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Severe Neonatal Presentation of Autosomal Recessive Renal Tubular Dysgenesis: A Case Report Underlining Genetic and Clinical Challenges

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1. Abstract

Background: Autosomal recessive renal tubular dysgenesis (ARRTD) is a rare and mostly fatal disorder caused by mutations in genes involved in the renin-angiotensin system, leading to disrupted renal perfusion and development. ARRTD typically presents with pulmonary hypoplasia, refractory hypotension, and persistent anuria, posing significant diagnostic and therapeutic challenges in the neonatal period. Methods: We describe a newborn with a severe clinical presentation of ARRTD, including refractory hypotension, persistent anuria, and complications related to oligohydramnios, who died within 19 hours of life. A comprehensive diagnostic workup, including genetic analysis and post-mortem investigations, was performed to confirm the diagnosis. The clinical course, management strategies, and outcomes were evaluated. Results: The patient exhibited hallmark features of ARRTD, including persistent anuria and hypotension unresponsive to vasopressors. Despite intensivesupportive care, his condition remained critical, underlining the challenges associated with ARRTD management and prognosis. Genetic testing identified a pathogenic homozygous mutation in ACE gene, and parental genetic analysis confirmed the autosomal recessive inheritance pattern of the disease. Conclusions: ARRTD should be considered in neonates presenting with refractory hypotension and persistent anuria, particularly in the context of a history of oligohydramnios. Genetic testing plays a central role in confirming the diagnosis. Given the poor prognosis and lack of targeted treatments, early recognition is essential for appropriate parental counseling and informed management planning.

2. Introduction

Autosomal recessive renal tubular dysgenesis (ARRTD) is a rare and mostly fatal disorder characterized by impaired renal tubular development [1], leading to severe complications such as oligohydramnios sequence with pulmonary hypoplasia, refractory hypotension, and anuria [2]. Since the initial characterization [1], over 150 cases of ARRTD have been reported, most of which resulted in neonatal death due to respiratory failure, refractory hypotension and/or anuric renal failure [3–5].

The pathogenesis of ARRTD involves mutations in genes related to the renin-angiotensin system (RAS), including angiotensinogen (AGT), renin (REN), angiotensin-converting enzyme (ACE), and angiotensin II receptor type 1 (AGTR1) genes [2,6]. These mutations disrupt the RAS pathway, which is essential for normal kidney development and function [7]. The resultant renal tubular dysgenesis leads to significant impairment in urine production, contributing to the oligohydramnios observed in affected pregnancies [2–5,7].

Prenatal suspicion typically arises from ultrasound findings of oligohydramnios starting from the 20th to 22nd gestational week [8–10], although a few cases with later onset of oligohydramnios have been described [11]. Unlike other conditions presenting with similar ultrasound findings, ARRTD usually shows normal renal morphology and maintains a normal fetal growth pattern [4,7,10,12,13].

Recent advances have elucidated the genetic background of this disease [2,6,7], enabling the identification of genetic mutations

associated with ARRTD through analysis of amniotic fluid samples collected via amniocentesis or amnioinfusion, providing a definitive prenatal diagnosis [8–10]. Such early diagnosis facilitates more informed prenatal counseling, enabling healthcare providers to discuss prognosis and potential therapeutic options with the parents [9,10,13].

We present a case report of a newborn with a severe clinical course of ARRTD, who died within 19 hours of life, precluding the administration of recommended treatments. The post- mortem genetic analysis confirmed ARRTD, highlighting the need for heightened awareness and early diagnostic intervention in similar cases.

3. Case Report

A male newborn was born to a healthy 25-year-old Egyptian woman, gravida 2 para 1 (G2P1). There was no history of maternal illness or exposure to teratogens. The family history was notable for fourth degree consanguinity (parents were first cousins) but was unremarkable for renal disease. The pregnancy was uneventful until anhydramnios was detected at 33 weeks of gestation, with a negative test for premature preterm rupture of the membranes. The woman was admitted to the Obstetrics and Gynecology Department of our hospital, where ultrasound of the fetus revealed a mild pericardial effusion, normally differentiated kidneys with regular cortico-medullary differentiation, and an unvisualized bladder. An amnioinfusion was performed, and karyotyping from the obtained amniotic fluid showed a normal male karyotype (46, XY). Considering the high risk of pulmonary hypoplasia, two doses of antenatal corticosteroids were administered.

The patient was delivered spontaneously at 36+1 weeks of gestation, presenting at birth with diffuse subcutaneous edema, clubbed feet, and cranial ossification defect. At delivery, he was hypotonic and cyanotic with poor respiratory effort, requiring positive pressure ventilation and subsequent support with nasal Continuous Positive Airway Pressure. His Apgar scores were 5, 7, and 7 at 1, 5, and 10 minutes respectively. Birth weight was 2950 g (68th centile), length was 49.0 cm (73rd centile) and head circumference was 35.0 cm (91st centile).

He was admitted to our Neonatal Intensive Care Unit (NICU) and was intubated at one hour of life due to severe mixed acidosis and respiratory failure. Subsequently, he developed bilateral pneumothorax, and two chest drains were placed, with no resolution of the condition. The patient exhibited severe hypotension soon after birth, with a mean arterial pressure (MAP) of about 20-30 mmHg, which appeared unresponsive to fluid boluses and inotropic support with norepinephrine and epinephrine. Hydrocortisone was started for persistent hypotension, showing a brief and transient improvement in blood pressure with MAP of about 40-45 mmHg. Fresh frozen plasma (FFP) was administered without any benefit. There was no urine output since birth, despite the administration of furosemide. Moreover, the patient developed progressively worsening electrolyte imbalances, specifically hyponatremia and hypocalcemia, which were refractory to intravenous supplementation. The patient remained anuric throughout his entire clinical course.

Several ultrasound examinations were conducted: an echocardiogram revealed a mild, non- tamponade pericardial effusion and no signs of pulmonary hypertension; a lung ultrasound displayed persistent bilateral pneumothorax despite chest drainage, and diffuse and confluent B-lines with pleural thickening consistent with respiratory distress syndrome; a cranial ultrasound showed bilateral grade I intraventricular hemorrhage; a renal ultrasound evidenced kidneys in normal anatomical position with the right kidney smaller in size, bilateral preserved parenchymal thickness, hyper-reflective echotexture, and an empty bladder.

The patient's oxygen saturation progressively worsened, and endotracheal surfactant administration did not provide any improvement. Severe hypoxia and hypotension persisted, unresponsive to maximal inotropic support with norepinephrine and epinephrine. At 18 hours of life, the patient developed a bradycardia, which progressively worsened. The patient died at 19 hours of life.

With parental consent, post-mortem investigations were conducted. The autopsy revealed findings consistent with the microscopic renal features of ARRTD, including an increase in the number of nephrons with dense renal glomeruli, absence of proximal convoluted tubules, uniform renal tubules, and thickening of the walls of renal arterioles. Genetic analysis of the newborn's blood sample revealed a homozygous mutation of ACE gene (c.1384dup (p. Ile462Asnfs*19; exon 9), associated with ARRTD. Moreover, a homozygous mutation of biotinidase gene (exon 4) was found. Genetic testing of the parents confirmed the autosomal recessive inheritance pattern of the disease.

4. Discussion

Autosomal recessive renal tubular dysgenesis is an uncommon and severe disorder characterized by impaired renal tubular development and renal dysfunction due to embryo-fetal renal hypoperfusion [1]. This condition leads to significant complications, including oligohydramnios and Potter sequence [2–5], which comprises distinctive facial features, cranial anomalies, limb deformities (clubbed feet), and most critically, pulmonary hypoplasia [14]. The insufficient amniotic fluid volume results in restricted fetal movement and compromised lung development, predisposing to respiratory failure at birth. Moreover, ARRTD is typically characterized by refractory hypotension, and anuria [2–5].

The pathogenesis of ARRTD involves gene mutations associated with the renin-angiotensin system, such as AGT, REN, ACE, and AGTR1, with ACE gene mutations being the most common [2,6]. In the RAS pathway, renin converts angiotensinogen into angiotensin I, which is then transformed by angiotensin-converting enzyme into the biologically active peptide angiotensin II. Angiotensin II plays an essential role in regulating blood pressure and fluid balance by increasing renal sodium reabsorption at the proximal tubules, stimulating aldosterone production in the adrenal cortex, which enhances sodium and water retention,

and promoting vasopressin release from the posterior pituitary gland, which helps to maintain vascular tone and water reabsorption in the kidneys [15]. The RAS pathway is critical for normal kidney development and its dysfunction results in the distinctive renal pathology observed in ARRTD, including absent proximal convoluted tubules, increased nephron number with dense glomeruli and renal arteriolar thickening [2,6,7].

Prenatal suspicion of ARRTD generally arises from ultrasound findings of oligohydramnios, which often begin to manifest between the 20th and 22nd weeks of gestation [8–10]. This early identification is critical, as ARRTD presents distinct characteristics compared to other conditions that also cause oligohydramnios. Fetuses affected by ARRTD typically exhibit normal renal morphology on ultrasound, without signs of obstructive uropathy, multicystic dysplastic kidneys, or renal agenesis. Furthermore, these fetuses usually maintain a normal growth pattern, differentiating ARRTD from other congenital anomalies that might present with reduced amniotic fluid volume [4,7,10,12,13]. Recent elucidation of the genetic background of ARRTD has significantly enhanced diagnostic capabilities [2,6,7]. Specifically, this genetic insight allows for prenatal identification of RAS pathway mutations through genetic analysis of amniotic fluid samples obtained via amniocentesis or amnioinfusion [8– 10]. Such testing provides a definitive prenatal diagnosis, enabling healthcare providers to offer more accurate prognostic information and engage in detailed prenatal counseling with parents [9,10,13]. This capability is important given the severe implications of ARRTD, including potential neonatal death due to respiratory failure, refractory hypotension, and renal failure.

Current perinatal management for ARRTD is primarily supportive, often involving renal replacement therapy, though this approach presents unique challenges in neonates and is not always feasible [12,16]. Notably, neonates with ARRTD are usually refractory to conventional supportive measures for hypotension and anuria, such as intravenous fluids, furosemide, catecholamines, and hydrocortisone [3,4,12,16,17]. Infusions of FFP have shown some efficacy in normalizing blood pressure in cases involving AGT mutations, though their effectiveness may be limited to this subset due to normal angiotensinogen levels in other ARRTD-related mutations [2,12]. In contrast, the administration of vasopressin has been effective in normalizing blood pressure and inducing diuresis in some neonates with ARRTD [4,12,16,17]. This treatment aims to bypass the defective components of the RAS, helping to restore vascular tone and water reabsorption functions, which are essential for stabilizing blood pressure and managing fluid balance in these infants [15]. However, this treatment does not have an impact on the concurrent deficiency of aldosterone, which is critical in cases of ARRTD with long-term survival. The use of fludrocortisone has been explored to compensate for the lack of aldosterone, with some cases showing promising results in maintaining blood pressure and electrolyte balance [4,12,16,17]. However, further research is needed to refine treatment protocols for this rare and challenging condition.

The clinical course observed in our case aligns with previous reports of ARRTD, where neonates often present severe and unresponsive hypotension, anuria, and respiratory distress, leading to high mortality rates. The prenatal findings of anhydramnios and the absence of urinary output post-birth were indicative of significant renal dysfunction, setting the clinical suspicion of ARRTD. The autopsy revealed findings consistent with the microscopic renal features of ARRTD, which was confirmed post-mortem by the genetic analysis showing a homozygous mutation in the ACE gene.

The prenatal detection of anhydramnios at 33 weeks, coupled with the absence of other significant renal anomalies, pointed towards ARRTD, also considering the consanguinity in the family history, which increases the likelihood of autosomal recessive conditions. However, the extremely rapid deterioration of the newborn's condition after initial stabilization in the delivery room (particularly due to severe pulmonary issues characterized by bilateral pneumothorax refractory to chest drainage) precluded the initiation of renal replacement therapy, which was not available at our center, and the administration of vasopressin, a medication not commonly used in our NICU. Consequently, the post-natal management relied on standard therapies to address hypotension and anuria, which proved ineffective. In this regard, our case highlights the challenges in managing such conditions, where the primary pathology severely limits therapeutic options and often leads to early neonatal death.

Recent advancements in the genetic backgrounds of ARRTD have allowed for more accurate prenatal diagnosis [2,6,7]. In our case report, the identification of homozygous mutations in the ACE gene has significant implications for future pregnancies of the couple. The autosomal recessive inheritance pattern necessitates genetic counseling for the family to discuss the risks of recurrence in subsequent pregnancies and the potential for prenatal diagnosis in future gestations. The severe and mostly fatal nature of ARRTD requires careful consideration of the potential outcomes and quality of life for the affected neonates. The ethical considerations in managing ARRTD are profound, particularly concerning the decision-making process around intensive care measures and the extent of intervention, even from the delivery room. Therefore, early genetic testing and counseling are utterly important for discussing with the family the prognosis and potential treatment limitations.

5. Conclusion

Autosomal recessive renal tubular dysgenesis presents a significant clinical challenge due to its severe and mostly fatal outcomes. The detection of oligohydramnios during pregnancy paired with normal renal morphology on ultrasound should raise the suspect for ARRTD, which can be confirmed by the genetic analysis of an amniotic fluid sample. The early prenatal diagnosis is crucial for providing valuable prognostic information and enabling timely counseling for families. Indeed, the clinical management of ARRTD remains complex, with current perinatal treatments being almost entirely supportive. On the other

hand, interventions like vasopressin and fludrocortisone show some promise, although further research is needed to establish standardized and targeted treatment protocols. Taken all together, the severe and mostly fatal nature of ARRTD requires careful consideration of the potential outcomes and quality of life for the newborns. Therefore, early genetic testing and counseling are essential for informed decision-making and providing support to the families.

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