Pruritus in Chronic Cholestatic Liver Disease

Chalermrat Bunchorntavakul, MD[a,b], K. Rajender Reddy, MD[a,*]

KEYWORDS

• Pruritus • Itching • Cholestasis • Liver disease • Pathogenesis • Management • Opioid antagonist • Cholestyramine

Pruritus is a troublesome complication of chronic liver disease and often occurs in those with cholestasis. It is commonly encountered and well recognized in chronic cholestatic conditions, such as primary biliary cirrhosis (PBC); primary sclerosing cholangitis (PSC); prolonged drug-induced cholestasis, with or without ductopenia; intrahepatic cholestasis of pregnancy (ICP); and cholestasis syndromes associated with genetic mutations, such as progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC). Further, it is also observed in other types of liver disease, such as intrahepatic or extrahepatic biliary obstruction and chronic viral hepatitis.[1,2] This clinical manifestation can significantly negatively affect patients' quality of life, resulting in sleep deprivation, emotional/psychological disturbance, and even suicidal ideation. At an extreme, severe refractory pruritus in patients with chronic cholestasis, and without overt liver failure, has been accepted as an indication for liver transplantation (LT) so that quality of life can be improved.[3]

In the past few decades, some progress has been made in elucidating the pathogenesis of cholestasis-related pruritus. As a result, several potential therapeutic targets have been proposed and treatments directed at them have been investigated. However, there is currently no single established pathogenetic explanation and all available antipruritic treatment options are empiric and are not consistently effective. Thus, the management of pruritus in cholestasis continues to be a challenge and it remains a cause of considerable distress among patients. Based on recent experimental and clinical data, this article outlines the clinical manifestations, pathogenesis, and management of pruritus in cholestasis. The current recommended approach is emphasized, and the experimental interventions are discussed. In addition, the management of pruritus in certain conditions including ICP and BRIC are briefly reviewed.

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[a] Division of Gastroenterology and Hepatology, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [b] Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, Rajavithi Road, Rajthewi, Bangkok 10400, Thailand

* Corresponding author. Hospital of the University of Pennsylvania, 2 Dulles, 3400 Spruce Street, Philadelphia, PA 19104.

E-mail address: rajender.reddy@uphs.upenn.edu

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MANIFESTATION AND NATURAL HISTORY

PBC has traditionally been the model for the study of pruritus in chronic cholestasis. Pruritus is a common presenting symptom of PBC and is reported in up to 70% to 80% of patients by 10 years after diagnosis; 75% of these patients reported this symptom preceding the diagnosis of PBC.[4,5] Similarly, in PSC, pruritus is a presenting symptom in 20% to 40% of patients and the frequency tends to increase during the course of the disease.[6,7] Pruritus is a prerequisite for the diagnosis of ICP. In patients with biliary tract obstruction, pruritus occurred in 17% of cases of nonmalignant obstruction and in 45% of patients with a malignant obstruction.[8] It has also been reported in 20% of patients with viral hepatitis and in 7% of patients with cirrhosis.[8]

Pruritus associated with cholestasis is often worse at night and can be transiently exacerbated by premenstrual state and psychological stress, whereas it often is relieved by cool temperatures.[4,5] It may be generalized or localized, particularly over the palms and soles, and often without any definable primary skin lesion. However, several cutaneous complications, such as folliculitis, excoriations, prurigo nodularis, and lichenification, can result from long-standing, vigorous scratching activity.[5,9] The intensity of pruritus varies and does not correlate with the severity of underlying liver disease. Once pruritus evolves in PBC, the severity may diminish over time. However, it is unlikely to disappear completely without treatment until a patient develops cirrhosis.[10]

PATHOGENESIS OF PRURITUS OF CHOLESTASIS

Itch-related nerve endings are found throughout the body surface and are inducible by many physical and chemical stimuli, either acting directly on the nerve endings or indirectly via histamine release.[4] The pruritus pathway involves the dorsal horn, the contralateral spinothalamic tract, and the thalamus. Apart from peripheral stimuli, central mediators, such as endogenous opioids, serotonin, and steroids, have also been postulated in the pathogenesis of pruritus.[9] The classic example is when a central phenomenon is invoked after the intrathecal injection of morphine, which then inhibits pain but is associated with pruritus.[11]

The pathogenesis of pruritus in cholestasis has not been clearly elucidated. It is assumed that cholestasis-related pruritus is induced by pruritogenic substance(s) that accumulate as a result of impaired secretion of bile, which either directly or indirectly affect signaling of the pruritus pathway.[4,9,12] This conventional wisdom is supported by an observation that pruritus generally disappears following resolution of bile duct obstruction, the use of procedures that remove substances from circulation, and LT. However, the causative factor(s) have not been conclusively identified. In the past, bile acids (BAs), which interact with peripheral nerve endings and induce an itching sensation, had been implicated as potential pruritogens. More recent attention has been drawn to the pathophysiologic alterations in cholestasis that induce pruritus, mediating mainly via the central pathways, and that include endogenous opioids, serotonin, and, most recently, lysophosphatidic acid (LPA).[4,9,12] Further, several genetic mutations have been shown to increase susceptibility for cholestatic liver disease; however, no genetic susceptibility specific for the occurrence of pruritus has been yet identified.

The Role of BAs

BAs accumulate in the tissue of patients with cholestasis, and they correlate linearly with the serum levels.[13] They are thought to be important pruritogens in patients with cholestasis, presumably by interacting with peripheral nerve endings. This notion