Hypothesis

An unusual association of contralateral congenital small kidney, reduced renal function and hyperparathyroidism in sponge kidney patients: on the track of the molecular basis

Giovanni Gambaro1,3, Antonia Fabris1, Lorenzo Citron2, Enrica Tosetto2,3, Franca Anglani2,3, Francesco Bellan2, Marilena Conte1, Luciana Bonfante2, Antonio Lupo1 and Angela D’Angelo2

1Division of Nephrology, Department of Biomedical and Surgical Sciences, University Hospital of Verona, 2Division of Nephrology and 3Laboratory of Molecular Biology, Department of Medical and Surgical Sciences, University Hospital of Padova, Italy

Abstract

Of unknown pathogenesis, sponge kidney (SK) is variably associated with nephrocalcinosis, stones, nephronic tubule dysfunctions and precalyceal duct cysts. Amongst 72 unrelated renal SK patients with renal stone disease, we detected one with unilateral bifid renal pelvis and six with unilateral small kidneys (longitudinal diameter difference >15%). Secondary causes of small kidney were excluded. Of the seven cases, four had reduced renal function (67 vs 7% in the entire cohort), and three developed hyperparathyroidism during follow-up (43 vs 4%). The pathogenesis of SK ought to explain why anatomical structures of different embryological origin are involved (the pre-calyceal and collecting ducts and the nephron) and why there is frequent association with hyperparathyroidism. In embryogenesis, the metanephric blastema synthesizes the chemotactic glial-derived neurotrophic factor (GDNF) to prompt the ureteric bud to branch off from Wolff’s mesonephric duct, and to approach and invade the blastema. The bud’s tip expresses the GDNF receptor (RET). RET–GDNF binding is crucial not only for the correct formation of ureters and collecting ducts (both of Wolffian origin), but also for nephrogenesis. We advance the hypothesis that SK results from a disruption in the ureteric bud–metanephric blastema interface, possibly due to one or more mutations or polymorphisms of RET or GDNF genes. This would explain: the concurrent alterations in precalyceal ducts and the functional defects in the nephron, the occasional association with size and the functional asymmetry between the two kidneys, some degree of renal dysplasia causing the reduction in the glomerular filtration rate and (given the role of RET in parathyroid cell proliferation) the association with hyperparathyroidism.

Keywords: hyperparathyroidism; MEN-2A; renal hypoplasia; RET; sponge kidney

Introduction

Sponge kidney (SK) is a renal malformation associated with: (i) a high risk of nephrocalcinosis and renal stones; (ii) a number of tubular function defects of acidification, concentration, calcium handling, maximum glucose reabsorption (Tmglucose) and maximum p-aminohippurate (TmPAH) secretion [1]; (iii) cystic anomalies of precalyceal collecting ducts; (iv) a possible risk of developing hyperparathyroidism; and (v) a moderate risk of developing urinary tract infections and renal failure.

Though rare, the disorder is relatively common in patients who have recurrent calcium nephrolithiasis. It generally occurs sporadically, but familial cases have been reported [2,3], and it has been described in patients with various developmental disorders.

The pathogenesis of the disorder has yet to be elucidated; meanwhile, we are still facing old hypotheses (anomalous congenital development of renal tubules with secondary cystic dilations; collecting duct dilation secondary to obstruction by calcium salts; renal manifestation of a systemic connective tissue disorder; or renal manifestation of primary hyperparathyroidism).

The association of SK with various malformations supports the conviction that it is a developmental disorder. However, the recent scheme proposed for
re-classifying developmental disorders of the kidney [4] does not consider SK at all.

The pathogenesis of SK ought to explain why anatomical structures of different embryological origin are involved (the collecting and precalyceal ducts, on the one hand, and the nephron, on the other) and why it is so often associated with hyperparathyroidism.

A few years ago, a patient was described who simultaneously had a medullary thyroid carcinoma and primary hyperparathyroidism (based on which a diagnosis of MEN-2a was advanced) together with SK and a RET gene mutation [5]. It was suggested that the association of SK and the RET mutation might be causal. It is worth noting that we can expect to find a RET gene mutation in a patient with a medullary thyroid carcinoma, since this occurs in 80% of these patients. Moreover, given the prevalence of the two conditions (as high as 10/100000 for the thyroid cancer and up to 1/100 for SK), a chance association (the low probability of which is up to 1 per million) is nonetheless a possibility. However, the idea of the existence of pathogenic mechanisms common to the two diseases is attractive, because the RET gene plays an important part in renal development.

During renal embryogenesis, through the synthesis of chemotactic molecules, i.e. glial-derived neurotrophic factor (GDNF), the metanephric blastema prompts the ureteric bud to branch away from Wolff's mesonephric duct (ureteral induction) and approach and invade the blastema [6]. The tip of the bud expresses a GDNF receptor, RET. The binding of RET and GDNF is essential not only for the correct formation of ureters and collecting ducts (the latter also of Wolffian origin), but also for the induction of nephrogenesis and kidney growth [6]. In particular, the transition of the mesenchymal cells of the metanephros to nephronic cells, the correct polarization of renal tubular cells and the specialization of different tubular segments of the nephron all need differentiation ‘messages’ originating from the ‘ureteric bud–metanephric blastema’ interface [6].

In light of these notions, we hypothesize that SK is the consequence of a disruption in the ureteric bud–metanephric blastema interface. This would explain the concomitant occurrence of the alterations in precalyceal and collecting ducts (ectasias, hypercalciuria, type 1 RTA and urine concentration defects) and of the functional defects in the renal tubule (hypercalciuria, and abnormal Tmglucose and TmPHA).

To confirm such a hypothesis demands molecular studies but, if this hypothesis holds, we would expect to see other renal developmental anomalies of processes that may depend on RET–GDNF binding in SK patients, such as unilateral renal agenesis, or unilateral or bilateral renal hypoplasia, or urinary tract duplication. It is worth noting that, in experiments involving the targeted inactivation of either the GDNF or RET genes, which leads to renal agenesis, some heterozygous animals develop unilateral renal agenesis or hypoplasia [7,8]. Anecdotal reports have also been published on the occurrence of horseshoe kidney [9] and unilateral renal aplasia [10] in SK patients. The first systematic analysis of SK patients to investigate this issue is reported herein.

**Patients and methods**

We retrospectively reviewed clinical records and X-ray films, and looked for unilateral renal agenesis, or unilateral or bilateral renal hypoplasia, or urinary tract duplication in a group of 72 patients, all of whom had SK (32 males, 40 females; age range 18–65 years) and who were routinely followed at the Nephrology Divisions of the University Hospitals of Padova and Verona. They were all sporadic (unrelated) cases, and all came to our attention because of calcium renal stones. SK was diagnosed during the work-ups of those patients for recurrent calcium nephrolithiasis, based on typical pictures obtained at intravenous urography. All patients had both kidneys involved, with typical nephrocalcinosis and linear striations in the papillae, or cystic collections of contrast medium in ectatic papillary ducts, giving blush or bouquet appearances to the papillae. The radiological criteria used for the diagnosis of SK have been described previously by others [11]. Briefly, the diagnosis is made if three or more linear collections of contrast material are evident within a papilla, and at least three papillae are involved bilaterally. Hypercalciuria was present in 67% of the studied patients, renal tubular acidosis (suspected on the bases of concomitant fasting urine pH > 6.0, hypocitraturia and normal serum bicarbonate) was present in 25%, and hypocitraturia alone in another 6% of the subjects. Renal hypoplasia was defined by a longitudinal renal diameter < 50% of that of the contralateral kidney [12] for unilateral hypoplasia, or renal lengths < 5 cm for bilateral hypoplasia. Small kidneys were arbitrarily defined as being < 9 cm long or, in the case of asymmetric kidneys, there being a > 15% difference between the longitudinal diameters of the two kidneys (i.e. 2 SD from the average longitudinal length) [13].

The following clinical and laboratory data were collected: serum calcium and phosphorus, parathyroid hormone, bicarbonate, creatinine clearance (established using the Cockcroft and Gault formula; considered abnormal when < 70 ml/min/1.73 m² in females, < 80 ml/min/1.73 m² in males), calcium, citruria, fasting urine pH and hypertension (repeatedly observed values > 140/90 mmHg in the sitting position after a 5 min rest, or therapy with antihypertensive drugs). In the few cases whose biochemical data were older than 2 years, blood analyses were repeated. Captopril renography and renal colour Doppler sonography were performed when appropriate.

**Results**

We observed one patient with unilateral bifid renal pelvis (patient no.1). None of the patients had unilateral renal agenesis, or unilateral or bilateral renal hypoplasia. We identified, however, six patients (three males) with one small kidney (Figure 1). The differences between the pole-to-pole lengths of each patient’s kidneys ranged between 16 and 28%.
One of these patients (no. 3) also had a modest degree of malrotation, with an anteriorized renal pelvis. In patient no. 7, the urographic pattern also suggested bilateral, multiple renal cysts imprinting calyces, a finding confirmed by renal ultrasonography. All the small kidneys were in their proper positions and appeared to have a normal number of papillae and a normal cortex. The morphologies of all of the small kidneys were regular, and no scarring was detected by intravenous urography. In one case only (no. 5), the larger kidney looked hypertrophic. The clinical and biochemical data of the six patients with small kidneys are given in Table 1. None of them had a history of obstructive uropathy, pyelonephritis or surgery (including minimally invasive procedures) in the small kidney, and none had ever had infectious/struvite/staghorn stones. One patient (no. 2) had come to our attention 6 years earlier for an episode of non-oliguric acute renal failure due to a ureteral stone contralateral to the small kidney. In this patient, after spontaneous resolution of the blockage (with the passage of a mixed calcium phosphate and oxalate stone), renal function recovered to a value of 72 ml/min. Patient no. 4, a woman, had a typical somatic hemihypertrophy. The two hypertensive women (nos 5 and 6) underwent captopril renography, with results negative for renovascular hypertension. Colour Doppler sonography showed no evidence of stenosis in the main renal arteries in the six patients with small kidneys.

Table 1. Clinical characteristic of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/gender</th>
<th>Bilateral SK</th>
<th>Developmental abnormality</th>
<th>PTH levels at diagnosis (intact mol pg/ml)</th>
<th>Hyperparathyroidism (intact PTH levels pg/ml, normal range 10–65)</th>
<th>Hemihypertrophy</th>
<th>Hypertension</th>
<th>Creatinine clearance (ml/min/1.73 m²)</th>
<th>Calcium (mg/24 h)</th>
<th>Acidification defect</th>
<th>Hypocitraturia (isolated) (&lt;300 mg/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1: RS</td>
<td>46/M</td>
<td>Yes</td>
<td>Bifid pelvis</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2: FG</td>
<td>30/M</td>
<td>Yes</td>
<td>Small kidney</td>
<td>Yes (125)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3: AZ</td>
<td>45/M</td>
<td>Yes</td>
<td>Small kidney + malrotation</td>
<td>Yes (95)</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4: MRA</td>
<td>47/F</td>
<td>Yes</td>
<td>Small kidney</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 5: PV</td>
<td>56/F</td>
<td>Yes</td>
<td>Small kidney</td>
<td>Yes (160)</td>
<td>No</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patient 6: MB</td>
<td>55/F</td>
<td>Yes</td>
<td>Small kidney</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 7: CS</td>
<td>41/F</td>
<td>Yes</td>
<td>Small kidney + extrapapillary cysts</td>
<td>No</td>
<td>No</td>
<td></td>
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</tbody>
</table>

SK = sponge kidney; PTH = parathyroid hormone.

Fig. 1. Right small, harmonious, hypofunctioning kidney in patient no. 3. The right kidney is 28% shorter than the left and shows a distinctly reduced concentration of the radioopaque contrast medium. Typical SK features can be observed in both kidneys.
Four of the six subjects had reduced renal functions (67 vs 7% in the group as a whole), three a mild glomerular filtration rate (GFR) reduction and one (no. 3) a GFR of 40 ml/min. None of the patients had radiological evidence of vesico-ureteral reflux (VUR).

When diagnosed with SK, six out of seven had hypercalciuria, three had renal acidification defects and one had isolated hypocitraturia, which were confirmed repeatedly during follow-up. During follow-up (range 1–12 years), three of the seven patients developed hyperparathyroidism (43 vs 4% in the group as a whole). None had had hypocalcaemia or hyperphosphataemia, or had used loop diuretics during the follow-up before the onset of hypercalcaemia, hypophosphataemia and hyperparathyroidism.

Discussion

According to Pubmed, to date, >450 papers have been published on SK in peer-reviewed medical journals. While few papers addressing metabolic abnormalities report findings on small patient populations, many report associations with a number of malformations. These anecdotal and unusual associations have not been fully considered to hint at possible derangements of development as the likely pathogenesis of the SK.

To overcome this drawback, we carried out a systematic analysis, the first, searching for concurrent renal malformations in 72 patients with SK and nephrocalcinosis, one of the largest SK populations ever described. The study highlights the existence of some apparently trivial morphological malformations in a subset of SK patients, namely small kidneys and bifid renal pelvis, that seem to be frequently associated with hyperparathyroidism and reduced renal function. We suggest that these data support a hypothesis that SK is due to a disruption of the ureteric bud–metanephric blastema interface. Our hypothesis is based on the following: (i) the role of the ureteric bud–metanephric blastema interface in the branching of the ureteral bud-derived structures and the development of the kidney; and (ii) the role of some of the molecules involved at the interface in parathyroid cell proliferation.

Abnormalities in the branching of the ureteral bud are thought to be responsible for urinary tract duplication, which includes the bifid renal pelvis (observed in patient no. 1). Although when discussing this case we cannot rule out a chance association with SK, our observation is not new [14] and fits quite well within the framework of our hypothesis.

Evaluating the small kidney always poses a problem, because of the difficulty in differentiating congenitally small, underdeveloped kidneys from secondarily small, atrophic kidneys. The criteria we chose to identify the six cases, however, seem adequate to rule out the latter condition. In fact, the patients’ histories exclude previous obstructive uropathies (a potential cause of renal hypotrophy, particularly in patients with urolithiasis), though this fact obviously relies to some degree on the patients’ recollections. Renal ischaemia was ruled out in the two hypertensive women by captopril renography; this is particularly important, because of the reported association of SK with renal artery fibromuscular dysplasia, a condition typical in hypertensive women. Furthermore, colour Doppler sonography in the six patients with small kidneys disclosed normal profiles, ruling out stenosis of the major renal arteries. The regular profiles of the small kidneys and the lack of calyceal deformities and scarring all support the assumption that these small kidneys are primarily underdeveloped, though according to our hypothesis SK could be associated with VUR. Indeed, the association of VUR and SK was reported previously [14]. The presence of VUR may actually point to defective branching processes during kidney–urinary tract development, but we found no sign of VUR by intravenous urography. Though this is not the gold standard diagnostic tool for such a condition, we cannot rule out the possibility that VUR had been present earlier and had resolved over time (as is generally the case).

Only patient no. 4 had congenital hemihypertrophy; the others had no somatic indicators of this condition. Congenital hemihypertrophy (OMIM 23500) is characterized by the asymmetric growth of the skull, face, trunk, limbs or digits, but it may also involve the viscera. In our opinion, this syndrome could not explain our findings, at least in five of our patients with one small kidney. This conviction is also supported by the observation that SK was bilateral in all subjects.

Renal failure is a possibility in patients with SK, though it is not particularly frequent. Renal failure in this disorder is believed to be related to renal infections, i.e. the formation of struvite stones, or to obstructive episodes or surgery [15]. In the whole group, the prevalence of reduced creatinine clearance was 7%, as in the literature [15], but all four patients with this finding were in the subgroup of patients with asymmetric kidneys and none of them had a history of infectious stones, obstruction or surgery, and they did not have abnormal main renal arteries. This would suggest that the renal anomaly detected in them is not just a trivial, modest reduction in the volume of one kidney, but that it may be a process affecting the entire parenchyma of both kidneys, reducing renal function globally. The derangement presumably is not limited to the typical precalyceal dilations of SK; it may be characterized by an insidious renal dysplasia responsible for the decline of renal function.

According to our hypothesis, i.e. that SK is due to a disruption of the ureteric bud–metanephric blastema interface, the transition of the mesenchymal cells of the metanephros to nephronic cells, or in other words the development of a normal renal parenchyma, ought to be impaired [6]. If this is the case, then it is hardly surprising that: (i) several carrier functions are altered, both in the nephron (of metanephric origin) and in the papillary and collecting ducts (of Wolfian origin); and (ii) most of our subjects have a reduced renal function.
SK is reportedly associated with a number of renal–ureteral malformations, e.g. with horseshoe kidney [9], with congenital mega-ureter and unilateral renal aplasia [10], and with familial co-segregation with different ureteral abnormalities (ureteropelvic junction obstruction, bifid pelvis, duplicated ureter and VUR) [14]. An association with Wilms’ tumour, RET, GDNF, etc. (e.g. Fallot’s tetralogy, rhythm disorders and sudden death syndromes) are due to non-lethal defects in genes expressed only during embryogenesis. If our findings are confirmed by molecular studies, SK might be the first renal disorder to join this category.

In the framework of our hypothesis, we consider the interaction of RET with GDNF to be the prime candidate for the pivotal pathogenic mechanism. That three out of seven of our patients developed hyperparathyroidism during follow-up may support the role of the RET gene, because its mutations cause MEN-2a, which includes, among other endocrine disorders, primary hyperparathyroidism.

If some RET gene mutation or polymorphism responsible for SK also weakens the control of parathyroid cell proliferation, a negative calcium balance (due to the renal leak hypercalciuria of SK patients, or vitamin D deficiency, etc.) or decreased renal function putatively might trigger parathyroid cell proliferation, leading to hyperparathyroidism.

Other candidate gene products may be considered, such as the glial-derived factor neurturin or the WT1 gene, and many others, including Eya-1, integrins, PAX2, laminin z5, AgtR2, FGFs, MT1-MMP, MMP9, TIMP1 and TIMP2, all involved in the process of nephrogenesis [6]. However, since most of them continue to be active after embryogenesis, they are less likely to be involved, because patients with SK do not manifest disorders due to mutations of these genes and generally look otherwise normal.

We now know that neurological and cardiac anatomical and functional malformational disorders (e.g. Fallot’s tetralogy, rhythm disorders and sudden death syndromes) are due to non-lethal defects in genes expressed only during embryogenesis. If our findings are confirmed by molecular studies, SK might be the first renal disorder to join this category.

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References

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