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A SYSTEMATIC APPROACH TO CHOLESTATIC ASSOCIATED PRURITIS AND UNDERSTANDING BASIC MECHANISM WITH THERAPEUTIC MANAGEMENT: AN UPDATE REVIEW

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ABSTRACT

This review is mainly focused on updating knowledge aboutcholestatic associated pruritis and understanding basic mechanism with therapeutic management. It summarizes the characteristics of clinical epidemiological studies, diagnostic approach and evidence based therapeutic recommendations regarding the form of pruritis. Cholestasis is defined as a decreasing bile flow due to impaired secretion by hepatocytes or obstruction of bile flow through intra or extra hepatic bile ducts. Therefore, the clinical definition of cholestasis in any condition in which substances normally excreted in to bile are retained. Pruritis is frequent symptom that accompanies several liver diseases, particularly cholestatic ones. It is extremely important to know about cholestatic pruritis to be sought by the patient when they experience the symptom. In addition to allowing an adequate diagnosis, a better pathophysiological; understanding of hepatic pruritis provides the identification of new therapeutic targets and optimization of approaching patients with this condition.

KEYWORDS: Pruritis, cholestasis.

INTRODUCTION

Cholestasis is defined as a decreasing biliary flow and impaired secretion by hepatocytes or the obstruction of this flow in the intra or extra hepatic bile ducts. On the otherhandthe detailed description of cholestasis in which substances normally secreted in the bile are retained. Serum levels of conjugated bilirubin and bile salts are the most commonly measured ones. The levels of serum alkaline phosphatase and gamma-glutamyl transferase that characterize cholestasis and require diagnostic investigations with above normal ranges. Clinically, the impaired bile flow can present as clotting disorder, jaundice, fat malabsorption, fatigue and pruritis.[1,2]

Pruritis is frequent symptom that accompanies several liver diseases, particularly cholestatic ones. It can be mild and tolerable, but it can also dramatically reduce the quality of life, sleep deprivation, depressive symptoms are most severely affected patients. This happens because it is very often considered this condition that is not worth infact assessing or treating. This evidence suggests that it is a symptom with a substantial impact on the quality of life of patients with cholestatic liver disease.[3]

EPIDEMOLOGY

PREVALENCE OF PRURITIS IN THE MAIN CHOLESTATIC DISEASES

DISEASE	PREVALENC OF PRURITIS
IHCP	100%
PBC/PSC	70%-80%
Lithiasis/ Tumor	16%-45%

According to relevant studies, the prevalence rate in other countries:
United states- pruritis occurs approximately in adults 20%. It is present in approximately 25% with jaundice and 50% receiving renal dialysis. Incidence rate in 20-70% and 38% of patients affected by cholestatic associated pruritis.

According to international levels, an underlying systematic disease is currently reported in 10-50% patients who seek medical attention for pruritis. In previous data shows 85% of patients on hemodialysis are affected, new reports suggest the rate is 22-66%.
Patients with polycythemia vera, 48-70%.

Rate of malignancy with generalized pruritis is less than 1-8%. In case of Hodgins disease approximately 35%

and non-Hodgin lymphoma with 10% during their clinical course.[4,5]

ETIOLOGY[6,7]

Cholestatic pruritis is particularly common with cholestasis caused by primary biliary cirrhosis, primary sclerosing cholangitis, chronic hepatitis c, obstructive carcinoma of pancreas/biliary system and end- stage liver disease of any cause.

Hematologic pruritis seen in association with following conditions:

- Polycythemia vera
- Iron deficiency
- Essential thrombocythemia

Endocrine pruritis seen in association with following disorders:

- Hyperthyroidism
- Hypothyroidism
- Hyperparathyroidism
- Hypoparathyroidism

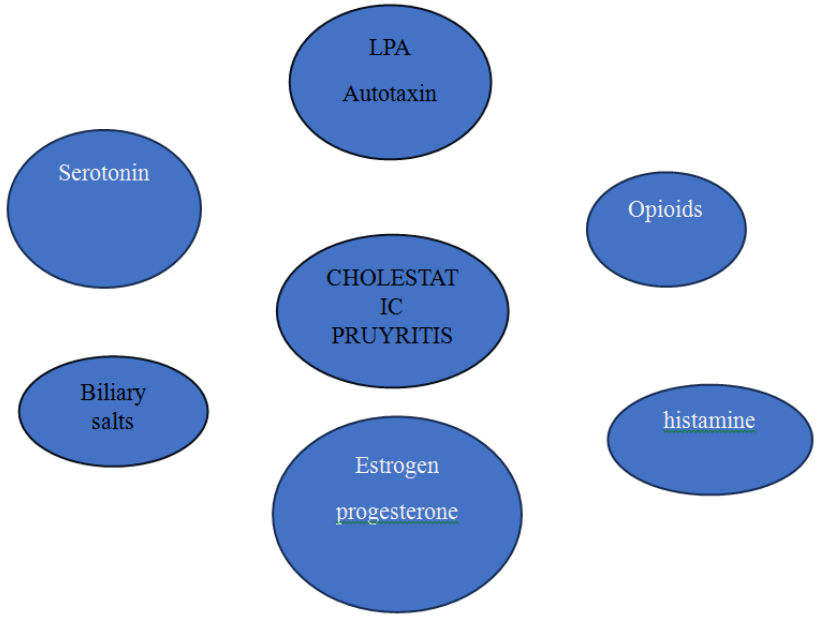
Following malignancies are known to have potential to cause itching:

- Hodgin's disease
- Non-Hodgin lymphoma
- Leukemia
- Cutaneous t-cell lymphoma

Systemic disorders associated with pruritis includes:

- Drug induced pruritis without a rash
- Scleroderma
- Dermatomyocitis
- Mastocytosis
- SLE

PATHOPHYSIOLOGY



The mechanism of cholestasis can be broadly classified into hepatocellular, where an impairment of bile formation occurs obstructive and imbidence of bile flow is formed. Typical of obstructive cholestasis is bile plugging of interlobular bile ducts, portal expansion and bile duct proliferation in association with centrilobular cholate injury. The transport of solute into the canaliculus by specific transporters creates chemical and osmotic gradience and promotes water flow by paracellular pathway.

The sensation of pruritis is transmitted through slow conducting unmyelinated C-polymodal and possibly type A data nociceptive neurons with free nerve endings located near dermo epidermal junction in epidermis. These neurons appears more superficially and sensitive to pruritogenic substances than pain receptors. Activators of these nerves include histamine, neuropeptide substance P, serotonin, bradykinin, proteases and endothelial. Impulses are transmitted from dorsal route ganglion to spinothalamic tract and eventually to thalamus.

BILE ACIDS

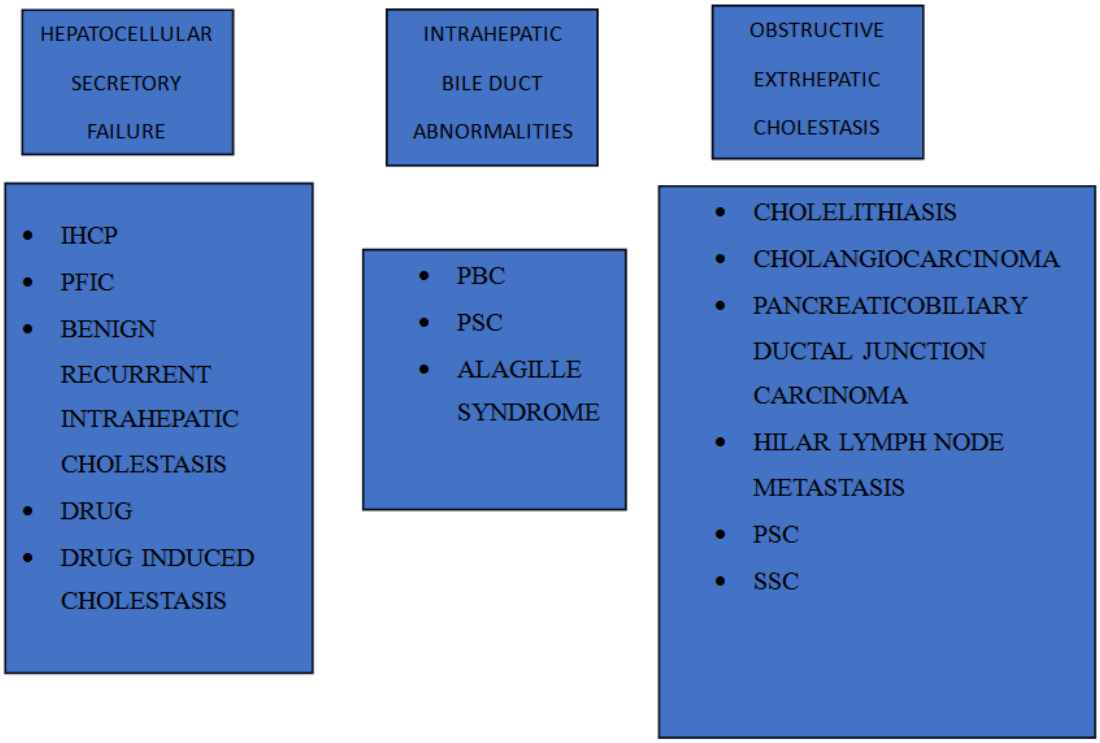
Bile acids have been implicated in the pathogenesis of cholestasis pruritis. Patients with liver disease under condition–bile acids have been reported to produce local itching. It results this symptom fluctuates regardless of the serum bile acid levels who experienced pruritis with synthetic bile acids.[8]

ENDOGENUS OPIOIDS

Opioids are known to modulate the sensation of pruritis both peripherally and centrally. Stimulation of opioid mu receptors, stimulation of kappa receptors and blockage of mu receptors suppress pruritis. As the liver disease progresses, liver clearence of endogenous opioids decreases, with a consequent increase in serum levels. However, pruritis severity does not corelate with endogenous opioid levels.

LPA (LYSO PHOSPHATIDIC ACID) and AUTO TAXIM (ATX)

It indicates that LPA, a potent neuronal activator, as well as ATX, the enzyme that produces LPA, are key elements in the pathophysiology of pruritis in cholestasis. Serum ATX activity corelates with pruritis intensity and response to treatment in patients with cholestatic pruritis, when it is associated with other etiologies. Patients who experienced with cholestasis and pruritis that ATX activity is significantly higher than in those with cholestasis without pruritis and ATX levels corelate with the severity of the symptom. The response to therapeutic interventions (bile acid binding resins or rifampicin) is associated with decreased serum auto- taxin activity, further supporting the role of auto taxin-LPA in the pathogenesis of pruritis in cholestasis. At the tissue level local deposition of excess bile salts was first suggested mechanism for pruritis in cholestatic disease. The proposed modulators of pruritic mechanism of cholestasis include bile salts opioids, histamine and lysophosphatidic acid-LPA, progesterone, estrogen and serotonin. The current evidence suggest that complex interaction of these substances and there are therapeutic agents for multiple targets.[9]

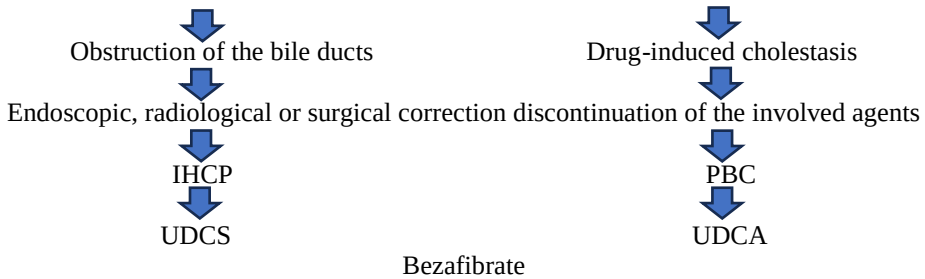


CLINICAL MANIFESTATION

The pruritis associated with cholestasis often exhibits a circadian rhythm, with patients reporting greater intensity in early hours of night. However, intense scratching can cause secondary alterations, such as excoriations, folliculitis and nodularis which occasionally lead to mis interpretation of its etiology as a primary skin condition. The dimensional pruritis severity scales include visual analog scale, numerical scale and verbal assessment scale, in addition to multidimensional questionnaires such as 5-D itch scale, pruritis severity scale and Eppendorf pruritis questionnaire.

Use of emollients and topical moisturizing and cooling agents (Eg: Emollients containing 1-2% menthol); Shortening of nails; encourage the use of light clothing made of natural fibers, such as cotton and avoid woolen or very tight clothing; Baths with cold water; Psychological interventions.

STEP 1: TREATMENT OF UNDERLYING HEPATOBILIARY DISEASE



STEP: 2 SYSTEMATIC TREATMENTS FOR PRURITIS

Cholestyramine
Rifaximin
Naltrexone
Sertraline

STEP: 3 EXPERIMENTAL TREATMENT FOR REFRACTORY PRURITIS

Plasmapheresis
MARS
Naso biliary drainage
UVB phototherapy
Opioid k receptor agonist
IBAT inhibitors
Auto-taxin inhibitors
Agonistas PPAR-Benzafibrato
SEVERE AND INTRACTABLE PRURITUS
Liver transplantation[10]

DISCUSSION

This review highlights the fact that for cholestasis associated pruritis, there are many possible pruritogens likely to play a role simultaneously. Due to different theories on the cause of cholestasis associated pruritis, different treatments exist of which none has yet shown to present the final solution. Research in this field should continue in order to clarify the mechanism and to provide a satisfying treatment for patients with cholestasis associated pruritis. One of the biggest challenges in cholestasis associated pruritis on the basis of multi organ aspect. Besides the affected liver, multiple other organs play a potential role in cholestasis associated pruritis, including the intestine with its entero-hepatic circulation of multiple unknown compounds, the blood with all its proteins, hormones and lipids, the skin with its receptors, barriers and nerves, and the brain which is still unknown. All of these aspects can affect the production, transport, accumulation, binding, metabolism and excretion of potential pruritogens.

We can interpret the complete enterohepatic circulation by partial external biliary diversion or remove hypothetical compounds from the circulation in which compound elimination is essential. Based on the most recent studies, we would expect higher levels of pruritogens in plasma and possibly even in bile of patients with chronic pruritis compared to people without chronic pruritis, elimination or filtration provides relief of pruritis. However, the possibility remains the pruritis is not caused by a change in the level of pruritogens but rather sensitivity to them. Thus, patients with cholestasis associated pruritis, there might be a change in sensory signaling involving receptor expression in neurons or the skin. These alternatives need to be investigated in details still.

CONCLUSION

Cholestatic pruritis is a complicated disease in which process that continues to be under treated and under recognized. In diseases like obstructive cholangiopathies, genetic conditions that causse cholestasis a majority of patients suffer from this condition. The recommended medications for treating cholestasis associated pruritis with cholestyramine that can be effective. As a step wise approach after cholestyramine, rifampin and naltrexone are the next recommendations. Therefore, second line of treatment can be recommended as bezafibrate. There are many new promising drug classes and agents in clinical trials, including PPAR agonists and IBAT inhibitors. With these promising agents, we hope that cholestatic pruritis may be a condition that may be adequately treated with the addition of asses to emerging therapies under the guidance of AASLD and EASL guidelines. As a result pruritis is a symptom that has a complete symptomatic control in most of the patients.[11]

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