Oxalosis & Hyperoxaluria Foundation
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INTERNATIONAL HYPEROXALURIA WORKSHOP 2026

ABSTRACT BOOK

INTERNATIONAL HYPEROXALURIA WORKSHOP

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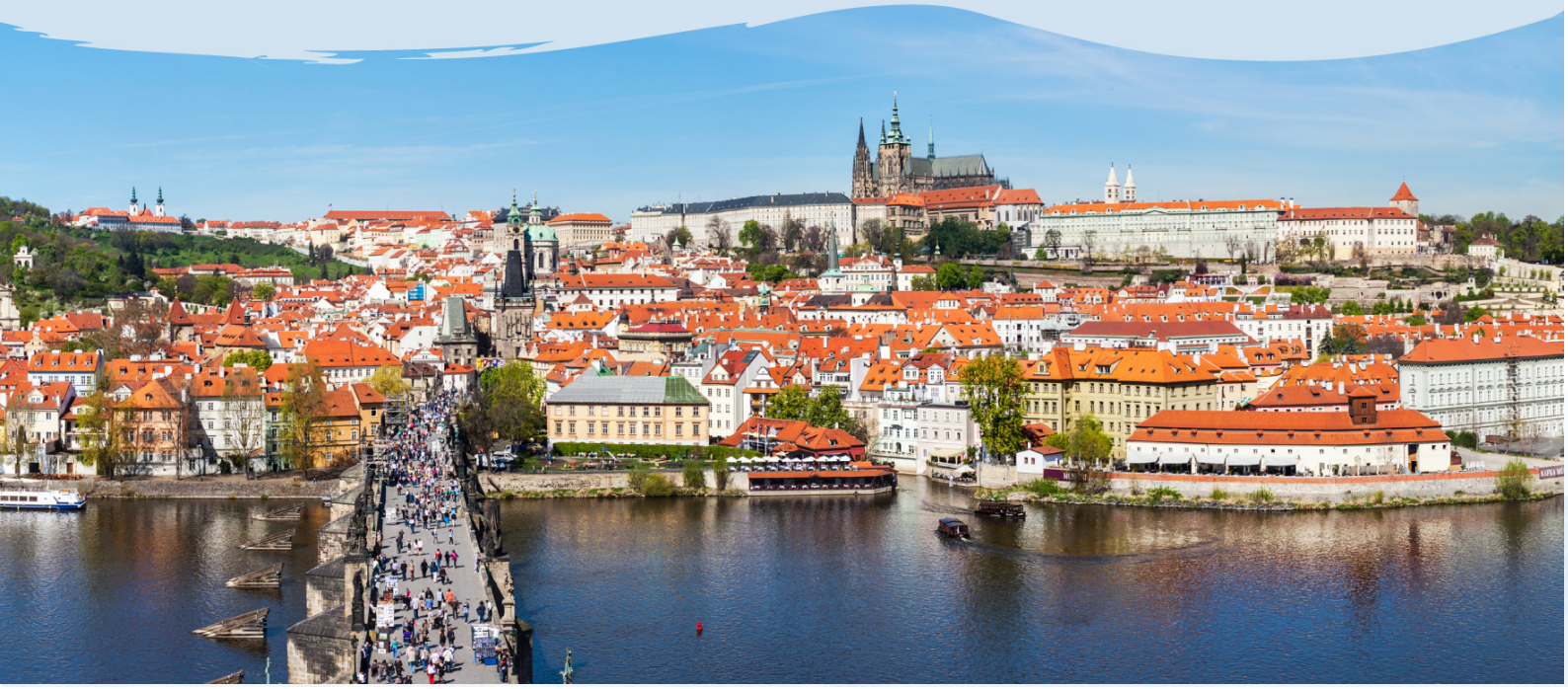

ORAL PRESENTATIONS

O 01 - YOLT-203, an In Vivo Gene-Editing Therapy for Primary Hyperoxaluria Type 1: Interim Results from Two Investigator-Initiated Trials

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Background and Objective: Primary hyperoxaluria type 1 (PH1) is a rare hereditary disease characterized by long-term excessive oxalate production that results in kidney failure and oxalosis. YOLT-203 is an in vivo gene-editing therapy targeting to the HAO1 gene to reduce hepatic oxalate production. Two ongoing investigator-initiated trials (IIT) have been conducted to evaluate the safety, tolerability, pharmacodynamics, and efficacy of YOLT-203.

Methods: Both IITs (NCT06511349, NCT06892301) adopted an open-label, single-dose escalation study design. Key eligibility criteria included a genetic diagnosis of PH1, an estimated glomerular filtration rate (eGFR) of ≥ 30 ml/min/1.73 m^2, and an elevated 24-hour urinary oxalate excretion (24h-UOx) of ≥ 0.70 mmol/day/1.73 m^2. The primary objectives for both IITs were safety and tolerability. The percent change in 24h-UOx was the primary measure of efficacy. Percent change in the 24-hour urinary oxalate:creatinine ratio (24h-UOx:UCr) was also evaluated.

Results: As of November 2025, a total of 11 participants have received one dose of YOLT-203 (two at 0.3 mg/kg, eight at 0.45 mg/kg, and one at 35 mg dosing) and completed over 24 weeks follow-up (range 24-52 weeks). Eight pediatrics and three adults were included (age range 2-59 years). YOLT-203 was well tolerated across all dose ranges. Transient adverse events (AEs) were reported in 5 (45.5%) participants, with fever being the most common (36.4%). Baseline 24h-UOx level was 2.29 mmol/day/1.73 m^2. At Week 24, percent change in 24h-UOx from baseline reached -31.1%, -53.0%, and -59.0% in the 0.3 mg/kg, 0.45 mg/kg, and 35 mg dosing group, respectively. Similarly, a 52.6% and 56.6% reduction of 24-week 24h-UOx:UCr from baseline was observed in the 0.45 mg/kg and 35 mg dosing groups, respectively.

Conclusion: Single-dose YOLT-203 showed favorable safety and tolerability in both pediatric and adult PH1 participants. YOLT-203 demonstrates significant potential for sustained reduction of urinary oxalate excretion.

O 02 - N-Propargylglycine Restores Survival by Preventing Calcium Oxalate Stone Formation, Tubular Injury, and Kidney Dysfunction in a Lethal Mouse Model of Primary Hyperoxaluria Type 2

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New therapeutics are needed to address the rapid progression of calcium oxalate (CaOx) nephrolithiasis and life-threatening renal failure afflicting infants and young adults with one of the three different genetic types of Primary Hyperoxaluria (PH) types 1, 2, and 3. Glyoxylate and hydroxypyruvate reductase knockout (*Grhpr* KO) mice recapitulate the pathophysiology of PH type 2 (PH2), developing accelerated hyperoxaluria and CaOx kidney stone formation. Previous studies have shown that this process can be mitigated by introducing an additional genetic knockout of the hepatic and renal mitochondrial enzyme, hydroxyproline dehydrogenase (Hypdh/Prodh2), which is responsible for the first step in liver production of glyoxylate and oxalate. We now show that oral administration of *N*-propargylglycine (*N*-PPG), a well-tolerated small-molecule inhibitor of Hypdh/Prodh2, significantly reduces hyperoxaluria and weight loss in *Grhpr* KO mice within three weeks, while preventing CaOx stone formation and renal tubular damage. In a 24-week survival study during which vehicle-treated *Grhpr* KO mice exhibit a median survival of only 15 weeks, daily treatment with *N*-PPG fully restores weight and survival in the *Grhpr* KO mice to that of wild-type controls. *N*-PPG suppresses hyperoxaluria during this extended treatment period, preventing CaOx stone formation, renal tubule injury, and loss of kidney function, achieving outcomes in this PH2 mouse model comparable to controls. These findings establish *N*-PPG as a promising therapeutic candidate for the long-term prevention of CaOx kidney stone formation and renal failure complications in PH2.

O 03 - Hepatic Knockout of Lactate Dehydrogenase and Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease in a Mouse model of Primary Hyperoxaluria type 1

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) can induce changes in the expression of enzymes involved in glyoxylate metabolism in mouse and human models, potentially leading to increased endogenous oxalate synthesis. A reverse relationship has recently been put forward, hypothesizing that increased hepatic endogenous oxalate synthesis may play a causative role in the acceleration of MASLD. *To test this hypothesis,* our study examines whether Crispr-cas mediated knockout of hepatic lactate dehydrogenase can reduce the progression of diet-induced MASLD in *Agxt* null and wild type mice.

Methods: Male, *Agxt* null mice and wild type littermates in the C57Blk6j background (N=8/group), were fed the Gubra-Amylin Western diet or a control diet, from the age of 9 weeks for up to 28 weeks to induce MASLD. Knockout of LDH was induced at 9 weeks *in Agxt* null mice and wild type littermates prior to Western diet feeding by a single intravenous dose (1mg/kg by tail vein) of Crispr-cas Ldha-LNP product (Arbor® Biotech, Cambridge, MA). The primary endpoint is the severity of MASLD assessed by histology (NAFLD Activity Score) and total liver triglyceride content at 14 and 28 weeks. Hepatic lactate dehydrogenase activity and urine oxalate will be measured to confirm effective reduction of endogenous oxalate synthesis. All diets are ultra-low in oxalate, allowing oxalate endogenous production to be estimated by measurement of urinary oxalate excretion.

Results: Experiments are ongoing and findings will be presented for all groups (N=4).

O 04 - Effect of Lumasiran in Hyperoxalaemic Patients on Maintenance Haemodialysis

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Background: Cardiovascular death remains the leading cause of death in people with ESKD, with limited improvement in cardiovascular mortality and morbidity compared to the general population. Previous cohort studies have shown that haemodialysis patients with elevated plasma oxalate concentrations have increased risk of cardiovascular events, particularly sudden cardiac death.

Methods: We investigated the efficacy and safety of lumasiran (3mg/kg) in haemodialysis patients with a non-primary hyperoxaluria cause of ESKD and a plasma oxalate concentration of >20uM in a randomised, double-blind placebo-controlled phase 2 trial. The primary outcome was the percentage change in pre-dialysis plasma oxalate levels from baseline to month 3- 6.

Results: The study was conducted in 29 patients with ESKD receiving haemodialysis for a minimum of 2 months. A total of 26 patients completed the trial period. For the primary end point of plasma oxalate percentage change; there was no statistically significant treatment effect at any of the time points. At month 6 the pooled pairwise comparison of placebo versus lumasiran was estimated at -11.19% change in plasma oxalate without significant a treatment effect (p= 0.184, 95% CI [-27.70, 5.32]). No significant differences were observed in the secondary end points. Two deaths were reported during this trial which were not related to the trial procedures or trial drug. There were no safety concerns and lumasiran was very well tolerated.

Conclusion: Although the primary endpoint was not reached, plasma oxalate concentrations improved in a subset of patients receiving lumasiran. This heterogeneity of response highlights the need to better refine dosing regimens in adult haemodialysis patients and to better define the role of hyperoxalaemia in cardiovascular pathology. The success of future studies will depend on accurately identifying those patients most likely to derive a clinical benefit.

O 05 - Inhibition of Hydroxyproline Dehydrogenase as a Therapy for Primary Hyperoxaluria

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The breakdown of hydroxyproline, a component of collagen, is a significant contributor to glyoxylate and oxalate levels. We have shown in normal individuals and patients with primary hyperoxaluria (PH) that hydroxyproline is converted to oxalate (18% for PH1, 47% for PH2, and 33% for PH3). These values are the largest known contribution to oxalate formation for any metabolite studied to date. We hypothesize that blocking the hydroxyproline pathway with an inhibitor will significantly lower the glyoxylate and oxalate burden of PH2 and PH3 patients, for which there are no available therapies. The target of this study is the first enzyme in the hydroxyproline degradation pathway, hydroxyproline dehydrogenase (HYPDH). This strategy is supported by the observation that individuals and mice that are deficient in HYPDH are normal and safely excrete the excess hydroxyproline into urine. A high throughput screening assay was used to identify potent inhibitors of HYPDH, and a cross screen using the *Escherichia coli* PutA, a proline-dependent enzyme, was used to identify non-selective compounds. Optimization of the scaffolds has generated novel compounds with improved potency, solubility, plasma and microsomal stability. Biochemical, cellular and animal studies will be presented that support the tractability of this novel approach to treat primary hyperoxaluria.

O 06 - Functional and In Silico Characterization of Common AGXT Variants as Potential Modifiers of Primary Hyperoxaluria Type 1

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Background: Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disorder of hepatic glyoxylate metabolism caused by pathogenic variants in the *AGXT* gene. Recent data suggest that common variants in several genes can be considered as disease modifiers [Hao et al 2023]. In this study the aim is to investigate whether this type of variants may influence PH1 clinical phenotype.

Methods: Candidate variants were selected among the most common one in gnomAD database and analyzed by in silico tools. Variants with predicted functional alteration were characterized through in vitro expression assays to assess protein stability and enzymatic function. The selected variants were then queried in the 100,000 Genomes Project (100KGP) database to investigate their occurrence and the associated clinical phenotypes in individuals.

Results: Some variants (e.g. p.Arg118His; p.Gly97Glu) were found to alter the protein expression or the protein function in *in vitro* analysis. 16/38 variants studied with functional analysis were found in 100KGP patients, but none of the patients were reported with recurrent kidney stones.

Conclusion: The rare occurrence of the functionally characterized variants in 100KGP indicates the need to extend the number of patients to be studied. Moreover, some variants found in 100KGP patients with kidney stones were not among the one selected for *in vitro* functional studies (e.g. p.Arg111Gln; p.Val339Ile). This suggest the necessity to extend the functional analysis to more variants commonly found in the population in order to discover possible disease modifiers.

O 07 - Data-Driven Metabolic Phenotyping of Calcium Oxalate Nephrolithiasis Using Model-Based Clustering

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Introduction: Calcium oxalate (CaOx) nephrolithiasis is the most common form of kidney stone disease and is associated with high recurrence rates and substantial morbidity. Although 24-hour urine testing is routinely used to guide prevention, management strategies remain largely uniform and do not account for biologically distinct subgroups of CaOx stone formers. The objective of this study was to apply model-based clustering to 24-hour urine data to identify data-driven phenotypes and evaluate their clinical relevance.

Methods: We performed a retrospective review of a prospectively maintained dataset of treatment-naïve patients with confirmed CaOx nephrolithiasis who underwent comprehensive metabolic evaluation, including 24-hour urine collection and relevant serum studies. Using an Expectation-Maximization (EM) clustering method, patients were stratified into phenotypically distinct groups based on urine chemistries and clinical risk factors. Primary outcomes included identification of clinically meaningful subgroups and associations between cluster membership and established risk factors. We hypothesized clusters would reflect distinct pathophysiologic mechanisms such as enteric hyperoxaluria and idiopathic hypercalciuria.

Results: A total of 153 patients were identified, of whom 49% were female with a mean age of 49.9 years old. EM clustering identified 4 distinct metabolic patterns (isolated hypocitraturia, hypocalciuria/hyperoxaluria, hypercalciuria, and a metabolic excess pattern). Subjects were then assigned group membership and meaningful clinical differences between groups were able to be shown. The isolated hypocitraturia group had features of a lower urine volume (1.3 L per day ± 0.5) and lower BMI (25.1±5). The hypocalciuria/hyperoxaluria group was more likely to have a CKD (44%) and malabsorptive GI history (66%). The metabolic excess group tended to have a higher rate of diabetes (41%), higher BMI (33.2±7), and higher dietary protein intake.

Conclusions: Clustering identifies clinically meaningful metabolic phenotypes not captured by conventional approaches. These findings support precision prevention strategies tailored to metabolic profiles.

Disclosures: None

O 08 - Urinary Biochemical Monitoring of Patients with Primary Hyperoxaluria: A Moroccan Experience

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Background: Primary hyperoxaluria (PH) remains underdiagnosed in Morocco. In our laboratory analysis of 614 urinary stones from children, 13.8% showed features consistent with primary hyperoxaluria.

Objective: To describe our Moroccan experience in urinary biochemical monitoring of patients with PH using accessible diagnostic and follow-up tools.

Methods: We conducted a retrospective analysis of 297 fresh first-morning urine samples from 59 Moroccan patients diagnosed with PH. The mean age during follow-up was 8.21 ± 4.57 years (range: 4 months - 20 years). Diagnosis was based on type Ic stone morphology, pure whewellite composition confirmed by infrared spectrophotometry, massive whewellite crystalluria (>200 crystals/mm³) under polarized light microscopy, and urinary oxalate ≥0.7 mmol/L. All patients received conservative management. Each sample was evaluated for crystalluria and urinary biochemical parameters including creatinine, calcium, phosphorus, magnesium, sodium, uric acid, citrate, proteins, urea, oxalate, pH, specific gravity, and the oxalate/creatinine ratio.

Results: All patients exhibited abundant whewellite crystalluria. Mean urinary oxalate concentration was 1.34 ± 0.81 mmol/L (reference <0.3 mmol/L), and the oxalate/creatinine ratio was 0.27 ± 0.25 mmol/mmol (reference <0.08 mmol/mmol), confirming persistent hyperoxaluria. Mean urinary citrate was 0.97 ± 0.98 mmol/L (reference >1 mmol/L), and mean specific gravity was 1014.25 ± 8.16 (reference <1012). Other biochemical parameters remained variable but within expected ranges for PH. Longitudinal follow-up demonstrated sustained oxalate burden in all patients, notably in one patient monitored from 4 to 20 years (mean oxalate 2.05 ± 1.32 mmol/L; oxalate/creatinine ratio 2.09 mmol/mmol) and in an infant diagnosed at 4 months, with oxalate levels of 2.8 mmol/L and an oxalate/creatinine ratio of 2.09 mmol/mmol (reference <0.36).

Conclusion: Persistent hyperoxaluria was observed despite conservative management, highlighting the need for earlier diagnosis, structured monitoring, and potentially intensified therapeutic strategies. This approach represents a feasible model for PH follow-up in resource-limited settings.

O 09 - Pregnancy During Active Lumasiran Therapy in Primary Hyperoxaluria Type 1

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PRELIMINARY
Limited human data exist on RNA interference therapy during pregnancy. We report on the first two women with primary hyperoxaluria type 1 (PH1) who continued lumasiran, a small interfering RNA targeting hepatic glycolate oxidase (GO), throughout gestation. Maternal kidney function remained stable, and no major congenital anomalies were identified. Both neonates required short-term intensive care support consistent with late-preterm adaptation. In both patients, plasma and urinary glycolate concentrations declined during pregnancy while urinary oxalate levels tended to increase slightly. These first-in-human observations on RNA interference exposure during pregnancy suggest gestational modulation of pharmacodynamic responses. Further data from this case series are forthcoming.

O 10 - Optimizing Access to Lumasiran in Primary Hyperoxaluria Type 1 Through a National Response-Guided Protocol

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Lumasiran is an effective yet costly therapy for primary hyperoxaluria type 1 (PH1), with uncertainty regarding long-term outcomes. We evaluated a national orphan drug access protocol in the Netherlands designed to enable early access, generate real-world evidence, and control costs.

A nationwide programme was launched in 2022, with centralized patient selection by a multidisciplinary indication committee based on European guidelines. Patients were stratified by kidney function, oxalate levels, and pyridoxine responsiveness. Treatment followed a stepwise evaluation model, with continuation based on predefined biochemical and clinical response criteria. Biochemical response was defined as reduction in urinary or plasma oxalate, while clinical response included stabilization or improvement of kidney function and systemic manifestations. Data were collected prospectively with longitudinal follow-up. Drug distribution was centralized, and pooling strategies were used to reduce waste and costs.

Between September 2022 and March 2026, 31 patients aged 3 months to 69 years were assessed, of whom 29 were formally evaluated. Treatment was mainly initiated in pyridoxine-unresponsive patients and/or those with advanced disease. Among pyridoxine-unresponsive patients with preserved kidney function, 8 of 9 were treated, showing a mean urinary oxalate reduction of 68%, with normalization in 4 patients and clinical improvement in all treated individuals. Most pyridoxine-responsive patients were not treated and maintained favorable outcomes. A small subgroup of pyridoxine-responsive patients with severe kidney impairment (eGFR <20) showed no response and discontinued therapy. In advanced disease, treatment reduced plasma oxalate and improved systemic manifestations.

The programme achieved substantial cost savings, including approximately €2.3 million through drug pooling and over €9 million by avoiding unnecessary treatment. This protocol demonstrates that careful patient selection enables personalized care while significantly reducing costs, and may serve as a model for other high-cost therapies in rare diseases.

O 11 - Contribution of Primary Hyperoxaluria in a High-Risk Pakistani Cohort: Genetic and Phenotypic Insights

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Background
Primary hyperoxaluria (PH) is an underdiagnosed cause of urinary stone disease (USD), particularly in populations with high consanguinity. We evaluated the contribution of PH within the broader genetic landscape of Pakistani patients suspected of monogenic USD.

Methods
Seventy-three patients with USD, attending Aga Khan University clinics and suspected of monogenic disease underwent targeted massively parallel sequencing of up to 160 genes associated with inherited stone disorders.

Results
A definitive molecular diagnosis was established in 14/73 patients (19.2%). Pathogenic variants in PH-associated genes accounted for 6/73 (8.2%) of the cohort and 6/14 (42.9%) of genetically resolved cases. Biallelic variants were identified in ***AGXT*** (PH1), ***GRHPR*** (PH2), and ***HOGA1*** (PH3) (two patients each, one *HOGA1* with the toxic +c.32C>T). Monoallelic pathogenic variants were observed in single individuals with PH2- and PH3-associated genes. One patient demonstrated a possible digenic contribution involving **AGXT** and an AD/heterozygous **SLC4A1** variant, with mixed stone composition.

Biochemical evaluation showed discordance with genotype: organic acid analysis was normal in three patients with genetically confirmed PH, while two exhibited additional suberic acid. Stone analysis revealed mixed compositions, including uric acid and ammonium urate components in some PH patients.

Clinical presentation was heterogeneous, with delayed diagnosis in some and variable biochemical profiles.

Conclusions
PH constitutes a substantial proportion of monogenic USD in this high-risk population. Significant genotype–phenotype discordance and limitations of conventional biochemical testing underscore the need for early genetic evaluation. These findings also suggest potential multigenic and modifying effects in stone pathogenesis.

O 12 - Lumasiran Treatment Outcomes in Infants with Primary Hyperoxaluria Type 1

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Aim: To describe real life outcomes of lumasiran treatment for infants with primary hyperoxaluria type 1 (PH1) in Israel.

Methods: A case series of 7 infants from three reference centers for PH1 in Israel.

Results: Three patients were diagnosed by screening (prenatally, at 2 weeks and at 6 months of age). Lumasiran was initiated upon diagnosis at 3 weeks - 7 months of age. Urinary oxalate (Uox) to creatinine ratio declined from ~10 times the upper limit of normal (ULN) to ~1.5-2 the ULN. Kidney function normalized and was stable on last follow up (3- 4 years). Two patients had nephrolithiasis and one required urologic intervention. All patients demonstrate normal growth and no signs of systemic oxalosis.

The other four patients presented with end stage kidney disease (ESKD) and started hemodialysis upon diagnosis at age 1-7 months. Lumasiran was initiated upon diagnosis in three patients *(early)* and after 10 months in one patient (*late*). Plasma oxalate (Pox) was above 100 micromol/L in all patients. Two of the *early* treated patients showed good response and outcome: Pox declined to ~ 75 micromol/L and both have mild or no signs of systemic oxalosis after 2 -2.5 years on dialysis. The third *early* treated patient did not respond well: Pox remained above 100 micromol/L, and the patient had severe dialysis complications and systemic oxalosis. The patient underwent liver-kidney transplantation, with stable grafts at the age of 4 years. One patient received *late* siRNA treatment, after 10 months on hemodialysis. She developed severe systemic oxalosis and dialysis complications and died at the age of 25 months.

Conclusions: siRNA therapy should be initiated as soon as possible in infants with PH1 as it may prevent severe infantile oxalosis. Pox, Uox and systemic oxalosis signs should be monitored to assess treatment response.

O 13 - Primary hyperoxaluria type 1 (PH1): Collaborative Retrospective Real-World Study Across Brazilian Regions

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Introduction: PH1 is a rare autosomal recessive metabolic disorder with variable prevalence worldwide, higher in regions with high consanguinity rates. Brazil has one of the world's largest admixed populations, shaped by diverse ancestry.

Methods: A collaborative study was undertaken comprising retrospective data of 33 (19M/14F) cases of PH1 from 26 families, obtained in a daily clinical setting involving biochemical data and genetic testing from distinct regions of Brazil. Parental consanguinity was evidenced in 10 patients (30.3%). According to their age at onset, median [IQR] diagnostic delay was 3.6 yrs [2.7-5.5] for group 1 (≤ 1 years old, 7M/0F), 8.0 yrs [1.3-15.5] for group 2 (1-12 yrs, 5M/5F) and 8.5 yrs [5.0-14.3] for group 3 (> 12 yrs, 7M/19F). Among clinical manifestations, failure to thrive (86%) and chronic kidney disease (CKD) signs/symptoms and oxalosis (43%) were more prevalent in group 1. Group 2 exhibited more renal colic and/or stone passage (60%) and group 3 more CKD stage 5 (%) and Post-Kidney Transplant recurrence (56%). CKD5 was evidenced in 63.6% of the whole sample (57%, 50% and 75% in groups 1, 2 and 3, respectively). The c.508 G>A variant was identified in 19 of all alleles (28.8%), most of them in group 3 (46.9%), followed by c.33dup/C in 7 (10.6%), mostly in groups 1 and 2 (15%) and c.731C>T in only one allele. Multivariable logistic regression showed that carriage of at least one c.508G>A allele was associated with later symptom onset (median 13.5 vs 3 years; p= 0.023), while male sex was independently associated with earlier onset (≈0.36-fold; p=0.046).

Conclusion: Genetic profile was more similar to Western European cohorts, with a higher prevalence of c.508 G>A in older patients, reflecting slower disease presentation besides progression. The percentage of CKD5 at PH1 diagnosis was similar to other series in the literature.

POSTER PRESENTATIONS

P 01 - Hyperoxaluria and Diet: Case Series Underscoring Nutritional Assessment Before Diagnosis

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Introduction: Hyperoxaluria, defined as excessive urinary oxalate excretion, is an important risk factor for calcium oxalate nephrolithiasis and renal injury. Distinguishing primary hyperoxaluria from enteric and dietary hyperoxaluria is the first step in evaluating a child with hyperoxaluria. Dietary hyperoxaluria results from excessive oxalate intake and is largely modifiable through nutritional management.

Methods: This report describes four pediatric cases characterized by markedly elevated oxalate levels at baseline assessment, highlighting the diagnostic challenges of differentiating primary and secondary etiologies.

Results: A 9-year-old female with Autism Spectrum Disorder and her brother were both initially found to have markedly elevated urinary oxalate concentrations (2 mmol/L and 1 mmol/L) during a random biochemical evaluation; however, the clinical utility of these first results was limited by pre-analytical factors, specifically the use of non-acidified samples and a lack of creatinine normalization. Follow-up testing using appropriate 24-hour acidified collection protocols confirmed persistent hyperoxaluria (0.81 mmol/day/1.73m2) and concurrent high urine glycolates (0.75 mmol/day/1.73m2), yet a subsequent period of strict low-oxalate dietary intervention resulted in the complete normalization of urinary levels for both siblings (0.49 and 0.24 mmol/day/1.73m2), suggesting a dietary etiology rather than a primary genetic defect. The third case is a 3-year-old boy with genetically confirmed hypochondroplasia and symptomatic urinary calculi, who also demonstrated hyperoxaluria (0.96 mmol/day/1.73m2) with normal glycolates that resolved upon dietary modification (0.61 mmol/day/1.73m2). Similarly, a fourth case involved a 4-year-old boy with renal calculi and significant hyperoxaluria (0.91 mmol/day/1.73m²) alongside elevated glycolates (0.74 mmol/day/1.73m2); following a dietary trial, his oxalate and glycolate levels normalized. The following case series illustrates the diagnostic challenges of hyperoxaluria in diverse pediatric presentations, emphasizing the critical role of pre-analytical protocols and dietary intervention.

Conclusions: Standardized 24-hour acidified urine collection and a controlled dietary challenge are essential to differentiate secondary, diet-responsive oxalate absorption from primary metabolic pathologies.

Keywords: dietary intervention, hyperoxaluria, urinary glycolates

P 02 - Searching for Lactate Dehydrogenase Inhibitors in the Phenolic Fraction of Olive Oil

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Extra virgin olive oil (EVOO), one of the cornerstones of the Mediterranean diet, is a plant-based fat that has attracted considerable interest for its significant cardiovascular benefits, attributed to its unique composition of monounsaturated fatty acids, particularly oleic acid, and bioactive phenolics, such as oleocanthal (OLCT) and oleacein (OLCN). Both phenolics are formed from ligustroside (LIG) and oleuropein (OL) (present in olive fruits), respectively, during olive oil production from olives via enzymatic hydrolysis. OLCT is known for being a powerful anti-inflammatory natural molecule with effects similar to ibuprofen,[1] and is believed to have anti-cancer, neuroprotective and cardioprotective properties.[2] OLCN is comparatively less studied than OLCT and stands out for its superior ability to combat inflammation and oxidative stress.[3]

In this communication are included (a) the protocol by which OLCT and OLCN were isolated from EVOO, (b) the semi-synthetic routes followed to prepare OLCT and OLCN, and their respective methylated derivatives (Met-OLCT and Dimet-OLCN), and (d) the evaluation of the lactate dehydrogenase (LDH) inhibitory activity of OLCT, OLCN, Met-OLCT, and Dimet-OLCN.

Regarding the activity evaluation, the inhibitory effect of the compounds listed over the human LDH type A (*h*LDHA) and type B (*h*LDHB), in the conversion of pyruvate to lactate, was determined using a kinetic fluorimetric assay at a single concentration of 50 µM. Of the four compounds tested, OLCN stood out with an inhibition percentage of 82% for *h*LDHA and 20% for *h*LDHB, indicating good selectivity that may be of interest in primary hyperoxaluria (PH).

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P 03 - Genetic and Clinical Insights into Familial and Sporadic Primary Hyperoxaluria Type I

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Aims/Purpose: Primary hyperoxaluria type I (PH1) is a rare metabolic disorder, affecting 1–3 individuals per million in Europe. It results from a deficiency of hepatic alanine-glyoxylate aminotransferase (AGT), leading to excessive oxalate production and recurrent nephrolithiasis. Early recognition remains challenging due to its nonspecific presentation and variable severity.

Methods: We report four PH1 cases diagnosed and monitored in our department between 2022 and 2025. Three were first-degree relatives, a 45-year-old mother, a 48-year-old father, and their 13-year-old daughter, while the fourth was a 14-year-old unrelated male. The family history of the daughter revealed additional affected relatives on both parental sides. In contrast, the sporadic case had no family history of stone disease, and diagnosis was delayed by the presence of a congenital renal malformation initially presumed to explain his lithiasis.

Results: The three related patients experienced recurrent nephrolithiasis, whereas the unrelated male presented with a single large calculus and severe concomitant epilepsy. Genetic testing identified heterozygous AGXT variants c.-169G>A in the mother and daughter and c.31C>G (p.Pro11Ala) in the father and daughter, confirming compound heterozygosity in the child. The unrelated patient carried the pathogenic homozygous variant c.508G>A (p.Gly170Arg). Based on genotype and phenotype correlations, lumasiran therapy (an RNA interference agent that reduces hepatic oxalate synthesis) was initiated in three patients, resulting in improved clinical and biochemical outcomes. The adult male declined treatment.

Conclusion: PH1 should be suspected in patients with recurrent calcium oxalate stones, especially when onset is early or family aggregation exists. Genetic confirmation guides management, and lumasiran represents a major therapeutic advancement substantially improving prognosis and quality of life.

P 04 - Development of a Cellular Model for Primary Hyperoxaluria Type I as a Platform for Therapeutic Evaluation

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The development of gene therapy has enabled new treatment options for genetic metabolic diseases with no cure, such as Primary Hyperoxaluria Type I (PH1). However, the rapid development of these advanced therapies is accompanied by a lack of suitable cellular models in which to test the real efficacy and feasibility of these treatments. Particularly, PH1 current available models, although valuable, do not stably express all the enzymes from the glyoxylate detoxification pathway.

In this work, we present a PH1 model, developed in the HepG2 cell line, characterized by the disruption of the *AGXT* gene via electroporation of CRISPR/Cas9 tools targeting the start site of the gene. This cell line was subsequently modified via lentiviral transduction to stably overexpress the *HAO1* gene, poorly expressed in HepG2 cells and necessary for glycolate detoxification. As an oxalate accumulation control model, we also transduced Wild Type (WT) HepG2 cells with the *HAO1* lentiviral vector.

To validate this cell line as a functional PH1 model, we assessed the expression of the *AGXT* and *HAO1* genes by qPCR and Western Blot. We also measured AGT activity and analysed oxalate accumulation in the medium after inducing the glyoxylate detoxification pathway adding glycolate. Twenty-four hours after the challenge, we observed a statistically significant oxalate accumulation in HepG2-PH1 cells compared to the HepG2 WT control cells.

By mimicking the main clinical hallmark of PH1, this model represents a valid *in vitro* platform for testing new therapeutic strategies. In our laboratory, we aim to use this model to compare the therapeutic strategies currently being pursued for PH1, whether in clinical use or at preclinical stage, and to evaluate the broader metabolic effects associated with each strategy, beyond correction of the glyoxylate detoxification defect.

P 05 - Liver Hydroxyproline Metabolism: New Insights from a Cellular Model of Primary Hyperoxaluria Type 3

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Hydroxyproline (HyPro) primarily originates from collagen turnover and is catabolized in the liver through the sequential action of four enzymatic steps resulting in the production of glyoxylate. Glyoxylate is highly reactive and in mitochondria and cytosol is reduced by the glyoxylate reductase (GRHPR) into glycolate that is converted to glycine in peroxisomes by alanine:glyoxylate aminotransferase (AGT) (1). However, glyoxylate may also be oxidated into oxalate and excreted in urine. Elevated endogenous oxalate production and excretion are the hallmarks of Primary Hyperoxaluria (PH), a group of inherited metabolic disorders characterized by calcium oxalate stone formation, progressive renal impairment, and systemic oxalosis (2,3).

PH type 3 (PH3) arises from deficiency of 4-hydroxy-2-oxoglutarate aldolase (HOGA1), a mitochondrial enzyme catalyzing cleavage of 4-hydroxy-2-oxoglutarate (HOG) into pyruvate and glyoxylate in the last step of HyPro catabolism. Despite the well-defined genetic defect, the mechanisms inducing oxalate overproduction in PH3 remain incompletely understood (4).

To investigate the metabolic role of HOGA1, we generated HOGA1 knock-out human hepatocarcinoma HepG2 cells by CRISPR/Cas9. Upon HyPro incubation, HOGA1-deficient HepG2 cells exhibited accumulation of 4-hydroxy-2-oxoglutarate (HOG), 4-hydroxy-glutamate (4-OHGlu), and dihydroxyglutarate (DHG) in the extracellular medium, and increased oxalate production, consistent with the metabolic profile of PH3 patients. Notably, these cells also displayed upregulation of AGT and GR expression and activity, suggesting a potential adaptive response and indicating previously unrecognized interactions between mitochondrial, peroxisomal, and cytosolic glyoxylate pathways.

Overall, these findings contribute to a more detailed characterization of the biochemical landscape associated with PH3 and provide a framework for further investigation into metabolic adaptations and inter-pathway connectivity relevant to glyoxylate homeostasis and disease.

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P 06 - Microbial Metabolites Intercept the Gut-Kidney Pathogenic Axis in Models of Secondary Hyperoxaluria

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Hyperoxaluria is characterized by increased urinary concentrations of kidney stone-forming oxalate. Primary hyperoxalurias are caused by pathogenetic variants in genes involved in the metabolism of glyoxylate, the precursor of oxalate, whereas secondary hyperoxalurias (SH) are due to multifactorial factors, hindering the development of therapeutic approaches. The gut is increasingly recognized as a central hub for the handling of dietary oxalate by regulating its microbial metabolism, fecal elimination, and mucosal absorption. Commensal microbes are especially capturing the interest for their proven efficacy to metabolize oxalate in the perspective of reducing its absorption. By producing a plethora of metabolites, commensal microbes regulate several functions of the host, potentially influencing oxalate handling. Based on these premises, we started from the prototypic tryptophan metabolite indole-3-aldehyde (I3A) to investigate whether microbial metabolites affect oxalate absorption from the gut and its biodistribution to the kidney. By combination of data in murine models, intestinal and renal cell lines, as well as a gut-kidney multi-organ-on-a chip model, we showed that microbial metabolites could restore microbiome composition and have anti-inflammatory activities in proximal tubular renal cells and podocytes. Taken together, these results might pave the way towards the development of novel, microbial metabolites-based, therapeutic approaches for SH.

P 07 - 4-Carboxyquinoline-Pyrimidine Hybrids as a Multi-Target Inhibition Strategy (LDHA, LDHB, and GO) for Potential Treatment of Primary Hyperoxaluria

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Substrate reduction therapy (SRT) for primary hyperoxaluria (PH) aims to suppress hepatic oxalate production by targeting critical enzymatic nodes, such as glycolate oxidase (GO), to deplete upstream precursors.[1,2] Additionally, liver lactate dehydrogenase type A (LDHA) is targeted as the main driver of the final conversion to oxalate.[2] However, the structural homology and functional redundancy between LDHA and LDHB can lead to compensatory metabolic escape, and so it may require double inhibition for full therapeutic efficacy.[3] Therefore, triple-target small molecules (LDHA/LDHB/GO) emerge as a high-efficiency strategy to reach the therapeutic ceiling for oxalate reduction.

Using structure-based drug design and target-oriented synthesis, a novel family of hybrids was optimized featuring a quinoline-4-carboxylic acid polar moiety. [1,4,5] Molecular docking simulations revealed that a U-shaped disposition is crucial for active-site positioning. So, an anilin-2-yl linker connects the polar fragment to apolar arylpyrimidinic residues, enabling key interactions with *h*LDHA residues Arg168 and Asp194. These acid derivatives were efficiently prepared via basic hydrolysis of ethyl ester precursors[4] in excellent yields (80–100%).

Kinetic fluorometric enzymatic assays confirmed that 2-((4-arylpyrimidin-2-yl)aminophenyl) quinoline-4-carboxylic acid hybrids inhibit *h*LDH. While ester precursors were *h*LDHA-selective,[4] most of tested acid hybrids acted as double *h*LDHA/*h*LDHB inhibitors (IC_{50} 1–20 µM). Significantly, 50% of synthesized acids also inhibited GO (IC_{50} 2-20 µM). A standout lead compound exhibited balanced potency (IC_{50} 1–3 µM) across all targets (*h*LDHA, *h*LDHB, *h*GO). This 4-carboxyquinoline-pyrimidine framework is a promising multi-enzymatic candidate for PH. Supported by PID2022-141783OB-C22/MCIN/AEI/10.13039/501100011033/FEDER, UE.

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P 08 - In Vivo Lentiviral Gene Therapy Enables Complete Metabolic Correction in Juvenile Primary Hyperoxaluria Type 1

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Primary hyperoxaluria type 1 (PH1), particularly in its infantile presentation, would require a therapeutic approach capable of providing permanent metabolic correction from early in life. Liver-directed *in vivo* lentiviral gene therapy is especially attractive in this setting because it enables stable genomic integration and sustained transgene expression after a single administration, with particular relevance for the growing paediatric liver.

We evaluated a hepatocyte-specific lentiviral vector (LV) encoding an enhanced AGT protein in *Agxt1* knockout mice. We previously showed that systemic LV administration at 2×10^{10} TU/kg achieved partial phenotypic correction in adult PH1 mice despite limited hepatocyte transduction. Vector dose escalation did not improve efficacy. Importantly, when LV delivery was optimized with the administration of dexamethasone (DXM) around the time of LV administration, urinary oxalate was significantly reduced in adult PH1 mice, including animals with only 5% corrected hepatocytes, revealing the strong therapeutic potential of this platform even at modest levels of liver gene transfer.

We then assessed this strategy in juvenile PH1 mice treated at 2.5 weeks of age. Under these conditions, liver gene transfer was markedly improved, reaching more than 50% AGXT-positive hepatocytes, as assessed by immunostaining. A complete normalization of urinary oxalate after a single administration was obtained and maintained over a 3-month follow-up, corresponding to a 67–82% reduction compared with untreated PH1 controls. Long-term safety studies with 1-year follow-up are currently ongoing.

These findings support *in vivo* LV gene therapy as a promising one-time treatment for early PH1 intervention. The complete reversal of hyperoxaluria in juvenile animals highlights the translational potential of this approach.

P 09 - A Multi-Organ Cell-based Platform for Primary Hyperoxaluria Research: From 2D to 3D Culture Systems

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Primary Hyperoxalurias (PHs) are rare genetic metabolic disorders arising from the deficit of enzymes involved in glyoxylate metabolism: AGT1, alanine:glyoxylate aminotransferase in PH1, GRHPR, glyoxylate/hydroxypyruvate reductase in PH2, and HOGA1, 4-hydroxy-2-oxoglutarate aldolase in PH3. These defects drive excessive endogenous oxalate synthesis, leading to recurrent nephrolithiasis, nephrocalcinosis, and possibly to end-stage renal disease (ESRD). Although RNAi-based therapies have expanded treatment options for PH1 patients, their availability is limited. Moreover, no therapies are available for PH2 and PH3. Therefore, developing suitable models to recapitulate human PHs pathophysiology and test new therapeutic strategies is an urgent need.
In this light we developed and validated a comprehensive cell-based platform to mimic the enzymatic deficits typical of PHs in liver and kidney, by CRISPR/Cas9 genome editing approaches. We selected single-cell clones knock-out for PH-associated genes in hepatoma-derived (HepG2) and proximal tubule-derived (HK-2) cell lines. Upon challenging with specific oxalate precursors, *i.e.* glycolate for PH1 and hydroxyproline for PH2 and PH3, we observed a significant oxalate accumulation, thus confirming that gene inactivation effectively mimics disease mechanisms. We then shifted from 2D cultures to 3D spheroids for HepG2-derived clones. Spheroids show increased expression of the hepatic differentiation marker albumin, as well as of the main genes involved in glyoxylate metabolism (*e.g.*, AGT1, GRHPR, HOGA1, GO, and LDHA), at both messenger RNA and protein levels. Moreover, they respond to glyoxylate challenge with oxalate excretion comparable to 2D culture systems.
Overall, our platform represents a versatile tool to better understand PH molecular pathology, identify novel drug targets, and perform preclinical tests of innovative therapeutic interventions. Experiments are ongoing to adapt the platform for microphysiological systems mimicking the human liver-kidney axis. This would make the platform a well-suited human-relevant alternative to animal models for drug testing and disease modelling.

P 10 - Exploring New Tags for Selective Degradation of Lactate Dehydrogenase and Glycolate Oxidase in Primary Hyperoxaluria

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Calcium oxalate has been linked to various conditions, including primary hyperoxaluria (PH) [1]. New treatments for PH type 1 involve the use of iRNA. Lumasiran inhibits the production of the enzyme glycolate oxidase (GO). Nedosiran inhibits the production of the enzyme lactate dehydrogenase A (LDH-A) [2].

The success of these drugs should not mask other potential strategies that could lead to new treatments with additional benefits (e.g., widespread *in vivo* distribution and utility in PH types 2 and 3 [3], lower cost). From this perspective, we are synthesizing new small-molecule drugs that induce the degradation of LDH-A and/or GO. Another important factor supporting the clinical development of this type of compound is its utility in treating highly prevalent diseases. For example, calcium oxalate plays a role in MASH and dual inhibitors of GO and LDH-A are effective in improving this phenotype [4].

Dual inhibitors of LDH-A and GO [5] modified with hydrophobic tags inhibit the enzymatic activity of LDH-A and GO, and also induce the *in vivo* degradation of LDH-A via the lysosomal pathway [6]. As a follow-up to this research, the incorporation of new tags that induce the degradation of GO and/or LDH-A has been evaluated in PH type 1 cell models, with the aim of reducing the formation of calcium oxalate.

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P 11 - Early Lumasiran Therapy Enables Recovery of Kidney Function in Infantile Primary Hyperoxaluria Type 1

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Background: Infantile onset of primary hyperoxaluria type 1 (PH1) is associated with rapid progression to kidney failure and is challenging to manage. Five-year data from the *ILLUMINATE* trials demonstrates that lumasiran stabilises or modestly improves eGFR (~10%); however, recovery to normal kidney function has not been clearly shown.

Case Presentation: We report a 3-month-old infant presenting with an 8-week history of vomiting and failure to thrive. Initial investigations revealed nephrocalcinosis and impaired kidney function (creatinine 57 µmol/L; eGFR 45 mL/min/1.73 m², Schwartz formula, k=0.45). Urinary spot oxalate: creatinine ratio was markedly elevated (> 2000 µmol/mmol), with metabolite profiling suggestive of PH1. Hyperhydration and pyridoxine were initiated.

Over the subsequent two weeks, whilst awaiting confirmatory genetic results, the patient deteriorated with progressive hypertension, hyperkalaemia, and oliguria (creatinine 81 µmol/L; eGFR 31 mL/min/1.73 m²). No precipitating factor other than progression of oxalosis was identified; infection screening was negative. Following urgent, national multidisciplinary discussion via the UK PH1 Rare Disease Collaborative Network, lumasiran was commenced empirically prior to genetic confirmation.

Results: Following initiation of lumasiran (6 mg/kg), kidney function and associated sequelae improved progressively. Genetic results confirmed PH1, with a genotype likely to be pyridoxine unresponsive. At three months, creatinine decreased to 32 µmol/L (eGFR 92 mL/min/1.73 m²). Continued improvement was observed alongside normalisation of growth and development. At 12 months, creatinine was 29 µmol/L (eGFR >90 mL/min/1.73 m²). Catch-up growth was observed (height SDS −2.7 to −1.2; weight SDS −2.0 to −1.1).

Conclusion: This case demonstrates significant recovery of kidney function following early initiation of lumasiran in infantile PH1 and rapidly declining eGFR. It highlights the importance of swift diagnostic pathways and timely access to targeted therapies. To our knowledge, this represents the first real-world report of recovery of kidney function to normal levels in this setting, underscoring the need for further real-world evidence.

P 12 - One Gene, Many Faces: Early and Variable Expression of Primary hyperoxaluria type 2 (PH2) with an Underreported GRHPR Mutation

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Aim: Primary hyperoxaluria type 2 (PH2) is a rare autosomal recessive disorder due to deficiency of glyoxylate reductase/hydroxypyruvate reductase, encoded by GRHPR. This defect results in hyperoxaluria leading to nephrolithiasis, nephrocalcinosis, and chronic kidney disease. Approximately 40 pathogenic variants have been described, with no clear genotype-phenotype correlation. We describe the clinical presentation, genetic findings, and outcomes of pediatric patients with PH2.

Methods: A retrospective study in two pediatric nephrology units. Data on clinical presentation, imaging, metabolic evaluation, genetic analysis, management, and outcomes were collected. The genetic evaluation included an NGS nephrolithiasis gene panel.

Results: Five patients with genetically confirmed PH2 (all Yemenite origin, homozygous for *GRHPR*, NM_012203.2: c.934A>G; p.Asn312Asp) were included. Median age at presentation was 0.84 years (range 0.07–5.5) and at last follow-up 5 years (range 0.73–8.4). Clinical presentation was heterogeneous. Two sisters presented in infancy with high-grade nephrocalcinosis, failure to thrive, and developmental delay in one. Three patients developed nephrolithiasis, two requiring multiple urological interventions. One had a dysplastic kidney, likely secondary to prolonged obstruction.

All patients exhibited persistent hyperoxaluria (initial urinary oxalate 138–150 mg/day/1.73m² or oxalate/creatinine 0.25–0.35 mg/mg; last follow-up 89–136 mg/day/1.73m²). Hypocitraturia and hypercalciuria were rare. Kidney function remained preserved in all patients (median eGFR 125 mL/min/1.73m² at presentation [100–138] and 125 [93.5–129.5] at last follow-up). Two patients with nephrocalcinosis had persistent proteinuria (protein/creatinine ratio up to 1.8 mg/mg; albumin/ creatinine 920 mg/gr), and one treated with ACE inhibitors. Management included hyperhydration and potassium citrate.

Conclusions: These cases expand our understanding of the clinical phenotype associated with GRHPR. Although no clear genotype- phenotype correlation has been established, all homozygotes for this specific pathogenic variant showed a severe clinical presentation. Further studies are needed in larger cohorts of patients with the same mutation.

P 13 - Reduction of Oxalate Levels in Metabolic Liver Diseases: A Therapeutic Approach for Primary Hyperoxaluria and MASH

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Oxalate overproduction represents a central pathological issue not only in *rare* genetic disorders such as primary hyperoxalurias (**PHs**) but also in the more prevalent metabolic-associated steatotic liver disease (**MASH**). Both conditions share alterations in the glyoxylate metabolic pathway, where the suppression of alanine-glyoxylate aminotransferase (AGXT) unbalances the metabolism toward lactate dehydrogenase (LDH-A) and glycolate oxidase (GO), causing excessive oxalate biosynthesis. This accumulation contributes to impaired fatty acid oxidation, lipotoxicity, and progressive liver inflammation and fibrosis in MASH, as well as systemic oxalosis and renal damage in PHs.

Two siRNA-based therapies targeting GO and LDH-A, *lumasiran* and *nedosiran* respectively, have been approved for the treatment of PH1. However, to date, no small-molecule inhibitors of enzymes involved in oxalate metabolism have received approval for any form of primary hyperoxaluria. In the context of MASH, *resmetirom*, a thyroid hormone receptor-β agonist, has recently been approved for pharmacological intervention, while *semaglutide*, a GLP-1 receptor agonist, is increasingly used in clinical practice; however, their overall clinical applicability remains limited. Recent studies highlight the therapeutic potential of targeting oxalate metabolism in both contexts. In MASH models, treatment with the dual inhibitor MDMG-935P reduced hepatic oxalate levels, attenuated pro-inflammatory signaling, and decreased fibrosis.[1] Similarly, in PH1 models, novel salicylic acid derivatives[2] with dual nanomolar inhibition of *h*GO and *h*LDHA not only lowered urinary oxalate but also promoted LDH-A proteolysis, reducing renal calcium-oxalate crystal deposition.[3]

These findings identify oxalate metabolism as a shared pathogenic axis in genetic and metabolic diseases and support dual-action inhibitors as a promising therapeutic strategy, particularly for MASH, a critical unmet need.

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P 14 - Expected Prevalence of Primary Hyperoxaluria In Italy: High Frequency from Multicenter Whole Exome Sequencing Data

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Primary hyperoxaluria (PH) is a rare, autosomal recessive disease of oxalate metabolism, caused by biallelic pathogenic variants in AGXT (PH1), GRHPR (PH2) and HOGA1 (PH3). Because symptoms are often attributed to "common" kidney stones, PH may be underdiagnosed.

Recently, a global carrier frequency of 1:229 for PH1, 1:465 for PH2 and 1:151 for PH3 and a global PH prevalence of 1:209.357 for PH1, 1:863.028 for PH2 and 1:90.834 for PH3 was estimated [Mandrile et al, 2025]. In Italy less than 200 PHs patients are known. Our study aims to estimate the disease prevalence in our Country, evaluating the carrier frequency of Pathogenic/Likely Pathogenic (P/LP) variants in PH genes across Whole Exome Sequencing (WES) cohorts. Of the 563 known P/LP PHs mutations, 55 were found in our cohort.

We retrospectively analysed data from WES performed for other indications than PH from different Centres. Variants were classified according to ACMG criteria and only P/LP were considered. We calculated carrier frequency and allele frequency for each gene and then obtained a disease prevalence using the Hardy-Weinberg model.

Among the 19.848 individuals analysed, we identified 195 heterozygous carriers of AGXT variants, corresponding to a carrier frequency of 0.00982 (≈1/100) and an expected disease prevalence of approximately 1/41.000; for GRHPR, 21 carriers were observed (0.001058, ≈1/945), with an expected prevalence of approximately 1/3.570.000; and for HOGA1, 86 carriers were identified (0.004333, ≈1/230), with an expected prevalence of approximately 1/212.000.

Thus, with an Italian population of 59.000.000, PH1 expected cases are around 1400. Although we cannot rule out the possibility of an overestimation of carrier frequency due to the inclusion of trio analyses, our data indicate that PH is certainly underdiagnosed. This highlights the importance of raising disease awareness, making better and earlier diagnosis, increasing the genetic screening in patients with recurrent stones.

P 15 - The Oxalate and Citrate Association in Humans

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Background: Basic science models have demonstrated transporter linkage between SLC26A6 and NaDC1 in the kidney, but it is not known if this exists in humans. Higher urine oxalate excretion has been associated with higher urine citrate excretion in humans. The mechanism for this association may be due to simultaneous intake of dietary oxalate and citrate or kidney SLC26A6-NaDC1 linkage.

Methods: Twenty-five participants were admitted to the clinical research center and given sodium oxalate. Timed pre-sodium oxalate (3) and post-sodium oxalate (6) urine samples were collected every hour. Twenty participants also consumed a low oxalate, low citrate breakfast and 5 participants remained fasting for the duration of the protocol. Mixed effects models were used to examine the association of oxalate and citrate.

Results: Thirteen of the 25 participants were female with mean age 55 years. After administration of breakfast and sodium oxalate both urine oxalate and citrate increased above baseline. In multivariate mixed effects models adjusting for gastrointestinal anion and time, higher oxalate excretion (in micromol/hr) was associated with higher urine citrate excretion in individuals who consumed breakfast after sodium oxalate (3.2 (95% CI 2.1 to 4.2) micromol/hr, p<0.00), and individuals who only consumed sodium oxalate (1.2 (95% CI 0.2 to 2.1) micromol/hr, p=0.02). Results were similar in a combined model with both groups. There was no correlation between fractional excretions of oxalate and citrate in either group but there was some individual variability.

Conclusion: After consumption of sodium oxalate, higher urine oxalate is associated with higher urine citrate excretion, and the magnitude of the association is higher for participants who also consumed breakfast. The oxalate and citrate association may be driven by both diet and kidney oxalate-citrate handling.

P 16 - Pediatric Urolithiasis Revealing Underlying SLC34A1-Associated Infantile Hypercalcemia: A Case Report

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Background: Pediatric urolithiasis is uncommon and warrants evaluation for underlying metabolic or genetic causes, particularly in early-onset or recurrent cases. Mutations in *SLC34A1* are associated with autosomal recessive infantile hypercalcemia and may predispose to nephrolithiasis.

Case Presentation: A 6-year-old girl, born at term via LSCS with an unremarkable perinatal history, presented at 2 years of age with recurrent flank pain, dysuria, fever, and intermittent vomiting. Urinalysis repeatedly showed leukocyte esterase, nitrites, and hematuria, although urine cultures remained negative.

Ultrasound KUB demonstrated a 10 mm calculus at the right pelviureteric junction with mild hydronephrosis. CT KUB with contrast confirmed an 11 × 5 mm obstructing proximal ureteric calculus (HU 441) causing moderate hydronephrosis. She underwent right percutaneous nephrolithotomy (PCNL), and DJ stent insertion. Intraoperatively, an impacted, soft, yellow proximal ureteric stone was identified. Stone analysis revealed calcium oxalate composition.

Further evaluation identified two pathogenic variants in the *SLC34A1* gene, consistent with autosomal recessive infantile hypercalcemia. Serial serum calcium levels showed persistent mild hypercalcemia (10.5–10.8 mg/dL).

Conclusion: This case highlights the importance of considering genetic etiologies such as *SLC34A1*-associated infantile hypercalcemia in pediatric urolithiasis. Early identification enables targeted surveillance and management to prevent recurrence and long-term renal complications.

P 17 - Recurrent Pediatric Nephrolithiasis Due to Primary Hyperoxaluria (GRHPR Mutation): A Case of Progressive Renal Damage

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Background: Primary hyperoxaluria is a rare autosomal recessive disorder leading to excessive oxalate production, recurrent nephrolithiasis, and progressive renal impairment. Early diagnosis is critical to prevent irreversible kidney damage.

Case Presentation: A 12-year-old girl, born at term to a consanguineous family, presented at 2 years of age with intermittent painless hematuria. Initial ultrasound revealed two left renal calculi, and CT pyelography demonstrated a staghorn calculus with mild hydronephrosis. She underwent open left pyelolithotomy in 2015, with successful removal of a large pelvic stone. Stone analysis confirmed calcium oxalate composition.

Despite initial management, she developed recurrent urinary tract infections and progressive nephrolithiasis. Follow-up imaging showed recurrent calculi in the left kidney. In 2022, genetic testing identified a homozygous pathogenic variant in the *GRHPR* gene (c.494G>A; p.Gly165Asp), confirming Primary Hyperoxaluria Type 2.

Disease Progression and Renal Impact: Serial imaging demonstrated increasing stone burden, culminating in a recurrent staghorn calculus extending into the pelvicalyceal system with moderate hydronephrosis. A DMSA scan revealed a small left kidney with cortical scarring and reduced function (23%), while the right kidney maintained normal function (77%).

Conclusion: This case highlights the aggressive course of Primary Hyperoxaluria and its association with recurrent staghorn calculi and progressive renal damage. Early metabolic and genetic evaluation in pediatric urolithiasis is essential for timely diagnosis and implementation of targeted management strategies to preserve renal function.

P 18 - PH3: A Rare Disease with Different Presentation

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Primary hyperoxaluria (PH) poses significant health risks due to excessive renal and systemic oxalate accumulation. The PH3 subtype, resulting from mutations in the mitochondrial 4-hydroxy-2-oxoglutarate aldolase (HOGA1) gene, is exceptionally rare and generally regarded as exhibiting a milder phenotype. However, progression to advanced renal failure has been reported, particularly in cases with delayed diagnosis.

These cases highlight both early severe and milder presentations, illustrating the disease's marked heterogeneity and the rarity of observing the only two cases diagnosed within a single year at an Italian center.

Cases: A two-month-old female infant (Pt 1) with bilateral renal stones and an eight-year-old girl (Pt 2) with unilateral multiple renal stones were referred to our center within one year. Initial metabolic evaluation showed hyperoxaluria in both, more pronounced in the younger patient (Pt 1: OxU/creatU 638, ref <174 µmol/mmol *versus* Pt 2: 116, ref <82 µmol/mmol). Cystine screening and calcium-phosphate metabolism were normal, despite prior vitamin D supplementation. Urinary glycolic acid levels were normal, while organic acids were elevated in both patients, especially in Pt 1 (4-HOG 8360 µmol/mmol; 4-HAG 35 µmol/mmol, ref <5 µmol/mmol). NGS revealed a homozygous HOGA1 mutation in Pt 1 and a compound heterozygous HOGA1 mutation in Pt 2.

Patients received maximum tolerable potassium citrate dose and intensive hydration. Pt 1 required repeated surgical treatment; recurrent stone events and limited reduction of oxaluria (OxU/creatU 432 *versus* 638 µmol/mmol at onset) induced us to place her a gastrostomy. Pt 2 was managed conservatively.

Early referral of children with renal stones to specialist clinicians is recommended to prevent delayed diagnosis or complex care. Early presentation, although associated with more frequent stone events, does not appear to increase CKD risk; however, more follow-up data in younger patients are needed. Conversely, mild initial presentations may be insidious if underdiagnosed or overlooked.

P 19 - Synthesis and Evaluation of 2-Oxa-8-azabicyclo[3.3.1]nonanes as hLDH Inhibitors

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Primary hyperoxaluria manifests with excessive oxalate production and the continuous calcium oxalate deposition leads to a remarkable tissues damage. The two existing RNAi-based therapies have effectively reduced urinary oxalate excretion only in PH1 patients but not in PH2 or PH3 patients.[1] An alternative or complementary strategy to generate chemical compounds inhibiting human lactate dehydrogenase (*h*LDH) might be a better option for the three types of PH. To date, there are no approved treatments for PH using small-molecule drugs, and encouraged by that, we have designed and synthesized LDH inhibitors.[2-5]

In the present work, we report on the synthesis of a new set of compounds with a 2-oxa-8-azabicyclo[3.3.1]nonane core and their *h*LDHA/*h*LDHB inhibitory activity. A two-step synthetic methodology has been followed: (a) synthesis of aromatic imines; (b) synthesis of tetrahydroquinolines from those imines through Povarov reaction, and addition of an oxygenated nucleophile, such as 4-hydroxycoumarin. Functional groups of different polarity are present in the synthesized compounds and the overall yields of syntheses are moderate (25-40%).

The inhibitory effect of the compounds synthesized over the *h*LDHA/*h*LDHB catalytic activity, in the conversion of pyruvate to lactate, was determined using a kinetic fluorimetric assay. The *h*LDHB inhibitory activity of the compounds has been measured in order to establish the selectivity of them. All of them were evaluated at a single concentration of 50 µM and those showing significant percentages of inhibition were tested at eight concentrations. So, a dose response curve fitting the logarithm of inhibitor concentration *vs* normalized enzymatic activity have allowed to determine IC_{50} values for each of them. Some of these 2-oxa-8-azabicyclo [3.3.1]nonanes showed IC_{50} values lower than 10 µM. Supported by PID2022-141783OB-C22/MCIN/AEI/10.13039/501100011033/FEDER,UE.

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P 20 - SIRT1 rs932658 Polymorphism and Serum Biomarkers as Predictors of Kidney Stone Susceptibility: A South Indian Case-Control Study with Machine Learning

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Nephrolithiasis is a multifactorial condition in which Fetuin-A, sirtuin-1 (SIRT1), and parathyroid hormone (PTH) play important roles in calcium metabolism and stone formation. Studies simultaneously evaluating genetic polymorphisms of these proteins alongside serum levels in Indian populations are lacking. This study aimed to compare genotype frequencies of Fetuin-A (766C>G, 742C>T) and SIRT1 (rs10509291, rs3740051, rs932658) polymorphisms between kidney stone patients and controls, assess serum biomarker differences, and develop machine learning models for kidney stone susceptibility.

This hospital-based case-control study enrolled 101 nephrolithiasis cases and 100 healthy controls at a tertiary care centre in coastal Karnataka, South India. Cases were predominantly male (78.2%) with a mean age of 44.8 ± 12.5 years. Five SNPs were genotyped by PCR-RFLP, and serum Fetuin-A, SIRT1, PTH, and calcium levels were measured. Logistic regression and random forest classifiers were evaluated by five-fold cross-validation.

Amongst the five SNPs, SIRT1 rs932658 (A>C) showed a significant genotype difference between cases and controls ($\chi^2 = 7.354$, $p = 0.025$). The CC genotype was observed exclusively in cases; the AA genotype was less prevalent in cases (16.8%) than controls (29.0%); and the AC genotype was more frequent in cases (78.6%) than controls (71.0%). No significant genotype differences were noted for the remaining four SNPs. PTH levels were significantly lower in cases (0.038 ± 0.041 pg/mL) than controls (0.079 ± 0.188 pg/mL; $p = 0.043$), whilst Fetuin-A ($p = 0.599$) and SIRT1 ($p = 0.229$) did not differ significantly. The random forest model achieved AUC = 0.667, outperforming logistic regression (AUC = 0.635). PTH, Fetuin-A, SIRT1 level, and serum calcium all exceeded the 0.05 feature importance threshold, whilst genetic variants ranked below it.

SIRT1 rs932658 is associated with kidney stone susceptibility in this South Indian cohort. Biochemical markers, particularly PTH, are more influential predictors than genetic variants in machine learning models.

P 21 - Adamantane-Tagged Salicylic Acids Targeting Oxalate Production Through Enzyme Inhibition and Degradation

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Primary hyperoxalurias (PHs) are rare genetic disorders characterized by oxalate overproduction due to mutations in enzymes involved in glyoxylate metabolism. The most severe form, primary hyperoxaluria type 1 (PH1), arises from mutations in hepatic enzyme *alanine glyoxylate aminotransferase* (AGT). AGT dysfunction leads to glyoxylate accumulation, which is oxidized to oxalate by lactate dehydrogenase A (LDH-A) [1]. Oxalate is excreted in urine and, when exceeding solubility limits, crystallizes, causing kidney damage, systemic oxalosis, and end-stage renal disease. A major glyoxylate source is glycolate, converted by *glycolate oxidase* (GO) [2,3]. Both GO and LDH-A are validated PH1 targets, currently addressed via *siRNA* therapies, which present limitations including high cost and parenteral administration.

Salicylic acid (SA) derivatives have emerged as promising alternatives, acting as dual GO/LDH-A inhibitors and reducing oxalate production in murine PH1 and MASH models after oral administration [2-4]. Structural optimization, guided by docking and molecular dynamics simulations, identified OPP-FSAs with submicromolar Ki values, further developed into bifunctional protein degraders while retaining *in vivo* efficacy [5]. Compound **1**, a hydrophobic-tag protein degrader (HyT-PD), inhibits GO/LDH-A and promotes selective LDH-A degradation in mice hepatocytes [5].

Based on this scaffold and aiming to achieve dual GO/LDH-A degradation, we designed and synthesized a series of novel HyT-PD degraders that retain the adamantane moiety while incorporating linkers of different lengths and natures. Overall, these compounds represent promising alternatives to *siRNA*-based therapies for PH1, combining a knockdown-like effect with oral bioavailability.

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P 22 - Long-term Lumasiran Treatment, Kidney Function, and Isolated Kidney Transplant Outcomes in Primary Hyperoxaluria Type 1

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Background: Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive disorder of hepatic oxalate overproduction that may lead to kidney failure, with historically poor graft survival rates after isolated kidney transplantation (iKT). Phase 2 (NCT03350451) and Phase 3 (ILLUMINATE-A, NCT03681184; ILLUMINATE-B, NCT03905694; ILLUMINATE-C, NCT04152200) trials showed sustained reductions in urinary oxalate and plasma oxalate (POx), with acceptable safety following treatment with the RNA interference therapeutic lumasiran. Long-term follow-up enables evaluation of native kidney survival and post-iKT outcomes in lumasiran-treated patients.

Methods: Characterization of changes in kidney function (eGFR) in eligible patients aged ≥12 months (M) and post-iKT outcomes.

Results: Regression-estimated mean annual eGFR change (slope [SEM] mL/min/1.73m^2/year [Y]) was −0.4 (1.0) over 54M in the Phase 2 trial (N=20; ages 6-43Y), −0.6 (0.7) over 60M in ILLUMINATE-A (N=39; ages 6-60Y), and 0.3 (0.8) over 60M in ILLUMINATE-B (N=18; ages 3-72M). Baseline eGFR ranged from 32-174 mL/min/1.73m^2.

ILLUMINATE-C enrolled patients with PH1 and advanced kidney disease into Cohort A (no hemodialysis; n=6) or Cohort B (hemodialysis; n=15). In Cohort A, three patients (baseline eGFR 8.6-16.5 mL/min/1.73m^2), required dialysis before M36, while three remained dialysis-free through M36. Two dialysis-free patients had mean annual eGFR declines of −2.3 and −0.9 mL/min/1.73m^2/Y, and one (aged >12M) had evaluable eGFR from M8, improving from 37.1 to 54.3 mL/min/1.73m^2 by M36. Five Cohort B patients underwent iKT before M36; all had POx reductions from baseline pre-transplantation with further reductions post-iKT, indicating improved POx clearance with functioning grafts. None had oxalate nephropathy, and all remained dialysis-free over 3-29M of follow-up while continuing lumasiran treatment.

Conclusions: Overall eGFR decline is expected in untreated patients with PH1. Long-term lumasiran treatment resulted in minimal annual eGFR decline over 54-60M in patients aged 3M-60Y, and lowered POx to allow iKT in some patients with end-stage kidney disease.

P 23 - When Healthy Eating Backfires: A Vegan Diet and Severe Hyperoxaluria - A Case Report

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Background: Aside from enteric hyperoxaluria, a small fraction (typically 5-10%) of ingested oxalate is absorbed under normal circumstances also depending on calcium, magnesium, fibers intakes and the gut barrier permeability.

Case Presentation: We report a case of severe hyperoxaluria in a 62 yrs old vegan patient, BMI 19.3 Kg/m^2 with a history of hemorrhagic stroke and residual motor and cognitive deficits in 2021. Upon admission at the Nephrology outpatient unit, serum creatinine 1.57 mg/dL and cystatin 1.22 mg/L were increased (eGFR 57.4 mL/min/1.73 m²) and a CT scan revealed bilateral kidney stones (up to 1.5 cm). Later workup labs showed normal calcium and citrate excretion (88 and 401 mg/day, respectively) and marked hyperoxaluria (148 mg/day) besides albuminuria 80.5 mg/day. No features of intestinal malabsorption or frequent use of antibiotics were evidenced. Two additional 24-hr urinary oxalate (uOx) results were 132 and 222 mg/day. No variants in *AGXT, GRHPR, HOGA1* and *SLC26A1* genes were detected in a targeted NGS panel (nephrolithiasis). The Registered Dietitian identified daily consumption in large quantities (more than 700 grams in total per meal) of foods rich in oxalate such as legumes, nuts, whole grains and beets, in addition to 3 liters of herbal tea per day. Estimated protein intake was 1.7 g/kg/day. Following dietary intervention that included increasing plant-based calcium sources at all meals, reducing consumption of teas and foods high in oxalate, as well as proper cooking methods to reduce oxalate content, uOx, uCa and estimated protein intake dropped to 51 mg/day, 68 mg/day and 0.6 g/kg/day, respectively.

Conclusion: This case highlights the significant impact of a vegan diet on oxalate excretion and the beneficial effect of dietary interventions in controlling secondary hyperoxaluria and stone formation. Continued metabolic and dietary follow-up is warranted to prevent progression to chronic kidney disease.

P 24 - Stone Analysis Supporting Etiologic Confirmation of Primary Hyperoxaluria Type 1 (PH1): A Case Report

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Background: Advances in metabolic evaluation and genetic testing now provide a more direct approach to etiological diagnosis of nephrolithiasis. Even when Fourier-transform infrared spectroscopy (FTIR), the current gold standard for determining stone composition, is employed, establishing the etiology of nephrolithiasis remains challenging as similar compositions may arise from distinct underlying disorders. Moreover, results of molecular analysis are also cumbersome, as variants may suggest more than one genetic disorder. Herein, we report a case illustrating that stone analysis may contribute to etiologic confirmation in particular clinical scenarios.

Case Presentation: A 10-year-old girl presented with recurrent bilateral nephrolithiasis from the age of 4 years, associated with repeated episodes of renal colic. Family history was notable for recurrent bilateral nephrolithiasis in her mother; her parents were non-consanguineous. Laboratory evaluation showed CKD stage 2, serum creatinine of 0.75 mg/dL, hypocitraturia, and marked hyperoxaluria, with 24-hour urinary oxalate excretion of 107.5 mg/1.73 m^2. Genetic testing identified compound heterozygous variants (pathogenic/likely pathogenic) in AGXT (c.508G>A; p.Gly170Arg /c.1400T>C; p.Met467Thr), consistent with primary hyperoxaluria type 1 (PH1), and a monoallelic likely pathogenic variant in SLC3A1 (c.1400T>C; p.Met467Thr), a gene associated with cystinuria. The presence of these digenic variants introduced potential diagnostic uncertainty. Although qualitative urinary cystine screening was negative, stone analysis by FTIR demonstrated pure calcium oxalate monohydrate, with no evidence of cystine, thereby supporting PH1 as the underlying cause of the stone phenotype.

Conclusion: This case highlights the importance of integrating clinical, biochemical, genetic, and stone composition data in hereditary nephrolithiasis. In the presence of potentially confounding molecular findings, stone analysis may provide relevant phenotypic information and contribute to etiologic confirmation.

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Boffa, Iolanda	P 05, P 06
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