The challenge of cholestatic pruritus

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Abstract

Pruritus can be the dominant symptom of cholestatic liver disease but is difficult to treat since unraveling its pathophysiology is a great challenge. Serum autotaxin activity correlates with pruritus intensity, but its causal relationship, expression pattern and exact mode of action during cholestasis remain to be established. The anion exchange resin cholestyramine, the PXR agonist rifampicin, the opioid antagonist naltrexone and the serotonine reuptake inhibitor sertraline are recommended by evidence-based guidelines as stepwise therapeutic approaches to treat itch in cholestasis. Rifampicin, the most effective antipruritic agent in cholestatic itch, has been shown to reduce autotaxin transcription *in vitro*. Experimental approaches include UVB phototherapy, extracorporeal albumin dialysis, nasobiliary drainage and in desperate cases even liver transplantation. Relevant clinical observations along with the different metabolic, neurologic and endocrine targets of available therapies in cholestatic pruritus are reviewed here. (Acta gastroenterol. belg., **2012**, 75, **399-404**).

Key words : cholestasis, pruritus, itch, autotaxin, bile salts, rifampicin.

Introduction

Quality of life

As in several other systemic disorders, pruritus can be the most burdensome symptom of chronic cholestatic disease. Quality of life studies indeed identify pruritus as a significant impact factor on both physical and mental impairment (1,2).

Pattern of pruritus in liver disease

The pruritic skin, initially often palms and soles, does not show any primary pathology but sometimes extensive secondary scratch marks. Complaints are the worst at night when patients seek for some fresh breeze, since warmth seems to aggravate itchy sensations.

Prognostic factors for pruritus in liver disease

Serum bilirubin levels and jaundice do not significantly differ between patients with and without cholestatic pruritus (3,4) and serum bilirubin levels are within the normal range in a substantial portion of patients with chronic cholestasis and itch (5,6). While serum alkaline phosphatase (AP) was found to be an independent risk factor for the occurrence of pruritus in a cohort of 355 PBC patients (4), other studies report no serum liver tests nor markers of inflammation to be predictive (7). The only parameter in serum of pruritic patients with different cholestatic diseases found to correlate with itch intensity is the enzyme autotaxin (ATX) and its product lysophosphatidic acid (LPA) (3,7,8). Increase of ATX activity had a positive predictive value of 70% to diagnose pruritus due to liver disease.

Prevalence of pruritus in liver disease

While intrahepatic cholestasis of pregnancy (ICP) is defined by the presence of pruritus, often with only mild cholestatic parameters, the prevalence of systemic itch in primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) is about 24-55% (1,4) and 40-70% (9), respectively. In PBC, pruritus is often most intense at stages 2-3, whereas it remarkably diminishes in late stage disease (7,10-12). Furthermore, pruritus can be observed in chronic hepatitis C and is a dominant symptom in hereditary cholestatic diseases such as benign recurrent intrahepatic cholestasis (BRIC), progressive familiar intrahepatic cholestasis (PFIC) types I and II or the multiorgan Alagille syndrome (13-18).

Pruritus as a prognostic factor for disease outcome

Pruritus was not investigated as an independent risk factor for disease outcome. Overall, asymptomatic patients have slightly better survival concerning death due to liver disease (19). Occasionally (4-7%) liver transplantation is performed for poor quality of life by means of fatigue and/or pruritus (20-22), counting for 42% of precirrhotic liver transplantations (23). Post transplantation occurrence of pruritus points into the direction of complications such as (non)anastomotic strictures or disease recurrence in the transplant (10).

Animal studies

In the expanding animal research on scratch behaviour, acute models predominate. Intradermal injection of pruritogenic compounds such as histamine, substance P,

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chloroquine, compound 48/80 and lysophosphatidic acid reliably elicit immediate scratch responses, contributing to the identification of itch pathways (24-26). Notably, the only (chronic) cholestatic model so far reported is ethynylestradiol induced cholestasis eliciting scratch activity in rats (27). One could think of differences in skin composition, bile salt pool, species-dependent receptor specificity and other yet unidentified metabolic factors between men and mice, impeding the investigation of cholestatic pruritus.

The mechanism of action of the limited number of medicinal and minimally invasive treatment options is largely to be elucidated. Here, along with current treatment targets, directions to the molecular mechanism of cholestatic pruritus are reviewed.

Disrupting enterohepatic cycling of pruritogens

Bile excretion is impaired in cholestatic disorders at different levels of the biliary tree. Thereby, together with other compounds normally excreted in bile, such as bilirubin and cholesterol (28), bile salt levels in the systemic circulation markedly increase. In case of post-hepatic cholestasis, dominant strictures may be resolved endoscopically to improve bile outflow (13). Total disruption of the enterohepatic cycle by nasobiliary or transcutaneous drainage of the accumulated bile markedly improves itch in cholestatic patients who do not respond to medicinal treatment or luminal drainage. A correlation with circulating total bile salts, however, remains controversial in the sparse cases reported in literature (3,29-31). Moreover, while bile salt levels rise to unprecedented levels in patients with end stage liver failure, a decline in pruritus is often reported at that time.

Bile salt sequestrants such as colesevelam and cholestyramine are regarded as first line treatment for pruritus in cholestasis (13). Early studies indeed show some efficacy (32,33) but the latest RCT concerning colesevelam proves no advantage over placebo, providing yet another argument against bile salts as a direct pruritogen in cholestasis (34). At the same time, however, these safe and inexpensive agents give some relief in pruritus due to other systemic diseases such as uraemia and polycythemia vera (35).

A modulating role of bile salts can be inferred from the fact that ursodeoxycholic acid (UDCA) improves serum liver tests and ameliorates itch in women suffering from ICP, where serum bile salt levels are usually only mildly increased. In contrast, worsening of itch may be observed during the first days of UDCA treatment in PBC where the agent is effective in slowing disease progression in two third of patients (36). Thus, while further exploration of the role of different bile salts in pruritus is desirable, a causative agent of pruritus may have to be sought in (a) different bile component(s). Notably, autotaxin protein could not be found back in drained bile, while its serum activity significantly decreases together with pruritus soon after starting drainage (3).

Detoxification

Altering enterohepatic pruritogen metabolism

Empirical administration of the antibiotic rifampicin improved pruritus in cholestatic patients and is considered as second line treatment in current guidelines (13). While clinicians might fear the occurrence of hepatitis associated with this drug, reviews on safety and efficacy of rifampicin monotherapy for cholestatic pruritus (37, 38) attribute the main risk in earlier reports to co-administration of anti-tuberculosis medication, for which rifampicin was initially registered. Still, some studies do report hepatitis with rifampicin monotherapy (39), especially when administered for a longer period of 4 to 12 weeks (25,40), making low dose (150 mg per day) initiation with monitoring of serum liver tests advisable (13). The molecular mechanism of the efficacy of rifampicin is still under investigation but could be looked at in multiple ways. First of all, cholestasis may induce transcription of pruritogen modulating factors being targeted by the Pregnane X Receptor (PXR, present in both hepatocytes and enterocytes). In vitro, rifampicin reduced autotaxin transcription in a PXR-dependent manner (3). In contrast, UDCA does not effectively modulate PXR during treatment of patients with PBC (41). Meanwhile, a PXR-independent mode of action of rifampicin cannot be ruled out. For example, its antimicrobial action could modify intestinal flora whereby influencing not only bile salt cycling and composition but also microbial metabolism of potential pruritogens (3). The nuclear Farnesoid X Receptor (FXR), present in hepatocytes and ileocytes, serves to modulate bile acid synthesis and protects the cell against overloads of toxic bile acids. Empirical therapeutic targeting of FXR by 6-ethyl-CDCA in cholestatic liver disease may provoke pruritus in PBC patients (42).

Detoxification of the systemic circulation : extracorporeal albumin dialysis

Extracorporeal albumin dialysis was originally used in acute liver failure and graft failure after transplantation (43). In addition, reports about its safety and immediate efficacy in treating resistant pruritus emerge (5,6, 44-47). Likely, during cholestatic liver disease either accumulated pruritogens themselves or downstream signaling factors overload the binding capacity of circulating albumin. It is posed that this demerit is reversed by the extracorporeal dialysis through an albumin rich solution. Thereby, substances binding to albumin (e.g. bile salts and bilirubin) are filtered out in particular before returning to the body. While some studies interpreted the subsequent decline of serum bile salts as the most probable mechanism of itch relief (5,6,48,49), others find correlation with autotaxin but not bile salts instead (3). Being a 125 kD protein, autotaxin will not be filtered out itself and thus a modulating compound will have to be sought for. The few studies reporting differences in

Table 1. — **Evidence based and experimental treatment options and concurrent proposed pathofysiology of cholestatic pruritus**

Proposed mechanism in pruritogenesis	Therapeutical intervention	Level of evidence*
Overflow of bile components in systemic circulation	- Bile salt sequestrants (e.g. cholestyramine)	II-2/B1 (13)
	- Nasobiliary drainage	II-3/B2 (3;29;30;31)
	- UDCA in cholestasis of pregnancy	I/B1 (13;73)
Decreased detoxification of pruritogens from portal circulation due to liver disease	- Rifampicin	I/A1 (13;37)
	- Extracorporeal albumin dialysis	II-3/B2 (5;6;44-47)
	- Liver transplantation	III/C1 (13)
Increased excitability of itch fibers	- Naltrexone	I/B1 (13)
	- Sertraline	II-2/C2 (13)
	- Abolish exogenous steroid hormones (e.g. oral contraceptives)	III/C2 (73;75)
	- Bright light therapy	III/C2 (11)
Pruritogen accumulation in the skin	- UVB light therapy	II-3/B2 (8;51-54)

*Evidence levels based on two grading systems : 1) Grades in level of evidence : I randomized controlled trials ; II-1 controlled trials without randomization ; II-2 cohort of case-control analytic studies ; II-3 multiple time series ; III opinions of respected authorities. 2) Grading of Recommendations Assessment Development and Evaluation (GRADE system (13)) : A : high quality, further research in very unlikely to change our confidence in the estimate of effect ; B : Moderate quality, further research is likely to have 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. 1 : strong recommendation ; factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost ; 2 : weak recommendation ; variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

circulating compounds before and after extracorporeal albumin dialysis come up with a broad spectrum of metabolites, cytokines and hepatic growth factors (50). In the only published investigation of the actual dialysate, proteomics identified 60 different extracted proteins of which 5 seem to be actually removed from serum of pruritic patients during extracorporeal albumin dialysis treatment (45). This will have to be explored in further studies, along with data supporting cost-effectiveness and tolerance of extracorporeal albumin dialysis as a bridge to or alternative for liver transplantation in patients that report greatly impaired quality of life despite the guidelines' medicinal treatment options.

Detoxification at the skin: phototherapy

Several attempts have been made to find the pruritogen of cholestasis in the skin, were it is hypothesized to accumulate and activate nerve endings. However still in experimental setting, Ultraviolet B (UVB) phototherapy has been shown to improve itch of cholestasis as it does in several other systemic diseases such as uremia (8,51-54). It is possible that UVB rays induce chemical modification of the pruritogen in the skin, whereas direct modulation of nerve endings was also proposed as the possible mechanism of action (8). Changes in conventional serum parameters of cholestasis were not evident to correlate with itch alleviation and data about serum autotaxin activity are lacking here. No severe side effects were reported (pronounced erythema in one and paresthesia in another). (Relative) contraindications could be the increased risk of skin cancer particularly in transplanted patients, concomitant administration of photosensitizing drugs and/or comorbid lupus erythematosus or xeroderma pigmentosum. One patient reported to keep control over pruritus by regular holidays at sunny destinations (8).

Modulating itch perception centrally of peripherally

Pain and itch are signalled through separate neurons. Still, as a reflex behaviour, pain induced by scratching seems to (temporarily) relieve itch sensation. The mechanism for this is the well-established inhibitory effect of pain signals on itch neurons at the level of the interneurons in the spinal cord (55,56). Within the sensory neuronal system, subsets of thin C-fibers have been identified to specifically react to pruritogens (57). Activation of receptors for histamine 1, serotonin, endothelin 1, IL-31 and gastrin-releasing peptide as well as ligand activation of PAR2 receptors and MrgX receptors is thought to activate the fibers (58,59) with a modulating role for phospholipase Cβ3 (PLCβ3) and TRPV1 (58). Centrally, a matching distinct spinothalamic pathway was proposed (60). While PLCβ3 seems to be specific for itch signalling, pain and itch neurons seem to share certain receptors such as the capsaicin receptor TRPV1, making clear-cut differentiation of nerve subsets an even greater challenge. TRPV1, a member of the transient receptor potential cation channels, seems to be an obligatory downstream integrator of both itch and pain, since knockout mice for this channel have reduced itch and pain perception. In contrast, recent data suggest that TRPV3 (61) and TRPA1 (62) play a more specific role in itch.

Moreover, clinicians have always encountered the occurrence of itch upon opioid treatment (63). In turn, the opiate antagonist naltrexone is advised in patients suffering from cholestatic itch resistant to resins and rifampicin (13,38,64,65). Still, the role of (endogenous) opioids in the pathophysiology of cholestatic pruritus is undetermined with the lack of correlation with itch severity (66,67). With the ability to modulate nociception, the serotonin reuptake inhibitor sertraline alleviated itch in one cohort of patients resistant to cholestyramine, rifampicin and naltrexone (68). If increased autotaxin activity in cholestatic patients indeed contributes to itch by means of LPA formation at the site of pruriceptors, research on the presence of LPA G-protein coupled receptors on itch nerves will have to be extended. Indeed, LPA injection in mice elicits a scratching response (67) that can be modulated by the histamine 1 receptor as well as TRPV1 and seems to be Rho-associated protein kinase dependent (69). LPA receptor 1 (70) and 5 (71) signalling were found to be involved in neuropatic pain in mice. Importantly, it was very recently reported that TRPV1 can be directly activated by LPA (72). This makes a role for LPA in activation of sensory neurons including itch neurons quite likely.

Endocrine targets for modulating pruritus of cholestasis

Several clinical observations make one wonder how female hormones could modulate pruritus. Within a few days after delivery, itch diminishes in intrahepatic cholestasis of pregnancy (ICP) patients (73). Here, besides the resolvement of the (mild) cholestasis, the abrupt changes in hormonal status may very well contribute. Moreover, it is most often women, typically premenopausal, that report itch during cholestatic diseases (74). Furthermore, de novo pruritus may occur during pregnancy in PSC patients (11) and hormone replacement therapy (73,75). Here, the only applicable data show that UDCA treatment for ICP, along with a decline of symptoms, decreases urinary excretion of progesterone disulphates (76). As does cholesterol, various steroids act as transcription factors by binding to intracellular receptors. Functional variants of FXR were proposed to increase susceptibility for ICP, when female sex hormones increase 100-200 fold, in a series of 92 patients (77). In mice however, estrogen hepatotoxicity seems to be modulated by ERα rather than FXR (78). Notably, in rats hippocampal Atx expression was shown to be induced by estrogen (79) and in healthy females taking oral contraceptives serum ATX is significantly higher than in controls (Kremer *et al.*, in preparation).

In addition, several endogenous steroid hormones and their metabolites exhibit neuromodulating properties, potentiating steroid metabolism to regulate (itch) nerve activation (80). In fact, ionotropic receptors found to be responsive to so called neuroactive steroids include those for generally inhibitory (e.g. GABA-A (81,82) and glycine (83)) and excitatory (e.g. glutamate (84) and serotonin (85)) neurons as well as TRPV1 (86). In line with all this, female mice show a stronger scratch response upon pruritogen application compared to males (87). Therefore, steroid hormones could very well modulate itch neuron excitability upon pruritogens during cholestasis. Thus far it has been insufficiently explored whether therapeutically targeting this mechanism in the treatment of pruritus might be beneficial, as is now proposed for neuronal (88) and psychiatric symptoms (89,90). In this context it is encouraging that neuroactive steroids have been shown to have antinociceptive effects in animal models (90,91) and are capable of reversing morphine tolerance in rats (92). In humans, gender differences in pain sensitivity and pharmacokinetics and pharmacodynamics of opioid analgesia have been encountered (93,94).

Perspectives

Both the striking observation that the occurrence of pruritus in cholestasis is hard to predict from available diagnostics and the trivial response to the limited number of current treatment options such as cholestyramine, rifampicin, naltrexone and sertraline, emphasize the urge to elucidate the fundamental mechanism of cholestatic itch. Experimental approaches will have to consider crucial differences between men and mice. It seems that pruritogens in cholestasis are subject to enterohepatic circulation and metabolism, hormonal status, local skin (partially photolabile) homeostatic factors and peripheral as well as central neuromodulation.

In addition, genome wide association studies (GWAS) on cholestatic diseases nowadays include pruritus questionnaires, hopefully bringing up susceptibility genes and concomitant new therapeutic targets in the nearby future.

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