A Case Report : Alagille Syndrome

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Abstract

Alagille syndrome consists of 5 major features comprising paucity of interlobular bile ducts, characteristic facies, posterior embryotoxon, vertebral defects and peripheral pulmonic stenosis. The female patient in this report met 4 of the 5 major features except ocular abnormality. The first clinical presentations were prolonged jaundice and generalized ecchymoses. She was treated by plasma replacement and vitamin supplement, particularly vitamin K1, which produced clinical improvement. This report also reviews the literature of Alagille syndrome.

Key word : Cholestasis, Arteriohepatic Dysplasia, Alagille

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CASE REPORT

A 6-month-old female infant had a history of jaundice first detected by her parents at the age of 2 weeks. There was no history of any acholic stool. At 2 months old, she was investigated with liver ultrasound at a primary hospital, and it was reported that the child had hepatitis. Thereafter, jaundice gradually increased during the first 6 months of life. Two weeks before being admitted to the hospital for complete evaluation, she had ecchymoses on her flank and extremities. Her birth weight was 3,050 g. There had been no complication during pregnancy and delivery, and no jaundice was observed at birth. Her developmental milestones were normal. There was no family history of cholestatic jaundice and congenital heart diseases. On physical examination, her weight, height and head circumference were 6.4 kg, 64 cm and 41.4 cm respectively. Moderate jaundice was observed on her conjunctivae and skin. Frontal bossing, deep-set-eyes and a small pointed chin were also noted. (Fig. 1) The ophthalmologic examination performed by an ophthalmologist was normal. There was a continuous murmur grade 2/6 at the left upper sternal border. The liver was slightly enlarged (2 cm below the right costal margin) with

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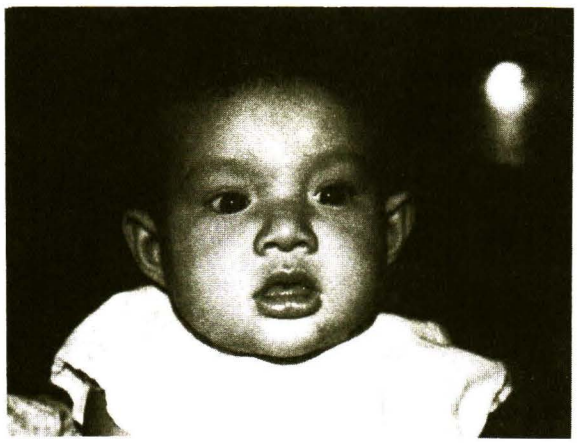

Fig. 1. The picture shows the characteristic facies of Alagille syndrome. Frontal bossing, deep-set-eyes and a small pointed chin were noted.

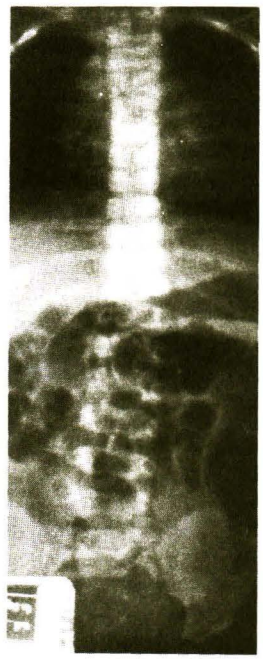

Fig. 2. The roentgenogram of the spine showed butterfly-like vertebrae and hemivertebrae.

a sharp edge and smooth surface, but the spleen was normal. Neither ascites nor superficial vein dilatation was noted. There were ecchymoses on her flank and extremities. She also had severe hearing loss at mid frequency in both ears, determined by using the BAEPs (brainstem auditory evoke potentials) test. Hematologic studies revealed hemoglobin 9.7 g/100 ml, hematocrit 31.7 per cent, white blood cell count 11,100 /mm^3, platelet 521,000 / mm^3, PT 20.8 sec (control 12.5 sec), PTT 64.3 sec (control 31.3 sec) and bleeding time 2 min. The liver function test included albumin 3.4 g/100 ml, globulin 3.1 g/100 ml, alkaline phosphatase 292 IU/L, gammaglutamyl transferase 198 U/L, AST 303 IU/L, ALT 332 IU/L, total bilirubin 21.41 mg/100 ml and direct bilirubin 13.86 mg/100 ml. Serology for CMV IgM and rubella were negative, but CMV IgG was positive at the titer 1:3,200, while the maternal CMV IgG titer was 1:400. By ultrasonography, the liver and kidneys appeared normal, however, neither bile duct nor gallbladder was detected. An HIDA scan showed no evidence of excretion of radioisotope into the bowel. A chest film and ECG were normal. Echocardiography revealed peripheral pulmonic stenosis. Roentgenogram of the spine showed butterfly-like vertebrae and hemivertebrae. (Fig. 2) A liver biopsy was performed, and the histopathology revealed paucity of interlobular bile ducts with evidence of cholestasis.

DISCUSSION

The first recognition of familial pulmonary arterial stenosis with neonatal liver disease, called arteriohepatic dysplasia, was described by Watson and Miller in 1973, however, the initial description of Alagille syndrome, thought to be similar to that described by Watson and Miller, was reported by Alagille et al in 1975[1,2]. He described 15 children having chronic cholestasis, characteristic facies, a mesosystolic murmur, vertebral arch defects, growth retardation and hypogonadism. The exact incidence is still unknown. Males and females are equally affected[2,3]. When reviewing 111 children for paucity of interlobular bile ducts (PILBD) in 1987, Alagille et al found that 72 per cent of these patients were classified into a syndromic type consisting of 5 major features; peculiar facies (95%), chronic cholestasis (91%), posterior embryotoxon (88%), butterfly-like vertebral arch defect (87%) and peripheral pulmonic stenosis or other complex heart diseases (85%)[4]. If the patients met all of the above major features, approximately 32 per cent would be categorized into the complete syndrome, otherwise, they would be categorized into a partial syndrome. Apart from the above mentioned patients, those with Alagille syndrome also had growth (50%) and mental (16%) retardation[4].

Chronic cholestasis reported by Dahms et al, resulting from the paucity of interlobular bile ducts, may be caused by destructive inflammation of bile duct epithelium found on the histopathologic study of patients with Alagille syndrome[5]. Furthermore, this study observed that half of the patients had a normal number of interlobular bile ducts as infants, which decreased with age. This result suggested an acquired process and may reflect variable penetrance of a genetic disorder. The characteristic facies consist of a prominent forehead, moderate hypertelorism with deep-set eyes, small chin pointed anteriorly and saddle or straight nose[4]. The vertebral defect includes the unfused anterior arches of one or several vertebrae resulting in a butterfly-like appearance[4]. A father and son with the syndrome of cholestasis and peripheral pulmonic stenosis has been reported[6]. This mode of vertical transmission supported a genetic etiology for this disease. Autosomal dominant inheritance was firmly supported when four generations of arteriohepatic dysplasia were reported[7]. It has been believed recently that Alagille syndrome is caused by a single gene defect resulting from microdeletion at 20p[8]. Laboratory findings related to chronic cholestasis revealed the elevation of cholesterol, triglyceride, lipoprotein, apoprotein B, total bile acids, alakaline phosphatase and gamma glutamyl transferase[4]. Complications seen in this syndrome included recurrent episodes of cholestasis, malnutrition, infection, kidney involvement and hepatocellular carcinoma[4,9-12].

Kidney involvement in Alagille syndrome may possibly be related to the hypercholesterolemia associated with cholestasis, such as mesangiolipidosis; or may result from abnormalities in renal morphogenesis, e.g. hydronephrosis with renal cyst, single kidney, dysplatic kidney, multicystic dysplasia and polycystic kidney[3,4,9]. Therefore, renal ultrasound is recommended for discovering evidence of kidney involvement in these patients.

The liver of patients with Alagille syndrome predisposes to develop hepatocellular carcinoma whether associated with cirrhosis or not[10-12]. This suggests that patients with Alagille syndrome are possibly at risk for the development of hepatocellular carcinoma after many years of chronic cholestasis, even in the absence of cirrhosis[11, 12]. The outcome of the patients depends on the severity and duration of the early cholestasis, degree of malnutrition, infection and the severity of diseases in the cardiovascular system. Alagille et al reported a 26 per cent mortality rate[4]. In contrast to previous studies, Hoffenberg et al reported only a 50 per cent long-term survival rate of Alagille syndrome cases without liver transplantation[3]. Nonetheless, this report included only patients with neonatal cholestasis, which is considered generally to be more severe.

Medical treatment with ursodeoxycholic acid improves pruritus, cutaneous xanthomas, serum total cholesterol and LDL[13]. Phenobarbital and cholestyramine can be used for this syndrome. Supplementation of adequate nutrition, particularly fat-soluble vitamins, is the mainstay therapy. Bleeding precautions should be recommended to the parents because the patient could die of intracerebral hemorrhage. Liver transplantation, especially in patients with severe liver failure, improved the long-term survival rate from 50 per cent to 87 per cent reported by Hoffenberg et al[3].

The patient in this report met 4 of 5 major criteria for the diagnosis of Alagille syndrome except the ocular abnormality. She had a bleeding tendency, however, it readily responded to vitamin K1 administration. Hearing loss in this patient was thought to be a result of CMV infection. Laboratory findings revealed mildly elevated alkaline phosphatase, GGT and liver enzymes. Symptomatic and supportive treatment were given to her with FFP transfusion, nutritional support, particularly fat-soluble vitamins, and the education of bleeding precautions. This patient was treated continuously with phenobarbital, she improved, and the ecchymoses disappeared.

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รายงานผู้ป่วย Alagille syndrome

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กลุ่มอาการ Alagille ประกอบไปด้วยลักษณะสำคัญ 5 อย่าง คือ ขนาดของท่อน้ำดีตับลดลง ลักษณะรูปร่างหน้าตาผิดปกติ มีความผิดปกติของตา และกระดูกสันหลัง และมีหลอดเลือดหัวใจส่วนปลายไปปอดตีบ รายงานนี้รายงานผู้ป่วยเด็กหญิงไทยอายุ 6 เดือน 1 ราย ที่มี 4 ลักษณะสำคัญของกลุ่มอาการนี้ ยกเว้น ความผิดปกติของตา โดยผู้ป่วยรายนี้มีอาการที่นำผู้ป่วยมาพบแพทย์ด้วยเรื่อง มีตัวเหลือง ตาเหลืองมาตั้งแต่อายุ 2 สัปดาห์ ร่วมกับมีจ้ำเลือดตามตัว ผู้ป่วยได้รับการรักษาด้วย วิตามิน เค ทำให้อาการดีขึ้น รายงานนี้ได้ทบทวนวรรณกรรมที่เกี่ยวกับ กลุ่มอาการ Alagille ด้วย

คำสำคัญ : Cholestasis, Arteriohepatic Dysplasia, Alagille

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