Apnea in a Child with Autosomal Recessive Polycystic Kidney Disease and Potter’s Phenotype

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INTRODUCTION
Autosomal recessive polycystic kidney disease (ARPKD) is a condition characterized by bilaterally enlarged kidneys often diagnosed during the perinatal period. Although the presentation can differ, severe cases presenting early in infancy commonly have a “Potter” phenotype while those who present later in life have less renal involvement and more severe hepatic abnormalities including congenital hepatic fibrosis. Electrolyte abnormalities and anemia may occur in ARPKD and are also known causes of apparent life-threatening events (ALTE). The 12-month-old infant in this case had severe ARPKD with Potter’s facies and was evaluated for an ALTE and admitted to the pediatric intensive care because of apnea.

CASE PRESENTATION
A 12-month-old male infant in his usual state of health presented to the emergency department after his mother witnessed the infant “stopped breathing” and “turned blue” for approximately two minutes. The mother stated that she heard him choking and went to check on him. He was rigid, with a fixed gaze, and not breathing. After mouth to mouth resuscitation by his father, the infant started breathing again and returned to acting like his “normal self.” Upon examination by the emergency department physician, he was noted to have wide-set eyes, low set ears, and a distended abdomen.

Further history revealed that the patient was born prematurely at 33 weeks and 6 days due to oligohydramnios. Renal abdominal ultrasound was performed and demonstrated multiple small renal cysts. A diagnosis of ARPKD was made based on his clinic findings and family history of ARPKD in 2 older siblings. The patient had been on multiple anti-hypertensive medications including enalapril, amlodipine, and metoprolol for chronic hypertension as a result of his renal condition. He was admitted for work-up of an ALTE. Differential diagnoses at the time included anemia, electrolyte imbalance, a cardiac arrhythmia such as wolf-parkinson-white or long QT syndrome, seizure, and dehydration.

On the first hospital day, the patient experienced a second apneic event with accompanying laryngospasm. This event was preceded by crying after feeding. His workup included chemistry panel, cell count, EKG, echocardiogram and EEG. He was hyponatremic [sodium = 122 mmol/L], hyperkalemic [potassium = 5.9 mmol/L], and anemic with a hemoglobin and hematocrit of 7.3 g/dL and 21.1%, respectively. His calcium and creatinine were within normal limits. The results of the EKG, echocardiogram, and EEG were unremarkable, making arrhythmia and seizures less likely diagnoses.

His electrolytes imbalance is a possible mechanism for the ALTEs; however, the severe anemia in this patient, which is a well-described sequel of severe renal disease, is likely the cause of his apneic events. The remainder of the patient’s hospital course was complicated by respiratory distress that did not require endotracheal intubation and deterioration of his renal condition, which ultimately required a bilateral nephrectomy. Multiple large cysts were identified in each kidney (Figure 1).

DISCUSSION
Autosomal recessive polycystic kidney disease (ARPKD)

The etiology of the apneic events in this infant was his underlying ARPKD, resulting in end stage renal disease (ESRD) and severe anemia. ARPKD is characterized by bilateral enlargement of the kidneys and abnormalities in the biliary duct, which induces congenital hepatic fibrosis. Its incidence is 1 in every 20,000 live births. This genetic condition results from a mutation in the PKHD1 gene on chromosome 6p21.1-p12, which encodes for fibrocystin (polyductin). Based on its structure, fibrocystin is thought to be a membrane receptor, but its exact function remains unknown. Molecular abnormalities observed in ARPKD include altered ciliary function, increased sensitivity to epidermal growth factor (EGF), persistent apoptosis, and altered location of EGF receptors, Na/K-ATPase, E-cadherin,

Figure 1: Left kidney of the patient demonstrating multiple cysts.

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cathepsin B, and matrix metalloproteinase 2. An aberration in polarity causes them to be found in the apical membrane instead of the basolateral membrane. The kidney enlargement is due to radially oriented cysts, consisting of dilated collecting tubules that retain connections to the nephron.1,2

Commonly used criteria to diagnose ARPKD are ultrasound characteristics of echogenicity and enlarged kidneys with one or more of the following clinical features: 1) pathoanatomical diagnosis of ARPKD in a sibling; 2) both parents lack renal cysts; 3) evidence of hepatic fibrosis; 4) parental consanguinity.2 Usually, the degree of liver and kidney involvement are inversely proportional. Patients who present later in life often have hepatosplenomegaly and less renal enlargement. At birth, 70-80% of patients show signs of impaired renal function and have large palpable kidneys, and severe cases have oligohydramnios and the “Potter” phenotype characterized by pulmonary hypoplasia, deformities of the limbs and spine, low set ears, and wide-set eyes. Patients frequently have urine concentrating defects, hypertension, transient hyponatraemia and hepatic fibrosis. Liver involvement can result in portal hypertension, and patients have an increased risk of developing cholangiocarcinoma.1

20-30% of ARPKD neonates die from pulmonary insufficiency. The patients that survive to one year have a 10-year survival rate of 82%, but approximately 50% of them will have ESRD by the age of 10. Currently, there is no treatment to prevent or stop cyst formation. Initial treatment commonly includes mechanical ventilation to stabilize respiratory function with unilateral and bilateral nephrectomy reserved for the severe cases. Associated hypertension is usually responsive to angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). Many patients experience growth retardation and have poor feeding for which gastrostomy or nasogastric tubes and growth hormone are used. Patients who develop ESRD require dialysis or a kidney transplant.1

Autosomal Dominant Polycystic Kidney Disease (ADPKD)
While not the case in this patient, there is another type of polycystic kidney disease that has an autosomal dominant inheritance. ADPKD patients can have thousands of cysts and progressively enlarging kidneys that can measure up to more than 1500mL in combined volume (kidney volume in men is normally 404mL). ADPKD commonly presents as hematuria following abdominal trauma, and ESRD appears in the 5th decade of life.5

ADPKD occurs in every 800 live births and is a result of inherited mutations in the PKD1 gene (85% of cases), PKD2 gene (10%), or a spontaneous mutation (5%).5 PKD1 on chromosome 16p13.3 and PKD2 on chromosome 4q21 code for polycystin-1 and polycystin-2, respectively. Polycystin-1 physically interacts with polycystin-2, which is a calcium permeable channel.7 Both proteins play a role in the development of the tubules and vasculature of the kidney, heart, brain, liver, and pancreas. An abnormal PKD1 results in a larger number of renal cysts and a faster progression to ESRD at the median age of 53, which is approximately 20 years earlier than those with a PKD2 mutation.5,5

The cysts form along various segments of the nephron and are expansions of the tubules that bud off to occupy the medulla and cortex. Extra-renal manifestations include liver, pancreatic, and splenic cysts, mitral valve prolapse, and cerebral aneurysms. Patients often exhibit hypertension, pyelonephritis, hematuria, nephrolithiasis, and flank pain.1

As in ARPKD, ADPKD abnormalities include altered ciliary function, EGF sensitivity, prolonged apoptosis, and channels located to the apical membrane instead of the basolateral membrane. Additionally, the Na+/K-ATPase a and β subunits retain the fetal αβ2 complex instead of transitioning into the adult form suggesting that ADPKD somehow inhibits the maturation process.

Diagnosis of ADPKD in a patient with a family history is established by the presence of a certain number of fluid filled cysts in both kidneys. The number of cysts needed is dependent on age, as seen in table 1.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Minimum # of cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>2</td>
</tr>
<tr>
<td>30-59</td>
<td>2 in each kidney</td>
</tr>
<tr>
<td>&gt;60</td>
<td>4 in each kidney</td>
</tr>
</tbody>
</table>

Table 1: Diagnosis of ADPKD in patients with a family history of ADPKD.5

For patients without ADPKD in the family, suggesting a spontaneous mutation, the diagnosis of ADPKD is made after ruling out acquired cystic disease, tuberculous sclerosis, and ARPKD.5

Treatment is focused on the symptoms and stopping the progression of renal failure. Blood pressure should be kept <130/80mmHg in adults and <75th percentile for kids. This is preferably done with ACE inhibitors or ARBs. Screening for cerebral aneurysms is only suggested for those with a family history of stroke or aneurysms. When renal insufficiency occurs, hemodialysis is preferred over peritoneal dialysis due to increased intra-abdominal pressure and risk of abdominal hernias.5 Many patients eventually require a kidney transplant after removal of their enlarged kidneys.5 Based on pre-clinical trials, caffeine, estrogen, thyropllinc, secretin, and β-adrenergic agonists should be avoided to prevent increasing the rate of growth of cysts.5

Apparent Life-Threatening Event (ALTE)
ALTEs are events that frighten the observer with the patient experiencing any combination of the following: apnea, cyanosis, pallor, erythema, altered muscle tone, gagging, and choking. The majority of ALTEs in infants is attributed to gastroesophageal reflex disease (GERD), seizures, and lower respiratory tract infection. Child abuse can be a cause and should always be ruled out.6 The studies suggested to identify occult ALTE causes include a chest X-ray, complete blood cell count, brain neuroimaging, urinalysis, urine culture, and screening for GERD.7

CONCLUSION
In the case described here, a patient with “Potter” phenotype and confirmed ARPKD presented with two episodes of apneic events. Continued on page 8
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Patients with ARPKD may develop renal dysfunctions early on, evident by the hypertension, electrolyte imbalances and severe anemia present in this patient. In this case, the severe anemia was most likely the culprit for his apneic events, highlighting the wide spread physiologic effects of ARPKD and the need to remember the basics when caring for a medically complicated child.

REFERENCES

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