PART XIV

NEPHROLOGY: Renal Pathology

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MEDULLARY SPONGE KIDNEY: ABNORMALITIES OF RENAL TUBULAR AND GLOMERULAR FUNCTION, AND THEIR RELATIONSHIP TO CLINICAL FEATURES

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Summary

This study confirms that medullary sponge kidney (MSK) has a good prognosis, but there is a considerable morbidity in patients with renal calcification; they suffer renal colic, ureteric obstruction, and frequently need operation. There is a high incidence of urinary infection in women. On follow-up, glomerular function is well maintained, although careful testing shows a mild depression of glomerular filtration rate in at least 40%. Proximal tubular function is normal, but abnormalities of distal tubular function are often seen: acidification defects occur in 24% and are associated with nephrocalcinosis, poor urine concentrating ability, and diminished glomerular function. Urine concentration defects occur in 73% and are probably secondary to nephrocalcinosis. Hypercalciuria was present in 19% and was not related to other defects.

Introduction

The term ‘medullary sponge kidney’ (MSK) describes a distinct structural abnormality of the kidney which is thought to be congenital. Multiple small cysts, 1 to 5 mm in diameter are found in the renal papillae, giving the kidneys a spongy appearance. These cysts are ectatic dilated collecting tubules, filled with a brown collagenous substance which is often calcified, and are lined with columnar or cuboidal epithelium. Although MSK was first clearly defined by Cacci and Ricci in 1949, it was not widely recognised until Ekström’s monograph appeared in 1959. The clinical diagnosis is usually made by intravenous urography (IVU), when dye can be seen filling the ectatic collecting tubules and cysts (Figure 1). When well developed this appearance is almost pathognomonic of the condition, but the diagnosis of mild degrees of MSK may be difficult. Radiological papillary nephrocalcinosis is also frequently present. The incidence of the condition on routine IVU examination is about 0.5%.

The main clinical features of MSK are renal colic, haematuria and urinary infection. Renal function is said to be well maintained, Ekström finding a
depressed glomerular filtration rate in only 2 of 16 cases studied\textsuperscript{1}, although in other series as many as 76\% of those studied were estimated to have a mild loss of glomerular filtration\textsuperscript{5}. It is necessary for a patient to have fairly good renal function in order to get good enough definition on an IVU to make a radiological diagnosis of MSK, so that patients who have a significant loss of renal function are unlikely to be diagnosed as having this condition. It is therefore necessary before drawing conclusions about prognosis to follow patients for a long period of time to see whether renal function changes; published series contain very few patients with long term follow-up.

Studies of tubular function in MSK have been on selected patients only and have not defined the overall incidence of abnormalities in MSK. Hypercalciuria\textsuperscript{2,6}, concentration defects\textsuperscript{2}, defects in urinary acidification\textsuperscript{7,8,9}, defects in urine ammonia excretion\textsuperscript{8,10}, and tubular reabsorption of sodium\textsuperscript{8}, have all been reported. This paper reports on 29 patients with MSK followed for up to 20 years, in whom renal glomerular and tubular function tests have been performed in order to define the incidence of abnormalities of renal function, and to see how the presence of each abnormality relates to the clinical features and prognosis of the condition.

Materials and Methods
The patients were identified from the hospital records system and were thus
selected only by the fact that they had presented with a symptom for which IVU was considered a suitable investigation. Each one was seen and investigated personally by the author. Proximal tubular dysfunction was sought by testing for urinary excess of small molecular weight substances normally filtered by the glomerulus and reabsorbed by the proximal tubule — glucose, amino-acids, and beta-2 microglobulin. Beta-2 microglobulin excess in the urine was detected by a gel diffusion precipitation method11, using a specific antibody and fresh urine which is concentrated 100 times or until the protein content of the sample is not more than 3 g per 100 ml. This technique correlates well with other methods for detecting excess beta-2 microglobulin in the urine. Urine acidification, and maximum concentration, were used as markers of distal tubular function. Urine concentration was measured after 14 hours of thirsting in 23 of the cases studied and after vasopressin and fludrocortisone administration12 in 3 other cases. Urine acidification was tested after a single oral dose of ammonium chloride, 0.1 g/kg; normal patients achieve a pH below 5.3213. Urine oxalate was estimated by the method of Hodgkinson and Williams14.

Results

Radiological sponge kidney was present bilaterally in 25 patients and unilaterally in 3; in 7 cases there was only patchy involvement of the affected kidneys. The remaining patient presented with haematuria, had 2 normal intravenous urograms, and was diagnosed by renal biopsy. There were 8 men and 21 women in the series, a reverse ratio to most series2,5, the first symptom appearing over a wide age range from 10 to 56 years. Urinary infection was detected at some time in 81% of the women and none of the men (p < 0.002), and did not appear to be related to the presence of nephrocalcinosis. Twenty-one of the patients had radiological nephrocalcinosis, in 14 of whom there were associated ureteric stones, and one patient had a renal stone with no nephrocalcinosis. In one of these patients a few specks of papillary nephrocalcinosis disappeared during the course of follow-up. The 7 remaining patients had no radiological calcification. Haematuria and hypertension (Table I) were equally common in the presence or absence of renal calcification. Renal colic was related to the presence of radiological calcification, and occurred in 68% of such patients, 7 of whom needed operation for relief of symptoms. Three patients without renal calcification

<table>
<thead>
<tr>
<th>Renal calcification</th>
<th>Colic</th>
<th>Haematuria</th>
<th>Infection (women only)</th>
<th>Hypertension</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present 22</td>
<td>15 (68%)</td>
<td>11 (50%)</td>
<td>13 (77%)</td>
<td>3 (14%)</td>
<td>4 nephrectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 lithotomy</td>
</tr>
<tr>
<td>Absent 7</td>
<td>0</td>
<td>3 (43%)</td>
<td>4 (100%)</td>
<td>1 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Total 29</td>
<td>15 (52%)</td>
<td>14 (48%)</td>
<td>17 (81%)</td>
<td>4 (14%)</td>
<td>7 (24%)</td>
</tr>
</tbody>
</table>

TABLE I. Relationship of Clinical Features to Renal Calcification in 29 Cases of Medullary Sponge Kidney

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suffered dull loin pain, which may be associated with urinary tract infection in
2, but is unexplained in the other.

Abnormal glomerular function, as indicated by a plasma creatinine above
113 μmol/L was found in 6 patients (29%) all with nephrocalcinosis; 5 of these
had a urine acidification defect, and the other had severe hypertension. Nine
patients with normal plasma creatinine had estimates of creatinine clearance
performed. Allowing for possible errors of urine collection in out-patients, and
therefore accepting a relatively low lower limit of creatinine clearance of 115 L/
24 hr, 4 patients were definitely abnormal, 2 were borderline, and 3 (including
the only 2 without nephrocalcinosis who were tested) were normal. The lowest
recorded creatinine clearance in any patient was 60 L/24 hr. Thus at least 38%
of the patients in this series have diminished glomerular filtration, and it is likely
that if all had had accurate tests of creatinine clearance the figure would be
higher (about 60%).

Nineteen patients in this series have been followed for more than 5 years, 9
of them for more than 10 years. Only 2 have shown any rise in plasma creati-
nine during follow-up; in one this was during the terminal stages of carcinomato-
sis with hypercalcaemia, and the other had a non-functioning kidney removed
which was found to be infiltrated by an undiagnosed granulomatous condition
which is probably affecting the other kidney also. These are the only 2 patients
whose serum creatinine has risen above 200 μmol/L. This is the first longitudinal
study to confirm the suggested good renal prognosis in these patients.

Only one patient showed any evidence of proximal tubular dysfunction on
the tests performed: this was the patient with a granulomatous renal infiltration,
who had excess beta-2 microglobulin in the urine. It seems, therefore, that proxi-
mal tubular dysfunction is not a feature of MSK.

Symptoms of thirst, polyuria or nocturia were only noticed by 4 patients, all
of whom had nephrocalcinosis. Urine concentrating ability was tested in 26
cases. Allowing for some error in patient compliance with thirsting, and there-
fore accepting a relatively low normal limit of maximal urine osmolality of 800
mOsm/L, only 7 patients (27%) were normal. It is significant that only 2 of 19
patients with nephrocalcinosis concentrated normally compared with 5 of 7
without nephrocalcinosis (p < 0.05), and these 2 had only minimal nephro-
calcinosis. A concentration defect is an almost universal finding in patients with
radiological nephrocalcinosis and is probably secondary to this rather than a
primary feature of MSK. One of the 2 patients in this series without nephro-
calcinosis who failed to concentrate normally had severe hypertension and
moderate glomerular dysfunction: it is possible that the other had sub-radiologi-
cal nephrocalcinosis.

A defect of urine acidification was found in 7 (24%) of 29 cases, 6 women
and one man. These patients all had nephrocalcinosis (which does not by itself
affect urinary acidification), 3 had systemic acidosis, and one of these was
hypokalaemic. Five (71%) of the 6 patients had an elevated serum creatinine
compared with one (5%) of the remaining patients (p < 0.01). From Figure 2
it can also be seen that these patients have a maximum urine osmolality signif-
ically lower than the others with nephrocalcinosis (p < 0.05). Urinary tract
infection does not seem to be a factor causing an acidification defect, as only 3
women with such a defect (50%) had urinary infections detected at any time, compared with 100% of the remaining women.

All the patients in this series had normal serum calcium, phosphate and alkaline phosphatase, and there was no evidence of hyperparathyroidism. Hypercalciuria, as judged by a 24-hour urine calcium greater than 7.5 mmol in women and 10 mmol in men\textsuperscript{16} was found in 5 (19%) of the 26 patients tested, 2 men and 3 women, including one of the 7 patients without nephrocalcinosis. None of these 5 patients had acidification defects, and their glomerular function and urine concentrating ability were not significantly different from the rest of the series. Twenty-four hour urine oxalate excretion was measured in 19 patients and was normal in all of them.

Discussion and Conclusions

Much of the morbidity of MSK derives from renal calcification, and in women from urinary infection. Therapy should be aimed at detection and rapid treatment of urinary infection, and prevention of accumulation of calcium in the kidney. For the latter aim it is important to identify and treat the two conditions which predispose to nephrocalcinosis. We treat hypercalciuria with mild dietary calcium restriction and cellulose phosphate. Patients with a renal tubular acidification defect are treated with sodium bicarbonate, which by elevating urine citrate excretion is probably helpful in preventing accumulation of calcium in the kidney, in both acidotic and in non-acidotic patients. By these measures it should be possible to prevent further accumulation of calcium in the kidneys of many patients diagnosed as having MSK and thus lower the morbidity of the condition.
Acknowledgments

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References

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Open Discussion

ZOUWEN (Utrecht) As you mentioned the most important clinical problem is the formation of stones and calcium deposits. Are you aware of any measures to decrease that problem?

FEEST I think it is sensible to lower urinary calcium excretion if it is elevated. If there is an acidification defect you should give bicarbonate, whether or not they have systemic acidosis because if their calcium excretion is high as shown in a lot of other patients, it will fall, and we elevate urinary citrate and lower the likelihood of stone formation. But until we have followed these patients under treatment for another 20 years, I won't know, and since we do not have a control group I will never know.

MASSRY (Los Angeles) There are some reports showing that serum calcium may be mildly elevated in these patients, and even a report suggesting an increased incidence of parathyroid adenoma. Resistant hypercalciuria can lead to secondary hyperparathyroidism, and I was wondering whether you have levels of serum calcium and parathyroid hormone, because excess parathyroid hormone could explain the tubular defects.

FEEST Yes, I am aware of that, but we have looked at the serum calcium, phos-
phate, and alkaline phosphatases which are normal in all these patients and I have data for the ionised calcium levels in 7 of them, and they have been normal. In the same set I have parathyroid hormone measurements and they are also normal. So in this series there is no evidence of hyperparathyroidism.

ANDREUCCI (Naples) Have you measured tubular reabsorption of phosphate?

FEEST No, I have not. The only other proximal tubular function I can comment on properly is bicarbonate, and none of them have the features of a bicarbonate-losing syndrome. I have not measured phosphate reabsorption.

ANDREUCCI You have not measured lithium reabsorption?

FEEST No.