Liver Transplant in a Case of Arthrogryposis-Renal Tubular Dysfunction-Cholestasis Syndrome With Severe Intractable Pruritus

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Abstract
Arthrogryposis-renal tubular dysfunction-cholestasis syndrome (MIM No. 208085) is a rare multisystem disorder involving the liver, kidney, skin, and central nervous and musculoskeletal systems. The syndrome is an autosomal-recessive trait, associated with germ-line mutations in the VPS33B gene. We report an Iranian boy of consanguineous cousin parents who had congenital deformities of the upper and lower extremities, severe ichthyosis, cholestasis, intractable pruritus, metabolic acidosis, and failure to thrive. Owing to cholestasis, severe intractable pruritus, and poor quality of life, he underwent a living-related liver transplant from his mother, and his ichthyosis and pruritus dramatically improved. To the best of our knowledge, this is a first case of someone with arthrogryposis-renal tubular dysfunction-cholestasis syndrome who underwent a liver transplant and is in good condition more than 5 years after surgery.

Key words: Arthrogryposis multiplex congenita, Cholestasis, Liver transplant, Child, Quality of life

Introduction
Arthrogryposis-renal tubular dysfunction-cholestasis (ARC) syndrome is a rare cause of cholestatic jaundice and skeletal abnormalities during the neonatal period.1, 2 It is a progressive and lethal disorder with autosomal recessive inheritance.3, 4 Autosomal recessive inheritance is suggested by the frequency of parental consanguinity and recurrence in siblings.5 Novel identification of the mutation in the VPS33B gene locus in ARC syndrome related to intracellular protein trafficking by regulation of vesicle-to-target sensory nerve action potential receptor family could explain the consistent combination of membrane fusion defects.6 Approximately half of the reported cases of ARC syndrome are associated with ichthyosis.6 In most cases, clinical features are accompanied by histopathological abnormalities of the liver and kidney.4 Renal tubular dysfunction ranges from isolated renal tubular acidosis to complete Fanconi syndrome. On the other hand, hepatic histology shows variable combinations of intrahepatic biliary hypoplasia, cholestasis, giant cell hepatitis, lipofuscin deposition, fibrosis and ultimately, cirrhosis.7 Additional features have been reported in some patients, including cerebral malformations, nerve deafness, neurogenic muscular atrophy, and nephrogenic diabetes insipidus. Most patients die by the age of 7 months, but those surviving longer show severe developmental delay.2, 7 There is no effective treatment for this syndrome. Living-donor liver transplant is an effective therapy for end-stage liver disease and has proven to be a major advance in treating progressive hepatic diseases in children.8 Here, we present a 12-year-old boy with ARC syndrome with cholestasis, severe intractable pruritus, and poor quality of life who underwent a living-donor liver transplant.

Case Report
A 12-year-old boy was admitted to the Nemazee Teaching Hospital affiliated with the Shiraz University of Medical Sciences in Shiraz, Iran, with arthrogryposis...
diagnosed at birth, chronic cholestasis, growth retardation, ichthyosis, and severe itching and scaling. He was the first child of healthy consanguineous cousin parents, born after an uneventful pregnancy by normal vaginal delivery. He had dry, scaly skin, ichthyosis, jaundice, and skeletal abnormalities including clenched hands, abduction contractures of the shoulders, and flexion deformities at the elbows and wrists. He also had flexion contractures at the knees and hips and was unable to walk. Based on these skeletal abnormalities, renal tubular acidosis, and cholestasis, his disease was diagnosed as ARC.

The boy had other clinical features including hypoplasia of the head of left femur, several fractures at the birth, multiple joint laxation, club foot, repeated episodes of septic arthritis, rickets, hypothyroidism, frequent dental abscesses, frequent urinary tract infections, photophobia, undescended testes, inguinal hernia, and severe hemorrhage with surgery.

Laboratory examination revealed metabolic acidosis and direct hyperbilirubinemia. Serum total bilirubin level was 316.35 μmol/L and conjugated bilirubin level was 210.33 μmol/L. He had elevated serum values of aminotransferases, alkaline phosphatase, and gamma-glutamyl transpeptidase, but serum levels of protein, albumin, and globulin were all within normal limits. The results of an amino acid analysis of the blood were normal, but heavy generalized aminoaciduria, phosphaturia, and glucosuria were seen in urine chromatography. The glomerular filtration rate of his kidneys was normal. No coagulopathy or portal hypertension was seen. Abdominal ultrasonography showed normal organs with regard to the shape and size, but relatively small kidneys also were notable. Microscopic examination of a liver biopsy specimen showed intrahepatic biliary hypoplasia, fibrosis with inflammation, and giant cell transformation.

The treatment regimen for his intractable pruritus included ursodeoxycholic acid (30 mg/kg/d), cholestyramine (200 mg/kg/d), phenobarbital (3 mg/kg/d), and rifampin (10 mg/kg/d) for more than 2 years, but no improvement was achieved.

Owing to cholestasis and severe intractable pruritus that did not respond to medical therapy and a poor quality of life, he underwent a living-related liver transplant from his mother. He had an uneventful postoperative period with no complications. His immunosuppressive regimen was composed of 4 mg/day tacrolimus and 10 mg/day prednisolone. Prednisolone was tapered and discontinued 3 months after liver transplant and the dosage of tacrolimus was adjusted to maintain the blood level of 10 to 12 ng/mL for the first year, 7 to 10 ng/mL for the second year, and 5 to 7 ng/mL thereafter. Currently, he takes 2 mg/day tacrolimus with normal graft function. There are no vascular, biliary, and infectious complications, nor any episodes of rejection during more than 5 years’ follow-up. The pruritus dramatically improved immediately after the liver transplant, and his scaly skin became normal 6 months after the liver transplant. Also, he gained more than 10 kg weight after liver transplant and at the time of this report, has a good nutritional and growth status.

Discussion

Arthrogryposis-renal tubular dysfunction-cholestasis syndrome is a rare multisystem disorder first described in 1979 and recently ascribed to a mutation in VPS33B whose product plays a role in intracellular trafficking. A membrane transport defect might explain the combination of neuromuscular dysfunction, skeletal abnormalities, cholestasis, and Fanconi syndrome. The phenotype in this syndrome varies, even within the same family members. Dry, scaly skin, clenched fingers, arthrogryposis, flexion deformities at the elbows and knees, abduction deformities of the shoulders, severe jaundice, ichthyosis, growth retardation, and weight loss are some of clinical features of the ARC syndrome. Other infrequent symptoms include diarrhea, platelet abnormalities, hypothyroidism, nephrogenic diabetes insipidus, hypothyroidism, and fractures at the birth. Recurrent febrile illness with normal serum immunoglobulin levels also has been described in most ARC patients like our case who have a history of recurrent episodes of septic arthritis and urinary tract infection.

The first diagnostic criterion for ARC syndrome is arthrogryposis multiplex congenita. These extremity anomalies are present at the birth in most patients, as it was in our case. Anomalies are the result of neurogenic muscle atrophy from anterior horn cells, and histopathologic examinations show rarefaction of motor neurons in the anterior horns of the spinal cord. Cholestatic jaundice and hepatomegaly are the most common symptoms in
ARC syndrome. Deal and associates reported that liver histology in these patients contain cholestasis and giant cell transformation of hepatocytes, but there is no lipofuscin deposition or bile duct hypoplasia. In our patient, the liver histology showed intrahepatic bile duct hypoplasia and fibrosis with inflammation and giant cell transformation.

The third component of the ARC syndrome is renal tubular dysfunction with glucosuria, phosphaturia, generalized aminoaciduria, and renal tubular acidosis. Failure to thrive is present in all of cases with weight loss of 20% to 50%. All of these were seen in the present case.

Jang and associates reported 10 cases of ARC syndrome in which 7 patients either died at 4 to 19 months of age or were presumed to have died. The remaining 3 patients remained alive at the time of the report and were aged from 7 to 23 months. All patients showed musculoskeletal symptoms and/or signs, which included vertical talus, pes calcaneovalgus, hip dislocation, pathologic fractures, and rigid kyphosis. The authors concluded that ARC syndrome should be included in the differential diagnosis of arthrogryposis, and because there is no specific effective treatment for renal dysfunction and cholestasis, orthopedic intervention should be postponed until long-term survival is expected, although this is unlikely.

Unfortunately, no curative therapy for ARC syndrome has 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 ursodeoxycholic acid can be given. Our patient underwent multiple orthopedic surgeries with some correction of his deformities, but he was unable to walk. He had severe intractable pruritus that impaired his quality of life but improved immediately after liver transplant. In conclusion, we believe that liver transplant may be a treatment option in cases of ARC syndrome with severe cholestasis and intractable pruritus.

References