Late occurrence of cysts in autosomal dominant medullary cystic kidney disease

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Abstract Medullary cystic kidney disease (MCD) is characterized by multiple renal cysts at the corticomedullary boundary area, by autosomal dominant inheritance, and by onset of chronic renal failure in the third decade of life. We report on a family with three affected individuals of both sexes in two generations presenting with end-stage renal failure at age 22–31 years. Primarily diagnoses considered included unclassified hereditary nephropathy and autosomal dominant polycystic kidney disease. Careful evaluation of all findings, initiated after investigation of renal morphology with CT, revealed features characteristic for MCD and led to the final diagnosis of MCD. We conclude that MCD is an important differential diagnosis for polycystic kidney disease in young adults with end-stage renal failure. Establishing the correct diagnosis has considerable impact for genetic counselling.

Key words: Medullary cystic kidney disease; autosomal dominant inheritance; diagnosis; corticomedullary boundary; end-stage renal failure; nephronophthisis

Introduction

Diseases of the nephronophthisis/medullary cystic disease (NPH/MCD) complex are inherited and characterized by a chronic sclerosing tubulointerstitial nephropathy with the later development of multiple cysts at the corticomedullary boundary of the kidneys [1–4]. Nephronophthisis (NPH) is autosomal recessive and leads to chronic renal failure at a median age of 13 years [5] and, as a rule, before age 25 years. Therefore, this disease is rarely observed in adults with end-stage renal failure. Medullary cystic kidney disease (MCD), a rare autosomal dominant cystic disease of the kidney, is indistinguishable from NPH on pathological grounds and leads to end-stage renal disease in the third to fourth decade of life [6]. Lack of experience with the diagnosis of MCD contributes in part to the fact, that the disease is diagnosed rarely. Another reason may lie in the fact that this diagnosis is based on clinical, radiological and histological findings of family members who often passed away years before an index patient is examined.

The term juvenile nephronophthisis (NPH1) is used for the recessive disease involving only the kidneys. Disease indistinguishable from NPH1 by renal histology, renal symptoms, and mode of inheritance may occur in association with extrarenal involvement. The most frequent association is retinitis pigmentosa. This disease entity is known as Senior–Loken syndrome (SLS) [7,8]. The gene underlying NPH1 has been localized on chromosome 2q13 [9,10], whereas the gene for SLS has not been mapped so far. The whole critical genetic region of the NPH1 gene has been cloned in YAC contigs [11,12]. Recently homozygous deletions have been reported in 80% of all familial cases with NPH1 [13], rendering a non-invasive diagnostic procedure in patients with suspected NPH1.

Subjects and methods

We have established a register of inherited diseases with chronic renal failure for the administration district of Freiburg (Regierungsbezirk Freiburg), in the south-west of Germany 1.9 million inhabitants. During this evaluation we were able to collect clinical, radiological and histological documents, which in the family described resulted in the new diagnosis of medullary cystic kidney disease (MCD).

Case reports

Clinical findings

The first careful evaluation of all findings in this family (Figure 1) was performed in June 1986. The index patient (II-1), female, born 1963, was first admitted to our hospital in 1984 because of dysuria...
Medullary cystic kidney disease

Fig. 1. Pedigree of the family with medullary cystic kidney disease. Filled symbols denote affected members. Numbers denote year of birth (upper right), age at death (lower right), and position in generation (lower left).

and flank pain. The 21-year-old woman of 166 cm height and 51 kg weight was normotensive. Renal function was found to be impaired with a serum creatinine of 5.1 mg/dl and a haemoglobin of 11.8 g/dl. Abdominal ultrasonography showed kidneys of normal size (10×5 cm) with slightly enhanced echogenicity but without cysts. Urinalysis was normal. Urinary protein analysis (0.13 g/day) revealed a pattern of tubular proteinuria. Ophthalmological investigations and audiometry results were normal. Five months later serum creatinine was found to be 6.9 mg/dl. Abdominal CT scan was performed and kidneys of normal shape and again no renal cysts were seen. Renal biopsy was regarded as non-diagnostic for a specific entity. Seven months later peritoneal dialysis had to be started. One year later the patient received a cadaveric kidney transplant, and serum creatinine declined to the normal range.

The brother (II-2), born 1964, was admitted to an army physician. 2 months after his sister was first seen, for specific nephrological investigations in order to check fitness for army service. His blood pressure was raised to 170/90 mmHg, serum creatinine was 1.2 mg/dl and creatinine clearance was normal. Proteinuria was 1 g/day, but at several consecutive measurements was normal; electrophoresis showed a tubular pattern of proteins. Abdominal ultrasound revealed normal findings of the kidneys and the liver. Ophthalmological investigations and audiometry results were normal. Eight months later serum creatinine was 1.4 mg/dl.

Family history: The father (I-1) had also been admitted to our hospital at age 29 in 1967 with end-stage renal failure. Twelve years earlier he had a febrile episode of ‘pyelonephritis’ and 7 years earlier hypertension was found. Renal biopsy tissue was insufficient for a histological diagnosis. He died at age 29 years, when placement of a peritoneal dialysis catheter caused excessive haemorrhage. The major autopsy renal findings were summarized as postpyelonephritis shrunken kidneys. Liver cysts have been absent. The mother (I-2) is living and healthy. The further family history especially from the father’s side is free of early deaths or uraemia. A working diagnosis of an ‘unclassifiable hereditary nephropathy’ was assigned at this time. A re-evaluation of all available documents of the family including the CT scans was performed in 1995.

The brother (II-2) was admitted again in 1995. He had denied regular controls of kidney function, and the last serum creatinine of 1.5 mg/dl dated from 1990. At admission he was in end-stage renal failure. Proteinuria was 2 g/day and electrophoresis showed a tubuloglomerular pattern of proteins. By abdominal ultrasound his kidneys measured 12.5×5 cm with corticomedullary cysts. CT scans of the kidneys using a third-generation scanner are shown in figure 2c and d. The shape of both kidneys was normal, and liver cysts were absent. Renal biopsy was not performed. Symptoms of salt loss were never observed. His sister (II-1) underwent CT examination 19 months after kidney transplantation. This CT scan showed in her native kidneys multiple cysts at the corticomedullary boundary area (Figure 2a and b) and autosomal dominant polycystic kidney disease was suspected. This CT however, did not show liver cysts. Besides an unilateral hemiovarectomy for a cyst she had a completely uneventful follow-up. Serum creatinine in 1996 was normal.

Histological findings
Histology of the kidneys of I-1 showed at autopsy (29 years) most of the glomeruli fibrotic, some enlarged with ectatic tubules and with thickened basement membrane, whereas the other tubules were atrophic. Glomerular loop scars and synechiae but no crescents or other signs of glomerulonephritis were found. Interstitial fibrosis with lymphohistiocytic infiltrates was noted.

Renal biopsy tissue of II-1 obtained at age 21 years (Figure 3a and b) contained six glomeruli and numerous tubules. Four glomeruli were normal, two were fibrotic. The prominent findings were ectatic tubuli and interstitial fibrosis with lymphohistiocytic infiltrates as well as irregular thickening of tubular basement membranes and a few Tamm–Horsfall protein deposits.

Final diagnosis
The diagnosis of MCD was based on the autosomal dominant mode of inheritance, the radiological finding of cysts in the corticomedullary boundary area in I-1 and II-2, the post-mortem findings of tubular cysts in I-1 together with the results of renal biopsy in II-1 compatible with MCD, and the occurrence of end-stage renal failure in young adulthood in all affected.

Genetic tests
We excluded nephronophthisis type 1 (NPH1) in this family by molecular genetic examination, demonstrating that the affected siblings were negative for the homozygous deletion described as diagnostic for NPH1 [13,14].
Fig. 2. CT scans of family members II-1 (a,b) at age 24 and II-2 (c,d) at age 30. Note the presence of several small renal cysts at the corticomedullary boundary in both kidneys and normal sizes and surfaces of the kidneys.

Discussion

We report on a family in which re-evaluation of clinical, histological, and radiological signs led to the diagnosis of MCD. The differentiation of disease entities within the NPH/MCD complex has considerable practical aspects, since transmission can be autosomal dominant as in MCD or recessive as in NPH and SLS. Consequently, the risk of an offspring of an affected individual for developing renal disease is 50% in MCD or less than 1% in NPH. Gardner and Evan [15] described in the USA a series of NPH/MCD families consisting of 30% families with MCD and 70% families with NPH. Eighty per cent of NPH families (56% of the total) had no extrarenal lesions.

Morphological findings from family studies or small case series have been reported by several authors [16–19]. The major characteristic finding were tubular cysts. Glomeruli are widely fibrotic, whereas the remaining functioning glomeruli can be considerably enlarged. Interstitial fibrosis with round cell infiltrates is typical, and the cortex is shrinking in parallel to progression of the disease. Cysts appear to develop late in the course of MCD, which has recently been described also in NPH [20]. So far, strict morphological criteria for the differentiation of NPH and MCD are not known [18].

The age of onset or detection of chronic renal failure is regarded as diagnostic and associated with either an autosomal dominant or recessive inheritance: patients with NPH develop end-stage renal failure at a median age of 13 years [11] and almost always before 25 years of age, while end-stage renal disease occurs in the third to fourth decade in MCD. In addition, symptoms of salt-losing nephritis, a typical feature of NPH, do not occur in MCD. Penetrance in MCD seems to be complete by the age of 50 years [16].

Histopathological findings in the described family included interstitial sclerosing nephropathy, thickening of tubular basement membrane, tubular ectasis and atrophy, and Tamm–Horsfall protein deposits, which all are consistent with NPH or MCD [18,19,21,22]. For NPH1 it has been described that cysts occur late in the course of the disease [19]. A similar finding was
Autosomal recessive polycystic kidney disease (ARPKD) may also be considered in patients with MCD. ARPKD, however, is extremely rare in adults and associated with periportal liver fibrosis [23]. Finally, patients undergoing dialysis have repeatedly been described with renal cysts. Thus, acquired renal cysts can also be considered but are unlikely in the described family, since such lesions are regarded to develop mostly after many years of dialysis treatment [24].

In summary, the diagnosis MCD is based on findings of several members of a family. Older documents should be checked carefully, but actual investigations, including CT scans or magnetic resonance tomography images, can contribute with essential information. Cysts at the corticomedullary boundary, onset of chronic renal failure in young adults, and the autosomal dominant mode of inheritance are diagnostic. So far, histopathology is unable to distinguish NPH and MCD; however, detection of a deletion in the NPH1 region may help to distinguish NPH1 from MCD in families lacking a clear autosomal dominant segregation pattern. Genetic counselling of families with MCD has to include (a) the autosomal dominant mode of inheritance, (b) a high risk of end-stage renal failure in young adulthood, (c) no risk for lesions of other organs. The MCD gene is unknown. So far, there is no candidate protein or chromosomal locus for MCD.

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