Novel VPS33B mutations of G514S gene cause an arthrogryposis, renal dysfunction and cholestasis syndrome

Seçil Conkar, Ebru Yılmaz, Sevgi Mir, Afig Berdeli

ABSTRACT

Introduction: Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare multisystem disorder first described in 1979 and recently attributed to mutation in VPS33B, whose product acts in intracellular trafficking. It shows wide clinical variability. The characteristic features of ARC core phenotype include arthrogryposis, spillage of various substances in the urine, and conjugated hyperbilirubinemia. In some patients, these features are sometimes accompanied by different manifestations, such as ichthyosis, central nervous system malformation, deafness, and platelet abnormalities. Many patients with different associations of cholestasis, renal tubular acidosis, and dysmorphic morphology may be underdiagnosed.

Case Report: We assessed the clinical characteristics of patients and investigated the VPS33B mutation in the gene G514S in a Turkish patient with ARC syndrome. We reported one Turkish patient with ARC syndrome, along with the presentations of renal tubular dysfunction, cholestasis, arthrogryposis, VPS33B Mutations in the gene G514S.

Conclusion: This case shows that the variability of different manifestations of ARC syndrome is well described. However, the presence of the mutations VPS33B in the gene G514S has not been reported before. Our findings advance the knowledge of the molecular pathways determining cell polarity and provide new evidence on the role of intracellular trafficking proteins in regulation of epithelial polarization. Further, the fundamental defects in growth and differentiation of epithelial tissues observed in ARC and in knockdown cell lines emphasize the importance of the VPS33B pathway for organ development and function. We found a novel mutation in a Turkish patient with ARC syndrome.
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Keywords: Arthrogryposis-renal dysfunction-cholestasis (ARC), Cholestasis, Renal tubular dysfunction, Mutations in VPS33B gene

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INTRODUCTION

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare autosomal recessive multisystem disorder with the association of arthrogryposis, renal
tubular dysfunction and cholestasis. It was first identified in 1973 by Lutz-Richner and Landolt, and in 1979, Nezeloff described new clinicopathologic findings [1, 2]. Most cases present arthrogryposis multiplex congenita, neonatal cholestatic jaundice, mild or severe forms of renal tubular disorder, and severe lamellar ichthyosis [3]. In addition, dimorphisms, recurrent infections, platelet dysfunction, growth retardation, nephrogenic diabetes insipidus, muscular atrophy, corpus callosum agenesis and rarely deafness are among the other findings described [4]. Most patients die within the first seven months. Severe growth retardation has been observed in those living longer [5]. Recently, it has been shown that the mutation in the VPS33B gene accounts for ARC syndrome [6]. VPS33B mutation was detected in 75% of individuals with ARC syndrome [7]. So far, 35 cases with ARC syndrome with VPS33B mutation were identified. Gene regions encoded and the gene protein products of these cases show variations [8]. In our case, the mutation has been identified in G514S codon of VPS33B mutation. The present case report aims to demonstrate the phenotypic characteristics of G514S mutation in the VPS33B gene. Detecting the VPS33B mutations in the G514S gene is important since a novel mutation in the gene causes an Arthrogryposis, renal dysfunction and cholestasis syndrome.

**CASE REPORT**

A 2.5-month-old male neonate, 2500 grams born by cesarean section in term, was admitted to our hospital due to respiratory distress, malnutrition at 2.5 months. In his history, it was found out that the patient was hospitalized in the neonatal unit for 33 days just after the birth by reasons of respiratory distress and jaundice. In the family history, there was no kindred relationship found between the mother and father. It was also found that the other son of the family had multiple fractures of the body and died at five days old. On physical examination, atypical facial appearance, dry skin, reduced turgor tonus, icterus, dehydration, ichthyosis and muscular atrophy were observed. Severe growth retardation was observed as the body weight was 2300 g (<3p), height was 49 cm (<3p). Severe adduction deformity of the foot and callus formation in both femurs was detected. In the whole body, X-rays of the case taken for multiple fractures, diffuse reduction in the density of bone structures, thinning in the diaphysis of long bones, slight inclination in both tibia and fibula were detected. Old crack and mal callus formation at the middle part of right femur, 1/3 proximal part of the left femur were found. At the middle part of the right tibia, callus formation occurred due to an old oblique fracture was detected. In the light of these findings, the laboratory values of the patient admitted with the pre-diagnosis of ARC syndrome was given in Table 1.

Despite the high levels of serum bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), Gamma Glutamyl Transferase (GGT) was detected within the normal levels. Toxoplasmosis, herpes viruses, cytomegalovirus (CMV) and rubella screenings were found negative. Plasma amino acid profile was normal. However, increase in urine amino acids was detected. Skin biopsy performed for ichthyosis was consistent with lamellar ichthyosis. Echocardiogram performed for possible cardiac abnormalities was found normal.

In the blood biochemistry examination, the findings were: pH 7.25, bicarbonate 11.3 mmol/l, base deficit 10.3, urine pH 5, potassium 2.8 mEq/L (3.5–5.5 mEq/L), chloride 126 mEq/L (98–106 mEq/L), phosphorus 0.7 mg/dl (1.36–2.26 mg/dl), sodium 151 mEq/L (135–148 mmol/L). In the urinalysis examined when the level of blood glucose was normal, glycosuria (1000 mg/l with dipstick) and proteinuria (22 mg/m²/hour) were detected. Urinary electrolytes were found as Na 13 mmol/L, K 41 mmol/L, Cl 48 mmol/L, Ca 0.41 mmol/L, PO 18 mmol/L, and creatinine 0.9 mg/dl, TPR 57%. The patient was evaluated as Fanconi syndrome. The eye consultation requested for a possible metabolic disease was normal.

On the abdominal ultrasound, 5.5 mm hemangioma located near the capsule was detected in the liver. The shape, size and echogenicity of the kidneys were within the normal limits. Cranial magnetic resonance (MR) taken for the associated cranial anomalies was normal. During the follow-up, severe metabolic acidosis, hypernatremia (Na 155 mEq/l), and polyuria (6 cc/kg/h) developed, and urine osmolality and blood osmolarity were detected as 124 mOsm/L and 371 mOsm/L, respectively. Desmopressin test was conducted following the development of diabetes insipidus in the patient. The patient, who was unresponsive to the desmopressin treatment, was considered as nephrogenic diabetes insipidus. The patient underwent replacement of erythrocytes due to anemia. Treatment of sodium bicarbonate and Shohl’s solution were performed due to metabolic acidosis. Despite all the support therapies, the patient died of dehydration and sepsis at the age of 3.5 months. Since the permission was not obtained from the family, an autopsy could not be performed.

As a result, our patient had a severe clinical course and died at the age of 3.5 months with the clinical signs of Fanconi syndrome, arthrogryposis, cholestasis with normal GGT levels despite the elevated levels of AST, ALT, GGT and bilirubin, multiple extremity fractures, muscular atrophy, ichthyosis, anemia which required erythrocytes transfusion and nephrogenic diabetes insipidus which manifested at the final stages of the patient. The notable features of our case were exhibiting the clinical manifestations at birth, clinical worsening at the age of 2.5 months, exitus at age of 3.5 months, ARC syndrome accompanied by severe components such
as nephrogenic Diabetes insipidus (DI) and multiple fractures. We detected VPS33B mutations in the G514S gene one month after exitus of the patient. After the VPS33B mutations in the G514S gene was detected, there was no change in the clinical management of the patient when he died.

Molecular Analysis

Genomic DNA (gDNA) from 2 ml of peripheral blood samples which were collected into ethylenediaminetetraacetic acid (EDTA) anticoagulated tubes by the standard venipuncture method was extracted using the QIAmp blood DNA isolation kit following manufacturer’s instructions. The DNA concentration was determined by using Thermo Scientific Nanodrop apparatus. 23 entire coding exons of VPS33B gene (Genbank NG_012162.1) were amplified by polymerase chain reaction (PCR) using flanking intronic primers (NCBI Reference Sequence NM_018668.3). All synthetic oligonucleotide primers synthesized and purchased by Invitrogen (Invitrogen, Paisley, UK) as the HPLC purification grade. Primer details are available from the authors upon request. The PCR amplification was carried out on Veriti gradient thermal cycler (Applied Biosystems, Foster City, CA) in a 25 µl reaction mixture containing 1 µl genomic DNA solution, 1.0 U platinum TAQ with Enhancer Buffer (Invitrogen, Paisley, UK), 50 µmol/l each of the dGTP, dATP, dTTP and dCTP (Promega, Madison, WI), 5 pmol each forward and reverse primers. The cycling conditions comprised a hot start at 95°C for 10 min, followed by 35 amplification cycles at gradient programme. Before cycle sequencing reactions the amplified PCR products were purified using Exo-SAP PCR purification Kit (Amersham Life Science). Cycle sequencing PCR was performed with using BigDye Terminator v.3.1 kit as manufacturers. (PE Applied Biosystems, Foster City, CA). Cycle sequencing PCR products after purification with BigDye XTerminator kit (PE Applied Biosystems, Foster City, CA) were analyzed an ABI 3130xl Genetic Analyser System. The DNA sequencing was performed in both directions, initiated from the forward and the reverse primers were used in the initial PCR reaction. For sequence evaluation, the SeqScape 2.0 sequencing analysis software was used with (NP_061138.3) protein reference sequence for comparison of newly identified sequence variations.

**DISCUSSION**

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare autosomal recessive multisystem disorder presenting with the association of arthrogryposis, renal tubular dysfunction and cholestasis. It was first described in 1973 by Lutz-Richner and Landolt. To date, there are more than 30 patients identified with ARC syndrome. The ARC syndrome is a rare entity and has been shown as an autosomal recessive disease [5, 9]. Gisses et al. detected VPS33B gene mutation at the locus of 15q26 in 1 in 14 children with ARC syndrome [8]. It has been identified that VPS33B gene contained sec 1 protein, which plays an important role in the membrane fusion/SNARE complex. Sec 1 protein plays part in the transport between the secretory cells. This protein is found in the kidney, liver, lung, heart, skeletal muscle and brain. It is considered that renal tubular dysfunction, cholestasis and arthrogryposis, a component of the neurogenic muscular atrophy, observed in ARC syndrome result from an incomplete function of Sec 1 protein, which is related to the VPS33B gene [1, 6, 7].

In our patient, liver function tests and GGT were found normal, while bilirubin was high. Additionally, cholestasis, ichthyosis, and renal Fanconi’s syndrome, arthrogryposis, multiple fractures, and nephrogenic diabetes insipidus were observed. The presence of multiple fractures present at birth, severe respiratory distress since birth, exitus at the age of 3.5 months suggest that the clinical course may be severe in the existence of this mutation.

In literature, 62 patients, 14 different ethnic groups have been reported with the diagnosis of ARC syndrome. There are 28 cases of ARC syndrome identified with the VPS33B mutation in literature [8]. In addition, there is one Turkish patient with the VPS33B gene mutation in literature. In this patient, renal Fanconi’s syndrome, arthrogryposis, ichthyosis and recurrent infections have been reported. Genetic mutation codon c.1406-1G>C was detected and the patient lived for 20 months. Another patient with ichthyosis, renal tubular acidosis, diabetes insipidus, cholestasis, hypothyroidism and large platelets was reported, but the VP33B mutation was not detected. This patient died of hypernatremia, dehydration and...
sepsis at the age of seven months [1]. Unlike the cases reported in literature, our case exhibits a more severe clinical course together with the multiple fractures. We believe that the G514S mutation in the VPS33B gene may be responsible for this clinical situation. The patients with ARC syndrome usually die within the first year. In the literature, there has been only one case reported that lived until the age of three [10]. Our patient died at an earlier age and had uncontrollable dehydration.

CONCLUSION

In conclusion, the VPS33B G514S mutation must account for this clinical course. It is possible that the different mutations in this gene may cause a more severe phenotype as seen in patients with ARC syndrome. As a result, in this study, we described the phenotypic characteristics of a patient with ARC syndrome presenting with VPS33B mutation. Today, ARC syndrome is considered a rare, incurable disease that requires a genetic counseling. Identifying more serious types of mutation will conclude the diagnosis of the disease in the literature.

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Author Contributions

Seçil Conkar – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Ebru Yılmaz – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Sevgi Mir – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Afig Berdeli – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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