Autosomal dominant medullary cystic disease: a disorder with variable clinical pictures and exclusion of linkage with the NPH1 locus

Francesco Scolari¹, Gian Marco Ghiggeri², Giorgio Casari³, Antonio Amoroso⁴, Daniela Puzzer⁴, Gian Luca Caridi², Brunella Valzorio³, Regina Tardanico⁵, Valerio Vizzardi¹, Silvana Savoldi¹, Battista Fabio Viola¹, Nicola Bossini¹, Elisabetta Prati⁶, Rosanna Gusmano², and Rosario Maiorca¹

¹Division and Chair of Nephrology, Spedali Civili and University, Brescia, ²Division of Paediatric Nephrology, G. Gaslini Childrens Hospital, Genova, ³Telethon Institute of Genetics and Medicine (TIGEM), S. Raffaele Biomedical Science Park, Milano, ⁴Chair and Service of Medical Genetics, University and IRCCS Burlo Garofolo, Trieste, ⁵Service of Pathology, Spedali Civili, Brescia, and ⁶Dialysis Service, Desenzano, Italy

Abstract

Background. The nephronophthisis–medullary cystic disease (NPH/MCD) complex represents a heterogeneous group of hereditary tubulointerstitial nephritis. The most common variant is juvenile recessive NPH, for which a gene locus (NPH1) has been mapped on chromosome 2q13. MCD is a less common dominant condition usually recognized later in life, which resembles NPH in many aspects, still presenting remarkable clinical differences. Nothing is known about the chromosome locus of MCD.

Methods. Five MCD families were studied. Diagnosis was made by inference from family history, type of inheritance, clinical signs and histology. Multipoint linkage analysis was performed by markers D2S293, D2S340 and D2S160 spanning the entire NPH1 locus.

Results. Diagnosis of MCD was made in 28 affected members (16 males; 12 females), belonging to five families. Histological diagnosis was available in 10 patients; clinical diagnosis in 11; seven deceased relatives had diagnosis of chronic nephritis. The age at diagnosis ranged from 8 to 65 years. Renal medullary cysts were found in a minority of patients. In family 1, the disease was associated with hyperuricaemia and gouty arthritis. Progression of renal disease presented intra- and extra-family variability with members of the same family showing mild elevation of creatinine or terminal renal failure. The NPH1 locus associated to recessive NPH was excluded from linkage to the dominant MCD.

Conclusions. MCD might be more common than previously assumed. Variability in clinical presentation and absence of histopathological hallmarks contribute to make the diagnosis uncommon. The most remarkable clinical difference with NPH is the age of onset in some kindreds and a delayed progression towards renal failure. The exclusion of linkage to the NPH1 locus suggests the existence of an MCD responsible locus, still to be mapped.

Key words: gout; hyperuricaemia; linkage analysis; medullary cystic disease; nephronophthisis; NPH1 locus

Introduction

The nephronophthisis–medullary cystic disease (NPH/MCD) complex represents a heterogeneous group of inherited renal diseases sharing some histopathological lesions and a few clinical similarities [1,2]. The most common variant is juvenile nephronophthisis (NPH), a disease with an autosomal recessive inheritance. Clinical signs of NPH typically are present in early childhood and invariably lead to end-stage renal failure within the second decade of life. A gene locus for the purely renal form of NPH (NPH1) has been located on chromosome 2q13, where 65–75% of NPH1 patients exhibit a large homozygous deletion (~250 kb) at which site a candidate gene has been identified [3–7]. NPH occurring in association with extrarenal symptoms, such as retinitis pigmentosa, does not map on 2q13 [3–5].

Medullary cystic disease (MCD) is a less common condition, with autosomal dominant inheritance. MCD is recognized later in life, usually in the third decade, and leads to end-stage renal failure at the age of 40–50 years [1,2]. Nothing is known about the chromosome loci or defective gene of the MCD.

The clinical heterogeneity of NPH/MCD complex has been a matter of debate. Originally, the diseases were assumed to be different disorders [8–10]. Subsequently, since the pathological findings of the two conditions are indistinguishable, it was suggested that they represented a single disorder [11–17]. Tubular...
Clinical and genetic features of MCD

atrophy, thickening of tubular basement membrane (TBM) with PAS-positive material, interstitial fibrosis, and interstitial infiltrates [1,2,18] are in fact frequent but not distinguishing histological features. Furthermore, also tubular cysts at the corticomedullary junction is a frequent but not invariable finding in both conditions, being most frequent in adults with MCD while only anecdotal in juvenile NPH [1,11,18]. The functional impairment in both disorders reflects the primary defects of tubular structures leading to a reduction in concentrating ability and in sodium conservation [1,2].

In this report we describe 28 patients belonging to five Italian families in which more than one case of MCD came to our attention. Detailed clinical informations demonstrated a quite variable clinical picture with respect to extrarenal symptoms, presence of cysts, age of onset, and rate of progression towards terminal renal failure. The molecular analysis of haplotypes excluded a linkage with chromosome 2q13.

Our data support the assumption of an underestimation of MCD in adults with chronic renal failure and stimulate further efforts to define the clinical and genetical features of the disease.

Subjects and methods

Patients

Five families of Italian ancestry (families 1–5; Figure 1) were studied in which more than one case of MCD came to our attention between 1972 and 1996. Families 1–4 were investigated at the Division of Nephrology of the Spedali Civili of Brescia; family 5 at the Division of Paediatric Nephrology, G. Gaslini Childrens Hospital, Genova. Clinical data and kidney specimens were re-examined. The families included 28 affected members (16 males and 12 females): 10 had clinical and histological diagnosis of MCD; 11 had clinical and histological diagnosis of MCD; seven deceased relatives had diagnosis of chronic nephritis on their death certificates. Genealogical data were obtained by interviewing family members.

Diagnostic criteria

Diagnosis of MCD was made by inference from family history, polyuria, nocturia, hyposthenuria, relatively normal urinalysis, presence of a smooth renal outline and normal or small kidneys on renal ultrasonography or intravenous pyelography. Occasionally, medullary renal cysts were found. Other disorders that can present with chronic renal failure and bland urinalysis, including pyelonephritis, urinary-tract infection, and polycystic kidney disease, were excluded on the basis of intravenous urography or renal ultrasonography findings. Histological confirmation of the diagnosis of MCD was available in at least one case for each family, based on the presence of areas of tubular atrophy, thickening of TBM with PAS-positive material, interstitial fibrosis, and interstitial infiltrates [1,2,17,18].

Genotype determination

DNA was extracted from peripheral blood samples by standard methods [20]. All genetic markers used in the present analysis were (CA)n microsatellites. Oligonucleotide primer sequences were as previously described [21,22]. PCR products were radiolabelled by incorporating 32PdCTP and separated by electrophoresis on 6% denaturant polyacrylamide gel. Gels were subsequently autoradiographed at ~80°C.

Two-point and multipoint linkage analysis has been performed by markers D2S293, D2S340, and D2S160 with the linkage software package [23], using intermarker distances, order and allelic frequencies as previously published [22]. Recombination frequencies were assumed to be equal between males and females; the disease was assumed dominant with incomplete penetrance (0.9); disease frequency is supposed 10−5. Deletion analysis of 2q13 was performed with 3 STS as previously described [4].

Results

Family reports

The pedigrees of the five families are shown in Figure 1. The overall clinical data are collected in Table 1.

Family 1

Index case (female, born 1948)

The index case was a 42-year-old woman (subject III-6), when first seen in December 1990 because of impaired renal function. In her past history, she had suffered from polyuria, nocturia, and occasional urinary infections. At age 26, the first pregnancy was complicated by severe pre-eclampsia. At age 30, she developed hyperuricaemia (9.2 mg/dl) and therapy with allopurinol (100 mg/day) was started; serum creatinine was 1.3 mg/dl. On admission, the patient was asymptomatic; blood pressure was 105/70. Audiogram and ophthalmological evaluation were negative. Biochemical liver abnormalities were not documented. Serum creatinine was 1.8 mg/dl; creatinine clearance 45 ml/min; uricaemia (on allopurinol) 7 mg/dl. Urinalysis showed no sediment abnormalities or proteinuria. The urine specific gravity was 1010 and urinary osmolality 315 mmol/kg. Renal ultrasonography, urography, and CT scan revealed small kidneys, a
normal collecting system, and no cysts. A percutaneous renal biopsy showed some foci of tubular atrophy and thickening of TBM with PAS-positive material. Significant focal areas of interstitial fibrosis, producing a picture of striped fibrosis, with modest inflammatory cell infiltration, were also seen. Renal cysts were not found. Two of nine glomeruli were globally sclerotic. Immunofluorescence was negative. In the subsequent years, the patient became hypertensive. At last follow-up, in July 1997, the clinical and laboratory picture was unchanged.

Patient 2 (male, born 1954)
Subject III-9, the youngest brother of the index case, presented at 19 years with pain and swelling in the left first metatarsophalangeal joint. Due to the concomitant presence of hyperuricaemia (10.5 mg/dl), gout was diagnosed. In the subsequent years, he presented several acute arthritis attacks affecting lower extremities, responding to oral non-steroidal anti-inflammatory drugs. In 1983, serum creatinine was 1.7 mg/dl; uricaemia 12 mg/dl. Treatment with allopurinol (150 mg/dl) was initiated; he did not experience further acute arthritis episodes. In 1992, the patient was referred for investigation of chronic renal failure. Polyuria and polydipsia had been present for many years. On admission, blood pressure was normal. Audiogram and ophthalmological evaluation showed negative results. Serum creatinine was 1.9 mg/dl; clearance creatinine 45 ml/min; uricaemia (on allopurinol) 6.5 mg/dl. Urinalysis was negative except for the urine specific gravity (1008); urinary osmolality was 295 mmol/kg. Renal ultrasonography and TC scan revealed small kidneys in the absence of renal cysts. Cystography did not show vesicoureteral reflux. A percutaneous renal biopsy showed groups of atrophic tubules with thickened TBM staining with PAS. Areas of interstitial fibrosis and inflammation were also present. Ten of 20 glomeruli were completely sclerotic, the remainder showing varying degrees of periglomerular fibrosis. Immunofluorescence study did not show staining in the glomeruli. By electron microscopy no electron-dense deposits were found, and while the average
Subject II-3, another maternal uncle of the index case, Subject I-1, the grandfather of the index case, also have had chronic renal disease and hypertension for failure requiring peritoneal dialysis. He died of heart failure in 1990.

Patient 4 (male, born 1921, died 1953)

Patient 5 (male, born 1922, died 1990)

Subject II-3, another maternal uncle of the index case, was admitted in 1976 for chronic renal failure. The patient had hyperuricaemia and repeated attacks of gout since the age of 48 and he was treated with a purine-restricted diet. There was a history of long-standing nocturia and polydipsia. Laboratory investigation disclosed chronic renal failure (serum creatinine 2 mg/dl; creatinine clearance 45 ml/min) and hyperuricaemia (12 mg/dl). Repeated urinalysis showed no abnormalities apart from a specific gravity always less than 1010. Urography revealed small kidneys with a thickness of the GBM was normal, TBM were markedly thickened. At last follow-up, in August 1997, the clinical and laboratory picture was unchanged.

Patient 3 (female, born 1923, died 1967)

The subject II-4, the mother of the index case, died of uraemia in 1967 at age 44. She was known to have suffered from renal disease for many years.

Patient 4 (male, born 1921, died 1953)

The subject II-1, a maternal uncle of the index case, died of uraemia in 1953 at age 41. He was known to have had chronic renal disease and hypertension for many years.

Patient 5 (male, born 1922, died 1990)

Subject II-3, another maternal uncle of the index case, was admitted in 1976 for chronic renal failure. The patient had hyperuricaemia and repeated attacks of gout since the age of 48 and he was treated with a purine-restricted diet. There was a history of long-standing nocturia and polydipsia. Laboratory investigation disclosed chronic renal failure (serum creatinine 2 mg/dl; creatinine clearance 45 ml/min) and hyperuricaemia (12 mg/dl). Repeated urinalysis showed no abnormalities apart from a specific gravity always less than 1010. Urography revealed small kidneys with a thickness of the GBM was normal, TBM were markedly thickened. At last follow-up, in August 1997, the clinical and laboratory picture was unchanged.

Patient 3 (female, born 1923, died 1967)

The subject II-4, the mother of the index case, died of uraemia in 1967 at age 44. She was known to have suffered from renal disease for many years.

Patient 4 (male, born 1921, died 1953)

The subject II-1, a maternal uncle of the index case, died of uraemia in 1953 at age 41. He was known to have had chronic renal disease and hypertension for many years.

Patient 5 (male, born 1922, died 1990)

Subject II-3, another maternal uncle of the index case, was admitted in 1976 for chronic renal failure. The patient had hyperuricaemia and repeated attacks of gout since the age of 48 and he was treated with a purine-restricted diet. There was a history of long-standing nocturia and polydipsia. Laboratory investigation disclosed chronic renal failure (serum creatinine 2 mg/dl; creatinine clearance 45 ml/min) and hyperuricaemia (12 mg/dl). Repeated urinalysis showed no abnormalities apart from a specific gravity always less than 1010. Urography revealed small kidneys with a thickness of the GBM was normal, TBM were markedly thickened. At last follow-up, in August 1997, the clinical and laboratory picture was unchanged.

Patient 3 (female, born 1923, died 1967)

The subject II-4, the mother of the index case, died of uraemia in 1967 at age 44. She was known to have suffered from renal disease for many years.

Patient 4 (male, born 1921, died 1953)

The subject II-1, a maternal uncle of the index case, died of uraemia in 1953 at age 41. He was known to have had chronic renal disease and hypertension for many years.

Patient 5 (male, born 1922, died 1990)

Subject II-3, another maternal uncle of the index case, was admitted in 1976 for chronic renal failure. The patient had hyperuricaemia and repeated attacks of gout since the age of 48 and he was treated with a purine-restricted diet. There was a history of long-standing nocturia and polydipsia. Laboratory investigation disclosed chronic renal failure (serum creatinine 2 mg/dl; creatinine clearance 45 ml/min) and hyperuricaemia (12 mg/dl). Repeated urinalysis showed no abnormalities apart from a specific gravity always less than 1010. Urography revealed small kidneys with a thickness of the GBM was normal, TBM were markedly thickened. At last follow-up, in August 1997, the clinical and laboratory picture was unchanged.

Patient 3 (female, born 1923, died 1967)

The subject II-4, the mother of the index case, died of uraemia in 1967 at age 44. She was known to have suffered from renal disease for many years.

Patient 4 (male, born 1921, died 1953)

The subject II-1, a maternal uncle of the index case, died of uraemia in 1953 at age 41. He was known to have had chronic renal disease and hypertension for many years.

Patient 5 (male, born 1922, died 1990)

Subject II-3, another maternal uncle of the index case, was admitted in 1976 for chronic renal failure. The patient had hyperuricaemia and repeated attacks of gout since the age of 48 and he was treated with a purine-restricted diet. There was a history of long-standing nocturia and polydipsia. Laboratory investigation disclosed chronic renal failure (serum creatinine 2 mg/dl; creatinine clearance 45 ml/min) and hyperuricaemia (12 mg/dl). Repeated urinalysis showed no abnormalities apart from a specific gravity always less than 1010. Urography revealed small kidneys with a thickness of the GBM was normal, TBM were markedly thickened. At last follow-up, in August 1997, the clinical and laboratory picture was unchanged.

Patient 3 (female, born 1923, died 1967)

The subject II-4, the mother of the index case, died of uraemia in 1967 at age 44. She was known to have suffered from renal disease for many years.

Patient 4 (male, born 1921, died 1953)

The subject II-1, a maternal uncle of the index case, died of uraemia in 1953 at age 41. He was known to have had chronic renal disease and hypertension for many years.

Patient 5 (male, born 1922, died 1990)

Subject II-3, another maternal uncle of the index case, was admitted in 1976 for chronic renal failure. The patient had hyperuricaemia and repeated attacks of gout since the age of 48 and he was treated with a purine-restricted diet. There was a history of long-standing nocturia and polydipsia. Laboratory investigation disclosed chronic renal failure (serum creatinine 2 mg/dl; creatinine clearance 45 ml/min) and hyperuricaemia (12 mg/dl). Repeated urinalysis showed no abnormalities apart from a specific gravity always less than 1010. Urography revealed small kidneys with a thickness of the GBM was normal, TBM were markedly thickened. At last follow-up, in August 1997, the clinical and laboratory picture was unchanged.

Patient 3 (female, born 1923, died 1967)

The subject II-4, the mother of the index case, died of uraemia in 1967 at age 44. She was known to have suffered from renal disease for many years.

Patient 4 (male, born 1921, died 1953)

The subject II-1, a maternal uncle of the index case, died of uraemia in 1953 at age 41. He was known to have had chronic renal disease and hypertension for many years.

Patient 5 (male, born 1922, died 1990)

Subject II-3, another maternal uncle of the index case, was admitted in 1976 for chronic renal failure. The patient had hyperuricaemia and repeated attacks of gout since the age of 48 and he was treated with a purine-restricted diet. There was a history of long-standing nocturia and polydipsia. Laboratory investigation disclosed chronic renal failure (serum creatinine 2 mg/dl; creatinine clearance 45 ml/min) and hyperuricaemia (12 mg/dl). Repeated urinalysis showed no abnormalities apart from a specific gravity always less than 1010. Urography revealed small kidneys with a thickness of the GBM was normal, TBM were markedly thickened. At last follow-up, in August 1997, the clinical and laboratory picture was unchanged.

Patient 3 (female, born 1923, died 1967)

The subject II-4, the mother of the index case, died of uraemia in 1967 at age 44. She was known to have suffered from renal disease for many years.
Subject III-3, a 31-year-old first-cousin of the index case, was investigated at 18 years of age for an episode of acute urinary-tract infection occurring during her first pregnancy. She had had nocturia and polyuria since the age of 10. Serum creatinine was 1.4 mg/dl and creatinine clearance 65 ml/min; uricaemia was 6.3 mg/dl. Urinalysis revealed a specific gravity of 1010 and urinary osmolality of 300 mmol/kg, in the absence of sediment abnormalities or proteinuria. Urography revealed small kidneys; cystography was negative. In 1983, she underwent percutaneous renal biopsy, which showed areas of tubular atrophy and thickening of TBM with PAS-positive material. Focal interstitial fibrosis accompanied by a sparse inflammatory infiltrate was also found. Five glomeruli were completely sclerosed; the remaining 15 showed periglomerular fibrosis. No cyst was detected. Immunofluorescence studies were negative. In subsequent years, the patient developed a moderate arterial hypertension and hyperuricaemia (9.6 mg/dl). In 1995, renal ultrasound showed two moderately reduced kidneys with increased echogenicity, loss of corticomedullary differentiation and no cysts. At last follow-up, in March 1997, serum creatinine was 1.8 mg/dl; creatinine clearance 50 ml/min.

Patient 9 (female, born 1974)

This 21-year-old patient (subject IV-6), the daughter of patient III-3, was found to have renal disease at age 16, during the third trimester of pregnancy, when she became hypertensive. In her history were polyuria and polydipsia. In April 1996, serum creatinine was 1.6 mg/dl, creatinine clearance 55 ml/min; uricaemia 5.5 mg/dl. Blood pressure was 105/70. Ophthalmological evaluation and audiogram gave negative results. Urinalysis showed no sediment abnormalities or proteinuria. The urine specific gravity was 1010; urinary osmolality 310 mmol/kg. Renal ultrasonography revealed small kidneys with loss of corticomedullary definition; cystography did not reveal vesicoureteral reflux. Renal biopsy was not performed.

Other family members

The grandmother of the index case, subject I-2, died in 1966 at age 73 of gastric neoplasia. One aunt (II-5) of the index case died in 1982 at age 55 of unknown causes. There was no evidence of renal disease. Another uncle (II-2) of the index case died in 1963 at age 35 of gastrointestinal haemorrhage. No further information was available on him.

Twelve other available family members (III-1, III-2, III-5, III-7, III-8, III-10, III-11, III-12, IV-2, IV-3, IV-4, IV-5) were screened for the disease and proved to be negative.

Family 2

Index case (female, born 1930)

This patient, subject II-1, was first seen at age 58 because of chronic renal failure. She had had a history of nocturia for many years. Serum creatinine was 2 mg/dl; creatinine clearance 40 ml/min; uricaemia 6.2 mg/dl. Urinalysis was negative; urinary specific gravity was 1010; urinary osmolality 310 mmol/kg. Blood pressure was 120/80 mm Hg. No ocular abnormalities were found. Renal ultrasound revealed two reduced kidneys with increased parenchymal echogenicity, loss of corticomedullary differentiation, and small medullary cysts. Renal TC scan confirmed the presence of cysts in both kidneys, located in the medulla, measuring approximately 0.5–1 cm in diameter. Cystourethrography was negative. Renal biopsy was a normal-looking interstitium alternating with areas of atrophic tubules with thickened TBM staining with PAS. Foci of interstitial fibrosis and inflammation were present. There were no cysts in the medulla. Eight of 16 glomeruli showed global or segmental sclerosis. Immunofluorescence was negative. Electron microscopy disclosed a homogeneous thickening of the TBM. At last follow-up, in February 1997, laboratory investigation revealed hyperuricaemia (9.5 mg/dl); the clinical picture and renal function were unchanged. Allopurinol (100 mg/day) was started.
Clinical and genetic features of MCD

not performed. At last follow-up, in January 1997, the clinical and laboratory picture was unchanged.

Patient 2 (female, born 1935)
Subject II-3, a younger sister of the index case, was found to have chronic renal failure at age 55. In her past history, she had suffered from urinary-tract infections. She had had nocturia since the age of 30. Serum creatinine was 1.7 mg/dl; creatinine clearance 60 ml/min; uricaemia 5.5 mg/dl. Urinalysis showed no sediment abnormalities or proteinuria. The urine specific gravity was 1010; urinary osmolality 305 mmol/kg. Blood pressure was 110/70 mmHg. Ophthalmological evaluation was negative. Renal ultrasound revealed two moderately reduced kidneys, with loss of corticomедullary definition. The left kidney presented a few small medullary cysts. Renal CT scan confirmed a few cysts on the left kidney, located in the medulla and corticomедullary junction. The average size of cysts was 1 cm. Cystourethrography did not reveal vesicoureteral reflux. A percutaneous renal biopsy demonstrated segmental zones of interstitial fibrosis containing groups of atrophic tubules with irregularly thickened TBM. No cysts were found. A few (5) glomeruli were present: three were completely hyalinized; the remainder showed a variable degree of periglomerular fibrosis. Immunofluorescence was negative. At last follow-up, in July 1997, the clinical and laboratory pictures were unchanged.

Patient 3 (male, born 1943)
Subject II-4, the brother of the index case, presented at 46 years with a history of polyuria and polydipsia for many years. Urinalysis was negative for blood and protein. Urinary specific gravity was 1012 and urinary osmolality 310 mmol/kg. Serum creatinine was 1.3 mg/dl; creatinine clearance 70 ml/min; uricaemia 7 mg/dl. By renal ultrasound and CT scan, kidney size was only moderately reduced and no cysts were apparent. The patient refused to allow renal biopsy. At last follow-up, in March 1997, renal function was unchanged.

Patient 4 (male, born 1905, died 1973)
Subject I-1, the father of the index case, died at age 68 with a history of chronic renal disease of several years’ duration. Death was attributed to pulmonary carcinoma.

Other family members
Subject I-2, the mother of the index case, died at the age of 78 from intestinal neoplasia. The available family members II-2, II-3, III-1, III-2, III-3, III-4, III-5 had no evidence of renal disease when screened in July 1996.

Family 3

Index case (male, born 1931, died 1996)
Subject II-2 was investigated at 42 years for chronic renal failure. He had had nocturia and polyuria for many years. Serum creatinine was 3 mg/dl; creatinine clearance 25 ml/min; uricaemia 9 mg/dl. Urinalysis revealed a specific gravity of 1008; no sediment abnormalities or proteinuria were found. Blood pressure was normal. Urography revealed small kidneys and a normal urinary tract. Audiogram was negative. Renal biopsy was not performed. In April 1975 haemodialysis became necessary. He died of heart failure in January 1996.

Patient 2 (female, born 1930)
Subject II-3 was referred in 1975 at age 45 for chronic renal failure. She had had nocturia from the age of 30. Serum creatinine was 2 mg/dl; clearance creatinine 40 ml/min; uricaemia 7 mg/dl. Urinalysis showed no sediment abnormalities or proteinuria. The urine specific gravity was 1010. Blood pressure was 110/70 mmHg. Audiogram and ophthalmological evaluation were negative. Urography and renal angiography revealed two reduced kidneys and the absence of anatomical urinary abnormalities and cysts. A percutaneous renal biopsy revealed a severe degree of tubular atrophy, associated with interstitial fibrosis and a moderate cellular infiltrate. Five of 10 glomeruli were globally sclerotic. Immunofluorescence was negative. In subsequent years, renal function deteriorated. In 1986, renal ultrasound disclosed two small kidneys which appeared hyperechogenic and without corticomедullary differentiation. A few small medullary cysts were seen in both kidneys. Haemodialysis became necessary in May 1988.

Patient 3 (male, born 1935, died 1977)
Subject II-1 was found to have chronic renal failure at 38 years. He had had nocturia for many years. Serum creatinine was 3.5 mg/dl; creatinine clearance 20 ml/min. Urinalysis showed no abnormalities, apart from a specific gravity always less than 1010. Roentgenological investigation revealed small kidneys with a normal collecting system. In 1975, he developed end-stage renal failure requiring dialysis. He died of heart failure in 1977.

Patient 4 (female, born 1938)
Subject II-4 was found to have arterial hypertension at the age of 50. There was a history of long-standing nocturia. In January 1997, serum creatinine was 1.4 mg/dl; creatinine clearance 55 ml/min. Urinalysis showed no abnormalities; specific gravity was 1005; renal ultrasound was negative. The patient refused to submit to further investigation.
Patient 5 (male, born 1904, died 1956)

Subject I-1, the father of the index case, died at age 52 from unknown causes. He was said to have suffered from chronic renal disease for many years.

Patient 6 (male, born 1968)

Subject III-2, the son of patient 3, was discovered to have chronic renal failure at age 24. Serum creatinine was 2 mg/dl; creatinine clearance 40 ml/min; uricaemia 9 mg/dl. He had had polyuria from infancy. Urinalysis showed no sediment abnormalities or proteinuria; the urine specific gravity was 1010; urinary osmolality 305 mmol/kg. Blood pressure was 130/70 mmHg. Audiogram and ophthalmological evaluation were negative. Renal ultrasound and TC scan showed two reduced kidneys in the absence of cystic formations. Cystourethrography did not reveal vesicoureteral reflux. A percutaneous renal biopsy showed groups of atrophic tubules with thickened TBM, staining with PAS, alternated with viable hypertrophic tubules. Some tubules, located in the medullary region, were dilated with formation of small cyst-like spaces. The tubules were separated by a marked interstitial fibrosis with significant inflammatory cell infiltration. Four of 8 glomeruli were hyalinized (Figure 2). Immunofluorescence studies showed no deposits. Ultrastructural studies confirmed the presence of dilated tubules and showed a homogeneous thickening of the TBM. In subsequent years, the patient has developed end-stage renal failure. Haemodialysis became necessary in May 1995.

Other family members

Subject II-2, the mother of the index case died at age 78 from unknown causes. Subjects III-1, III-3, III-4, III-7 were screened for renal disease and were negative.

Family 4

Index case (male, born 1977)

Subject III-1 was found to have renal insufficiency at age 10, when he was investigated for anaemia. He had polyuria and polydipsia for many years. Laboratory investigation showed serum creatinine 1.8 mg/dl; creatinine clearance 40 ml/min; uricaemia 6 mg/dl. Urinalysis revealed a maximum specific gravity of 1009; urinary osmolality 290 mmol/kg; pH 5.0; no protein and sediment abnormalities. Blood pressure was normal. Renal ultrasound and urography showed small kidneys; cystography did not reveal vesicoureteral reflux. Ophthalmological evaluation and audiogram were negative. An open renal biopsy showed focal areas of tubular atrophy and segmental zones of interstitial fibrosis with a mild inflammatory cell infiltrate. Ten of 17 glomeruli were sclerotic. Immunofluorescence showed an aspecific entrapment of IgM in mesangial areas. During the next 8 years, renal function deteriorated and arterial hypertension occurred. Peritoneal dialysis became necessary in 1995. The patient underwent renal transplantation in February 1998.

Patient 2 (female, born 1958)

The mother of the index case (Subject II-2) was referred for investigations of chronic renal failure in April 1990. In her past history, she had suffered from polyuria and nocturia. At age 20, although renal function was already slightly impaired (serum creatinine 1.4 mg/dl), she had a normal pregnancy. On admission, blood pressure was 105/70 mmHg. Ophthalmological evaluation and audiogram were negative. Serum creatinine was 1.7 mg/dl; clearance of creatinine 55 ml/min; uricaemia 6.9 mg/dl. Urinalysis showed no sediment abnormalities or proteinuria; urine specific gravity was 1010; urinary osmolality 310 mmol/kg. Ultrasonographic investigation revealed small kidneys without cysts. Cystography showed negative results. An open renal biopsy showed segmental zones of interstitial fibrosis containing variable areas of tubular atrophy. A sparse interstitial cell inflammatory infiltrate was also found. Eight of 23 glomeruli were sclerotic (Figure 3). Immunofluorescence was negative. At last follow-up, in April 1996, the patient presented a slight deterioration of renal function (serum creatinine 2.1 mg/dl; creatinine clearance 40 cc/min.) and a moderate degree of arterial hypertension.

Other family members

Subjects I-1, II-1, II-3 were studied and had no kidney disease.

---

Fig. 2. Atrophic tubules with thickened TBM staining weakly with PAS; some tubules, located in the medullary region, are dilated with formation of small cyst-like spaces; interstitial fibrosis with significant inflammatory cell infiltration. Light microscopy; PAS stain (×25).
Clinical and genetic features of MCD

urine specific gravity was 1010; urinary osmolarity was 295 mmol/kg. Ultrasonography revealed small hyperechogenic kidneys with a few cysts of 1 cm in diameter localized at the corticomedullary junction. No follow-up was available.

**Patient 4 (male, born 1945)**

Subject II-3, the younger brother of the patient II-4, was found to have chronic renal failure in 1993, with subsequent development of uraemia. No clinical data are available. At age of 50, he underwent renal transplantation, which is still functioning.

**Patient 5 (male, born 1895; died 1928)**

Subject II-2, the brother of patients II-3 and II-4, died at age 37 from end-stage renal failure. He was known to suffer from chronic nephritis with renal insufficiency from age 20 but no clear information is available.

**Other family members**

Subject II-I died at 6 years from unknown causes. The subjects I-2, II-1, III-3 were studied and had no kidney disease. No information was available for subject III-1.

**Exclusion of linkage of MCD with NPH1**

Linkage analysis was performed using markers surrounding the previously described recessive NPH1 locus on chromosome 2 (D2S293, D2S340, and D2S160) to test for locus heterogeneity between recessive NPH and dominant MCD [24]. LOD score values relative to family 1 are shown in Table 2. Multipoint linkage analysis was achieved by using the same three informative markers on families 2, 4, and 5 were marginally informative for the used

<table>
<thead>
<tr>
<th>Marker</th>
<th>Recombination unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>D2S293</td>
<td>−5.43</td>
</tr>
<tr>
<td>D2S340</td>
<td>−5.50</td>
</tr>
<tr>
<td>D2S160</td>
<td>−4.75</td>
</tr>
</tbody>
</table>

**Family 5**

**Index case (male, born 1988)**

Subject IV-1 was found to have renal insufficiency (serum creatinine 1.1 mg/dl; creatinine clearance 60 ml/min; uricaemia 7.5 mg/dl) at age 8, when he was investigated for polyuria. Urinalysis was negative; urine specific gravity was 1010; urinary osmolality 300 mmol/kg. Ultrasonography demonstrated kidneys with size at lower range of normality, without cysts; the liver appeared normal. Cystography did not reveal vescicoureteral reflux. Ocular investigations did not demonstrate sign of retinitis pigmentosa. Biochemical liver abnormalities were not documented. Renal biopsy showed some atrophic tubules while others were enlarged. Tubular basement membrane was intensely PAS positive. Interstitium was markedly fibrotic with some areas of mononuclear infiltration. Four of 10 glomeruli were obsolete, with the remaining showing periglomerular fibrosis. Immunofluorescence study was negative. At last follow-up, in August 1997, serum creatinine and other parameters were unchanged.

**Patient 2 (female, born 1965)**

Subject II-2, the proband’s mother, was referred in 1994 for chronic renal failure. In her past history she had suffered from polyuria. At the time of presentation, serum creatinine was 3 mg/dl; uricaemia 6 mg/dl. Urinalysis showed no abnormalities; urine specific gravity was 1008; urinary osmolality 305 mmol/kg. Ultrasonographic investigation revealed small kidneys without apparent renal cysts. Biochemical liver abnormalities were not found. At last follow-up (July 1997), serum creatinine was 3.1 mg/dl.

**Patient 3 (male, born 1932)**

Subject II-4, the proband’s grandfather, was found to have chronic renal failure (serum creatinine 3 mg/dl; uricaemia 8 mg/dl) in 1992. He had had polyuria and polydipsia for many years. Urinalysis was negative;
MCD [12,25,26], the significance of this association is not well established. In particular, it is not clear whether this association identifies a single nosological entity [25,26]. It is possible that hyperuricaemia and gout exist in our family independent of MCD; alternatively, the defects producing hyperuricaemia and MCD might be inherited together or represent two clinical features inherent to the same genetic defect.

A second point of interest is the wide range of age at onset of MCD in respect to recessive NPH which is usually diagnosed under 10 years [1,2]. In our series the age of onset of the disease was extremely variable, ranging from 8 to 65 years; moreover, the age at which end-stage renal disease developed was also quite variable, and ranged from 18 to 73 years. Juvenile and adult onset of MCD coexisted in families 4 and 5, suggesting that an age limit is difficult to delineate. This indicates, in agreement with previous reports [11,13], that the age of onset cannot be considered of diagnostic value.

Fig. 4. Multipoint linkage analysis of families 1 and 3 showing exclusion of linkage between MCD and NPH1 locus.

markers. Deletion analysis of the 3 STS present at 2q13 was in all cases negative (data not shown).

Discussion

The term nephronophthisis historically includes renal diseases with various clinical features, different age at onset, rate of progression towards renal failure and different patterns of inheritance. However, since the clinical and genetic heterogeneity does not necessarily imply different diseases, the majority of the authors prefer to refer to NPH/MCD complex [1,2,11–17]. While the recessive form of NPH in its pure renal form or associated with extrarenal symptoms represents a more homogeneous entity, confusion exists in the literature regarding MCD [1].

In this report we describe five new families containing 28 patients presenting with clinical, histological, and genetic features consistent with the diagnosis of MCD. The renal clinical characteristics common to NPH/MCD, including polyuria, polydipsia, normal urine analysis, and slow progression to renal failure, were seen in our families. Moreover, a histopathological picture of chronic tubulointerstitial nephritis was observed. Extrarenal lesions usually found in the recessive form of the disease, such as tapetoretinal degeneration, central nervous dysfunction, skeletal involvement and liver disease, were not present.

Since our study population represents a homogeneous group with clinical and histological criteria fitting the diagnosis of MCD, this give us the opportunity to outline the aspects of the disease which appear fragmentary in the literature.

The first point we would like to discuss is the association of MCD with hyperuricaemia and gout in family 1. Although the occurrence of hyperuricaemia and gout has been reported in some families with MCD [12,25,26], the significance of this association is not well established. In particular, it is not clear whether this association identifies a single nosological entity [25,26]. It is possible that hyperuricaemia and gout exist in our family independent of MCD; alternatively, the defects producing hyperuricaemia and MCD might be inherited together or represent two clinical features inherent to the same genetic defect.

Two final points deserving consideration are the presence of cysts and histology. Although the presence of cysts (which has given rise to the term ‘medullary cystic disease’ in the American literature) has been historically considered a cardinal feature of NPH/MCD complex [9,10,14,27], from the introduction of ultrasonography it became apparent that they appear later in the course of the disease [28,29]. Since the development of cysts later may not be unique to NPH/MCD, as has been observed in patients with end-stage renal disease due to other aetiologies [30,31], some authors believe that it is not appropriate to consider NPH/MCD as a cystic disease [1]. In our families, renal cysts were documented in a minority of patients, the finding being not homogeneous within families. Sonographic and/or TC scan evidence of cysts, mainly localized in the medulla and at the corticomedullary junction, was found in one patient of family 1, in two affected sisters of family 2, in one patient of family 3, and in one patient of family 5. By renal biopsy, a diagnostic tool with considerable limitations [1], cystically dilated tubules were seen in the medullary region of an additional patient of family 3, who had negative renal sonography. These findings suggest that, despite the appellation of the disease, the presence of medullary cysts, although helpful, is not required for the diagnosis of MCD.

The histological changes seen on renal biopsy were at the same time not pathognomonic for MCD. The most frequent histological lesions in our patients were represented by focal areas of tubular atrophy and segmental zones of interstitial fibrosis. Groups of atrophic tubules with thickened TBM staining with periodic acid–Schiff alternated with viable hypertrophic and dilated tubules. Atrophic tubules were surrounded by fibrotic interstitial tissue, accompanied by a sparse inflammatory infiltrate. Glomeruli were often normal, although some were completely sclerotic and other showed varying degrees of periglomerular fibrosis. Significant vascular lesions were not observed. Immunofluorescence studies were negative. These
findings further support that a specific histological diagnosis of MCD is often not possible on needle biopsies, and a confrontation with the clinical and familial history is necessary.

Based on all these observations, it is clear that the diagnosis of MCD may be difficult on purely clinical grounds, and in this view the genetic approach is critical. Evidence obtained from the study of present families indicates, according to Mendelian principles of segregation, a dominant mode of inheritance. A vertical transmission of the disease was observed, with the condition being recognized in members of two or more generations. One parent of each affected member had symptomatic renal disease. Male to male inheritance also occurred, ruling out the possibility that the lesion is located on the X chromosome. Finally, the absence of consanguinity further supports the hypothesis of a dominant trait.

Multipoint linkage analysis conducted with markers flanking the NPH1 locus showed exclusion of linkage with MCD. Therefore the heterogeneous inheritance pattern reflects a condition of locus heterogeneity for recessive NPH and dominant MCD, with the dominant gene(s) still to be mapped. At present we cannot exclude genetic heterogeneity inside MCD, notwithstanding the above-mentioned renal clinical homogeneity of the disease.

In summary, we have described five new families with autosomal dominant MCD. The diagnosis was based on the presence of a hereditary tubulointerstitial nephritis, with an autosomal dominant mode of inheritance. While the recessive form of NPH/MCD is a major cause of end-stage renal failure in children [32], the dominant condition is considered to be a very rare disease. Up to 1992, about 30 families had been reported in the literature [1]. Although it is currently difficult to determine if in adults this disease is overlooked as a cause of end-stage renal failure, our study suggests that MCD families are more common than previously assumed. According to some authors, lack of experience with the diagnosis of this condition might partially explain the fact that the disease is rarely diagnosed [29]. We suggest that the traditional emphasis on the diagnostic value of the medullary cysts and of adult onset might have further contributed to the disease underestimation.

At the time of writing, nothing is known about the chromosome loci or defective gene of MCD. The exclusion of linkage to the NPH1 locus in our families suggests the existence of a different gene for dominant MCD. Molecular biology investigation of large kindreds will probably answer this question. We think that our families provide an ideal model for the detection of a genetic anomaly linked to the expression of the disease.

References


Received for publication: 10.2.98
Accepted in revised form: 3.6.98