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Management of cholestatic pruritus in children with Alagille syndrome: Case report and literature review

Traitement du prurit dans le syndrome d'Alagille : à propos d'un cas

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Summary

Alagille syndrome causes intractable pruritus and disfiguring xanthomas because of retained bile acids and cholesterol. Drug therapy in addition to surgical intervention may be effective in many patients in reducing serum bile acids, cholesterol levels, pruritus, and skin xanthomas. In this report, we describe a child with Alagille syndrome who presented with severe pruritus and xanthomas as a consequence of severe hypercholesterolemia and discuss the treatment modalities.

Résumé

Le syndrome d'Alagille, ou paucité ductulaire syndromique, est une affection multisystémique héréditaire, de transmission autosomique dominante. Il est caractérisé par l'association d'une cholestase chronique à une atteinte cardiaque, oculaire, squelettique et un faciès caractéristique. Il est souvent associé à prurit et à la formation de xanthomes secondaires à l'hypercholestérolémie. Nous discutons à travers une observation les modalités thérapeutiques chez ces patients souffrant souvent de prurit invalidant.

1. Introduction

Alagille syndrome (AGS), also known as arteriohepatic dysplasia, is a multisystem autosomal dominant disorder caused by defects in components of the Notch signalling pathway, most commonly due to a mutation in *JAG1* (AGS type 1), but in a small proportion of cases (1–2%) to a mutation in *NOTCH2* (AGS type 2). The main clinical and pathological features are chronic cholestasis due to a paucity of intrahepatic bile ducts, peripheral pulmonary artery stenosis, minor vertebral segmentation anomalies, characteristic facies, posterior embryotoxon/anterior segment abnormalities, pigmentary retinopathy, and dysplastic kidneys [1,2]. Expression of AGS varies from a mild phenotype to severe diseases of the heart or kidney and to the consequences of chronic cholestasis, including liver failure. Intractable pruritus and disfiguring xanthomas from cholestasis markedly reduce the quality of life of these children.

2. Case report

This male baby was admitted at the age of 2 months for evaluation of persistent neonatal jaundice. He was born at full term, to nonconsanguineous parents. His family history was negative for any childhood diseases or hereditary disorders. On physical examination, he weighed 3800 g (< 5th percentile), and was 52 cm tall (< 5th percentile). He had a triangular face with a broad forehead, hypertelorism, and a small pointed chin. Skin examination was significant for jaundice including the mucous membranes associated with acholic stools and dark urine. Cardiac examination revealed a

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systolic ejection murmur. The abdomen was soft, nondistended and the liver's edge was felt 1 cm below the right costal margin with no splenomegaly. Laboratory values showed elevated liver enzymes with aspartate aminotransferase 460 U/L (reference value, 15–50), alanine aminotransferase 361 U/L (10–25), γglutamyltransferase 433 U/L (11–48), and alkaline phosphatase 1278 U/L (150–380), total bilirubin of 194 μmol/L (0–1.2 [conjugated 105]) and total cholesterol level 7.3 mmol/L (3–6 mmol/L). The prothrombin time was normal. Abdominal ultrasonography showed moderate hepatomegaly with empty gallbladder and no expansion of the intrahepatic bile duct. Bilateral nephromegaly was also noted. The ophthalmologic exam was significant for bilateral posterior embryotoxon. Radiography of the spine was normal. An echocardiogram revealed mild stenosis of the pulmonary artery. A diagnosis of AGS was made on the basis of the association of four major features of this disease. A genetic study was not performed. The management of the patient was based on hypercaloric nutrition regimen, a supplementation of fat-soluble vitamins (A, D, E, K), and the prescription of ursodeoxycholic acid (15 mg/kg per day). At the age of 15 months, he presented with intense pruritus. Xanthomas were noted on the extensor surface of the fingers and palmer creases *(fig. 1)*. Evaluation of plasma lipids revealed hypercholesterolemia 25.7 mmol/L (3–6 mmol/L) and hypertriglyceridemia 5.1 mmol/L (0.5–1.5). Rifampin (15 mg/kg per day) and an antihistamine agent were started, followed shortly by cholestyramine (8 g/day). However, symptoms continued to progress with extension of xanthomas (ears, inner canthus, extensor surface of elbows) in spite of a decrease in the cholesterol level to 17 mmol/L (*fig. 1*; informed consent obtained). Surgical options were discussed, and a liver biopsy was performed as part of his presurgical evaluation. The biopsy showed cholestasis, mild fibrosis, and a paucity of bile ducts. Partial external biliary diversion was offered to the family for progressive xanthomas and intractable pruritus. The family was opposed to a permanent ostomy and refused this option. At 2 years of age, the patient underwent ileal exclusion with a

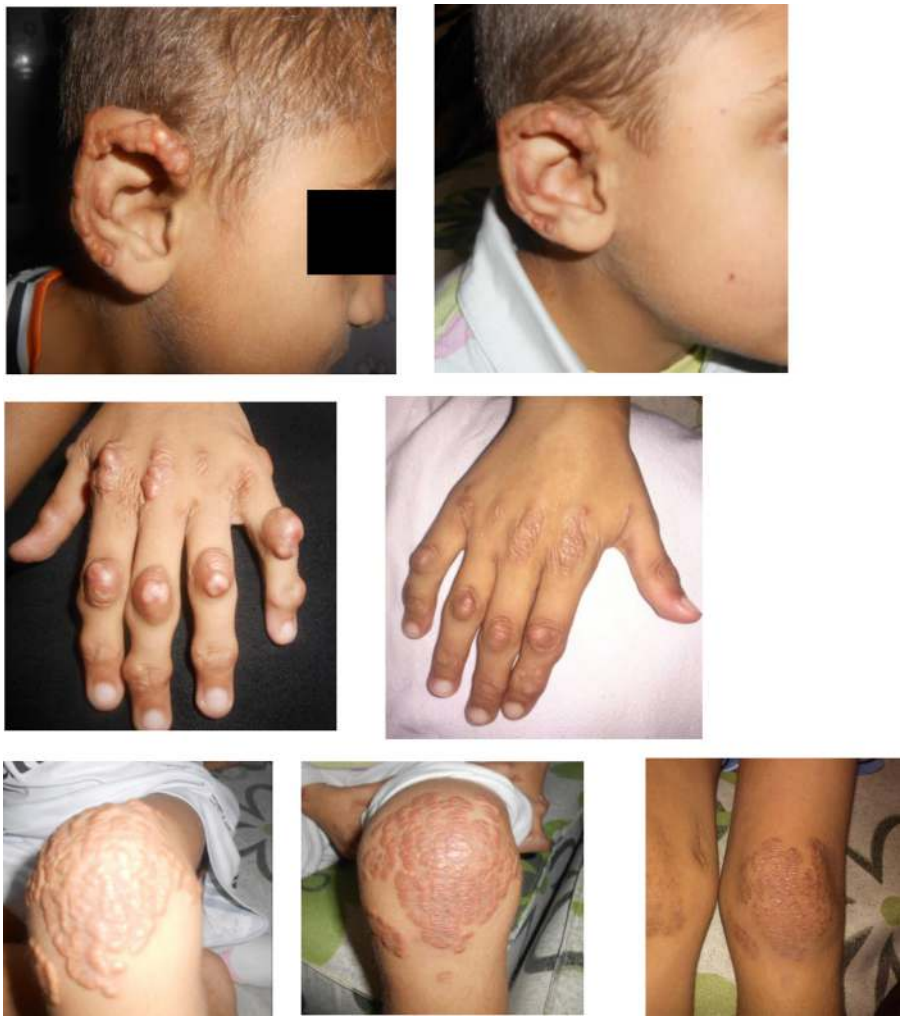

Figure 1. Xanthoma before treatment (Zoloft, vitamin C, and aloe vera) and 6 months later. Informed consent was obtained for use of these photographs.

slight benefit. Because of severe nonresponsive pruritus, he was listed at age 2.5 years for liver transplantation. At the age of 3 years 6 months, a treatment with sertraline (Zoloft®) was initiated, at progressively increasing doses from 1 to 3 mg/kg per day, with vitamin C (250 mg/day). Improvement of pruritus was reported 6 months later and for the first time the child was able to sleep through the night without scratching. At 4 years, the mother added an aloe vera preparation. *fig. 1* demonstrates the degree of improvement in the xanthoma burden. Total and LDL cholesterol levels were reduced by 41% and 39%, respectively. The patient is now 8 years old, and the family continues to report significant improvement in pruritus and xanthomas (on ursodeoxycholic acid, cholestyramine, rifampicin, vitamin C, sertraline, and aloe vera).

3. Discussion

Chronic cholestasis is a principal feature of AGS and most commonly presents in the neonatal period or the first 3 months of life, with jaundice due to conjugated hyperbilirubinemia. Serum bile acids and liver function tests are high, pruritus and growth failure may occur, and xanthomas may be present [1]. The pruritus seen in AGS is among the most severe of any chronic liver disease. It is rarely present before 3–5 months of age but is seen in most children by the 3rd year of life. It is often debilitating, disturbing sleep, daily activities, and cognitive development [3]. The etiology of pruritus associated with cholestasis is unclear. It has been postulated that it may be caused by the accumulation of toxic bile acids, steroid-derived metabolites, histaminergic pathways, or even neurogenic endogenous ligands that interact with central opiate receptors [4,5]. Xanthomas typically form, as seen in our case, on the extensor surfaces of the fingers, the palmar creases, the nape of the neck, the ears, the popliteal fossa, the buttocks, and around the inguinal creases. They are typically worse in areas of friction, such as the diaper area. They tend to occur with serum cholesterol levels greater than 500 mg/dL. Xanthomas increase in number during the first few years of life and may disappear subsequently as cholestasis improves. Xanthomas are cosmetically disfiguring and may interfere with fine motor function, although they are not considered painful [3,6]. The hypercholesterolemia of AGS is often staggering; however, this high level of plasma cholesterol is largely associated with lipoprotein-X. Lipoprotein-X is in the low-density lipid range and resists oxidation, thereby protecting against atherosclerosis. Thus, the hypercholesterolemia of AGS does not appear to carry an increased risk of cardiovascular disease [3].

Management of chronic cholestasis in AGS depends on severity and may include nutritional support, medical therapy, and surgery or liver transplantation in severe cases. Treatment options for pruritus and xanthoma remain limited to a few evidence-based and several experimental medical and interventional therapies. Current standard therapy in this setting consists of bile acids binding resins, antihistamines, phenobarbital, rifampicin, and ursodeoxycholic acid, singly or in various combinations [4]. Choleretics such as ursodeoxycholic acid may promote bile excretion in some patients. The use of ursodeoxycholic acid has been studied in children with AGS with improvement in pruritus, xanthomas, and biochemical markers of cholestasis. Narkewicz et al. [7] conducted a 2.5-year open-label crossover study in a group of cholestatic children, four of whom had AGS, with improvement in pruritus scores. Phenobarbital is rarely used due to its sedative effect. Rifampin reduces itching in some patients, perhaps by decreasing bile salt production [3]. Cholestyramine binds bile acids in the intestinal lumen, increases fecal excretion of these substances, and interrupts the enterohepatic bile-acid cycle. Significant reductions in bile acids and LDL-C are achievable during treatment with cholestyramine in about 50% of eligible children [4]. In the present case, we failed to control symptoms and pruritus remained intractable even with combined medical treatment. The opioid antagonists, naloxone and naltrexone, as well as the serotonin-reuptake inhibitor (sertraline), have also been shown to alleviate pruritus from cholestasis[4]. Naltrexone has been shown to be effective against pruritus in cholestatic adults. Zellos et al. [5] reported on the moderately successful use of oral naltrexone in four children for debilitating pruritus secondary to cholestasis and refractory to other antipruritic medications. The naltrexone dosage used was 1–2 mg/kg orally once daily with a maximum daily dosage of 50 mg. Sertraline was moderately effective in reducing itch intensity in our patient, whereas it was effective and well tolerated in a study of 21 adults with chronic pruritus due to liver disease [8]. In a retrospective review of 62 patients diagnosed as having AGS, 51 (82.3%) patients experienced pruritus and 50 (80.6%) received antipruritic medication. Ursodeoxycholic acid was the most frequently prescribed drug (n = 40). Other drugs were rifampicin (n = 39), cholestyramine (n = 18), naltrexone (n = 14), alimemazine (n = 13), nonsedating antihistamine agents (n = 7), ondansetron (n = 5), and phenobarbitone (n = 1) [9]. Aloe vera is a botanical with immunomodulatory properties. Aloe preparations improve the absorption of vitamin C and the total cholesterol-lowering effects noted in the present report may be due to the antioxidative properties of vitamin C [10]. There are currently several randomized controlled trials underway that are analyzing the antipruritic effects of bile acid transporter inhibitors in acquired (primary biliary cirrhosis) or genetic (AGS, progressive familial intrahepatic cholestasis) hepatobiliary diseases [11]. Nor-ursodeoxycholic acid (norUDCA) is a side-chain-shortened derivate of ursodeoxycholic acid and appears to be one of the most promising novel treatment approaches targeting the liver and the bile duct system at multifactorial and multicellular levels [12].

Surgical techniques that divert the biliary system and interrupt enterohepatic circulation have become increasingly used to treat refractory symptoms and improve quality of life. Partial external biliary diversion allows for external drainage of bile by creating a conduit between the gallbladder and the skin using a segment of jejunum, resulting in a permanent ostomy [13,14]. Ileal exclusion creates an end-to-side ileocolostomy by bringing the proximal ileum to the right colon and, therefore, excluding the terminal ileum [15]. Recently, a surgical technique, namely partial internal biliary diversion, has been described in a child with AGS to decrease cholestasis and itching [16]. In cases of refractory pruritus, liver transplantation is indicated.

4. Conclusion

The management of cholestatic pruritus in AGS is difficult and often suboptimal. The anion exchange resin cholestyramine, the PXR agonist rifampicin, the opioid antagonist naltrexone and the serotonin reuptake inhibitor sertraline are recommended by evidence-based guidelines as stepwise therapeutic approaches to treat itch in cholestasis [14]. Pruritus may remain intractable even with combination medical treatment, and at this stage, surgery or liver transplantation is indicated [9].

Disclosure of interest

The authors declare that they have no competing interest.

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