Glomerulocystic Kidney
One Hundred-Year Perspective
Jochen K. Lennerz, MD, PhD; David C. Spence, MD; Samy S. Iskandar, MBBCh, PhD; Louis P. Dehner, MD; Helen Liapis, MD

Context.—Glomerular cysts, defined as Bowman space dilatation greater than 2 to 3 times normal size, are found in disorders of diverse etiology and with a spectrum of clinical manifestations. The term glomerulocystic kidney (GCK) refers to a kidney with greater than 5% cystic glomeruli. Although usually a disease of the young, GCK also occurs in adults.

Objective.—To assess the recent molecular genetics of GCK, review our files, revisit the literature, and perform in silico experiments.

Data Sources.—We retrieved 20 cases from our files and identified more than 230 cases in the literature under several designations.

Conclusions.—Although GCK is at least in part a variant of autosomal dominant or recessive polycystic kidney disease (PKD), linkage analysis has excluded PKD-associated gene mutations in many cases of GCK. A subtype of familial GCK, presenting with cystic kidneys, hyperuricemia, and isosthenuria is due to uromodulin mutations. In addition, the familial hypoplastic variant of GCK that is associated with diabetes is caused by mutations in TCF2, the gene encoding hepatocyte nuclear factor–1β. The term GCK disease (GCKD) should be reserved for the latter molecularly recognized/inherited subtypes of GCK (not to include PKD). Review of our cases, the literature, and our in silico analysis of the overlapping genetic entities integrates established molecular-genetic functions into a proposed model of glomerulocystogenesis; a classification scheme emerged that (1) emphasizes the clinical significance of glomerular cysts, (2) provides a pertinent differential diagnosis, and (3) suggests screening for probable mutations.

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Figure 1. Glomerular cysts are traced back to the 19th century. This is the first depiction of glomerulocystic kidney in a newborn male in a pathology textbook. A, Spongolike gross appearance (size: 12.5 x 9 x 5 cm). B, Round or elongated and irregular glomerular cysts are seen microscopically. a, collecting ducts; b, dilated collecting ducts; c, cysts with glomeruli; d, glomerulus; e, large cyst (Flemming's safranin, original magnification x45).

Figure 2. Age distribution of patients with glomerulocystic kidney reported in the literature and here (bold numbers beside columns). Approximately two-thirds of cases occur in males and more than two-thirds occur before age 21 years. Abbreviations: PN, prenatal (27 weeks' gestational age to birth); *, oldest reported case (case 19).

SUMMARY OF THE LITERATURE

Among 234 cases in the literature, patients were predominantly male (62%), with ages ranging between 20 weeks’ gestational age to 78 years. There were 64 adults (23%) and approximately 168 (72%) children (Figure 2). We identified 10 cases with asymmetric, unilateral, or segmental involvement. Kidney size was available in 181 cases; 69 cases (~38%) were associated with enlarged kidneys (8 of which had sizes 2 standard deviations above the mean for age), whereas in 38 cases (~20%) the kidneys were small for age. In 50 cases (~40%) there was focal involvement and 73 cases (~60%) had diffuse involvement (123 cases used for evaluation). In 26 cases, nonspecific liver changes were reported, while 16 cases (22%) had cystic bile ducts or ductal plate malformation (72 cases used for evaluation). Table 2 shows the GCK-related conditions and syndromes and Table 3 lists the GCK-associated findings and malformations sorted by organ system. The most commonly reported cases fall under either sporadic (type V) or syndromic (type III) category, with the most common syndromic associations being tuberous sclerosis and Zellweger syndrome. Of note, syndromes with renal dysplasia are considered under obstructive GCK (Table 1). Many unusual associations, for example, neurocristopathy,1,2,7,26 neureillemoblas-tosis,26 or hypomelanosis of Ito,26,30 are considered under sporadic GCK (type V), even though some may eventually be proven hereditary (eg, hypomelanosis of Ito).

There are currently 13 GCKD cases reported with defined molecular abnormalities (type II). In many reports genetics are not clear, but there is a strong suggestion of autosomal dominant inheritance,31,32 either representing type I (GCK in PKD) or type II (GCKD). Surprisingly, we did not find a case of GCK associated with trisomy 21, which makes our case 14 the first reported. The most common reported dysmorphic feature was prognathism.26–30

We identified 5 definitive cases of GCK in the Western literature reported before 1950.36–43 The subsequent decades saw a steady increase in case reports (eg, 28 before 1970, 50 before 1990, and 62 before 2000). To our knowledge, our 20 cases in this review constitute the largest reported series.

CLINICAL MANIFESTATIONS

Glomerulocystic kidney can be divided into “early onset,” more common in neonates, and presenting with renal insufficiency44,45 and “late onset,” more common in adults, with less severe renal impairment.46–50 Early-onset GCK may follow a blastic course for several years44,45 or progress to end-stage renal disease in as short a time as 3 years.31,51,52 In adults, renal injury may be discovered incidentally, late in life;53 thus, it has been speculated that adult GCK may be more frequent than previously thought.20,45,46,49,54,55 A possible explanation for the different
clinical presentations and variability in rate of progression is that glomerular cysts may affect only a minority of the glomeruli, but the fact remains that most cases progress to end-stage renal disease.\textsuperscript{54,56,57} Other authors\textsuperscript{58} have questioned the role of acquired factors, such as superimposed glomerulonephritis, in the progression to end-stage renal disease. Bernstein\textsuperscript{9} remarked that "it remains to be determined if the different age groups and their clinical course are distinct diseases." Molecular insights into GCKD in the last decade appear to justify this remark.

Table 1. Diagnostic classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Common features</th>
<th>Subcategories</th>
<th>Key features in subcategory</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>GCK in PKD</td>
<td>PKD genes</td>
<td>ARPKD (PKHD1)</td>
<td>Inheritance pattern, age, shape, size, bilateral, Liver and or other organ cysts</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ADPKD (PKD1-3)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>GCKD = hereditary GCK</td>
<td>GCKD genes</td>
<td>ADGCKD (UMOD)</td>
<td>Inheritance pattern, and GCKD specific features</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FHVCKD (TCF2)</td>
<td></td>
<td>e.g. MODY5 and other features in TCF2 (Fig. 8)</td>
</tr>
<tr>
<td>III</td>
<td>Syndromic GCK</td>
<td>Recognized syndrome, absence of dysplasia</td>
<td>Too numerous to list (see Table 2)</td>
<td>Malformation syndrome with typical manifestations</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Localized GCK</td>
<td>Obstruction</td>
</tr>
<tr>
<td>IV</td>
<td>Obstructive GCK</td>
<td>Urinary tract abnormalities</td>
<td>With dysplasia</td>
<td>Smooth muscle collarettes, cartilage, IM (see Table 4)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Without dysplasia</td>
<td>Urinary tract abnormalities, uni- or bilateral</td>
</tr>
<tr>
<td>V</td>
<td>Sporadic GCK</td>
<td>No familial pattern</td>
<td>Ischemic GCK</td>
<td>Vascular changes, usually unilateral, age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No dysplasia</td>
<td>Drug-induced GCK</td>
<td>Bilateral, history of drug exposure</td>
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<tr>
<td></td>
<td></td>
<td>No syndrome</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>No obstruction</td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: ADGCKD, autosomal dominant glomerulocystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; FHGCKD, familial hypoplastic glomerulocystic kidney disease; GCK, glomerulocystic kidney; GCKD, glomerulocystic kidney disease, synonymous with heritable/familial GCK; GCKD (NOS), glomerulocystic kidney disease, not otherwise specified (see text); IM, immature mesenchyme; MODY5, maturity-onset diabetes of the young type 5; PKD, polycystic kidney disease; PKD1-3, ADPKD genes; PKHD1, ARPKD gene; TCF2, FHGCKD gene encoding hepatocyte nuclear factor–1β (HNF1β); Figure 8; UMOD, uromodulin, ADGCKD gene.

In adults the radiologic diagnosis of GCK is less problematic, but glomerular cysts are frequently missed because their detection is below the threshold of ultrasonography or computed tomography. Magnetic resonance imaging (MRI) is regarded as more advantageous.\textsuperscript{84} In the presence of focal, diffuse, segmental, or even asymmetrically distributed glomerular cysts, the distinction between GCK and renal dysplasia can be subtle and defined only by a thorough pathology examination, when possible.\textsuperscript{46,69–71}

PATHOLOGY

Glomerulocystic Kidney in PKD (Type I)

Polycystic kidney disease can occasionally present as GCK and the diagnosis can be easily missed. Seven of our 20 cases (35%) were diagnosed as such only retrospectively; 5 were ARPKD (cases 1–5) and 2 were ADPKD (case 6 and 7), demonstrating that PKD is the most important entity in the differential diagnosis of GCK.

ARPKD Presenting as GCK.—Classic ARPKD presents in neonates with severe acute renal failure and symmetrically enlarged kidneys, dilated collecting ducts, and congenital hepatic fibrosis. Such babies often die shortly after birth. Atypical ARPKD may occur (1) in adults, predominantly with liver instead of kidney failure; (2) in newborns, with absence of liver disease; and (3) in

Abbreviations: ADGCKD, autosomal dominant glomerulocystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; FHGCKD, familial hypoplastic glomerulocystic kidney disease; GCK, glomerulocystic kidney; GCKD, glomerulocystic kidney disease, synonymous with heritable/familial GCK; GCKD (NOS), glomerulocystic kidney disease, not otherwise specified (see text); IM, immature mesenchyme; MODY5, maturity-onset diabetes of the young type 5; PKD, polycystic kidney disease; PKD1-3, ADPKD genes; PKHD1, ARPKD gene; TCF2, FHGCKD gene encoding hepatocyte nuclear factor–1β (HNF1β); Figure 8; UMOD, uromodulin, ADGCKD gene.
newborns, with GCK and only focal collecting duct dilatation, with absence of liver disease.

A combination of the latter findings was present in 1 of our cases, that of a newborn female (case 1) who died shortly after birth from respiratory failure. Kidneys were cystic and slightly enlarged bilaterally. Histologically, glomerular cysts were present (Figure 3, A) but cysts were also seen in the medulla; these cysts were focally fusiform and suggested a tubular origin (Figure 3, B). The liver showed no ductal plate abnormality (Figure 3, C). The case was initially interpreted as "GCK," but genetic testing of tissues from the newborn and of blood from the parents established the diagnosis of ARPKD.

Typically, in ARPKD collecting tubules are elongated and lie at right angles to the renal capsule; however, oval or spherical glomerular cysts may overshadow this classic presentation. An example of ARPKD presenting as GCK is shown in case 2, that of a 10-week-old male infant born with bilateral kidney enlargement, in which essentially all glomeruli were cystic (Figure 4, A through C). Presence of dilated bile ducts in the liver strongly suggested the possibility of ARPKD (Figure 4, A [inset]). An almost identical combination was present in case 3 in which a premature (30 weeks' gestational age) female with oligohydramnios had enlarged, diffusely cystic kidneys. Sections showed numerous glomerular cysts and focally immature mesenchyme and ductal plate malformation typical of ARPKD (not shown). The diagnosis of ARPKD was confirmed via genetic analysis in both of these cases.

In ARPKD, kidneys are typically enlarged bilaterally but any combination of size and laterality, even unilateral agenesis or segmental cysts, have been reported.

Case 4 is an example of such; an 11-day-old newborn female presented with asymmetric kidney enlargement, hepatomegaly, and cortical glomerular cysts. Subsequent immunohistochemistry and histochemical staining allowed recognition of elongated medullary cysts as being of tubular origin (Figure 5), and liver sections revealed congenital hepatic fibrosis. This case illustrates that cystic involvement of the medulla in GCK is a helpful diagnostic feature that should raise the possibility of ARPKD. Nonetheless, absence of medullary cysts does not exclude the possibility of ARPKD, as seen in case 5, that of a 27-week-old male twin who died shortly after birth. The predominant cortical distribution of glomerulocysts affected approximately 10% of glomeruli bilaterally. The karyotype was normal, and initially no information was available on the sibling(s) or parents; however, subsequent genetic testing confirmed the diagnosis of ARPKD, emphasizing that GCK in a newborn or infant must primarily raise the possibility of ARPKD in the differential diagnosis. Besides ARPKD, other entities that combine hepatic fibrosis with renal cysts include renal dysplasia, GCKD, early-onset ADPKD, and familial juvenile nephronophthisis. While glomerular cysts are seemingly the consequence of alterations in different and multiple developmentally regulated genes (eg, TCF2, NPHP3, TSC2), it is the presence of hepatic abnormalities that helps to formulate a differential diagnosis and narrows down potential genetic testing.

ADPKD Presenting as GCK.—There are 2 peaks in the age distribution of ADPKD: 1 at the time of birth and 1 around 40 to 50 years. In classic ADPKD, cysts are of tubular origin and typically spherical, filled with dark eosinophilic fluid. At birth, ADPKD often presents as GCK. In fact, the

| Table 2. Glomerulocystic Kidney (GCK) and Related Conditions |
| a. GCK in malformation syndromes |
| - Tuberosclerosis |
| - von Hippel-Lindau disease |
| - Otofaciodigital syndrome, type 1 (OFD1 or Papillon-Leage–Pseudoaneurysm; Xp22.2–Xp22.3) |
| - Brachymesomelia–renal syndrome |
| - Short rib–polydactyly syndromes |
| - Asphyxiating thoracic dysphoria syndrome (Jeune syndrome) |
| - Zellweger cerebrohepatorenal syndrome |
| - Familial juvenile nephropathies (chronic progressive tubulointerstitial disease) |
| - Trisomy 18 |
| - Congenital nephritic syndrome |
| - OEIS complex |
| - MODY5 |
| - Cornelia de Lange syndrome |
| - Marden-Walker syndrome |
| - Phocomelia syndrome (Pseudoholidiomide syndrome) |
| - Smith-Lemli-Opitz syndrome |
| - Finnish type of infantile nephrotic syndrome (NPHS, nephrin, autosomal recessive) |
| b. Glomerular cysts in dysplastic kidneys |
| - Glomerular cysts in renal dysplasia associated with congenital obstruction |
| - Zellweger syndrome (autosomal recessive; see also Table 3) |
| - Meckel syndrome (cystic dysplasia of Meckel) |
| - Dandy-Walker malformation (Goldston syndrome) |
| - Asphyxiating thoracic dysphoria syndrome (Jeune syndrome) |
| - Diffuse cystic dysplasia |
| - Renal-hippatic-pancreatic dysplasia |
| - Familial renal dysplasia |
| - Glutaric aciduria, type II |
| - Short rib–polydactyly syndromes |
| - Congenital nephrotic syndrome type II (Majewski syndrome) |
| - Congenital nephrotic syndrome type I (Saldino-Noonan syndrome) |
| - Acrocephalopolycystic dysplasia (Elejalde syndrome) |
| - Chondroectodermal dysplasia (Ellis–van Creveld syndrome) |
| - Smith-Lemli-Opitz syndrome |
| - Trisomy 9 |
| - VATER association |
| - Branchio-oto-renal (BOR) syndrome (EYA1) |
| c. GCK secondary to ischemia |
| - Progressive systemic sclerosis |
| - Hemolytic uremic syndrome |
| - Henoch-Schönlein purpura |
| - Systemic lupus erythematosus |
| - Nephrotic syndrome |
| - Nephritic syndrome (mesangial glomerulonephritis) |
| - Wegener granulomatosis |
| - Siøgren syndrome |
| - Thrombotic renal vascular lesion |
| - Renal vascular disease |

Abbreviations: MODYS, maturity-onset diabetes mellitus of the young; OEIS, omphalocele-exstrophy-imperforate anus-spinal defects; TCF2, developmentally regulated genes (eg, corticosteroids, lithium) are excluded (see text; eg, case 14). In contrast, primary GCK is either GCK disease or sporadic (same as nonsyndromal) GCK; some authors list obstruction under “secondary category.” |

Entities listed under ischemia share autoimmune-inflammatory, nephrotic, and postinflammatory components; however, ischemia can be viewed as the overriding pathomechanistic principle.
glomerular cysts are the most common feature of early-onset ADPKD. Although some authors estimated that about 50% of presumed GCK diagnoses described in infants are examples of early-onset ADPKD, however, not all cases of early-onset ADPKD are predominantly glomerulocystic and genetic heterogeneity, mutation position in, for example, PKD1 modifier genes, as well as environmental factors, account for the substantial variability of manifestations. Notably, hepatic abnormalities of the “ductal plate type” affect 10% of infants with ADPKD and about 10% of ADPKD cases are due to new mutations. Therefore, if glomerular cysts are encountered, careful assessment and evaluation via genetic counseling is recommended to exclude ADPKD. This is illustrated in the case of a 3-year-old boy (case 6) who presented with bilaterally enlarged kidneys interpreted as “infiltrative masses” consistent with Wilms tumor (Figure 6, A). After failure of the condition to respond to chemotherapy, a subsequent renal biopsy revealed GCK (Figure 6, B). Genetic counseling revealed ADPKD with intrafamilial variability, a known feature of ADPKD. Although the exact mutations in case 6 are currently unknown, it was the pathologic examination that triggered the diagnosis in this family.

In our experience, glomerular cysts can be readily found in adult ADPKD, but the typical case poses few diagnostic difficulties. For all practical purposes, absence of tubule-derived cysts virtually excludes the possibility of classic ADPKD, but not the genetic predisposition. This is exemplified by case 7.

Case 7 is that of a 68-year-old woman who presented with chronic renal failure, hypertension, and history of renal cell carcinoma treated with partial nephrectomy of the left kidney. Both kidneys were moderately enlarged (Figure 7, A) but neither liver/pancreatic cysts nor brain or skin lesions were present. Sections revealed numerous glomerular cysts, multifocal smooth muscle proliferation, and thick-walled vessels within cyst walls and in the renal parenchyma (Figure 7, B). In addition, there were focal micropapillary epithelial proliferations with abundant eosinophilic fluid within some of the cysts (presumably derived cysts) that virtually excludes the possibility of classic ADPKD, but not the genetic predisposition. This is exemplified by case 7.

Table 3. Glomerulocystic Kidney–Associated Findings by Organ System

<table>
<thead>
<tr>
<th>Hepatobiliary and gastrointestinal</th>
<th>12, 146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular adenoma</td>
<td>19, 146</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>3, 516</td>
</tr>
<tr>
<td>Hepatic cysts</td>
<td>10, 46</td>
</tr>
<tr>
<td>Hepatic cysts in combination with congenital hepatic fibrosis</td>
<td>17</td>
</tr>
<tr>
<td>Intrahepatic biliary dysgenesis and similar lesions</td>
<td>16, 201, 316</td>
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<tr>
<td>Anagenesis of gallbladder</td>
<td>16, 194</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td>16</td>
</tr>
<tr>
<td>Colonic anagenesis</td>
<td>16</td>
</tr>
<tr>
<td>Accessory spleen</td>
<td>1, 273</td>
</tr>
<tr>
<td>Abdominal visceral transposition</td>
<td>273</td>
</tr>
</tbody>
</table>

Genitourinary

| Obstructive uropathy               | 31, 293 |
| Uterus duplex                     | 16, 194 |
| Double or distorted collecting system | 161 |
| Megacystis-megaureter syndrome     | 26 |
| Renal dysplasia                   | 274 |
| Hypoplastic kidneys               | 161 |
| Pelvic kidney                     | 271 |
| Cryptorchidism                    | 11 |
| Atypical cysts and acquired renal cystic disease | 122 |
| Glomerulonephritis                | 49 |
| Mesangioproliferative glomerulonephritis | 49 |
| Type I tubular renal acidosis     | 321, 322 |
| Glutaric aciduria type II         | 11 |
| Olignephronia (olignephronic hypoplasia/oligomeganephronia) | 324 |
| Congenital abnormalities of the kidney and urinary tract | 105 |
| Atypical familial juvenile hyperuricemic nephropathy | 265 |

Cardiothoracic

| Congenital heart disease          | 192, 315 |
| Hypoplasic aortic arch            | 161 |
| Coarctation of the aorta          | 273 |
| Patent ductus arteriosus          | 161, 315 |
| Patent foramen ovale              | 92, 290 |
| Double mitral valve               | 61 |
| Atroventricular canal malformation/completely atroventricular canal | 9 |
| Lung hypoplasia                   | 11 |
| Rhombomandria (± tuberous sclerosis) | 85, 88 |
| Hypertrophic (± obstructive) cardiomyopathy | 26, 327 |
| Pentalogy/tetralogy of Fallot    | 278 |

Table 3. Continued

<table>
<thead>
<tr>
<th>Musculoskeletal and multiple malformations</th>
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<tbody>
<tr>
<td>Prognathism</td>
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<td>Facial clefts</td>
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<tr>
<td>Orofaciodigital syndrome type I (X-dominant; Table 2)</td>
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<tr>
<td>Brachymesosomella-renale syndrome</td>
</tr>
<tr>
<td>Short rib-polydactyly syndrome (Majewski type; autosomal recessive)</td>
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<tr>
<td>Cerebrohepatorenal syndrome (Zellweger syndrome)</td>
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<tr>
<td>Interstitial fibrosis and horseshoe kidney</td>
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<tr>
<td>ARC syndrome</td>
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<tr>
<td>CNS/brain</td>
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<tr>
<td>Hydrocephalus</td>
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<tr>
<td>Aneurysms of cerebral arteries (~10%)</td>
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<tr>
<td>Agenesia of olfactory bulbs</td>
</tr>
<tr>
<td>Retinitis</td>
</tr>
<tr>
<td>Retinal hypoplasia</td>
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<tr>
<td>Mitochondrial disease (mainly affecting the nervous system)</td>
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<tr>
<td>Necrotizing encephalomyelopathy</td>
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<tr>
<td>Subacute necrotizing encephalomyelopathy (SNE; Leigh disease)</td>
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<tr>
<td>Pearson syndrome</td>
</tr>
<tr>
<td>Leukoencephalopathy, hearing loss (case 8; MTND5 ± GCKD?)</td>
</tr>
</tbody>
</table>

Abbreviations: ARC, arthrogryposis renal dysfunction cholestasis syndrome; CNS, central nervous system; GCKD, glomerulocystic kidney disease; SNE, subacute necrotizing encephalomyelopathy (Leigh disease).
Figure 3. A, Glomerular cysts in case 1; arrows indicate cysts with vascular tufts. B, Elongated (medullary) cysts (similar to epithelial membrane antigen in Figure 5). C, Liver is normal (hematoxylin-eosin, original magnifications ×10 [A], ×20 [B], ×63 [C]).

Figure 4. Autosomal recessive polycystic kidney disease presenting as glomerulocystic kidney (case 2). A, Diffuse cortical involvement. Inset, biliary dysgenesis (hematoxylin-eosin, original magnifications ×4 and ×40 [inset]). B, Immunofluorescence: PGP 9.5 (red), Dolichos biflorus agglutinin (green), Hoechst 33258 (blue); arrows indicate vascular tufts (original magnification ×20). C, Parietal epithelium and proximal tubules; arrows indicate vascular tufts (PAX2 immunohistochemistry, original magnification ×20).

Figure 5. Epithelial membrane antigen immunohistochemical staining for distal tubules and collecting ducts highlights cylindrical cysts; asterisk indicates tortuously dilated tubular cyst that simulates glomerular cysts (case 4) (original magnification ×20).
genesis of GCK, more significant aspects exist for pathologists. It is important to (1) raise the possibility of an underlying heritable disease and (2) initiate a genetic workup that includes entities in the differential diagnosis of GCK.

**Hereditary GCK Synonymous With GCKD (Type II)**

From the start, hereditary GCK was thought to be an autosomal dominant disorder. Some authors related the dominant pattern of inheritance to ADPKD presenting with glomerular cysts. This notion was supported by the finding of intrahepatic anomalies similar to ADPKD in 10% of GCKDs. Bernstein suggested that GCKD is an allelic disorder of classic ADPKD; however, multiple linkage studies have excluded PKD1 and PKD2 as causative for ADGCKD. Likewise, a murine cystic kidney locus (jck) was excluded via linkage markers in the human homologues. Human molecular genetic studies have redefined GCKD as an autosomal dominant trait, distinct from ADPKD. For example, Collins et al demonstrated an 11.1-cM telomeric interval to marker D11S909 in the same cohort as originally reported by Sharp et al. Currently, GCKD encompasses ADGCKD due to uromodulin mutations and “familial hypoplastic GCKD” due to TCF2 (HNF1β) mutations. Although several reference laboratories offer TCF2 (HNF1β) testing (typically listed as RCAD [renal cysts and diabetes]), routine diagnostic testing is currently not available.

**Autosomal Dominant GCKD.**—Autosomal dominant GCKD was first described by Rampoldi et al who reported it in a family segregating ADGCKD, with mutations in the UMOD gene encoding uromodulin (previously known as Tamm-Horsfall protein). A missense mutation, 943T>C transition in the UMOD gene, was predicted to result in a cysteine-to-arginine substitution at position 315 (C315R). This finding, in combination with an absence of TCF2(HNF1β) mutations, places ADGCKD in the category of “uromodulin disorders,” which also include autosomal dominant medullary cystic kidney disease (MCKD) types 1 and 2 (MCKD1, Mendelian Inheritance in Man [MIM] 174000; and MCKD2, MIM 603860, respectively) and familial juvenile hyperuricemic nephropathy (MIM 162000). Within the family of uromodulin disorders, more than 30 different mutations have
been described and 28 were found in exon 4, suggesting a "hot spot." Sequencing of UMOD exon 4 has been proposed as a preliminary diagnostic test for patients with this phenotype. However, it remains to be determined if other genetic abnormalities segregate with ADGCKD, as indicated by markers on chromosome 11. Nonetheless, ADGCKD represents 1 of the entities for which the term glomerulocystic kidney disease is deemed appropriate. Kidneys in ADGCKD are either hypoplastic, enlarged, or normal size. There are currently only 3 documented cases of GCKD (UMOD), which most likely underrepresents the true proportion of patients with UMOD mutations who have glomerulocystic kidneys. While studies are under way to determine this proportion, this finding reiterates the importance of morphologic recognition of glomerular cysts.

**Familial Hypoplastic GCKD.**—This is the second familial GCK for which the term glomerulocystic kidney disease is applied. This entity is linked to heterozygous mutations in the TCF2 gene, encoding for HNF1β. The syndrome is also known as familial hypoplastic GCKD (MIM 137920), renal cysts and diabetes syndrome (RCAD), or familial hypoplastic GCK. In addition to small kidneys with irregular enlarged collecting systems or absent calices, and occasional Müllerian tract malformations in females, affected families also have maturity-onset diabetes mellitus of the young (MODY5; MIM 604284). The clinical tetrad with an example of a MODY family tree is shown diagrammatically in Figure 8. The original reports provide evidence that the familial hypoplastic GCKD is associated with heterozygous mutations in the TCF2 gene, and it is noteworthy that individuals without hypoplastic kidneys do not harbor such mutations. In excess of 40 different mutations have been identified in the TCF2 gene, with most in the first 4 exons, particularly in exon 2. Different mutations in TCF2 may contribute to the morphologic diversity of renal abnormalities. There is great variation in both the frequency and geographic occurrence of the described mutations, suggesting the need for careful clinical analysis before recommending molecular testing.

**GCKD (Not Otherwise Specified).**—This group encompasses cases due to new mutations that do not fall in the above categories and is designated GCKD not otherwise specified (Table 1). Case 8 is that of a 12-year-old girl who initially presented with autoimmune hemolytic anemia, diabetes mellitus, and leukoencephalopathy. A renal biopsy revealed diffuse glomerulocystic change and the PKD workup was initiated but was complicated by the fact that the girl was adopted. She developed repeated urinary tract infections and presented most recently with fever, emesis, and flank pain. Other pertinent findings included atrial septal defect, bilateral hearing loss, recurrent middle ear infections, hypothyroidism, and malignant hypertension. Full bidirectional sequencing of the longest open reading frame of PKHD1 and TCF2 genes showed no pathogenic alterations, but mitochondrial genome sequencing showed a heteroplasmic uncoupling mutation in the mitochondrially encoded NADH dehydrogenase 5 (MTND5) gene at position 14091 (14091A>T) resulting in K585N (lysine-to-asparagine substitution at position 585). This mutation is most likely related to the girl’s hearing loss as modifier roles for MTND5 and MTND mutations have been reported. Interestingly, 1 previously reported case of Pearson syndrome associated with renal cortical cysts and focal glomerulocystic change showed a 3.5-kilobase MTND5 deletion. The significance of these MTND5

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mutations in the context of GCK is unknown and the case could be assigned to the syndromic GCK group. Nevertheless, ciliary (dys)function and hearing (loss), as well as a multitude of other conditions are intimately linked, and this case may provide an interesting starting point to explore new mutations causing GCKD, currently listed under GCKD, not otherwise specified, in our classification.

**Syndromic GCK (Type III)**

**Definition.**—If glomerulocystic kidneys occur as a component of a known and phenotypically well-characterized entity without dysplasia, the term syndromic GCK is appropriate (dysplasia carries distinct clinical significance and warrants classification as GCK type V [see below]). At least 43 syndromes have been reported in association with GCK and the extended list of syndromes appears at first glance to be heterogeneous; however, commonalities are present (Table 2). Importantly, many of the diseases are multiorgan genetic diseases, the most common of which is tuberous sclerosis.

**GCK in Tuberous Sclerosis.**—Tuberous sclerosis is a hamartomatous autosomal dominant syndrome leading to overgrowth of indigenous cells or matrix components in various organs (tubers). Typically, it presents in infancy with cardiac rhabdomyomas or as bilateral cystic kidney disease. In some cases, the cystic kidneys are composed predominantly of glomerular cysts, which are recognized as part of the hamartomatic syndrome, but are infrequently documented on imaging studies. We present a unique case diagnosed by MRI of the retroperitoneum of a 34-year-old woman (case 9) in the course of an infertility evaluation. The MRI showed subcapsular cortical cysts bilaterally (Figure 9, A). Hyperintensity in the T2-weighted images, in the absence of T1-weighted enhancement (after gadolinium), excluded renal masses. Subsequently, the patient had a twin pregnancy, during which an enlarging renal mass was identified in the left upper pole that proved to be an angiomyoma (Figure 9, B). One of the twins had a cardiac mass detected in utero, which was resected after birth and was diagnosed as a rhabdomyoma and tuberous sclerosis. In this case, tuberous sclerosis in the mother was missed and subcortical renal cysts were interpreted as GCK on the basis of the imaging findings.

Both tubular and glomerular cysts occur in tuberous sclerosis, are asymptomatic at birth (or for life), and vary in size and distribution. The lining of the glomerular cysts in tuberous sclerosis is cuboidal or hyperplastic, with a resemblance to proximal tubular epithelium. Although not specific, the presence of hyperplastic epithelium within glomerular cysts should raise suspicion for tuberous sclerosis and/or ADFPKD. Tuberous sclerosis should also be considered in the differential diagnosis of GCK in neonates. The cysts may be unilateral or localized in older children and adults and may coincide with left-sided cardiac rhabdomyomas or splenic hemangiomas. The presence of cutaneous angiofibromas is not mandatory in this young age group, since these may appear years after other lesions have developed.

In addition to tuberous sclerosis, we also identified GCK in trisomy 21 (Down syndrome) and prune belly syndrome, undoubtedly well-recognized syndromic entities. The presence of dysplasia in these cases led us to emphasize this critical finding by classifying such cases into obstructive GCK (type IV; see below).

Taken together, the diagnosis of syndromic GCK should be made to reflect and emphasize extrarenal manifestations of well-established entities with significant clinical implications such as tubers, even when the underlying syndrome is not clinically apparent at the time (case 9).

**Localized GCK.**—Definition.—Unilateral or segmental GCK.

In general terms, unilateral (localized) renal cystic disease is reported mainly as a radiologic diagnosis. In many cases the contralateral kidney contains cysts that may be below detection threshold. Nevertheless, its distinction from polycystic kidney disease is based on absence of family history, absence of hepatic cysts, asymmetrical presentation, and small kidney size. Bisceglia and Creti reported a rare glomerulocystic variant of localized cystic kidney disease. The differential diagnosis includes hygroma renalis (lymphangioma), vascular ischemia, and tuberous sclerosis. Although GCK is usually bilateral, 3 unilateral cases and 1 segmental case are reported in the literature. It is noteworthy that all but 1 of these cases occurred with tuberous sclerosis (synonymous with syndromic GCK). The fourth case was associated with neonatal ADPKD. Interestingly, the genes TSC2 and PKD1 that cause these 2 diseases lie immediately adjacent to each other on chromosome arm 16p and a contiguous gene syndrome has been described.

Although localized cystic kidney disease is reported as a separate entity, there are strong indications for a genetic basis. We have thus preliminarily placed localized GCK under the syndromic category (type III). More importantly, the presence of glomerular cysts in unilateral localized cystic kidney disease emphasizes the complexity of disease associations in the rarest of all cases, which is the unilateral/segmental GCK.

**Obstructive GCK (Type IV)**

**Definition.**—Glomerulocystic kidney associated with renal dysplasia or urine flow obstruction without renal dysplasia in the absence of a heritable condition.

The rationale for this combination is that most cases of GCK with urine flow obstruction will have evidence of renal dysplasia, if diligently sought. Moreover, renal dysplasia is most frequently a nonheritable condition (with very few exceptions).

Renal dysplasia is by definition the histologic evidence of smooth muscle collarettes, primitive ductlike structures, or islands of cartilage (found in approximately 30% of cases). Numerous causes of dysplasia are known; however, obstruction during embryogenesis appears to be the common denominator. Although obstruction is common in adults, dysplasia is only seen in newborns or children. This indicates a certain developmental potential as a prerequisite for renal dysplasia, reflected in the immature mesenchymal components seen microscopically.

Overall, renal dysplasia is a common finding in GCK and in our series was the second most frequent diagnosis after PKD. Dysplastic kidneys are often cystic and represent an important differential diagnosis of GCK, known as multicystic dysplastic kidney (MCDK).
Bilaterality does not exclude MCDK; however, MCKD is usually unilateral and compatible with life unless the contralateral kidney is impaired or absent. In our cohort, we saw a 22-week-old male infant with right-sided renal aplasia (case 10) and glomerular cysts in the left kidney along the nephrogenic zone (Figure 10; nephrogenic rests may be present in approximately 5% of cases. In some cases, an atretic ureter may accompany an atrophic kidney with minimal renal parenchyma. Case 11, that of an 11-day-old newborn male, is such an example, with findings of disorganized mesenchyme on the left side (Figure 11). Additional sections revealed additional pathognomonic features of renal dysplasia.

Figure 10. Subcapsular glomerular cysts in early metanephric kidney (midgestation; case 10) (hematoxylin-eosin, original magnification ×10).

Figure 11. Obstructed kidney (case 11) with disorganized parenchyma (hematoxylin-eosin, original magnification ×20).

Figure 12. A, Bilateral subcapsular cysts (“whole mount,” scale bar: 0.5 cm). B, Glomerular cysts in varying shapes (case 12) (hematoxylin-eosin, original magnification ×10).

Figure 13. Prune belly syndrome (case 13). A, Cystic kidney (ultrasonography). B, Gross appearance (scale bar: 1 cm). C, Whole body x-ray in prune belly syndrome. D, Giant glomerular cysts; arrow indicates vascular tuft. E, Focal mesenchymal collarettes found in the medulla (hematoxylin-eosin, original magnifications ×10 [D], ×40 [E]).
Renal dysplasia and GCK may occur as part of a well-recognized syndrome or sequence. We have seen 3 cases of syndromic GCK for which careful review showed features of renal dysplasia. In this setting, the finding of dysplasia should make one question the presence of obstruction. For example, case 12 was that of a 2-day-old newborn male with Potter sequence (respiratory failure secondary to oligohydramnios and typical facial features). Both kidneys had glomerular cysts with the entire spectrum of shapes and tuft configurations (Figure 12, A and B). In addition to cortical glomerular cysts, primitive tubules and mesenchymal collarettes were present focally (not shown). Although we were not able to demonstrate

Abbreviations: AAA, abdominal aortic aneurysm; AIHA, autoimmune hemolytic anemia; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; BKE, bilateral kidney enlargement, defined as >1.5 normal size for age; BUD, bilateral ureteral dilatation; CH, clinical history; C/M, cortical and medullary cysts; CHD/PM, ductal plate malformation/congenital hepatic fibrosis; EMH, extramedullary hematopoiesis; G/C, genetic counseling/cytogenetics; GCKD, glomerulocystic kidney disease; GCKDm, mitochondrial mutation in setting of GCKD; HIE, hypoxic ischemic encephalopathy; HMD, hyaline membrane disease; IM, immature mesenchyme; KT, karyotype; L, left; LE, leukoencephalopathy; lob., lobulation; MRI, magnetic resonance imaging; N/A, not available for review; OH, oligohydramnios; PBS, Prune belly syndrome; PN, partial nephrectomy; POC, products of conception; PUV, posterior urethral valve; R, right; RAS, renal artery stenosis; RCC, renal cell carcinoma; RD, respiratory distress; SMP, smooth muscle proliferation; TSC, tuberous sclerosis; UKE, unilateral kidney enlargement; UTI, urinary tract infection; wga, weeks gestational age; "WT", initial presentation with infiltrative masses interpreted as Wilms tumor; --, not available.

1 No evidence of elongated medullary cysts.
2 Patient declined genetic testing.
3 Patient has mitochondrial disorder in the absence of classical TFC2 or PKHD1 mutations.

Renal dysplasia and GCK may occur as part of a well-recognized syndrome or sequence. We have seen 3 cases of syndromic GCK for which careful review showed features of renal dysplasia. In this setting, the finding of dysplasia should make one question the presence of obstruction. For example, case 12 was that of a 2-day-old newborn male with Potter sequence (respiratory failure secondary to oligohydramnios and typical facial features). Both kidneys had glomerular cysts with the entire spectrum of shapes and tuft configurations (Figure 12, A and B). In addition to cortical glomerular cysts, primitive tubules and mesenchymal collarettes were present focally (not shown). Although we were not able to demonstrate urinaiy tract obstruction, the finding of renal dysplasia is indicative of early in utero disturbance of nephrogenesis.

Case 13 is similar and is that of a 6-week-old male infant who had hyperechogenic kidneys (Figure 13, A), which were bilaterally enlarged at birth (780 g) (Figure 13, B). There was also absence of abdominal musculature (Figure 13, C), hydronephrosis, and intra-abdominal undescended testes. This classical constellation is known as prune belly syndrome but is also reported as ’’triad,’’ Eagle-Barrett,143 Obrinsky,144 and Fröhlich syndrome.145 The infant died at 4.5 months because of respiratory insufficiency. Diffusely cystic kidneys (Figure 13, B) and a dilated bladder were present at autopsy; however, an
anatomic obstruction was not found and there was no associated liver disease. Microscopically, a substantial number of cysts had diminutive glomerular tufts (Figure 13, D), and mesenchymal collarettes surrounding tubules were focally found in the medulla (Figure 13, E).

Case 14 is a term newborn male who died on the first day of life due to respiratory complications. At autopsy, cardiomegaly (with patent ductus arteriosus), hyaline membrane disease, and hydrenephrosis of the right kidney were present. The normally sized kidneys were glomerulocystic with bilateral peritubular collarettes, diagnostic of renal dysplasia (not shown). The adrenal glands showed findings suggestive of transient neonatal myeloproliferative syndrome, usually associated with trisomy 21. Cytogenetics confirmed the diagnosis of the latter condition (Table 4). Although several cases of GCK with other trisomies have been reported, it seems unlikely that this represents the first case of GCK occurring in the setting of Down syndrome. However, to our knowledge, such has not been reported.

All 3 cases were diagnosed as obstructive GCK with dysplasia to emphasize the underlying, nonhereditary problem (eg, intrauterine obstruction). It should be emphasized that urine flow obstruction may not be apparent pathologically in all cases and/or the diagnostic features of renal dysplasia may be subtle or very focal. When these correlates are absent, we suggest additional dissection and extra sectioning of the kidney; radiologic (re)evaluation, if available, is often helpful.

We have seen a 2-day-old newborn male with hyaline membrane disease (case 15) and a 9-week-old male infant with hypoxic ischemic encephalopathy (case 16), both with bilateral kidney enlargement found at autopsy. In both cases, histologic analysis was essentially identical and remarkable for glomerular cysts (20% and 30%, respectively) without dysplasia. In these cases, thorough gross examination and review of available imaging studies are paramount. In case 15, MRI was helpful in identifying ureteral dilatation. In case 16, we were able to find gross evidence of posterior urethral valves. Subsequent additional sections were helpful in case 15 and demonstrated small islands of primitive tubules, focally surrounded by undifferentiated mesenchymal cells, diagnostic of renal dysplasia. In the absence of immature mesenchymal component in case 16, we diagnosed obstructive GCK without dysplasia (Table 4).

Analogous to ARPKD, hepatic findings are also helpful. Although in most cases liver findings are normal (cases 13, 15, and 16) or nonspecific (cases 10 and 12), many exceptions exist. The most important differential diagnosis is renal-hepatic-pancreatic dysplasia (RHPD) caused by NPHP3 mutations. The latter condition represents a most difficult problem, namely when renal dysplasia is the kidney abnormality within a distinct heritable condition. For example, multicystic kidneys erroneously called MCDDs were proven to be examples of GCDD instead. In very few of the familial cases with TCF2 mutations (syndromic with familial hypoplastic GCDD), abnormalities included renal dysplasia as well as grossly cystic kidneys with glomerular cysts. The typical inheritance pattern and associations, for example, maturity-onset diabetes of the young (MODY5), severe pancreatic hypoplasia, or pylorocystic abnormalities can be very helpful in this setting (Figure 8). Such rare cases should be designated as “GCK” with the complete differential diagnosis, until genetic counseling and testing allows definitive assignment to a specific type.

The obvious “grey zone” when encountering GCK and dysplasia is reflective of the complexity of either phenotype. Currently, there are at least 17 syndromes reported to show glomerular cysts in dysplastic kidneys (Table 2); in all reviewed cases, an obstructive component was present. Although, for some of the entities, candidate genes for the underlying syndrome are emerging (EYA1 or established (NPHP3)), at this point the genetic basis for dysplasia evolves around TCF2, PAX2, and uroplakin2(140,141) and requires a more systematic approach. However, the finding of dysplasia in nonheritable GCK perhaps indicates a common pathogenesis (eg, TCF2; see below). From a diagnostic perspective, obstructive GCK represents the principal entity in the differential diagnosis after heritable conditions are excluded.

**Sporadic GCK (Type V)**

**Definition.**—In the absence of (1) a recognizable pattern of inheritance, (2) diagnostic features of renal dysplasia, (3) obstruction, and (4) syndromic associations, cases of GCK are assigned to the sporadic type, which may be the most commonly reported class (Tables 1 through 3).

Case 17 is that of an 8-month-old male infant who had a complicated postnatal course with bronchopulmonary dysplasia, retinopathy of prematurity, sensory hearing loss, and seizures (likely related to the history of meningitis), severe gastroesophageal reflux, and bilateral inguinal hernias. Prominent subcapsular macrocytes were visible grossly and the renal parenchyma had a spongblike appearance (Figure 14, A and B). The kidneys were slightly enlarged. Importantly, the classic cylindrical medullary cysts of ARPKD were absent; however, glomerular cysts were apparent, consistent with GCK (Figure 14, C). The family history revealed that several members had neurodevelopmental delay but no history of renal disease or other features suggestive of type I or II GCK. The karyotype was normal and in the absence of diagnostic features of renal dysplasia or obstruction, this case was assigned to the sporadic category. Cases such as this may, upon further study, be shown to be due to gene mutations; however, to our knowledge, this case was not.

Like case 17, many cases of sporadic GCK are reported with findings of questionable relationship (eg, mobile cecum, gastroesophageal reflux). Here we suggest that this term be restricted for cases without well-discernable or well-described findings in other organs. Based on the literature review of sporadic cases, the findings indicate that 2 causes—ischemia and exposure to certain drugs—are encountered most often. Some authors refer to the latter categories as “secondary.”

**Ischemic GCK.**—Unilateral and some cases of bilateral GCK occur in the setting of ischemia, such as progressive systemic sclerosis or hemolytic uremic syndrome(20,35,156) (Table 2). Progressive systemic sclerosis is characterized by severe inflammatory narrowing of renal arteries, and hemolytic uremic syndrome is characterized by endothelial cell damage and arteriolar thrombosis. Ischemic damage is thought to cause outflow obstruction resulting in glomerular cyst formation. Examples of glomerular cysts secondary to ischemic injury are seen in cases 18 and 19. Case 18 was identified as GCK in a donor kidney of a 20-year-old man (not shown). This constellation has
previously been reported once\textsuperscript{158}; however, the genetic profile of the donor’s family remains unknown. Case 19 reports an abdominal aortic aneurysm and renal artery stenosis in a 78-year-old woman (oldest reported patient).

In both cases, despite the glomerulocystic change, the major underlying abnormality was vascular ischemia (Figure 15, A and B). It has been speculated that GCK, in general, may be caused by ischemia and subsequent...
In contrast to the subcortical region, there is little objective evidence for a causative mechanism of glomerular cyst formation. Alternative theories for so-called secondary GCK involve an immunologic insult or a combination of factors. The complexity of findings in sporadic GCK and incomplete understanding of contributing factors resulted in this questionable “etiologic” subcategorization, including secondary GCK. Although the term secondary implies a mechanistic or temporal relation and can be useful in the pathophysiologic context, we feel that, as a diagnostic category, it has little clinical meaning.

Drug-Induced GCK—The diagnostic challenge of GCK is illustrated in case 20, that of a 53-year-old woman who presented with bile duct obstruction caused by a gallstone and who was incidentally found to have numerous renal cysts bilaterally in normally sized kidneys (Figure 16). She had been treated with lithium for bipolar disorder, with resulting lithium nephropathy and the development of GCK. The main renal complications of lithium toxicity/nephropathy are glomerular in nature and include focal segmental glomerulosclerosis, interstitial fibrosis, and glomerular or tubular cysts. Cyst formation was originally reported in up to 40% of patients treated with lithium, but GCK due to lithium toxicity appears underappreciated. The mechanism of lithium-induced cystogenesis was studied in animal models. Hypotheses range from focal segmental glomerulosclerosis, interstitial fibrosis, altered enzyme function, cell cycle activation to atubular glomeruli. Nevertheless, lithium-induced GCK is sometimes missed on imaging studies (Cary L. Siegel, MD, oral communication, February 2009).

**SUMMARY OF THE 20 CASES REPORTED HERE**

We identified 20 cases from our files (Lauren V. Ackerman Laboratory of Surgical Pathology and St Louis Children’s Hospital, Washington University Medical Center, St Louis, Missouri). The demographic and salient clinicopathologic data are shown in Table 4. The patients were predominantly male (12/20) and the ages ranged from 30 weeks’ gestational age to 78 years. Five were adults, while most were children (n = 15). The percentage of involved glomeruli in our GCK cases varied widely, but most cases had greater than 50% glomerular cysts, although it is unusual to find global glomerular involvement. Two such examples were cases 2 and 10 (Figures 4, A and 10), ARPKD and renal dysplasia, respectively. Most had bilateral kidney involvement (n = 17) and 16 of 17 cases had enlarged kidneys, defined as 1.5 times the normal size for age. Unilateral cases were associated with urine flow obstruction (cases 11 and 13, prune belly syndrome), contralateral aplasia (case 10), and ipsilateral renal artery stenosis (cases 18 and 19) (Table 4). Polycystic kidney disease was the most common entity in our series and ARPKD/ADPKD was diagnosed retrospectively via genetic testing in 6 cases (1 patient declined genetic testing). The second most common condition was obstructive GCK with dysplasia, in fact, the most common entity in neonates and young children in our series (n = 6). Since genetic testing was not available for all reported cases, it remains to be determined what percentage of patients harbor UMOD or TCF2 mutations.

**Histopathology**

Glomerular cysts in general are spherical, oval, or polygonal (Figure 17, a through i) and range from less than 0.1 cm to more than 1 cm. Usually, not all cysts have a readily identifiable vascular tuft because of the diminutive nature of the nublike tuft and the plane of section through the cyst(s). Remarkably, the glomerular tuft can sometimes be seen in very large cysts (Figures 13, D and 17, l). A degenerated and/or atrophic tuft may be composed of only a few cells attached to the cyst wall in a grapelike or dotlike fashion (Figures 12, B and 17, e). The cysts may be filled with debris, minimal proteinaceous fluid (Figures 7, C and 17, g), or appear empty after processing (Figures 12, A and B, and 13, D). Occasionally, 2 or more tufts are present in a single cyst. The latter is referred to as “dysplastic glomerulus” (Figures 12, B and 17, d). Irrespective of configuration, at least 5% of the glomeruli should be found to be cystic before a kidney is designated as a GCK. A single layer of either cuboidal or,
In ADPKD it is assumed that proliferation of epithelial proliferations in GCK may represent ADPKD or tuberous sclerosis.\textsuperscript{1,85–89}

**Immunohistochemistry**

Recognition of glomerular cysts is mostly dependent on the presence of glomerular tufts; the difficulty arises when the tufts degenerate as the cysts enlarge (Figures 6, B; 12, B; 13, D; and 17, d through i). In these cases, the glomerular origin of the cysts is inapparent and the cysts may be interpreted as tubular in origin. The demonstration of the glomerular origin of the cysts is facilitated by immunohistochemistry.\textsuperscript{180,184} We have used antibodies for PGP 9.5\textsuperscript{185,186} and PAX2\textsuperscript{187} to highlight parietal Bowman capsule epithelium (Figure 4, B and C). When used in combination with the lectin DBA (Dolichos biflorus agglutinin) for proximal versus distal tubules, the panel is helpful in delineating the origin of cysts as glomerular.\textsuperscript{184,189} In a cohort of 20 cases, using Tamm-Horsfall protein (THP), Lotus tetragonolobus lectin (LTA), DBA, PAX2, and PGP 9.5, we found strong PAX2 and weak THP, LTA, DBA, and PGP 9.5 staining in most glomerular cysts\textsuperscript{188} (Figure 4, A through C). Even though no one antibody alone distinguished glomerular from tubular cysts, medullary cysts with vague cylindrical shapes may be better visualized with immunohistochemistry (eg, Figure 4, A through C represents ARPKD). For example, epithelial membrane antigen that stains collecting duct and distal tubular epithelia can reveal the cylindrical nature of medullary cysts coexisting with glomerular cysts (Figure 5). Occasionally, the epithelium of a tortuously dilated tubular cyst simulates glomerular cysts, but epithelial membrane antigen immunoreactivity establishes the tubular origin (Figure 5).

Given the size of cysts in some cases, it has been suggested that cysts in GCK may consist of multiple nephron segments.\textsuperscript{85} However, it is clear that the lack of tubular involvement is a key feature that distinguishes GCK from classic ARPKD and ADPKD in which the cysts are primarily derived from tubules.\textsuperscript{88} Absence of cysts in other organs and/or concurrent hepatic fibrosis helps exclude classic PKD.\textsuperscript{85,88,190}

**PATHOGENESIS OF GLOMERULAR CYSTS**

Glomerular cysts were originally classified as a component of polycystic kidney disease (Potter IV)\textsuperscript{4,191} associated with urinary tract obstruction.\textsuperscript{13} However, most reported GCKD cases lack demonstrable lower urinary tract obstruction.\textsuperscript{4} Although selective dilatation of the Bowman capsule remains largely unexplained, intrarenal medullary inflammation\textsuperscript{81,192} and/or intrarenal medullary obstruction during the last 10 weeks of gestation has been postulated as one mechanism.\textsuperscript{17,148} This adaptation combines (1) Virchow’s “retention” or “papillitis theory,”\textsuperscript{40} in which an interstitial inflammatory process results in tubular occlusion, with (2) the “Anlagedefehler theory” of Hanau\textsuperscript{17} in which aplasia of the papilla is thought to be the culprit. Increased pressure in the Bowman space as the cause of glomerular cyst formation is indirectly supported by electron microscopy.\textsuperscript{192} Sessa et al\textsuperscript{20} proposed that an alteration in the collagen component of the Bowman capsule may underlie the structural abnormality; however, in many of the reported cases ultrastructural alterations are lacking. Nevertheless, in some aspects, this “collagen theory” follows an older notion first proposed by Borst.\textsuperscript{192,200} The postulate is that an imbalance between epithelium and stroma results in an unregulated epithelial growth into the connective tissue. Such developmental alterations from nephrogenic blastema to glomeruli and proximal convoluted tubules may explain some of the immunohistochemical\textsuperscript{11,188} and ultrastructural\textsuperscript{11,188} variations in GCK,\textsuperscript{11,188} as well as alterations of epithelial-mesenchymal interactions.\textsuperscript{200,201} Another proposed mechanism for cyst formation is stenosis at the glomerulotubular junction.\textsuperscript{202} Although serial sectioning provides some evidence for the latter,\textsuperscript{20} recently, 3-dimensional reconstruction and image analysis have excluded stenosis/obstruction at the level of the glomerulotubular neck.\textsuperscript{203} Consequently, the original speculation that fluid and cyst formation may occur when fetal glomeruli begin to function coincides with the ingrowth of the vascular tuft. While the glomerulotubular junction is a known target in renal disease\textsuperscript{188} and regains acceptance as “atubular glomeruli,”\textsuperscript{204} the link to GCK has not been established. This is surprising given the morphologic similarity in animal models\textsuperscript{200} and in lithium nephrotoxicity.\textsuperscript{8}

Intrarenal obstruction during fetal development is a modification of the above-mentioned theory but, predominately, cortical distribution of cysts provides weak evidence.\textsuperscript{17} In ADPKD it is assumed that proliferation of the tubular epithelium, fluid accumulation, and remodeling of the extracellular matrix are the main events in the formation of cysts.\textsuperscript{17} It is possible that the same factors underlie cyst formation in GCK. Environmental factors such as intrauterine drugs (eg, gestational maternal phenacetin), toxin exposure, infections, or drugs (eg, lithium) and chemicals have all been postulated.\textsuperscript{185,186,201–205}

Although cystic kidneys with glomerular cysts in humans show remarkable resemblance to those induced by long-acting corticosteroids in rabbits,\textsuperscript{192,193,213,214} the contribution of steroids is vague in humans.

**UMOD** mutations inactivate a calcium-binding epidermal growth factor–like domain and ultrastructurally, fibrillar material accumulates in the endoplasmic reticulum.\textsuperscript{90} In combination with vitro cell culture models, uromodulin mutations have been shown to affect the intracellular trafficking through the endoplasmic reticulum.\textsuperscript{90} The pathogenic mechanism remains speculative, as uromodulin is expressed only in the thick ascending limb of the loop of Henle and the most proximal part of the distal convoluted tubule.\textsuperscript{94,96,215–217} However, in combination with the abnormal presence of uromodulin within glomerular cysts,\textsuperscript{218,219} a possible mechanism for glomerular cyst formation has been proposed as follows: tubular obstruction and subsequent reflux of prourine, containing uromodulin, into the Bowman space causes glomerular cysts.

**HNF1β, TCF2**-encoded protein, is a transcription factor of the homeodomain-containing superfamily\textsuperscript{220} with early expression in liver, bile ducts, thymus, genital tract, lung, intestine, and kidney;\textsuperscript{116} this transcription factor is involved in collecting duct and cortical mesenchyme development.\textsuperscript{113} Similar distribution of cysts in the liver and kidney suggests dysregulation of shared develop-
mentally regulated programs. Most recently, insertional mutagenesis in the homeobox gene vhnf1 in zebrafish (equivalent to TCF2-encoded HNF1β in humans) demonstrated such developmental regulation in an organ-specific manner, which involves wt1 and pax2 in the glomerulus and tubules, and more ubiquitous regulators such as shh and pdx1 in the gut. These data have been linked to ciliary motility via phenotype comparisons. The Wilms tumor suppressor protein WT1 has been implicated because ablation of splice isoforms is associated with the development of glomerular cysts in animal models. Among numerous mouse models for cystic kidney diseases, GCK is evident in 25% of aged +/jcpk heterozygotes and$jcpk$ and mm1633 genes are implicated in mouse GCK. While such animal models offer the possibility to study GCK, Sharp et al excluded GCKD disease-susceptibility genes that cosegregate with markers of the candidate intervals for the human jcpk homologue on either chromosome band 10q21 or 22q11. As previously discussed above for TCF2 and UMOD, recent molecular-genetic advances have improved our understanding of the familial GCKD variants. From evidence and speculation to implementation of molecular testing about a decade ago, our current understanding of cystic renal disease has greatly advanced in the past decade. However, the exact pathogenesis of GCK is not yet clear. An interesting mechanistic link derives from Wwtr1−/− mice, which develop cystic dilatation of the Bowman space and atrophy of the glomerular tuft, reminiscent of GCKD in humans. Wwtr1 is a 14-3-3 binding protein that regulates the activity of several transcription factors; in its absence there is loss of ciliary integrity within the epithelial kidney compartment. Although it remains to be determined whether Wwtr1 represents a candidate gene for GCKD in humans, the link from glomerulocysts—via the transcriptional modulator Wwtr1/TAZ—to ciliary dysfunction has most recently been substantiated via Glis3 signaling–deficient mice. These and other studies implicate defects in the primary cilium as a shared abnormality underlying cystic diseases of the kidney. Importantly, ciliary dysfunction links mechanical forces to cell and tissue differentiation pathways. According to this ”unifying theory of renal cystogenesis,” mutated proteins that cause renal cystic disease are expressed in primary cilia or related structures. Although many ”cystogens” remain to be charted in a similar fashion, at this time more than 20 cystoproteins have been linked to this theory, for example, via localization to primary cilia of renal tubules (nephrocystin-1, inversin/NPHP2).

References 220, 252, 258, 350, 351.

Figure 18. Synopsis of the genetic alterations underlying glomerulocystic kidney (GCK) and some known associations. Based on in silico data, the selected “locus-gene-protein-disease-associations” (vertical axis: tap to bottom) illustrate 4 of the connections (filled areas, corresponding to text) that suggest a common pathway of glomerulocystogenesis.

* Familial forms of glomerulocystic kidneys (same as glomerulocystic kidney disease or GCKD) with renal cysts and diabetes syndrome (RCAD) and maturity onset diabetes mellitus of the young (MODY5) represent a subset of familial hypoplastic GCKD (FHGCKD). Abbreviations: ADGCKD, autosomal dominant GCKD; ADPKD, autosomal dominant polycystic kidney disease; AN, adult nephronophthisis; ARPKD, autosomal recessive polycystic kidney disease; FJN or FJHN, familial juvenile hyperuricemic nephropathy; FJHNa, FJHN adult type; GCK, presenting as glomerulocystic kidney disease; IN, infantile nephronophthisis; MCKD, medullary cystic kidney disease; PKDTS, polycystic kidney disease and tuberous sclerosis; RHPD, renal-hepatic-pancreatic dysplasia.

Wwtr1 is a 14-3-3 binding protein that regulates the activity of several transcription factors; in its absence there is loss of ciliary integrity within the epithelial kidney compartment. Although it remains to be determined whether Wwtr1 represents a candidate gene for GCKD in humans, the link from glomerulocysts—via the transcriptional modulator Wwtr1/TAZ—to ciliary dysfunction has most recently been substantiated via Glis3 signaling–deficient mice. These and other studies implicate defects in the primary cilium as a shared abnormality underlying cystic diseases of the kidney. Importantly, ciliary dysfunction links mechanical forces to cell and tissue differentiation pathways. According to this “unifying theory of renal cystogenesis,” mutated proteins that cause renal cystic disease are expressed in primary cilia or related structures. Although many “cystogens” remain to be charted in a similar fashion, at this time more than 20 cystoproteins have been linked to this theory, for example, via localization to primary cilia of renal tubules (nephrocystin-1, inversin/NPHP2). The formal link between ciliopathies and human GCK is pending; however, as noted previously, 14-3-3 binding proteins are reasonable candidates. Two novel genes in ciliogenesis and cyst formation encode tumor suppressor (pVHL) and collectrin, a homologue of angiotensin-converting enzyme 2. Collectrin is transcriptionally regulated by HNF1β, implicated in familial hypoplastic GCK.
On the basis of these data, we used a comprehensive in silico approach to determine connections of different disease entities and associations (Table 2, OMIM [Online Mendelian Inheritance in Man]) with a common denominator “glomerular cyst/GCK.” In brief, mapping of involved gene–protein axis into biologic networks was performed with 2 proprietary, manually curated databases of human gene–protein interactions (Ingenuity Pathway Analysis, Ingenuity Systems, Mountain View, California; MetaCore Gene Expression and Pathway Analysis [version 4.5; GeneGo, St Joseph, Michigan]) by using “shortest pathway” and custom algorithms. Manual deconvolution of networks and interrogation with clinical entities exposed at least 4 important connections in the molecular context of GCK (Figure 18).

1. HNF1β acts upstream of PKHD1 and UMOD. The former is evidenced by an evolutionarily conserved HNF1β binding site in the proximal promoter of the mouse Pkhd1 gene and the absence of Pkhd1 transcripts in cyst-lining cells in dominant-negative tcf2 mutant mice, proving direct contribution of HNF1β via Pkhd1 to the formation of renal cysts.246 The link to UMOD and PKHD1 is supported by evidence that HNF1β acts as a tumor suppressor in chromophobe renal cell carcinogenesis.246 In cases with biallelic HNF1β inactivation, expression of PKH1 and uromodulin was turned off.246 In this context, the transcriptional network of PKD247 and the transcriptional control of PKHD1 and UMOD246,247 can be used to link the 2 recognized familial types of GCKD with ARPKD.

2. Tuberous sclerosis and ADPKD/GCK are linked on multiple levels, including genetic loci with large-scale deletions on the short arm of chromosome 16 (involving TSC2 [tuberin] and PKD1 [polycystin] (“contiguous gene syndrome”)),236 expression profile,246–251 protein–protein interaction,252 and disease associations in children253,254 and adults.255,256 The finding that tuberin is responsible for functional localization of polycystin-1323 accentuates the function of the polycystin complex as a key regulator253 in the development of renal cysts. In contrast to TSC2, mutations in TSC1 (hamartin) are typically not associated with kidney cysts, angiomylipomas, retinal hamartomas, and liver angiomylipomas.258 The latter emphasizes the known function of TSC genes as tumor suppressor genes.259-261

3. The overlapping phenotype of nephronophthisis (eg, familial juvenile nephronophthisis, medullary cystic kidney diseases, and ADGCKD) is provided via uromodulin (“uromodulin storage diseases”).94,95,263,264 Our attempts at functional clustering in canonical pathways are at this time limited because the causative gene for MCKD1 is unknown. However, high-resolution haplotyping in 16 kindred and mutational analysis of 37 positional candidates260 revealed 3 genes: a neurofilament homologue (AK000210, part of FLJ20203) with potential involvement in regulation of kidney morphogenesis,260,262; SCAMP3, a gene encoding endocytosis/membrane trafficking protein downstream of epithelial growth factor receptor260; and CCT3, a gene encoding chaperonin, for which interactions with tubulin260 and inversin (NPHP2)250 have been described. Interestingly, CCT3 and SCAMP3 have also been implicated in hepatocarcinogenesis.271 In the absence of other common links between familial juvenile nephronophthisis, MCKD, and GCK, the main cell-biologic target—ciliary function—forms the most appealing link.74,220,231 Recently, a heterozygous sequence change in the UMOD gene (149G>C: Cys50Ser), involving the first epidermal growth factor–like domain of the protein, has been reported to be associated with immature renal structures.272 This suggests a link between uromodulin storage diseases and glomerulocystic dysplasia and indicates the importance of UMOD in renal development.

4. Pathway analysis in nephronophthisis (NPHP3; renal-hepatic-pancreatic-dysplasia, RHPD)230 and GCK revealed Wnt signaling and interactions of the nephrocystins/ inversins proteins.230 This interaction of nephrocystin-3 with inversin (NPHP2) was demonstrated via direct inhibition of canonical Wnt signaling.232 The same group showed that nephrocystin-3 deficiency leads to planar cell polarity defects in Xenopus laevis (equivalent to situs inversus) and provide the link to Meckel-Gruber-like syndrome,232 abdominal visceral transposition,273 and RHPD.192 While this finding substantiates the link to ciliopathies, there is an additional facet in GCK. NPHP3 mutations that cause RHPD192,193 illuminate the pathogenesis of glomerular cysts and renal dysplasia.146 This molecular basis also partially explains liver findings in GCK.

In summary, these 4 connections appear to converge in a common pathway of glomerulocystogenesis. We do not wish to speculate on the exact molecular targets (eg, tumor suppressor genes, transient receptor potential ion channels) or altered machinery (eg, centriole/cilia), but these relationships have important diagnostic and potentially therapeutic implications.274 Diagnostically, the molecular genetic link between GCK and renal dysplasia can be viewed as one that makes renal dysplasia an overriding feature that sometimes is linked to diseases with genetic mutations (TCF2, sporadic and syndromic GCK), even

**Figure 19.** Rationale for glomerulocystic kidney (GCK) classification follows the key diagnostic questions regarding presence or absence of dysplasia, a familial pattern, syndromic findings, ischemia, and drug history. Currently, dysplasia has been described in several syndromes and in TCF2 mutations and requires exclusion of the latter and careful review of the former before assignment to type IV. The arbitrary borders between hereditary, syndromic, and acquired (dotted lines) types can be used as a conceptual framework for dysplasia in the context of GCK. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; GCKD, glomerulocystic kidney disease; PKD, polycystic kidney disease; TCF2, gene encoding hepatocyte nuclear factor-1β; UMOD, gene encoding uromodulin.
though most frequently it is not (obstructive GCK) (Figure 19).

Glomerulocystic changes were previously enigmatic conditions with little understood pathogenesis. This is now reversed because of advances in cell biology and genetics. These insights have led us to reorganize into a classification scheme some of the entities described under GCK. For diagnostic pathologists, meeting histopathologic criteria for GCK and recognizing glomerular cysts is not the end of a case. The significance of GCK lies in concrete understanding of disease associations. Adult GCK is more common than anticipated (~23%) and significant causes include ADPKD variants, tuberous sclerosis, vascular ischemia, and lithium toxicity. Irrespective of age, clinicopathologic correlations, genetic counseling, and molecular testing, when appropriate, are the only means to accurate diagnosis.

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