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Case Report

Arthrogryposis, Renal Tubular Dysfunction and Cholestasis (ARC) Syndrome: A Case Report

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Abstract

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome, the association of arthrogryposis, renal tubular dysfunction, and cholestasis, is a rare autosomal recessive multisystem disorder. This syndrome results from mutations in VPS33B gene. In some patients, ichthyosis, central nervous system malformations, deafness, and platelet abnormalities may be seen. Many patients with different associations of cholestasis, renal tubular acidosis, and dysmorphic morphology may be underdiagnosed. We describe novel mutations (Gly496Arg and Gly514Ser) in VPS33B gene in an affected fortyfive-month-old female infant with ARC syndrome from Turkey.

Key words: Arthrogryposis, renal tubular dysfunction, cholestasis ARC syndrome, VPS33B gene

Introduction

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome was first described in 1973 and refers to an association between arthrogryposis, tubular dysfunction and cholestasis [1]. It is an autosomal recessive multisystem disorder that may be associated with germline VPS33B mutations on chromosome 15q26 [2]. Other features variably reported include ichthyosis, failure to thrive, mild dysmorphic signs, absent corpus callosum and neurogenic muscular atrophy. Recurrent infections result in severe metabolic acidosis, worsening diabetes insipidus and rarely liver failure [1,3,4]. In the present paper, we describe a fortyfive-month-old girl with ARC syndrome who initially presented with cholestasis associated with homozygote Gly496Arg and Gly514Ser genetic mutations in VPS33B gene.

Case report

A fortyfive-month-old female infant was transferred to our hospital for further evaluation and management of hypotonia and jaundice. She was born at 40th week of gestation from non-consanguineous parents, via cesarian section because of macrosomy with a birth weight of 4100 gr. She was the second child of healthy Turkish parents. On the 8th day of life jaundice was recognized and she was hospitalized on 35th day in another hospital with the diagnosis of prolonged jaundice. On physical examination body temperature was 36.5 ^{0}C, heart rate 140 per minute, respiratory rate 28 per minute, weight 3000 gr, length 53 cm and head circumference was 37 cm. She had dry and scaly skin like ichthyosis, lax skin on the neck and jaundice. Muscle bulk

Fig. 1. Manifestation of ARC syndrome. Ichthiyosis, lax skin, reduced muscle bulk, flexion contractures of knees and limbs, equinovarus, talipes calcaneovalgus, radial deviation of the wrists, bilateral arthrogryposis

of deltoid and triceps was notably reduced. Flexion contractures of knees and limbs, equinovarus, talipes calcaneo-

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valgus, radial deviation of the wrists, bilateral arthrogryposis, proximally inserted thumps and big toes were detected (Figure 1).

Liver was palpable 4 cm from the costal margin. On laboratory examination, hemoglobin was 8.1 g/dL, leucocyte: 18.200/mm^3, platelet: 497.000/mm^3 (giant-sized platelets were seen in peripheral blood smear), serum total bilirubin level was 10 mg/dL, conjugated bilirubin level 3.8 mg/dL. Serum values of transaminases, gamma glutamil transferase, protein and albumin were within the normal limits but alkaline phosphatase was 4 times above the normal value (1438 U/L). Protrombin time (18 seconds) and activated partial tromboplastine time (76.8 seconds) were prolonged. Serologic investigations for hepatitis and viral infections were negative. Thyroid function tests were within normal limits. Plasma alpha 1 anti-tripsin, alpha feto protein, aminoacid analysis of blood and urine were all normal. Urine electrolytes were as follows: Na 40 mmol/L, K 27 mmol/L, Cl 37 mmol/L, Ca 8.2 mg/dL and P 23 mmol /L. A search of common mutations for cystic fibrosis was negative. She was diagnosed as Fanconi syndrome with blood pH of 7.32, HCO_3^- of 11 mmol/L, base excess of 14 and urine pH of 6.5 with proteinuria (> 300 mg/dL), calciuria (6.8 mg/kg/day), phosphaturia (TPR: % 45) and glucosuria (48 mg/dL) with normal serum glucose. Urinalysis showed tubular proteinuria [N-acetyl glucoseaminidase: 22 U/L (normal: 1.5-6.1 U/L), beta 2 microglobulin 77.7 mg/L (normal: 0.02-0.2 mg/L)]. Abdominal ultrasound showed bilateral moderate renal hyperechogenity, nephrolithiasis in left kidney and minimal hepatomegaly. A radionucleotide scan of biliary system (HIDA scan) revealed excretion to the bowel after 24 hours. Liver biopsy showed giant cell hepatitis. Cranial MRI and echocardiographic studies showed encephalomalacia and atrial septal defect (< 3 mm), respectively. With all signs and laboratory findings ARC syndrome was diagnosed. We have screened all 23 exons and exon–intron boundaries of the VPS33B gene and mutation analysis revealed homozygote Gly496Arg and Gly514Ser mutations in VPS33B gene.

After treatment with Scholl solution, acidosis was partially improved (blood pH: 7.38, HCO_3^-: 18 mmol/L, base excess: -4). Despite treatment with intravenous antibiotics, total parenteral nutrition and appropriate fluids, she died at the age of 4 months from dehydration and sepsis. Autopsy could not be performed because her parents did not give permission for religious reasons.

Discussion

Arthrogryposis-renal dysfunction-cholestasis syndrome is a multisystem disorder with a wide clinical spectrum. This rarely seen syndrome is characterized by arthrogryposis, renal tubular dysfunction and cholestasis [1]. To the best of our knowledge, we report the fourth patient from Turkey who presented with Fanconi syndrome, cholestasis and renal tubular acidosis.

In this syndrome, the first diagnostic criterion is arthrogryposis and it is thought to be secondary to neurogenic muscle athrophy [6]. It has been reported that fractures in extremities due to muscle athrophy and strain [7]. Evidence of denervation was obtained from electromyographic studies as well as from muscle biopsies [8]. Severity varies from talipes equinovarus to severe hip dysplasia [3]. Our patient just had flexion contractures of knees and limbs, equinovarus, talipes calcaneovalgus, radial deviation of the wrists, bilateral arthrogryposis, proximally inserted thumps and big toes (Figure 1).

Cholestatic jaundice and hepatomegaly are the most common symptoms at presentation and the second major component of the syndrome. Reportedly, all patients had conjugated hyperbiluribinemia and level of bilirubin in an individual patient fluctuated between extremely high or normal levels. Normal or mildly elevated transaminases with normal GGT level are a constant and early feature of ARC syndrome. Appropriate laboratory investigation should be done to rule out the other causes of conjugated hyperbilirubinemia in infancy. Our patient had conjugated hyperbilirubinemia with normal transaminase and GGT levels. In a study 14 out of 15 patients had non excreting biliary isotope studies suggesting biliary obstruction or severe intrahepatic cholestasis as HIDA scan of our patient revealed excretion to the bowel after 24 hours [3]. Liver biopsy shows paucity of bile ducts, lipofuscin deposition, bile plugs and giant cell hepatitis [9]. Therefore, liver biopsy has nonspecific findings and this procedure could be dangerous due to bleeding. In our patient, however, liver biopsy revealed giant cell hepatitis.

Renal dysfunction in ARC syndrome is characterized by multiple features of Fanconi syndrome including aminoaciduria, glycosuria, phosphaturia and bicarbonate wasting as well as by nephrogenic diabetes insipidus [10,11]. Gissen *et al*. [3] found poor corticomedullary differentiation in 6 patients, nephrocalcinosis in 6 patients and tubular atrophy in 2 patients. Our patient was also diagnosed as Fanconi syndrome and she showed tubular proteinuria which is the most striking clinical abnormality. Also, in our patient, renal ultrasound showed nephrolithiasis which is an occasional sign of this syndrome.

Abnormally, large platelets have been described in ARC patients as in our patient but trombocytopenia is unusual [1]. Although, despite normal clotting studies hemorrhagic events can be encountered after interventional procedures, such as kidney or liver biopsies, in our patient, we performed liver biopsy, uneventfully. However, later on, intracranial bleeding was detected during sepsis.

Congenital heart disease has been reported in ARC patients [2]. Our case had an ASD less than 3 mm. with no clinical significance.

Unfortunately, curative therapy for this rare syndrome has not been reported [2]. The current treatment of ARC patients includes the use of fluids and caloric administration such as total parenteral nutrition or medium-chain triglyceride-rich formulas, monthly vitamins A-D-E-K and ursodeoxyhcolic acid. Most patients do not live longer than 7 months after birth despite supportive care for metabolic acidosis and cholestasis [12]. Death usually occur secondary to sepsis and severe dehydration and acidosis [6]. Our patient died at 4 month of age, due to sepsis.

Novel identification of the mutation in VPS33B in this syndrome, which involves intracellular protein traffick-

ing by regulation of vesicle-to-target sensory nerve action potential receptor (SNARE) family, might explain the consistent combination of membrane fusion defects [5,13]. The reported cases and also mutations are few in the literature due to the new discovery of gene locus of disease. The mutation analysis for ARC syndrome is important because it eliminates the need for diagnostic organ biopsies which results in life threatening hemorrhage over 50 % of patients. The syndrome is inherited in an autosomal recessive pattern and most of the reported cases are from the regions where the consanguineous marriage rates are high, as in our country [2]. Recently, Gissen *et al*. [5] mapped the disease to 15q26.1 and identified germline mutations in the VPS33B gene in 14 kindred with ARC syndrome. Furthermore, Gissen *et al*. found that, in 7 apparently unrelated consanguineous families of Pakistani origin with ARC syndrome, a 1311C-T transition in the VPS33B gene resulting in an arg438-to-ter (R438X) mutation and in a consanguineous Pakistani family with ARC syndrome an arg532-to-ter (R532X) mutation [5]. Gissen et al. [13] also characterized clinical and molecular features of 62 individuals with ARC from 35 families (11 of which had been previously reported). Germline VPS33B mutations were present in 28 of 35 families (48 of 62 individuals); however, VPS33B mutations were not detectable in approximately 25% of patients, suggesting the possibility of a second ARC syndrome gene [13]. Our case is the forth patient reported from Turkey and twenty-first patient who was determined VPS33B mutation by this time [5,13]. Mutation analysis revealed a 1405G-C transition resulting in homozygote Gly496Arg mutation and a 1540 G-A transition resulting in Gly514Ser mutation in VPS33B gene. We, therefore, identified novel mutations in our Turkish patient with ARC. Identification of population-specific mutations improves the ability to provide rapid molecular diagnosis and makes molecular studies more affordable.

Conclusion

Arthrogryposis-renal dysfunction-cholestasis syndrome is a severe multisystem disorder leading to death in infancy. However, the traditional method of diagnosis such as liver biopsy is associated with a substantial risk of morbidity and mortality. Direct sequencing of VPS33B is a good method to provide molecular diagnosis in ARC patients.

Conflict of interest statement. None declared.

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