

Gaining a comprehensive understanding of pruritus

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ABSTRACT

Pruritus is a common symptom associated with many dermatoses, systemic abnormalities, and psychiatric / psychosomatic diseases. Additionally, pruritus is one of the most intractable symptoms due to its complex pathogenesis involving an increasing number of mediators and receptors, undefined neurophysiologic pathways, unclear cerebral processing, and psychophysiology interaction. Clinically, the first challenge of dermatologists is how to get general and interdisciplinary vision of pruritus and to preliminarily figure it out whether there might be underlying systemic or psychosocial disorders. The second challenge is to select efficient individual tailored anti-pruritic treatment, which includes targeted drugs and cognitive-behavioral therapy.

Key words: Classification, pruritus, pathogenesis, treatment

INTRODUCTION

Pruritus or itch refers to an uncomfortable sensation and emotional experience associated with an actual or perceived disturbance to the skin that provokes the desire to scratch.^[1] Chronic pruritus and induced scratching behavior could have a significant impact on disease course, life quality, and healthcare costs.^[2]

Though common and important, pruritus has not received much interest until the current decade, and management of pruritic conditions is still a challenge for physicians due to its multifactorial causes and complex pathophysiology. Here, we highlight a comprehensive way of understanding pruritus, including new findings on pathogenesis of pruritus, fast-emerging pruritic mediators and receptors, pathological interaction between pruritus and psychosomatic cofactors, and firstly put forward a psychosomatic cofactors-pruritus-psychiatric comorbidity cycle.

PATHOGENESIS OF PRURITUS

Pruritus is a complex process provoked by exogenous or endogenous, localized or systemic pruritogenic stimuli (chemically, electrically, mechanically, thermally, and/or psychologically). The stimuli act directly as or cause the release of peripheral or central pruritogens from various intracutaneous cell types or specific subtypes of peripheral nerve endings. After pruritogens binding with their relevant receptors, the signal generated is relayed by subsets of C fibers and second-order neurons expressing gastrin-releasing peptide receptor (GRPR) as well as spinothalamic track (STT) neurons in the spinal cord.^[3] These spinal neurons form their own transmission pathway from dorsal horn to the ventrocaudal part of the nucleus medialis dorsalis (MDvc)^[4] in the thalamus, which eventually project the electrochemical information (including stimulus intensity and location) to certain brain areas: Anterior cingulate cortex, insular cortex, primary and secondary somatosensory cortices,^[5] and some motor areas^[6] resulting in the perception of itch and an acute or chronic scratch response. Acting on any factor along the pathway of transmission of itching sensation could cause pruritus. On the other hand, psychophysiological factors could profoundly influence pruritus.

Briefly speaking, pruritus can be intracutaneous or central pathomechanisms or both. And, chronic

Access this article online

Quick Response Code:



Website:

www.ijdv.com

DOI:

10.4103/0378-6323.100516

PMID:

22960808

How to cite this article: Zhang H, Yang Y, Cui J, Zhang Y. Gaining a comprehensive understanding of pruritus. Indian J Dermatol Venereol Leprol 2012;78:532-44.

Received: October, 2011. **Accepted:** June, 2012. **Source of Support:** Nil. **Conflict of Interest:** None declared.

pruritus is always associated with central mechanism and exacerbated by itch-scratch cycle.

Pruritus and pain share many similarities. Recently, it was found that GRPR is an itch-specific gene in the spinal cord. GRPR⁺ neurons, different from the spinothalamic tract (STT) neurons (mediate both pain and itch sensation), confer the specificity of itch sensation mediated by glutamate.^[7] This may elucidate how pruritogens—received by cutaneous sensory receptors, relayed by primary afferents, and discriminated and transmitted by the spinal cord—are ultimately perceived by the brain as pruritus, which could distinguish itself from pain.^[8]

MEDIATORS AND RECEPTORS

Pruritogens, also known as itch mediators, could induce an itch after being generated within or exposed to the skin. Pruritogens^[9-12] act peripherally, centrally or both, and their receptors have been found in various intracutaneous cell types, peripheral and central nerves, as well as sensory neurons [Table 1]. Conventional dermatological therapies are mostly symptomatic and lack in efficacy. The fast-emerging pruritogens (e.g. interleukin-31^[13,14] autotoxin^[15]) and receptors [(histamine H4-receptor^[16] neurokinin-1 receptor (NR1-R)] serve as potential therapeutic targets for the development of imminent novel anti-pruritic drugs [e.g. interleukin-31 inhibitors, histamine H4-receptor antagonists, clonidine,^[17] PI3Kγ inhibitor AS605240,^[18] Cholecystokinin7S (CCK7S) and CCK8S,^[19-21] aprepitant.^[22]

CLASSIFICATION OF PRURITUS

Differentiation and an early accurate diagnosis of pruritus subtypes are imperative for revealing the underlying disorders and choosing targeted treatment. For differential diagnostic purposes, a classification of 6 categories of pruritus is proposed^[23]: Category I: Dermatological diseases; Category II: Systemic diseases including diseases of pregnancy and drug-induced pruritus; Category III: Neurological; and Category IV: Psychiatric / psychosomatic diseases. Category V: Mixed overlapping and coexistence of several diseases; Category VI: Undetermined origins.

What are the features of each subtype of pruritus and how to diagnose them are the initial questions.

CATEGORY I: PRURITUS FROM DERMATOLOGICAL DISEASES

Pruritus is the most common accompanying symptom of many dermatological diseases, such as inflammatory diseases [e.g. atopic dermatitis (AD), psoriasis, urticaria], infectious diseases (mycotic, bacterial and viral infections, scabies, pediculosis, insect bites, folliculitis), autoimmune diseases (e.g. dermatitis herpetiformis, bullous dermatoses), neoplastic disorders (cutaneous T-cell lymphoma, cutaneous B-cell lymphoma, and leukemic infiltrates), and genodermatoses (e.g. ichthyosis vulgaris, Netherton syndrome).^[23,24]

Mechanism

Pruritus is generated in the epidermis and papillary dermis on nociceptors of unmyelinated C-fibers.^[25]

Many receptor systems are functionally expressed on these afferences. Moreover, many intracutaneous cells (keratinocytes^[26]) and immune cells (mast cells,^[27] eosinophils^[28]) in the skin express a number of pruritus-associated receptors and could release inflammatory and pruritogenic substances under stimulation and finally lead to pruritus. These mechanisms are normally associated with pruritus caused by inflammatory, autoimmune, and neoplastic dermatological diseases, which are mostly characterized by chronic and severe pruritus. Recently, more mediators associated with AD, psoriasis, prurigo nodularis and lichen simplex chronicus have been elucidated [Table 2].

Diagnosis

Diagnosis is dependent on specific skin lesions (predisposing cause, timing of onset, location, morphology, and quality). Skin examination, dermatographism, microscopic examination, and skin biopsy are sometimes needed. The diagnosis of pruritus with non-specific skin lesions may be difficult. Detailed medical history, system review, and a complete physical examination aimed at detecting information and signs suggestive of underlying systemic cause should be performed.^[24]

Management of pruritus from dermatological diseases

Because of long duration and a frequent combination of psychological factors and itch-scratch cycle, chronic pruritus (e.g. AD and psoriasis) caused by inflammatory, autoimmune, and neoplastic dermatological diseases is quite challenging. In order to adopt more efficacious

Table 1: Pruritogens, corresponding receptors and treatment modalities

Pruritogen	Site and Receptors	Treatment modalities
	Skin and Peripheral nervous system	
Ach	Nicotinic receptor (nAChR) Muscarinic receptor (mAChR)	Botulinum toxin (subcutaneous and topical)
CCK7S and CCK8S	CCK receptor	-----
CGRP	CGRP receptors	-----
Chloroquine	Mas-related G-protein-coupled receptor	-----
CRH and POMC	CRH-R1 and -R2 (through nerve growth factor and neuropeptide Y)	Tanezumab, Psychological management (Behavior feedback or psychotropic agents)
Cytokines (e.g. IL-1,2,6,8,31)	Cytokine receptors	Anti-IL-31 antibody
Endocannabinoids	Cannabinoid receptor (CB1, CB2) CB1: anandamide, CB2: PEA	Fatty acid amide hydrolase inhibitors: URB597 (KDS-4103) (centrally active); URB937 (peripherally-restricted)
Endothelin	ET receptors (ETA, ETB)	-----
Endovanilloids	TRPV1 TRPV3	8% Capsaicin (Qutenza), Tacrolimus ointment -----
Histamine	H1, H3, H4 histamine receptor	Topical Antihistamines Systemic: First/second/third generation Antihistamines JNJ-7777120 (promising H4 antagonist)
Kallikreins (cathepsin S, trypsinase)	PARs (proteinase-activated receptor serine proteases, cysteine protease)	Antibodies: - SAM-11,- P2pal-2135 Antagonists: ENMD-106836, Tetracyclines, AS605240
Kinins	Bradykinin receptors (B1R, B2R)	B2R antagonists
Leukotriene B4	Leukotriene receptors	Leukotriene receptor-antagonists such as: Zafirlukast, zileuton, Montelukast
Neurotrophins (NTs) (e.g. NGF and BDNF)	High-affinity receptor: Trk Low-affinity receptor: NTR	Trk inhibitors:K252a, AG879 NGF antibody: Tanezumab
Opioids	μ -opioid receptor κ -opioid receptor	Methylnaltrexone, Alvimopan Asimadoline, SA14867, ICI
Prostanoid (PGD2, PGE2,TA2)	Prostanoid receptors	Topical Salicylic Acid
	Peripheral/central nervous system	
Opioids	MOR: μ -opioid receptor KOR: κ -opioid receptor	Topical antagonist: 1% Naltrexone cream Systemic: Naloxone, Naltrexone, Nalmefene, Butorphanol, Nalbuphine Topical: Butorphanol (liposomal formulation) Systemic: Bremazocine, GR8969649, Nalfurafine, Butorphanol and Nalbuphine
	Spinal cord	
Bombesin/ Glutamine/ GRP	GRPR	-----
PAR-2 activating peptide	Bradykinin receptor-1 and -2	
Histamine	Histamine receptor-1, 2, and 3	First/second/third generation Antihistamines
Substance P (SP)	neurokinin receptor-1 (NKR-1)	Aprepitant
	Spinal cord/Cerebrum	
Glutamate/SP	N-methyl-D-aspartate breceptor (NMDAR)	Aprepitant, Dapitant, Ezlopitant, Fosaprepitant, Lanepitant, L-733,060, Orvepitant
Serotonin	Serotonin receptor (5-HT)	SNRI: Venlafaxine, Desvenlafaxine, Duloxetine SSRI: Sertraline, Paroxetine, Fluvoxamine
-----	α -adrenoceptors	clonidines

BDNF: Brain-derived neurotrophic factor, CGRP: Calcitonin gene-related peptide, CRH: Corticotropin-releasing hormone, Endovanilloids include heat, acidosis, histamine, bradykinin, and various neurotrophins, NGFN: Nerve growth factorm POMC: Pro-opiomelanocortin, TA2: Thromboxane A2, Trk: Tropomyosin-related kinase A, SNRI: Serotonin–norepinephrine reuptake inhibitors, SSRI: Selective serotonin reuptake inhibitors

therapy, we need to be aware of the general principles, each double-edged anti-pruritic management, and potential new targeted drugs.

General Principles: It is experimentally and clinically demonstrated that some factors may exacerbate pruritus by lowering the threshold of an itch or impairing the skin

barrier layers, and some others can alleviate pruritus by elimination of trigger factors or by improving the skin barrier function, irrespective of the underlying causes. General principles including avoiding aggravated factors and applying appropriate protective measures are essential parts of an effective treatment. [Table 3]

Etiological Therapy: Further adoption of the etiological therapy (aimed at inhibiting the production of pruritogens or antagonizing receptors peripherally or centrally) is crucial for a long-term control of pruritus.

Present anti-pruritic therapies usually direct against a variety of targets including the epidermal barrier, immune system, or the nervous system [Table 4]. With a better understanding of the pathological mechanisms

of itch processing, identification of new medications targeting specific mediators and neuronal pathways offers a promising approach to manage pruritus more effectively. Recently, aprepitant, a NK1-R antagonist, showed rapid confirmed anti-pruritic efficacy in a small clinic experiment.^[22] And, histamine H4 receptor antagonists are on their way to the clinic. Many other potential targeted drugs (e.g. anti-interleukin-31 antibody, anti-NGF antibodies, TrkA inhibitors) are under investigation and may enter the clinic in the near future.

Given that there are few specialists with sufficient expertise in chronic pruritus, and many patients have no access to advanced therapeutic options, specialized pruritus clinics are recommended.^[29]

Pruritus caused by infectious diseases is commonly acute, mild or moderate, localized and is of short duration. Mechanical stimulation and/or immune cell infiltration contribute to the pathological mechanisms of pruritus. Elimination of triggering factors together with an early and specific treatment based on the primary pathogens is efficacious.

Pruritus is also a common symptom of genetic ichthyoses, which are caused by certain gene mutation leading to generation of abnormal structural proteins (keratins, filaggrin, loricrin, cornified cell envelope, etc.), deficient enzymes or transport proteins essential for the lipid metabolism in the epidermis (cholesterol sulphatase, transglutaminase, fatty acid dehydrogenase, lipoxygenases, ABCA12, etc.)^[27] and finally form keratinizing disorders characterized by excessive scaling on the skin. The scale clogs the pores of the sweat glands and traps the sweat. The trapped sweat irritates the

Table 2: Emerging pruritogens and potential new targeted therapies of some dermatological pruritic diseases

Atopic dermatitis	
Histaminergic pathway	H4 histamine receptor antagonists
Protease pathway	Serine protease inhibitors
	Cysteine protease inhibitors
	PAR-2 antagonists and antibodies
Opioid system	Topical and systemic, peripheral and centrally-acting mu-receptor antagonists and kappa-receptor agonists
IL-31	Anti-IL-31 antibody
Cannabinoids	FAAH inhibitors (centrally and peripherally acting agents)
	Neurotrophins
Cerebral processes	Esmirtazapine
Malignancy associated itch (especially cutaneous T-cell lymphoma)	
Substance P–NKR-1	NKR-1 antagonists
Cerebral processes	Esmirtazapine
Prurigo nodularis and lichen simplex chronicus	
Opioid system	Topical naltrexone
	Topical butorphanol
	Kappa-receptor agonists (centrally and peripherally)
TRPV1	8% Capsaicin
IL-31	Anti-IL-31 antibody
Neurotrophins	Anti-NGF antibodies

Table 3: General principles Legend: Some other exogenous factors (molds, fur, wool fiber, alcoholic beverages, caffeine, hot drinks, spicy food, and some drugs) as well as some endogenous factors (emotional stress, depression, obsessive compulsive disorders, perspiration, viral infections, and staphylococcal infections) also aggravate pruritus.

	Factors	General principles
Aggravate itch	Incessant scratching	Cutting off of the fingernails, Wet-wrap dressings
	Xerosis	Emollients (immediately after bathing), Humectants (glycerin, urea), Occlusives (cosmoline, mineral oil, silicon oil), Humidifier. Avoiding overusing soap, high concentration of disinfectants and excessive bathing.
	Sleep	Short-term (and sometimes long-term) use of hypnotics (typically benzodiazepine receptor agonists). Alternatives include clonidine, chloral hydrate and melatonin.
Relieve itch	High temperature (sweat)	Keep the environment cool, wipe the sweat away immediately.
	High pH of skin surface	Avoiding using high pH cleaners.
	Scratching and rubbing	Transcutaneous nerve stimulation (TNS) and cutaneous field stimulation
	Cold	Topical camphor, menthol and menthol lactate. Cool baths with tar or oatmeal, Cool compresses with menthol or camphor. Keep cool and dry environment are recommended.
	Low pH	Low pH or neutral soaps, Low pH lotion and moisturizers

Table 4: The treatment of dermatological pruritus

	Medical	Comments (side effect/precautions)
Topical antihistamines	Doxepin	high incidence of allergic contact dermatitis, increased skin fragility and petechiae
Topical corticosteroids		with caution: combined with UV-light therapy
Topical calcineurin inhibitors	Tacrolimus ointment Pimecrolimus cream	children <2 years of age immunocompromised patients
Topical anesthetics	Pramoxine Benzocaine	maximum of 3 days avoid using in patients with atopic eczema
Topical Vitamin D modulators	Calcitriol ointment	cutaneous irritation in sensitive areas
Capsaicin		localized burning and stinging sensation
Systemic Antihistamines	First/second/third-generation Loratadine, Cetirizine, Olopatadine	sedating (the first generation) proarrhythmic (the second generation)
Systemic glucocorticoids	Prednisolone	should be used as a short term
Other immunosuppressants	Cyclosporine	close clinical follow-up and laboratory tests
Leukotriene receptor antagonists	Zafirlukast, Montelukast	headache and gastrointestinal upsets
Thalidomide		teratogenesis and peripheral neuropathy

skin and leads to itchiness, redness, and occasionally small blisters. Moreover, the abnormality of certain enzymes could cause accumulation of certain molecules (e.g. leukotrienes), which can also stimulate itching. Netherton syndrome and ichthyosis vulgaris may also experience AD, and the former is a predisposition to allergies, such as asthma or food allergies. As we all know, AD and allergies always accompany pruritus. With regard to diagnose, family history and genetic counseling are important. So far, the treatment of genetic ichthyoses remains mainly symptomatic and is empirically based on the use of topical medication to ameliorate hydration, lubrication, and keratolysis, and in more severe cases, oral retinoids (vitamin A analogues), oral histamine and topical immunomodulator are also used. Recently, new drugs such as Dexeryl® and 10% N-acetylcysteine emulsion prepared in urea 5%^[30] showed pleasing efficiency and good tolerance.

CATEGORY II: PRURITUS FROM SYSTEMIC DISEASES

Systemic pruritus arises from “diseases of organs” other than the skin and certain multifactorial (e.g. metabolic) states or drugs.^[23] Among the diseases that can cause pruritus are renal insufficiency, cholestasis, lymphoma, polycythemia vera, solid tumors, and many others. Diseases of pregnancy and drug-induced pruritus are also divided into this group.

An underlying systemic disease is reported in 14-24% of patients who seek medical attention for pruritus.^[31] And, pruritus is probably a hint to latent systemic diseases, especially when there are no signs of primary dermatological diseases. Up to 80% of patients with primary biliary cirrhosis (PBC) experience pruritus,^[32]

which is also the initial symptom in almost half of the patients with this disease. 15–49% of patients with chronic renal failure and up to 90% of patients receiving dialysis suffer from pruritus.^[33] The prevalence of chronic pruritus has been reported as 30% in patients with Hodgkin's disease,^[34] and 15% of patients with non-Hodgkin's disease.^[35] Approximately, 30–50% patients with polycythemia vera (PV) suffer from temperature-induced itching, which may precede development of disease by several years.^[36]

Mechanism

The mechanism underlying systemic pruritus is multifactorial and still poorly understood. At least 4 main hypotheses for the pathogenesis of uremic pruritus have been proposed: Dermatological abnormalities, an immune-system derangement that results in a proinflammatory state, an imbalance of the endogenous opioidergic system, and a neuropathic mechanism.^[37] And, Fallahzaden *et al.*^[38] recently found that interleukin-2 serum levels were elevated in patients with uremic pruritus.

Accumulation of bile salts, histamine, substance P, progesterone metabolites, or endogenous opioids has been controversially postulated as potential pruritogen in cholestasis in the past, but showed little convincing correlation. Most recently, lysophosphatidic acid (LPA) and autotoxin (an enzyme that produces LPA) were identified as a potent pruritogen in pruritus of cholestasis and presented better correlation with occurrence and extent of itch perception.^[15,39] Cytokines (such as interleukin-6^[40] and interleukin-8^[41]) are found to be closely related to pathophysiology of pruritus of lymphoma.

Diagnosis

When it comes to diagnosis, a thorough history, system review, and physical examination (thyroid gland, lymph nodes, liver, and spleen) are needed. If the probability of systemic disease is low based on the above examination, a 2-week trial of symptomatic therapy (following general principles plus using conventional anti-histamine and topical corticosteroids) may be prescribed before proceeding to laboratory testing and radiological investigation. In the following 3 circumstances: Positive test, symptomatic therapy fails, or pruritus recurs, further checkups (liver / renal / thyroid panel, glucose, HIV antibody, tumor markers, and radiological investigation) are proposed. Treatment is often palliative with unsuccessful diagnosis. Here are some indications, which may increase concern for underlying systemic conditions: Old age, generalized pruritic sites, secondary skin lesions (excoriation, lichenification, prurigo nodularis) rather than primary skin lesion (e.g. wheal, papule) and itch preceding rash rather than rash before or parallel with itch.^[42]

Treatment

The first step of treatment is optimizing the control of

the primary diseases and following general principles. The second step is applying targeted anti-pruritic therapy (commonly neuroleptics, opioid receptor antagonists, and anti-depressant drugs). Therapeutic ladders of pruritus in end-stage renal disease (ESRD), chronic liver disease, and lymphoma are proposed.^[43] [Figure 1] However, adverse effects of opioid receptor antagonists (gastrointestinal, cardiovascular, neurologic), and costs lead to considering these drugs as a second line approach to chronic systemic pruritus. And, they should not be used in drug addicts or in patients receiving opioid analgesics and opioid-containing medicines (cough, cold, and anti-diarrheal preparations). The most typical side effects of anti-depressant drugs are xerostomia, sleeping disorders, and sexual dysfunction. Available choices for the treatment of pruritus in pregnancy dermatoses are limited. When systemic corticosteroid treatment is necessary in pregnancy, only non-halogenated corticosteroids should be administered.^[44] Ursodeoxycholic acid (UDCA) is the only treatment for intrahepatic cholestasis of pregnancy, which has been shown not only to reduce maternal pruritus but also to improve fetal prognosis.^[44-46] Other bile acid exchange

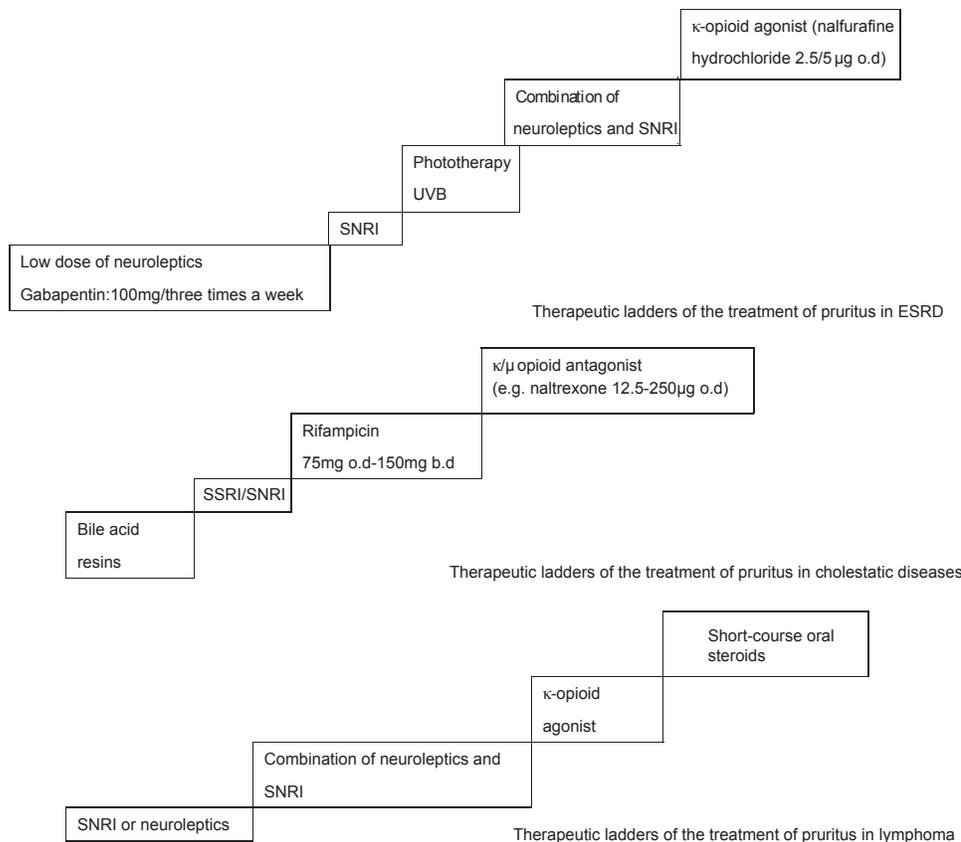


Figure 1: Therapeutic ladders of the treatment of systemic pruritus

resins should be avoided due to the risk of causing malabsorption of vitamin K with possible consecutive bleeding complications.^[47]

Recently, nalfurafine hydrochloride (a novel κ opioid receptor agonist) demonstrated efficacy in a phase III, randomized, double blind and placebo controlled study in treating refractory uremic pruritus.^[48] Novel imminent anti-pruritic strategies (ATX inhibitors and LPA receptor blockers for cholestatic pruritus,^[19-21] aprepitant for uremic pruritus^[22]) based on specific underlying mechanisms are being developed or under evaluation and may present more efficacy and better tolerance in clinic.

CATEGORY III: NEUROLOGICAL PRURITUS

Neurological or neuropathic pruritus terms as pruritus arising from diseases or disorders of the central or peripheral nervous system, e.g. nerve damage, nerve compression, and nerve irritation.^[23] Common peripheral neuropathic pruritic diseases are postherpetic neuralgia (PHN), brachioradial pruritus (BP), Notalgia paraesthetica, keloid, and burn scars. Central neuropathic pruritic diseases include spinal tumors, Creutzfeldt-Jakob disease,^[49] and multiple sclerosis. The itch sensation in most cases is chronic, persistent, and always accompanied with painful qualities (burning, stinging, biting, piercing, or tingling) and sensory damage (experienced as parasthesia, hyperesthesia, or hypoesthesia) in the affected areas.

Mechanisms

Mechanisms are incompletely understood. Some of the proposed mechanisms include itch associated with local nerve damage; central neuronal deprivation of afferent input, and central hypersensitivity of nerve fibers.^[50]

Diagnosis

In terms of diagnosis, itch combined with pain sensation, suggestive past history and neurologic exam indicating associated sensory abnormalities may support neurological origin. Further evaluation with electromyography, nerve conduction studies, and magnetic resonance imaging is needed to locate suspected nerve impingement and to rule out space-occupying lesions.

Treatment

Therapeutic options for neuropathic itch are sparse. Neuroleptic drugs were proven to be effective in neuropathic pain, such as gabapentin and pregabalin. Side effects include sedation, neurotoxicity and/or coma in patients with reduced renal function and withdrawal symptoms with pregabalin.^[51]

Botulinium toxin A injection has been reported to be successful for notalgia paraesthetica and PHN neuropathic pain.^[52-54] Clinical efficacy and side effects need to be assessed in further studies.

Novel drugs (Anti-NGF antibodies, TrkA inhibitors) targeting neurotrophin-induced pruritus pathway may shed new light on neurological pruritus therapy.

CATEGORY IV: PRURITUS WITH PSYCHIATRIC / PSYCHOSOMATIC DISEASES

In some circumstances, chronic pruritus is indeed unrelated to skin diseases, and the skin lesions are simply secondary to scratching behavior and are highly associated with mental state.

Psychiatric pruritus is considered psychiatric in origin, which is characterized as an excessive impulse to scratch, gouge, or pick at normal skin.^[50] It was found that 30% of the inpatient population with schizophrenia had pruritus with no organic basis.^[55] And, patients with obsessive and compulsive disorders or eating disorders also showed high incidence of pruritus. There are actually few well-defined entities where itching is a form of psychiatric disorder (e.g. delusions of parasitosis and tactile hallucinations). Psyche-pruritus-scratch cycle is the main cause of psychiatric pruritus.

Psychological factors may perplex itch perception even in the absence of a true psychiatric morbidity. The most frequent diagnosis is “psychological impact on or psychosomatic cofactors in pruritus” (46.8%).^[56]

Clinically, it has long been recognized that both acute stress (stressful life events) and chronic psychoemotional stress can precipitate or exacerbate pruritus and the scratching response.^[57,58] Gupta *et al*,^[59] found a direct correlation between depression and pruritus severity in patients with AD, psoriasis, and chronic idiopathic urticaria (CIU). And, a close association between pruritus severity and anger in CIU was also showed.^[60]

Mechanisms

The underlying mechanisms possibly involve the interaction of the skin, endocrine, nervous, and immune systems.^[61] A wealth of mediators are released systemically or locally^[62,63] in response to negative emotions. Such a release has been suggested to increase sensory innervations, co-stimulate other pruritogens, perpetuate inflammation, and lower the itch threshold.

Stress activates the nervous system in a number of ways. SP-NKR1 pathway has been shown to be activated in response to stressful stimuli, both in the central and peripheral nervous system.^[64] SP is an important pruritogen in the induction and maintenance of pruritus by binding to NKR1.^[65,66] And, a correlation between pruritus intensity and number of SP-positive nerves in lesional skin of psoriasis patients was observed.^[67] Interestingly, the Beck's Depression Inventory (BDI) score of the patients positively correlated with the number of SP and NKR1-positive cells in lesional skin.^[66] These indicate that stress and depression may influence pruritus via substance P and NKR1. In line with these findings, it was recently reported that depressive symptomatology strongly correlated with substance P in sweat patches and plasma in patients with major depressive disorder in remission.^[68] Meanwhile, stressors can activate the stress response system in the brain (hypothalamic-pituitary-adrenal axis; HPA axis) and release corticotropin-releasing hormone (CRH) into the bloodstream. Under stress, CRH is also released from dorsal root ganglia directly in the skin and could induce mast cell degranulation (releasing pruritogens: e.g. histamine, IL-31^[67]) and subsequently potentiate pruritus signaling.^[69]

Moreover, the noradrenergic system, which is highly relevant to emotional reaction, was found to play a

role in itch transmission. Descending noradrenergic system exerts a tonic inhibition of itch transmission in the spinal cord mediated by α -adrenoceptors.^[17,70]

Psychosomatic cofactors –pruritus- psychiatric comorbidity cycle

Recently, a biopsychosocial model^[71] of pruritus was described, which focused on the effects of personality characteristics, external stressors, cognitive disposition, behavioral and social factors, and the possible mediating role of physiological processes on pruritus. [Figure 2] Certain personality traits (less narcissistic in psoriasis patients, dissatisfaction in urticaria patients, and need for power and social influence in AD patients^[72]), negative affectivity (e.g. depression, anxiety, neuroticism, and dissociative states), and external stressors (negative life events) are associated with the development or exacerbation of skin disorders. And, specific cognitive disposition (helplessness and worrying negatively, acceptance beneficially), behavioral (scratch and avoidant coping behavior negatively) and social factors are assumed to mediate a persons' skin reactivity and response to pruritus.

On the other hand, patients with a pruritic disease have a high level of psychosocial (e.g. depression, suicidal ideation, public fear, sexual impairment) and occupational (absenteeism and productivity loss) morbidity.^[73] Clinically, it was found that patients with prurigo nodularis and psoriasis had a high frequency of psychiatric morbidity (18% cases of anxiety and 22% cases of depression).^[24,74] Put these together, it will form a vicious psychosomatic cofactors-pruritus-psychiatric comorbidity (PPP) cycle.

Heightened itch sensation, that doesn't completely correspond to pathophysiological findings, may

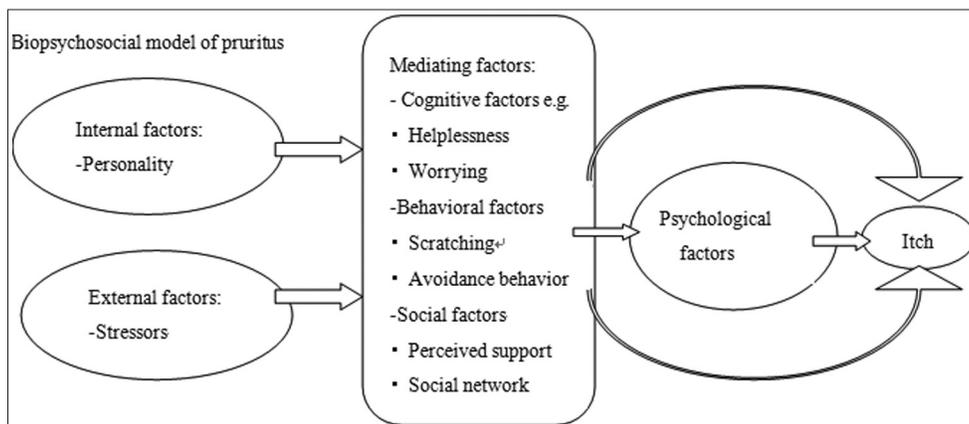


Figure 2: Biopsychosocial model of Pruritus

indicate the existence of psychosomatic cofactors. Unlike most other pruritic diseases, which cause nocturnal awakening, psychogenic pruritus rarely disturbs sleeping. And, secondary skin changes in varying stages associated can be seen, commonly on body areas that are most accessible to hands such as extensor surfaces of the arms, legs, abdomen, thighs, upper parts of the back, and shoulders with scalp and face being the most common sites.^[75-77]

Diagnosis

When it comes to diagnosis of psychiatric pruritus, ruling out of systemic, neuropathic, and dermatological causes of itch should be given priority. An evaluation of whether the disease is just psychiatric, or in a combination with other pruritic diseases should also be determined. Referral to a psychiatrist or a psychologist is highly recommended after the initial evaluation by the dermatologists.^[50]

In terms of psychosocial comorbidity, considering the presence of the PPP cycle, we suggest that physicians who encounter patients with pruritus should be aware of possible psychophysiological problems, and use the biopsychosocial model to evaluate the personality profiles, stressors, and the possible mediators of highly suspected patients.^[78]

Treatment

Somatic treatment with anti-pruritus drugs (see the treatment of dermatological pruritus), and psychosomatic treatment including pharmacological and non-pharmacological treatment are needed.

Pharmacological treatment

Tricyclic anti-depressant (TCA), such as doxepin, amitriptyline, and trimipramine, has additional anti-histaminic effects and is of benefit in dermatological conditions such as urticaria and pruritus. And, the generally more favorable side-effect profile of the SSRIs (selective serotonin reuptake inhibitors) has made them the first-line agents in the management of psychiatric morbidity in dermatological disorders.^[79] Neuroleptic medications are useful for the treatment of delusions of parasitosis, and the current drug of choice is pimozide.^[80] New anti-psychotics (e.g. risperidone) are effective for psychotic syndrome and have a much safer adverse effect profile.^[80]

Non-pharmacological therapy

Cognitive therapy: Besides pain, it was recently found

that itch nocebo effects can be induced by only giving verbal suggestions, and a placebo effect of verbal suggestions indirectly decreased the intensity of pruritus. In the long term, these findings may facilitate the development of therapeutic strategies to reduce itch by manipulating patients' expectations.^[81]

Since catastrophizing (Inability to foresee anything other than the worst possible outcome) and helpless coping were found to be significantly related to itch,^[82] patients should try to change the negative way of evaluating things.

Besides, patients and the public should be educated that chronic pruritus diseases (such as AD, psoriasis and urticaria) are not contagious, so as to reduce the social fear of the patients and to ameliorate their interpersonal relationships with their families and others.

Behavior therapy: Scratching counteracts itch (probably via segmental and suprasegmental circuits, which engage glycine and GABA-mediated inhibition of spinal itch signaling neurons^[83]). On the contrary, persistent scratching eventually damages skin, causes disfigurement, and compromises barrier function that opens the door to infection and other complications.^[84]

Behavioral therapy have to be initiated in time to break the vicious circle of itching and scratching.^[85]

Several techniques of relaxation, behavioral modifications, and biofeedback (a technique that involves monitoring the changes in physiologic responses to one's thoughts or feelings) have been reported to reduce itch scratching patterns, improved their skin status, and reduce the use of dermatological care.^[86]

Given that attention focus on bodily sensations is associated with higher levels of experienced itch, distracting maneuver should be taken.^[87]

Combined therapy: A literature review prompted the implementation of a multidisciplinary itch coping program that comprised of a broad scope of cognitive behavioral methods (self-monitoring, guidance in skin care, and coping skills to manage itch and scratch triggering factors, stress management methods with relaxation techniques, and habit reversal).^[88,89]

And recently, an integrative program, including

psychological, complementary and alternative medicine (CAM), and medical therapies was showed to be a novel, efficacious approach to decrease itch, scratching, pain, and anxiety of children suffering AD.^[90]

CATEGORY V: PRURITUS FROM MIXED OVERLAPPING AND COEXISTENCE OF SEVERAL DISEASES

Patients, especially elderly patients with chronic pruritus, always have multifactorial origins, among which, metabolic, endocrine, or hematological disturbances are most common.^[91,92] In the study of Sommer *et al.*,^[93] 10.7% patients had 2, 1.9% patients had 3, 0.7% patient 4, and 0.4% patient had 5 pruritogenic pathological conditions. A high incidence of psychogenic pruritus has also been described in conjunction with pruritus due to dermatological or systemic diseases.^[94] As a consequence, treatment of these patients with anti-pruritic substances exhibits several difficulties such as contraindication due to pre-existing systemic diseases, increased side effects in elderly patients, or interaction with other drugs.^[95] Since the psychogenic nature of the pruritus is in most cases secondary or comorbid with severe and longstanding dermatological or systemic diseases,^[96] drugs targeting primary diseases and high consideration should be given before taking psychiatric medications. And, dry skin, reduced sweating, decreased production of sebum, thicker stratum corneum, impaired skin barrier have been suggested as causes of itch in elderly people, non-specific treatment following general principles gains a significant role.^[97]

CATEGORY VI: PRURITUS OF UNDETERMINED ORIGIN

Chronic pruritus with no detection of the underlying origin after completion of diagnostic tests is called PUO, which accounts for up to 45% of all cases.^[93,95,98] Subclinical or subsided diseases are common reasons for PUO, and an association of as-yet unrelated diseases with pruritic conditions should be considered. Eisendle *et al.*,^[98] found that subclinical cholestasis was involved in the pathogenesis of PUO, and evaluation of total serum bile acid levels should be included in the diagnostic work-up of these patients. A recent study by Sonja *et al.*,^[99] showed that lactase deficiency might be an independent causal factor in the elicitation of chronic pruritus and a lactose-free diet offers a low cost, efficient, and specific therapy in patients with this kind of chronic pruritus. For older patients, the

itch sensation may be due to reduced water content of the skin without overt dryness.^[100,101]

General principles should be followed before non-specific topical or oral anti-pruritus therapy (anti-histamine, corticosteroids). Opioid antagonists (naltrexone hydrochloride), and SSRIs were found to be effective treatment of severe PUO,^[102-104] and gabapentin is recommended for treatment of PUO unresponsive to the usual treatment modalities.^[105]

DISCUSSION AND CONCLUSION

Pruritus is not a diagnosis, but a symptom that associated with multiple etiologies. Clinical physicians should gain a holistic understanding of pruritus. Stepwise multi-disciplinary assessment is needed to search the underlying systemic, neural, and psychophysiological disorders. So far, effective amelioration of pruritus is still far from satisfactory. Traditional methods, such as topical treatments, UV, and systemic anti-histamine medication are symptomatic and sometimes fail to work. Novel therapeutic intervention based upon better understanding of the mediators, receptors, as well as the neurophysiological and molecular pathways is a real prospect. Although evidence-based improved treatment modalities are emerging, many of these targeted treatments appear to be effective against pruritus in animals. And, judging from the reported case number, particularly carefully-designed-controlled clinical trials are needed. The cutis and the psyche are inseparable.^[103] A combination with drugs that counteract itch perception and modulate emotions is beneficial.^[24] And, non-pharmacological therapy, such as psychological counseling and management of emotional or psychological problems contributing to the symptoms with cognitive-behavioral methods, is of great help, both in the short and long term.

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Multiple Choice Questions

1. Which of the following systemic diseases has the highest incidence of pruritus:
 - a. Polycythaemia vera.
 - b. Renal failure
 - c. Primary biliary cirrhosis.
 - d. Hodgkin's disease
2. Which of the following molecules is considered specific itch-signaling molecule:
 - a. Calcitonin gene-related peptide (CGRP)
 - b. Gastrin-releasing peptide (GRP)
 - c. Neurokinin-1(NK1)
 - d. All of the above
3. Which of the following interleukin is found to be closely related to pathogenesis of uremic pruritus:
 - a. Interleukin-2
 - b. Interleukin-6
 - c. Interleukin-8
 - d. Interleukin-31
4. Which of the following factors can relief itch:
 - a. Sleep
 - b. Low pH
 - c. High pH
 - d. Alcoholic beverages
5. Which of the following is not μ -opioid receptor antagonists (MORA):
 - a. Naloxone
 - b. Naltrexone
 - c. Nalfurafine
 - d. Nalmefene
6. Which opioid receptor antagonist showed anti-pruritic effects and could be used in hemodialysis patients with uremic pruritus:
 - a. Naltrexone
 - b. Nalfurafine
 - c. Nalmefene
 - d. All of the above
7. Which of the following antidepressants has additional antihistaminic effect:
 - a. Amitriptyline
 - b. Sertraline
 - c. Paroxetine
 - d. Fluvoxamine
8. All the following areas are commonly sites of secondary skin lesions seen in pruritus with psychiatric/psychosomatic diseases EXCEPT:
 - a. Hands
 - b. Lower parts of the back
 - c. Scalp
 - d. Face
9. Which of the following mechanisms is associated with pruritus with psychiatric/psychosomatic diseases:
 - a. SP-NKR1 pathway
 - b. Gene mutation
 - c. Immune cell infiltration
 - d. All of the above
10. All the followings act as a psychosomatic cofactor that could trigger or aggravate pruritus EXCEPT:
 - a. Neuroticism
 - b. Helplessness
 - c. Dissatisfaction
 - d. Public fear

1.(c), 2.(b), 3.(a), 4.(b), 5.(c), 6.(b), 7.(a), 8.(b), 9.(a), 10.(d)

Key

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