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MINI REVIEW

Pathophysiology and current management of pruritus in liver disease

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Summary Pruritus is frequently reported by patients with cholestatic hepatobiliary diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy and hereditary cholestatic syndromes, but may accompany almost any other liver disease. Increased concentrations of bile salts, histamine, progesterone metabolites or endogenous opioids have been controversially discussed as potential pruritogens in cholestasis in the past. Most recently, novel insights unravelled lysophosphatidic acid (LPA), a potent neuronal activator, as a potential pruritogen in pruritus of cholestasis. Nevertheless, the pathogenesis of pruritus in cholestasis is still not clearly defined and current antipruritic treatment strategies provide relief only in a part of the affected patients. Based on recent experimental and clinical findings, this review outlines the actual insight in pathogenesis of pruritus in cholestasis and summarizes evidence-based and experimental therapeutic interventions for cholestatic patients suffering from itch.

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Definition and prevalence

The observation that pruritus accompanies jaundice has already been made by the ancient Greek physician Aretæus the Cappadocian in the 2nd century BC [1]. Today, itch is well known as a frequent and agonizing symptom accompanying many types of liver diseases, particularly those with cholestatic features [2–4]. In these disorders, cholestasis may be due to:

- impaired hepatocellular secretion as observed in intrahepatic cholestasis of pregnancy (ICP), benign recurrent intrahepatic cholestasis (BRIC), progressive familial intrahepatic cholestasis (PFIC), toxin- or drug-induced cholestasis, and chronic viral hepatitis B and C infections;
- intrahepatic bile duct damage and secondary hepatocyte secretory failure as seen in primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and paediatric cholestatic syndromes such as the Alagille syndrome;
- obstruction of the intrahepatic or extrahepatic bile duct system as found in choledocholithiasis and hepaticolithiasis, PSC, cholangiocellular carcinoma, obstructive tumours of the pancreatic head or enlarged lymph nodes located in the hilar region, bile duct adenomas, or biliary atresia [5].

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The prevalence of pruritus between the different liver diseases varies considerably. While ICP is defined by the presence of pruritus [6], it is a pre-eminent symptom in 25–80% of patients with chronic cholestatic liver disorders such as PBC and PSC and experienced by at least 80% of patients at any time during the course of their disease [7–10]. Obstructive jaundice is less frequently accompanied by pruritus and was reported to occur in 16% of patients with benign biliary obstruction such as choledocholithiasis and up to 45% of those with malignant obstruction such as carcinoma of the head of the pancreas [11]. Itching was noted in 5–15% of patients suffering of chronic hepatitis C infections [12–14], whereas it is rarely seen in chronic hepatitis B patients, non-alcoholic fatty liver disease, alcoholic or non-alcoholic steatohepatitis even when cholestasis is present [15].

Clinical picture

Although pruritus is frequently undervalued by clinicians, it is often the major burden of the cholestatic patient and can dramatically reduce quality of life. Pruritus may be mild and tolerable, but does, in some patients, limit activities of daily life and cause severe sleep deprivation resulting in lassitude, fatigue, depression and even suicidal sensation. In rare cases, intractable pruritus may become a primary indication for liver transplantation even in the absence of liver failure [4,16–18].

One characteristic feature of pruritus in cholestatic patients is its circadian rhythm with the highest intensity reported in the evening hours and early at night [5]. A diurnal variation of itch intensity has been objectified by measuring the scratching intensity in PBC patients using piezo-film technology [9]. Circadian fluctuations – as described, e.g., for cortisol – of yet unknown substances that either aggravate or attenuate pruritus might be responsible for this phenomenon. Although cholestatic pruritus may be generalized, another specific feature is its localisation at the limbs and in particular at the palms and soles [9,19]. Scratching of the skin surface barely alleviates itch intensity in cholestasis and patients tend to rub rather than to scratch. In contrast to dermatological pruritus, primary skin lesions are not detectable in these patients, however, intense scratching activity may cause secondary skin lesion such as excoriations and prurigo nodularis [20]. In female cholestatic patients, pruritus commonly exacerbates premenstrually, during hormone replacement therapy, and in late pregnancy indicating a role of female sex hormones in the pathogenesis of pruritus.

Pathogenesis

Bile salts

Aretæus, the Cappadocian, explained the itchy skin in jaundiced patients by prickly bilious particles [1]. More than two millennia later, his hypothesis is at least partly still valid as the removal of bile from the body either by external biliary diversion [21–23] or nasobiliary drainage [24–26] quickly and dramatically alleviates severe cholestatic pruritus. Thus, certain biliary substances contribute either

directly or indirectly to the onset of itching. During cholestasis, many cholephiles, among which are bile salts and bilirubin, accumulate in circulation and tissues. The insightful observation of physicians in the 19th century that pruritus may precede the appearance of jaundice, which is now recognized commonly in ICP [6] and PBC patients [27], suggested substances other than the pigment of bile, bilirubin, as causative pruritogens [28]. Bile salts being discovered during that era [29] were, therefore, regarded as primary candidates [30,31]. This idea was supported by the facts that feeding of bile salts to cholestatic patients aggravated their pruritus [32,33], intradermal injection of bile salts caused pruritus in healthy volunteers [34,35] and anion exchange resins, which bind bile salts inside the intestinal lumen, ameliorate pruritus [36–39]. Further support to a causative role of retained bile salts in cholestatic pruritus was lent by the observation that long-lasting intractable pruritus subsided rapidly in desperate cholestatic patients after ileal exclusion surgery [23,40], transcutaneous [21,22,41–43] and nasobiliary drainage of bile [24–26]. In addition, increased levels of total bile salts have been reported in patients with non-cholestatic disorders being associated with pruritus such as uraemia [44,45]. These experimental and clinical observations favoured back then [15,46] – and still in current literature [47] – increased concentrations of bile salts as causative pruritogens in liver diseases (Table 1).

However, various observations dispute bile salts as a key mediator for the pruritus of cholestasis. Even with the most sophisticated technique, no correlation between the concentration of any naturally occurring bile salt in the circulation, urine or skin and severity of pruritus could be proven [15,48–51]. Furthermore, frequency and intensity of cholestatic pruritus does not correlate with the severity of cholestasis [20]. Itching in patients with primary biliary cirrhosis may be the initial presenting symptom in early stages of the disease when bile salts are low. However, in patients with terminal liver failure when cholestasis is most severe and bile salts reach their highest levels, pruritus is often lost [5]. Many patients, particularly those with obstructive cholestasis, have highly elevated levels of serum bile salts but never experience pruritus [52]. In contrast, women with intrahepatic cholestasis of pregnancy presenting with the mildest imaginable form of cholestasis with marginally increased bile salt concentrations do all suffer from pruritus [6]. In some cholestatic patients, itching spontaneously ameliorates or even vanishes despite ongoing cholestasis and unaltered raised levels of bile salts [20,52]. Cholestyramine which binds bile salts but also many other amphiphilic substances in the gut, improved pruritus not only in cholestasis but also in polycythemia *rubra vera*, a haematological disorder being not associated with elevated bile salts [53]. The modern anion exchange resin colesevelam efficiently decreased serum bile salt concentrations by approximately 50% in a well-defined cohort of pruritic patients but improvement of pruritus was similar to that of placebo [54]. The enzyme inducers phenobarbital and rifampicin effectively improved pruritus without changing or with only temporarily decreasing the levels of serum bile salts [55–57]. Anecdotal treatments included androgens such as methandrostenolone, which relieved pruritus but worsened cholestasis and raised serum bile salts [58,59]. Finally, bile salt concentrations did not correlate with itch

Table 1 Conflicting data about the relationship between pruritus and potential pruritogens in cholestasis.

| Pros | Literature | Cons | Literature |
|--|-----------------|--|------------|
| <i>Histamine</i> | | | |
| Key pruritogen of allergic reactions | | Typical histamine-induced skin lesion lacking | [2–5] |
| Increased concentrations in pruritic cholestatic patients | [95] | No correlation between severity of itch and histamine concentrations | [51] |
| | | Antihistamines mostly ineffective | [2–5] |
| <i>Bile salts</i> | | | |
| Increased concentrations during cholestasis | [30,31] | Pruritus observed in patients with normal levels of bile salts | [15] |
| Experimental induction of pruritus by application to the skin | [34,35] | No correlation between severity of itch and concentrations of bile salts in circulation and skin | [15,48–51] |
| Aggravation of pruritus by bile salt feeding | [32,33] | Obstructive cholestasis often associated with highest bile salt levels but not pruritus | [52] |
| Improvement of pruritus by bile acid binding resins | [36,39,120,121] | ICP women have mildest increases of bile salts, yet all suffer from pruritus | [6] |
| Relief of pruritus by external or nasobiliary biliary drainage in various cholestatic disorders | [21–25,40–42] | Spontaneous amelioration of pruritus despite ongoing cholestasis | [20,52] |
| Increased concentrations in uremia associated with pruritus | [44,45] | Inefficacy of bile salt sequestrant colesevelam | [54] |
| | | Phenobarbital improves pruritus without reducing bile salt levels | [55] |
| | | Androgens improve pruritus and increase bile salt concentrations | [58,59] |
| <i>Endogenous opioids</i> | | | |
| Increased concentrations in pruritic cholestatic patients | [79,80] | No correlation between severity of itch and concentrations of endogenous opioids | [51,80] |
| Induce pruritus upon spinal application | [75] | Endogenous opioids are increased in advanced stages of PBC, while pruritus is typically seen in early stages | [80] |
| μ -opioid antagonists moderately improve pruritus | [79,85–91] | μ -opioid activity not increased in ICP compared to pregnant controls | [51] |
| Spinally administered plasma extracts of pruritic cholestatic patients induce facial scratching in monkeys | [81] | Antinociceptive effect of cholestasis in mice is mediated peripherally, not centrally | [94] |
| <i>Lysophosphatidic acid</i> | | | |
| Increased concentrations in pruritic cholestatic patients | [51] | ATX inhibitors or LPA antagonists yet unavailable and unproven to reduce pruritus | |
| Intradermally application induces scratching behaviour in experimental animals | [51,110] | | |
| ATX, the enzyme forming LPA, correlates with itch intensity | [51,111] | | |
| Therapy efficacy correlates with ATX activity | [51,111] | | |

intensity in PBC patients undergoing nasobiliary drainage [25]. In summary, rather the type of hepatobiliary disease and not simply the level of bile salts or the magnitude of cholestasis may determine itching in cholestasis. Bile salts and their metabolites play – if any – an indirect role in the pathogenesis of pruritus of cholestasis (Table 1).

Steroids

Steroid hormones and their metabolites have been discussed as mediators of cholestatic pruritus [5] as these compounds influence many ionotropic receptors such as transient receptor potential vanilloid 1 (TRPV1) [60], GABA-A [61], glycine [62], glutamate [63–66], and serotonin receptors [67]. These speculations were based on the following observations. Female mice scratched more often compared to male mice upon intradermal injection of different pruritogens [68]. Female cholestatic patients reported a more intense and more frequent pruritus compared to men [69]. The highest concentrations of steroids and steroid metabolites are seen in pregnant women [70] and intrahepatic cholestasis of pregnancy, which typically occurs during the third trimester of pregnancy is defined by the presence of pruritus [6,71,72]. After delivery, pruritus rapidly disappears and serum liver tests normalize. Interestingly, urinary levels of disulphated progesterone metabolites correlated slightly with the improvement of pruritus in ICP patients treated with ursodeoxycholic acid, whereas neither bile salt metabolites nor other steroid metabolites showed a similar correlation [71,73]. Thus, steroid hormones might modulate neuronal excitability of pruritoceptive and/or nociceptive fibres in cholestatic patients.

Endogenous opioids

Since the early 1980s, endogenous opioids such as Met- and Leu-enkephalins have been discussed as pruritogens in cholestasis [74]. Opiates, particular those being epidurally or spinally administered, are indeed capable of inducing itch in humans [75] and facial scratching in monkeys [76]. Increased levels of endogenous opioids were found in bile duct-resected rats [77,78] as well as in plasma of cholestatic PBC patients [79,80]. Spinally administered plasma extracts from four patients suffering from cholestatic pruritus induced facial scratching behaviour in monkeys, which could be abolished by coadministering the μ -opioid-antagonist naloxone [81]. In different parts of the brain of bile duct-resected rats opioid receptors were shown to be downregulated, which was explained by the authors as a consequence of increased exposure of opioid receptors to endogenous opioids [82]. The source of the increased opioids in cholestasis may be the liver itself as mRNA expression of preproenkephalin was increased in liver of bile duct-resected rats [83] and Met-enkephalin immunoreactivity was raised in the periportal areas and proliferating bile ductules of cholestatic rat livers [84]. The importance of the altered endogenous opioid system in pruritus of cholestatic patients is underlined by the moderate antipruritic effect of μ -opioid receptor antagonists such as naloxone, naltrexone, and nalmefene [79,85–92].

Nonetheless, several arguments question the role of endogenous opioids as direct pruritogens in cholestasis. A correlation between itch intensity and endogenous opioid concentrations has never been shown [80]. Opioid levels were similar in PBC patients without pruritus compared to those with pruritus [51] and correlated with the stage of disease in PBC patients rather than with the presence of pruritus [80]. In PBC patients, methionine-enkephalin concentrations were significantly raised in histological stage 3 and 4, however, pruritus typically occurs in the early stages of the disease and rather improves in end-stage liver disease [5,80]. Furthermore, μ -opioid activity was similar in women with ICP compared to gestation-matched pregnant controls [51]. The antinociceptive and pruritoceptive effect of raised concentrations of endogenous opioids in cholestasis have been explained by a central mode of action [93]. However, it was recently shown that the antinociceptive effect of endogenous opioids in a cholestatic mouse model was due to local effects at the level of peripheral sensory nerve endings, but not centrally mediated [94]. Therefore, the endogenous opioid system is certainly altered in cholestasis, but endogenous opioids are not likely to be the causative pruritogens in cholestasis (Table 1).

Histamine

Histamine, the main mediator of allergic reactions, which originates particularly from mast cells and basophils, has also been discussed as potential pruritogen in cholestasis [46]. Indeed, increased plasma concentrations of histamine have been measured in chronic cholestatic liver disorders with the highest concentrations in pruritic patients [95]. Similarly, histamine levels were raised in cholestatic animal models [96] and bile salts, in particular, the hydrophobic deoxycholate and chenodeoxycholate and their conjugates, were shown to release histamine from mast cells [97,98]. However, bile salt-induced histamine release occurred at bile salt concentrations that are much higher than those generally observed in cholestatic patients. In addition, patients with cholestatic pruritus do not respond to antihistamines. Tryptase levels, which represent a specific marker for activation of mast cells, were also unchanged in pruritic compared to non-pruritic cholestatic patients [51]. Furthermore, typical histamine-induced skin alterations such as erythema, urticaria and flares are not seen in cholestatic patients suffering from pruritus and antagonists of the histamine-1-receptor do, in most instances, not improve cholestatic pruritus [46]. Thus, histamine is unlikely to represent a causative factor in the pathogenesis of cholestatic pruritus.

Serotonin

The biogenic amine serotonin has also been reported to induce scratching behaviour in mice [99,100] and itch sensations in humans upon intradermal injection [101,102]. The selective serotonin reuptake inhibitors sertraline [103,104] and paroxetine [105] have been used to treat cholestatic pruritus with moderate success. In contrast, clinical studies using the 5-HT₃-receptor antagonist ondansetron resulted in conflicting results regarding the improvement of itch intensity [106–109]. This paradoxical effect may be explained

by the dichotomous effects of serotonin on central versus peripheral nervous system. Cholestasis may alter serotonin homeostasis and, thereby, influence itch perception or signalling, but serotonin seems not to be a direct mediator of pruritus in chronic cholestatic disorders.

Lysophosphatidic acid

Screening blood of pruritic cholestatic patients for neuronal activation in various cell lines, we could recently identify lysophosphatidic acid (LPA), a potent neuronal activator, as potential pruritogen in cholestatic patients [51]. Serum LPA concentrations were increased only in those cholestatic patients who suffered from pruritus. Intradermally injected LPA, but not the vehicle control, induced scratching behaviour in mice in a dose-dependent manner [51,110]. LPA is formed from lysophosphatidylcholine by the enzyme autotaxin (ATX). ATX activity and protein content were markedly increased in sera of ICP women compared to pregnant controls and in sera of cholestatic patients with versus without pruritus. Furthermore, in contrast to all other substances discussed as potential pruritogens in the past ATX activity significantly correlated with the itch intensity [111]. Strikingly, in PBC patients with otherwise intractable pruritus who underwent nasobiliary drainage both, itch intensity and autotaxin activity decreased during drainage and returned to increased levels when pruritus had returned [51]. These data suggest that autotaxin and its product, LPA, play a key role in cholestatic pruritus (Table 1).

Management

Treatment options for pruritus in cholestasis remain limited to a few evidence-based and several experimental medical and interventional therapies. Therapeutic interventions should primarily focus on an adequate therapy of the underlying hepatobiliary disease, as this may result in relief of pruritus.

The rationale for medical and interventional therapeutic approaches is:

- to remove the pruritogens from the enterohepatic cycle by non-absorbable, anion exchange resins such as cholestyramine, colestipol, and colesevelam in mild pruritus or interventions such as nasobiliary and transcutaneous drainage or external biliary diversion in desperate cases;
- to alter the metabolism of the presumed pruritogens in the liver and/or the gut by biotransformation enzyme inducers such as rifampicin;
- to modify central itch and/or pain signalling by influencing the endogenous opioidergic and serotonergic system via μ -opioid-antagonists and selective serotonin re-uptake inhibitors, respectively;
- to remove the potential pruritogen(s) from the systemic circulation by invasive methods such as anion absorption, plasmapheresis or extracorporeal albumin dialysis.

Table 2 highlights the current therapeutic recommendations of the 2009 EASL Clinical Practice Guidelines for the management of pruritus in cholestatic patients [2].

Ursodeoxycholic acid (UDCA) exerts beneficial anticholestatic effects and is, therefore, administered to several cholestatic disorders such as primary biliary cirrhosis, primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, cystic fibrosis-associated liver disease, and paediatric cholestatic syndromes. Although UDCA was reported to effectively diminish itching in some paediatric cholestatic disorders [112–114], it did not convincingly improve pruritus in randomized, placebo-controlled trials for treatment of PBC or PSC [115,116]. UDCA was well-tolerated and alleviated pruritus in women with ICP and also restored serum liver tests, time to delivery, and birth weight of the neonates [73,117,118].

The anion exchange resins cholestyramine and colestipol have been extensively used to treat cholestatic pruritus and ameliorated pruritus in small trials within 2 weeks [36–39,119–122]. Cholestyramine is recommended as a 4 g dose 1 hour before and after breakfast and may be extended to 4 × 4 g/d. Resins should, however, be taken at least 4 hours prior to any other medication as they may interfere with their intestinal absorption [123]. Adverse effects

Table 2 Current therapeutic recommendations for the management of pruritus in cholestasis [2].

| Approach | Drug/Therapy | Final dosage | Evidence |
|----------|--|--------------------|-------------------|
| 1st line | Ursodeoxycholic acid (UDCA) ^a | 10–15 mg/kg/d (po) | I/B1 ^a |
| 2nd line | Cholestyramine | 4–16 g/d (po) | II-2/B1 |
| 3rd line | Rifampicin | 300–600 mg/d (po) | I/A1 |
| 4th line | Naltrexone | 50 mg/d (po) | I/B1 |
| | Sertraline | 100 mg/d (po) | II-2/C2 |

po: peroral.

Categories of evidence: I: randomized controlled trial; II-1: controlled trials without randomization; II-2: cohort or case-control analytic studies; II-3: multiple time series, dramatic uncontrolled experiments; III: opinions of respected authorities, descriptive epidemiology. Evidence grading: A: high quality; further research is very unlikely to change our confidence in the estimate of effect; B: moderate quality; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; C: low quality; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain.

Recommendation: 1: strong; factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost; 2: weak; variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

^a Evidence and recommendation for intrahepatic cholestasis of pregnancy.

include abdominal discomfort, bloating, diarrhoea, hypertriglyceridemia, and rarely bleeding after long-term use. The novel anion exchange resin colesevelam, which has superior binding affinities for bile salts than cholestyramine and colestipol was, however, not more effective than a placebo in alleviating the severity of pruritus of cholestasis [54]. It may be that cholestyramine binds the “real” pruritogen more efficiently in the gut lumen than colesevelam, but these results certainly question bile acid resins as first line treatment.

The pregnane X receptor (PXR) agonist, rifampicin, is recommended as second line therapy and is thought to exert its antipruritic effect by the induction of phase I, II and III biotransformation enzymes and transporters such as CYP3A4, UGT1A1, SULT2A1 and MRP2 [124,125], thereby enhancing metabolism and/or secretion of potential pruritogens. Additionally, rifampicin may alter intestinal metabolism of potential pruritogens by its antibiotic effect on the intestinal flora. The antipruritic effect of rifampicin cannot only be due to increased CYP3A4 activity as phenobarbital similarly induced CYP3A4 but was inferior in diminishing pruritus [126]. Various prospective randomized, placebo-controlled trials have proven that rifampicin at doses of 300–600 mg/d [56,126,127] and 10 mg/kg per day [57], respectively, is an effective and safe treatment of cholestatic pruritus. Hepatotoxicity, after treatment for several weeks or months, may be an adverse effect of rifampicin in up to 12% of cholestatic patients [57], requiring the monitoring of serum transaminase levels at regular intervals [128].

If rifampicin is ineffective, the μ -opoid antagonist naltrexone should be regarded as third line therapy. Several clinical trials showed a moderate antipruritic effect of naltrexone at doses of 25–50 mg/d [87,88,90,91]. This drug is mostly well-tolerated during long-term treatment. Naltrexone should, however, be started at doses of 12.5 mg/d as severe opiate withdrawal-like reactions may occur in some cholestatic patients during the first days of treatment [79]. To prevent a breakthrough phenomenon with concomitant reoccurrence of pruritus naltrexone treatment can be interrupted for 1 or 2 days per week [87].

Finally, the serotonin-reuptake inhibitor (SSRI) sertraline [103,104] was moderately effective in reducing itch intensity in cholestatic patients and is, therefore, recommended as fourth line therapy.

If all the above-mentioned drugs are ineffective, experimental treatments can be considered. These treatment options include phototherapy such as UVA and UVB light on the skin and bright light directed towards the eyes. As experimental drug therapies propofol [129], lidocaine [130], phenobarbital [126], flumecinol [131], stanzolol [132], ondansentron [107], dronabinol [133] and butorphanol [134] have been used in the past with variable success. Furthermore, invasive procedures such as plasmapheresis [135], molecular adsorbent recirculating system therapy [136–138], plasma separation/anion absorption [139], transcutaneous and nasobiliary drainage [24,25] have been beneficial in severe, otherwise, untreatable cholestatic pruritus in case series. For these experimental approaches, the reader is referred to reference [5]. Finally, future strategies might include LPA-receptor blockers and autotaxin inhibitors (which are currently developed) if the pathophysiological

role of lysophosphatidic acid and autotaxin in pruritus can be further substantiated.

Conflict of interest statement

The authors have no conflicts of interest that are directly relevant to the content of this review.

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