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Is Genotype the Major Outcome Parameter of Kidney Failure in Patients With Primary Hyperoxaluria Type 1?

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Kidney Int Rep (2023) **8,** 2187–2190; https://doi.org/10.1016/j.ekir.2023.09.012

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The primary hyperoxalurias are a group of autosomal recessive inherited rare inborn errors of glyoxylate metabolism. Three different deficient enzymes result in endogenous overproduction of oxalate and type-specific further metabolites. Oxalate, which is inherently not degraded in humans, is primarily eliminated by the kidneys inducing urinary calcium-oxalate supersaturation which leads to recurrent urolithiasis, progressive nephrocalcinosis, and eventually chronic kidney disease (Figure 1). Primary hyperoxaluria type 1 (PH-1) is caused either by deficiency of the liver specific peroxisomal alanine-glyoxylate aminotransferase or its mistargeting from the peroxisome to the mitochondria, where it is ineffective. Diagnostic evaluation includes urine analysis of both oxalate and glycolate, and genetic confirmation by *AGXT* gene variants. PH-1 accounts for 70% to 80% of all primary hyperoxaluria cases; however, it still seems to be underdiagnosed, according to genetic calculations. PH-1 is the most severe form, frequently causing rapid decline in kidney function and eventually early kidney failure even in newborns (infantile oxalosis).[1] Patients therefore need renal replacement therapy and consecutively transplantation. While waiting for transplantation, they develop systemic oxalate depositions merely everywhere in the body (Figure 1). Standard of care treatment includes hyperhydration, citrate medication, and vitamin B6 (VB6) medication for patients with genotypes being sensitive to that treatment.[2] Recently, an era of new therapeutic possibilities has emerged, when the first RNA interference medication for treatment of PH-1 was launched.[3] For that reason, it is of utmost importance to diagnose and treat patients early, and to know the determinants for treatment decisions based on (multiple) outcome parameters, one of which definitively is the genotype/phenotype correlation. In addition, other markers such as urinary and plasma oxalate levels, kidney stones or nephrocalcinosis, treatment and treatment adherence, time of diagnosis, and center-specific differences are of significance.[2]

The study by Metry *et al.*[4] published in the October issue reports on the largest database available on real-world observational data in patients with PH-1. The study puts special emphasis on a specific determinant of kidney function, as it examines the impact of genotype, be it VB6 sensitive or not, on phenotype, namely kidney failure. VB6 sensitivity was assumed based on DNA sequence change (missense), or mitochondrial mistargeting in 2 genotypes, c.508G>A (p.Gly170Arg) and c.454T>A (p.Phe152Ile) and evidence of *in vivo* VB6 response in another c.731T>C (p.Ile244Thr). The relationship between nephrocalcinosis and urolithiasis with kidney outcomes was also investigated; and the connection between urinary oxalate and glycolate excretion, and the onset of kidney failure was explored.

The ability of a clinician to predict phenotypic behavior based on genotypic variants is always rewarding and more so in detrimental disorders such as PH-1. Previous OxalEurope studies observed a better prognosis of the p.Gly170Arg variant.[5] Hopp *et al.*[6] reported that the *AGXT* p.G170R induced mistargeting was associated with a milder PH-1 phenotype; however, other putative *AGXT* mistargeting variants were associated with a more severe (fully penetrant) disease. One of the standout findings of the study by Metry *et al.* is the identification of specific genetic variants that correlate with the risk of kidney failure. The highest risk was found in 175 VB6 unresponsive ("null")

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Received 24 August 2023; accepted 4 September 2023

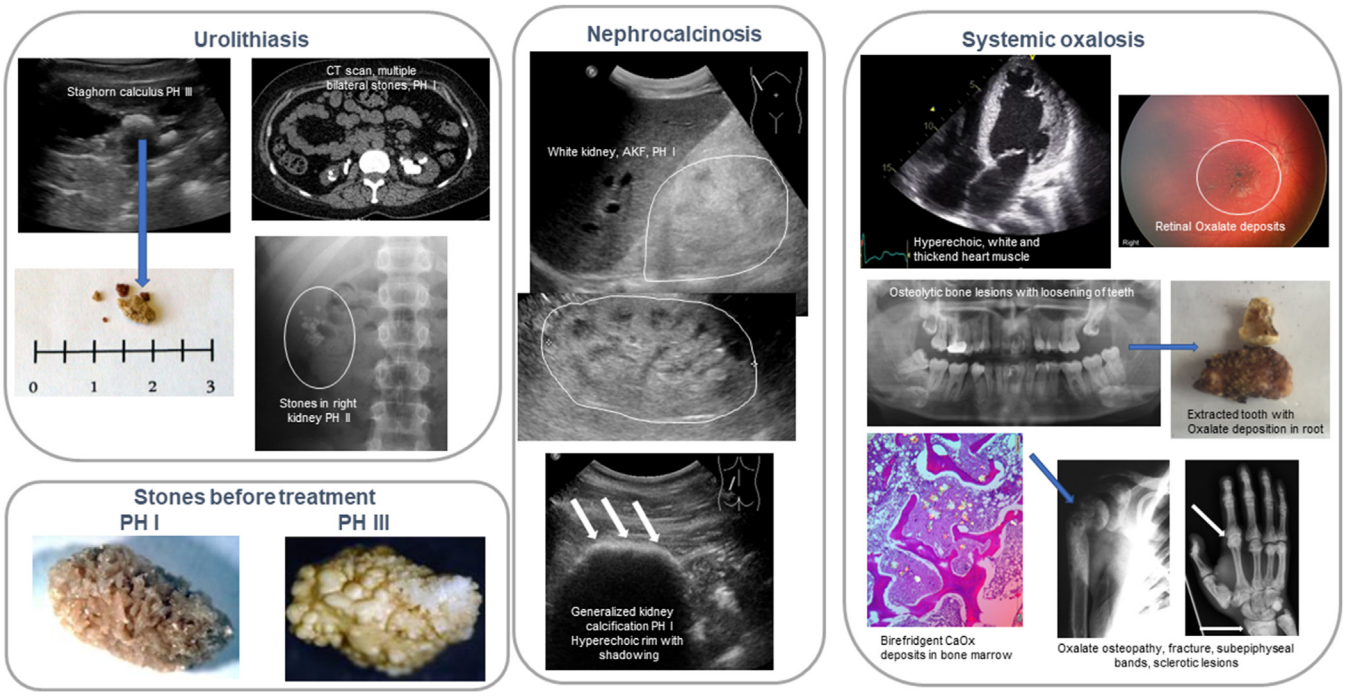

Figure 1. Urolithiasis or nephrocalcinosis and systemic oxalate depositions in patients with primary hyperoxaluria.

homozygotes, with kidney failure beginning at a median age of 7.8 years. In contrast, 155 patients with the variants c.508G>A and c.454T>A had the lowest risk, with a median age of onset of 31.8 years. VB6 unresponsive null homozygotes had a 2.5 times amplified risk of developing kidney failure than VB6 responsive homozygotes. This finding highlights the significance of in depth genetic testing in the diagnosis and treatment of PH-1.

It is established fact that a subset of patients with specific PH-1 genotypes (c.508G>A and c.454T>A) will respond to pyridoxine, as defined by a >30% decrease in urinary oxalate excretion.[2] In a Tunisian study, the only known genotype-phenotype correlation in PH-1 was the response to pyridoxine in patients with Gly170Arg and Phe152Ile variants, which may improve renal prognosis.[7] A key takeaway in the study by Metry *et al.*[4] is that VB6 responsiveness is not uniform across all patients and must be considered in conjunction with specific genetic variants and clinical factors. This must take into consideration that VB6 sensitivity is not equal in all patients with such variants, even not within families. It must also imply, that patients' adherence to treatment, treatment control by centers, and additional medication plus hyperhydration are nonnegligible parameters, when considering kidney failure as outcome.

There is dispute on whether specific genotypes, for example, with *in vivo* VB6 responsiveness here (e.g., c.731T>C) are truly showing VB6 sensitivity.[2] In this regard, it was interesting to read that there was no specific difference in kidney survival curves between this and the c.508G>A variant and that it even had a better kidney survival than the c.454T>A variant. Nevertheless, patients with other potentially VB6 responsive variants had worse outcomes. This indicates that VB6 responsiveness alone may not be a sufficient predictor of outcome. This is also reflected by the fact that data on outcome and VB6 sensitivity of the specific variants reported are different in the literature,[2] although numbers of patients reported are smaller than the number depicted by Metry *et al.*,[4] which may confirm superiority of the latter data collection.

Another crucial finding of the study by Metry *et al.*[4] is the association between nephrocalcinosis and kidney failure. With a 3.17 hazard ratio, this result cannot be ignored. Nephrocalcinosis has been known to cause kidney issues for a long time; however, this study quantifies its effect in the context of PH-1. This relevant observation is consistent with the conclusion of a Chinese study that nephrolithiasis and nephrocalcinosis are pathophysiologically distinct entities and nephrocalcinosis is associated with an increased risk for kidney failure.[8] It was also interesting, though, that time of diagnosis did not change the significance of the finding. Patients with nephrocalcinosis do not have overt symptoms, like the patients with stone disease. Therefore, diagnosis is often made late, and this may explain why patients with PH-1 with

nephrocalcinosis have a worse outcome. This provides evidence why newborns and infants with PH-1 and nephrocalcinosis are with a special risk to develop early kidney failure; and this should make clear that this group of patients, much more than others, need early diagnosis and treatment. As PH-1 became a treatable disease with the new RNA interference medication lumasiran, with which infantile oxalosis can be prevented, postnatal screening should even be considered.[3]

There is substantial evidence that the degree of hyperoxaluria is a primary predictor of loss of kidney function. A recent study had shown that patients with the highest quartile of oxalate excretion at diagnosis had a worse renal outcome, whereas those in the lower quartiles trended toward substantially better prognosis.[9] The current study also explored the association between urinary oxalate and glycolate excretion and the onset of kidney failure. Patients who subsequently developed kidney failure had a higher urinary oxalate excretion, but glycolate levels did not correlate. However, this finding was mitigated by a 41% intraindividual variation in urinary oxalate, resulting in wide confidence intervals. In addition, there was no specific difference between urinary oxalate-to-creatinine ratios for those with or without kidney failure. All these demonstrate the difficulty of using urinary oxalate as a reliable indicator of the risk of kidney failure, especially if outcome is related to only 1 urine value and not to a variety of measurements. We know that sometimes there is a huge intraindividual variation of urinary oxalate excretion; therefore, we have to carefully consider its value proposition. It definitively necessitates additional study to refine the influence of urinary (and even more plasma) oxalate on outcome.

The extensive number of patients included in the OxalEurope registry provides a wide spectrum of real-world data. There is profound evidence that genotype correlates with kidney failure, which provides detailed insights into genetic influences on the disease. However, many more individual risk factors needed to be added to the risk evaluation of each patient to really consider the differences between the groups examined, which were only related to possible VB6 sensitivity. Time of diagnosis, kidney function at diagnosis, treatment, treatment adherence (e.g., to VB6 treatment), stone events, stone removal procedures, grading of nephrocalcinosis, intervals of concomitant diseases (e.g., dehydration), and quality of care provided were not all included. Data on urinary oxalate and glycolate excretions were, in contrast to the genetic data, not sufficient to draw adequate conclusions. In addition, the wide confidence intervals due to intraindividual variation in urinary oxalate made the observations less definitive.

Nevertheless, this study on determinants of kidney failure in PH-1 has opened new avenues for understanding and treating this complex condition. However, it has also highlighted gaps that require further exploration. Advances in research, focusing on enhanced genetic testing, standardization of measurements, early interventions, longitudinal studies, collaborative multidisciplinary efforts, and patient-centered approaches could bridge these gaps. Standardization of urinary measurements and early intervention strategies are also crucial. It clearly shows that early diagnosis is mandatory, which may help to open doors for postnatal (genetic) screening.

Longitudinal studies and registries can provide valuable real-world data on the disease's progression and the effectiveness of interventions. However, they are only as good as the data included in such registries. Considering that there are missing data, for example with regard to urinary excretion parameters, plasma oxalate values and clinical follow-up, conclusions may still have a bias.

DISCLOSURE

BH was a former employee of Dicerna Pharmaceuticals, a NovoNordisk subsidiary; he currently is consultant to NovoNordisk, Arbor Pharmaceuticals and Avanzanite. PSV has declared no conflicting interest.

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