The nephrologist and nephrolithiasis. Take it or leave it?

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Nephrolithiasis is a disorder that the human being has suffered since ancient times. Calculi have been found, for example, in Egyptian mummies[1] and in the inhabitants of what is now Arizona. From the time of Aulus Cornelius Celsus (ca. 25 BC-50 AD),[2] different lithotomy techniques have been designed to remove bladder stones. Until the arrival of the X-ray, calculi located in kidneys and the urinary tract could not be diagnosed *in vivo*. We know the names of some people who underwent lithotomy or cystolithotomy, such as the Holy Roman Emperor St. Henry II (973-1024) in the monastery of Monte Cassino (1022).

In Spain, the Spanish physician Julián Gutiérrez de Toledo wrote the book *Cura de la piedra y dolor de la ijada* (*Cure of the stone and flank pain*) (1498) and, almost a century later, the famous physician from Alcalá de Henares, Francisco Díaz (1527-1590) wrote his *Tratado nuevamente impresso de todas las enfermedades de los riñones, vexiga, y las carnosidades de la verga y urina (New treatise of all diseases of the kidneys, bladder and flesh of the* [sic] *penis and urine* (Madrid, 1588).[3] This book is considered the world's first written treatise on urology and, consequently, also the first Urology book in Spain.[4] In 1612, Spain established the first chair of "urology" in the history of medicine; as such, "La cátedra se erixe, funda e instituye para la enseñanza y práctica de sacar piedras" (The chair is established, founded and instituted for the teaching and practice stones removal).[5,6]

Many historical figures suffered from the "stone disease" such as Erasmus of Rotterdam, Michel de Montaigne, Pope Clement XI, King Philip IV, Samuel Pepys, Goethe, Napoleon Bonaparte and Federico de Madrazo. Many lithotomists, generally "professional" travelling practitioners, have been remembered in history, such as William Cheselden[7] (1688-1752) and Jacques Beaulieu (1651-1714), better known as "Frère Jacques". The latter is known for the famous phrase "I've removed the stone, now I'll leave it to God to heal the patient". This is why he had to travel. The lithotomy operation was so well-known in society that Marin Marais (1656-1728) wrote a musical piece entitled *The table size operation for viola da gamba and continuo in E minor*, in which he describes the various stages of the operation.

In general, the quality of life of patients with calculi was lamentable and depressing. Erasmus wrote: "Back in February, the stone afflicted me so vigorously with vomiting that since that time my little body has become increasingly meagre". Michel de Montaigne said that "it is the worst of diseases, the most sudden, the most deadly, the most irremediable, on which medicine is lost, through which I reconcile and familiarise myself with death". The physician Thomas Sydenham, also suffering from calculi, wrote: "The patient suffers until being consumed by age and disease and the poor man wishes to die." Considering these circumstances, one could only put themselves in the hands of "St Liborius, *Cenonense* Bishop , against flank pain, kidney stones and urinary retention".

The treatment of patients suffering from calculi improved when Jean Civiale introduced an apparatus in 1824 (*lithotripter trilabium*), which allowed lithotripsy, transurethral lithotripsy or the reduction of calculi to fragments in the bladder[8] to be performed. The first lithotripsy in Spain, using Dr Civiale's method, was performed in 1834.[9] In the last quarter of the 19th century, two significant leaps forward took place in the field of stone disease. The first was disclosed in a modest letter to the Director, which stated that the urinary deposits had genetic bases.[10] The second was the ability to diagnose calculi in the kidneys and the urinary tract thanks to the introduction of the X-rays.[11]

The twentieth century brought many advances that allowed mechanisms involved in lithiasis to be understood and effective means were provided for its prevention and treatment. Apart from extracorporeal lithotripsy, we want to recall some milestones, among many others, that we believe to be well-known. Firstly, the discovery by Alexander Randall of papillary plaques where the lithiasis process

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begins.[12,13] Secondly, a description of the association between morphological lesions, metabolic abnormalities causing calculi and calculi formation itself; we refer to the medullary sponge kidney or Cacchi-Ricci disease.[14,15] Thirdly, and due to Hispanic associations, the description of megacalycosis or hypoplasia of the renal medulla by Antonio Puigvert in 1963.[16]

Another aspect noteworthy for its influence in the understanding of lithiasis is the gradual discovery of the different substances that are involved in the metabolic aetiology of calculi. Initial findings occurred when the first chemists who came together by chance, began to work on problems related to medical practice. Karl Wilhelm Scheele (1742-1786), Swedish pharmaceutical chemist, discoverer of many elements and chemical substances (barium, chlorine, manganese, molybdenum, tungsten), described the presence of oxalic acid in some roots and cortices of plants and especially rhubarb. In 1776, the same author discovered, on analysing some urinary calculi, a substance (lithic acid) which turned purple upon contact with nitric acid. Years later, a Frenchman named Fourcroy observed that this substance was rich in carbon and nitrogen but poor in oxygen and hydrogen ($C_5H_4N_4O_3$) and he renamed it uric acid. In 1810, William Hyde Wollaston (1776-1828) observed a new type of calculus that was composed of hexagonal plates and was alkali-soluble. He named the new substance cystic oxide believing that it was exclusively vesicular in origin. Alexandre Marcet (1770-1822) showed in 1817 that this type of calculi could form in kidneys.[18] Subsequently, the name cystic oxide was replaced by cystine. Along with calcium, the three above listed substances (uric acid/urate, oxalate and cystine) are the major cause of calculi when they are present in urine in high concentrations.

The most common metabolic abnormalities that produce calculi when they have a low concentration are magnesium and citrate. Citric acid was also discovered by Scheele. In the mid-19th century, its properties were observed as an inhibitor of crystallisation. Thus, Spiller noted that citric acid had a special ability to maintain calcium in solution. In the presence of citrate, calcium was not precipitated by carbonate, phosphate or oxalate.[19] When some of these precipitates were formed, they could be brought back to solution by adding citrate. Subsequently, it was learned that hypocitraturia is a major cause in the formation of calculi. Citrate treatment would become, over time, one of the most effective methods for preventing calculi formation. At the start of the 20th century, it was found that the citraturia could be a marker of the acid-base balance. Thus Östberg described for the first time that the levels of citrate in human urine increase when there is alkalosis and, conversely, decrease in cases of acidosis.[20] In 1960, Bibus and Luis Cifuentes showed that drug treatment with citrate eliminates uric acid calculi. [21]

Reaching supersaturation of solutes responsible for and/or a deficit of inhibitors, associated or not with changes in pH, there is a formation of the first crystals which can occur in three environments, the 'Randall's plaques' (all causes of calcium oxalate calculi, primary hyperparathyroidism, patients with ileostomy and resected small intestine),[22] inside the tubules (almost all causes of lithiasis)[23] and the free crystallisation in solution (cystinuria, hyperoxaluria).[24] If the right conditions persist, an increase of size of the particles formed either by crystal growth or by their combination is observed.

The most important types of salts that make up the structure of the calculi have been known since the late 18th and early 19th centuries. As such, Antoine François Fourcroy and Louis Nicolas Vauquelin published notable studies in which they reported the chemical composition of around 600 calculi: uric acid, ammonium urate, calcium phosphate, magnesium ammonium phosphate, calcium oxalate and "animal material" (gelatine); stones could be pure or be formed by a mixture of any of these substances.[25,26] More recently, a certain relationship has been established between the composition of the stone and the underlying metabolic abnormality. As such, a whewellite calculus (calcium oxalate monohydrate) should raise suspicions of primary hyperoxaluria or other hyperoxaluric states. Lithiasis due to weddellite (calcium oxalate dihydrate) or mixed weddellite and whewellite is usually more common in idiopathic hypercalciuria. Calculi with high calcium phosphate content should suggest primary hyperparathyroidism, complete or incomplete distal renal tubular acidosis or infection due to ureolytic bacteria (urinary alkaline pH situations). Purine calculi will be observed in cases of hyperuricosuria, xanthinuria, adenine phosphoribosyltransferase deficiency and in repeatedly acidic urinary pH. In any case, in cystinuria, calculi are obviously cystine calculi.

At present, in any of our hospitals, a child may be referred to a paediatric nephrologist on a preferential basis, sometimes urgently, after having observed calcium oxalate crystals in their urine sediment and, however, their mother, from whom they inherited the condition has had a few cases of renal colic and nobody has performed a urinary metabolic and renal function study. The reasons can be surmised. On the one hand, for centuries, when there were no nephrologists, surgeons dedicated to urology were always considered to be the physicians who treated calculi, since they were responsible for their removal, which was urgent in many cases.

Nephrology is a very young specialty. It has been around for just over 50 years now. In an effort to establish and consolidate the specialty, the separation from the "mother" stem of internal medicine occurred when nephrologists showed that they possessed their own specific techniques, that is, those related to renal replacement therapy. The

various techniques of dialysis and subsequent renal transplantation are so complex that they have required preferential attention to the detriment of other nephrology issues such as lithiasis. However, in the early eighties, an idea was consolidated that children could be diagnosed who were predisposed to kidney stones, preferably in adulthood. This genetically-based situation has been called "prelithiasis" though there have been some reservations about the term, since not all prelithiasis patients eventually developed calculi. The bottom line in this situation is that there is nothing to operate upon, in order that the nephrologist, in this case the paediatrician, has their own specific workspace, which is not shared with the surgeon.

The key to this concept, the association between haematuria and idiopathic hypercalciuria, was begun by two works published in the same issue of *The Journal of Pediatrics*.[27,28] Since then, it has been known that idiopathic hypercalciuria, the most common cause of kidney stones at any age, can present in childhood as a macro or microscopic haematuria, sterile dysuria, urinary frequency, urinary urgency, urinary incontinence, nocturnal enuresis, turbid urine, recurrent abdominal pain "not typical of renal colic" or sterile leukocyturia. The frequency of urinary tract infection is much higher in these children than in controls, for an unknown reason. We have even described the association between prelithiasis (hypercalciuria and/or hypocitraturia) and simple renal cysts.[29] The full involvement of the paediatric nephrologist with lithiasis rests, moreover, on the fact that some causes of nephrocalcinosis are tubulopathies which are usually diagnosed in childhood, such as Bartter's disease, distal renal tubular acidosis, Dent's disease and hypomagnesaemia with hypercalciuria and nephrocalcinosis. Also, diseases such as oxalosis and cystinuria are clinically notable to such an extent that they often present in childhood. To demonstrate the difference between the two spheres of nephrology, we must point out that in the XLII National Congress of the Spanish Society of Nephrology (Gran Canaria, 2012) two abstracts on lithiasis were presented, except in cases of error or omission (2/660 abstracts; 0.3%). By contrast, in the 38th National Congress of Paediatric Nephrology (Pamplona, 2012) seven abstracts on lithiasis and another seven on diseases with nephrocalcinosis were presented (14/90 abstracts, 15.5%).

Apart from the fact that calculi form in the renal parenchyma, in our opinion, the decisive intervention of the nephrologist in this issue is based on clear and convincing arguments:

1. Quantification of the excretion of substances involved in the development of calculi must be carried out by a nephrologist. Arguably, to request 24-hour urine, it is not necessary to have specialist studies. However, it is necessary in order to know if the urine has been collected properly, since the calculation of urinary ratios for each substance must qualitatively match the recorded urine result. Furthermore, it is increasingly accepted that 24-hour urine, at least in some of the substances studied, is a *totum revolotum*, since its excretion may vary during the day, as with other body parameters, including blood pressure. It is therefore very appropriate to calculate urinary ratios in isolated urine samples or, better still, fractional excretions. The urinary excretion of calcium and citrate, for example, changes dramatically at different times of the day; these differences are more pronounced during the night. It has been confirmed that calculi form at night because the lack of water intake is, in many patients, combined with an increase in urinary calcium and a reduction in citraturia. Therefore, the first urine collection of the day that records what happened during the night must be studied separately from the 12-hour urine collected during the day or another isolated sample collection, usually after diner. Moreover, one may not be lithogenic, if citraturia is reduced as well as calciuria. That is, urine is particularly lithogenic when there is an imbalance between the components which cause calculi and those which protect against it. This is the reason for the importance of the calcium/citrate ratio. Values of this ratio that are greater than 0.33 indicate that the urine is potentially lithogenic, regardless of the age and the time of collection.[30,31] In a study we conducted in children with prelithiasis, the calcium/citrate ratio corresponding to the night urine increased in 33.3% of samples however, the same ratio in the first urine of the day increased in 70.8%. This was the only parameter calculated which was also related to a family history of lithiasis.[32]

2. Some lithiasic patients, especially those with nephrocalcinosis or associated parenchymal loss, may have chronic kidney disease, and therefore, in order to calculate the glomerular filtration rate, a functional nephrology test is necessary.

3. The renal management of water is the first parameter that changes in many nephrological disorders,[33] and lithiasic patients are not an exception.[34,35] Hypercalciuria[36] has been implicated as the reason. This is difficult to understand, since children with idiopathic hypercalciuria have a normal concentration that deteriorates gradually, in adults with the same profile,[37] probably due to a chronic tubulointerstitial lesion caused by crystal deposits. In this sense, discovering a progressive deterioration of renal concentrating capacity may be an indication to initiate preventive drug therapy.

4. The ability of renal acidification is one of the functional parameters which is most disrupted in lithiasis. At this point, we would like to remember and pay tribute to the studies some Spanish urologists carried out on the subject, particularly Dr. Luis Cifuentes Delatte.[38,39] Distal

renal tubular acidosis presents with nephrocalcinosis secondary to hypercalciuria and hypocitraturia. Conversely, lithiasic patients very often have acidification defects.[40-46] In the latter case, it is difficult to know if lithiasis is the cause or the consequence of a partial acidification defect, such as incomplete distal tubular acidosis.[47-49] It has also been suggested that hypercalciuria may produce secondary renal tubular acidosis;[50,51] however, these are old publications whose hypotheses have not been confirmed. We observed in children with idiopathic hypercalciuria a paradoxical response to two stimuli, that is, they cannot acidify with furosemide, but pCO_2 test, carried out with acetazolamide and bicarbonate is usually rigorously normal.[52] In any case, when there is a significant acidification defect, which must be shown with corresponding tests performed by a nephrologist, hypercalciuria and hypocitraturia often exist, which is a clear indication of the beginning of prolonged alkalising treatment.

In short, from what is listed above, we believe that the nephrologist should actively intervene in the diagnosis, treatment and follow-up of all patients with stone disease, since nephrolithiasis is a nephrological and sometimes, urological disease. Of course, the creation of Lithiasis Units in which nephrologists, urologists, biochemists and radiologists work together would be ideal. In these units, the criteria for receiving patients would be decided. In any case, when surgery is not necessary, we believe that in the first visit, the patient should be referred to the nephrologist, as occurs in paediatrics, just as arrhythmias are referred to a cardiologist or chronic headaches, to a neurologist, and not to their corresponding surgical units.

Lastly, although it is dangerous to prophesy in medicine, we can predict the patient's future in our example, who presented with crystalluria. Surely, before the age of 30, they will have their "first" nephritic colic because preventive dietary recommendations given to the diagnosis of prelithiasis are usually eliminated from adolescence. These recommendations basically consist of increasing the intake of food containing natural stone formation preventive elements (water, fruit, vegetables, oily fish, whole grain cereals) and not abusing those that contain elements that cause calculi (dairy and other proteins, salt). In the case of their mother, from whom they would have inherited the condition, when she is in her seventies she will have her "first" hip fracture. In lithiasis, reduction in bone mineral density is very common.[53] However that is another story.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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