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ORIGINAL ARTICLE

Management of genetically determined kidney stone disease: consensus from a panel of urologists and nephrologists

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ABSTRACT

BACKGROUND: Available evidence suggests that monogenic causes of kidney stones are likely under-diagnosed, particularly in young adults, needing expert multidisciplinary recommendations to improve diagnosis, management and therapeutic outcomes. To increase the awareness among the medical community on the recognition of the signs and symptoms of genetically determined kidney stone disease in adult patients, with a special focus on primary hyperoxaluria (PH), a group of nephrologists and urologists started a consensus process through the Delphi method.

METHODS: A list of 40 statements (23 regarding genetically determined stone disease and 17 regarding primary hyperoxaluria) was defined by the authors and included in an online Delphi survey, which was sent to 16 urologists and 22 nephrologists with expertise in managing patients with kidney stone disease. An agreement threshold of 75% was established for consensus.

RESULTS: After two rounds of Delphi voting, consensus was reached for 33 statements, 18 regarding genetically determined stone disease and 15 regarding PH.

CONCLUSIONS: The Delphi process highlighted several areas of agreement with regard to the characteristic or anamnestic data suggesting diagnostic investigation, optimal diagnostic patterns, treatment strategies and management of patients with genetically determined nephrolithiasis. The process also highlighted some grey areas, which deserve further investigation and highlight the need for educational initiatives focused on rare diseases in the field of kidney stones.

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KEY WORDS: Cystinuria; Genetics; Kidney calculi; Nephrolithiasis; Hyperoxaluria, primary.

Kidney stone disease represents a major health burden, variably affecting people worldwide depending on geographic, socio-economic and climate conditions.[1] Kidney stones are commonly recurrent, with up to 30% of individuals experiencing a second episode within 10 years of their initial presentation.[2, 3] Calcium nephrolithiasis is the most frequent stone type. It may be associated with multiple predisposing urinary abnormalities influencing the solubility of calcium salts, such as hyperoxaluria, hypercalciuria, hypocitraturia and inability to acidify urine.[4-6] In most patients, the underlying etiology is thought to be multifactorial, with environmental, dietary, hormonal and genetic components to be considered.[7] Monogenic disorders may cause stone formation in a significant proportion of patients, more frequently in children than adults (9.6% *vs.* 1.6%), mainly due to metabolic alterations triggering the precipitation of urinary salts.[7-9] Accordingly, recent evidence suggests that up to 15% of patients in specialist kidney stone clinics and ~30% of recurrent stone formers under the age of 25 years may have a monogenic disease.[8, 10-12] Unfortunately, clinical and biochemical red flags suggesting the presence of genetic defects underlying stone disease in adults are often poorly recognized. Among these poorly recognized conditions, cystinuria is the most frequent, followed by primary hyperoxaluria (PH).[9]

PH is a group of autosomal recessive disorders characterized by impaired glyoxylate metabolism in the liver, resulting in excessive production of oxalate, which increases the urinary supersaturation for calcium oxalate.[13, 14] This leads to the formation of kidney stones and nephrocalcinosis, which in turn decrease the ability of the kidney to clear oxalate from blood,[15] progressing in over 70% of cases to end-stage kidney disease.[16] Recent data reported a prevalence of PH of about 1 in 60,000 individuals, more than traditional estimates of 1-2 cases per million, suggesting a significant number of undiagnosed cases that are likely to occur in the adult setting.[17] It is, therefore, necessary to increase awareness among the medical community on recognition of the signs and symptoms of monogenic stone disease, in order to promptly establish the treatment strategy and to improve the patients' management and quality of life.

To address this issue, a group of nephrologists and urologists with experience in the diagnosis and management of kidney stone disease started a consensus process through the Delphi method, with the aim to provide recommendations for the recognition and management of adult patients with genetically determined kidney stone disease, with a particular focus on PH.

Materials and methods

Based on the literature review and clinical experience, the authors defined three areas of interest, according to the two main topics of the study (genetically determined kidney stone disease and primary hyperoxaluria), relevant to provide consensus recommendations on managing adult patients with genetically determined kidney stone disease (see Table I for details). Statements for each area of interest were proposed by the authors and discussed during a meeting in April 2023. A list of 40 statements was included in

TABLE I.—*Areas of interest relevant to providing consensus recommendations on recognizing and managing adult patients with genetically determined kidney stone disease.*

A. Genetically determined kidney stone disease
1. Which clinical characteristic or anamnestic data (*e.g.*, recurrence, age of onset, bilaterality, familiarity, type/morphology of the stone, others) should lead to the suspicion of a genetically determined kidney stone disease and, therefore, should orient to a diagnostic investigation?
2. What type of investigation (metabolic investigations, genetic characterization, others) and when should it be carried out?
3. What should be the optimal management of the patient? (Taking charge, timing of investigations, referrals, others)
B. Primary hyperoxaluria
4. Which clinical characteristic or anamnestic data (*e.g.*, recurrence, age of onset, bilaterality, familiarity, type/morphology of the stone, others) should lead to the suspicion of a PH and, therefore, should orient to a diagnostic investigation?
5. What type of investigation (metabolic investigations, genetic characterization, others) and when should it be carried out?
6. What should be the optimal management of the patient? (taking charge, the timing of investigations, referrals, others)

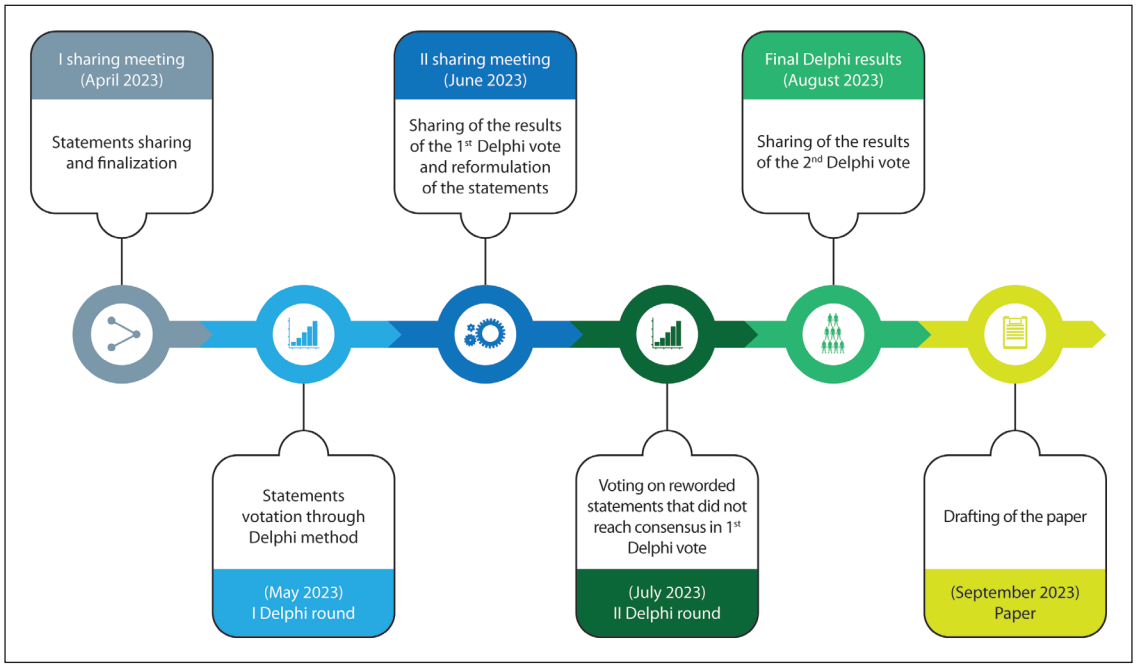

Figure 1.—Project workflow.

an online survey. The Delphi survey was sent in May 2023 to 38 Italian clinicians (16 urologists and 22 nephrologists) with expertise in managing patients with kidney stone disease and who met the following criteria: ≥10 years' clinical experience, ≥5 relevant scientific publications in this field and/or regular speaking activity at national/international congresses. A timeline of 21 calendar days to answer was established.

After the first Delphi round, the Authors met in an online meeting to review and discuss the outcomes and provide an alternative formulation for statements that did not reach consensus, considering the comments received from the Delphi panel. A second Delphi round was carried out in July 2023. The project workflow is reported in Figure 1.

Delphi method

The Delphi method is a standard method of consensus, which iteratively and anonymously evaluates the level of agreement using a Likert scale (1-5; 1=total disagreement; 5=total agreement). Consensus on the agreement is reached when ≥75% of voters express a vote equal to 4 or 5.[18] Within this project, the Delphi method was developed using the SurveyMonkey® (2024 version) software and conducted through online voting.

Statistical analysis

All data were analyzed with descriptive statistics.

Results

During the first Delphi round, consensus on the agreement was reached for 28 out of 40 statements (70%). With regard to genetically determined stone disease, the consensus was reached for 6 out of 10 statements from the area 1 (1.1, 1.3, 1.5, 1.7, 1.8, 1.10), 6 out of 9 statements from the area 2 (2.1, 2.2, 2.3, 2.5, 2.6, 2.9) and all the 4 statements from the area 3 (Supplementary Digital Material 1: Supplementary Table I). With regard to PH, a consensus was reached for all the statements from areas 4 and 6 (Supplementary Digital Material 2: Supplementary Table II). None of the statements from area 5 reached a consensus (Supplementary Table II).

After the first Delphi round, the Authors de-

cided to reduce the statements of area 5 due to related/similar content: definitive statements from this area were 3. Finally, 10 statements were reformulated and voted on in the second Delphi round. Consensus was reached on 5 out of 10 (50%) statements (blue statements in Supplementary Table I and Supplementary Table II), while the other 5 statements (Supplementary Table I and Supplementary Table II) did not reach an agreement.

At the end of the Delphi voting, consensus was reached for 33 statements, 18 regarding genetically determined stone disease and 15 regarding PH.

Discussion

Available evidence suggest that monogenic causes of kidney stones are likely under-diagnosed, particularly in young adults, needing expert multidisciplinary recommendations to improve diagnosis, management and therapeutic outcomes.[9, 19] To increase the awareness among the medical community on the recognition of the signs and symptoms of genetically determined kidney stone disease in adult patients, with a special focus on PH, a group of nephrologists and urologists produced a list of consensus statements. They followed the Delphi approach and provided recommendations for the management of adult patients with a particular focus on the clinical characteristics or anamnestic data, suggesting when and which diagnostic investigations to perform, and optimal patient management. A summary of the recommendations is reported in Supplementary Digital Material 3: Supplementary Table III.

Genetically determined kidney stone disease

Characteristic or anamnestic data suggesting diagnostic investigation

An early onset of nephrolithiasis, family history, recurrence, bilaterality, nephrocalcinosis, the association of young age and eGFR<60 mL/min/1.73 m^2, as well as sensorineural hearing loss, rickets deformities and severe bone disease were widely recognized as useful hints for suspecting potential genetic causes for kidney stones. Otherwise, a first urinary stone episode occurring before 25 years or the presence of consanguineous parents in a young (<25 years) stone forming patient were not deemed essential factors for the suspicion of a genetically determined disease (statements 1.2 and 1.4, consensus not reached).

According to guidelines, an extensive metabolic (urinary) evaluation at the first stone is not required and generally not performed.[20, 21] Statement 1.2 proposed a metabolic evaluation in very young adults in consideration that calcium idiopathic stones generally occur in older subjects, in the range 30-50 years. On the other hand, there are data showing a decreasing age trend in the first stone occurrence in idiopathic stones, and this may have been the reason for not accepting the statement.[22]

Since a number of monogenic disorders causing renal stones are autosomal recessive,[23] their occurrence in siblings of consanguineous parents is more likely than in unrelated parents. The panel suggested statement 1.4 for this reason, considering also that an increasing number of immigrants in western countries come from ethnic groups with common marriages of familial-related individuals. Of note, the perception of this problem is different between urologists and nephrologists.

In reference to the need to collect stone fragments for the analysis on composition, a consensus was reached mainly among nephrologists (91% *vs.* 75% among urologists). Urologists' reluctance to collect stone fragments is surprising because do not align with Urological Societies Guidelines suggestions.[21] Some reasons could justify the urologists' stance: the use of dusting laser lithotripsy technique with difficulty in collecting significant fragments, the historical low interest on further evaluation after surgery (13% of urologists totally disagreed on the useful role of stone fragments analysis in kidney stone patients); the fact that only 2,8-dihydroxyadenine (DHA) – very rare – and cystine in a stone are distinctive compositions that address specific disorders.

The morphological characteristics of the stones during endoscopy were not deemed useful by urologists for the identification of geneti-

cally determined diseases (57.14% *vs.* 77.27% of nephrologists), probably as a consequence of recent studies showing the low performance of identifying stone composition from endoscopic observations.[24]

Diagnosis: type of investigations

A wide agreement between urologists and nephrologists was reached on the need to investigate patients with suspicion of genetically determined kidney stones with a metabolic evaluation (24 h urine and blood), urine sediment analysis and infrared spectroscopy for stone composition. Moreover, a broad agreement was reached for the need of further investigations due to the risk of genetic causes underlying kidney stone in case of low serum phosphate, low serum potassium, high serum calcium, metabolic acidosis, and primary hyperparathyroidism in a young patient.

As in the previous area, significant differences between nephrologists and urologists led to the non-approval of some statements (statements 2.4 and 2.7). That was the case of persistent urinary pH>6 leading to the suspicion of renal tubular acidosis. While nephrologists were widely convinced, over 50% of urologists were not, although the EAU guidelines underline the importance of urinary pH as the first step to diagnose renal tubular acidosis. In our opinion, this could reflect the scarce interest of urologists, even experts with high volume of stone treatments, to go beyond the surgical treatment with an evident low experience in catching metabolic signs and symptoms. As an additional consideration, it can be highlighted that 50% of the responders indicate 3 as the reply, thus probably reflecting a grey area around this topic.

The same consideration regards the indication to screen for cystinuria any patient with an active formation of stones of unknown composition and adolescent or young adult patients at their first episode of stones, where the agreement was not reached. It must be acknowledged that in 28% of cases, cystinuria evaluation allows the diagnosis of the disorder and that delay in the diagnosis raises the risk of CKD and of unnecessary urological procedures.[25]

Although finding cystine crystals in the urinary sediment has been indicated as pathognomonic of cystinuria,[26] the relative statement (2.6) was approved only due to the very wide agreement between nephrologists (95%) while a significant percentage of urologists was not convinced (35% of 1+2+3 replies).

Optimal patient management

The referral to qualified centers of patients with a history of recurrent or severe kidney stone disease, or suspected genetic disorders, for thorough metabolic assessment and clinical follow-up was widely recognized as necessary, as well as the need for a close collaboration of a multidisciplinary team (statements 3.1 and 3.2).

If a diagnosis of monogenic nephrolithiasis is established, relatives should be tested for the same disorder and, depending on the disorder, the involvement of organs other than the kidney should be investigated (statements 3.3 and 3.4).

Primary hyperoxaluria

Characteristics or anamnestic data suggesting diagnostic investigation

A wide agreement was reported on the red flags to suspect PH, such as high recurrence of kidney stones, nephrocalcinosis, stones onset before 20 years, bilateral stones, progressive loss of kidney function of unknown origin, end-stage kidney disease of unknown origin, and any of the above in siblings (statement 4.1). A diagnostic algorithm including these red flags was recently proposed and validated in a cohort of adult PH patients on dialysis treatment, suggesting that this prediction model can be considered as a screening tool to identify adult patients with high likelihood of PH, who could then undergo further testing to achieve a diagnosis of certainty.[19]

In a significant proportion of patients, PH can remain asymptomatic or pauci-symptomatic until adulthood, occurring even relatively later in life.[27] Thus, suspicion of PH should not be ignored in adult patients. Agreement was reached on the indication of a diagnostic workup for PH also if calcium oxalate nephrolithiasis appears in childhood or adolescence, in dialysis patients with undiagnosed nephropathy, medical history of recurrent nephrolithiasis and/or nephrocalcinosis and in patients with calcium oxalate

nephrolithiasis and urine oxalate excretion >100 mg/24 h or between 45 and 99 mg/24 h (statements 4.2, 4.3, 4.4, 4.6).

High values of urinary oxalate excretion should also be confirmed by assessing the oxalate-to-creatinine ratio, either in 24 h or fasting/spot urine samples (statement 4.5). Interestingly, urine oxalate from spot urine samples shows an acceptable correlation with 24h urine values, especially if urine creatinine is estimated based on the patient's characteristics.[28]

For most statements in this area, the agreement among urologists was remarkable lower that in nephrologists. On our opinion, this substantial disagreement might depend on a scarce knowledge by urologists of the range of different clinical presentations of PH and of its recessive mendelian inheritance. This would advocate for initiative aimed at increasing the knowledge of PH.

Type of investigations

In patients with suspicion of PH, the determination of glycolate and glycerate excretion have been reported as useful investigations to provide additional information on the pathophysiology of hyperoxalurias (statement 5.1). In agreement with the most recent recommendations, in patients with an established PH diagnosis and eGFR lower than 30 mL/min/1.73 m^2, measurements of the serum concentration of oxalate and oxaluria in a 24-hour urine sample adequately acidified were indicated as fundamental to assess the risk of oxalosis (statements 5.2 and 5.3).[13]

Optimal patient management

Patients with PH should be addressed to a center with nephro-urological care facilities to reduce the probability of progression of kidney disease up to kidney failure and should be managed by a multidisciplinary team (statements 6.1 and 6.2). Referral laboratories to investigate patients with suspicion of PH and clinical centers for the patients' follow-up should be clearly identified (statement 6.3).

A genetic test for siblings of PH patients is recommended (statement 6.4), as well as investigations for systemic oxalosis in all patients on dialysis with oxalate-related diseases (statement 6.5), even if consensus was not reached among urologists on these indications (69% of consensus for both).

Conclusions

A joint effort of specialists dedicated to the diagnosis and care of kidney stone disease highlighted several areas of agreement with regard to optimal diagnostic patterns and treatment strategies in patients with genetically determined nephrolithiasis. The process also highlighted some grey areas, which deserve further investigations and that highlight the need for educational initiatives focused on rare diseases in the field of kidney stones, similar to our consensus activity. There is a need for multidisciplinary teams with structured cooperation between urologists, nephrologists and other specialists to offer patients tailored treatments and follow-up. We firmly believe that this is the key to preventing the poor prognosis of most of these genetic forms of kidney stones.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
All authors contributed to the definition and contextualization of the paper's contents, critically edited the manuscript. All authors read and approved the final version of the manuscript.

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Supplementary data
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