Alagille syndrome: Resolution of xanthomas

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Alagille syndrome (arteriohepatic dysplasia) is an autosomal dominant disorder characterized by chronic cholestasis due to paucity of intrahepatic biliary ducts, characteristic facies, peripheral pulmonary stenosis, ocular posterior embryotoxon and skeletal abnormalities. Very little information is available on the cholestatic, lipid and lipoprotein profiles in individuals with Alagille syndrome. The course of xanthomatosis and the lipid-lipoprotein profile of a 15-year-old male with incomplete Alagille syndrome with marked xanthomatosis and extremely elevated cholesterol secondary to cholestasis is reported. He showed gradual resolution of xanthomas beginning at age 12 years with a concurrent reduction in his total serum cholesterol. The lipid studies showed that the majority of cholesterol was found in low density lipoprotein (LDL) with lesser amounts in lipoprotein (Lp)-X, a lipoprotein precursor complex seen in patients with cholestasis, and high density lipoprotein (HDL). With resolution of xanthomas, LDL and Lp-X decreased while HDL-cholesterol and apolipoprotein (Apo) A-I increased. Gamma glutamyltransferase and bilirubin decreased but remained 15- and threefold elevated, respectively.

Key Words: Alagille syndrome, Cholesterol, Cholestyramine, Intrahepatic cholestasis, Lipoprotein X, Xanthoma

 Syndrome d’Alagille : résolution de xanthomes

RÉSUMÉ : Le syndrome d’Alagille est une maladie rare à caractère autosomique dominant caractérisée par une choléstase chronique attributable à la perte perméabilité des voies biliaires intrahépatiques, par un faciès typique, une sténose pulmonaire périphérique, un embryotoxon postérieur et des anomalies du squelette. Très peu de renseignements sont disponibles sur les profils cholestéatiques, lipidiques et lipoprotéiques des sujets atteints du syndrome d’Alagille. L’évolution de la xanthomatose et le profil des lipides et des lipoprotéines d’un garçon de 15 ans atteint d’un syndrome d’Alagille partiel avec xanthomatose marquée et cholestérol extrêmement élevé secondaire à la choléstase ont été présentés ici. Le patient a manifesté une résolution graduelle de ses xanthomes vers l’âge de 12 ans, avec réduction concurrente de son cholestérol sérique total.

CASE PRESENTATION

The patient was a 15-year-old Caucasian male. The perinatal course was unremarkable. He was born at term, birth weight 2.7 kg (10%), and had ‘mild jaundice’ that did not require treatment. He was discharged home on day 3 of life and had difficulties, with poor feeding irritability and increased...
jaundice. At three months of age he was found to have bleeding from his right ear, increased jaundice and loose fatty stools. Investigations revealed a three- to fourfold elevation in aspartate aminotransferase and alanine aminotransferase (ALT), a 20- to 30-fold elevation in gamma glutamyltransferase (GGT) and a three- to fourfold elevation in total bilirubin (60 to 80% conjugated) reflecting an obstructive picture. Liver biopsies at three and nine months showed cholestasis but were inconclusive for Alagille syndrome.

When the patient was five years old a repeat liver biopsy showed the characteristic paucity of intrahepatic bile ducts that is seen in Alagille syndrome. Additional features included the characteristic facies of Alagille syndrome with prominent forehead, deep set eyes, hypertelorism, straight nose and small pointed chin. He had a III/VI systolic murmur and a widely split S2 diagnosed as peripheral pulmonary artery stenosis by echocardiogram. Ophthalmic examination showed no posterior embryotoxon and skeletal surveys at age two and 15 years were normal. He developed problems with xanthomatosis and pruritus around age two years. The xanthomas began on the flexor surface of his forearms and gradually increased in size and spread to the extensor surfaces. By age 12 years he had extensive red-brown xanthomas covering most of the extensor surfaces of his arms, the dorsal aspect of his hands, the anterior and posterior aspects of his thighs, and the posterior aspect of his buttocks and lower back (Figure 1). He had extensive xanthomas on the helices and the posterior aspect of the ears (Figure 2) and small lesions on the buccal mucosa. He had bilateral arcus adiposus and fundoscopic findings of silver wiring, and small tortuous arteries and veins. Exercise tolerance testing and coronary arteries on echocardiogram were normal at age 12 years. Neurological examination and development were normal and he had honours standing in school. At age 15 years he had Tanner II development. Renal function, ultrasound of the liver and alpha-fetoprotein were normal at age 15 years. Chromosome studies were normal with no evidence of a deletion on the short arm of chromosome 20 (20p). Small deletions of 20p can be seen in some individuals with Alagille syndrome.

There was no family history of Alagille syndrome. His parents had normal lipid profiles, and clinical examination showed no evidence of Alagille syndrome. The patient was treated with supplemental vitamins and cholestyramine for pruritus on an intermittent basis before age 10 years. At age 12 years, while undergoing investigations for elevated cholesterol and xanthomas, the patient was placed on a high soluble fibre diet with 30% fat, 140 mg/day cholesterol, 20% protein and 50% carbohydrates. At age 12.5 years he was started on cholestyramine 4 g bid on a regular basis.

METHODS

Blood samples were drawn after a 12 h fast. HDL cholesterol was assayed after precipitation of LDL and very low density lipoprotein (VLDL) by sodium phosphotungstate-Mg++. Serum apolipoprotein (apo) A-I and apoB were determined by single radial immunodiffusion (Tago Diffu-Gen apoA or apoB, California) (8). Lp-X was quantitatively determined by the method of Panteghini and colleagues (9). Phospholipids were fractionated chroma-
tographically (10) and quantified by the method of Bartlett (11). High resolution chromosome analysis was performed on peripheral lymphocytes (12).

**RESULTS**

Lipid and apolipoprotein profiles are illustrated in Figures 3 to 5. Total plasma cholesterol (Figure 3) was the extremely high level of 37 mmol/L at age eight years. The patient was lost to follow-up between ages eight and 11 years. At age 12 years, the plasma total cholesterol level was 19 mmol/L, well above the upper normal level of 4.9 mmol/L. Lipoproteins that comprise the total plasma cholesterol are illustrated in Figure 4. Low density lipoprotein cholesterol (LDL-C), the majority of the total cholesterol, was well above the upper normal level of 3.18 mmol/L until age 14 years. High density lipoprotein cholesterol (HDL-C) initially was below normal levels but rose steadily to above the normal range (0.88 to 1.53 mmol/L) until age 14 years. Lp-X, a low density precursor lipoprotein, was present in plasma and gradually declined. ApoB (normal 0.67 to 1.17 g/L) declined in parallel with LDL-C and rose when LDL-C increased at 15.3 years (Figure 5). Apoprotein A-I (normal 0.67 to 1.17 g/L) shows a steady rise with a concomitant rise in HDL-C (Figure 5). Total bilirubin, ALT and GGT are illustrated in Figure 6. They were all well above the normal range, with only slight improvement after age 12 years.

The GGT levels were compatible with an obstructive pattern as were bilirubin levels, which fluctuated between 39 and 85 µM/L.

Figure 2 illustrates the presence of xanthomas on the patient’s right ear and their resolution from ages 12 to 15 years. The resolution occurred gradually over the course of a number of months starting at 12.2 years of age. Overall, the patient had clinical resolution of xanthomas from age 12 to 13 years with a concomitant decline in total plasma cholesterol, LDL-C and associated apoprotein B. This was associated with a slight increase in HDL-C and the associated apoprotein A-I.
DISCUSSION

Alagille syndrome is an autosomal dominant disorder with features of chronic cholestasis due to paucity of intrahepatic biliary ducts (91%), characteristic facies (95%), peripheral pulmonary stenosis (85%), posterior embryotoxon (prominence of Schwalbe’s line 88%) and skeletal abnormities (87%) including butterfly-like vertebral arch defects or lack of increase in the interpedicular distance of the lumbar spine and short distal phalanges (1,13). A deletion of chromosome 20 (p11.2, p12.3) has been detected in some individuals with Alagille syndrome (14-18), most of whom show evidence of developmental delay and dysmorphic features suggestive of a contiguous gene syndrome. Much variability has been noted in families with evidence of ‘anticipation’ which is the increased severity in subsequent generations (14,19).

REFERENCES