

Hepatobiliary scan in Alagille syndrome; arteriohepatic dysplasia

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Abstract

Arteriohepatic dysplasia or congenital paucity of interlobular bile ducts - Alagille Syndrome, is a well defined syndrome characterized by five major features, including chronic cholestasis, posterior embryotoxon, butterfly-like vertebral arch defects, peripheral pulmonary artery hypoplasia or stenosis and facial dysmorphism. The disease is very rare. Only three cases have been reported in Greece and none with renal involvement. Hepatobiliary scan was a fundamental tool in the patients diagnosis and therefore we present the following case.

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Introduction

Arteriohepatic dysplasia, or congenital paucity of interlobular bile ducts-Alagille syndrome (AS), is a well defined syndrome characterized by five major features, including chronic cholestasis, posterior embryotoxon, butterfly-like vertebral arch defects, peripheral pulmonary artery hypoplasia or stenosis and facial dysmorphism [1-3].

It is the second most common cause of intrahepatic cholestasis in infancy. The disease is very rare with a frequency 1 in 100000 live births and with no gender predilection [4]. Only three cases have been reported in Greece and none with renal involvement [5, 6]. Hepatobiliary scan was a significant tool in the patient's diagnosis and therefore we present the following case.

Case report

A male newborn 43 days old was admitted to Paediatric Clinic of the University Hospital of Alexandroupolis with a prolonged neonatal jaundice. The baby was delivered after a caesarean section at 38 weeks of gestation, because of failure to progress and maternal chronic active hepatitis B. His birth weight was 2,600gr. Immediately after birth, he received one dose of specific hepatitis B globulin and one dose of hepatitis B vaccination to compensate for maternal chronic hepatitis B. His growth and development, during the first month of his life, have been satisfactory. The last few days his stools were pale. On admission, the infant was alert with good tone and obvious jaundice both at the sclera and skin. He had a peculiar face with prominent forehead and hypertelorism. The liver was palpable 1.5cm below the costal margin. Primary reflexes were present and the rest of physical examination was unremarkable. The diagnostic work up revealed: Normal full blood count. Abnormal liver function tests: aspartate aminotransferase (AST)131U/L-normal values 15-48U/mL-, alanine aminotransferase (ALT) 78U/L-normal values 13-40U/L-, lactic dehydrogenase (LDH) 471U/L-normal values 230-460U/L-, alkaline phosphatase (ALP) 463-normal values 53-128-, bilirubin 7.9mg/dL-normal values 0.2-1.2mg/dL-, conjugated bilirubin 6.8mg/dl- normal values <0.3 mg/dl-. Coombs test was negative. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood gases, clotting time and thyroid function tests were normal.

Hepatitis screening-virology: hepatitis B surface antigen (HBsAg) was negative, anti hepatitis B surface antigen (anti-HBsAg) was >1,000IU/L-normal values >10-, HBeAg negative, anti-HBe positive, IgM antibodies for hepatitis A, C, for toxoplasma, rubella and cytomegalovirus (CMV) were negative. IgG antibodies for CMV and rubella were positive, attributed to maternal infection in the past. Sweat test was negative for cystic fibrosis.

Urine culture obtained after suprapubic needle aspiration, was positive for *Klebsiella oxytoca* (>10⁶). Kidneys ultrasound and renal scintigraphy with 34 MBq intravenously (i.v.) injected dose technetium-99m dimercaptosuccinic acid, (^{99m}Tc-DMSA-Fig. 1), showed dysplas-

tic right kidney. Urinary tract infection (UTI) was diagnosed. The diagnostic work up also included: magnetic resonance cholangio-pancreatography (MRCP), heart ultrasound, ophthalmological examination and liver biopsy.

The infant was successfully treated with amikacin intravenously (i.v.) for ten days. Subsequent biochemistry showed that transaminases were persistently elevated: AST131-184U/L, ALT78-106UI/L and also hyperbilirubinaemia, mainly due to increased conjugated bilirubin between 6.8-8.1mg/dL (normal

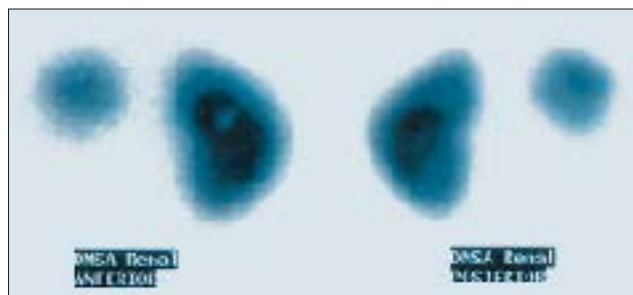


Figure 1. Static renal scintigraphy with ^{99m}Tc-DMSA. Dysplastic right kidney.

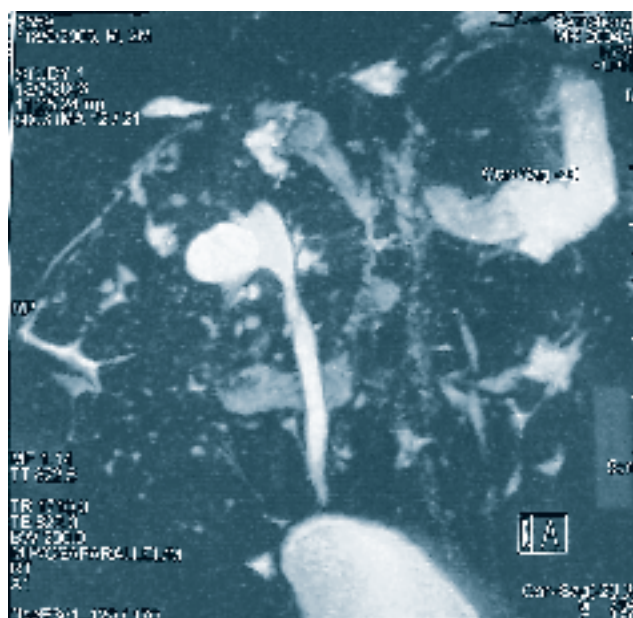


Figure 2. MRI with MRCP protocol. Normal bile ducts are absent.

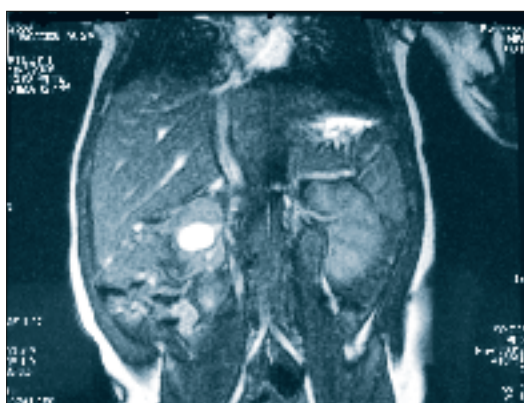
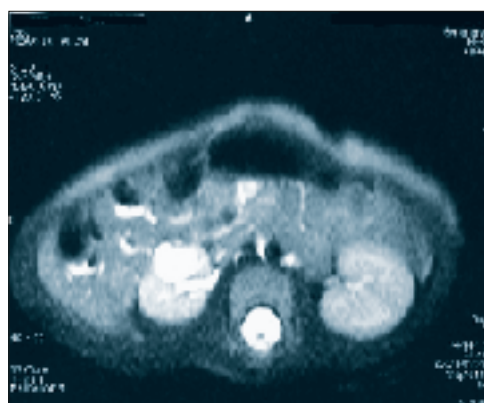


Figure 3. T2 weighted MR images on axial (A) and (A) coronal planes. Hypoplastic right kidney with a cystic lesion of high signal intensity; in the anterior view.

values <0.3). Persisting obstructive jaundice could not be attributed to UTI, hepatitis or other congenital neonatal infection.

Upper abdominal MRCP (Fig. 2 and 3) and 40 MBq i.v. injected dose ^{99m}Tc-bromo iminodiacetic acid (^{99m}Tc-BRIDA) liver scan were performed for further evaluation. Before hepatobiliary scanning, the patient received per os phenobarbital (5mg/kg/day) divided in two daily doses for 3 days. The infant was not fed for 1h before and 2h after the injection of ^{99m}Tc-BRIDA. Anterior images of the abdomen were obtained at 5min intervals up to 1h after injection. Thereafter, images were obtained at 2, 4, 8 and 32h post injection. All scans were evaluated independently by two medical imaging specialists. There was no excretion of radiolabeled tracer into the small intestine 32h after injection (Fig. 4).

With the suspicion of intrahepatic cholestasis, the infant was referred to a special Pediatric Gastroenterology Center for further investigation. The patient's study revealed the following: a) Cholestasis, with paucity of interlobular bile ducts, by the liver biopsy. b) Pulmonary artery stenosis, diagnosed

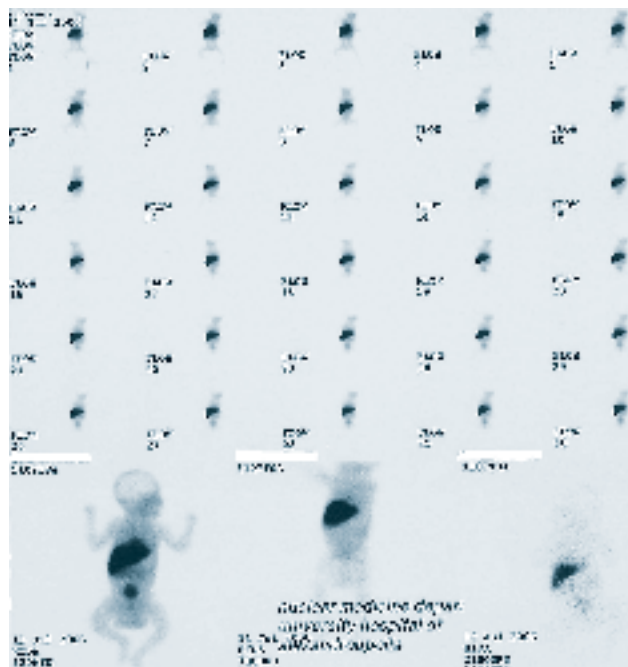


Figure 4. Dynamic cholescintigraphy with ^{99m}Tc-BRIDA. No bile draining is shown.

by the heart ultrasound. c) Embryotoxon found on slit lamp ophthalmological examination. d) Dysplastic right kidney, by the U/S and by ^{99m}Tc -DMSA renal scintigraphy.

The above fulfilled the criteria for the diagnosis of Alagille syndrome with 4 major features and 1 minor.

The infant was started on supplementation with lipid soluble vitamins (A, D, E, K) and treatment with cholestyramine and ursodeoxycholic acid for cholestasis and cefaclor for prophylaxis against UTI and followed up regularly by pediatric gastroenterologists. The child is still alive, with deteriorating liver function and in the list for liver transplantation.

Discussion

Alagille syndrome is an autosomal dominant disorder. The disease gene has been mapped at chromosome 20-band p12 with a deletion of the short arm of chromosome 20 [7-9]. The clinical spectrum of this syndrome includes: a) Chronic cholestasis due to intrahepatic bile duct hypoplasia. b) Characteristic facies consisted of prominent forehead, moderate hypertelorism with deep-set eyes, small chin pointed anteriorly and saddle or straight nose. c) Cardiovascular abnormalities with most common pulmonary artery stenosis. d) Vertebral arch defects with most common the non-fusion of the anterior arches of one or more dorsal vertebrae resulting a butterfly-like appearance. e) Posterior ocular embryotoxon. f) Less associated abnormalities that are considered as minor criteria for diagnosis are, growth retardation, mental retardation, renal abnormalities, skeletal abnormalities and high-pitched voice.

Our patient had cholestasis due to paucity of intralobular bile ducts, characteristic facies, pulmonary artery stenosis, embryotoxon and dysplastic right kidney, consistent with a complete form of the disease.

Recent reports indicate that patients with this syndrome are at risk for serious clinical problems, including heart failure, liver failure and hepatocellular carcinoma [10-12]. Early diagnosis of the disease and appropriate follow up are important. It is imperative to differentiate surgically correctable lesions from paucity of interlobular bile ducts (like in Alagille syndrome).

Hepatobiliary scanning is a useful diagnostic method for differentiating cholestatic jaundice in neonates, as non draining scans may indicate either severe neonatal hepatitis, or interlobular bile duct paucity [13-15]. In patients with non draining scans and possible Alagille syndrome, liver biopsy will confirm or exclude cholestasis due to paucity of intrahepatic bile ducts.

The prognosis of the disease is related to the severity and duration of cholestasis, the severity of cardiovascular abnormalities and the deterioration of liver function.

Treatment consists of nutritional supplementation and antipruritic treatment [10]. When cirrhosis becomes uncompensated, liver transplantation is the treatment of choice [7, 16, 17]. When the syndrome is complicated by liver tumour, transplantation is less likely to succeed and most patients die within 3 years as a result of tumour recurrence [16].

In conclusion, Alagille syndrome is the second most common cause of intrahepatic cholestasis. It is imperative to differentiate paucity of interlobular bile ducts from surgically correctable lesions. Hepatobiliary scan was important for diagnosis.

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