Medullary sponge kidney (Lenarduzzi–Cacchi–Ricci disease): A Padua Medical School discovery in the 1930s

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The introduction of radiological contrast media and intravenous (i.v.) urography in clinical diagnostics in the 1930s enabled the discovery of several diseases, including the medullary sponge kidney (MSK). MSK is a renal malformation characterized by cystic anomalies of precalyceal ducts, which is frequently associated with nephrocalcinosis and renal stones. Although it was first recognized by G Lenarduzzi in 1939, its thorough description was the result of the *ante litteram* multidisciplinary cooperation between a radiologist (Lenarduzzi), a urologist (Cacchi), and a pathologist (Ricci), all at the Padua University Hospital. These authors 'established' the paradigm for its diagnosis that is still used today. I.v. urography is the gold standard for the diagnosis of MSK, but as the technique is used less and less, there is a concrete possibility of this renal condition being forgotten in the future. Although the pathogenesis of MSK has yet to be elucidated, its association with different malformative conditions supports the idea that it is a developmental disorder. Recent findings suggest that MSK may be the consequence of a disruption of the ureteral-bud/metanephric-blastema interface.

Kidney International (2006) **69,** 663–670. doi:10.1038/sj.ki.5000035; published online 4 January 2006

KEYWORDS: renal embryogenesis; precalyceal ducts; sponge kidney; urography

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Received 23 March 2005; revised 20 June 2005; accepted 14 July 2005; published online 4 January 2006

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney (MSK) is a renal malformation associated with a high risk of nephrocalcinosis and renal stones, with urinary acidification and concentration defects, cystic anomalies of precalyceal ducts and a moderate risk of developing urinary infections and renal failure. It generally occurs sporadically, but familial cases have been reported.

Although relatively uncommon, the disorder is not rare in patients suffering from recurrent calcium nephrolithiasis. The prevalence in the general population is not exactly known, as no systematic autopsy search has been performed on the condition, and some of the radiographic features are very subjective. In a large series of intravenous (i.v.) urographies performed for any reason,[1] pictures ranging from a clearcut MSK to faint radiological signs of MSK, for example, papillary 'blush', were found in 0.5–1%. Of course, this only tells us the prevalence among people submitted to i.v. urography (for which there must have been a reason), so we can safely assume that these prevalences are too high. About 3–5% of renal stone formers have MSK, although much larger proportions (up to 20%) have also been reported.[2] Differences are probably due to the intensity of investigation, the interpretation of papillary 'blush' and the selection of the case population.

The diagnosis of MSK is radiographic, and i.v. urography is still the cornerstone. Typical pictures reveal collections of contrast medium in ectatic papillary ducts, giving the appearance of a blush (in the mildest cases) or linear striations, or of bouquets of papillae, when cystic dilation of the collecting ducts is seen in the full-blown cases. Medullary nephrocalcinosis is frequent, but not always present, and it is not mandatory for diagnosis. Typical cases involve all renal papillae bilaterally, but involvement may also be unilateral or affect only a few papillae, the latter cases being the more bewildering to diagnose. The disease is interesting in many respects: (1) the impact of imaging techniques on its diagnosis, both in the past and in the future, when they will probably change our approach to the disorder; (2) the elusive pathogenesis: we are still facing old and generic 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; renal manifestation of primary hyperparathyroidism), despite its possible association with developmental disorders suggesting a malformative origin – but a recent proposal for a re-classification of developmental disorders of the kidney[3] astonishingly does not consider MSK at all.

DISCOVERY OF MSK

The discovery of MSK needs to be set in its historical framework, that is, the introduction of radiological contrast media and i.v. urography in clinical diagnostics.[4] Ever since 1906, various chemical compounds had been suggested to radiocontrast the kidney and urinary tract, but none were satisfactory. Some (colloidal silver, colloidal silver iodide, and thorium nitrate) triggered severe reactions and even death.[5,6] Although the striking lack of toxicity of sodium iodide was well established in the treatment of syphilis, it was only in 1918 that Cameron[7] proposed using sodium iodide to depict the urinary tract.

Beforehand, the only tool for the radiological investigation of the urinary tract was ureteral catheterization and direct imaging after inducing a pneumoperitoneum. Ureteral catheterization could be very difficult and painful at times, and it could cause severe complications. However, while pyelography was clearly capable of delineating the renal pelvis, it could not reveal the outline of the kidney itself. Kidneys could be clearly outlined only by inducing a pneumoperitoneum, but this procedure was not practised generally and was cumbersome.

In 1923, Osborne *et al.*[8] at the Mayo Clinic started to investigate the feasibility of performing i.v. urography by infusing 5–20 g of sodium iodide. Results were not good enough, however. The contrast was effective in delineating the bladder, but it was only partially successful in depicting the renal pelvis and ureter. Furthermore, it was almost invariably useless for renal imaging, enabling the size, shape, and position of the kidney to be determined at best.

Although it had been established that radio-opacity depended on the presence of iodine, it was impossible at that time to synthesize a well-tolerated, organic compound suitable for i.v. use. In the context of studies on the development of bacteriostatic agents at Shering in Germany in 1930, a well-tolerated radio-opaque medium, 5-iodine-pyridone-*N*-acetic acid ('Uroselectan'), was obtained by binding an iodine to a pyridine ring. But it was only after the introduction of a second iodine atom in the pyridine ring (Perabrodil by Bayer in 1931, and Uroselectan B by Shering in 1932), which considerably improved its radio-opacity, that urography could be launched in clinical practice.

Just like the more recent introduction of computed tomography or nuclear magnetic resonance in diagnostics, the exploration of the new diagnostic technique coincided with a period of scientific fervor and enthusiasm. Urography was a very powerful tool for investigating the kidney and urinary system, arriving at diagnoses hitherto achievable only in surgical or autoptic theaters. A few diseases were also discovered. In the X-ray of Figure 1, a normal-appearing calyceal system and pelvis are associated with a previously unknown anomaly: the opaque medium reveals dilated tubules in the pyramidal portion in the shape of blushes, some of which contain calcium deposits.

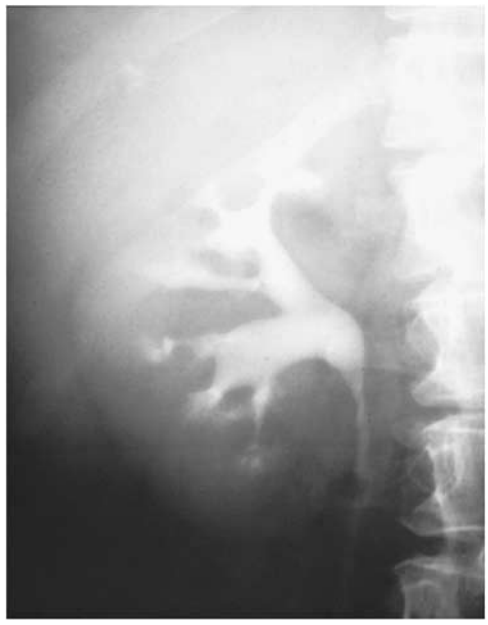

Figure 1 | Representative urographic appearance of MSK. Typical pyramidal blushes are evident, containing small radio-opaque spots.

THE 40-YEAR-OLD ABYSSINIAN WAR VETERAN AND THE FIRST DESCRIPTION OF MSK

The first description of this 'uncommon pyelographic finding (dilation of the intrarenal urinary tract)' was published by Lenarduzzi[9] in 1939 in an abstract form, in the Proceedings of the Venetian Regional Association of Radiologists (Figure 2). The patient was very probably the one described a decade later as the '*Premier case – C… Rino, âgé de quarante ans…*' in the first detailed account of the condition by Cacchi and Ricci.[10] Indeed, Cacchi and Ricci themselves wrote that this case had been diagnosed 11 years earlier.

C… Rino was a 40-year-old Italian veteran of the Abyssinian war, who was repatriated due to typhus complicated by pyelonephritis. Lenarduzzi performed both urography and retrograde pyelography using Uroselectan B. The latter demonstrated intrarenal reflux of the contrast medium. He concluded 'The radiologist believes that the opaque spots are due to stagnant urine in the dilated urinary tract upstream from the renal pelvis.' There is no image of this case in the Archives of the Institute of Radiology at the University of Padua; in their paper, Cacchi and Ricci[10] showed one poor-quality image of this case with a schematic explanatory drawing clearly representing an MSK condition (Figure 3). According to Professor Romani (personal

LENARDUZZI. — *Reperto pielografico poco comune (dilatazione delle vie urinarie intrarenali).*

In un paziente, che presentava segni clinici e di laboratorio di pielite bilaterale, durante la pielografia endovenosa comparvero numerose piccole chiazze opache nel parenchima dei due reni, con distribuzione tale da far ricordare quelle delle piramidi del Morgagni.

I bacinetti e gli ureteri apparivano regolari.

Con pielografia ascendente, si confermò il reperto dei bacinetti ed ureteri; si ebbe però passaggio in alcuni canali papillari.

L'O. crede di poter interpretare le chiazze opache come ristagno di orina opacata dall'Uroselectan nelle vie escretrici dei reni assai dilatate a monte dei bacinetti.

Figure 2 | Summary from the communication presented by G Lenarduzzi in 1939.[9] Uncommon pyelographic finding (dilation of the intrarenal urinary tract). In a patient with clinical and laboratory signs of bilateral pyelitis, i.v. urography disclosed many small radio-opaque spots with a distribution resembling Morgagni's pyramids. Renal pelvis and ureters looked normal. Normal renal pelvis and ureters were confirmed by ascending pyelography, but the passage (of the contrast) was observed in a few papillary ducts. The radiologist believes that the opaque spots are due to stagnant urine in the dilated urinary tract upstream of the renal pelvis.

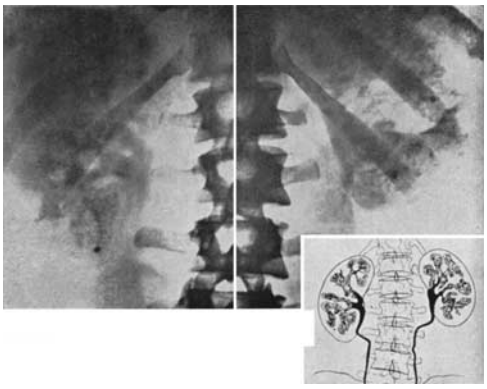

Figure 3 | Urographic film and schematic drawing from the first case of MSK described by Lenarduzzi. The picture was published by Cacchi and Ricci[10] in their first exhaustive report.

communication), former Professor of Radiology at the same University and one of Lenarduzzi's pupil, when Cacchi and Ricci asked for a picture of that first case, he gave them one of the available films, but not the best one, that he was unwilling to part with.

Lenarduzzi correctly interpreted the radiological finding of MSK. He clearly realized that the radio-opaque spots were ectatic collecting ducts, not papillary cysts. Indeed, cysts are closed cavities, so they should not communicate with the urinary system, whereas in MSK the pyramids are like a sponge after the water has been squeezed out of it – hence the name of the condition.

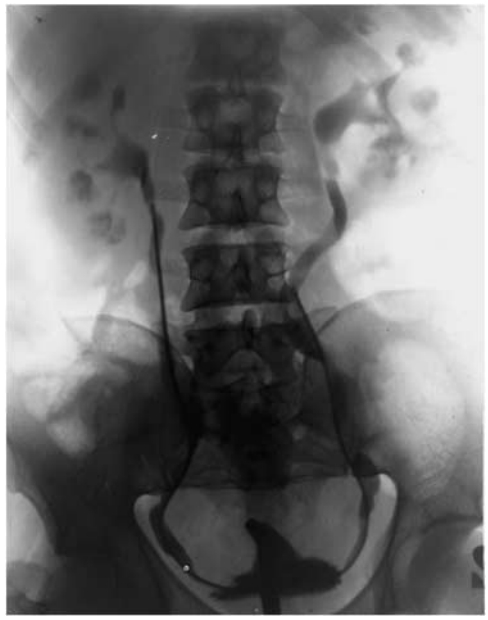

Figure 4 | Retrograde bilateral pyelogram performed in 1934 showing a mislabeled MSK case. This retrograde bilateral pyelogram of 27 December 1934 shows dilation of the upper urinary tract and ureters with bilateral urinary stones (coral calculus). Numerous small calculi are evident in front of enlarged calyces. At the time, the diagnosis was renal tuberculosis, but there was no evidence of ureteral stenosis. Although retrograde pyelography may produce non-specific findings in MSK (due to intrarenal backflow), and is no longer performed to diagnosing this condition, present-day review of this case suggests a diagnosis MSK, which was unknown in 1934 (from the 'Archaeoradiology' collection of the Chair of Radiology, Department of Medical and Diagnostic Sciences, University of Padua).

Interestingly, some previous cases of MSK had already been investigated by Padua radiologists, but they had been incorrectly labeled (Figure 4).

GUERRINO LENARDUZZI (1902–1985)

Lenarduzzi (Figure 5) was born in Pinzano al Tagliamento (Pordenone) and graduated in Medicine at the University of Padua in 1927. In the 1930s, he was working as a radiologist in a surgical division of the University Hospital in Padua. There was no distinct radiology section in Italy then; radiology was considered a diagnostic facility in surgical or medical wards. Lenarduzzi had to interrupt his scientific career after the outbreak of the Second World War, since he was enrolled in 1941 as a medical officer (captain) in the Army. In August 1942, he joined the Italian North Africa corps in Darnah, Libya, and was appointed director of the seventh radiological auto-ambulance. Following the rout of the Italian and German armies in North Africa, after the second battle in El Alamein (during the defense of Northern Tunisia), he was made prisoner in May 1943 and interned in a British camp, then in a British military hospital in Tunis, where he worked as a radiologist. After the end of the war and his return home (March 1946), he became chief of the radiological department. In 1954, he was appointed professor of radiology at the University of Padua Medical School,

Figure 5 | Guerrino Lenarduzzi in 1946. Picture taken during a Meeting of the Venetian Radiologists held in Venice on 19 May 1946. Lenarduzzi is in the front row, holding a hat and briefcase.

where he founded a school and his many disciples were infected by his interest in imaging the kidney and urinary tract, and in neuro-radiology. He retired in 1972.

ROBERTO CACCHI AND VINCENZO RICCI

Cacchi was a fellow under Professor Ravasini, founder of the Institute of Urology in Padua, when Lenarduzzi was operating and describing MSK at the same School of Medicine. They certainly shared some MSK patients. It was for a suspect urographic image and severe functional defect of the right kidney (investigated by administering i.v. indigo-carmine and then cystoscopically determining its appearance in the urine coming from the two ureters) that the fifth MSK patient described by Cacchi and Ricci,[10] a 30-year-old lady, was right nephrectomized by Cacchi. Ricci was an assistant in the pathology department directed by Professor Bompiani in Padua and performed the histopathological examination on the kidney, confirming Lenarduzzi's intuition, that is, the existence not of true cysts, but of tubular, precalyceal ectasias.

At the end of the 1950s, Cacchi was appointed professor of urology at the University of Ferrara, while Ricci became professor of otorhinolaryngology at the University of Verona in the 1970s.

FIRST DESCRIPTIONS OF MSK OUTSIDE ITALY

Since the first detailed account of the condition was written in French,[10] it is hardly surprising that the first person to describe MSK outside Italy was Neveu, in France, in 1950,[11] who was followed by many other French colleagues. A report was published in Portuguese in 1953[12] and in Spanish in 1955.[13] It was only in 1959 that the first article in English was published by Lindvall, a radiologist working at the Karolinska Institute in Stockholm.[14] Lindvall correctly recognized that Lenarduzzi had been the first to describe this condition, coining the term 'medullary sponge kidney' in 1938, and this was only possible because Cacchi and Ricci[10] had given a correct account of Lenarduzzi's abstract. The British literature received a first contribution a few months later.[15] Although Vermooten had described congenital cystic dilation of the renal collecting ducts as a new disease entity in 1951,[16] the first American report clearly referring to MSK was published in 1960 by Abeshouse and Abeshouse.[17] Many reports appeared in the American literature early on, including those by Palubinskas[1], who suggested that a continuum exists between benign dilation of the collecting ducts and the cyst-like changes resulting in symptomatic MSK. The first paper in German was published in 1961,[18] and in Japanese in 1962.[19]

Thus, more than 20 years elapsed between Lenarduzzi's discovery, presented in a 90-word abstract at an obscure local meeting, and the worldwide recognition of MSK – made possible by the work published in French by Cacchi and Ricci,[10] which enabled the information to circulate further in the French-speaking world, and Lindvall's contribution in English in a well-renowned journal.[14] In those times, it was highly unusual for Italian investigators (in the medical research field at least) to publish their papers in English-language, peer-reviewed journals. If they did not use Italian, they were more likely to write in French or German, where they used to go for internships. In fact, judging from the PubMed database, only two of Lenarduzzi's 17 papers were published in foreign journals (one in German and one in French) and, to our knowledge, Cacchi only wrote the paper describing MSK in the *Journal d'Urologie*.[10] This certainly hindered the international diffusion of original contributions from Italian medical researchers. It was only after the first generations of Italian medical professionals or investigators, who went to the US or the UK to specialize or do research in the late 1960s and early 1970s, had returned to Italy that the Italians started writing their scientific medical articles routinely in English. Indeed, some of the most famous Italian nephrologists published in English for the first time in their scientific careers only in 1969 (Professor Giuseppe Maschio), 1970 (Professor Claudio Ponticelli) and 1972 (Professor Giuseppe D'Amico).

THE MANY NAMES OF MSK

Sponge kidney (*Rene a spugna*) was the term coined by Lenarduzzi to describe this condition. Since then, many different names have been used, that is, precalyceal canalicular ectasia, cystic dilation of renal collecting ducts, sponge pyramid kidney and MSK.[20] They are all correct. Conversely, although Cacchi and Ricci[10] correctly described the pathology in their paper in the *Journal d'Urologie* as ectasic precalyceal tubules, their designation of the condition as a '*maladie kystique multiple des pyramids rénales*' (multiple cystic disease of the renal pyramids) is wrong. The two most frequently used names are sponge kidney and MSK, although the eponyms are also occasionally employed. In the early literature, Cacchi and Ricci were mentioned more frequently in the French literature, while the Scandinavian and

Anglo-American literature generally referred to Lenarduzzi. Since 1952, however, in the over 500 papers dealing with MSK found in PubMed (using the words Cacchi and Ricci or sponge kidney or spongy kidney), 'Cacchi and Ricci' occurs 27 times and 'Lenarduzzi' only once.[21]

As early as 1960, Professor Ravasini recognized the role of both Lenarduzzi and Cacchi and Ricci in describing this renal disease, and suggested using all three names in the eponym. Indeed, in his preface to Cacchi's essay 'Il Rene a Spugna',[22] he wrote, 'The sponge kidney is the outcome of the bright, but independent investigations of a radiologist, and of a urologist in cooperation with a pathologist, and this condition should properly be indicated in the literature as the 'Lenarduzzi, Cacchi and Ricci' disease'. We agree with him entirely and suggest that the eponym for MSK be 'Lenarduzzi, Cacchi and Ricci disease' (Lɛna:dʊtsi–Cakki–Ri:t∫i).

CLINICAL ASPECTS

Although MSK may be silent, its anatomical characteristics and association with functional alterations mean that it is frequently complicated by nephrolithiasis and pyelonephritis. Other, less frequent manifestations are gross and microscopic hematuria, renal failure and primary hyperparathyroidism.

Recurrent calcium nephrolithiasis and nephrocalcinosis are the most common signs. The association with renal hypercalciuria, distal tubular acidosis, and hypocitraturia (in conjunction with urinary stasis in the papillary duct ectasias) triggers the formation of calcium phosphate and/or calcium oxalate stones.

Hyperparathyroidism is frequently associated, and was thought to cause MSK and also trigger stone formation in these patients.[23] However, in most patients, hypercalciuria, nephrocalcinosis, and renal stones clearly precede the onset of hyperparathyroidism by many years. It was also suggested that renal hypercalciuria triggers the parathyroid gland stimulation leading to hyperplasia.[24] Nevertheless, we now believe that both hyperparathyroidism and stones might be secondary to common disorders.

In addition to the morphological abnormalities of the precalyceal ducts, MSK is associated with other abnormalities of the lower tubule, such as a defective urinary concentration, distal renal tubular acidosis and hypocitraturia, and also of the upper nephron (in the proximal tubule), that is, maximum reabsorption of glucose (TmGlucose) and maximum secretion of P-aminohippurate (TmPAH).[25]

The risk of renal failure seems to be modest in MSK and related to renal infections and the formation of struvite stones.[26,27]

Familial cases have been reported,[28–31] sometimes associated with renal agenesia, other renal malformations or abnormalities in the urinary tract.[32] An autosomal dominant pattern of inheritance has been suggested in familial cases.[30–32]

WILL MSK NO LONGER BE DIAGNOSED?

The growing tendency to reduce the diagnostic use of urography since the introduction of imaging techniques that do not depend on radio-opaque contrasts (ultrasound, spiral computed tomography, nuclear magnetic resonance) will probably mean that fewer cases of MSK are diagnosed. Although it has been suggested that kidney ultrasound can diagnose MSK,[33] it does not produce the typical images disclosed at urography, which are considered specific of the disorder. Ultrasound merely shows very nonspecific signs of hyperechoic medulla due to nephrocalcinosis.[34] The sensitivity of computed tomography in detecting MSK is markedly lower than that of urography, as computed tomography can only show images pointing to the possibility of MSK even in the most florid cases of the disease.[35] Recent preliminary data have suggested that multiphasic helical computed tomography may be more sensitive than urography; however,[36] nuclear magnetic resonance imaging does not seem to be sensitive enough to disclose the typical signs of MSK.[37] Thus, MSK emerged with the introduction of urography in clinics and, like a carsic river, seems destined to disappear again (i.e. to be diagnosed less and less).

Although the condition and its complications have no specific treatment, its recognition in recurrent stone formers is certainly useful in tailoring stone prophylaxis and for a proper approach to the diagnosis and treatment of the frequently associated hyperparathyroidism. Hence, our conviction that urography should still be considered as a necessary step in the diagnostic workup for recurrent calcium stone formers.

A MODERN LOOK AT MSK: ON THE TRACK OF ITS MOLECULAR BASES

Although the pathogenesis of MSK has yet to be elucidated, its association with different malformative conditions (Table 1) supports the idea that it is a developmental disorder. The most important of these associated conditions are hemihypertrophy and the Beckwith-Wiedemann syndrome.[38] When MSK is associated with Wilms' tumor, this generally occurs in the context of a hemihypertrophy/Beckwith-Wiedemann syndrome. About one in eight patients with Beckwith-Wiedemann syndrome has some degree of hemihypertrophy, rising to 40% in those with associated tumors. In a pediatric case population with Beckwith-Wiedemann syndrome, hypercalciuria was found in 22% (as opposed to a predicted rate of 7–10% in the general population) and most patients had nephrocalcinosis (suggesting that they also had MSK).[39] Chesney *et al.*[40] have even suggested that MSK and hemihypertrophy represent a subtle form of Beckwith-Wiedemann syndrome. So there is a sort of triangulation between MSK, Wilm's tumor, and hemihypertrophy/Beckwith-Wiedemann syndrome. The latter are known to be associated with a locus on chromosome 11p15,[41] whereas Wilm's tumor is associated with alterations in the *WT-1* gene at 11p13. Thus the two loci are very close, supporting the view that the overlap between the three disorders could depend on a derangement occurring in the 11p chromosome area, along the lines of the so-called 'contiguous gene syndromes'.

Table 1 | Disorder associated with MSK

	Prevalence (%)	Reports in PubMed	Text books
Beckwith-Wiedemann syndrome	13% (Choyke *et al.*[38])[a]		
Congenital hemihypertrophy		15	
Wilm's tumor		5[b]	
Horse-shoe kidney		2	
Polycystic renal disease[c]		5	
Other urinary tract malformations	10% (Gambaro *et al.*[47])[d]		
Caroli syndrome and congenital Hepatic fibrosis	~70% (Kerr *et al.*[42])[e]		
Anodontia		1	
Ehlers-Danlos syndrome		1	
Marfan syndrome		1	
Young's syndrome (immotile cilia)		2	
Congenital pyloric stenosis		1	
Renal artery fibromuscular dysplasia			Yes

The association between MSK and the listed disorders is indicated as prevalence whenever the datum is available, or as number of case reports if the former is not available, or as textbook (*Oxford Textbook of Nephrology*) citation when no case report is retraceable in the PubMed database.
[a]Prevalence of MSK in a cohort of patients with Beckwith-Wiedemann syndrome.
[b]Always in association with the Beckwith-Wiedemann syndrome or congenital hemihypertrophy.
[c]It is not clear whether inheritance of the polycystic condition was recognized in all case reports, thus making the ADPKD diagnosis uncertain. On the other hand, 15% out of a case population of 71 ADPKD with renal stones has been reported to have evidence of precalyceal tubular ectasia supporting that ADPKD and MSK may truly coexist.[44]
[d]Prevalence of malformations in a cohort of MSK patients.
[e]Prevalence of MSK in a cohort of patients with congenital hepatic fibrosis.

A second group of conditions associated with MSK includes congenital dilation of intrahepatic bile ducts and hepatic fibrosis,[42] and autosomal dominant polycystic kidney disease (ADPKD). Regarding the association with liver conditions, it is worth noting that the excretory ducts in both organs derive from the endoderm, and liver fibrosis has been reported in association with ADPKD too.[43] Several case reports have been published in which MSK occurred together with cortical cysts in polycystic kidney disease, but more interestingly 15% of a population of 71 ADPKD cases with renal stones reportedly had evidence of precalyceal tubular ectasia, supporting the idea that ADPKD and MSK may truly coexist.[44]

The other associated conditions listed in Table 1 are uncommon or anecdotal. Although some of these may be chance associations, it is intriguing that some form syndromes of local tissue hypertrophy,[2] which reinforce the potential triangulation with MSK and more generalized hypertrophic disorders.

The pathogenesis of MSK should explain the involvement of anatomical districts (the collecting and precalyceal ducts on the one hand and the nephron on the other) of different embryological origins. It should also explain why it is so often associated with primary hyperparathyroidism.

A few years ago, a case was described of a medullary thyroid carcinoma presenting with concomitant primary hyperparathyroidism (prompting the diagnosis of MEN-2a) together with MSK, and a *RET* (rearranged during transfection) proto-oncogene gene mutation, and it was claimed that the MSK/*RET* mutation association may be causal.[45] However, we expect to find a *RET* mutation in a patient with a medullary thyroid carcinoma, since this occurs in 80% of cases. Moreover, given the prevalence of the two conditions (as high as 10/100 000 for the former, up to 1/100 for MSK), the probability of a chance association (up to 1 per million people), though very low, is nonetheless a possibility. The idea of common pathogenic mechanisms in the two diseases is attractive, however, since *RET* plays a huge part in renal development.

In renal embryogenesis, through the synthesis of chemotactic molecules, that is, the glial-derived neurotrophic factor (GDNF), the metanephric blastema prompts the branching of the ureteral-bud from Wolff's mesonephric duct, which approaches and invades the blastema.[46] The top of the bud expresses a GDNF receptor, RET. Binding between RET and GDNF is essential not only for correct ureter and collecting duct formation (they also are Wolffian in origin), but also for the induction of nephrogenesis, morphogenesis, and kidney growth.[46] In particular, the transition of mesenchymal cells of the metanephros to nephronic cells, the correct polarization of renal tubular cells, and the specialization of the different tubular segments of the nephron, all need differentiation 'messages' originating from the ureteral-bud/metanephric-blastema interface.[46]

We have hypothesized that MSK may be the consequence of a disruption of said interface:[47] this would explain the concomitant occurrence of alterations in precalyceal and collecting ducts, and functional defects in the nephron tubule. Moreover, if the disruption of the ureteral-bud/metanephric-blastema interface depends on some derangement in RET function, then the hypothesis would also explain the abnormal parathyroid function, in view of this oncogene's role in controlling parathyroid cell proliferation,[48] and the association of MSK with liver disorders due to its possible role in the development of the liver excretory system.[49] But other candidate genes may be suggested for this abnormal embryological development,[46] such as the glial-derived factor neurturin, which is also capable of promoting ureteric-bud branching; or the *WT1* gene which is involved in ureteral-bud induction; and many others, including Eyes absent 1 (*Eya-1*), integrins, *PAX2*, laminin α5, *AgtR2*, *FGFs*, *MT1-MMP*, *MMP9*, *TIMP1*, *TIMP2*, all involved in the process of nephrogenesis. However, as most of them continue to be active after embryogenesis, they are less likely to be involved because patients with MSK do not reveal disorders due to mutations of these genes. On the other hand, the WT1 gene is much more intriguing as a possible candidate because of the association of MSK with Wilms' tumor and hypertrophic disorders.

Abnormal interfacing of the ureteral bud with the blastema may be secondary to environmental influences (drugs, viruses, etc.) during pregnancy. It may also be genetically driven, however, despite the rarity of cases of

familial MSK. Even germline mutations might cause sporadic forms of MSK via a number of mechanisms: (1) incomplete penetrance; (2) if a two-hit phenomenon is needed for the onset of MSK (as in ADPKD or other developmental kidney disorders, such as von Hippel–Lindau syndrome or tuberous sclerosis); (3) if MSK is due to unfavorable genotype combinations, for example, between specific *RET* and *GDNF* alleles; (4) if a concomitant mutation of the *GDNF* ligand gene is needed; and finally (5) if MSK is not a simple Mendelian trait, but follows a polygenic pattern of inheritance affected by modifier genes, as in another RET-associated disorder – Hirschprung's disease – which also occurs quite often in sporadic forms, like MSK.[50]

Along with this wide range of possibilities, it may also be that the differentiative abnormality occurs throughout both kidneys, only in one kidney, or even in just a few papillae.

Molecular studies are needed to confirm the hypothesis but, if it proves correct, we would expect to find other renal developmental abnormalities of processes depending on RET/GDNF binding (i.e. unilateral renal agenesia, or unilateral or bilateral renal hypoplasia, or renal district duplication, etc.) much more frequently in MSK patients than the few anecdotal cases of horse-shoe kidney, unilateral renal aplasia,[51] and familial cosegregation of various ureteral abnormalities.[32] We ourselves have observed six cases of congenital, monolateral small kidneys in a systematic analysis of 72 MSK patients.[47]

ACKNOWLEDGMENTS

We thank General A Oliva, Strategical Sc. Dr, Padua, for his help in historical research in the military archives. The paper is based on a lecture given by G Gambaro at the International Congress on the History of Nephrology, Taormina, Italy, November 2001.

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