Etiopathogenesis of pruritus due to systemic causes: Implications for treatment

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Pruritus is one of the most troublesome symptoms seen in dermatologic practice. Severe pruritus can undoubtedly affect quality of life and can have serious psychological implications. Satisfactory management of pruritus unassociated with any skin lesions still remains a distant goal though breakthroughs in our understanding of pruritus are on the horizon.

Cutaneous inflammatory disorders are associated with release of chemical mediators like histamine. That skin inflammation leads to pruritus is clear from the fact that anti-inflammatory agents including steroids relieve pruritus in such patients. Antihistamines provide relief from pruritus in allergic disorders by competitively or non-competitively blocking histamine and by producing sedation.

However, when pruritus is not due to any primary skin disease, dermatologists find themselves on less familiar ground. Proven causes of pruritus due to systemic diseases are: uremic pruritus, hepatobiliary pruritus, pruritus due to hematological causes like polycythemia vera, leukemia, lymphomas (especially Hodgkin's disease), multiple myeloma, pruritus due to endocrine disorders and multiple sclerosis. The less proven causes are carcinoid syndrome, iron deficiency anemia, diabetes and intestinal parasites. Our understanding of the pathomechanism of pruritus of systemic origin has considerably improved in the last few years. Drugs based on these mechanisms are likely to produce better results than the use of antihistamines alone.

UREMIC PRURITUS

The link between uremia due to chronic renal failure and pruritus is an established one. However, in uremia associated with acute renal failure, pruritus is classically absent. Uremic pruritus is of multifactorial origin and common causes suggested are uremic xerosis, secondary hyperparathyroidism, hypervitaminosis-A, uremic neuropathy, elevated serum histamine levels and iron deficiency anemia. Of these, uremic xerosis is perhaps the most important cause of uremic pruritus.[1]

The level of uremic pruritus is directly proportional to the severity of uremic xerosis; the more intense the xerosis, the greater the amount of pruritus.[2-5] Uremic xerosis is secondary to full-thickness skin dehydration resulting from diminished sweating and low levels of skin surface lipids due to atrophy of the eccrine and sebaceous glands respectively. However, Yosipovitch *et al.*[6] and Ståhle-Bäckdahl *et al.*[7] did not find a correlation between the severity of pruritus and objective parameters of skin dryness. Nevertheless, it illustrates that even if uremic xerosis is not 'the' cause of uremic pruritus, it can adversely affect pruritus by reducing the threshold for itch. Impaired perfusion of the skin demonstrated in patients of medical renal disease may also contribute to the skin dehydration process.[8] Liberal application of emollients improves cutaneous hydration and relieves pruritus in a significant proportion of patients with uremia.

Pruritus appears at advanced stages of renal failure. Uremia causes severe paroxysms of pruritus (especially during the summer) in 25% of patients with chronic renal failure.[9] Generally, dialysis, both hemodialysis and peritoneal dialysis, helps in treatment of pruritus. Occasional concern is about complement activation by dialyzer membrane and

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aggravation of pruritus. Now, with the use of increasingly more biocompatible membranes the problem is more theoretical than practical.

Nordal *et al.* reviewed the relationship between secondary hyperparathyroidism and uremic pruritus and suggested the treatment of secondary hyperparathyroidism for the amelioration of uremic pruritus. Secondary hyperparathyroidism leads to calcium phosphate deposition in the skin that causes degranulation of mast cells and release of serotonin and histamine. Uremic patients with pruritus were found to have numerous mast cells in the skin, elevated serum histamine, parathyroid hormone and serum ferritin levels as compared to uremic patients without pruritus.[10] Despite the evidence for release of histamine, there was no correlation found between plasma histamine levels and severity of itching in uremic patients suggesting that plasma histamine does not play a significant role in uremic pruritus.[11] Probably for the same reason, the role of antihistamines is best described as marginal in the treatment of uremic pruritus. However, serotonin antagonists like ondansetron and granisetron were found to be effective, safe and well tolerated for the treatment of uremic pruritus in Hemodialysis patients in some recent trials.[12] Similarly, mast cell stabilizer and anti-serotonin drug, ketotifen also gives encouraging results in the treatment of uremic pruritus.[12,13]

The hypothesis that release of cytokines initiates uremic pruritus is supported by the successful use of narrow band UVB therapy (NB-UVB) in the treatment of uremic pruritus. The NB-UVB therapy supposedly depletes the mast cell in the uremic skin to reduce the itching.[14] Renal transplantation is curative in uremic pruritus and uremic changes of the skin and generalized pruritus disappear upon restoration of kidney function after renal transplantation.[15]

HEPATOBILIARY PRURITUS

Pruritus is one of the common disabling symptoms of hepatobiliary diseases. Although, in the majority of cases, it is associated with jaundice, it may occur in the absence of it. Pruritus in cholestatic hepatobiliary diseases is due to bile acid, bile acid derivatives or endogenous opiates that undergo enterohepatic circulation.[13,16] Opiates are thought to be involved in the development of hepatobiliary pruritus because opiate agonists induce opioid receptor-mediated scratching activity of central origin. Further, the increase in central opioidergic tone in cholestasis and reduction of scratching activity by opiate antagonists (naltrexone) in cholestatic patients support their role.[14,17] Naltrexone (50 mg/day), an opiate antagonist, is found to be beneficial but only in small controlled trials.[18] Bile acid binding resin like cholestyramine (4-6 g taken 30 min before meal) still remains the drug of choice for the pruritus associated with primary biliary cirrhosis and primary sclerosing cholangitis.[19] Malabsorption, constipation and decreased absorption of other medications are some unwanted effects of cholestyramine. In cases of 'surgical' jaundice, surgical intervention will relieve obstruction in the extrahepatic biliary tree to improve pruritus. The common causes include gall stones, calculus cholecystitis, carcinoma of head of pancreas and obstruction of biliary tree by metastases. Biliary stenting by endoscopic retrograde cholangiopancreatography (ERCP) provides another therapeutic option in inoperable malignancies affecting the extra-hepatic biliary tract.

Ursodeoxycholic acid (USDA), 13-15 mg/kg/day is a choleretic bile acid that replaces naturally occurring taurate- and glycate-rich bile acids and improves pruritus in intrahepatic cholestasis of pregnancy but is not useful for other forms of cholestatic jaundice.

Pruritus of primary biliary cirrhosis and pediatric cholestatic disorders has shown improvement with rifampicin, but the underlying mechanism and magnitude of benefits are not clear.[18] Limited data on the efficacy and potential for hepatotoxicity precludes its routine use in these conditions.

PRURITUS OF ENDOCRINE CAUSES

Common endocrine disorders associated with pruritus are hypothyroidism and hyperthyroidism. Skin in hypothyroidism is dry, coarse and myxedematous. It is postulated that decrease in sebaceous gland activity, decreased sweat secretion and low epidermal sterol synthesis contribute to xerosis.[20] Supplementation of thyroid hormone and use of emollients is helpful. In hyperthyroidism, skin becomes warm and moist. Vasodilatation leads to increased blood flow of the skin and increase in skin temperature that decreases the threshold for itching.[20]

Contrary to popular belief, diabetes mellitus is not a cause of generalized pruritus. However, localized pruritus due to anogenital candidiasis is certainly common in diabetics.

PRURITUS AND HEMATOLOGICAL DISORDERS

A large number of hematological disorders are associated with pruritus in the absence of 'itchy skin lesions'. Causes

include polycythemia vera, Hodgkin's disease, myeloma and leukemia. 'Bath itch' of polycythemia occurs after contact with water and lasts for about 30-60 min, the exact mechanism of which is unknown. While normal serum tryptase levels is a good evidence against mast cell degranulation in these cases, elevated histamine levels are consistently observed.[21] Despite this, the role of antihistamines in the relief of pruritus is limited. Venesection and aspirin have been used with variable results.

Pruritus is a well-recognized symptom of Hodgkin's lymphoma (HD) that is present in approximately 30% of cases of HD.[22] Paroxysms of generalized itching and hyperhidrosis have been observed. Pruritus in HD was earlier considered as a sign of active disease warranting aggressive chemotherapy, but this is no longer accepted today. Pruritus in HD is reported to resolve after the initiation of chemotherapy indicating strong etiologic association.[23]

Neurogenic pruritus

Causes of central neurogenic pruritus are multiple sclerosis, stroke and spinal tumors. The mechanism of central pruritus and central pain appears the same in such cases.[24]

CONCLUSION

Better understanding of the pathophysiology of pruritus invariably has implications for specific treatment. With increasing understanding of the role of chemical mediators, central neural mechanisms, immune cells and cytokines, newer drugs are being explored for the alleviation of pruritus. Thus, in future, we may use specific drugs to treat each of the systemic causes of pruritus providing succor to our distressed patients.

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