

Pruritus Responsive to Naltrexone in a Patient with Cholestatic Liver Disease

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KEY WORDS: Alagille syndrome, pruritus, cholestatic liver disease, naltrexone, children

IMAJ 2011; 13: 111–112

Alagille syndrome (OMIM 118450) is an autosomal dominant disorder associated with abnormalities of liver, heart, bones, eyes, kidneys and characteristic facies (broad forehead, triangular face, prominent zygomatic arch). Mutations in either the jagged-1 or notch-2 genes are seen in patients with AS and result in multiple phenotypic expressions. Cholestatic liver disease of varying degrees characterized histopathologically by a paucity of intrahepatic bile ducts is the hallmark of the syndrome. One of the most incapacitating symptoms in patients with AS is cholestasis-induced pruritus, which can interfere with sleep, nutrition and growth, diminish quality of life and can even lead to severe automutilation. Pruritus is therefore considered one of the leading indications for liver transplantation in AS.

We present a 3.5 year old girl with AS and severe recalcitrant pruritus, who was listed for transplantation but dramatically improved on treatment with the opioid antagonist naltrexone.

PATIENT DESCRIPTION

A 3.5 year old Jewish girl was diagnosed with AS in early childhood. Diagnosis was

based on typical facial appearance, cholestatic liver disease, peripheral pulmonary artery stenosis, severe failure to thrive and typical liver biopsy. She presented in infancy (1 month old) with cholestasis and restlessness which later presented as intractable pruritus. Her pruritus failed to respond to several accepted regimens, including ursodeoxycholic acid, various first- and second-generation antihistamines and rifampin.

In the subsequent years her pruritus worsened, causing considerable deterioration in her quality of life, manifested as severe sleep deprivation and automutilation. Physical examination revealed jaundiced skin and sclera, and multiple linear crusted excoriations scattered on her skin, mainly on the extremities. Because of severe non-responsive pruritus she was listed at age 2.5 years for liver transplantation. As a last resort, while waiting for the transplantation, we initiated treatment with oral naltrexone in addition to antihistamines, rifampin and ursodeoxycholic acid. The drug was introduced at a very low evening dose (0.25 mg once daily, 0.02 mg/kg/day) and gradually increased with no adverse events or opioid withdrawal symptoms. After the second day of treatment, substantial improvement was reported; and for the first time in 2.5 years the child slept through the night without scratching. However, daytime symptoms were still uncontrolled, and an additional morning dose was administered. Currently, 6 months on treatment, she receives 0.5 mg twice daily (0.08 mg/kg/day). Both her own quality of life and that of her family

have improved significantly. According to the child's mother, scratching activity score (scale from 1 = no symptoms, to 10 = child's worst historical symptoms) decreased from 10 before treatment to 1 after treatment was begun. In the light of these new circumstances we withdrew her from the transplantation list.

COMMENT

Although the pathogenesis of pruritus in cholestatic liver disease is still poorly understood, it is a result of complex interplay of pruritogens and their receptors, nerve fibers, neural pathways, as well as cerebral processing [1]. Besides classic pruritogens such as bile acids, other agents were suggested including progesterone metabolites and histamine [1]. Because at this time the mechanisms leading to pruritus are unresolved, several therapeutic interventions have been used with varying degrees of success in children, including rifampin, phenobarbital, ursodeoxycholic acid, bile-binding resins and antihistamines, as well as surgical procedures, such as partial external biliary diversion. [2]

Moreover, studies have demonstrated that endogenous opioids in the central nervous system may have an important role in pathogenesis of the pruritus. It has been suggested that opioids bind to the μ -opioid receptor and presumably induce pruritus centrally [1].

The usefulness of opioid antagonists was first documented in the late 1970s; administration of the opioid receptor antagonist naloxone led to the dramatic amelioration of otherwise intractable

AS = Alagille syndrome

pruritus in a patient with cholestatic liver disease. Since these initial reports, several studies have shown that treatment with opioid antagonists can lead to relief of pruritus in patients with cholestatic liver disease. However, it must be emphasized that all clinical trials that we are aware of were performed in adults, and only two of them involved a total of three pediatric patients [3,4] whose data were not analyzed separately. To the best of our knowledge, there is only one published case report of naltrexone use in children [5]. Chang and Golkar [5] describe a 17 month old child with congenital biliary atresia and generalized pruritus refractory to conventional treatment whose condition improved remarkably with the addition of naltrexone.

Opioid antagonists are well tolerated during long-term treatment, but severe opiate withdrawal syndrome can occur at the initiation of treatment – possibly as a result of an enhanced opioid tone in cholestatic patients, similar to that seen in opiate abuse [1]. Therefore, opioid receptor antagonists should be administered at very low doses and increased slowly [2].

In summary, we describe the dramatic resolution of symptoms in a 3.5 year old girl with AS treated with naltrexone, such that we withdrew her name from the transplantation list. In addition, we provide anecdotal data on dosage and scheduling of naltrexone. The effectiveness of this drug in children should be studied prospectively.

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