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A New Aberration in the VPS33B Gene Leads to Full-Symptom ARCS1

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, newborn
Final Diagnosis: ARCS1
Symptoms: Cholestasis and/or gallbladder dysfunction
Medication: —
Clinical Procedure: —
Specialty: Pediatrics and Neonatology

Objective: Rare disease
Background: ARCS1 is an acronym for arthrogryposis, renal dysfunction, and cholestasis. It is a congenital malfunction with autosomal recessive inheritance, and, unfortunately, its prognosis is still poor. It is believed that VPS33B is altered in 75% of cases and that the VIPAR gene is altered in approximately 25% of them.
Case Report: An affected child was born from the first pregnancy of 26-year-old mother and a 30-year-old father with no previous medical history and no genetic conditions. The first clinical symptoms were observed at the end of the child's second week of life. The mother reported the child has decreasing body weight and loss of appetite. After admission to the ward, the child was apathetic and sleepy. Symptoms of conjunctivitis, pale and dry skin, and mild face and mild body dysmorphism were observed.
Conclusions: Laboratory tests revealed proteinuria of up to 1.36 g/l and glycosuria of up to 28 mmol/l, as well as fluctuating metabolic acidosis. The bilirubin level reached 6.62 mg/dl, along with alkaline phosphatase at 470 U/l. Moreover, hypothyroidism with TSH at 16.71 uU/ml was observed. Because of the co-occurrence of cholestasis and renal dysfunction, molecular testing was done. The 17th exon of VPS33B was sequenced by Sanger DNA sequencing method. To the best of our knowledge, this is the first report of homozygotic mutation c.1235_1236delinsG (p.Pro412ArgfsTer7) in the VPS33B gene. The risk of transfer of the mutation to future descendants was calculated as 25%.
Due to the wide landscape of molecular alternation in the 17th exon of the VPS33B gene, we propose using Sanger whole-exon sequencing as a first-choice diagnostic test.

Keywords: Arthrogryposis • Arthrogryposis Renal Dysfunction Cholestasis Syndrome • VPS33B Protein, Human

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/932769>



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Background

ARCS1 syndrome is an acronym that was proposed by Horslen for arthrogryposis, renal dysfunction, and cholestasis. It is a multi-organ congenital malfunction with autosomal recessive inheritance, and, unfortunately, its prognosis is still poor [1]. It was first described by Lutz-Richner and Landolt in 1973 [1,2]. The main life-threatening conditions that it involves are serious dehydration, recurrent infection, metabolic acidosis, and internal bleeding [3]. The pathogenesis of ARC was first described by Gissen in 2004 and is based on the VPS33B gene located on 15q26.1, as well as the VIPAR gene, which interacts with VPS33B protein and acts as an apical and basolateral polarity regulator. It is believed that VPS33B is altered in 75% of cases and that the VIPAR gene is altered in approximately 25% of them [2,3].

The VPS33B gene is a member of the Sec-1 family and contributes to the carrying of signals between cell compartments. It is believed to act as a cytoplasmic transducer and as an intercellular exosome that influences neighboring cells [4-6]. In normal circumstances, VPS33B controls pattern-recognition receptors (PRR) for endosomal cooperation. Toll-like receptors (TLR) are a type of PRR that activate mitogen-activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) to start the immunological response. The precise prevalence is still unknown, and no more than 100 cases have been reported so far.

Case Report

A child was born from the first pregnancy of 26-year-old mother and a 30-year-old father with no previous medical history and no genetic conditions. All routine pregnancy tests showed normal results. At 32 gestational weeks, a risk of premature delivery was observed, which led to hospitalization of the patient for 17 days. Finally, spontaneous labor occurred at 36 gestational weeks. The male newborn had a weight of 2620 g, length of 48 cm, head circumference of 33 cm, chest circumference of 31 cm, and Apgar scores of 8/8/9 points.

All serum blood test results were normal. Ultrasonography of the abdominal cavity and central nervous system did not reveal any anatomical abnormalities. In the clinical examination, bilateral valgus deformity of the ankles was noted. The newborn was discharged on the fifth day after delivery; he was breast-fed by the mother, and his body weight increased.

The first clinical symptoms were observed at the end of the child's second week of life. The mother reported the child's body weight was decreasing and he had loss of appetite. After admission to the ward, the child was apathetic and sleepy. Symptoms of conjunctivitis, pale and dry skin, and mild face

and body dysmorphism were observed. Laboratory tests revealed proteinuria of up to 1.36 g/l and glycosuria of up to 28 mmol/l, as well as fluctuating metabolic acidosis with pH 7.2 to 7.31 with capillary base excess -2.2 mmol/dl and bicarbonates 20.9 mmol/dl. Moreover, rising hyperbilirubinemia was observed, with bilirubin levels reaching 6.62 mg/dl and serum bile acid ranging from 52.5 μ mol/l to 75.7 μ mol/l, along with alkaline phosphatase at 470-818 U/l and hypothyroidism with TSH at 16.71 uU/ml. The serum creatinine was elevated at 0.86 mg/dl. Urine acid and BUN tests were normal.

Extended tests excluded inherited CMV, *Toxoplasma* infection, galactosemia, tyrosinemia, and α -1 antitrypsin deficiency, and there were still no pathological findings in ultrasonographic examination. Because of the progression of apathy, MRI of the central nervous system was performed. Hypoplasia of the corpus callosum was noted. A urine test showed phosphaturia ranging from 4.21 mmol/l to 24.71 mmol/l, with normal calcium levels (Ca total 1.21 mmol/l to 3.37 mmol/l), which suggested a defect of the proximal tube. No change in urinary anion gap was observed. The urine calcium to urine creatinine ratio was 0.12. The levels of urine organic acids were not raised (the GC-MS test result was negative), and there were no glycosylation disturbances (the CDG test result was also negative). A control renal ultrasound revealed correct size and location of the kidneys, with raised echogenicity of the peripheral parts of pyramids. The first conclusion was ARCS1 syndrome based on the permanent hyperbilirubinemia with a high level of biliary acid reaching 75.7 μ mol/l, and slightly elevated GGTP up to 57 U/l, which are in line with renal tubulopathy, metabolic acidosis, and valgus ankle deformity.

The clinical outcome presented a recurrent infection of the urinary and respiratory tracts. Severe pneumonia caused the patient's death 13 months after diagnosis.

The 17th exon of VPS33B was sequenced by a Sanger DNA sequencing method. In the presented case, we noted homozygotic mutation c.1235_1236delinsG (p.Pro412ArgfsTer7) in the VPS33B gene. Genetic tests were extended to the parents to analyze the VPS33B gene mutation carrier. The report confirmed parental asymptomatic carrier status of c.1235-1236delinsG/p.Pro4127ArgfsTer7/ in 1 allele in a heterozygotic fashion. This causative alternation is new and has never been reported in the files of dbSNP, gnomAD, HGMD, and ClinVar. The molecular feature with preterm termination of translation suggests a pathological impact. The risk of transfer of the mutation to future descendants was calculated as 25%. Moreover, the risk is unchangeable for any future pregnancy for the couple.

Discussion

Molecular insights into the pathogenesis of ARCS1 have explained the disease's underlying pathway. It seems that the clinical symptoms of arthrogryposis are caused by malfunction of the spine's motor neurons [7]. As mentioned above, PRR acts as a synaptic neurotransmitter. Kidney malfunction is caused by abnormal polarization of the proximal tubules' epithelium, which leads to the dysregulation of endocytosis. This manifests clinically as glycosuria, hyperphosphaturia, proteinuria, and even full-symptom Fanconi disease. Similarly, the incorrect polarization of hepatocyte membranes underlies jaundice, hepatocyte injury with the elevation of ALT and AST, and also cholestasis with a low level GGT [1,3,4,7,8].

The histopathological pattern is unspecific. Periductal fibrosis, giant cell hepatitis, and even liver cirrhosis have been described. Notably, there is a risk of bleeding after liver biopsy. It can cause platelet dysfunction by a lack of α -granules, even if the serum level of platelets is normal [1,3,4,8-10]. Although arthrogryposis is the most typical dysmorphic symptom, others have been reported. Rarely, there can be occipital prominence, low-sitting ears, a flat nose, oblique folds, gothic palate, dry skin or ichthyosis, cardiac malformation, and generally many symptoms of dyscollagenosis of the skin, tendons, and joints [1,3,7,11].

For a long time, molecular testing of ARCS1 syndrome was tested by PCR focusing on a well-established point mutation, which could lead to false-negative results. The progress made in molecular solutions, especially sequencing, provided a possibility to detect other molecular abnormalities. Our case, however, caused by unreported mutation, had a typical clinical

outcome. Two years ago, an unusual case of twins was published with deleted clinical manifestation. First symptoms of jaundice, pruritus, and biliary atresia were observed at age 2 years, and full symptomatic liver cirrhosis and lethal visceral bleeding occurred at age 7 years. The authors presented c.1157A>C (p.His386Pro) as the first reported mutation [1].

There has been progress in treatment of symptom, but the prognosis of ARCS1 is still poor. Patients usually die in their seventh month of life. The manner of death is usually reported as serious recurrent infection, dehydration, metabolic acidosis, or internal bleeding [1,4,12].

Conclusions

Implication for practice. Being aware the wide landscape of molecular alternation into 17th exon of VPS33B gene resulting in clinical symptoms mosaicism, we propose testing of all cases of neonatal hyperbilirubinemia and renal dysfunction. In our opinion, Sanger whole-exon sequencing should be a first-choice diagnostic test.

Statement of Ethics

This study with the use of human tissue was in accordance with the ethical standards of the declaration of Helsinki with its latest revision in 2004.

Conflict of Interest

Nothing to declare.

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