Clinical and pathological aspects of ARC (arthrogryposis, renal dysfunction and cholestasis) syndrome in two siblings

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We describe the first family report of ARC syndrome (arthrogryposis multiplex congenita, renal dysfunction, and cholestasis) diagnosed in Turkey. ARC syndrome is a rare cause of cholestatic jaundice and skeletal abnormalities in the neonatal period. Fanconi-like renal tubular dysfunction completed the clinical picture. Consanguinity and affected membership are the other typical components of this rare disorder, and possibility of autosomal recessive transmission was considered. A broad spectrum of histopathological abnormalities have been described in the liver and kidney. In this report, we describe two male siblings with ARC syndrome who had cholestatic jaundice, arthrogryposis multiplex congenital-like joint contractures and renal involvement with additional clinical features. Clinical and pathological aspects of the syndrome are discussed and compared with the other cases in the literature.

Key words: ARC, arthrogryposis multiplex congenita, cholestasis, renal tubular dysfunction.

Association of the arthrogryposis multiplex congenital, cholestasis and renal tubular dysfunction was first reported in 1973[1] and described as a new clinicopathologic entity by Nezelof et al[2]. in 1979. It is a fatal, progressive disorder that has autosomal recessive inheritance and has been termed ARC syndrome[3,4]. In most cases, clinical features are accompanied by histopathological abnormalities of the liver and kidney[4].

We present the first family report with the typical clinical picture that was diagnosed in Turkey, and compare our cases with other cases that have been published to date.

Case Reports

Case 1

At the twenty-first day of life, a male infant was admitted to the Newborn Unit with jaundice and umbilical hemorrhage. He was the third child of healthy the consanguineous parents. After a normal pregnancy, he was born via cesarean section because of breech presentation, with a birth weight of 2200 g. On the third day of life, jaundice was observed by his parents and it slightly increased in the following days. On physical examination, he was pale, had loose skin and diminished subcutaneous fat tissue. Body temperature was 36.2°C, heart rate 100 beats/minute, respiratory rate 60 per minute, weight 2230 g, length 49 cm, head circumference 34 cm, and anterior fontanel diameter 1x1 cm. He had dry and scaly skin like ichthyosis, jaundice, and skeletal abnormalities such as clenched fingers, abduction contractures of shoulders, and flexion deformities at the elbows. Flexion of the knee and hip joints was limited (Fig. 1). Based on these skeletal abnormalities, he was diagnosed as arthrogryposis multiplex congenita. Laboratory examination revealed metabolic acidosis and direct hyperbilirubinemia. Serum total bilirubin level was 26.5 mg/dl; conjugated bilirubin level was 21.2 mg/dl. Serum values of transaminases, gamma-glutamyltranspeptidase (GGT), protein, albumin and globulin levels were all within normal limits. Microbiologic evaluation for the antibodies against toxoplasmosis, cytomegalovirus (CMV) rubella and herpes simplex, and antigens

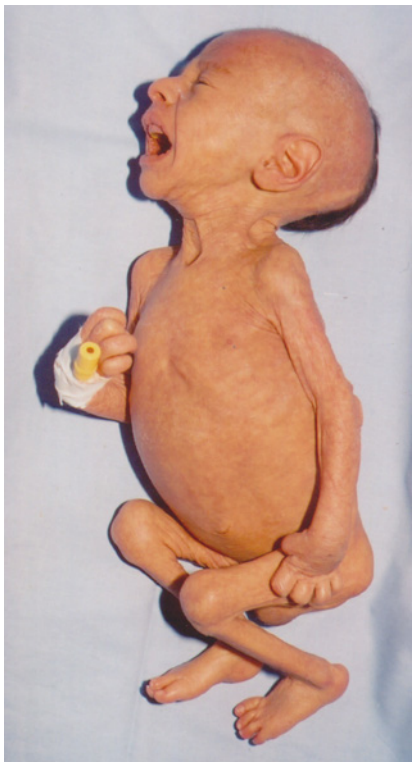

Fig. 1. 55th day of life. He had dry and scaly skin, arthrogryposis multiplex congenita (clenched fingers, abduction deformities of shoulders, flexion deformities at the elbows), excessive jaundice and weight loss.

and antibodies against hepatitis viruses A, B and C were negative. Klebsiella pneumoniae grew in blood culture. Plasma alpha-1-antitrypsin level and sweat chloride concentrations were normal. Amino acid analysis of blood was normal, but heavy generalized aminoaciduria and glucosuria were present in urine analysis on paper chromatography. Abdominal ultrasonography showed hepatomegaly with normal echogenicity and scintigraphic examination of the biliary tract was normal. Two hundred ml/kg/day parenteral fluid, bicarbonate, and broad-spectrum antibiotic therapy was given for correction of dehydration and metabolic acidosis and against infection. Tubular phosphate reabsorption was 55% in 24-hour urine analysis. In the echocardiographic evaluation, patent ductus arteriosus (PDA) was detected. The infant was fed with medium chain triglyceride oil-containing formulas supporting parenteral nutrition. Ursodeoxycholic acid (10 mg/kg) was added to therapy. On the 52nd day of the hospitalization, hepatomegaly, splenomegaly and excessive skin lesions like ichthyosis were present. Conjugated bilirubin level was 36 mg/dl. Percutaneous liver biopsy demonstrated brown-yellowish pigment deposition, especially granular types, in hepatocytes (Fig. 2). He died at 70 days of age from sepsis. Postmortem necropsy specimens showed renal tubular degeneration.

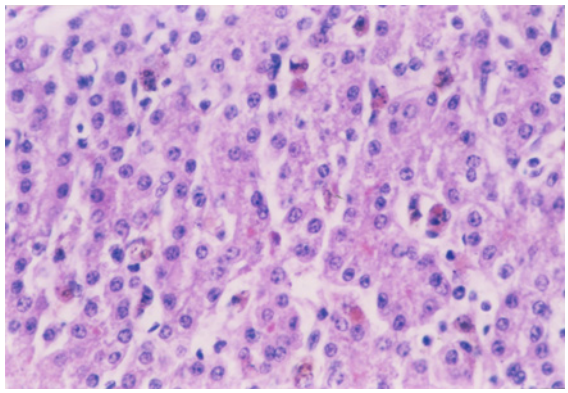

Fig. 2. Microscopic examination of the liver on the 60th day f life. Intracytoplasmic granular pigment deposition in hepatocytes.

Case 2

This male sibling of Case 1 was admitted at the 55th day of life with jaundice, bloody secretion from mouth, respiratory distress and seizures. He was born at 39 weeks of gestation with a birth weight of 3300 g. On admission his weight (2780 g), length (52 cm) and head circumference (35 cm) were at the 3rd centile. He was stuporous, had retractions with a respiratory rate of 64/minute, a heart rate of 148 beats/minute and bleeding from puncture sites. Skin was dry and scaling and jaundice was evident. Liver was 4 cm and spleen 1 cm palpable below the respective costal margins. Low-set nuchal hairline, low-set ears, high-arched palate, flexion contractures at kness, elbows and wrists, hip abduction, pes varus on left foot, internal rotation of shoulders, and clenched hand deformity were noted. Laboratory examination showed Hb 7.6 g/dl, WBC 22,300/mm^3, platelets 674,000/mm^3, and abnormally large platelets in blood smear. Total bilirubin concentration was 28.9 mg/dl (22.94 conjugated), AST 73 IU, ALT 23 IU, GGT 7 IU, alkaline phosphatase 1134 IU, blood pH 7.27, and HCO_3 9.4 mEq/L, with a base deficit of -19.5 mEq/L. Renal insufficiency with BUN

73 mg/dl and Cr 1.09 mg/dl was present. Urinalysis revealed proteinuria >300 mg/dl, hematuria with 27 erythrocytes and generalized aminoaciduria. ELISA test results were negative for TORCH agents and hepatitis A, B, C. PT and PTT were prolonged. Management of bleeding from upper gastrointestinal tract was attempted by nasogastric decompression, fresh frozen plasma, and ranitidine. He died at the 60th hour of hospitalization. Autopsy of the cases was performed. Histological section from liver displayed pigment granules in the hepatocytes and Kupffer cells and calcium deposits in the lumen of dilated medullary tubules were domnstrated in the kidney (Fig. 3). There was moderate degree of hyperkeratosis and keratotic follicular plugs in skin specimens.

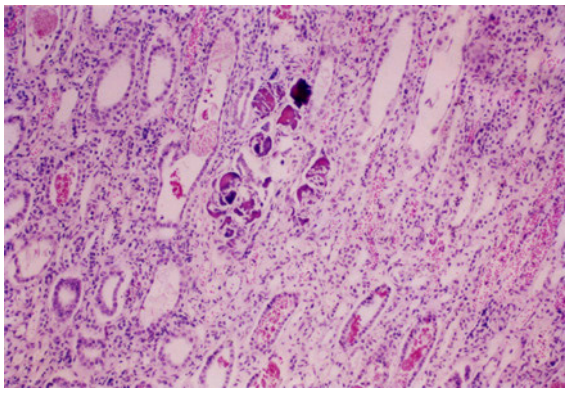

Fig. 3. Microscopic examination of the kidney demonstrating calcium deposits in the lumen of dilated medullary tubules.

Discussion

Association of arthrogryposis multiplex congenita, cholestasis and renal tubular dysfunction was first reported in 1973 in two male siblings[1]. Since 1973, the reported cases, including ours, have not exceeded 30. Nearly all had consanguineous parents and affected family membership[2-5]. Nezelof et al.[2] suggested X linked inheritance, but strong family history and reported female cases have suggested autosomal recessive inheritance[4-7]. Most of the reported cases are from the regions where the consanguineous marriage rate is high[3,8-10]. The ARC acronym was first used by Horslen et al.[3] for this rare entity.

The first diagnostic criterion for ARC syndrome is arthrogryposis multiplex congenita. These extremity anomalies were present at birth in most of the patients, as in our cases. Anomalies were the result of neurogenic muscle atrophy from anterior horn cells, and histopathologic examinations showed rarefaction of the motor neurons in anterior horns of the spinal cord[4,6].

Cholestatic jaundice and hepatomegaly are the most common symptoms in ARC at presentation. Appropriate investigations should be done to rule out the other causes of the conjugated hyperbilirubinemia in the neonatal period. Two different histopathological appearances of the liver biopsy suggested the possibility of two different syndromes sharing the same clinical picture[3]. One is intrahepatic biliary paucity and the other pigmentary deposit in hepatocytes[4]. Di Rocco et al.[4] reported occurrence of both types of changes in the same patient and suggested that these features were not distinctive of two different diseases but represented non-specific liver changes. Lipofuscin deposition is similar to that in Dubin-Johnson syndrome[4]. Intracytoplasmic pigment deposition in hepatocytes was shown in both of the cases.

The third and last component of the syndrome is renal tubular dysfunction accompanied by glucosuria, phosphaturia, generalized aminoaciduria and renal tubular acidosis[1-8]. Renal histology is variable[2,3]. While tubular degeneration was present in our first case, nephrocalcinosis was evident in the second.

Eastern et al.[10] pointed out that ARC syndrome exhibited clinical variability and was associated with additional clinical features such as dysmorphism, ichthyosis, diarrhea, recurrent febrile illnesses, and abnormal platelets. Ichthyosis-like skin features were present in both of our cases. Dysmorphic features of the second case were low-set ears, high-arched palate and low-set nuchal hairline. In 1997, Coleman et al.[11] reported cerebral anomalies and nephrogenic diabetes insipidus with ARC syndrome. Cerebral anomalies were hypotonia, microcephaly, deafness and corpus callosum anomalies. Congenital heart disease was reported in three cases including atrial and ventricular septal defect[3,11]. Our case had PDA, but cardiac involvement was not defined as a component of the syndrome.

Failure to thrive was present in all of the cases with a 20-50% weight loss[2,6]. Our first case was 2200 g at birth and 2250 g at 55th day at life, while the second case was 3300 g at birth and weighed 2780 g on admission.

All of the reported cases have died within several days or months. One case died at three years and delayed motor-mental retardation and cirrhosis in long-term surveillance were observed[11]. Almost all of the patients died from sepsis; Papadia et al.[7] suggested that these cases had immune dysfunction. Our first case diet at two months of age from sepsis, but we could not demonstrate immune dysfunction. Our first case had umbilical hemorrhage and the second case had gastrointestinal bleeding on admission. Tendency to bleed has been reported ant it was speculated that functional disturbance of abnormal platelets may play a role[10]. Eastham et al.[10] demonstrated abnormally large platelets in their six patients, which was also present in our second case.

Unfortunately, curative therapy for this rare syndrome has not been reported. High fluid and caloric administration such as total parenteral nutrition or medium chain triglyceride-rich formulas, monthly vitamin A-D-E-K and ursodeoxyhcolic acid can be given.

Although multisystem involvement suggests metabolic disturbance, it has not been proven. Since similar clinical and laboratory findings are observed both in ARC syndrome and progressive familial intrahepatic cholestasis (PFIC), Gissen et al.[12] performed linkage analysis to PFIC-I and II genes, but ARC syndrome was not found as an allelic condition to PFIC I or II. Further research is required to identify the gene causing this syndrome. On the basis of genetic, biochemical and histopathologic improvements, the cause of the ARC syndrome can be clarified, and therapy may be possible.

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