Seminars in Fetal & Neonatal Medicine xxx (2016) 1–6

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

# Chronic kidney disease in the neonate: etiologies, management, and outcomes

Jason Misurac*

*Pediatric Nephrology, University of Iowa Children's Hospital, Iowa City, IA, USA*

*Keywords:*
Chronic kidney disease
Etiology
Neonate
Preterm

SUMMARY

Neonatal chronic kidney disease (CKD) occurs with an estimated incidence of 1 in 10,000 live births, whereas the incidence of neonatal end-stage renal disease (ESRD) is about 7.1 per million age-related population. The most frequent etiologies are renal hypoplasia/dysplasia, posterior urethral valves, and other congenital anomalies of the kidney and urinary tract. Other etiologies include polycystic kidney disease, cortical necrosis, and renal vascular thrombosis. Management of CKD focuses primarily on replacing renal functions such as erythropoietin, 1,25-hydroxylation of vitamin D, electrolyte homeostasis/excretion, and, in ESRD, waste product removal. Nutrition and growth monitoring are of utmost importance, with the majority of ESRD infants requiring gastrostomy tube for nutrition. Outcomes of neonates (<31 days) started on dialysis continue to improve, with large cohort studies showing 2–3-year survival rates of 79–81%. As in other neonatal disciplines, the gestational age and size limits for safe provision of dialysis continue to decrease.



## 1. Etiologies of neonatal chronic kidney disease

Neonatal chronic kidney disease (CKD) may broadly be defined as a decrease in kidney function which manifests in the neonatal period and is longstanding or is expected to be longstanding. The incidence of neonatal CKD is difficult to ascertain, as there have been few systematic studies. Wedekin et al. retrospectively analyzed all neonates at a single center with serum creatinine >100 μmol/L (1.13 mg/dL), dividing them into acute kidney injury (AKI) and CKD cohorts. During ~5 years of study, 49 infants with CKD were identified, for an incidence of 1 in 10,000 live births in the geographical area of the study [1]. More data are available regarding incidence and etiologies of neonatal end-stage renal disease (ESRD), the most severe presentation of neonatal CKD. The ANZDATA registry showed an incidence of ESRD of 7.1 per million age-related population in infants aged 0–2 years, consistent with rates reported elsewhere [2,3]. A study of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) database identified the causes of ESRD in the modern era (2000–2012) among 98 neonates aged <31 days: (i) renal dysplasia in 28%, (ii) obstructive uropathy in 21%, (iii) reflux nephropathy in 3%, and (iv) other causes in 46% [4]. Etiologies of ESRD in neonates from a combined database study representing 40 countries and 264 patients showed that the most frequent causes of neonatal ESRD were: (i) congenital anomalies of the kidney and urinary tract (CAKUT) in 55%, (ii) cystic kidney disease in 13%, (iii) cortical necrosis in 11%, and (iv) congenital nephrotic syndrome in 6% [3].

Preterm neonates are at a higher risk of CKD for several reasons. First, they are born with a smaller complement of nephrons. Renal development begins at 5 weeks of gestation, with the first permanent nephrons appearing at about 9–10 weeks. However, >60% of glomeruli form in the third trimester, and nephrogenesis plateaus at 36 weeks [5,6]. Furthermore, nephrogenesis does not continue normally after preterm birth. Sutherland et al. demonstrated this by examining kidney tissue collected at autopsy from 28 preterm neonates with postnatal survival ranging 2–68 days. The estimated gestational age ranged 24–35 weeks, and these kidneys were compared to 32 stillborn controls matched to postconceptional age [7]. The preterm kidneys demonstrated accelerated postnatal renal maturation with a much higher proportion of abnormal glomeruli compared to kidneys from the stillborn infants [7]. Providing further evidence that nephron endowment is lower in preterm neonates, Hughson et al. showed that birth weight was directly correlated to number of glomeruli many years later in autopsy study of teens and adults without kidney disease [8].

* Address: 200 Hawkins Dr, 4019 BT, Iowa City, IA 52242, USA. Tel.: +1 319 356 7249.
*E-mail address:* jason-misurac@uiowa.edu.

http://dx.doi.org/10.1016/j.siny.2016.09.003
1744-165X/

Please cite this article in press as: Misurac J, Chronic kidney disease in the neonate: etiologies, management, and outcomes, Seminars in Fetal & Neonatal Medicine (2016), http://dx.doi.org/10.1016/j.siny.2016.09.003

Second, preterm neonates are frequently exposed to nephrotoxic medications and other risk factors for AKI. Exposure to nephrotoxic medications interrupts and impairs nephrogenesis by causing AKI. Indeed, in-vitro evidence has shown that gentamicin has direct effects on reducing nephron endowment in rats [7,9]. It is increasingly recognized that AKI frequently leads to increased risk of later development of hypertension, proteinuria, and CKD. This occurs through pro-fibrotic healing pathways during AKI recovery.

Finally, CKD is more prevalent in preterm neonates because prenatal kidney disease leads to a higher risk of preterm delivery. This may be related to oligohydramnios and the associated increase in risk for preterm delivery, or to the various syndromic causes of CKD in children, which often have extra-renal manifestations that may themselves make preterm delivery more likely.

The increased risk of CKD in the preterm neonate is neatly summed up by two recent studies. The first, a systematic review, compiled observational studies which examined the link between birth weight and the development of CKD defined as albuminuria, low estimated glomerular filtration rate (GFR <60 mL/min/1.73 $m^2$), or end-stage renal disease (ESRD). There was a significant association between low birth weight and risk of CKD at 20–50 years of age, with overall odds ratio of 1.73 (95% confidence interval 1.44–2.08) [10]. Thus, preterm delivery in itself is a risk factor for CKD development. Second is an analysis from the Chronic Kidney Disease in Childhood (CKiD) study, demonstrating that 17% of the cohort with CKD had a history of low birth weight, compared with 8% in the general population. Additionally, 40% of these children with CKD were hospitalized in the neonatal ICU immediately after birth [11].

### 1.1. Congenital etiologies of neonatal CKD

#### 1.1.1. Cystic kidney disease and renal ciliopathies

*1.1.1.1. Autosomal dominant polycystic kidney disease.* Autosomal dominant polycystic kidney disease (ADPKD) is caused by a mutation in either *PKD1* or *PDK2* [12]. Penetrance is near 100%, but disease severity is widely variable due to gene, allele, and gene modifier effects. Severe ADPKD can present in neonates or in utero and can even mimic autosomal recessive polycystic kidney disease (ARKPD) in its presentation [13]. However, most patients with ADPKD present as young adults, and the progression to ESRD is much slower than ARPKD [12]. The overall incidence is ~1 in 1000, making ADPKD the most prevalent heritable kidney disease [12]. Family history is positive in about 90% of patients, with a presumed de-novo mutation rate of 10%. The cysts in ADPKD arise from any part of the nephron, and range in size from microscopic to very large. Cyst formation is thought to occur following random somatic loss of heterozygosity, and more cysts appear gradually over time. The prevalence of hypertension in children with ADPKD is 20%, and may be present from early in childhood, even with normal renal function [14]. Negative imaging (ultrasound, magnetic resonance imaging, etc.) does not rule out ADPKD, and routine imaging or genetic testing is not currently recommended due to the lack of accepted disease-specific treatment [13,15].

*1.1.1.2. Autosomal recessive polycystic kidney disease.* Autosomal recessive polycystic kidney disease (ARPKD) is a genetic disorder caused by a mutation in the *polycystic kidney and hepatic disease 1* gene (*PKHD1*), located on chromosome 6p21 [12]. ARPKD is often identified during the prenatal and neonatal periods due to strikingly large, poorly functioning, echogenic kidneys. Kidney size is typically +2 to +4 standard deviations above the normal for gestational age, in contrast to the normal or small echogenic kidneys seen with mutations of *hepatocyte nuclear factor 1β* (*HNF1β*) [16,17]. ARPKD occurs at a frequency of 1 in 10,000 to 1 in 40,000 live births, and affects males and females equally [12].

The cysts in ARPKD are not generally visible on ultrasound or gross examination of the kidneys, and are all similar in size. They arise exclusively from the collecting tubules, and they affect all of the collecting tubules [17]. Over time, larger cysts may develop.

The severity of ARPKD ranges from ESRD at birth with severe pulmonary hypoplasia and congenital hepatic fibrosis to mildly decreased kidney function with gradual but inexorable progression to ESRD [12,18]. Overall, 14% reached ESRD by 5 years of age, 29% by 10 years, and 58% of patients reached ESRD by 20 years of age. Whereas ARPKD was once considered a uniformly fatal disease, 70% of patients now survive beyond the newborn period, and mortality in the neonatal period is most usually due to pulmonary disease [12]. More than 80% of those patients who survive the neonatal period survive beyond 10 years of age [18].

There are no known disease specific treatments to slow the progression of cyst formation in ARPKD. Hypertension is a common feature: one series of patients showed that angiotensin-converting enzyme (ACE) inhibitors were used in 82% (18/22) of patients with ARPKD, and three or more antihypertensive drugs were required in 32% (7/22) [18]. Unilateral or bilateral nephrectomy may be needed due to impingement of the abdominal compartment on the diaphragm in patients with pulmonary hypoplasia or to allow space within the peritoneum for peritoneal dialysis. However, management of an anephric infant with ARPKD and pulmonary hypoplasia is very challenging, so the decision to proceed with nephrectomy must be carefully considered. Portal hypertension due to hepatic fibrosis occurs in about half of patients who survive the neonatal period, and early involvement of hepatology is important in patients with hepatomegaly or other signs of hepatic involvement [12].

*1.1.1.3. Other renal ciliopathies.* There has been substantial and growing interest in the role of cilia in the pathogenesis of certain kidney diseases since the 1999 discovery that proteins from *Caenorhabditis elegans* (nematode worm) genes *PKD-2* and *LOV1* localize to the worm's flagellum [19,20]. Further work demonstrated that many of the genes implicated in various forms of heritable cystic kidney disease have products which localize to or interact with the primary cilia on renal epithelial cells [19]. The following heritable kidney diseases are now considered ciliopathies: ADPKD, ARPKD, juvenile nephronophthisis, Joubert syndrome, Bardet–Biedel syndrome, oro-facial digital syndrome type I, Jeune syndrome, and Meckel–Gruber syndrome [19]. A detailed review of these syndromes is beyond the scope of this article, but the importance of cilial function is illustrated by the multi-organ impact of almost all of these syndromes.

#### 1.1.2. Renal dysplasia

Renal dysplasia falls within the larger category of congenital anomalies of the kidneys and urinary tract (CAKUT). Genetic defects, lower urinary tract obstruction, and certain teratogens/drugs may cause renal dysplasia, but it is most often idiopathic [21]. By definition, dysplastic kidneys are deficient in normal renal tissue (nephrogenic zone, glomeruli, collecting ducts). Dysplastic kidneys have been characterized as having primitive tubules with surrounding metaplastic cartilage and stroma, dysmorphic vessels, and cysts [21,22]. Multicystic dysplastic kidney (MCDK) is a severe form of renal dysplasia in which the kidney is comprised of multiple cysts with no functional renal tissue [21].

CAKUT are mostly considered polygenic or non-heritable. However, recent genetic studies of CAKUT cohorts have identified a number of single genes which may lead to CAKUT [23,24]. This fits with the observations that some CAKUT segregate in family cohorts,

Please cite this article in press as: Misurac J, Chronic kidney disease in the neonate: etiologies, management, and outcomes, Seminars in Fetal & Neonatal Medicine (2016), http://dx.doi.org/10.1016/j.siny.2016.09.003