechanisms of pruritus has shown significant progress. However, this development is limited to animal model studies [13]. Much remains to be elucidated about the pathophysiology of human pruritus. From skin to brain, pruritus transmission occurs via multiple pathways, which are regulated by numerous cells, mediators, and receptors [14].

From skin, pruritus is transmitted through specific nerves: a) unmyelinated C-type fibres and b) myelinated Aδ-type fibres. The cell bodies of those fibres reside to the spinal root ganglia. A complex interaction is developed between nerve fibres and the skin. The pruritus initiation involves the binding of endogenous and exogenous pruritic agents to the receptors of these sensory nerve fibres [14].

Two main families of pruritus receptors have been reported: a) G protein coupled receptors and b) the transient receptor potential channels (TRP channels). TRP channels include TRP vanilloid 1 (TRPV1) and TRP ankyrin 1, and activate sodium channels thus, promoting pruritus signalling [14].

Histaminergic pathways transmit acute itch through histamine secretion from mast cells, basophils, and keratinocytes. After its release, histamine is binding to nerve receptors H1 and H4, and activates TRPV1.

Non-histaminergic pathways result from a variety of nerve receptors that are activated by other mediators [14,15,16].

The cytokines which have been studied in the pathogenesis of pruritus are IL-4, IL-13 and IL-31. The epidermal cells may also release IL-33 and thymic stromal lymphopoietin which can induce itch directly.

Other cytokines, involved in pathogenesis of itch are, IL-17 (in psoriasis) and IL-22. These cytokines may induce pruritus by releasing GRP (Gastrin Releasing Peptide) [17,18,19].

In the pathogenesis of uremic pruritus, the cytokines that have been implicated are, IL-2 and IL-33 [20]. Mediators following those inflammatory cytokines are the intracellular pathways, Janus kinases (JAK). Blocking especially JAK1 can be an interesting therapeutic option due to its role in itch pathogenic pathways [21].

Substance P (SP) and the neuropeptide Calcitonin gene related peptide (CGRP) may also be released from activated sensory nerves provoking neurogenic inflammation and degranulation of the mast cells in dermis. Once released, SP binds to NK1R (neurokinin 1 receptor) which is found on free nerve endings of sensory nerves, keratinocytes, and other immune cells [22,23].

Opioids are also well documented pruritic agents and can bind to μ- and κ-opioid receptors on sensory nerves. Opioid induced pruritus is a result of activation of μ-opioid receptors and its suppression results from activation of κ-opioid receptors [24].

Various proteases can induce pruritus by binding to protease activated receptors, which belong to G protein coupled receptors family. These proteases are: kallikrein, tryptase, trypsin and cathepsin S. Autotaxin, an important enzyme for the generation of lysophosphatidic acid is likely to be involved in the pathophysiology of cholestatic pruritus [24].

Pruritus is transmitted through dorsal root ganglion cells in the posterior horn of the spinal cord. The activated sensory nerves release GRP which binds to the corresponding receptor in the spinal cord [25].

Abnormalities of the spinal cord may cause localized neuropathic pruritus. Diseases of the spine roots have been associated with brachial pruritus, paresthesia notalgia, and paresthesia myalgia [26].

After the spinal cord, pruritus signal ends up in the thalamus and nuclei and on areas of the cere-

bral cortex, via the spinothalamic bundle [27]. The perception of pruritus occurs in the primary and secondary somatosensory cortex, the island of Reil and the cortex of the anterior part of the afferent gyrus. By scratching, areas such as the isle of Reil and the cortex of the anterior part of the afferent gyrus, associated with this unpleasant feeling, are inhibited [14,28]. Scratching achieves the feeling of itch relief by activating areas of the brain's excitatory system that include the striatum and the ventral tegmentum area [29].

3.1. Clinical classification of pruritus

Clinical classification is a very important step to identify CP. According to IFSI there are three groups of patients:

Group I – Pruritus on primary skin lesions (primary diseased or inflamed skin). Causes of itch are cutaneous disorders.

Group II – Pruritus with no skin lesions (non-diseased, non-inflamed skin).

Group III – Pruritus on skin with abrasions as a result of scratching, rubbing or pinching.

The causes of pruritus in patients of groups II and III may be systemic, neurological, psychiatric diseases, mixed or other diseases (itch of unknown origin) [30].

A list of diseases that can cause pruritus are showed in Table I.

Table I

Etiology of Pruritus [3,4,8,12,14,30,31]

Cutaneous Diseases				
Dermatitis / Eczema	• Atopic dermatitis • Contact dermatitis (allergic / irritant) • Dishydrotic eczema • Neurodermatitis • Nummular dermatitis • Photodermatitis • Seborrheic dermatitis • Venous stasis dermatitis • Xerotic eczema	**Autoimmune disorders**	• Bullous pemphigoid • Dermatitisherpetiformis • Dermatomyositis • Epidermolysis bullosa pruriginosa • Linear immunoglobulin A disease • Scleroderma	
Papulosquamous disorders	• Psoriasis • Lichen planus • Pityriasis lichenoides • Pityriasis rosea • Pityriasis rubra pilaris	**Pregnancy**	• Atopic eruption of pregnancy • Intrahepatic cholestasis of pregnancy • Pemphigoid gestationis • Pruritic urticarial papules and plaques of pregnancy	
Infections	• Folliculitis • Fungal Infections • Impetigo • Insect bites • Pediculosis (lice infestation) • Scabies • Viral infections	**Genodermatoses**	• Darier disease • Hailey-Hailey disease • Ichthyosis • Sjögren-Larsson syndrome	
Malignancies	• Basal cell carcinoma • Bowen disease • Cutaneous T-cell lymphoma • Cutaneous B-cell lymphoma • Leukemia cutis • Paget disease • Squamous cell carcinoma	**Others**	• Anal Itching • Aquagenic pruritus • Cutaneous mastocytosis • Drug eruptions • Erythrotherma • Intertrigo • Grover disease • Kyrle disease • Lichen simplex chronicus • Lichen sclerosus and atrophicus Miliaria rubra	• Pigmented purpura (Capillaritis) • Polymorphic light eruption • Postburn pruritus • Prurigo nodularis • Reactive perforating collagenosis • Senile pruritus • Scars, keloids • Urticaria • Xerosis (Dry skin) • Wells syndrome

Systemic Diseases

Hematologic diseases	• Hemochromatosis • Iron deficiency anemia • Mastocytosis • Plasma cell dyscrasias • Polycythemia vera	**Metabolic & Endocrine diseases**	• Carcinoid syndrome • Diabetes mellitus • Hyperthyroidism • Hyperparathyroidism • Hyperphosphatemia • Hypothyroidism • Malabsorption • Perimenopausal pruritus
Hepatobiliary diseases	• Biliary cirrhosis • Chronic pancreatitis • Drug-induced cholestasis • Hepatitis C • Sclerosing cholangitis	**Malignancies**	• Leukemia • Lymphoma (Hodgkin, non-Hodgkin) • Multiple myeloma • Paraneoplastic syndromes secondary to solid tumors • Plasmacytoma • Solid tumors (cervix-prostate-colon etc.)
Infectious diseases	• HIV • Infectious hepatitis • Parvovirus B19 Infection • Prion diseases • Parasitic infections: ➢ Ascariasis ➢ Filariasis ➢ Helminthiasis ➢ Onchocerciasis ➢ Schistosomiasis ➢ Trichinosis	**Others**	• Drug-induced pruritus • Fibromyalgia • Pruritus of unknown origin • Swimmer's itch • Sjögren syndrome • Weight loss (rapid) in eating disorders
Renal diseases	• Chronic kidney disease – associated pruritus		

Neurological Diseases

• Anogenital pruritus • Brachioradial pruritus • Cerebral abscess • Cerebral tumor • Creutzfeldt-Jakob disease • Multiple Sclerosis • Neuropathic itch	• Notalgia paresthetica • Post-herpetic neuralgia • Poststroke • Scalp dysesthesia • Small fiber neuropathy • Vulvodynia

Psychiatric Diseases

• Anxiety • Bipolar disorder • Delusional parasitosis • Depression • Drug abuse (opium, cocaine, amphetamines)	• Neurotic excoriations • Obsessive - compulsive disorder • Schizophrenia • Somatoform disorders

4. APPROACH

A complete history and careful clinical examination are the keys to the diagnostic approach and determining management and treatment steps. Dermatological examination is essential and should include skin, scalp, genitalia, perineal area, mucous membranes, and nails.

Dermatologist should differentiate primary skin lesions from lesions secondary to scratching, such as excoriations, lichenification, pruritic nodules, etc, which may point out a probable underlying non - dermatologic etiology [31].

Pruritus characteristics such as, duration, location, mode of onset, time of appearance, form and triggering factors must be considered for the correct diagnosis. More information such as medication, personal and family history, pets, etc. must also be reported from the patient. In patients of groups II and III (IFSI), extensive laboratory testing must be carried out [30].

Pharmacologic and non-pharmacologic treatments are available in patients with CP.

Non-pharmacologic interventions for the pruritus relief, are useful. Regardless itch etiology, all patients should undergo proper skin hygiene

and elimination of potential itch triggers. The use of gentle cleansers (pH 5.5) while bathing and moisturizing creams or lotions, at least once daily, are recommended. Bath water should ideally be lukewarm. Muscle relaxation techniques have been shown to relief itch by decreasing stress. Comfortable, light clothes and nail clipping are suggested to avoid traumas from scratching [32].

5. CONCLUSION

Pruritus is produced mainly through histaminergic and non-histaminergic pathways. It is transmitted from skin, through the nerve fibers of unmyelinated C-type fibers and myelinated A-type fibers. The regulation of itch transmission from skin through spinal cord to the certain areas of brain is achieved by a cooperation between the immune and nervous systems. However, the exact pathogenetic mechanisms from various underlying disorders remain unclear.

CP can be associated with skin diseases or numerous underlying diseases of systemic, neurologic or psychiatric origin. Itch of unknown origin accounts approximately for 20% of CP cases. The presence of primary or secondary skin lesions is important in distinguishing between dermatologic and non-dermatologic causes. Localized pruritus is treated with topical treatment, generalized pruritus requires diagnostic approach and systemic treatment.

Due to the complexity in the presentation of this symptom, its obscure pathophysiology and multifactorial etiology, and the absence of clearly defined therapeutic goals, CP remains a diagnostic and therapeutic challenge.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. Rothman S. Physiology of itching. *Physiol. Rev* 21(2):357-81 (1941). **https://doi.org/10.1152/physrev.1941.21.2.357**

2. Ikoma A., Steinhoff M., Stander S., Yosipovitch G., Schmelz M. the neurobiology of itch. *Nat Rev Neurosc* 7(7):535-47(2006). **http://dx.doi.org/10.1038/nrn1950**

3. Stander S., Sun Y.G., Schmelz M. Editorial: Pruritus *Front Med* (Lausanne) 8:763667 (2021). **https://doi.org/10.3389/fmed.2021.763667**

4. Roh Y.S., Choin J.C., Sutaria N., Shawn G.K. Itch: Epidemiology, clinical presentation, and diagnostic workup. *J Am Acad Dermatol* 86(1):1-14 (2022). **http://dx.doi.org/10.1016/j.jaad.2021.07.076**

5. Weisshaar E. Itch: A global problem? *Front Med* (Lausanne) 8:665575 (2021). **doi: 10.3389/fmed.2021.665575**

6. Hay R.J., Johns N.E., Williams H.C., Bolliger I.W., Dellavalle R.P., Margolis D.J., Marks R., et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 134(6):1527-34 (2014). **http://dx.doi.org/10.1038/jid.2013.446**

7. Whang K.A., Khanna R., Williams K.A., Mahadevan V., Semenov Y., Kwarta S.G. Health-Related QOL and Economic Burden of Chronic Pruritus. *J Invest Dermatol* 141(4):754-60. e1 (2021). **http://dx.doi.org/10.1016/j.jid.2020.08.020**

8. Dalgard F.J., Svensson A., Halvorsen J.A., Gieler U., Schut C., Tomas-Aragones L., et al. Itch and Mental Health in Dermatological Patients across Europe: A Cross-Sectional Study in 13 Countries. *J Invest Dermatol* 140(3): 568-73 (2020). **http://dx.doi.org/10.1016/j.jid.2019.05.034**

9. Weisshaar E., Szepietowski J.C., Dalgard F.J., Garcovich S., Gieler U., Gimenez-Arnau A.M., et al. European S2k Guideline on Chronic Pruritus. *Acta Derm Venereol* 99(5):469-506 (2019). **http://dx.doi.org/10.2340/00015555-3164**

10. Bartus C.L., Parker S.R. Hodgkin lymphoma presenting as generalized pruritus in an adolescent. *Cutis* 87(4):169-72 (2011).

11. Weiss M. Mettang T., Tschulena U., Weisshaar E. Health-related quality of life in haemodialysis patients suffering from chronic itch: results from GEHIS (German Epidemiology Haemodialysis Itch Study). Qual Life Res 25:3097-106 (2016). **http://dx.doi.org/10.1007/s11136-016-1340-4**

12. Weisshaar E. Epidemiology of itching. *Curr Probl Dermatol* 50:5-10 (2016). **DOI: 10.1159/000446010**

13. Pan H., Fatima M., Li A., Lee H., Cai W., Horwitz L., et al. Identification of a Spinal Circuit for Mechanical and Persistent Spontaneous *Itch Neuron* 103(6):1135-49 (2019).**http://dx.doi.org/10.1016/j.neuron.2019.06.016**

14. Sutaria N., Adawi W., Goldberg R., Roh Y.S., Choi J., Kwarta S.G. Itch: Pathogenesis and treatment. *J Am Acad Dermatol* 86(1):17-34 (2022). **http://dx.doi.org/10.1016/j.jaad.2021.07.078**

15. Wang F., Trier A.M., Li F., Kim S., Chen Z., Chai J.N., et al. A basophil-neuronal axis promotes itch. *Cell* 184(2):422-40. e17 (2021). **DOI: 10.1016/j.cell.2020.12.033**

16. Meixiong J., Anderson M., Limjunyawong N., Sabbagh M.F., Hu E., Mack M.R., et al. Activation of Mast-Cell-Expressed Mas-Related G-Protein-Coupled Receptors Drives Non - histaminergic Itch. *Immunity* 50(5):1163-71. e5 (2019). **http://dx.doi.org/10.1016/j.immuni.2019.03.013**

17. Lou H., Lu J., Choi E.B., Oh M.H., Joeng M., Barmettler S., et al. Expression of IL-22 in the Skin Causes Th2-Biased Immunity, Epidermal Barrier Dysfunction, and Pruritus via Stimulating Epithelial Th2 Cytokines and the GRP Pathway. *J Immunol* 198(7): 2543-55 (2017).
http://dx.doi.org/10.4049/jimmunol.1600126

18. Oetjen L.K., Mack M.R., Feng J., Whelan T.M., Niu H., Guo C.J., Chen S., et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. *Cell* 171(1):217-28 (2017).
http://dx.doi.org/10.4049/jimmunol.198.supp.63.3

19. Wongvibulsin S., Sutaria N., Kannan S., Alphonse M.P., Belzberg M., Williams K.A., et al. Transcriptomic analysis of atopic dermatitis in African Americans is characterized by Th2/Th17-centered cutaneous immune activation. *Sci Rep* 11(1):11175 (2021).
http://dx.doi.org/10.1038/s41598-021-90105-w

20. Belzberg M., Alphonse M.P., Brown I., Williams K.A., Khanna R., Ho B., et al. Prurigo Nodularis Is Characterized by Systemic and Cutaneous T Helper 22 Immune Polarization. *J Invest Dermatol* 141(9):2208-18 (2021).
DOI: 10.1016/j.jid.2021.02.749

21. Kwatra S.G. Breaking the Itch-Scratch Cycle in Prurigo Nodularis. N. Engl. J. Med 382(8):757-8 (2020).
http://dx.doi.org/10.1056/nejme1916733

22. Azimi E., Reddy V.B., Pereira P.J.S., Talbot S., Woolf C.J., Lerner E.A. Substance P activates Mas-related G protein-coupled receptors to induce itch. *J Allergy Clin Immunol* 140(2):447-53 (2017)
http://dx.doi.org/10.1016/j.jaci.2016.12.980

23. Skoff A.M., Adler J.E. Nerve growth factor regulates substance P in adult sensory neurons through both TrkA and p75 receptors. *Exp Neurol* 197:430–6 (2006).
http://dx.doi.org/10.1016/j.expneurol.2005.10.006

24. Melo H., Basso L., Iftinca M., MacNaughton W.K., Hollenberg M.D., McKay D.M., Altier C. Itch induced by peripheral mu opioid receptors is dependent on TRPV1-expressing neurons and alleviated by channel activation. *Sci Rep* 8(1):15551 (2018).
http://dx.doi.org/10.1038/s41598-018-33620-7

25. Mishra S.K., Hoon M.A. The cells and circuitry for itch responses in mice. *Science* 340(6135):968-71 (2013).
http://dx.doi.org/10.1126/science.1233765

26. Ross S.E., Mardinly A.R., McCord A.E., Zurawski J., Cohen S., Jung C., et al. Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mu¬tant mice. Neuron 65(6):886-98 (2010).
http://dx.doi.org/10.1016/j.neuron.2010.02.025

27. Mu D., Deng J., Liu K.F., Wu Z.Y., Shi Y.F., Guo W.M., et al. A central neural circuit for itch sensation. *Science* 357(6352):695-9 (2017).
DOI: 10.1126/science.aaf4918

28. Papoiu A.D.P., Nattkemper L.A., Sanders K.M., Kraft R.A., Chan Y.H., Coghill R.C., et al. Brain's Reward Circuits Mediate Itch Relief. A Functional MRI Study of Active Scratching. *PLoS one* 8(12): e82389 (2013).
http://dx.doi.org/10.1371/journal.pone.0082389

29. Setsu T., Hamada Y., Oikawa D., Mori T., Ishiuji Y., Sato D., et al. Direct evidence that the brain reward system is involved in the control of scratching behaviors induced by acute and chronic itch. *Biochem Biophys Res Commun* 534:624-31(2021).
http://dx.doi.org/10.1016/j.bbrc.2020.11.030

30. Stander S., Weisshaar E., Mettang T., Szepitowski J.C., Carstens E., Ikoma A., Bergasa N.V., et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol* 87:291-4 (2007). **http://dx.doi.org/10.2340/00015555-0305**

31. Lipman Z.M., Ingrasci G., Yosipovitch G. Approach to the Patient with Chronic Pruritus. *Med Clin North Am* 105(4):699-721 (2021).
http://dx.doi.org/10.1016/j.mcna.2021.04.007

32. Mack M.R., Kim B.S. The Itch-Scratch Cycle: A Neuroimmune Perspective. *Trends Immunol* 39(12): 980-91 (2018). **DOI: 10.1016/j.it.2018.10.001**