Genetic kidney stones disease in adults

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An adequate diagnostic evaluation of an adult patient with recurrent nephrolithiasis is mandatory to find the pathophysiological basis of the kidney stone(s). Sadly, this is only infrequently done even though the approach is implemented in urological guidelines [1]. The stone is just a symptom of a disease and not the disease itself. Of course, knowing the basis of the disease makes a better and preventive treatment possible, rather than just repeated stone removal procedures. Also, new medications have become available in a variety of metabolic diseases leading to kidney stones [2, 3]. However, rare metabolic diseases are all clearly underdiagnosed. Why is this still the case?

The paper published in this issue of NDT on the prevalence and characteristics of genetic disease in adult kidney stone formers deals with this topic [4]. Whole-exome screening was done in 787 adult patients to find the genetic reason for their recurrent nephrolithiasis. Although the major finding of the paper suggests that only a minority of adult patients (only 2.9%, or 23 of 787 patients examined), have a genetic or Mendelian reason for kidney stone formation, it nevertheless emphasizes the necessity and importance of diagnostic evaluations in adults with recurrent nephrolithiasis.

It is of the utmost importance to recall again and again that a missing diagnosis in recurrent nephrolithiasis can end in a disastrous situation such as kidney failure, isolated kidney transplantation and transplant failure due to disease recurrence. Even if the majority of adult patients did not have a genetic diagnosis in the current paper, there are still patients who left the study evaluations with a diagnosis, and therefore with a better treatment possibility. More risk factors can be detected though, if more basic diagnostic evaluation is performed. Not all patients with cystinuria, for example, also carry mutations in one of the known genes, but urine or stone analysis will prove the diagnosis [5].

In our pediatric kidney stone center the need to find the reason for the kidney stone event is evident and imprinted. Up to 75% of pediatric patients do have a metabolic reason—what a disaster it would be were these not to be diagnosed and treated [6]. However, as adult patients with rare metabolic diseases leading to kidney stones are also treated in our pediatric center, we are aware of how often disasters do occur because the diagnosis is not made.

In a recent retrospective data analysis performed in an adult community, we found a possible reason for nephrolithiasis/nephrocalcinosis in the majority of adult patients (83%). This was not a genetic study, but was done by examination of urinary lithogenic risk factors first (Fig. 1). We evaluated data from 24-h or spot urines of adult kidney stone-formers randomly sent for analysis to a reference lab in Cologne, Germany. A total of 288 laboratory reports of urine samples collected between January 2020 and March 2021 from 243 adult patients (age range 18–87 years of age) with either nephrolithiasis or nephrocalcinosis were viewed retrospectively and anonymized. The most prevalent risk factors were hypocitraturia and hyperoxaluria (found in 38% of patients, each), and a low magnesium excretion (in 30%). Hypercalcemia was found in 15.2% of patients and hyperuricosuria was observed in 15.2%. The combination of two or three risk factors was seen in 18.9% of patients. This clearly showed that risk factors can easily be detected also in an adult kidney stone–forming community, even easier, as with primary genetic testing and also in agreement with urology guidelines proposing to examine urine for lithogenic substances and, if available, kidney stones for their composition. The need to do this was later strengthened by diagnosing a number of adult patients with rare monogenic diseases: for example patients with hereditary hypophosphatemia, rickets and hypercalciuria syndrome (genes: SLC34A3/NPT2c), infanilile hypercalcemia and hypercalciuria (genes: CYP24A1 or SLC34A1), primary hyperoxaluria (PH) type 1 (gene: AGXT) or PH type 3 (gene: HOGA1). All of them had recurrent kidney stones and were not diagnosed beforehand. One patient with PH type 1, for example, had 15 and one patient with PH type 3 had >50 stone removal procedures before diagnosis was finally made by pediatric nephrology at ages 34 and 60 years, respectively. Since diagnosis and installment of treatment they both are without any further stone development.

The paper from Anderegg and colleagues describes nephrolithiasis as a global healthcare problem [4]. This is quite true, as numbers are increasing for both adult and pediatric patients [7, 8]. The paper puts emphasis on genetic diagnostics given the fact that family history was positive in the majority of patients. This underlines that there definitely is a treatable risk in this community of patients, which needs to be diagnosed adequately. The easy and minimally invasive stone removal procedures may give rise to belief that diagnostic evaluation is not necessary, however, in believing so it is overlooked that the underlying disease still may cause harm, and that the repeated stone removal procedures also can induce deterioration of kidney function or other unwanted problems. The most dramatic scenario is that of late diagnosis in a metabolic/genetic disease only after an isolated kidney transplantation has failed because of disease recurrence [9]. This makes it very obvious that it is not enough to remove stones, one must also perform diagnostics. We should not just let the patient hyperhydrate himself and come back if there is a new stone for removal—we should be dealing with the situation as we learned in medical school: find the diagnosis and treat adequately.
We are in complete agreement with the paper from Anderegg et al. that there needs to be an easy diagnostic procedure for adult stone formers and we should not be discouraged by the few diagnoses made in the cited study. However, diagnostic evaluation can be easier, more personalized and cheaper than using whole-exome sequencing. For that reason, let us be reminded of the urology guidelines: specific metabolic evaluation requires collection of two consecutive 24-h urine samples in patients with a high risk of recurrence (Turk et al. [1] and European Association of Urology guidelines updated 2023; 4.1.2. Urine sampling: https://uroweb.org/guidelines/urothiathiasis/chapter/metabolic-evaluation-and-recurrence-prevention). We have adapted that procedure into an easy workflow to detect the stone risk factor by routine urine collections. We ask patients to collect three 24-h urines on consecutive days, the first under a normal diet (and always under a normal fluid intake), the second under a low oxalate diet and the third with a diet high in oxalate [10]. At the first collection a pH daytime profile can be added. Using that procedure we are able to interpret diet, fluid, pH and especially the lithogenic factors, and then introduce further diagnostics, e.g. more personalized genetic testing (Fig. 1).

Nevertheless, larger genetic testing may also have its place, for example in postnatal screening. Broader postnatal screening is not possible by urine collection and analysis, but can be done nicely with genetic evaluations. Our experience here is encouraging based on a pilot trial in primary hyperoxaluria with early diagnosis in two newborns, preventing early kidney failure in one. At the same time, but outside the postnatal screening study, two other infants experienced kidney failure by age 4 months and only then were diagnosed with PH type 1. This underlines the utmost importance of performing diagnostic evaluations in patients with (recurrent) kidney stones as early as possible. This must be done in pediatric as well as in adult patients, and guidelines should always be followed. As mentioned, repeated urine analysis of lithogenic substances and/or prompt stone analysis followed by personalized genetic testing may prove the suspected diagnosis. However, a patient with a cystine stone has cystinuria, no matter on whether a genetic background is later found [5]. Diagnostic evaluation can be easy in recurrent kidney stone formers, and it has to be done (Fig. 1). Hence, the paper by Anderegg and our commentary are in agreement that there is huge potential for early (genetic) testing to direct patients to personalized treatment. This is further substantiated by the fact that new treatment options in rare metabolic diseases are now available and patients can be better treated to prevent disastrous outcomes [2].

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

