Congenital Limb Anomaly as a New Presentation of Arthrogryposis-Renal Problems-Cholestasis (ARC) Syndrome in an Iranian Infant: A Case Report

Mitra Basiratnia¹, Forough Saki²

¹ Shiraz Nephrology-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.  
² Endocrinology and Metabolism Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Background: Arthrogryposis-Renal Problems-Cholestasis (ARC) syndrome is a rare autosomal recessive disease mostly presenting with arthrogryposis, renal problems and cholestasis. We present the first report of ARC syndrome in Iran manifested in a 4-month-old male infant. Case Report: A 4-month-old male infant was admitted in our hospital with jaundice, poor feeding, tachypnea and lethargy. He has a history of congenital limb anomaly in his feet and jaundice on fifth day of birth. Laboratory and imaging studies revealed renal tubular acidosis, nephrocalcinosis and cholestasis. Despite antibiotic therapy, he died at the third day of hospitalization due to sepsis of pseudomonas aeruginosa and Escherichia coli co-infection and upper gastrointestinal bleeding secondary to coagulopathy of liver failure. Conclusion: ARC syndrome has various and rare clinical manifestations such as lower limb congenital anomaly, hypothyroidism, liver failure and nephrocalcinosis. [GMJ. 2015;4(3):117-21]

Keywords: Lower limb anomaly; Arthrogryposis-Renal Problems-Cholestasis (ARC) syndrome; Hypothyroidism

Introduction

Arthrogryposis, Renal problems and Cholestasis (ARC) syndrome is a rare autosomal recessive disorder; it was first described in 1973 in a consanguineous family by Lutz-Richner and Landolt [1]. Due to variability in signs and symptoms, they have been classified into complete and incomplete forms [2]. Up to now, about 60 cases have been reported in the literature. Other clinical manifestations of ARC syndrome include ichthyosis, congenital heart disease, cerebral malformation, sensory hearing loss, diarrhea, recurrent febrile illness and abnormal platelet morphology and function [3,4]. We present the first report of ARC syndrome in Iran manifested with arthrogryposis, renal problem, cholestasis and liver failure, hypothyroidism, congenital limb anomaly and ichthyosis. In addition, we compare our case with other reports of this syndrome published to date.

Case Presentation

A 4-month-old male infant was admitted in our hospital with jaundice, poor feeding, tachypnea and lethargy. He was the second
child of consanguineous parents and product of cesarean section due to breech presentation at term, after an uneventful pregnancy. His first and fifth minutes Apgar score were good. His birth weight was 2700 g, birth length was 49 cm and birth head circumference was 34 cm. He had a congenital limb anomaly in his feet (absence of one toe and overriding of the 1st and 4th toes on the 2nd and 3rd ones) (figure 1). He also had dry and scaly skin, jaundice and flexion contracture in both upper and lower extremities (figure 2). Five days after birth, he developed jaundice and clayed color stool that slightly increased in the following days, so he was referred to a physician when he was 20 days old with yellowish skin and sclera and mild hepatomegaly; laboratory examination showed mild normal anion gap metabolic acidosis and direct hyperbilirubinemia (serum total bilirubin level was 21.5 mg/dl; conjugated bilirubin level was 18.1 mg/dl). Serum level of aspartate aminotransferase (AST) was 55 IU/L, alanine aminotransferase (ALT) was 1u/L, gamma glutamyltransferase (GGT) was 7 IU/L, Alkaline phosphatase was 454 IU/L and Albumin was 3.5 mg/dl. Thyroid function test revealed TSH=10.39 µIU/ml, T3=0.3 nmol/L and T4=48 nmol/L. Microbiologic studies for antibodies against toxoplasmosis, cytomegalovirus (CMV), rubella and herpes simplex; antigen and antibodies against hepatitis viruses A, B and C were negative. Urine and blood cultures were negative. Plasma alpha-1-antitrypsin level and sweat chloride tests were normal. Analysis of serum amino acids was normal. Complete blood count was normal. Hepatobiliary scan with TC 99m showed good liver uptake without appropriate excretion even 24 hours post-injection that was in favor of biliary atresia. Abdominal sonography showed hepatomegaly with normal echogenicity. On 37 days of life, exploratory laparotomy, intra-operative cholangiography and liver biopsy were done for him. It revealed patent hepatic and common bile ducts and no sign of biliary atresia. Liver biopsy demonstrated deposition of brown-yellowish pigments in hepatocytes especially granular types (figure 3). In addition, it showed lobular disarray and giant cell transformation and severe cholestasis. Portal tracts were unremarkable. There was no fibrosis. Bile duct numbers were adequate. So, the patient was treated with levothyroxin, phenobarbital, multivitamin and ursodeoxycholic acid.

Two months later (when he was 4 month old), he developed poor feeding, tachypnea, lethargy and diarrhea, so he was referred to our hospital for further evaluation. On physical examination, he had dry yellowish and scaly skin with decreased subcutaneous fat tissue and was lethargic. He also had edematous extremities and scrotum. Body temperature was 36.4°C, heart rate was 110 beats/minute, respiratory rate was 64 per minute, weight was 3220 g, head circumference was 35 cm and length was 55 cm. He had low-set ears. His liver was palpated 4 cm below the costal margin. Laboratory investigations showed electrolyte imbalance (serum Na=164 meq/L, K=3.1 meq/L, Cl=131 meq/L, Calcium = 7.1 mg/dl, Ph = 5.4 mg/dl, Albumin = 2.1 mg/dl, BUN=54 mg/dl and Cr=1.5 mg/dl). Also, he had normal anion gap metabolic acidosis (Hco3=12 meq/L, Anion gap = 12.) Urine analysis showed 2+ proteinuria. The measured urine calcium to creatinine ratio was 2.7 and urine albumin to creatinine ratio was 0.8. Urine specific gravity was 1.006 and urine output was 6cc/kg/hr. Serum PT and PTT were prolonged. Abdominal sonography showed increased parenchymal echogenicity of both kidneys more in the medulla typically seen in medullary nephrocalcinosis. Parenteral fluid, electrolyte, fresh frozen plasma, bicarbonate and broad spectrum antibiotic
therapy were started to correct metabolic aci-
dosis, dehydration coagulopathy and infec-
tion. Unfortunately, he died at the third day of
hospitalization due to sepsis of pseudomonas
aeroginosa and Escherichia coli co-infection
and upper gastrointestinal bleeding secondary
to coagulopathy of liver failure. His parents
did not agree with genetic studies. Their first
child had died due to prolonged jaundice in
the second month of life due to an unknown
cause.

Discussion

ARC syndrome is a hereditary fetal disease
with a wide range of clinical manifesta-
tion [5]. It has three key presentations including
arthrogryposis, renal tubular dysfunction and
cholestasis [3]. Nearly all 60 patients with
ARC syndrome that have been reported since
1973 had consanguineous parents and auto-
sonal recessive inheritance [6,7]. Most of the
reported patients with ARC syndromes were
from Pakistan [3], but some have been re-
ported from Saudi Arabia [3,4], Turkey [5,6],
United Kingdom [8,9], Italy[4], Portugal [4]
and Iran [2].

We report the third case of ARC syndrome
in Iran [2], which manifested with arthrogry-
posis, renal problem, cholestasis, diarrhea,
failure to thrive and dry skin. In addition, our
case is the first case presented with congenital
lower limb anomaly. One of the most com-
mon manifestations of ARC syndrome is ar-
throgryposis which was present at birth in our
case. This anomaly might be due to rarefac-
tion of the motor neurons in the anterior horn
of the spinal cord [6]. It may include talipes
equinovarus, radial deviation of the wrists,
club feet and hip dislocation. Our patient had
flexion contracture of the knees and elbows.
Another common manifestation of ARC syn-
drome is cholestatic jaundice and hepatomeg-
aly. In previous reports, liver disease was ac-
companied with normal GGT, mild elevation
of the liver enzymes (AST or ALT) and direct
hyperbilirubinemia. Most of them showed
evidence of biliary obstruction or severe in-
trahepatic cholestasis. One infant developed
acute liver failure at the age of 6 weeks during
an episode of sepsis. Findings of liver biopsy
may include cholestasis with multinucleate
giant cell change of hepatocytes, intrahepat-
ic biliary hypoplasia and lipofuscin deposi-
tion [9]. Liver biopsy of our patient showed
lobular disarray, giant cell transformation of
hepatocytes, severe cholestasis and granular
type brown-yellowish pigments in hepato-
Our patient developed liver failure at age of 4 months, presenting with coagulopathy, hypoalbuminemia and elevated liver enzymes which were the cause of death. The third manifestation of ARC syndrome is renal problem. Renal involvement in ARC patients is complex. Many abnormalities include glomerular involvement, proteinuria, hypernatremic dehydration, nephrogenic diabetes insipidus (NDI), dysplastic kidney and renal tubular acidosis (RTA) as described for these patients [2]. Nephrocalcinosis in our patient was one of our purposes in presenting this case. Our case presented with normal anion gap metabolic acidosis, hypokalemia, proteinuria and hypercalcemia that are manifestations of RTA. In addition, our patient had medullary nephrocalcinosis and secondary nephrogenic diabetes insipidus. It was manifested with hypernatremic dehydration, polyuria and low urine specific gravity. It was reported only in two cases of ARC syndrome [2]. One unique presentation of our case was congenital anomaly in his toes. He had four toes in each foot and abnormal overriding of the first and forth toes on the second and third ones. The only dysmorphic feature of the limbs that was previously reported in a Pakistani ARC patient was large hands and proximally inserted thumbs [4], but no lower limb anomaly has been reported for ARC syndrome till now. Another interesting finding in our patient was congenital hypothyroidism, which was treated with levothyroxin. Hypothyroidism was reported in three cases of ARC syndrome [4,5]. All of them were primarily of congenital type and treated with low doses of levothyroxin. Our patient also had low-set ears, which was previously reported in some cases [4,5]. Ichthyosis is another presentation of our patient, as reported in 17 cases of ARC syndrome. Choi , suggested that the defective secretion of the lamellar bodies in the epidermis, which might be mediated by sensory nerve action potential receptor protein complex, might be the cause of the ichthyosis phenotype in ARC syndrome [10]. Our patient did not have brain or hematologic manifestations.

**Conclusion**

In conclusion, ARC syndrome has various clinical manifestations. Lower limb congenital anomaly, hypothyroidism, liver failure and nephrocalcinosis are other rare presentations of ARC syndrome, which was manifested in our patient.

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**Conflict of Interests**

There is no conflict of interests between authors.

**References**


