Cortical microcystic disease of the kidney with dominant inheritance: a previously undescribed syndrome

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SUMMARY We report a family in which the father and all three children had symptomless chronic renal failure and, in the case of the children, normocytic, normochromic anaemia. None had hypertension, proteinuria, or abnormality of urinary deposit. Renal biopsy specimens showed microcysts confined to the renal cortex; some cysts contained vestigial glomerular tufts.

This family appears to represent the first known example of hereditary cortical microcystic disease. The distribution of the disease suggests dominant inheritance without sex linkage.

Cysts of the renal cortex are common but are usually large, solitary, and of little clinical importance except in differential diagnosis.

The various forms of polycystic disease are much less common. The familial types so far described have been either in the infantile nephrotic syndrome or part of a multisystem disorder. In this paper we describe a previously unrecognised form of the condition with no extrarenal abnormality and without the nephrotic syndrome. The father and all three children are affected.

Family S

Initially the three children were seen because of transient minor ailments by their family doctor, who found they were anaemic. Both parents and children felt well and even systematic questioning failed to elicit any symptoms. The children and father were pale, but the mother was of normal complexion. All were of normal stature except for the middle child, NS, whose height was only 1.25 m (below the third centile of age) and weight was 25.2 kg (third centile). Detailed examination of major systems revealed no abnormality. Blood pressures were normal as were optic fundi, and urine tests were negative for protein, blood, and glucose.

The parents (JS and TS) came from the west of Ireland and their marriage was not consanguineous. Neither was aware of renal disease affecting parents

or siblings, but they did not wish the rest of the family to be investigated.

Investigations

HAEMATOLOGICAL (Table 1)

Moderate anaemia was confirmed in the children, but the father (despite pallor) and mother had normal haemoglobin concentrations.

The anaemia was normocytic and normochromic and there was no reticulocytosis. Serum iron and iron binding capacities were below or only just within the normal ranges, but serum B12 and folate concentrations were normal. Total and differential white cell counts and platelets were all normal.

RENAL

Mid-stream urine samples from all the family had normal deposits and were sterile on culture.

Renal function (Tables 2 and 3).

The blood urea of the mother was low normal (Table 2), and as there was no physical or haematological abnormality it was concluded that she was healthy, and she was not investigated further.

The main finding was that the father and all three children had moderate, chronic renal failure (Table 2), with raised serum urea concentrations and reduced creatinine clearances. Serum potassium concentrations were raised and electrocardiograms showed high voltage peaked T-waves, consistent

Table 1 Haematological data

	Sex	Age (yr)	Hb concentration (g/dl)	PCV (%) (38–50)	MCV (fl) (76–92)	MCH (pg) (27–31)	MCHC (g/dl) (32–36)	Serum iron ($\mu\text{mol/l}$) (14–36)	Iron binding capacity ($\mu\text{mol/l}$) (45–70)
WS	M	13	9.2	27.3	81	27.3	33.7	4	44
NS	M	11	8.2	24.3	80	27.7	33.6	14	46
MS	F	7	9.8	29.0	85	28.7	32.9	12	47
JS	M	39	13.2	40.0	88	29.2	32.6	—	—
TS	F	39	13.8	41.2	94	32.0	33.8	—	—

Hb = haemoglobin; PCV = packed cell volume; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration. Values in parentheses = normal ranges.

Table 2 Renal function

	Serum urea (mmol/l) (3.0–8.3)	Serum creatinine ($\mu\text{mol/l}$) (44–133)	Creatinine clearance (ml/min) (85–125)	Uric acid (mmol/l) (0.12–0.36)	Serum sodium (mmol/l) (130–150)	Serum potassium (mmol/l) (3.3–5.8)	Phosphate (mmol/l) (0.8–1.45)	Calcium (mmol/l) (2.2–2.6)	Alkaline phosphatase (IU/l) (20–130)
WS	13.7	106	54.4*	0.44	136	5.8	1.61	2.36	220
NS	26.5	148	24.2*	0.50	135	7.1	1.72	2.39	144
MS	11.9	84	55.0*	0.43	136	6.3	1.61	2.46	219
JS	15.6	182	41.0	0.52	144	5.6	1.06	2.39	71
TS	3.9	—	—	0.30	144	4.5	—	—	—

*Corrected /1.73 m².

Values in parentheses = normal ranges.

with hyperkalaemia. Raised serum uric acid and phosphate concentrations were consistent with moderate renal impairment, and calcium and alkaline phosphatase concentrations were normal.

Urine concentration (Table 3) was impaired after overnight water deprivation, with osmolalities of 409–625 mosmol/kg (lower limit of normal 800 mosmol/kg). Sodium excretion was normal in the children (<150 mmol/24 h), but increased to

197 mmol/24 h in JS. Potassium excretion was normal.

Acid-base studies (Table 4) showed moderate metabolic acidosis (pH <7.36), uncompensated in JS and sons WS and NS, but compensated in MS (pH 7.37). Urine acidification after ammonium chloride loading was normal (pH <5) in the chil-

Table 3 Urine concentration and electrolyte excretion

	Volume (ml/24 h)	Osmolality (mosmol/l)	Sodium (mmol/24 h)	Potassium (mmol/24 h)
WS	900	625	71	58
NS	800	409	39	26
MS	1400	506	57	34
JS	2100	461	197	47

Table 4 Acid-base studies

	Arterial blood				Urine
	pH (7.36–7.44)	Standard bicarbonate (mmol/l) (24–32)	pCO ₂ (kPa) (4.5–6.1)	Base deficit (mmol/l)	pH
WS	7.31	18	4.0	8.7	4.9*
NS	7.24	15	3.8	12.2	5.0*
MS	7.37	20	4.1	5.5	4.8*
JS	7.33	22	5.4	2.9	4.9†

*After ammonium chloride loading.

†Average of three random samples.

Values in parentheses = normal ranges.

Fig. 1 Low power view of renal biopsy specimen from JS (father) showing cortex containing many small cysts filled by colloid-like material. Between these cysts are small areas of normal tubules and other small areas of very small thin walled empty cysts. Haematoxylin and eosin. Original magnification $\times 40$.

dren; in the father the mean pH of three random urine samples was 4.9.

Amino acid chromatography of the urine was normal.

Intravenous urography showed reduced concentration of radio-opaque medium, but the kidneys were of normal size and shape and there was no evidence of obstructive uropathy.

Renal ultrasonography showed no abnormality.

Other normal investigations comprised liver function tests, serum complement (C3, C4), antinuclear factor, and audiometry.

Renal biopsies

After these investigations renal biopsies were performed on the father (JS) and the eldest child (WS).

The biopsy specimen from JS consisted of a large needle core with renal cortex at either end and medulla in the middle. It contained only six glomeruli, however, because much of the cortex was replaced by cysts. There were numerous cysts in the cortex at either end of the specimen (Fig. 1). The mean diameter of 11 cysts measured was 328 μm , range 208 μm –500 μm . A point count showed that 50.3% of the area of the cortex was occupied by cysts.

The cysts contained colloid-like material which was eosinophilic, showed positive periodic acid Schiff (PAS) staining, and had an ill defined foamy consistency (Fig. 2). The cysts were rather larger in

the peripheral cortex than in the juxtamedullary cortex. The biopsy specimen was completely serial sectioned and the cysts were examined at many levels. In one cyst only there was a collection of capillaries resembling a small glomerular tuft (Fig. 3).

Between the larger cysts in the peripheral cortex were groups of much smaller cysts 20–25 μm diameter. They had extremely delicate walls, appeared empty, and did not contain the colloid material present in the larger cysts (Fig. 2).

In the small areas of cortex between the cysts the glomeruli and tubules, even those immediately adjacent to the cysts, appeared normal. There were, however, a few very small foci of shrunken atrophic tubules with thickened PAS-positive basement membranes.

There was appreciable hyaline thickening of many arterioles. The medulla appeared normal and contained no cysts.

The biopsy specimen from WS consisted of cortex and medulla and contained 20 glomeruli. The cysts in the cortex were smaller and more widely separated from one another than in the specimen from the father (Fig. 4). The mean diameter of the cysts was 172 μm , range 77 to 339 μm . A point count showed that the cysts occupied 7.8% of the area of the cortex.

The cysts had thin walls, quite like the Bowman's capsules in normal glomeruli. They contained the same foamy PAS-positive material as was present in

Fig. 2 JS. Renal biopsy specimen showing cortical cysts containing finely vacuolated, colloid-like material. Below centre is a group of small, empty, thin walled cysts. Haematoxylin and eosin. Original magnification $\times 100$.

Fig. 3 JS. Cyst in renal cortex with small collection of glomerular like capillaries arising from its wall. Periodic acid – methenamine silver. Original magnification $\times 100$.

Fig. 4 WS. Cysts are smaller than in JS with greater amounts of normal cortex between them. Haematoxylin and eosin. Original magnification $\times 100$.

Fig. 5 WS. Parts of three normal glomeruli, normal tubules, and no interstitial fibrosis. Small cyst in centre with a group of rudimentary capillaries in the wall. Periodic acid Schiff. Original magnification $\times 250$.

the larger cysts in the father's specimen. There were no groups of very small empty thin walled cysts. In several of the cysts there were small groups of capillaries projecting from the wall into the lumen of the cyst. They were covered by epithelium and resembled rudimentary glomerular capillaries (Fig. 5).

The tubules were normal and there was no appreciable interstitial fibrosis. The blood vessels were normal, but surprisingly there were a few completely hyalinised glomeruli despite the fact that the small arteries and arterioles appeared normal.

Discussion

The distribution of affected members of this family suggests a condition of autosomal, non-sex-linked, dominant inheritance. The main finding was symptomless chronic renal failure. This almost certainly explained the children's anaemia but it was not clear why the father was not also anaemic. Despite the renal failure, hypertension, proteinuria, and abnormal urinary deposits were conspicuous by their absence. Hyperkalaemia was an unexpected finding in the presence of only moderate renal failure. Two of the children (NS and MS) had low plasma renin concentrations and the possibility of hyporeninaemic hypoaldosteronism is being investigated.

The pathological changes were confined to the renal cortex. Microcysts constituted the most striking abnormality and the changes were more severe in the father than the son. The percent volume of the

cysts in the father was about seven times that in the son: they occupied 50.3% of the cortex in the father compared with 7.8% in the son.

A small tuft of capillaries was found in only one of the many cysts present in the biopsy specimen from the father. Several cysts in the specimen from the son contained similar tufts of capillaries. These groups of capillaries resembled glomerular capillaries, and it is therefore suggested that the cysts were glomerular in origin. An extensive search of many serial sections from both specimens, however, produced no evidence of even the most atrophic remnants of proximal tubules arising from them.

From a comparison of the appearances in the father and the son it would appear that the cysts have slowly enlarged, compressing and destroying the intervening cortex. During this process the rudimentary glomerular capillaries appear to have atrophied in many of the cysts in the father.

In these two patients the correlation between the changes in the renal biopsy specimens and the impairment of renal function was not close. In the father the damage to the renal cortex was quite severe (Figs. 1 and 2), 50% of the cortex being replaced by cysts, and for this degree of damage the impairment of renal function was not very severe. In the son, on the other hand, the structural damage, 8% of the cortex being occupied by cysts, was relatively slight for the degree of impairment of the renal function. In the son, however, were appreciable numbers of completely hyalinised glomeruli, which may have contributed to the impairment of renal function.

CLASSIFICATION

Cystic diseases of the kidney have been classified into seven groups by Bernstein;¹ cortical cysts are described in four of them.

In group I (renal dysplasia) cortical cysts with rudimentary glomeruli occur only as an occasional minor feature. The prominent, characteristic changes, which were absent in our patients, are cartilaginous metaplasia and obstructive uropathy.

In group II (hereditary cystic diseases) the two common conditions are infantile polycystic disease and adult polycystic disease. In both, cysts are not confined to the renal cortex and appear to originate from tubules rather than glomeruli. There are other important differences: the kidneys enlarge greatly and are of irregular shape, owing to differences in the size of the cysts. Infantile polycystic disease is of recessive inheritance and the liver is always affected.² Although adult polycystic disease is inherited in a similar manner to our patients' condition, the histological changes are sufficient to distinguish them.

Glomerular microcysts occur occasionally as a minor feature in group III diseases (multisystem heredofamilial syndromes with renal cysts), which are typically recessive. Renal involvement has been described in Ehlers-Danlos syndrome (dominant)³ and in the oral-facial-digital syndrome (sex-linked dominant).⁴ Multisystem involvement was absent in our family.

Group IV includes all other known conditions with predominant cortical cystic involvement. The majority are large solitary cysts which do not lead to renal failure. Diffuse cortical microcystic disease is uncommon. It is typical of the Finnish type of infantile nephrotic syndrome, but this is recessive;⁵ the cysts are tubular in origin and mainly situated at the corticomedullary junction. Other examples of cortical microcystic disease occur only sporadically, are without any known heritable tendency, and many have other abnormalities, particularly congenital cardiac defects.⁶

Bernstein's other groups do not include cortical cysts, but it is important to consider group VB, uraemic medullary cystic disease,⁷ known as juvenile nephronophthisis in Continental Europe, because the clinical features are remarkably similar to those in our family: insidious progression of renal failure with absence, or only late development, of hypertension and proteinuria.

The nephronophthisis complex includes several different genetic pedigrees, some associated with retinal abnormalities.⁸ In some families the inheritance appears to be autosomal recessive but in

others it is autosomal dominant. The pathological changes include much reduced kidney size; severe, diffuse, chronic damage to the cortex; glomeruli which are completely hyalinised or show considerable periglomerular fibrosis; severe loss of tubules and surviving, atrophic tubules which are slightly dilated and contain cast material; and severe interstitial fibrosis throughout the cortex. There are no cysts in the cortex but numerous cysts in the outer medulla close to the cortex.

In conclusion, we cannot find reference to any patients with the combination of clinical and pathological changes comparable to that in our family. We suggest that the condition should be classified as a separate entity in Bernstein's group II of hereditary cystic diseases.

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Addendum

The second son, NS, now 17 years old, has recently (January 1984) come under medical care and a renal biopsy has been performed. It shows cortical microcystic disease intermediate in severity between the biopsies of JS and WS.

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