

PRURITUS IN THE ELDERLY. PATHOPHYSIOLOGICAL, CLINICAL, LABORATORY AND THERAPEUTIC APPROACH

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PRURITUS IN THE ELDERLY. PATHOPHYSIOLOGICAL, CLINICAL, PARA-CLINICAL AND THERAPEUTIC APPROACH (Abstract): Generalized pruritus is a common symptom in elderly patients, with severe impact on the quality of life. The diagnosis of senile idiopathic pruritus is made after the exclusion of a systemic disease such as chronic renal disease, hepatobiliary disease with cholestasis, thyroid dysfunctions, drug-induced hypersensitivity reactions, visceral or hematological neoplasia, and primitive dermatological distinct conditions. The pathophysiological mechanisms are still unclear. A critical role is considered to be played by changes related to skin aging, cutaneous nerve supply and other nervous system components. The clinical approach requires a thorough assessment of general health status. In primary skin conditions, a biopsy and direct immunofluorescence (DIF) are required, while in pruritus associated with a systemic disorder, the assessment of hematological, biochemical and immunological parameters and imaging are necessary. The treatment of a patient with chronic pruritus is often palliative and individualized, with emollients, sedating and non-sedating antihistamines, tricyclic antidepressants, gabapentinum, and narrow-band UVB phototherapy. Pruritus associated with systemic disease may be alleviated by etiologic treatment. **Keywords:** PRURITUS, PATHOPHYSIOLOGY, ELDERLY, SYSTEMIC DISEASE, TREATMENT

Generalized pruritus is a common symptom in elderly patients, with severe impact on their quality of life. It is an annoying symptom, considered an "alarm system" or a self-defense mechanism, the same as other cutaneous sensations such as pain, tactile sensation, vibrations, cold or hot.

Pruritus is a symptom occurring in about 20% of the adult population.

An underlying systemic disease is reported in 10 - 50% of the patients who see a doctor for pruritus. Thus, it occurs in 22 - 66% of the hemodialysis patients, 30% of

the patients with chronic renal failure not undergoing dialysis, 60% of the patients with primary biliary cirrhosis, 48-70% of the patients with polycythemia vera, 4 - 11% of the patients with untreated Graves disease, 35% of the patients with Hodgkin's disease, 10% of the patients with non - Hodgkin lymphoma.

The malignancy rate in patients with generalized pruritus is thought to range between 1 and 8%. Pruritus occurs in very few cases of diabetes, hypothyroidism and leukemia (1, 2).

PATHOPHYSIOLOGY

Various mechanisms involve a complex network of cutaneous cells (keratinocytes, mast cells, inflammatory infiltrate cells: lymphocytes, eosinophils), which interact with unmyelinated slow-conducting polymodal C fibers and A-delta nociceptive neurons, with free terminations, located in the vicinity of the dermoepidermal junction or in the epidermis (2, 3, 4, 5).

The following mediators were found to play an important role: histamine, serotonin, bradykinin, protease (for instance mast cell tryptase), endothelin, NGF, brain-derived neurotrophic factor, neurokinins, neuropeptides (substance P), gastrin-releasing peptide, cytokines such as IL31, autotaxin, histamine H₄ receptors (6).

Senile pruritus or Willan's itch is induced by age-related tegument changes and cutaneous nervous fibers distribution alteration. Also, any increase in the expression of the vanilloid transient receptor 1 (TRPV1), which is a member of the non-selective cation channel family whose activation determines an influx of bivalent and monovalent cations (for instance, Ca²⁺, Na⁺, Mg²⁺) in aged human skin, would be suggestive of the involvement of this receptor in different senile cutaneous symptoms such as pruritus and neurogenic inflammation (2, 6, 7).

In renal pruritus (chronic renal failure, especially in hemodialysis patients), pruritus is rather due to the high level of bivalent ions (calcium, magnesium, phosphate), also detected in patients with cutaneous pruritus of different etiology, than to the high level of circulating histamine associated with a large number of mast cells in various organs. Other factors that may be involved in renal pruritus are: lower transepidermal release rates of pruritogenic

substances, xeroderma, higher bile acid levels in the serum, higher vitamin A levels in the epidermis, serum serotonin increase. Also, in chronic renal failure, pruritus may be a possible symptom of peripheral neuropathy. Enolase-positive non-specific nerves were found to proliferate in the epidermis of uremia patients. Also, opioid substance accumulation and μ -opioid receptor over-expression and activation could account for renal pruritus. Another hypothesis supports the role of systemic inflammatory reactions in these patients, which trigger the over-expression of activated Th1 lymphocytes, which secrete the IL2 responsible for pruritus; hence, the efficiency of the UVB phototherapy, and thalidomide and tacrolimus treatment, which target inflammation mediators. Pruritus severity in uremia patients is correlated with high ferritin and low transferrin and serum albumin levels (2, 6).

In cholestatic pruritus, the accumulation of specific pruritogenic intermediaries in bile salt synthesis is thought to determine hepatic lesions and pruritogenic substance release. Rifampin and ursodeoxycholic acid diminish the intrahepatic concentration of bile salts and ameliorate hepatic pruritus. This would also involve the accumulation of endogenous opioids, which play a certain role in pruritus modulation and cerebral opioidergic tonus increase; therefore, cholestatic pruritus is partially ameliorated by opioid antagonist delivery (2, 6).

In hematologic pruritus, iron deficit may lead to pruritus occurrence through a variety of metabolic pathways. In *polycythemia vera*, pruritus is influenced by the large number of circulating basophils and skin mast cells, and it is typically enhanced when the contact with hot water ceases. In addition to iron, other major hematologic

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pruritus mediators are mast cell prostaglandins and platelet degranulation products, which induce serotonin and prostanoid release (2, 6).

In endocrine thyroopathy pruritus, the thyroid hormone hypersecretion specific to hyperthyroidism may activate the kinins resulting from high tissue metabolism or it may reduce pruritus threshold as a result of heating and vasodilation. In hypothyroidism, pruritus follows xerosis. In diabetic patients, pruritus is correlated with metabolic anomalies, anhidrosis, diabetic neuropathy and autonomic dysfunction (2, 6).

Pruritus associated with malignant processes may be accounted for by the release of tumor toxins. Pruritus mediators in Hodgkin's disease are leukopeptidase and bradykinin released as a self-immune response directed against malignant lymphoproliferative cells. In carcinoid syndrome, pruritus is triggered by serotonin (2, 6).

CLINICAL APPROACH

The detailed history and thorough general physical and tegument examination play a critical role in determining the cause of pruritus.

The detailed history should include the onset, duration, severity, location and temporal relation with triggering factors such as drugs, bath, emotional stress, and data on possible alcohol abuse, which may indicate a chronic hepatic disease. The history should also provide information on patient's mental health in order to exclude a possible psychiatric cause of their pruritus.

The clinical examination may reveal xeroderma as a possible cause or just as a coincidental symptom, as well as signs that allow differentiating systemic causes from primary dermatological conditions. Thus, the skin may look normal or it may exhibit

secondary lesions: excoriation, prurigo nodularis, lichen simplex chronicus, signs of secondary suprainfection, "butterfly sign" (hypo-pigmented or normal skin area on the postero-median thorax and post-inflammatory pigmentation areas which are easy to reach by patient's hands).

Renal pruritus may be accompanied by: diffuse xerosis, "half and half nails" associated with signs of peripheral neuropathy and uremia.

Signs of hepatic condition present in cholestatic pruritus are: jaundice, spider angiomas, white nails, xanthelasma, Dupuytren's contracture, gynecomastia in males, ascites, splenomegaly.

Hematological pruritus determines: paleness (anemia, hyposideremia), glossitis and angular cheilitis, "red face" (perioral, cheek, nose and ear erythema), whereas in polycythemia vera it also associates hypertension and splenomegaly.

Well-defined hyperpigmentation, ichthyosis, painless lymphadenopathy and splenomegaly are characteristic of paraneoplastic pruritus in Hodgkin's disease.

Diagnostic keys: generalized pruritus due to a systemic disease has an insidious onset; generalized pruritus in an old man with iron deficit but without anemia raises the suspicion of a neoplasm.

The causes of pruritus occurrence in systemic diseases are partially elucidated. Bile salts, histamine, opioids and unidentified pruritogenic substances in injured hepatocytes are thought to be involved in cholestatic pruritus. Pruritus may be correlated with primary biliary cirrhosis cholestasis, sclerosing cholangitis, chronic virus C hepatitis, choledocholithiasis, obstructive pancreas or bile duct carcinomas, pregnancy, and terminal hepatic illnesses regardless of etiology. Also, pruritus may be

associated with drug-induced cholestasis: chlor-propamide, salbutamol, phenothiazine, anabolic steroids, oral birth control pills, and erythromycin.

Hematologic prurits may either be induced by iron deficit, or occur in polycythemia rubra vera, hypereosinophilic syndrome, primary thrombocythemia, myelodysplastic syndromes.

Endocrine pruritus accompanies hypo/hyperthyroidism, diabetes mellitus, hyperparathyroidism, hypoparathyroidism.

Pruritus associated with neoplastic conditions occurs in Hodgkin's disease, non-Hodgkin lymphomas, leukemia, paraproteinemia, carcinoid syndrome, SIPPLE syndrome (multiple endocrine neoplasia), solid tumors (gastro-intestinal tumors, SNC, pulmonary tumors).

Other conditions that materialize in pruritus are drug-induced rash-free pruritus (pruritus sine materia), mastocytosis, HIV infection, AIDS.

LABORATORY APPROACH

Whenever primary cutaneous lesions are present (dermatitis herpetiformis, bullous pemphigoid, mastocytosis), cutaneous biopsy and possibly direct immunofluorescence and special stains are required.

Suspicion of a systemic cause requires: hematologic, biochemical and immunological tests (complete blood count, leukocyte differential count, ESR, electrolyte dosage, total protein test and protein electrophoresis, functional renal tests, glycemia, hepatic enzymes, uric acid, serum iron, alkaline phosphatase, bilirubin (high in cholestasis), hepatitis B and C serology, thyrotropin and thyrosine indicative of thyroid dysfunctions, IgE, PSA, urine exam for hydroxyindol-acetic acid (5-HIAA) and mast cell metabolites, folic acid dosage, zinc, vita-

min B₁₂, porphyrin, antimitochondrial antibodies (positive and with 98% specificity in primary biliary cirrhosis), parathormone level, coproparasitologic exam, hidden hemorrhage); diagnosis confirmation procedures: retrograde cholangio-pancreatography, colonoscopy; necessary imaging investigations: chest X-ray, abdominal ultrasonography, tumor detecting CT/IMR, ganglion ultrasonography.

THERAPEUTIC APPROACH OF PRURITUS

Possible treatment stages include: when the cause is not identified: avoid triggering factors, emollients, symptomatic therapy (non-sedating H₁ antihistamines), topical corticotherapy; when the cause has been detected: etiologic treatment; when the cause is unclear and the patient has not responded to previous therapies, and when secondary lesions are present: administer capsaicin, calcineurin inhibitors, cannabinoid agonists, naltrexone, gabapentinum, UV therapy, immunosuppressants (cyclosporine), tricyclic antidepressants (doxepin) and tetracyclic antidepressants (mirtazapine).

Elderly patients in whom pruritus is suspected to have a systemic cause are given: gastroenterological exams (to detect hepatobiliary conditions), hematologic/oncologic exams (to detect malignant hematologic conditions, organic neoplasm), nephrological exams (to detect chronic renal conditions), endocrine exams (to detect thyroid conditions), surgical procedures (for renal/hepatic transplant or obstruction removing stent in primary sclerosing cholangitis).

ETIOLOGIC TREATMENT

Therapeutic options available in renal pruritus are represented by physical, topical

and systemic treatment. Physical treatment - UVB phototherapy - reduces cutaneous phosphorus, decreases the number of dermal mast cells, and reduces vitamin A level in the epidermis. Topical treatment is used in localized pruritus and includes 0.025% capsaicin cream, 0.03% tacrolimus ointment (calcineurin inhibitor able to decrease Th1 lymphocytes differentiation and reduce IL2 production), 3-6% gabapentinum cream (ameliorates localized neurogenic pruritus), gamma-linolenic acid. Systemic treatment: the most common therapy of renal pruritus in dialysis patients is narrow-band UVB phototherapy associated with activated carbon administered orally. Another option in patients not responding to conventional therapy is thalidomide which decreases Th lymphocytes and inhibits TNF alpha production, or nicergoline and free fatty acids as the ones found in common evening primrose, gabapentinum or opioid antagonists, butorphanol and nalufafine (2, 8, 9).

Cholestyramine is the first line therapy in cholestatic pruritus. It is followed by rifampine (rifadin, an antibiotic inhibiting RNA synthesis in bacteria and also hepatic biliary acid re-uptake, by detoxifying them), opioid antagonists (i.v. naloxone or oral naltrexone or oral butorphanol), ursodeoxycholic acid and s-adenosyl-methionine (efficient in pregnancy cholestasis and generally in patients with intrahepatic cholestasis) (2, 8).

Iron therapy in hematologic pruritus normalizes ferritin levels. The first therapeutic option in polycythemia vera is aspirin, which decreases platelet degranulation and serotonin and prostaglandin release. Other therapeutic options are cimetidine, danazol, UVB phototherapy, cholestyramine. In Hodgkin's disease, pruritus may

be ameliorated by thalidomide (2, 8).

Pruritus due to hypothyroidism is ameliorated by topical therapy with emollients, whereas systemic pruritus responds well to substitution thyroid hormones.

Pruritus associated with chronic dermatosis responds to basic disorder therapy or to non-specific treatments such as topical cannabinoid agonists.

Uncontrollable pruritus may be reduced by UVB phototherapy, cholestyramine, naloxone and activated carbon.

Limited data suggest that gabapentinum, focal/zonal cutaneous stimulation, serotonin antagonists and UVB phototherapy may ameliorate senile idiopathic pruritus (6, 7).

PATIENT EDUCATION AND PROGNOSIS

Common cutaneous xerosis in the elderly enhances pruritus. Consequently, recommendations include emollients, avoidance of excessive bathing, dry environments, alkaline soaps and irritating fabrics.

Prognosis depends on complications, which are: debilitating insomnia, suicidal ideation, prurigo nodularis, and lichen simplex chronicus.

Poor prognosis is correlated with symptom severity. Thus, generalized pruritus is an example of long-term mortality marker of approximately 3 years in hemodialysis patients and it has poor significance in Hodgkin's disease patients. The recurrent nature of pruritus after visceral neoplasm therapy is a marker of cancer recurrence.

CONCLUSIONS

Pruritus is a common symptom in the elderly, yet age, just as sex, does not correlate with pruritus occurrence in patients with systemic conditions.

Idiopathic senile pruritus is an exclusion diagnosis, which requires investigation of a basic systemic disease (thyroid, hematologic, cholestatic or chronic renal condition, or more rarely as paraneoplastic phenomenon or cerebral infarction aftermath). Initially negative paraclinical tests do not exclude a systemic disease and the screening must be repeated every 3-6 months if the clinical suspicion remains.

Pruritus in old age is a difficult symptom to treat. The elucidation of the pathological mechanisms involved may have therapeutic advantages both in idiopathic senile pruritus and in pruritus triggered by systemic diseases.

A symptomatic patient-specific therapy

is preferred in the absence of an etiological diagnosis, especially considering that the mere use of emollients may be impossible because the physical disabilities proper to seniors and the adverse effects of therapy are more common in seniors, since the associated diseases may alter drug metabolite pharmacokinetics and polypragmasia increases the risk of adverse reactions correlated with drug interactions, and failing cognitive functions induce low therapy compliance in the elderly.

The therapeutic options in severe therapy-resistant pruritus of systemic origin are: IL31 antagonists, neurokinin 1 receptor antagonists or anti H4 which are still under clinical study.

REFERENCES

1. Ward J.R., Bernard J.D. Willan's itch and other causes of pruritus in the elderly. *Int. J. Dermatol.* 2005; 44(4): 267-273.
2. Cassano N., Tessari G., Vena G.A., Girolomoni G. Chronic pruritus in the absence of disease: an update on pathophysiology, diagnosis and therapy. *Am. J. Clin. Dermatol.* 2010; 11(6): 339-411.
3. Kuraishi Y. Diverse mechanisms of itch. *Nihon Shinkei Yakurigaku Zasshi* 2005; 25(4): 197-201.
4. Anboh T. Importance of epidermal keratinocytes in itching. *Nihon Shinkei Yakurigaku Zasshi* 2006; 26(6): 403-408.
5. Stander S., Steinhoff M., Schmelz M., Weisshaar E., Metze D., Luger T. Neurophysiology of pruritus: cutaneous elicitation of itch. *Arch. Dermatol.* 2003; 139(11): 1463-70.
6. Raap U, Ständer S, Metz M. Pathophysiology of itch and new treatments. *Curr. Opin. Allergy. Clin. Immunol.* 2011; 11(5): 420-427.
7. Lee Y.M., Kang S.M., Chung J.H. The role of TRPV1 channel in aged human skin. *J. Dermatol. Sci.* 2012; 65(2): 81-85.
8. Lonsdale-Eccles A., Carmichael A.J. Treatment of pruritus associated with systemic disorders in the elderly: a review of the role of new therapies. *Drugs Aging* 2003; 20(3): 197-208.
9. Ruiz Villa Verde R., Sanchez Cano D. Idiopathic senile pruritus – therapeutic response to gabapentin. *Rev. Esp. Geriatr. Gerontol.* 2009; 44(6): 355-356.