REVIEW

Journal of Pre-Clinical and Clinical Research, 2011, Vol 5, No 2, 47-49
www.jpccr.eu

Pruritus in liver disease – pathenogenisis and treatment

Agata Michalak[1], Magdalena Hanc[1], Aleksandra Fatyga[1], Aleksandra Skublewska[1], Andrzej Prystupa[2], Jerzy Mosiewicz[2]

[1] *Student Scientific Association, Department of Internal Medicine, Medical University, Lublin, Poland*
[2] *Chair and Department of Internal Medicine, Medical University, Lublin, Poland*

Abstract

Pruritus often constitutes a most irritating ailment in patients suffering from chronic liver diseases, especially when cholestasis plays a prominent role. The exact pathogenesis is not entirely recognized. Nevertheless, several mechanisms have been proposed: pruritus connected with a central/peripheral origin, itch caused by mast cells' hyperactivity, or determined by the intrahepatic cholestasis of pregnancy. This article concentrates on the pruritus accompanying advanced liver disorders. Its pathogenesis and treatment are also discussed.

Key words

pruritus, liver, cholestasis, pathogenesis, treatment

INTRODUCTION – PRURITUS OF CHOLESTASIS

Pruritus (from the Latin verb *prurire*, to itch) is known as a common syndrome of various systemic diseases. The huge clinical and psychological importance of this symptom in many branches of medicine is widely emphasized. It happens due to the influence of the chronic itch on the quality of life and its multiple origin. Pruritus is an interdisciplinary problem universally observed in dermatology, neurophysiology and neuropharmacology. However it is also the symptom of more complex states, such as endocrine disorders, hyperthyroidism and hypothyroidism, iron deficiency anaemia, illnesses of the central nervous system, such as cerebrovascular accidents, brain abscesses, multiple sclerosis and malignancies (lymphomas, gastric and breast carcinoma). Moreover, intractable pruritus is reported to be the prevalent manifestation of liver diseases. Itch is the complication of liver disorders, in particular those characterized by cholestasis. Primary billiary cirrhosis (PBC) has traditionally been the gold model for the study of pruritus [1]. It is an autoimmune liver disease with progressive destruction of interlobular bile ducts leading to a chronic cholestasis and eventually, cirrhosis. Women are mainly affected (female to male ratio of 9:1), with a peak incidence between the ages of 40-60 years [2]. Pruritus touches nearly 70% of PBC patients. Once itching occurs in a person with this illness, it is unusual for it do disappear spontaneously. Its perception seems to vary among patients; itch can be intermitted or persistent, localized to specific parts of body (mostly the palms and the soles) [3]. What is more, it appears to be more irritating in hot, humid weather, at night, and under constricting clothes. The exacerbation of pruritus may also occur as the consequence of premenstrual state plus hormonal replacement therapy in women, and psychological factors (e.g. excitation). Nevertheless, no correlation of intensity or incidence of itch with the severity of cholestasis has been noted. It s also worth mentioning that PBC-connected pruritus resembles the itch in extrahepatic biliary obstruction, secondary biliary cirrhosis, and primary sclerosing cholangitis; in conclusion, they can be discussed together.

Pathogenesis. The origin of pruritus in cholestatic liver diseases is poorly understood. Despite numerous theories, the definite molecular pathogenesis of this phenomenon still remains unknown; however, there are plenty of views on this subject [4, 5].

The concept of putative peripherally-acting pruritogens. Cholestasis leads to the accumulation of various substances in systemic circulation that are physiologically secreted into the bile, and pruritus subsides within 24 h when the mechanical obstruction of the large bile duct is removed. Due to the impaired secretion of bile, the mentioned pruritogenic substances tend to interact with the nerve endings of the skin and induce the sensation of itching [3].

Bile acids and bile salts. Bile acids and bile salts were thoroughly tested as potential sources of pruritus, and was discovered that their level in patients with cholestasis was elevated [3]. Furthermore, this theory is consistent with the beneficial effects of cholestyramine, testosterone and biliary drainage on itch. In conclusion, it has been suggested that the presented pruritogenic compound thereafter acts within the peripheral nervous system to promote the perception of itch [1].

Cutaneous mast cells and histamine. Another interesting issue is the role of cutaneous mast cells in cholestasis [6]. It is unclear whether they can contribute to itch in this case, although their influence on the discussed symptom in other conditions is commonly recognized. With regard to cholestatic liver disease, plasma histamine levels are higher in patients with pruritus than without pruritus [3]. Subsequently, bile acids are known to be potent activators of mast cells. As a result, the degranulation of mast cells induced by bile acids and histamine's excretion in consequence might also constitute the reason for itch.

Corresponding author: Andrzej Prystupa Chair and Department of Internal Medicine, Medical University, Lublin, Staszica 16, 20-081 Lublin, Poland.
E-mail: aprystup@mp.pl

Received: 23 August 2011; accepted: 30 November 2011

The idea of pruritus of central origin. In 1990, the hypothesis that the pruritus of cholestasis is centrally mediated by increased opioidergic tone was published [7, 8]. How opioidergic transmission is increased in cholestasis still remains undefined. However, evaluated plasma levels of Met and Leu-enkephalin, 2 of the endogenous opiod peptides, has been reported in the serum of patients with liver diseases, including those with PBC [6]. The source of peripheral endogenous opioids in liver disorders is not clear. In spite of the fact that the liver is not considered to be a prominent root of opioid peptides in the physiological state, this organ can contribute to the increased availability of opioids in cholestasis [4]. This is suggested by the expression of the gene that codes Met-enkephlin in the liver of rats with acute cholestasis. With regard to the entry into the CNS of periphery-derived endogenous opioids, according to the latest hypotheses they are transported by the special proteins found in the basolateral domain of hepatocytes. These are also found in the choroid plexus and in the blood-brain barrier which can transport opiats *in vitro* [8]. Other considerable evidence that supports the concept of opioids is the oral administration of a potent opioid antagonist to cholestatic patients. In such circumstations, an opioid withdrawal-like reaction takes place. It is usually transient and subsides spontaneously after 2-3 days, despite continued drug administration and does not occur when opioid antagonist is administrated in high doses to healthy subjects [9]. Moreover, in a rat model of acute cholestasis, μu-opiod receptors in the brain are down-regulated, possibly in a response to changes in opioid receptor kinetics as a consequence of increased availability of endogenous opioid agonists at opioid receptors. In the mechanism of pruritus of central origin, there might also be involved another neurotransmitter system. Cholestasis-related altered opioidergic tone may lead to changes in the serotonin system [6]. Such secondary changes may also contribute to the pruritus of cholestasis. Furthermore, increased serotonin release leads to elevated Met-enkephalin levels in the hypothalamus [1]. As a result, the serotonin system, by analogy with the opioid system, may also modulate the perception of pruritus. In conclusion, the idea of pruritus of central origin is a complicated and uneasy theory to explain, and demands to be confirmed by detailed research. Nevertheless, its participation in the development of pruritus in cholestasis seems to be authentic.

Management of primary biliary cirrhosis. The complicated pathogenesis of pruritus in PBC resembles its multiple treatment strategies [1]. Unfortunately, no specific and helpful diet or lifestyle modifications are recommended in patients with liver diseases and pruritus. There are only 2 general prescriptions: namely to keep the finger nails short and filed to avoid severe excoriations, and to be in the hands of a dermatologist in the case of skin disorders connected with scratching. What is more, psychiatric or psychological evaluation and support should be sought for patients in whom the pruritus interfaces with regular activities, and in those who manifest depression and/or suicidal intentions. However, pharmacologic treatment remains a very important element in fighting itch [8]. As the etiology of pruritus of cholestasis is still unknown, its treatment has been largely empirical. Numerous interventions have been used to manage this symptom, with varying efficiancy. Evaluation of medicines is also hard because of the subjective character of pruritus: it is not easy to quantify its perception directly. Many clinical trials have been carried out, with the result that several therapies have been tested many times. Consequently, it was discovered that there are various hypothetical methods for treating pruritus.

Cholestyramine, colestipol and colesevalan. The most widely used conventional treatment for pruritus of cholestasis are anion exchange resins, aimed at the removal of pruritogens from the body. Numbered substances are hydrophilic, water-insoluble, non-absorbable agents that bind bile acids, preventing their absorption from the terminal ileum through the intrahepatic circulation [10]. It is worth noting that to date there has been no randomized study on the effectiveness of cholestyramine. On the other hand, clinical experience is positive and the drug seems to relieve or ameliorate pruritus in the majority of patients. Side-effects of cholestyramine are quite common, but usually not serious. Poor compliance appears to be the major issue due to the unpleasant taste of the drug. It can also contribute to fat malabsorption, constipation, abdominal discomfort and anorexia [8]. Moreover, cholestyramine interfaces with the bio-availability of several drugs, such as Ursodeoxycholic acid (UDCA), thyroxin, digoxin, and oral conceptive hormones. It must be emphasized that at least 4 h should elapse between ingestion of this medicine and any other medication.

Rifampicin. This semi-syntethic antibiotic produced by *Streptomyces mediterranei* has also been studied for the treatment of pruritus in cholestasis [1]. It acts as a rapid and strong inducer of the enzymes which belong to the microsomal drug-oxidizing system, which in consequence promotes the metabolism of the discussed endogenous pruritogenic compounds [10]. Furthermore, rimfapicin tends to compete for the uptake of bile acids into the hepatocyte, eliminating their detergent effect. It has been even shown that this medication also modifies the synthesis of secondary bile acids in the intestinal lumen, thanks to its antimicrobal action, and as a result reduces the amount of hepatotoxic litocholic acid. However, rifampicin has been associated with severe idiosyncratic hypersensitivity reactions, such as haemolytic anaemia, renal failure and thrombocytopenic purpura. To conclude, further assessment is necessary with more studies to explore its side-effects.

Opioid antagonists. The ameliorating effect on pruritus of cholestasis with the administration of opiate antagonists supports the hypothesis that endogenous opioids contribute to itch [2]. They have been intensively explored in the treatment of pruritus of cholestasis over the last decade, and the majority of studies showed beneficial effects. Their function is to avoid binding endogenous opioid agonists, which are elevated during cholestasis [9]. Medications aimed at this process are: nalmefene, naloxone and naltrexone. As many trials have proved, infusion of these opiate antagonists was associated with a decrease in scratching activity, and in the perception of pruritus. On the other hand, the administration of this drugs to cholestatic patients (but not to normal subjects) leads to an opioid withdrawal-like reaction [1]. It may begins within one hour from administration of the medicine, is always temporary, often becoming minimal after 2-3 days, despite continued administration of the drug. Among other side-effects, nausea, colicky abdominal pain, anorexia, cool

skin, and increase in blood pressure are mostly enumerated. Nalmefene, in comparison with naloxone, has a greater bio-availability, more potent action, and longer plasma half-life [11]. Because of its association with hepatotoxicity, the value of naltrexone needs to be further investigated in longer and larger researches. Nevertheless, there is a define role for opiate antagonists in the treatment of pruritus in cholestasis, and studies exploring this topic should continue to be conducted.

Serotonin antaganonists. As mentioned, serotonin might also take part in the pathogenesis of pruritus in liver diseases [5]. According to this hypothesis, some data, series of cases and several trials, support the use of ondansetron – a serotonin type 3 antagonist [2,10]. The anti-pruritic effect of this drug seems to be manifested; however, experience with ondansetron is limited, variable, and needs many more studies.

Extracorporeal albumin dialysis. The MARS (molecular adsorbent and recirculating system) procedure is an extracorporeal haemofiltration system using an albumin-enriched dialysate to remove albumin-bound substances in patients with liver failure. In several reports, its efficiency in the treatment of pruritus appears to be quite satisfying [12], although before using this invasive treatment modality, the practise of a stepwise medical approach is recommended, based on optimized administration of the different drugs [9].

PRURITUS IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY

General description of the medical condition. Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is the most frequent (occurrence 0.5-1%) in pregnant women, mainly in the third trimester of gestation [1], is the cause of hepatic disease in pregnancy, and is associated with foetal distress, spontaneous preterm labour, and stillbirth. Its origin is unknown, although genetic, hormonal and exogenous factors are suspected to play a role [13]. Genetic determination of the condition is implied by the fact that the prevalence of ICP varies greatly according to country. The pruritus that often accompanies ICP may cause lack of sleep, anorexia and malnutrition. Itching originally affects palms and soles of the patients and suggests ICP, which must be confirmed by biochemical tests of liver enzymes. These encompass: total bile acids (tBA), alanine aminotransferase (ALT), aspartate aminoransferase (AST), alkaline phosphatase, bilirubin, of which ALT and tBA are the most sensitive. Very promising studies on the significance of gluathione S-transferase have been conducted – its measurement provides a test of liver dysfunction that distinguishes women with ICP from those with a more benign form of pruritus gravidarum, caused by dermatitis or idopathic [14]. The latter is observed in 20% of pregnant women. On detection of abnormal liver functions, possible alternative causes must be excluded by testing anti-smooth muscle antibodies, anti mitochondrial antibodies, Epstein Barr virus, cytomegalovirus, hepatitis A, B, C [14]. Women affected by Intrahepatic Cholestasis of Pregnancy present with intense itching without a rash, that increases in the evening, and does not respond satisfactorily to anti-histamines, accompanied by elevated concentrations of the above-named liver function tests. Other symptoms of the obstruction of the flow of bile to the duodenum may be recorded, although less commonly: darker urine, lighter stools, prolonged clotting time (due to vitamin K deficiency), and jaundice. As far as the impact of hormones is concerned, progesterone administered for risk of premature delivery (premature uterine contractions or cervical modifications), as well as estrogen oral contraceptives, are associated with ICP. Both exacerbate pruritus.

Treatment. Various medications have been used to fight ICP. As mentioned above, antihistamines and cholestyramine are usually not well tolerated and ineffective. The role of S-adenylosyl methionine in the treatment of ICP is debatable, although it alleviates pruritus, the foetal/neonatal outcome needs to be studied. Women with ICP are most successfully treated with ursodeoxycholic acid, which provides subjective improvement, or even complete resolution of pruritus, and does not show any adverse side-effects in mothers or babies [1].

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