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ORIGINAL ARTICLE

Arthrogryposis-renal dysfunction-cholestasis syndrome diagnosed from a case of neonatal cholestasis - a case report

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Abstract

Arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome is a rare autosomal recessive syndrome, with multisystemic manifestations and mainly characterized by arthrogriposis, renal dysfunction and cholestasis. The prognosis is poor and most patients die within the first year of life. This is a case report of a female infant, 37 days old, referred to a tertiary hospital due to neonatal cholestasis. Upon evaluation, she also presented with Fanconi syndrome, arthrogryposis, malnutrition, ichthyosis and agranular platelets, thus receiving the clinical diagnosis of ARC syndrome. The liver biopsy showed signs of neonatal hepatitis. Her admission was complicated by dehydration, worsening of metabolic acidosis and acute respiratory failure. The infant was discharged at the age of 3 months, in palliative care, and later died. As it is a very rare disease, knowledge of its characteristics is crucial for appropriated diagnostic evaluation and differential diagnosis with other causes of cholestasis, as well as adequate management.

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INTRODUCTION

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is a rare, fatal multisystem disease characterized primarily by the presence of arthrogryposis, renal tubular dysfunction, and cholestasis. This recessive autosomal syndrome has had tens of mutations reported since it was first described in 1973[1,2]. Prognosis is poor and most patients die within the first year of life due to complicated disease[3]. Early diagnosis is instrumental in providing proper support to patients, advice to family members, and guidance over the need to seek genetic counseling. Although rare, one of the main manifestations in ARC syndrome is neonatal cholestasis, a condition of great relevance in pediatrics. This article describes the case of a 37-day-old infant referred to a tertiary hospital for neonatal cholestasis. The patient also presented with Fanconi syndrome and arthrogryposis. A diagnosis of ARC syndrome was established based on a multidisciplinary review. The patient was placed on palliative care and eventually died.

CASE REPORT

A female 27-day-old infant was referred to our center due to neonatal cholestasis. The infant was born from a Cesarean section at 42 weeks of gestation. She was small for gestational age and weighed 2755g at birth. Her parents were nonconsanguineous. She had jaundice since the first day of life and was initially treated with phototherapy for eight days, although tests revealed she had cholestasis (total bilirubin: 11.1mg/dl; direct bilirubin: 6.94mg/dl) and elevated transaminases (aspartate transaminase: 257 U/L; alanine transaminase: 202 U/L). Her neonatal life was marked by dehydration and poor weight gain, although she was breastfed and given a formula. Thirty-five days after birth the infant showed signs of dehydration and jaundice, which prompted a referral to a tertiary center for assessment. No limb deformities or arthrogryposis were noted.

On admission, the patient had signs of severe malnutrition, pallor, jaundice, and ichthyosis. She did not have an enlarged liver or spleen. Her mother's account indicated that the patient had acholia, was adynamic, ate poorly, and was unable to gain much weight. The patient weighed 2770g, and had a Z-score below -2 for her sex and age. Workup tests showed she had cholestasis with elevated transaminase and alkaline phosphatase (ALP) levels, although her gamma-glutamyl transferase (GGT) was normal. Other findings included severe anemia, hemolysis, agranular platelets, acute kidney injury, metabolic acidosis, and hypothyroidism. The results of the main lab tests are shown in Table 1. Percutaneous liver biopsy revealed chronic liver disease associated with intra-hepatocytic and cholestasis with Kupffer cell activation and extensive giant cell transformation of hepatocytes. As the patient was being sedated for the procedure, we noticed she was unable to fully extend her right knee, which characterized arthrogryposis.

Table 1. Lab tests on admission and in the last outpatient visit.

Tests \ Age	1 month	4 months
Hemoglobin (g/dL)	6.1	7.9
Hematocrit (%)	19.3	24.7
Platelets (/µL)	409000	-
Reticulocytes (%)	3.8	-
TB (mg/dL)	15.62	-
DB (mg/dL)	12.61	-
AST (U/L)	655	-
ALT (U/L)	815	-
ALP (U/L)	1201	-
GGT (U/L	34	-
Albumin (g/dL)	3.5	2.9
pH in venous blood gas	7.29	7.25
Bicarbonate in venous blood gas (mmol/L)	15.4	18
Lactate in venous blood gas (mmol/L)	1.8	2
Sodium (mmol/L)	138	147
Potassium (mmol/L)	4.5	4.6
Phosphorus (mg/dl)	3	3,7
Magnesium (mEq/dl)	1,88	1,74
Creatinine (mg/dL)	0,65	0,57
Urea (mg/dL)	25	22

TB = total bilirubin; DB = direct bilirubin; AST = aspartate transaminase; ALT = alanine transaminase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; - = not available.

The patient was diagnosed with Fanconi syndrome during hospitalization. She required a nasogastric tube for nutritional support and fluid and electrolyte replacement. The patient was dehydrated and her anemia, metabolic acidosis, and acute respiratory failure worsened. She received a transfusion of packed red blood cells, antibiotics (ampicillin and sulbactam), and antiviral therapy with oseltamivir. The patient was sent to the Pediatric Intensive Care Unit; she was intubated and connected to a ventilator. Her condition improved after the introduction of support measures.

The infant was assessed by the gastroenterology, pediatric hepatology, pediatric nephrology, dermatology, and genetics teams and was diagnosed with ARC syndrome. Genetic tests were not performed since they are not routinely reimbursed by the Brazilian Public Healthcare System; the patient was diagnosed based on clinical findings. She was discharged with a nasogastric tube when she was three months old, placed on palliative care at home, and followed at the outpatient clinic The patient was taken to a visit for the last time when she was five months old, without the nasogastric tube, significantly malnourished, weighing 2520g, a Z-score below -3 for her sex and age, which made the arthrogryposis in her knees more evident (Figure 1). She eventually died.

Figure 1. Infant with decreased fat tissue and muscle mass in her legs and skin folds consistent with malnutrition, knee arthrogryposis. Her skin was dry and scaly, consistent with ichthyosis. The patient also had jaundice.

DISCUSSION

ARC syndrome is a fatal multisystem disorder that affects the musculoskeletal system, the kidneys, the liver, and the central nervous system from birth. Most of the cases reported involve individuals from Pakistan and Saudi Arabia, given the high prevalence of consanguineous marriages in these regions, although cases have also been described in other countries[4-6]. Although the parents were not consanguineous, the patient had the classical traits described in other studies: arthrogryposis, renal tubular acidosis, and neonatal cholestasis. Other findings may include ichthyosis (50%), platelet anomalies (25%), agenesis of the corpus callosum (20%), congenital heart defects (10%), hearing loss, recurrent infection, difficulty to gain weight, hypothyroidism, and bleeding due to coagulation disorders[3]. Thrombocytopenia is not a characteristic finding in ARC syndrome, but the presence of agranular platelets favors the diagnosis of the condition and explains platelet dysfunction and increased risk of bleeding[7]. One of the most commonly described kidney conditions, Fanconi syndrome causes aminoaciduria, glycosuria, phosphaturia, and mainly bicarbonate loss leading to tubular acidosis[8,9].

Liver involvement is apparently related to altered canalicular proteins involved in biliary secretion and causes increases in transaminase and alkaline phosphatase levels, with normal or decreased levels of gamma-glutamyl transferase, which might be useful in the differential diagnosis against other causes of neonatal cholestasis, such as biliary atresia[10]. Several histology alterations have been described. The main findings described by *Eastham et al.* were cholestasis and giant cell transformation of hepatocytes, which were also observed in the present case[9].

ARC syndrome is one of the rarest etiologies of neonatal cholestasis, with cases occurring at a rate of 1:7 relative to biliary atresia according to Jang *et al*.[11] Workup alterations seen in ARC syndrome may be similar to the ones observed in progressive familial intrahepatic cholestasis (PFIC) and genetic tests may be needed in diagnosis[12]. Analysis of platelet morphology may be useful in differential diagnosis against other causes of neonatal cholestasis, since agranular platelets are a common finding in ARC syndrome and may be used as a noninvasive diagnostic marker of disease[7].

Although they were not performed for the patient described in this article, genetic tests are a valuable diagnostic tool, since ARC syndrome has been linked to mutations in genes VPS33B in about 75% and VIPAR in about 25% of the cases[13]. Most patients die after two to seven months of birth,[6] primarily of sepsis, severe anemia, acidosis, and dehydration[14]. Correlations between genotypes and phenotypes are still being studied[7]. Some patients survive with the disease for longer, and a new mutation in the VPS33B gene has been linked to milder disease, with moderate kidney involvement and progressive liver disease[15].

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