IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Case Report

Arthrogryposis-renal Dysfunction-cholestasis Syndrome

Ziba Mosayebi[1], Ameneh Lamsehchi[1*]

1. Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare autosomal recessive disorder mostly affecting the liver, kidney, skin, as well as central nervous and musculoskeletal systems. This multisystemic disease results from mutations in the vacuolar protein sorting 33B (VPS33B) or VPS33B- interacting protein, and apical-basolateral polarity regulator (VIPAR) genes. This is a lethal disorder from which few patients can survive at the first year of their life. This syndrome exhibits a wide range of phenotypes, such as ichthyosis, hypothyroidism, agenesis of the corpus callosum, and congenital cardiovascular anomalies.

Case report: Here, we present the case of a 32-day-old male neonate with respiratory distress admitted to Children's Medical Center Hospital in Tehran, Iran, in August 2019. He had ichthyosis, cholestasis with arthrogryposis as bilateral clubfeet, developmental dysplasia of the hip, and flexion contractures in upper limbs. During hospitalization, he received Shohl's solution for metabolic acidosis, intravenous antibiotics, fat-soluble vitamins, and levothyroxine. Other presentations in our case included ichthyosis, failure to thrive, congenital heart disease, and hypothyroidism.

Conclusion: Timely diagnosis, supportive care and genetic counseling should be provided for better outcome.

Keywords: Developmental dysplasia of the hip, Hypothyroidism, Ichthyosis, Vacuolar protein sorting 33B

Introduction

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a genetic disorder affecting different organs, such as liver, kidney, skin, central nervous, and musculoskeletal systems(1). This multisystemic disease results from mutations in the vacuolar protein sorting 33B (VPS33B) or VPS33B interacting protein, apical-basolateral polarity regulator (VIPAR) gene (1-4). The accurate incidence of ARC syndrome has not yet been described; nonetheless, to the best of our knowledge, about less than 100 cases have been reported worldwide (5). This rare and fatal disorder(6) has numerous clinical features, such as ichthyosis, nephrogenic diabetes insipidus (5), renal Fanconi syndrome (7), platelets abnormalities(8, 9), hypothyroidism, agenesis of the corpus callosum, congenital cardiovascular anomalies, hearing impairment(10), and recurrent sepsis(11). For exact diagnosis of this disease, early targeted exome sequencing is needed, along with processing clinical presentations. There is no cure for this disease yet, and the prognosis is poor (1, 11).

In this report, we present the case of a 32-day-old male neonate with respiratory distress and cholestasis who had arthrogryposis and hyperchloremic metabolic acidosis as ARC syndrome with additional manifestations.

Case report

A 32- day-old male neonate with severe respiratory distress was admitted to Children's Medical Center Hospital affiliated to Tehran University of Medical Sciences in August 2019. Immediately, endotracheal intubation was performed in the emergency room and the patient was transferred to the neonatal intensive care unit. He was delivered at term (38 w+3 d) by cesarean section with a birth weight of 3130 g. His parents had consanguineous marriage, and according to the history of three previous abortions, his mother had received enoxaparin during her pregnancy. Nuchal translucency was high in prenatal screening; however, amniocentesis and the karyotype were reported normal. The pregnancy was also

* *Corresponding author:* Ameneh Lamsehchi, Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran. Tel: 09128147886; Email: lamsehchila@gmail.com

Please cite this paper as:
Mosayebi Z, Lamsehchi A. Arthrogryposis-renal Dysfunction-cholestasis Syndrome. Iranian Journal of Neonatology. 2021 Apr: 12(2). DOI: 10.22038/ijn.2020.46808.1794

Figure 1. Ichthyosis of the skin

complicated by polyhydramnios.

The newborn had a history of two hospitalization due to poor feeding, jaundice, sepsis, and respiratory distress, he did not gain weight during the first month of his life. Upon admission, he weighed 3000g. Physical examination showed dry and icteric skin with decreased subcutaneous fat tissues, and the scaly lesions on his abdomen looked like ichthyosis (Figure1). The abdomen was soft without hepatosplenomegaly, and there were multiple contractures, including dislocated hips, bilateral clubfeet, flexion contractures in the upper limbs, and muscle atrophy. Both feet were in casts extending from the upper thigh to the toes to correct the clubfeet deformity (figures2 and 3). Table 1 displays the laboratory findings.

The patient suffered from leukocytosis and anemia; therefore, he had twice received 10 mL/kg of packed red blood cell transfusion. Peripheral blood smear (PBS), Prothrombin Time (PT), and Partial Thromboplastin Time (PTT) were reported normal. The serum level of gamma-

Table 1. Laboratory Findings

Time	Laboratory Test	Result	Normal Range
	White blood cell count, $10^3/\mu L$	36.1	5 - 19
	Neutrophil, %	53.1%	53-62%
	Hemoglobin, g/dl	4.7	12-16
	Platelet,$10^3/\mu L$	656	150-450
	BUN, mg/dl	16	5-20
	Creatinine, mg/dl	1.1	0.3 – 0.7
	Aspartate aminotransferase, U/L	37	Up to 37
	Alanine aminotransferase, U/L	33	Up to 41
	Bill total, mg/dl	6.9	0.1-1.2
	Bill direct, mg/dl	6.4	≤0.5
	Gamma-glutamyl transpeptidase, IU/ L	38	15-132
	alkaline phosphatase, U/L	1100	180-1200
	Albumin, g/dl	2.8	3.5-5.2
	Sodium,meq/L	154	135 - 145
	Potassium, meq/L	4.2	3.5 – 5.2
	Chloride, mg/dl	132	90-110
	Blood culture	Negative	–
	PH	7.25	7.35 – 7.45
	HCO3, meq/L	13.7	22 - 26
	BE, meq/L	-9.5	-2 - +2
	Pco2, mmHg	35.5	35-45
	25 OH vitD3, ng/ml	10	30-100

Figure 2, 3. Flexion contractures in upper and lower limbs in the patient with the arthrogryposis-renal dysfunction-cholestasis syndrome

glutamyl transpeptidase (GGT) was normal, and he had conjugated hyperbilirubinemia with normal liver function.

This patient had hypoalbuminemia and hypothyroidism, and the latter was treated with levothyroxine before admission. Arterial blood gas analysis showed hyperchloremic metabolic acidosis with a normal anion gap. The serum level of creatinine was high; however, Ammonia, lactate, and pyruvate were within normal limits. The serum level of 25 OH Vitamin D3 was deficient. Both the TORCH study and metabolic evaluation were negative. Blood and urine culture were negative as well. He was polyuric with a urinary output of 6.5 cc/kg/h. The urinary analysis revealed glycosuria (3+). Urine-specific gravity was 1005. Brain and abdominal ultrasonography was normal. Cardiac echocardiography sisplayed a small patent foramen ovale (PFO), patent ductus arteriosus (PDA), mild pulmonary hypertension (PH), and mild left ventricular hypertrophy (LVH).

According to main clinical features (e.g., arthrogryposis, cholestasis, and renal dysfunction), along with some additional features and laboratory findings, ARC syndrome was the most accurate diagnosis; nevertheless, exact diagnosis needs targeted exome sequencing. Although a genetic counselor talked to parents, they refused the genetic studies. During hospitalization, he was extubated after 5 days and received Shohl's solution for metabolic acidosis, intravenous antibiotics, fat-soluble vitamins, and levothyroxine. Before the completion of treatment, parents discharged the infant from the hospital due to financial issues; nonetheless, they filled the consent form to give us permission for reporting the case. However, the patient was lost to follow-up.

Discussion

The ARC syndrome is an autosomal recessive and lethal disorder with such cardinal features as arthrogryposis, renal dysfunction, and cholestasis. Moreover, it has some other clinical manifestations, including ichthyosis, diarrhea, hypothyroidism, agenesis of the corpus callosum, congenital cardiovascular anomalies, deafness, and recurrent sepsis (1). The ARC syndrome was firstly reported in 1973 by Lutz-Richner and Landolt (5). It is a rare disorder and to the best of our knowledge, very few cases have been reported worldwide. Her, we described an Iranian male infant with ARC syndrome characterized by clubfeet and hip dislocation, renal dysfunction, cholestasis, failure to thrive, ichthyosis, hypothyroidism, and congenital heart disease.

One of the main clinical symptoms of ARC syndrome is arthrogryposis which has different orthopedic manifestations, such as vertical talus, pes calcaneovalgus, hip dislocation, muscular atrophy, rigid kyphosis, and limb contractures. Infants with joint contractures have a deficit in the normal range of motion in their joints due to decreased fetal movement, which might be secondary to the degeneration of motor neurons in the anterior horns of the spinal cord (11, 12). Our case as an ARC syndrome suffered from congenital hip dislocation and contracture of upper limbs, bilateral clubfeet, and muscular atrophy. In a similar vein, renal dysfunction as an obligatory feature of ARC syndrome has many symptoms, such as renal tubular acidosis, nephrogenic diabetes insipidus, glycosuria, aminoaciduria, and phosphaturia, as a result of Fanconi syndrome (6, 7, 11). Our patient had normal anion gap metabolic acidosis, hypernatremia, polyuria, and low urine specific gravidity, which could be related to a nephrogenic diabetes insipidus; however, formal testing was not performed. Hypernatremia, dehydration, and polyuria have been mentioned in numerous cases of ARC syndrome (5).

Another main phenotype of this syndrome is cholestasis with a normal or low level of GGT and normal or slightly high levels of aspartate aminotransferase and alanine aminotransferase. Patients with ARC syndrome who develop cholestatic jaundice usually present no biliary obstruction (13). This patient had normal GGT and liver transaminases despite elevated conjugated bilirubin and alkaline phosphatase level. Although the association of high GGT with ARC syndrome has been rarely detected, Gupra et al. reported the case of a term newborn with ARC syndrome and a high level of GGT (14).

In addition to major clinical features of ARC syndrome, our patient has some other manifestations, including ichthyosis, failure to thrive, congenital heart disease, and hypothyroidism. Ichthyosis has been observed in 50% of reported cases, and it is assumed that the defective secretion of the lamellar bodies in the epidermis, mediated by soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins might be the cause of ichthyosiform phenotype in ARC syndrome. Furthermore, the lack of free fatty acid absorption which is critical for the differentiation of epidermis is an additional cause of ichthyosis in this syndrome(11, 15).

The majority of patients with ARC syndrome fail to thrive despite enough enteral caloric intake.

Failure to thrive might be due to increased caloric demand according to recurrent episodes of dehydration, sepsis, and chronic diarrhea secondary to cholestasis (16). Our case did not gain weight appropriately during the first month of life. He had dehydration, polyuria, and renal tubular loss with a history of two episodes of sepsis which might be contributed to his weight loss.

Another presentation of the patient was small PFO, PDA, PH, and mild LVH in echocardiography. Congenital heart diseases are reported in 10% of ARC syndromes (17); furthermore, ventricular and atrial septal defects have been reported(18). Another additional presentation was congenital hypothyroidism which was treated with levothyroxine. Before his current admission, he was under medical treatment for hypothyroidism which is a rare presentation of this syndrome; nonetheless, a few cases of congenital hypothyroidism have been reported by other studies (18).

There was no brain or hematological findings in our patient. The prognosis of this disorder is not favorable. In fact, most of these patients die within their first 12 months of life(19). There is no cure for this syndrome yet; however, the quality of life could be better with supportive strategies. Aggressive orthopedic interventions are not recommended since the mortality rate is high in this syndrome. A liver transplant may be considered when there is a failed response to supportive therapy. Dehghani et al. carried out a liver transplant on a boy with severe cholestasis and intractable pruritus with ARC syndrome in Iran to improve his quality of life and is deemed to be successful even after five years of follow-up(17).

Conclusion

The present study indicated that although ARC syndrome has three cardinal features of arthrogryposis, renal dysfunction, and cholestasis; moreover, it may exhibit an expanding range of phenotypes. Other presentations in our case were ichthyosis, failure to thrive, congenital heart disease, and hypothyroidism. Family history, classical clinical findings, and genetic tests together can facilitate the diagnosis of ARC syndrome. Despite the fatal outcome of ARC syndrome, early detection, supportive interventions, and genetic counseling can be of great help in the control of this disease. With advancements in molecular genetics and medical technologies, gene therapy would be a promising treatment option in the near future for managing or even curing this syndrome.

Acknowledgments

We would like to thank all staff nurses who have a critical role in caring for this patient.

Funding

This study received no specific grant.

Conflicts of interest

The authors declare that they have no conflict of interest.

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