Clinics and Research in Hepatology and Gastroenterology (2017) xxx, xxx–xxx

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MINI REVIEW

An update on the physiopathology and therapeutic management of cholestatic pruritus in children

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KEYWORDS
Cholestasis;
Pruritus;
Children;
Treatment

Summary Pruritus is a disabling symptom accompanying chronic cholestasis. In extreme cases, the refractory nature of pruritus can result in a need for invasive therapies including liver transplantation. The pathogenesis of pruritus in cholestatic disease is poorly understood. It may involve a specific neural pathway (similar to that associated with pain) regulated by several pruritogenic substances such as bile acids, opioids, serotonin, and the more recently identified lysophosphatidic acid. While the therapeutic management of cholestatic pruritus is well established in adults, there is no consensus in children, in light of the difficulty of conducting controlled clinical studies. The currently recommended strategy to manage cholestatic pruritus in children is based on several lines of specific therapies that should be associated with skin hydration and with non-specific treatment of cholestasis including ursodeoxycholic acid. Pruritus should be assessed as objectively as possible between each line of therapy. Rifampicin, a potent CYP3A4 inducer, is the first-line treatment of cholestatic pruritus. Second-line therapies require evaluation of the child in an expert center and are discussed on a case-by-case basis depending on the underlying disease and the experience of the center. These include inhibitors of serotonin reuptake (sertraline), opioid antagonists (naloxone), or ASBT inhibitors. Invasive therapies such as biliary diversion or liver transplantation can also be proposed in the most severe cases. The aim of the current update is to review the physiopathologic mechanisms implicated in cholestatic pruritus and to propose potential therapeutic strategies in children.

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http://dx.doi.org/10.1016/j.clinre.2017.08.007
2210-7401/

Please cite this article in press as: Thébaut A, et al. An update on the physiopathology and therapeutic management of cholestatic pruritus in children. Clin Res Hepatol Gastroenterol (2017), http://dx.doi.org/10.1016/j.clinre.2017.08.007

Introduction

Pruritus is a characteristic symptom of several serious diseases, including cholestasis. Cholestatic pruritus can be disabling to such extent that liver transplantation may be proposed. The frequency and severity of pruritus vary according to the underlying cause of cholestasis. In children, Alagille syndrome, progressive familial intrahepatic cholestasis (PFIC), and less commonly, biliary atresia and sclerosing cholangitis, are typically associated with particularly severe pruritus. While therapeutic management of cholestatic pruritus is well established in adult patients there is currently no consensus in children [1,2].

Physiopathology of cholestatic pruritus

Neuronal pathways

The physiopathology of cholestatic pruritus is poorly understood. One neuronal pathway specifically involved in pruritus conduction has been characterized. It starts with slow-conducting afferent C-fibers, which are sensitive to activating endogenous and exogenous substances such as histamine (Fig. 1) [3]. These connect to a second neuron in the posterior horn of the spinal cord, which is sensitive to the neurotransmitter neuropeptide natriuretic polypeptide b (Nppb). Synaptic transmission to a third neuron occurs via gastrin-releasing peptide (GRP) neurotransmitter, through its specific receptor GRP-R [4,5]. This latter neuron enters the spinothalamic tract reaching the thalamus then the cerebral cortex (prefrontal and anterior cingulate cortex) [6].

In parallel to the ascending sensory pathways, descending central regulatory pathways are mediated by opioids and serotonin, as is the case for pain transmission pathways. The two pathways (proprioceptive and nociceptive) are distinct, but are parallel and linked by a mechanism of reciprocal inhibition. Inhibition occurs within the posterior horn of the spinal cord via afferent neurons and/or descending regulatory signals [7].

The specific mediators implicated in cholestatic pruritus have not been definitively identified. They may include accumulation of specific pruritogenic substances presumably with biliary elimination, with increased plasma concentrations as a result of cholestasis (primarily bile acids), stimulating peripheral sensitive fibers within the cutaneous neuronal terminal, and/or disruption of the homeostasis of central regulatory systems (serotonergic or opioidergic systems).

Mediators of pruritus

Bile acids

Cholestatic pruritus is attributed, at least in part, to the stimulation of cutaneous nerve terminals, as a consequence of bile acid retention in the skin. Recent studies suggest that the excitatory effect of bile acids occurs by the co-activation of the TGR5 membrane receptor (expressed by the initial peripheral afferent neuron) and the TRPA1 calcium channel, inducing fiber depolarization [8,9].

Pruritus improves with approaches designed to reduce serum bile acid concentrations, irrespective of whether this is oral administration of chelators (cholestyramine), nasobiliary drainage or surgical biliary diversion [10]. In addition, patients suffering from a primary bile acid synthesis defect do not experience pruritus, despite the presence of hepatocellular cholestasis, and furthermore, pruritus has been reported in these patients in cases of cholic acid overdose (a primary bile acid used to treat the disease) [11]. A correlation between the concentration of serum bile acids and the intensity of pruritus has nonetheless never been demonstrated.

Opioids

Opioids, both endogenous (met-enkephalin and leu-enkephalin) and exogenous (morphine and morphine derivatives), can affect pruritus signaling pathways via their central receptors situated within the posterior horn of the spinal cord [12]. This modulation occurs via an interaction between the proprioceptive and nociceptive pathways. Pruritus signaling is controlled by the inhibition of the afferent pain neurons, which are themselves inhibited by the release of opioids. Thus morphine, an opioid agonist, can induce pruritus. This pruritus is partially reversible after administration of morphinic antagonists such as naloxone, whose efficacy against cholestatic pruritus has been demonstrated in several small clinical studies [13—15]. An increase in the plasma concentration of endogenous opioids was reported in patients suffering from cholestatic pruritus, but once again correlation with intensity was not apparent [16].

Serotonin

Serotonin is a neurotransmitter within the central nervous system. It is active in nociceptive regulation, and as such in the regulation of pruritus signaling pathways. Homeostasis of the serotoninergic system appears to be deregulated in chronic cholestasis patients, thus modifying itch perception and signaling [17].

Lysophosphatidic acid

Recently, lysophosphatidic acid (LPA), a neuronal activator implicated in the transmission of neuropathic pain, was identified as a pruritogenic agent. LPA is produced from lysophosphatidylcholine by the enzyme autotaxin (ATX), a lysophospholipase implicated in angiogenesis and neuronal development. Intradermic injection of LPA also induces scratching in mice [18]. An increase in ATX (correlating with plasma LPA) proportional to the intensity of the pruritus, has been demonstrated in several series of cholestatic patients [19,20]. A correlation between the decrease in ATX and decreased intensity of pruritus was seen after treatment with rifampicin or biliary diversion [21], making it the first mediator to correlate with pruritus intensity.

Histamine

Pruritus of a cutaneous origin (urticaria, eczema) is principally mediated via histamine. The cutaneous sensitive afferent fibers respond to histamine via the specific receptor H1-R. While elevated serum histamine concentrations have been reported in some cases of chronic cholestasis

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