Glomerulocystic kidney disease in a family

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Abstract

Background. Glomerulocystic kidney disease (GCKD) is a rare renal disorder, the identity of which has long been discussed. GCKD can occur in a familial form with autosomal dominant transmission. The presence of GCKD in families affected with autosomal dominant polycystic kidney disease (ADPKD) has lent support to the hypothesis that GCKD may be an early manifestation of ADPKD. In families with hypoplastic forms of GCKD, the HNF-1β gene has recently been identified.

Methods. Three members of a family were evaluated: a girl (case 1) and her brother (case 2), who were aged 11 and 12 years, respectively, at the beginning of the study, and, subsequently, the girl’s son, when he was 4 years old (case 3). They all had mild renal insufficiency. Clinical, morphological and genetic evaluations were performed on 11 members of the family.

Results. Case 1. A mild reduction in renal length with modest dysmorphology of renal calyces and hyper-echogenic parenchyma were present when the patient was 11 years old. At the age of 29 some small renal cysts were identified, which remained unchanged over the next 8 years. Renal dysfunction remained stable. Case 2. A slight reduction in size of a hyperechogenic kidney was found. Cysts were seen at the age of 38. Renal dysfunction remained unchanged. Case 3. Kidneys were of normal size. Small cysts were found at the age of 9 years. In cases 1 and 2, histopathology was highly consistent with GCKD. In none of the cases associated pathological conditions could be identified. Haplotype reconstruction allowed the exclusion of PKD1 and PKD2 genes. No mutation of the HNF-1β gene was found.

Conclusions. The morphological data from the three cases are suggestive of GCKD. The involvement of PKD1, PKD2 and HNF-1β gene mutations was excluded.

Keywords: familial autosomal dominant; genetics; glomerulocystic kidney disease

Introduction

Glomerulocystic kidney disease (GCKD) is a rare renal disorder that occurs in both sporadic and familial forms. Its identity has long been discussed. Glomerular cysts have been observed in various renal cystic diseases, such as autosomal dominant polycystic kidney disease (ADPKD), cystic renal dysplasia and autosomal recessive polycystic kidney disease (ARPKD) [1]. Familial GCKD can be associated either with hypoplastic or normal sized kidneys. Therefore, GCKD must be diagnosed by excluding other cystic renal disorders. This can be done by identifying any associated extra-renal pathological conditions that define syndromic renal anomalies, through renal ultrasound imaging and, in non-sporadic forms, careful evaluation of other members of the patient’s family.

Previous studies have aimed to identify the genetic abnormality responsible, or at least to exclude the known genes associated with, various cystic renal diseases. The presence of genes for ADPKD, PKD1 and PKD2 has been ruled out in one Italian family [2]. A study of a large African–American family has confirmed that the active mutation of GCKD involves a genetic locus other than PKD1 and PKD2 genes or the human GCKD homologue of the mouse cystic kidney mutations described [3]. In two families with hypoplastic GCKD associated with non-insulin-dependent diabetes, a mutation in the hepatocyte nuclear factor-1β (HNF-1β) mutation has recently been reported [4].

Familial GCKD transmission is autosomal dominant. Our findings in the Italian family we describe here may help to clarify the nosographic position of the disease and define its autonomy.

Patients and methods

The index case was an 11-year-old Italian girl. All members of her family were born in a small town in the south of Italy.
The family tree is shown in Figure 1. Eleven members were characterized on a clinical basis, and DNA samples were obtained during their clinical and genetic work-up.

Case 1. Individual III-3

This girl was born in 1963. Her parents were unrelated. Her father died of renal failure due to an undefined cause at the age of 33. While his death cannot be precisely attributed to GCKD, no urinary abnormalities, hypertension or renal masses were recorded. He was not known to suffer from diabetes.

In 1974, the girl was found to have mild renal insufficiency and was referred to our Department of Pediatric Nephrology at G. Gaslini Children’s Hospital in Genoa. No bouts of fever, pain, dysuria, anaemia or growth disturbances were reported. Physical examination was normal. Blood pressure and urinalysis were normal. An i.v. urogram and an open renal biopsy were performed during her first evaluation. During periodic follow-up examinations she had regular renal ultrasound evaluations.

This woman had two children. The first is affected (case 3); the second proved to be normal on ultrasonographic and renal function examinations. During her two pregnancies, no gestational diabetes was reported. Genetic analysis was performed.

Case 2. Individual III-2

This boy was born in 1962. In 1974, following the discovery of his sister’s renal insufficiency, he underwent examination at our department. He was reported to have always been in good health. Physical examination and urinalysis were normal. Routine biochemical tests indicated that the boy had mild renal insufficiency. In 1974, an i.v. urogram and an open biopsy were performed. Ultrasonographic evaluations were made during regular follow-up examinations. From 1974 to May 2000, his renal function remained stable. Genetic evaluation was performed.

Case 3. Individual IV-1

This boy was born in 1987 after normal gestation. Mild polydipsia and polyuria were noticed during his first year of life. Examined at our centre when he was 4 years old, he showed evidence of anaemia and mild renal insufficiency. Urinalysis was normal. No hyperglycemia or glycosuria were detected. Ultrasound examinations of his kidneys were performed. A renal biopsy, performed at the age of 5 years, did not yield sufficient tissue for diagnosis. Genetic evaluation was performed.

The data on all three cases are shown in Table 1. Clinical, urographic and sonographic evaluations

Molecular analysis

Blood samples were obtained from all available family members for DNA extraction and evaluation of candidate genes. DNA was extracted using standard protocols. In order to rule out the involvement of PKD1 and PKD2 genes in the pathogenesis of GCKD, the following polymorphic markers were used: KG8, SM6, KM17, D16S664, D16S663 for the PKD1 locus and D4S1334, D4S2929, D4S1563, D4S2460, D4S414 for the PKD2 locus. These markers were amplified following methods already reported [5,6] or under standard conditions. The microsatellites were amplified by labelling one primer with a fluorescent amidite. The corresponding PCR products were loaded into an automated sequencer ABI mod. 377A (ABI, Perkin-Elmer, Foster City, CA, USA), and allele size was determined by means of Genescan software. For HNF-1β, direct gene-based mutational analysis was performed as described by Bingham et al. [4,7].

Results

Clinical, urographic and sonographic evaluations

Eleven members of the family were characterized clinically. One brother of the index case, her mother, three siblings of the father and one cousin were normal. No members of the mother’s family were available for the study.

Intravenous urogram, performed at the first evaluation of case 1 (III-3) at 11 years of age, showed a mild reduction in renal length with a modest dysmorphology of renal calyces. No additional further i.v. urograms were performed. Renal sonography revealed hyperechogenic parenchyma. At 29 years of age, some renal cysts of 0.6–0.8 mm diameter were identified in the cortex of the right kidney (Figure 2). During follow-up, both kidneys remained slightly hypoplastic; the diameter of the cortical cysts at the upper pole of the right kidney remained unchanged. Renal function remained diminished but stable over the years. No hyperglycemia or glycosuria was ever found. At the last follow-up examination, in February 2001, the glucose tolerance test was normal.

In case 2 (III-2), i.v. urogram showed that kidney length was slightly below the range of normal and that cortical thickness was reduced. Ultrasound evaluations confirmed that the kidney volume was reduced, and showed hyperechogenicity. At his last follow-up examination in May 2000, at 38 years of age, some cysts of 0.5–1 cm diameter were found in both kidneys. No hyperglycemia or glycosuria was found. At the last examination, the glucose tolerance test was normal.

In case 3 (IV-1), slight increases in serum creatinine, urea and uric acid were detected during follow-up. We deliberately did not perform an i.v. urogram.
Glomerulocystic kidney disease in a family

(a)

(b)

ADPKD2

ADPKD1
Ultrasound examination performed at the age of 4 years showed kidneys of normal size possessing hyperechogenic parenchyma with slight loss of corticomedullary differentiation. At the age of 9 years, small cysts of 4–5 mm diameter were detected at the upper poles of both kidneys. Their diameters reached 8 mm by the age of 11 years (Table 1). Urinalysis remained normal during follow-up. At the latest follow-up examination, in February 2001, renal function was stable and the glucose tolerance test was normal.

In all three cases, liver morphology was normal on sonography. We identified no other coexistent pathological conditions.

**Histopathological evaluation**

In two patients (case 1 and case 2), renal tissue was examined by light microscopy. In the specimen from case 1, 87 glomeruli were observed, of which ~40% showed marked dilation of Bowman’s spaces. The glomerular tufts were reduced or rudimentary; most glomerular tufts were attached to the cyst walls. Cysts were lined by flattened epithelial cells. In some markedly expanded Bowman’s spaces two tufts were present, indicating the fusion of two adjacent cysts (Figure 3). No periglomerular fibrosis was observed in the specimen. No tubular dilation was seen. Diffuse and very mild interstitial fibrosis was present. No dysplastic elements were observed.

The renal histology of case 2 was similar. Approximately 25% of glomeruli displayed marked dilation of Bowman’s spaces; some remnants of glomerular tufts were present in the majority of glomeruli. Glomerular cysts were lined by flattened epithelial cells; no hyperplastic epithelial cells were seen. This specimen also showed very mild interstitial fibrosis. Tubules were not dilated. No dysplastic elements were present.

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### Table 1. Clinical data at the first and follow-up examinations

<table>
<thead>
<tr>
<th>Case (individual)</th>
<th>Age (years)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Blood pressure</th>
<th>Diuresis</th>
<th>Intravenous urogram</th>
<th>Sonogram</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case 1 (III-3)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.77</td>
<td>Normal</td>
<td>Normal</td>
<td>Slight reduction in size of kidneys</td>
<td>Kidneys reduced in size (&lt;10th percentile for age and height)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>1.82</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>1.98</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Case 2 (III-2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.97</td>
<td>Normal</td>
<td>Mild polyuria</td>
<td>Slight reduction in size of kidneys</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>2.24</td>
<td>Normal</td>
<td>Mild polyuria</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>2.31</td>
<td>Mild hypertension</td>
<td>Mild polyuria</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Case 3 (IV-1)</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.43</td>
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<td>Mild polyuria</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
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<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>1.36</td>
<td>Normal</td>
<td>Mild polyuria</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>1.36</td>
<td>Normal</td>
<td>Mild polyuria</td>
<td>–</td>
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</tr>
</tbody>
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**Fig. 2.** Renal sonogram of individual III-3. Dyshomogeneous hyperechoic kidney with loss of corticomedullary differentiation. Small cortical cyst. Caliceal dysmorphology.
Immunofluorescence studies were negative. Electron microscopy studies were not performed. The findings in both cases were highly consistent with GCKD.

Genetic evaluation

As shown in Figure 1, the disease in the family described here is inherited as an autosomal dominant trait. In the individuals we studied, haplotype reconstruction led to the exclusion of the PKD1 and PKD2 genes in the family members by means of linkage analysis. Exclusion of the PKD1 gene was achieved on the basis of different haplotypes inherited by the two affected individuals, III-2 and III-3. Furthermore, the PKD2 gene was excluded, since the two affected individuals, III-2 and III-3, and their unaffected brother, III-1, had inherited the same haplotype from the affected father. No mutation was observed in the HNF β1-gene.

Discussion

This paper reports data from an Italian family with three members with GCKD, in whom linkage for PKD1 and PKD2 was excluded. Our report helps, therefore, to clarify an issue that has been discussed since the disease was defined. It was first described in 1941 [8], and 35 years later it was termed GCKD by Taxy and Filmer [9] who underlined, however, that glomerular cysts can be found in many renal diseases. Dominant inheritance was first reported in a family in 1984 [10]. GCKD is a rare disease, and the paucity or lack of symptoms may render its recognition difficult. Only in a few cases are polyuria and polydipsia signs of the disease. Its evolution can be very slow, sometimes silent, and its progression is not always unfavourable. Furthermore, adults who are affected by multiple renal cysts do not usually undergo biopsy, and are assumed to be affected by the more common and well known ADPKD.

GCKD has been described as sporadic or familial, most frequently in children, but has also been found in adolescents and adults [11]. GCKD has also been subdivided into two groups: (i) early onset, more common in neonates, sometimes with severe renal insufficiency [12]; and (ii) late onset, in adulthood, with less severe renal damage [13]. Some cases described in adults with advanced renal insufficiency or end-stage renal failure, however, cast doubt on this differentiation. As noted by Bernstein, it remains unclear whether adult and infantile forms are the same disease or not. The same doubt remains with regard to sporadic and familial forms [10].

In both sporadic and familial forms, the kidneys have been described as hypoplastic, normal-sized or massively enlarged. The variable enlargement of the kidney is probably related to the degree of cyst formation. The cysts may be diffuse or clustered. Uneven cyst development can lead to an asymmetrical form. In some families with a positive history, vertical transmission and histological findings of glomerular cysts, i.e. urograms have revealed small kidneys with coarse or absent calyces lacking papillae [14,15]. These structural anomalies have prompted researchers to differentiate these cases from the usual GCKD.

Ultrasonograph can be useful in the diagnosis of GCKD. Kidneys are frequently enlarged, although normal or hypoplastic ones may also be observed. The cortex is hyperechogenic, with a characteristic hypoechoic rim. Sometimes, tiny isolated cysts are seen in the echogenic renal cortex. As no cysts are seen in the medulla, their absence can help to differentiate GCKD from ADPKD. In ADPKD, multiple cysts of varying size, usually larger than those seen in GCKD, can be observed in both the cortex and the medulla [16].

Histopathological analysis in suspected cases of GCKD may reveal a variable number of glomeruli with markedly dilated Bowman’s spaces. Glomerular tufts attached to the capillary wall may be reduced, rudimentary or collapsed. Epithelia covering the walls of Bowman’s capsules are flattened. Periglomerular fibrosis and diffuse mild interstitial fibrosis have been described in only a few cases. The lack of dysplastic elements is a strong factor in the differentiation of primary GCKD from the glomerular cysts, which may be present in renal dysplasia.

In our patients, the morphological data are suggestive of GCKD. In all three cases, sonograms show hyperechogenic kidneys, and over time small cysts became more evident in the cortex. The reduced kidney size in two of the three cases and the mild calyceal dysmorphology found in only one of the three affected subjects suggest that the hypoplasia and abnormality of calyces and papillae described in some cases [14,15] might not constitute a significant variation from the usual GCKD. Renal histopathology gives the precise image of what is defined as a glomerular cystic kidney [1,17]. Glomerular cysts are considered to be the basic and predominant lesions of GCKD (in our cases, the cysts were the only lesions). No dilation of tubules is present; the absence of tubular dilation excludes the
diagnosis of ADPKD. Dysplastic elements were absent in our cases. The lack of evident periglomerular and interstitial fibrosis in our cases is probably the basis of the mild renal insufficiency.

The main cause of glomerular cyst development could be stenosis at the glomerulo-tubular junction. Three-dimensional imaging analysis has recently excluded stenosis or obstruction at the level of the glomerulo-tubular neck [18]. No signs of obstruction of the urinary tract were observed in our three cases using i.v. urograms or sonograms.

The transmission modality of the disease is autosomal dominant. Some observations relate dominant familial GCKD to ADPKD [19], and the appearance of some cases of GCKD in ADPKD-affected families has given support to the notion that, in some instances, GCKD is an early manifestation of ADPKD. The occurrence of intra-hepatic anomalies, which are described in 10% of cases of GCKD, is considered to support this hypothesis. The question has been raised of whether GCKD is an allelic disorder of classic ADPKD or a different disease [1]. The genes for ADPKD, PKD1 and PKD2 have been excluded by linkage studies in the Italian family previously described [2]. In a study of a large African–American family with the autosomal dominant trait and a distinctive phenotype of GCKD, the linkage data excluded PKD1 and PKD2 as the genes of disease susceptibility [3] along with the human homologue of Gck and mm 1633 mouse glomerulocystic kidneys [20,21].

In two previously described families [14,15] affected by the familial hypoplastic form of GCKD, a novel heterozygous mutation in the gene encoding the hepatocyte nuclear factor 1β (HNF-1β) has recently been identified [4]. In both families, the mutation co-segregated with the hypoplastic subtype of GCKD, which was characterized by small kidneys, absent calyces and irregular, enlarged collecting systems in the Italian family [15], and by small kidneys associated with calyceal abnormalities in the African–American family [16]. Furthermore, it should be underlined that, in both families, all the affected individuals had shown maturity onset of diabetes of the young (MODY). In contrast, a mutation in the HNF-1β gene was not found in two families harbouring the non-hypoplastic form of GCKD without diabetes [4].

The members of the family we studied did not show morphological elements of the hypoplastic form of GCKD or diabetes. The lack of mutation of the HNF-1β gene thus supports the exclusion of hypoplastic GCKD.

The rarity of the disease, combined with the variable renal phenotype, which ranges from sonographic abnormalities to end-stage renal disease, will inevitably hamper making a precise diagnosis and, consequently, the identification of the responsible genetic anomaly.

References


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