Cystic Kidney Disease: An Early Manifestation of a Rare Syndrome

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Abstract

Pediatric cystic kidney diseases include a diversity of hereditary or non-hereditary conditions, whose phenotypic presentation can vary from asymptomatic to end-stage renal disease.

We report a case of a male with a prenatal diagnosis of pyelectasis. Throughout the first two years of life, serial renal ultrasound showed regression of pyelectasis, but increased renal echogenicity, first identified at three months-old. The family history of renal diseases was negative. Voiding cystourethrography showed no signs of vesicoureteral reflux and the MAG3 renogram revealed equally functioning kidneys. At 29 months-old, elevated transaminases and two cortical cysts were detected, raising the suspicion of a cystic kidney disease. A hepatic biopsy showed no signs of fibrosis. He was tested for autosomal recessive polycystic kidney disease (ARPKD), which was negative. Renal ultrasound showed an increase in the number of cysts bilaterally, with diffuse hyperechogenicity and reduction of parenchymal-sinus differentiation. Throughout the years, he maintained normal blood pressure and elevated transaminases, with rising serum creatinine from the age of 13 years. A NGS panel for cystic diseases detected 17q12 deletion syndrome, which causes renal cysts and other urinary tract malfunctions, and may also present with mature-onset diabetes of the young type 5 (MODY5) diabetes, hyperparathyroidism, altered hepatic function and behavioral and psychiatric conditions. On the last appointment (15 years-old), ultrasound showed bilateral cysts (10 mm), worsened renal function (glomerular filtration rate (GFR) of 71 mL/min/1.73 m2), hypomagnesemia under treatment, and normal transaminases and glycemia.

In this case, an atypical presentation of cystic kidney disease led to an extended investigation resourcing to other genetic panels, allowing the etiological diagnosis and enabling the early identification and monitorization of possible extra-renal comorbidities commonly associated with this syndrome.

Keywords: Child; Chromosomes, Human, Pair 17; Kidney Diseases, Cystic; Pyelectasis

INTRODUCTION

Neonatal and pediatric renal cystic diseases affect 0.44-4.1 in 10 000 children, depending on the underlying disease.[1] Clinical presentation can range from benign simple cysts, to chronic kidney disease and, in rare occasions, even rapidly progressive disease leading to kidney failure, with symptoms appearing at different ages. It includes a variety of hereditary or non-hereditary conditions.[2] In most cases, there is a genetic base, with a monogenic cause identified in 50%–70% of children with ≥two cysts and/or increased echogenicity, usually associated with systemic symptoms and extrarenal involvement.[3]

With an estimated prevalence of 1.6 per 100 000, 17q12 deletion syndrome is a rare chromosomal anomaly, with high penetrance and variable expressivity.[4] It affects the long arm of chromosome 17, with the deletion of more than 15 genes, including *HNF1B*, that plays a central role in the development of the pancreas, the kidneys, and the liver.[5] These chromosomal microdeletions can be inherited in an autosomal dominant manner or appear *de novo* (70%). Children of an affected individual have a 50% chance of inheriting the deletion.[6]

Renal phenotypes of HNF1B-associated disease are highly heterogenic, with cystic disease being the most common. Other renal phenotypes include congenital anomalies of the kidneys and urinary tract (CAKUT) and collecting system abnormalities.[7] Renal function varies accordingly, from normal (59%) to chronic kidney failure (41%), including cases requiring renal replacement therapy.[7] Extrarenal phenotypes include maturity-onset diabetes of the young

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type 5 (MODY5), pancreatic hypoplasia, hepatopathy characterized by elevated liver enzymes,[8] genital tract malformations and neurodevelopmental or neuropsychiatric disorders (58% and 27%, respectively), such as autism spectrum disorders and cognitive impairment.[9]

We report a case of a 17q12 deletion syndrome that presented antenatally with CAKUT. Genetic testing allowed us to make a diagnosis and closely monitor renal and extrarenal symptoms.

CASE REPORT

Our patient was a male, who had a prenatal diagnosis of pyelectasis detected by ultrasound at 22 weeks gestation. Amniocentesis was performed, reporting a normal karyotype.

He was born at 39 weeks gestation to a healthy couple, via vaginal route, with no perinatal complications. Birth weight was 2335 g (low for gestational age, <P10), length 48.5 cm (P15) and head circumference 36 cm (P85). The parents were non consanguineous and there was no report of renal diseases within the family. He was discharged at three days of life, with trimethoprim prophylaxis. The first postnatal ultrasound was performed at four weeks of life, with right pyelectasis of 10 mm and left of 11 mm.

Throughout the first two years of life, he was submitted to serial renal ultrasounds, for pyelectasis follow-up. Despite having reached its maximum at three months of age (10-12 mm on the right-left kidney, respectively), the dimensions began to decrease from then on, stabilizing at 8 mm when he was 19 months-old. Increased renal echogenicity was firstly identified at the age of three months. Voiding cystourethrography showed no signs of vesicoureteral reflux and MAG3 renogram revealed equally functioning kidneys and excluded obstruction of the urinary tract. He maintained trimethoprim until he was 12 months-old, with no reported urinary tract infections in the first year of life.

At 29 months-old, he presented with two *de novo* cortical cysts on the right kidney (5.7 mm and 3.5 mm diameter), and his transaminases levels began rising, reaching their maximum within 18 months (AST 215 U/L and ALT 179 U/L), raising the suspicion of cystic kidney disease. At this point, genetic tests for autosomal recessive polycystic kidney disease (ARPKD) were performed, but with a negative result. Blood pressure values remained below P90 (according to the 2017 American Academy of Pediatrics guidelines), with a systolic and diastolic of 88/53 mmHg, respectively, with normal creatinine levels (0.60 mg/dL), but elevated urea (51 mg/dL). Alpha-fetoprotein level was within normal range, as well as alpha-2 antitrypsin. Celiac disease was also ruled out, with negative screening tests. Liver ultrasound showed no abnormalities, and hepatic biopsy performed at the age of six years had no signs of fibrosis.

Renal ultrasounds started showing an increase in the number of cysts, with bilateral reach, as well as diffuse hyperechogenicity and reduction of parenchymal-sinus differentiation.

At seven years-old, he began showing mild learning difficulties at school and attention-deficit/hyperactivity disorder (ADHD). No other neuropsychiatric symptoms have emerged.

Throughout the years, he maintained normal blood pressure and elevated, but gradually decreasing, transaminases. From the age of 13 years-old, serum creatinine levels began rising gradually, going from 0.76 mg/dL to a maximum of 1.03 mg/dL in 2.5 years' time. Transient secondary hyperparathyroidism was treated with supplementation, with normalized values after a six-month course of cholecalciferol treatment. A Next Generation Sequencing (NGS) panel for cystic diseases was performed and detected 17q12 deletion syndrome. Parents were also tested afterward, but no genetic variant was found.

As part of the syndrome multidisciplinary assessment, he was referred to multiple consults. He was evaluated by a Pediatric Endocrinologist at 14-year-old and MODY5 diabetes was discarded.

An echocardiogram was performed to exclude congenital heart defects, as well as an electrocardiogram, and both were normal.

On the last appointment (15 years-old), blood pressure and glycemia remained normal and transaminase values had already normalized. At the moment, he is being treated for hypomagnesemia, firstly with 1500 mg of daily oral magnesium, later doubled to 3000 mg as he maintained hypomagnesemia, reaching a minimum value of 1.3 mg. Renal function kept worsening, with a GFR of 71 mL/min/1.73 m^2 (using Schwartz equation)and renal ultrasound showed bilateral cysts with 10mm of maximum diameter, hyperechogenicity and loss of corticomedullary differentiation.

DISCUSSION

We determined this to be a sporadic case of renal cystic disease based on 17q12 deletion syndrome.

This syndrome has a multisystemic effect and a variable phenotypic presentation, even within members of the same family. Predominant features include renal or urinary tract abnormalities (~85%), metabolic implications such as MODY5 and hyperparathyroidism (~50%), as well as neurodevelopmental and psychiatric conditions, including intellectual disabilities or behavioral disorders (~50%) like autism, autism spectrum disorder.[6]

Less frequent clinical findings encompass eye abnormalities (~40%), such as strabismus, horizontal nystagmus, congenital heart defects (20%), liver involvement spanning from asymptomatic elevation of hepatic transaminase enzyme levels to neonatal and adult-onset cholestasis (~35%) and seizures (14%).[6]

In this case, the clinical presentation included neonatal onset, with a prenatal diagnosis of pyelectasis accompanied

by hyperechogenicity noted from the early months of life, along with the development of renal cysts and elevated liver enzymes. Initially, these findings led to the consideration of ARPKD. However, the absence of hypertension and the insidious evolution of cysts cast doubt on this hypothesis. Ultimately, genetic testing yielded negative results, confirming the need to explore alternative diagnoses. In fact, structural anomalies of the kidneys or urinary tract may be found prenatally in patients with 17q12 deletion syndrome. Hence, this genetic condition should be considered as a potential hypothesis in patients presenting with CAKUT along with renal cysts.

Additionally, elevated liver enzymes are a common finding in 17q12 deletion syndrome, and have been reported in 48% of individuals in cohorts ascertained for kidney involvement, diabetes mellitus, and uterine malformations.[4,10] Liver involvement has a wide spectrum, ranging from elevation of transaminase levels to the development of cirrhosis. Our patient had no other relevant clinical or analytical findings: transaminase levels stabilized over time and other important hepatic diseases were ruled out through biopsy, such as hepatic fibrosis, a condition documented in 17q12 syndrome patients.[11]

Despite the absence of developmental delay or documented cognitive impairment, he began exhibiting learning disabilities during elementary school, which were attributed to ADHD.

Remarkably, case reports have documented instances of neurodevelopmental manifestations of ADHD in patients with 17q12 deletion syndrome, suggesting that this feature is part of the syndrome, instead of an unrelated condition. Overall, approximately half of individuals with the 17q12 deletion exhibit some degree of learning disability.[12] Additionally, some studies have found a broader spectrum of need for special support, ranging from mild to moderate delay. Tested IQs have been in the 50-85 range, but can vary widely.[13] Other neuropsychiatric disorders, such as autism spectrum disorder, schizophrenia or bipolar disorder have also been reported in association with the syndrome.

From a metabolic perspective, hyperparathyroidism, found in more than half of tested patients in some studies, was promptly identified and managed with cholecalciferol supplementation.[14,15] He was also referred to the Endocrinology department due to a higher risk of MODY5. Although MODY5 typically manifests before the age of 25 years, cases presenting later in adulthood are not uncommon. Because of this well-known risk, annual glycated hemoglobin should be performed as part of the regular screening of people with a 17q12 deletion, as well as inquiry of symptoms, such as polyuria and polydipsia. While our patient displayed no clinical signs of diabetes or abnormal insulin levels, ongoing monitoring is crucial, as the prevalence of MODY5 can reach 50% in 17q12 syndrome.[7] Regarding other less common abnormalities, cardiac evaluation was also normal.

When it comes to prognosis, our patient currently remains stable and without medication or directed treatment, besides magnesium supplementation. However, there has been a gradual and slow worsening in his kidney function. Concerning the eventual impact, while the majority of children with this syndrome maintain normal kidney function, the wide spectrum of presentation and evolution mandates a close follow-up, as the potential for progression to end-stage renal disease is non-neglectable.

In recent years, genetic tests have been a helpful tool in challenging cases, with no certain diagnosis. It has become increasingly prominent in contemporary medical practice as a go-to exam, potentially surpassing clinical criteria in diagnostic utility.

With the advent of cost-effective NGS-based panels, rapid sequencing of a large number of genes is now feasible, enabling multiple diagnoses. In the field of renal cystic diseases, where genetic etiology predominates and close surveillance is imperative for those at risk of poor long-term outcomes, integrating genetic testing early in the diagnostic process is essential.

Parents' screening tests returned negative for this mutation, making this a *de novo* case, as the majority reported in the literature. Thus, we suggest that a comprehensive genetic panel should be considered in all patients presenting with progressive renal cystic disease. Obtaining a definitive and clear diagnosis is of major importance, as it allows us to perform less invasive exams, such as renal biopsy, and facilitates the identification of potential extra-renal manifestations necessitating further evaluation and follow-up. This proactive approach enables the anticipation of treatment needs for potential complications, thus optimizing patient care and outcomes, not only for the patient himself but also for future offspring.

Prizes and Previous Presentations

The authors state that this case report was previously presented at *VII Congresso Hispano-Português de Nefrologia Pediátrica XLVI Congreso Espanõl de Nefrologia Pediátrica.*

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