Arthrogryposis, Renal dysfunction, Cholestasis (ARC) Syndrome with A Novel Mutation in two siblings

Rahiya Rehman[1], Leslia Gonzalez[1], Kelsey Kolbe[1], William Brucker[1], Mohammed Faizan[2], and Carolina Cerezo[1]

[1]Brown University Warren Alpert Medical School
[2]Warren Alpert Medical School of Brown University

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Introduction:

Arthrogryposis renal dysfunction cholestasis (ARC) syndrome is a rare autosomal recessive condition caused by mutations in the VPS33B and VIPAR genes. Several mutations have previously been described and associated with either a severe or mild phenotype, with the severity correlating with fatality. Given the spectrum of phenotypes, milder presentations can be elusive and more difficult to diagnose. Our case illustrates a mild presentation of ARC syndrome with cholestasis that improved over time in the setting of a novel, pathogenic variant (c.1609 del, p. Asp538Metfs*17).

Case history and examination:

Patient 1 : A 4-month-old female with intrauterine growth restriction, arthrogryposis multiplex congenita, and sensorineural hearing loss was referred to pediatric gastroenterology clinic for poor growth and feeding problems. She was born at 40 weeks of gestation to a healthy, non-consanguineous, biracial Hispanic-Asian couple. Mother had alpha thalassemia trait and hemoglobin E trait, and paternal half-brother had lipoprotein deficiency. Patient's birth weight was 2.72 kg. She had postnatal growth failure with weight of 4.23kg (0.03 %tile, Z score -3.40) and length of 52.8cm (<0.01 %tile, Z score -4.07) at 4 months of age. On examination, she had mild jaundice, microcephaly, ocular hypotelorism, micrognathia, highly arched palate, bilateral hearing loss, bilateral transverse palmar creases, dry skin without ichthyosis, enlarged liver, mild hypotonia, and bilateral rocker bottom feet (Figure 1: a,b,c).

Patient 2: Patient was born at 39 weeks of gestation to the same biological parents as sibling 1. Her birth weight was 2.72kg. Subsequently, she was also found to have growth failure, with a weight of 2.70 kg (<0.01%tile, Z score -3.90) and a length of 46.7cm (<0.01 %tile, Z score -4.31) at 1.5 months of age. On examination, she had microcephaly, bilateral hearing loss, bilateral transverse palmar creases, dry skin without ichthyosis, mild hypotonia, and bilateral rocker bottom feet (Figure 1: d,e).

Investigations and Treatment:

Patient 1: Labs upon presentation showed fasting hypoglycemia and cholestatic hepatitis (Table 1). She was also found to have severe Vitamin D deficiency rickets based upon her labs and wrist X-rays. Abdominal ultrasound (US) showed hepatosplenomegaly as well as bilateral increased renal echogenicity surrounding the medullary pyramids. MRI brain revealed thin corpus callosum with overall decreased volume of cerebral white matter. MRI spine was normal. Renal tubular dysfunction was identified on labs that showed acidosis, proteinuria and glucosuria. She had a normal coagulation profile and negative infectious hepatitis panel

Differential diagnosis initially included a genetic or metabolic syndrome given the vast array of findings. A clinical diagnosis of ARC syndrome was made that was later confirmed by genetic testing. A commercial genetic cholestasis panel was ordered that identified variants in VPS33B: c.1225+5G>C and c.1609del p. Asp538Metfs*17, with the c.1225+5 G>C previously described in association with a milder presentation of the disease. Another rare variant was positive, designated c.1609del, that has not been described in the literature or reported in a large population database. She was also found to have a heterozygous pathogenic variant in SERPINA1 (c. 863 A>T, p. Glu288Val) conferring a carrier state for alpha-1 antitrypsin (A1AT) deficiency. Her A1AT phenotype was MS with normal level.

Our patient's vitamin D deficiency improved over time with supplementation and repeat labs showed normal Vitamin D, calcium, and phosphorus. Her acidosis improved with sodium citrate supplementation. She was started on ursodiol for cholestasis and her total and direct bilirubin levels also normalized.

Patient 2: Patient's mother had undergone amniocentesis during pregnancy that confirmed biallelic pathogenic variants in VPS33B: c.1225+5G>C and c.1609del p. Asp538Metfs*17, which were also seen in her sibling (patient 1) confirming a diagnosis of ARC syndrome, as in patient 1. She did not have any additional mutations. Initial laboratory tests, including bilirubin and thyroid profile, were within normal range. Overtime, she also developed hepatitis and experienced fasting hypoglycemia, similar to her older sibling (Table 1). Abdominal ultrasound (US) revealed a congenital gallbladder anomaly (multiseptated gallbladder), without any associated hepatosplenomegaly or renal defects. MRI brain was normal. Renal tubular dysfunction was identified on labs that showed acidosis, proteinuria and glucosuria. She had a normal coagulation profile.

She was started on DEKA vitamins early on, and fortunately, did not develop Vitamin D deficient rickets, as seen in her sibling. She is now 11-month-old. For her failure to thrive, she is currently receiving supplemental enteral feeds via a gastrostomy tube, and she is on sodium citrate supplementation for her acidosis.

Outcome and Follow up:

Patient 1: Since diagnosis, her course has been dominated by chronic malnutrition requiring gastrostomy tube placement, hypothyroidism (requiring levothyroxine) and complications from arthrogryposis multiplex congenita. She continues to have chronic fluctuating hepatitis (overall improving) with stable hepatomegaly and elevated serum bile acids leading to pruritus for which she is being treated with ursodiol and odevixibat. She is also on DEKA vitamins. Despite these complications, child is a happy toddler approaching 3 years of age, and otherwise stable.

Patient 2: Similar to her sibling she also has chronic fluctuating hepatitis and elevated serum bile acids leading to pruritus for which she is being treated with ursodiol and odevixibat. While her clinical features are somewhat less severe compared to her sibling, the presence of similar mutations suggests that she is likely to follow a comparable course of the condition.

Discussion:

Arthrogryposis renal dysfunction cholestasis (ARC) syndrome is a rare multisystem disorder involving liver, kidney, musculoskeletal, skin, and central nervous systems with early mortality and poor prognosis seen with severe forms. ARC is characterized by autosomal recessive mutations in the VPS33B (vacuolar protein sorting 33 homolog B) and VIPAR (VPS33B-interacting protein, apical basolateral polarity regulator) genes which are involved in the intracellular protein sorting and vesicular trafficking pathways.[1] These are expressed in several organs and mutations lead to disruption of cell polarization that is crucial to cellular development and function.

There are various described phenotypes associated with ARC syndrome with the three core features being arthrogryposis, renal dysfunction, and cholestasis. Different genetic mutations are associated with different phenotypic variations. The prognosis of ARC syndrome is poor especially in cases with severe mutations. Most patients usually die within the first year of life after developing acidosis, recurrent infection, or internal bleeding. [2,3]

Our patients' genetic testing identified pathogenic variants in VPS33B (c.1225+5G>C) and (c.1609del p. Asp538Metfs*17), with the latter not described in the literature or reported in a large population database previously. The phenotype of our patients is unique in that on presentation there was no ichthyosis or sepsis like illness that is typically life limiting before one year of age. Table 2 illustrates the differentiating factors of a classic ARC patient as compared to our patients (Image 1) with a milder phenotype. Hepatitis and hepatomegaly with giant cell transformation, biliary plugs, and portal fibrosis can be seen to varying degrees in this disorder in part due to disruption in trafficking of bile components. While severe cholestasis is one of the core findings in ARC syndrome, proband 1 only had mild elevation in total and direct bilirubin that resolved overtime. Proband 2 also followed a similar course which may be explained by milder phenotype associated with this unique mutation. [1,2,4] Both patients continue to have intermittently elevated serum bile acids and pruritus that is currently treated with selective inhibitor of the ileal bile acid transporter (odevixibat). These features along with fasting hypoglycemia and rickets are clinical features less described in literature in the setting of a novel mutation (c.1609del, p. Asp538Metfs*17).

This current case series adds to the spectrum of ARC-associated variants. Increased awareness and early genetic testing for ARC are suggested in cases with failure to thrive, renal tubular dysfunction, and rickets even when the degree of cholestasis is mild.

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