Medullary sponge kidney: state of the art

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ABSTRACT

Medullary sponge kidney (MSK) is a kidney malformation that generally manifests with nephrocalcinosis and recurrent renal stones; other signs may be renal acidification and concentration defects, and pre-calyceal duct ectasias. MSK is generally considered a sporadic disorder, but an apparently autosomal dominant inheritance has also been observed. As MSK reveals abnormalities in both the lower and the upper urinary tracts, renal imaging and renal function tests should be performed in patients with a suggestive clinical presentation. Medical or surgical treatment is warranted in symptomatic patients or when complications like renal insufficiency, hypertension or infection occurs. MSK is generally considered a benign condition. The natural history of MSK is favorable, with an overall good prognosis.

REFERENCES

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nephron and is often associated with urinary tract developmental anomalies, its pathogenesis should probably be sought in one of the numerous steps characterizing renal morphogenesis. Given the key role of the GDNF-RET interaction in kidney and urinary tract development and nephrogenesis, anomalies in these molecules are reasonable candidates for explaining a disorder such as MSK. As a matter of fact, we detected two, hitherto unknown, rare variants of the GDNF gene in MSK patients. We surmise that a defective distal acidification has a central role in MSK and is followed by a chain of events including defective bone mineralization, hypercalciuria, hypocitraturia and stone formation.

INTRODUCTION

Medullary sponge kidney (MSK) is a kidney malformation that generally becomes manifest with nephrocalcinosis and recurrent renal stones; other signs may also be renal acidification and concentration defects, pre-calyceal duct ectasias (erroneously diagnosed as cysts) and neglected proximal tubular defects. MSK is generally considered a sporadic disorder.

Although its prevalence in the general population is not precisely known, it is considered an uncommon condition. In a large, unselected radiological series [1], pictures containing from clear-cut to weak radiological signs of MSK were observed in 0.5–1% of cases. The condition is relatively well represented among renal stone patients, however. Indeed, MSK has been observed in up to 20% of recurrent renal calcium stone formers [2], and 12% of our own case series of such patients have the condition [3].

Table 1. Renal and extra-renal malformative conditions identified in patients with MSK

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (%)</th>
<th>Reports in PubMed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckwith–Wiedemann syndrome</td>
<td>13 (Ref. 59)</td>
<td>15</td>
</tr>
<tr>
<td>Congenital hemi-hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilm’s tumour</td>
<td></td>
<td>5b</td>
</tr>
<tr>
<td>Rabson–Mendenhall syndrome</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Polycystic renal disease</td>
<td>15 (Ref. 28)</td>
<td></td>
</tr>
<tr>
<td>Cakut syndrome</td>
<td>10 (Ref. 10)d</td>
<td></td>
</tr>
<tr>
<td>Caroli syndrome and congenital hepatic fibrosis</td>
<td>70 (Ref. 29)e</td>
<td></td>
</tr>
<tr>
<td>Young’s syndrome (immotile cilia, or obstructive azoospermia and chronic sinopulmonary infections)</td>
<td>2</td>
<td></td>
</tr>
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</table>

The association between MSK and the above-listed disorders is indicated in terms of prevalence where this information is available, or otherwise as the number of case reports. Only associations with two or more published case reports are listed.

bAlways in association with the Beckwith–Wiedemann syndrome or congenital hemihypertrophy.

Prevalence of MSK in a cohort of: apatients with Beckwith–Wiedemann syndrome; cpatients with congenital hepatic fibrosis; and dADPKD patients.

cPrevalence of malformations in a cohort of MSK patients.
During nephrogenesis, GDNF synthesized by the metanephric blastema, induces ureteric bud outgrowth and branching from Wolff’s duct. GDNF requires a receptor tyrosine kinase (RET) and a co-receptor (GFRα1) for the downstream signalling pathway (Figure 2).

\textbf{In vivo} experiments with GDNF or RET homozygous inactivation resulted in animals with renal agenesis due to the ureteric bud failing to develop from the Wolff’s duct, and the animals died shortly after birth. Conversely, animals heterozygous for a GDNF or RET null allele were both fertile and viable [12–14]. While the RET and GFRα1 heterozygotes demonstrated a near-normal renal phenotype, the GDNF heterozygotes showed an array of renal phenotypes ranging from smaller kidneys (many with abnormal shapes and cortical cysts) to unilateral renal dysgenesis, indicating that GDNF dosage influenced kidney development, and that the loss of one allele suffices to give rise to a particular renal phenotype, though it may become evident only later in life. RET ectopic expression in transgenic mice resulted in small cystic kidneys [15].

RET mutations were found in 37% of fetuses with bilateral renal agenesis and in 20% of fetuses with unilateral renal agenesis [16], also associated with a GDNF mutation in one case. Very recently, GDNF variants have been disclosed in patients with urinary tract malformations [17].

Given the key role of the GDNF–RET interaction in kidney–urinary tract development and nephrogenesis, anomalies in these molecules could be reasonable candidates for explaining a disorder such as MSK, which discloses abnormalities in both the lower and the upper nephron, and is often associated with urinary tract developmental anomalies. Interestingly, an anecdotal report in a woman has described MSK together with multiple endocrine neoplasia (MEN 2A) due to a RET mutation [18].

\textbf{MSK as a genetic disease}

MSK is considered a sporadic disease, though a handful of familial clusters of cases of MSK have been reported [19–21], in which MSK segregated as an autosomal dominant trait. The observation of familial clusters of MSK is nonetheless an experience shared by many nephrologists. In an effort to establish whether MSK is indeed an inheritable disorder, we have recently performed a systematic investigation on relatives of MSK patients in our cohort by means of interviews, renal

\textbf{FIGURE 1:} Bilateral MSK and left kidney megacalycosis. Typical blushes are visible in all papillae in the right and left kidneys; the left kidney is remarkable, however, for the associated dilated calyces (megacalycosis) with a normal renal pelvis, which rules out any obstructive cause and suggests a malformative origin.

\textbf{FIGURE 2:} Schematic representation of the interplay in the nephrogenesis between the RET receptor on the ureteric bud and its ligand GDNF produced by the metanephric mesenchyme.
imaging and biochemical studies. We observed familial clustering of MSK in 50% of cases with an autosomal dominant inheritance with a reduced penetrance and variable expressivity [22]. If MSK is a developmental disorder, then genes governing renal development might be considered good candidate genes. We hypothesized that MSK might result from a disruption at the ‘ureteric bud–metanephric mesenchyme’ interface, probably due to disease-causing mutations or specific polymorphisms of GDNF and RET genes, or particular GDNF/RET genotype interactions. Studying 55 apparently sporadic MSK cases and 85 healthy controls, we detected eight MSK patients heterozygous for two, hitherto unknown, rare variants of the GDNF gene located in a putative binding domain for PAX2, i.e. the c.-45G > C and c.-27 + 18G > A variants, which were both found significantly associated with MSK [23].

Being located in the 5’UTR region of the gene, the two variants might cause quantitative changes in mRNA expression and/or an altered response to regulatory factors, given that both the GDNF variants are located in a domain that binds the transcription factor PAX2, which has a well-known crucial role in nephrogenesis [24]. In fact, we found GDNF gene expression significantly higher in the papillary tissue of a patient carrying the c.-27 + 18G > A variant than in controls [23].

An altered GDNF response to PAX2 might affect the development both of the nephric ducts (leading to the formation of ‘cysts’) and of the metanephric tubules, thus causing an altered renal cell polarization with mis-targeting of the carriers in- volved in acidification and ion handling, and the consequent anatomical and functional abnormalities observed in our patients [23]. That GDNF is involved in dysplastic/cystic renal disorders has been known ever since it was found up-regulated patients [23]. That GDNF is involved in dysplastic/cystic renal disorders has been known ever since it was found up-regulated.

Analysing a further 57 unrelated MSK patients confirmed the association and disclosed the low-penetrant GDNF mutation R93W in one patient, thus reinforcing our previous results. In all, 12% of our MSK cohort was found to be heterozygotes for rare GDNF variants (unpublished data).

Finding 12 patients with the same GDNF variants prompted us to hypothesize a founder effect. We consequently examined apparently normal parents and relatives of five GDNF heterozygotes and discovered that the mutations were inherited and co-segregated with the MSK phenotype [23].

The proportion of cases attributable to GDNF mutations is small; however, the pathology of the remainder of the cases remains unclear. That some patients in our MSK cohort should have no GDNF mutations, and some patients have no family history of MSK, point to a genetic heterogeneity, but does not rule out the possibility of MSK being a complex disorder involving major susceptibility genes, one of which would be GDNF. The existence of non-genetic forms of MSK cannot be ruled out, however. We previously hypothesized that environmental factors (drugs, viruses, etc.) during pregnancy could also have a role in the interaction between the ureteral bud and the blasteme, giving rise to MSK [4].

Carboni et al. [26] recently described two patients with syndromic autosomal recessive distal renal tubular acidosis (dRTA) apparently associated with MSK. They suggested that MSK might be part of the clinical phenotype of autosomal recessive dRTA and be caused by the same gene. The typical clinical phenotype of recessive dRTA is very different from the one observed in characteristic MSK of adulthood; however, dRTA is common, but generally in its incomplete form; MSK patients do not fail to thrive or suffer from growth retardation in childhood; and sensorineural hearing loss has never been reported in typical MSK patients. In familial cases of MSK, moreover, the inheritance is autosomal dominant rather than a recessive trait. On the other hand, it is not uncommon for patients with multiple renal calcifications—as in complete dRTA—to be diagnosed as having MSK; the urographic diagnosis of MSK is not as easy as it might generally seem.

**MSK and ciliopathies**

Gunay-Aygun et al. recently suggested that MSK could be a ciliopathy [27], based on the observation that MSK has been reported in association with conditions determined by non-motile cilia disorders. MSK has actually been observed in association with ADPKD [28] and congenital hepatic fibrosis [29]. The association between MSK and Young’s syndrome [30] could also be added to the list. Gunay-Aygun et al. [27] also identified an increased medullary echogenicity in some obligate heterozygotes for PKHD1 mutations that, in the homozygous state, are responsible for the autosomal recessive polycystic kidney disease (ARPKD). While this hypothesis is intriguing, there is nothing to show that the medullary echogenicity seen in parents of patients with ARPKD coincides with nephrocalcinosis and dilated papillary collecting ducts. In addition, only the pre-calyceal and collecting ducts are dilated in MSK, at odds with the situation seen in ARPKD.

**CLINICS**

Although MSK may be silent, its anatomical characteristics and association with tubular dysfunctions explain its most common manifestations, i.e. nephrolithiasis and pyelonephritis. Macro- and micro-haematuria, renal failure and hyperparathyroidism can also occur, though less frequently.

The disease affects both genders in equal proportions and is generally diagnosed in adulthood, as a result of recurrent calcium nephrolithiasis and nephrocalcinosis, the signs that dominate the clinical history of most MSK patients. It is rarely manifest in children, but when this happens, the disease is rather severe and the bone-related consequences of dRTA prevail, with failure to thrive, short stature and rickets-like symptoms [31, 32].

We suspect that MSK is diagnosed mainly in adulthood because of its progressive nature. In fact, we have the impression that ‘cysts’ and nephrocalcinosis worsen over time, although this has not been specifically ascertained in any longitudinal investigation. Anecdotal evidence to support this impression comes, for instance, from the case of Dr. H.M. Saxton, Department of Radiology, Guy’s Hospital, London presented by Cameron [33].
Nephrocalcinosis is a very frequent finding in MSK patients, though we have seen a few cases without it despite a typical papillary pattern at urography. Hypercalciuria and hypocitraturia are also very common. In our experience, 100% of typical MSK patients had hypercalciuria and 83% had hypocitraturia [3], although others have reported lower rates of their occurrence (58 and 19%, respectively) [34]. Hypercalciuria, a relatively high urine pH, hypocitraturia and urinary stasis in the dilated papillary duct trigger the formation of calcium phosphate and/or calcium oxalate stones. Chemical analyses on our MSK patients’ stones showed that 67% of them were mainly calcium phosphate and 33% were calcium oxalate [3].

Stones recurred frequently in our cohort, with one episode every 2 years on average, but <3% of our patients needed urological intervention (extracorporeal shock wave lithotripsy in all cases). So, despite frequent recurrences, stone disease in MSK is characterized by small stones that pass spontaneously, as reported elsewhere [3].

MSK may also be silent or take an indolent clinical course with a history not dominated by stones. This was true of one in four of our patients [3], whose MSK was diagnosed as a result of symptoms unrelated to stones (haematuria, vague loin pain or burning sensation), or as an incidental finding during a diagnostic work-up for other reasons. In a recent study from the Mayo Clinic, 32% of MSK patients were diagnosed while they were being assessed for microscopic or gross haematuria, urinary tract infections or renal masses [34]. No stones formed during these ‘silent/indolent’ MSK patients’ follow-up either [3], and it is worth stressing that they did not have the typical urinary metabolic abnormalities predisposing to stone formation, i.e. hypercalciuria and hypocitraturia, or a biochemical profile suggestive of dRTA (marginally low serum potassium levels, fasting urinary pH > 5.5 and hypocitraturia) [3].

Very rarely, the MSK patient may have a clinical course dominated by pain, not necessarily associated with the passage of a stone or macro-haematuria. They experience an intractable, sometimes shooting pain, often against background dullness in the loin, that does not irradiate to the groin. This picture might bring the ‘loin-pain haematuria syndrome’ to mind but, strictly speaking, this is a diagnosis of exclusion, reached after ruling out other conditions (including MSK). These patients gain little from preventive stone treatment.

Although they are not particularly frequent (0.1 episodes a year per patient) [3], urinary tract infections are considered the second most common clinical problem (after renal stones) in MSK. Pyelonephritis may be the first sign of the disease in some MSK patients [35] and is certainly favoured by the particular anatomical derangement caused by the disorder.

Infectious episodes may complicate the renal stones picture, leading occasionally to secondary struvite stones and/or pyelonephritis, which are probably the most common causes of ESRD in MSK patients [36]. A mildly reduced GFR has been observed in MSK patients with contralateral congenital small kidneys [10], but such patients are definitely few in number, accounting for <10% of our cohort [10]. In any case, renal failure and ESRD are infrequent outcomes in MSK patients; hence, causes of ESRD other than MSK should be suspected in ESRD patients with nephrocalcinosis (e.g. complete dRTA and Dent’s disease, among other, much rarer conditions).

Hyperparathyroidism is also reportedly associated with MSK, and we too have observed it in a few patients [10]. It has even been suggested that hyperparathyroidism is a cause of MSK and triggers nephrolithiasis in these patients [37], but in our experience hypercalciuria, nephrocalcinosis and renal stones precede the onset of hyperparathyroidism. Dlabal et al. [38] advanced the hypothesis that the negative calcium balance due to renal hypercalciuria stimulates the parathyroids, leading to hyperplasia: we are of the same mind as concerns its effect, but disagree on the genesis of the negative calcium balance. Incomplete and overt dRTA are reported in up to 40% of MSK patients [39–41], though a prevalence of the overt form has been reported in only 2.9% of cases [42]. In Daudon’s large series of stones from MSK patients [41], the prevalent carbapatite and brushite composition supports the impression that distal acidification defects must be very common in MSK. We found that >80% of our MSK patients had a biochemical profile suggestive of incomplete dRTA, i.e. marginally low serum potassium levels, fasting urinary pH > 5.5 and hypocitraturia [43]. In addition, 58 and 14% of MSK patients have a dual-energy X-ray absorptiometry profile of osteopenia and osteoporosis, respectively, unrelated to any of the most common causes of bone demineralization (particularly, hyperparathyroidism and menopause) [43].

We have yet to conduct a specific study in our MSK patients to confirm their high prevalence of incomplete dRTA and validate the previously described biochemical profile suggestive of dRTA. The real prevalence of dRTA in our cohort thus remains to be seen. We also cannot rule out the possibility of MSK patients having a primary renal calcium leak, though we feel that the finding that treatment with alkali citrate corrected the above-described biochemical profile supports our interpretation, for patients with dRTA at least. In particular, alkali citrate treatment dramatically reduced calciuria and improved bone mineral density [43]. The drop in calciuria induced by potassium citrate treatment in our MSK cohort may be due both to a higher luminal pH activating TRPV5 (the epithelial calcium channel) in the distal nephron [44], and to their decreased sodiuria [3]. We estimated, however, that the two mechanisms together could explain no more than 40% of the observed decrease in calciuria [3]. To explain such a marked reduction in calciuria, we therefore concluded that, by correcting incomplete dRTA (which we believe is frequent in MSK patients), long-term treatment with alkali citrate improves bone mineralization and thus reduces bone calcium mobilization and calciuria.

We surmise that a defective acidification has a central role in MSK and would be followed by a chain of events including defective bone mineralization, hypercalciuria, hypocitraturia and stone formation. Oster et al. [45] also suggested that a distal renal acidification defect plays a pivotal part in the genesis of hypercalciuria in MSK, and Higashihara et al. showed that correcting these patients’ acidosis with bicarbonate reduced their calciuria [46]. Having said that we cannot rule out the possibility of this acidification defect being...
secondary to repeated ‘micro-obstructive’ episodes due to stones, although the intriguing observation that MSK patients carrying the previously described GDNF variants have a more severe acidification defect [23] supports the impression that it is a primary phenomenon. Whether this subtle acidosis is primary or not, our data suggest that—once established—it has a strong and highly prevalent impact on bone mineralization and on the urinary stone risk profile [3, 43].

**TUBULAR ABNORMALITIES**

In addition to the already-described morphological abnormalities and dRTA, MSK is associated with other tubular defects of the lower and upper nephron. Among the former, a defective urinary concentration has been reported [33]. Hypocitraturia is most likely an epiphenomenon of dRTA. MSK may also involve a number of dysfunctions of the upper nephron (of the proximal tubule), however. The maximum glucose re-absorption (TmGlucose) and maximum secretion of P-amino-hippurate (TmPAH) are reportedly affected [47]. We too found that 40% of our cohort of MSK patients had LMW proteinuria and low plasma phosphate levels due to a lower Tm for phosphate (A. Fabris, unpublished data).

These proximal tubular abnormalities in MSK patients mean that the whole nephron is indeed deranged in this condition. This was not unexpected, based on our assumption that MSK is a developmental embryological disorder of the interface between the ureteral bud and the metanephric blastema [4]. As the transition of mesenchymal cells from the metanephros to nephronic cells and the correct polarization and specialization of renal tubular cells necessitate differentiation ‘messages’ originating from the ‘ureteric-bud/metanephric-blastema’ interface [48], a disruption of said interface would explain the concomitant occurrence of alterations in both the distal and the proximal nephron.

**DIAGNOSIS**

The diagnosis of MSK is radiographic, and i.v. urography is (or was) the gold standard. Typical pictures reveal collections of contrast medium in dilated papillary ducts (Figure 3), giving the appearance of a blush or linear striations in the mildest cases, or of bouquets of flowers when cystic dilation of the collecting ducts is seen in full-blown cases (Figure 4).

As already mentioned, medullary nephrocalcinosis is common (Figure 5), but not always present, and it is not essential for diagnostic purposes.

MSK typically involves all renal papillae bilaterally (Figure 4), though it may also be unilateral or affect only a few papillae (Figure 6), and this can be bewildering when it comes to diagnosis.

The severity of the disease (symptomatic stone rate and numbers of hospital admissions and procedures required) correlates with the extent of the urographic signs [49].

Urography has been almost completely replaced by spiral computed tomography (CT) (with no i.v. contrast medium) because of the latter’s better diagnostic performance in cases of renal colic [50]. This has led to fewer and fewer cases of MSK being diagnosed. Unfortunately, spiral CT cannot disclose the typical MSK ‘cysts’ and, in cases of nephrocalcinosis, it is often unable to reveal its spotty distribution, giving a
picture of gross calcifications instead [51]. Although a 20-year-long comparison between urography and CT (with and without i.v. contrast medium) showed that the latter’s sensitivity in detecting MSK was markedly lower than urography [52], the latest CT equipment is highly sensitive and uroCT can disclose cystic dilations of the pre-papillary collecting ducts [53, 54], albeit at the price of a distinctly higher X-ray exposure than urography. It has been said that renal ultrasound (US) can diagnose MSK [7], but it cannot reveal the typical urographic images that are the hallmark of the disorder; US only shows nonspecific signs of hyperechoic medulla due to nephrocalcinosis and stones [55, 56]. We have used US to diagnose MSK in familial cases, but only in families with at least one case of MSK already diagnosed using gold-standard imaging techniques (urography or uroCT). In such conditions, we believe that a diagnosis of MSK is very likely if medullary hyperechogenicity and/or multiple hyperechogenic spots in the pyramids are discovered. NMR imaging is not sensitive enough to disclose the typical signs of MSK [57], though no specific studies on its use have been performed, as far as we know. In a very recent case report, it was suggested that remarkable hyperintensity on fat-saturated $T_2$-weighted MR images and aggregation of cystic structures on MR urography enable a diagnosis of MSK to be established [58].

**TREATMENT**

Although there is no specific treatment for MSK, and despite the difficulty of obtaining a correct diagnosis these days, recognizing MSK in recurrent stone formers is certainly useful for the purpose of tailoring their stone prevention treatment.

Given the pivotal role in lithogenesis of metabolic abnormalities in the urinary tract (i.e. hypercalciuria and hypocitraturia, together with a relatively high urinary pH), treatment with alkali citrate is a rational choice on the strength of our assumption that an incomplete dRTA is the primary functional defect in MSK. In actual fact, we generally recommend oral potassium citrate (2–4 g/day, i.e. 10–20 mmol/day divided into two or three doses) in patients who have MSK and at least one urine abnormality (hypercalciuria, hypocitraturia, hyperuricosuria and/or hyperoxaluria). We start with 2 g/day and gradually step up the dose in patients who fail to achieve the target citruria level of 450 mg/24 h, adding 1 g at a time until this citruria level is reached, providing their urinary pH in a 24-h collection is <7.5 (to prevent the risk of exacerbating any calcium phosphate lithogenesis). Patients are followed up once a month until the treatment’s dosage has been fine-adjusted, then 6-monthly. Our experience with this treatment has been quite positive: in a cohort of 61 MSK patients, the stone rate decreased from 0.58 to 0.10 per year [3], with an improvement in their bone mineral density [43]. These effects were achieved in parallel with a 50% decrease in their calciuria and a 75% rise in their citrate levels.

Other prophylactic measures, such as increasing water intake, reducing dietary sodium and proteins, increasing vegetable and fruit intake, are also generally recommended. Thiazides to reduce calciuria have also been used, though they may reduce citruria. We generally add thiazides in patients who continue to pass stones or have hypercalciuria despite receiving the maximal dose of alkali citrate.

In MSK patients with very frequently recurring stones, and in selected symptomatic patients, some urologists (F. Zattoni, Padua, Italy, and N. Buchholz, London, UK, personal communications) have occasionally opted for the prophylactic removal of small stones from the pre-papillary ‘cysts’ to give the patient a ‘break’ from stone colics.

**CONFLICT OF INTEREST STATEMENT**

None declared. This paper has not been published previously in whole or part.

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