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CLINICAL NOTE

ARC syndrome accompanied with glaucoma in one of two affected siblings

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Arthrogryposis-renal dysfunction-cholestasis syndrome (ARCS, OMIM#208085) is a rare autosomal recessive disorder caused by variants in vacuolar protein sorting 33B (*VPS33B*; MIM#608552) or VPS33B-interacting protein, apical–basolateral polarity regulator (*VIPAR*; MIM#613401).[1] Characteristic ARCS presentation includes neonatal cholestatic jaundice, renal tubular acidosis, arthrogryposis, and severe failure to thrive, with no studies to date reporting ocular involvement. Here, we present the cases of two relatively long-lived siblings with ARCS, one of whom developed congenital glaucoma.

Case 1 was the older sister born at 39 weeks of gestation by cesarean section without asphyxia in another hospital. She had congenital bilateral glaucoma, elevated intraocular pressure (IOP) measured using tonometry, optic nerve atrophy observed through fundus examination, arthrogryposis of extremities, hip dislocation, rocking chair-like heels, jaundice, and marked xerosis. Interventions included fluid replacement (>350 mL/kg/day) for polyuria (12 mL/kg/h) and diarrhea and electrolyte replacement for renal tubular acidosis (base excess, −10 mEq/L; HCO_3^-, 15 mEq/L), hypophosphatemia, and hypokalemia. Serum alanine aminotransferase level was mildly elevated with normal gamma-glutamyl transpeptidase level. Ursodeoxycholic acid was administered for cholestasis. Enteral nutrition did not progress, and diarrhea persisted. She underwent goniotomy twice. During surgery, she exhibited a marked bleeding tendency, and electron microscopy revealed the absence of platelet alpha granules, suggesting abnormal platelet function. G-band chromosome analysis revealed a normal 46, XX karyotype. *VPS33B* genetic analysis revealed a novel compound heterozygous mutation in exon 6 [c.402A>C(p.Gly134Gly)] and a previously reported splice-site mutation in intron 6 (NM_018668.5:c.403+2T>A)[2] for which the father and mother were heterozygous, respectively. She was transferred to our hospital at 3 months of age and underwent trabeculotomy. Cholestasis improved at 6 months but relapsed and worsened at 2 years of age (maximum total bilirubin, 32 mg/dL). Recurrent gastrointestinal and nasal bleeding necessitated transfusions. Latanoprost eye drops were initiated at 1 month of age and maintained IOP between 20 and 45 mmHg in both eyes. She died at 5 years and 10 months of age due to worsening renal failure, liver failure, and pneumonia (Figure 1a).

Case 2 was the younger brother born at 38 weeks of gestation in our hospital who was clinically diagnosed with ARCS based on the clinical presentation similar to that of the sister. The parents did not request prenatal genetic counseling or postnatal genetic testing. After birth, he developed polyuria, diarrhea, poor weight gain, and cholestasis, which was not as advanced as that observed in his sibling. He also had a bull's eye in the setting of normal IOP (9 mmHg). He died of malnutrition, heart failure, and pneumonia at 5 years and 5 months of age (Figure 1b).

Although life expectancy is longer in some patients with ARCS depending on the *VPS33B* variant,[3] most patients experience severe failure to thrive and die early in the first 6 months of birth.[1] ARCS is refractory to treatment due to cholestatic liver failure, renal failure, platelet hypofunction,

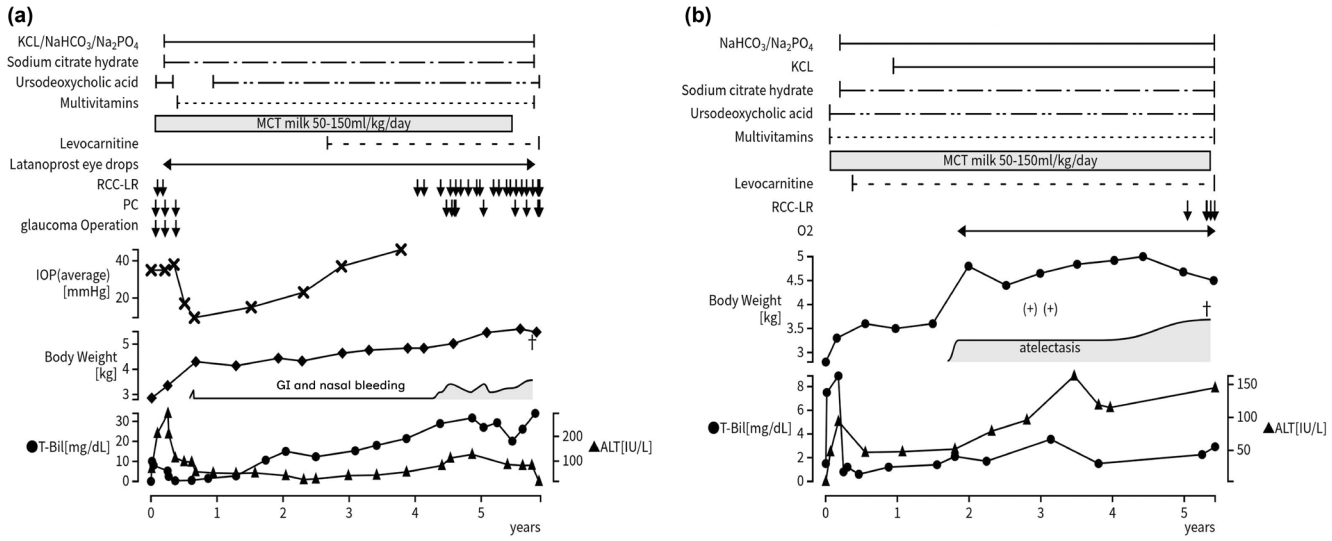

FIGURE 1 (a) Clinical course of Case 1, the older sister. (b) Clinical course of Case 2, the younger brother. KCL, potassium chloride; $NaHCO_3$, sodium bicarbonate, Na_2PO_4, disodium phosphate; MCT, medium chain triglyceride; RCC-LR, red cells concentrates-leukocytes reduced; PC, platelet concentrate; IOP, intraocular pressure; GI, gastrointestinal; T-Bil, total bilirubin; ALT, alanine aminotransferase.

and nutritional disorder; however, long-term survival can be expected with appropriate symptomatic therapy. Furthermore, aggressive treatment such as living-donor liver transplantation might be considered in the future.[4]

Given that siblings with the same ARC syndrome show varying symptom severity in nonocular organs and considering the role of genetic variants in congenital glaucoma, genetic modifiers, epigenetic differences, and environmental factors likely influence the glaucoma development.[5] The timing and degree of developmental abnormalities in the anterior chamber angle could vary between siblings, which can lead to differences in trabecular meshwork dysfunction and extent of IOP elevation. *VPS33B*, which encodes SNARE proteins crucial for intracellular trafficking, could be disrupted by variants, affecting procollagen transport and trabecular meshwork turnover.[6] Reduced autophagy due to these variants can lead to cellular stress and dysfunction, which could further elevate IOP.

In ARCS, effective management of repeated gastrointestinal and nasal bleeding, fractures, and infections can improve long-term survival whereas complications of congenital glaucoma may become a major issue related to quality of life in older patients.

AUTHOR CONTRIBUTIONS

T.O. was responsible for conceiving this case report and writing the manuscript. M.T., S.S., N.H., and Y.O. contributed to data collection and performed critical revisions. All the authors have approved the final version to be published.

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CONSENT

Written informed consent was obtained from the patients' parents for publication of this case report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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