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The Itch of Liver Disease

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Itch is a complication of liver disease. It is hypothesized that this type of itch is mediated, at least in part, by increased central opioidergic tone; a peripheral component may coexist. The role of serotonin, bile acids, substance P, and lipophosphatidic acid and the activity of the enzyme that generates it, autotoxin, has been proposed in the pathogenesis of itch. Scratching activity was significantly suppressed in association with the placebo tablet in a controlled, double-blind study; this finding supports the exploration of the placebo effect on the itch sensation and the inclusion of behavioral methodology in clinical trials in patients with this complication of liver disease.
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Cholestasis is defined as impaired secretion of bile.[1] It is a consequence of all types of liver diseases, including those caused by the inflammatory destruction of intra- and extrahepatic biliary structures and those associated with hepatocellular injury.[2] Specific characteristics do not seem to separate the itch or pruritus that results from cholestatic liver diseases from the itch that results from hepatocellular diseases.

Seventy percent of patients with primary biliary cirrhosis, a cholestatic liver disease, experience itching at some point in the course of their disease,[2] whereas, in retrospective studies, 5% of patients with chronic hepatitis C presented with itching.[3] Patient experiences of the itch from liver disease were studied in a survey conducted via the Internet among members of the PBCers, an organization that supports education and research in primary biliary cirrhosis (http://pbcers.org/).[4] Two hundred thirty-nine patients with primary biliary cirrhosis responded to the survey, 164 of whom reported itch (68%). Seventy-five percent of the patients reported that they had experienced itch before they were diagnosed with primary biliary cirrhosis, and most stated that they had been itching for 2-5 years before their diagnosis. This finding highlights the importance of considering primary biliary cirrhosis, and surely other liver diseases, in patients who present with this symptom, in the absence of primary itchy skin lesions; in these cases, a prompt liver disease workup and referral to a hepatologist are indicated. Seventy-four percent of the patients who experienced itch reported that their sleep was disturbed by this symptom, and 11% reported that nothing relieved the itch. Indeed, the itch from liver disease can be so severe that it is an indication for liver transplantation even in the absence of liver failure.[2]

The idea that the pruritogen(s) and/or cofactors to the pruritogen(s) are made in the liver is supported by the following clinical observations: (i) patients who have itch before undergoing liver transplantation report complete relief after their liver has been replaced by the graft, and (ii) when patients with cholestasis progress to liver failure, the itch tends to cease,[5] suggesting that the pruritogen(s) and/or its cofactor(s), are made in the liver and that some degree of liver function is necessary for these substance(s) to be synthesized and/or for the itch to be perceived.[6] It has been inferred the pruritogen(s) are excreted in bile and that, because of cholestasis, they accumulate in plasma and other tissues mediating stimuli perceived as itch.[6] In support of this idea is the relief of itch secondary to bile duct obstruction in association with relief of the obstruction.[6]

Increased neurotransmission via the endogenous opioid system has been proposed to contribute to the itch of cholestasis. Three lines of evidence support the idea that in cholestasis there is increased opioidergic tone in the central nervous system: (i) the opiate withdrawal-like reaction experienced by patients with cholestasis after the intake of opiate antagonists[7-9]; (ii) the state of antinociception that is stereospecifically reversed by an opiate antagonist (i. e., naloxone) in an animal model of cholestasis[10]; and (iii) the altered expression of opioid receptors in the brain of rats with cholestasis.[11,12] Increased opioidergic tone is associated with itch. For example, the pharmacologic increase in opioidergic tone, as it occurs after the administration of morphine and other drugs with agonist activity at the opioid receptor, intrathecally, is associated with itch, which can be prevented or effectively

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treated by opiate antagonists.[13,14] Clinical observations[13,14] and animal studies[15] suggest that the itch in human beings and scratching behavior in laboratory animals associated with the administration of morphine and opiate drugs is centrally mediated. The opiate-withdrawal like syndrome precipitated by opiate antagonists in patients with cholestasis suggests that in cholestasis there is increased central opioidergic tone; accordingly, there is a rationale to support the hypothesis that states that the itch of cholestasis is centrally mediated by increased opioidergic tone, at least in part.[16] Itch, however, seems to be independent from the degree of cholestasis, as measured by current methods (i. e., high fasting and two-hour postprandial serum bile acids). This observation suggests that there may be patient-specific characteristics that contribute to the perception of itch.

To explore why not all patients with cholestasis experience itch, genetic polymorphisms were studied in 101 samples from a group of patients with primary biliary cirrhosis from Italy and from the United States who did and did not report itch.[17] A novel mutation (t3563a) in codon 1188 of exon 25, which resulted from the substitution of valine by glutamate (V1188E), was identified in the gene codes that for MRP2. V1188E was found in 19.5% of the samples from patients who reported itch and in 7.8% of those who did not ($P = 0.02$, relative risk 2.51, 95% confidence interval 1.13-5.69). Single nucleotide polymorphisms in the *MRP2* gene may be associated with a decrease in the in vivo function of the protein;[17] thus, V1188E may alter the ability of the transporter to transport substrates into the biliary canaliculus, and it may lead to the accumulation of pruritogens in plasma, or to an increased availability of pruritogens in the central nervous system, because MRP2 is also located in the blood–brain barrier.[17]

Stimulation of the mu opioid receptor is associated with scratching behavior in laboratory animals.[18] The polymorphism Al18G found in exon 1[19] of the gene that codes for the mu opioid receptor was detected in 27.6% samples from the group of patients with primary biliary cirrhosis and itch and in 30.6% from the group of patients without itch ($P = 0.7$).[19] In the samples from the United States, A118G was found in 27.6% samples from the patients with itch and in 40.7% of the patients without itch ($P = 0.3$). A118G changes the effect of receptor activation; accordingly, this polymorphism may be protective from itch in cholestasis. Although the presence of A118G was not significantly different from that in patients with itch, the small sample size clearly limited this study; thus, studies of this type, including a large sample may be revealing and seem warranted.

Pathophysiology of the Itch of Liver Disease

The hypothesis stating that the pruritus of cholestasis is mediated by increased opioidergic tone[16] is supported by results of clinical trials. If cholestasis is associated with increased opioidergic tone, and increased opioidergic tone mediates the itch, at least in part, the administration of opiate antagonists should decrease the itch. Indeed, this effect has been demonstrated in clinical studies. The administration of the opiate antagonist nalmefene to patients with cholestasis and pruritus was associated with an opiate withdrawal-like reaction; in addition, the patients reported relief of their itch, as measured by a visual analogue scale.[7] The results of two controlled clinical trials revealed that the infusion of naloxone, an opiate antagonist, was associated with a decrease in scratching behavior,[20,21] thus supporting the hypothesis that increased opioidergic tone contributes to the itch of cholestasis.[16] In short-term studies, the administration of opiate antagonists was associated with a decrease in hourly scratching activity in an average of 89% of the patients (range, 82.8%-100%).[8,9,20,21] Opiate antagonists were also associated with decrease in the perception of pruritus, as measured by a visual analogue scale for pruritus.[7-9,20-23]

A question arises: how does the liver contribute to the increase in opioidergic tone in cholestasis? There is evidence to suggest that in cholestasis the liver may be a source of endogenous opioids. Met-enkephalin is one of the endogenous opioids coded by the pre-proenkephalin gene; in this context, there is increased expression of Met-enkephalin immunoreactivity in the liver of patients with liver disease, including primary biliary cirrhosis, a liver disease characterized by cholestasis and pruritus.[24] Studies in the liver from rats with cholestasis secondary to bile duct resection also support the idea that the cholestatic liver may be a source of endogenous opioids.[25,26] Thus, the cholestatic liver may contribute to increased opioidergic tone by increasing the availability of endogenous opioids in the circulation and to the opioid receptor.

Furthermore, in some patients with liver disease, including primary biliary cirrhosis,[7,27] their serum concentration of Met-enkephalin is greater than that of control subjects.[7,27] The increase in the serum concentration of endogenous opioids in patients with cholestasis by itself, however, should not be interpreted as the only piece of evidence for increased opioidergic tone in cholestasis; instead, it is the opiate-withdrawal like reaction[7] which suggests that in cholestasis there is increased opioidergic tone. Can liver-derived opioid peptides act on the brain and increase central opioidergic neurotransmission? The answer to this question appears to be yes, as the presence of MRP2 in the blood-brain barrier tends to suggest that the pathways to allow the entrance of opioid peptides into the central nervous system are in place.[28,29] In addition, neurogenic signals attributable to inflammation may be transmitted from the liver to the brain, contributing to a central component of the itch sensation.

A central component of the itch of cholestasis may also result from central sensitization for itch, as the emerging consensus proposes in conditions associated with chronic scratching[30]; accordingly, it may be speculated that the accumulation of substances in plasma and tissues from cholestasis may exert constant stimuli of C-pruriceptors, leading to the central sensitization for pruritus, contributing to a central component of the itch of liver disease. In addition, hepatic nerve fibers may transmit to the brain signals triggered by

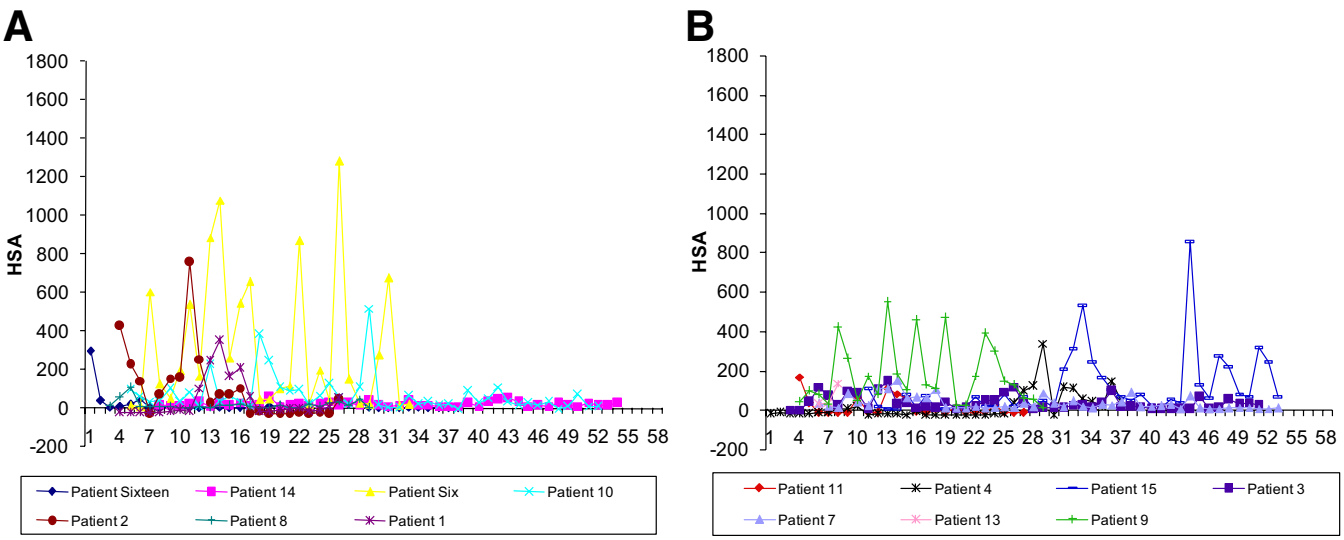

Figure 1 Mean hourly scratching activity (HAS) from patients who participated in a randomized, double-blind, placebo-controlled study of gabapentin for the pruritus of cholestasis (n = 89). All patients underwent baseline continuous recording of scratching activity for at least 24 hours, after which they were randomized to receive gabapentin or placebo. Mean baseline HSA is depicted from the patients who were subsequently randomized to gabapentin (A) and to placebo (B). Reproduced with permission from Bergasa et al.[40]

inflammation, contributing to a central component of the itch of liver disease.

In further support of a central origin of the pruritus of cholestasis are data from brain scans by single-photon emission computed tomography and functional magnetic resonance imaging methodology in patients with pruritus of cholestasis during periods of itch and no itch. It was reported, in abstract form, that itch was associated with sensory cortex activation, and the increasing severity of itch was reported to correlate with activity in the prefrontal cortex, orbital frontal cortex, putamen, globus pallidus, insular cortex, and orbital anterior and posterior cingulate cortex but not with activation of the sensory cortex. On the basis of the pattern of activation, the authors concluded that the limbic system is the primary central nervous system pathway involved in the perception of itch and stated that the findings support a central origin for this type of pruritus.[31]

Other neurotransmitter systems may be involved in the mediation of the itch from cholestasis.[6] In the context of

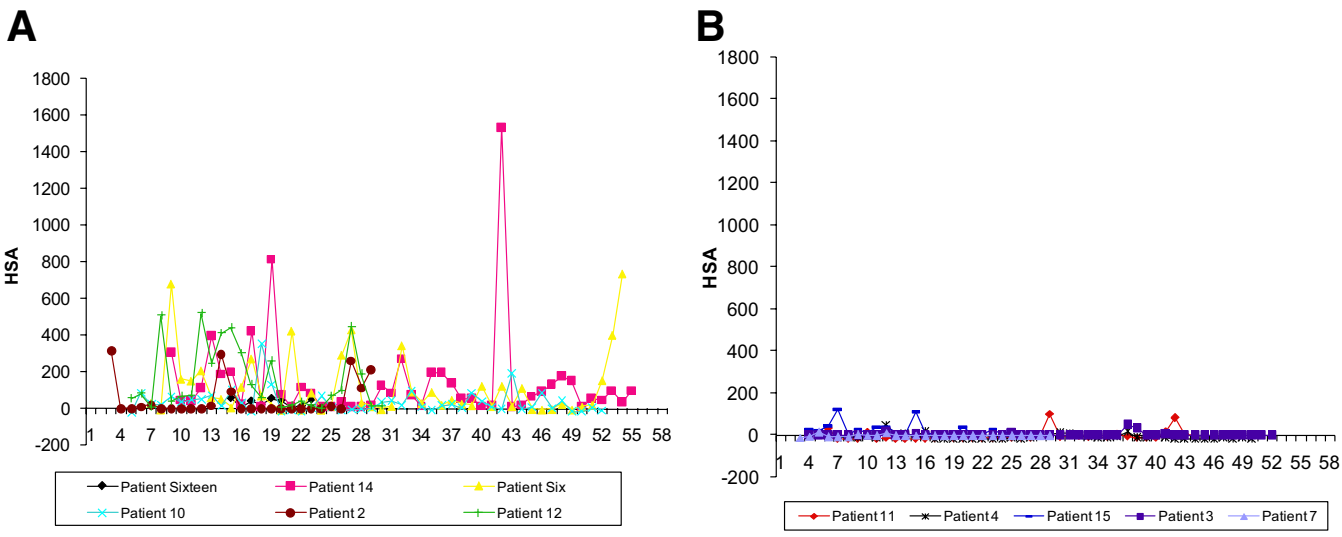

Figure 2 Mean hourly scratching activity (HAS) from patients who participated in a randomized, double-blind, placebo-controlled study of gabapentin for the pruritus of cholestasis.[40] After the patients had been randomized to the study drug (gabapentin or its placebo) and had been on treatment for at least four weeks, scratching activity was recorded for a period of at least 24 hours. Gabapentin was not associated with an amelioration in hourly scratching activity; in fact, it was associated with an increase (A); in contrast, the placebo tablet was associated with a significant reduction of hourly scratching activity (B). Reproduced with permission from Bergasa et al.[40]

serotonin neurotransmission, which is involved in nociception, serotonin type 3 receptor antagonists have not been consistently associated with amelioration of the itch from liver disease.[32,33] The serotonin reuptake inhibitor sertraline, by contrast, was reported to be associated with a decrease in the itch in patients with liver disease.[34] Substance P is an excitatory neurotransmitter that acts through the NK-1 receptor synthesized in primary afferent nociceptors and released into the spinal cord after noxious stimuli[35]; the mean serum concentration of substance P was significantly greater in patients with chronic liver disease and pruritus than in patients with chronic liver disease without pruritus and in control subjects[35]; these data suggest that substance P may mediate some manifestations of liver disease, including pruritus; thus, there is a rationale to study the effect of substance P antagonists on this symptom of liver disease, in studies that include behavioral methodology.

A role of lipophosphatidic acid and the activity of the enzyme that generates it, autotaxin, was proposed recently to be involved in the itch of cholestasis because the serum concentration of the former and the activity of the latter were reported to be greater in the serum of patients with cholestasis and itch than in the serum of those with cholestasis without itch.[36] Evidence in support of a role of these compounds in the pathogenesis of the pruritus of cholestasis, however, has not been provided.

Bile acids, which accumulate in tissues of patients with cholestasis, have been proposed as pruritogens in cholestasis[37]; however, their role on the itch of cholestasis has not been demonstrated.[6,16] A certain bile acid profile in the cholestatic liver milieu, or in the serum, and not total serum concentration of bile acids, may be relevant, by contrast. A recent study published in abstract form revealed that the administration of obeticholic acid to patients with primary biliary cirrhosis was associated with itch, in contrast to the placebo intervention. Obeticholic acid is a synthetic derivative of chenodeoxycholic acid, which is an agonist at the farsenoid nuclear receptor and which has choleretic properties.[38] Farsenoid nuclear receptor is a bile acid sensor associated with a decrease in bile acid production.[39] The relevance of this observation to the itch from liver disease is unknown.

Lessons from Behavioral Methodology

Itch results in the action of scratching in most humans. This behavior can be measured objectively by methodology that records scratching behavior independently from gross body movements.[20,21] In a double-blind randomized placebo controlled study of naloxone infusions for the pruritus of cholestasis, a 24-hour rhythm in scratching behavior that tended to peak from 1200 to 1600 hours was detected in some patients[21]; accordingly, the interpretation of data obtained from subjective methodology (i. e., visual analogue scales, diaries, questionnaires) may be inaccurate because the timing of collection will affect the result. Another striking revelation came from a double-blind, randomized placebo-controlled study of gabapentin for the itch of cholestasis (Figs 1, 2A-B); in this study the placebo intervention was associated with a significant reduction of scratching activity,[40] in contrast to the study drug. Several important conclusions have been derived from these results: (i) the placebo effect, confirmed in this study, can have an impact on the specific behavior that results from itch, scratching; and (ii) expectations, which can affect the response to a placebo intervention, should be assessed in the study participant before their enrollment in clinical trials of itch.[40]

A diagram displaying a hypothetical itch-scratch circuit in cholestasis is depicted in Fig. 3.

Selected Therapies for the Treatment of the Itch of Cholestasis

Therapies for the treatment of the itch of cholestasis, which have been included in the guidelines on the treatment of primary biliary cirrhosis from the American Association for the Study of Liver Disease[41] are provided in Table 1. Other interventions that have not been studied in controlled studies or that have been published from limited experience have been reported to be associated with relief of the itch from cholestasis and are used randomly; they include the following treatments: (i) extracorporeal liver support systems, such as molecular adsorbent recirculating system, which his aimed at the removal of the pruritogen(s)[42], (ii) phototherapy to the

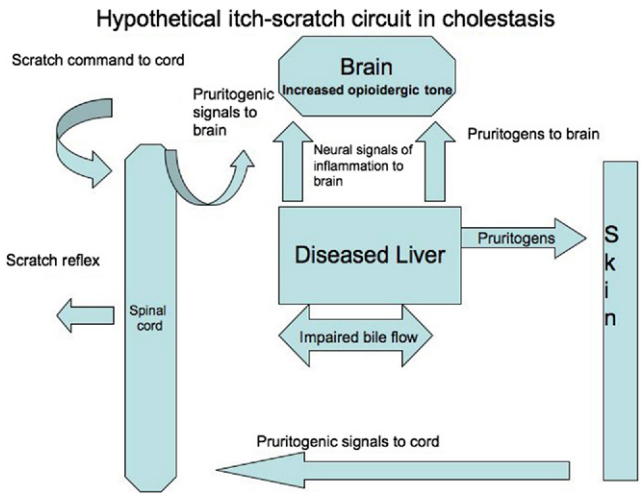

Figure 3 The diagram is a hypothetical itch-scratch circuit in liver disease. Cholestasis, or impaired secretion of bile, is a result of liver disease. Because of cholestasis, pruritogens accumulate in plasma and may enter the brain, where they change neurotransmission. Signals conveying inflammation travel via neural networks from the liver to the brain. Pruritogens stimulate itch receptors in the neural skin fibers, which transmits itch stimuli from the skin to the spinal cord and subsequently to the brain. All these possible ascending messages mediate changes in neurotransmission, including the increase in opioidergic tone. The processing of pruritogenic stimuli is associated with a descending message that mediates scratching behavior.

Table 1 Selected Publications on the Treatment of Itch From Liver Disease

Medication	Aim	Dose/Mode of Administration/ Frequency	Type of Study/Duration	n	End Points on Pruritus and/ or Scratching	Results	Reference
Cholestyramine	Removal of pruritogen(s)	3.3-12 g/PO/day	Single blind, open-label/ placebo-controlled crossover/* 6-32 mo	27	Not reported	Twenty-three patients experienced relief of pruritus*	52
Rifampicin	Unknown	150 mg PO/BID if serum bilirubin >3 mg/dL; 150 mg P.O/TID if serum bilirubin <3	Double-blind, randomized placebo controlled crossover/ 4 wks†	9	Change in VAS*	Highly significant decrease in the 7-d summed VAS†	53
Naloxone	To decrease opioidergic tone	0.2 μ/kg/min/IV continuous infusions preceded by 0.4-mg IV bolus	Double-blind, placebo-controlled, randomized crossover/4 consecutive days	29	Change in HSA	Geometrical mean HSA 34% lower on naloxone than on placebo	21
Naltrexone	To decrease opioidergic tone	25 mg PO/BID on day 1 followed by 50 mg PO daily	Randomized placebo controlled/4 wks‡	16	Change in VAS	Daytime VAS down by 54% and nighttime VAS down by 44%	22
Sertraline	To change serotoninergic tone	75-100 mg PO daily	First phase, dose finding study/4 wks second phase, randomized, double placebo controlled, crossover design/6 wks	21 12	Change in VAS, decrease in skin excoriations	Decrease in mean VAS by 53% in first phase and decrease in mean VAS by 33% from baseline on sertraline	34

BID, twice daily; HSA, hourly scratching activity; n, total number of patients; IV, intravenously; PO, orally; TID, three times a day; VAS, mean visual analogue score.
*Compared with an observational control group that did not receive cholestyramine but which received norethandrolone or no treatment.
†The use of cholestyramine was allowed to continue; the number of cholestyramine packs per day that the patients used was counted. Mean change in VAS not reported; VAS graphed per patient.
‡Concomitant use of antipruritic medications were allowed.

skin (a rationale for the use of this intervention is not apparent)[43-45], (iii) bright light phototherapy (10,000 lux) indirectly aimed towards the eyes, in a pilot study in patients with chronic liver disease, in whom a decrease in scratching activity, in particular, in a decrease in the number of scratching outbursts was documented[47]. Circadian rhythms are regulated by light[46]; the 24-hour rhythm in scratching behavior displayed by some patients with cholestasis suggested a circadian nature of this behavior,[21] and thus, provided a rationale for this study, and (iv) lidocaine infusions.[48] It was suggested the ameliorating of the itch of liver disease by the use of lidocaine might have been mediated via the vanilloid receptor-1[6] on the basis of interesting recent publications.[49-51]

The development of effective therapy for the itch of liver disease is a research priority. The use of behavioral methodology offers the opportunity to gain insight into the well-conserved reflex of scratching and has provided information not apparent from studies that used questionnaires and visual analogue scales as the sole methodology including, the 24-hour rhythm in scratching behavior exhibited by some patients with cholestasis, and the amelioration of this behavior in association with the administration of a placebo intervention. In the absence of behavioral methodology in clinical trials, the use of yes or no, as a measure of success from an antipruritic medication, may suffice.

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