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Original Paper

Genetically Confirmed Hyperoxaluria in Iranian Children- A Multicenter Survey

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Introduction. Primary hyperoxaluria (PH) is a rare autosomal recessive disorder characterized by a heterogeneous presentation that leads to kidney failure and involvement of other organs. The aim of this study was to determine the number of cases with suspected PH in Iran that have had a genetically verified diagnosis.
Methods. A survey distributed among members of Iranian society of pediatric nephrology (IranSPN) to collect overall data on hyperoxaluria (HOX) in their centers, as well as those who performed whole exome sequencing (WES) or sanger sequencing genetic study. Data is presented as frequency and number blocks.
Results. Nineteen out of 130 members filled out the questionnaires. About two-thirds of the responders were suspected to have HOX in the presence of recurrent multiple kidney stones. PH was genetically confirmed in 80 children above 10 years. Alanine-Glyoxylate Aminotransferase (AGXT) was the most frequent reported genetic abnormailtiy. The majority of their patients required kidney replacement therapy. Combined or sequential liver- kidney transplantation was less frequent. Conservative treatment was the only therapy applied to all children prior to end-stage kidney disease.
Conclusion. This simple survey revealed that definitive diagnosis of PH occurs at older age accompanied with higher rate of kidney transplantation.

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Keywords. Primary hyperoxaluria; Kidney replacement therapy; Genetic testing, Combined or sequential liver and kidney transplantation

INTRODUCTION

Primary hyperoxaluria (PH) is a rare autosomal recessive disorder characterized by recurrent kidney stones, kidney failure, and nephrocalcinosis. Excessive production of oxalate crystal may precipitate in several organs leading to kidney failure and morbidity.[1,2] Biochemical evaluation is less accurate than genetic analysis for diagnosis, which makes genetic testing the preferred diagnostic method.[3]

In Iran, the reported prevalence of urolithiasis is 2.86%.[4] Among Iranian children with kidney stones, urinary metabolic assessments revealed a wide variation in the prevalence of hyperoxaluria (HOX), ranged from 5% to 36%.[5-9] In addition, 8% of children on continuous ambulatory peritoneal dialysis (CAPD) had a history of kidney calculi including HOX.[10] PH represents 1.4% of chronic kidney disease cases in southwestern Iran.[11] There are only a few case reports of recurrence of HOX in transplanted graft or successful sequential liver kidney transplantation.[12-14]

The management of PH includes high fluid intake, potassium citrate solution and in certain instances high doses of pyridoxine. Patients with kidney failure are recommended to undergo a sequential liver and kidney transplant. New mRNA medicines revolutionize patient quality of life and kidney survival.[1] There are no data on the number of suspected PH cases in Iran that have been confirmed via genetic analysis. Therefore, we carried out a survey to determine its prevalence.

MATERIALS AND METHODS

From December 2023 to March 2024, each center was provided with a questionnaire to collect data on; the total number of patients with HOX, the diagnostic method used, the number of genetically confirmed cases of HOX, age, sex and the distribution of genetic disorders within each center classified as a block of numbers. Questionnaires were shared by email or social media to 130 members of the Iranian society of pediatric nephrology, working at different centers in Iran. The data are presented as frequency and block of numbers. This was a preliminary survey on behalf of Iranian Tubulopathy Registry (rkdireg.com) that The study protocol has been reviewed and approved by the Ethics Committee of Iran University of Medical Sciences (IUMS) (IR.IUMS.REC.1403.554). It was conducted according to the 1964 Declaration of Helsinki.

RESULTS

Diagnosis

Out of 19 responses, three were excluded due to the absence of genetic study and one was excluded for duplication. The estimated total number of HOX in their center was 182 cases and the total number of kidney stones diagnosed was 2807. Out of them, 80 patients had PH confirmed by genetic study. Ninety-three percent of responders confirmed that genetic study was the gold standard for definitive diagnosis while, 67% of responders suspected HOX in cases of recurrent multiple microlithiasis or urolithiasis, sudden kidney failure, nephrocalcinosis, with a family history of recurrent kidney stones. Over half of the patients had consanguineous parents.

Stone analysis, 24-hour urine oxalate excretion or urine oxalate to creatinine ratio were used frequently to discover the cause. Moreover, kidney sonography and less frequently KUB x-ray were obtained. Twenty-eight percent of responders considered all clinical clues, imaging, and biochemistry assessment before suspecting HOX.

Demography

The survey revealed that the disease was more frequent in males. In response to the question of the age at diagnosis, surprisingly, the genetic study was more frequently performed at ages above one year and to a large extent above 10 years, that may be due to screening of recipients prior to kidney transplantation (Figure 1).

Genetic Study

Figure 2 summarizes the frequency of genetic findings identified in patients. The survey revealed that Alanine--Glyoxylate Aminotransferase (AGXT) was the most frequently reported genetic abnormailty. Hyperoxaluria type 2 and 3 were uncommon. Genetic assessment valuable in those suspected cases (Figure 2).

Medical treatment:

We asked about the treatment protocols in patients with PH at each center. All centers used Pyridoxine for the management of PH. In addition, 86% prescribed Potassium Bicitrate solution.

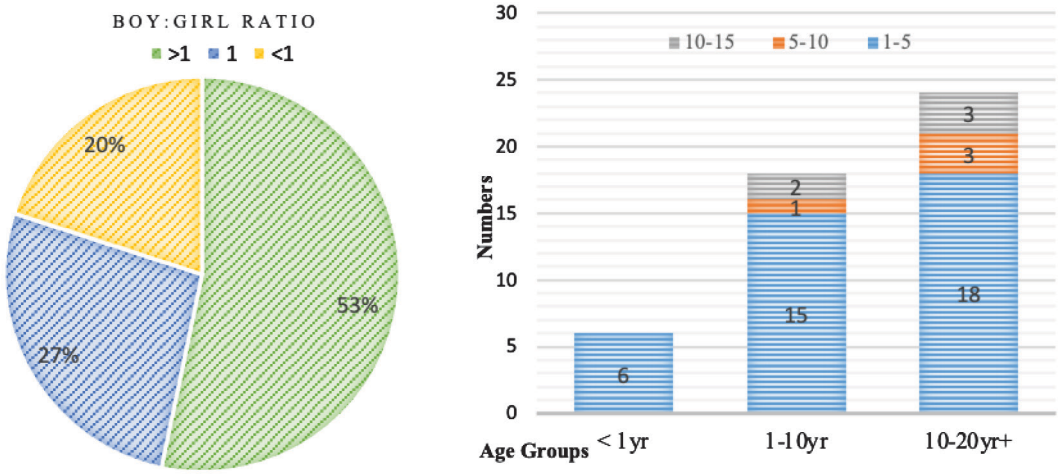

Figure 1. Pie chart shows the frequency of Boy to Girl ratio. Bar chart represented the distribution of age categories classified to block groups of numbers based on five (Blue for one to five cases, Orange five to ten cases, and gray for more than ten cases).

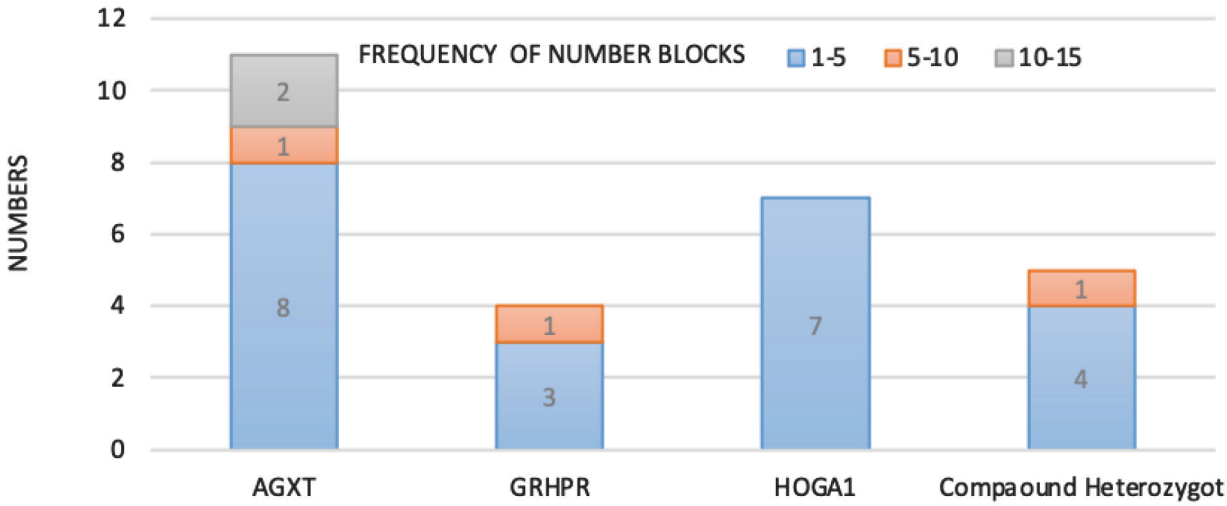

Figure 2. The figure shows the frequency of each detected genetic mutation. AGXT (Alanine--Glyoxylate Aminotransferase), GRHPR (Glyoxylate/Hydroxypyruvate Reductase), HOXA1(4-hydroxy-2-oxoglutarate aldolase 1). The color coding of classification according to block groups of numbers based on five (blue for cases less than five, orange for five to ten cases, and ten to fifteen cases in gray).

Unrestricted fluid intake and limitation of external sources of oxalate (food or medication) were recommended by 71% of informants.

Outcome

The survey focused on the kidney and patient outcomes. As expected, the majority of centers disclosed that their patients required kidney replacement therapy. Combined or sequential kidney-liver transplantation has been performed less frequently. Remarkably, the number of kidney transplants outpaced liver transplants (Figure 3). The graft lost data, genetic evaluation following failure of graft function is recommended in urolithiasis (Figure 3).

In response to the need for treatment of HOX with double-stranded small interfering ribonucleic acid (siRNA), most centers strongly supported this request.

DISCUSSION

Due to discrepancies between the genotype and phenotype of primary hyperoxaluria, genetic evaluation is of primary importance for diagnosis. The frequency of PH was 2.85% with a prevalence 1.6 per million population (PMP) among individuals under 30 years of age compared to the worldwide estimation of 1-3 PMP.[1] Figure 4 illustrates the frequency of HOX among children with urolithiasis from different regions of Iran.[2-11] Interestingly, none

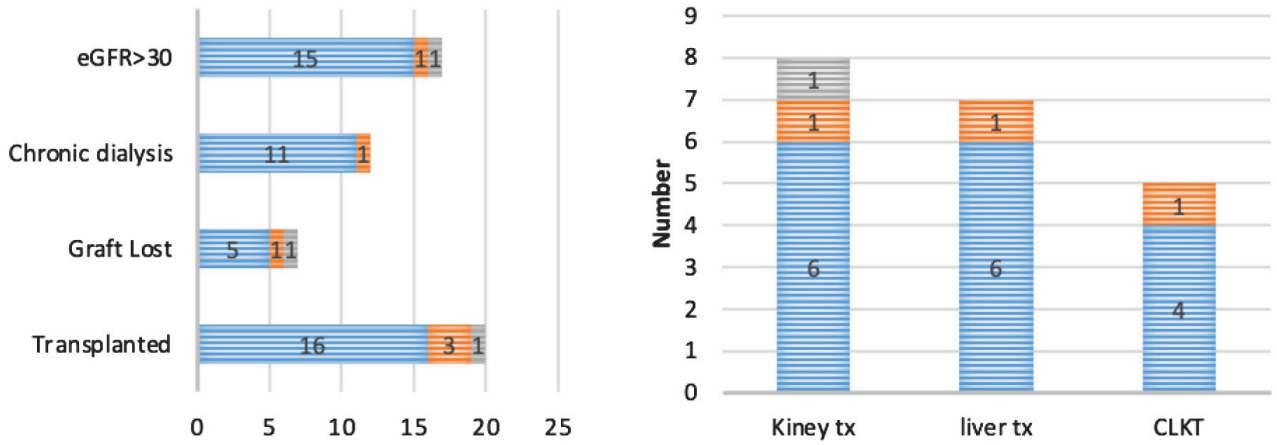

Figure 3. The figure shows kidney function (left) and the frequency of the type transplantation (Right). Data expressed as the frequency of blocks of numbers based on five. (Blue represented one to five, orange 5-10 cases, and gray more than 10 cases.) Tx = Transplant, CLKT = combined liver kidney transplant, eGFR = estimated glomerular filtration rate.

Figure 4. White ellipse shows the number of responders to the survey in each province of Iran. The orange rectangle represents the percentage of hyperoxaluria in metabolic assessment of children with urolithiasis, adopted from literatures. [2-11,13,18]

of the centers were from the provinces with high frequency of HOX. Their reliance on clinical and biochemical assessment instead of genetic study to confirm diagnosis may be attributed to the high cost of genetic testing. Urolithiasis was reported to be the cause of end-stage kidney disease in 2.8% and 12% of Iranian children.[10,12-13] In this case, PH should be included in kidney transplantation

evaluation in those who are suspected of having a hereditary kidney stone.[14] Furthermore, a cohort of 64 patients with PH revealed a delay in age of onset and genetic assessment from 1.2 years in children to 30 years in adults.[15] There are some case reports of accelerated graft failure due to HOX recurrence in patients with a history of recurrent kidney urolithiasis or unexplained kidney failure.[16,17]

The most cases with identified genes were over than 10 years old according to the survey. This suggests that the genetic analysis is conducted either prior to the kidney transplantation evaluation or following graft failure because of disease recurrence. Improving patient outcomes and preventing the progression of the disease depend on timely diagnosis and intervention. Genetic evaluation is crucial for early diagnosis due to the clinical heterogeneity and unusual presentations of PH.

AGXT was the most commonly detected genetic mutation, which is also associated with worse prognosis, although the current survey did not look for detail of mutations. Patients with severe PH have oxalate deposits in bone and heart. Furthermore, multi-organ involvement in the infantile type of oxalosis is detrimental to the eye, kidney, and heart.[1] Specific mutation of PH (c.508G > A and c.454T > A) would respond to high doses of vitamin B6. All centers prescribed pyridoxine to their patients, regardless of the genetic mutation. Lumasiran, a novel RNAi treatment for PH1, was recently approved in the United States, Europe, and the United Kingdom. Lumasiran reduces the production of glyoxylate and oxalate by inhibiting glycolate oxidase.[19] Nedosiran, another RNAi agent, that inhibits hepatic lactate dehydrogenase A, is currently FDA-approved (29 Sep 2023) for the treatment of PH1 in patients above 9 years old.[20] These medications reduce the necessity for liver transplantation and improves renal outcomes.

In the case of inaccessibility of RNAi medicines, liver and sequential kidney transplantation or combined kidney and liver transplantation are suggested.[14] Total native hepatectomy generally precedes liver transplantation in PH. A successful sequential liver and kidney transplantation was reported in a 17- years old boy with PH by Naderi *et al.* in 2011.[21] Dehghani *et al.* reported the outcome of 18 cases with PH who underwent liver transplantation. Four–year survival was 61% with the mortality rate of 40%. The most common complications were hepatic artery thrombosis, biliary complications, infection and graft rejection.[22]

Current research includes pharmacological chaperon therapy, gene therapy, pluripotent stem cell therapy, and oral small-molecule drugs that target the protein using Crispr-cas9 technology.[23] Furthermore, there are ongoing trials on immunoregulation and enzyme replacement therapy as additional management modalities.[24]

The limitations of this study were: 1. the style of questionnaire was incomprehensive, 2. the frequency was represented as blocks of numerical intervals and vague figures 3. the genetic mutation was not collected in details. We are planning to collect more precise data by collaboration of IranSPN members to find genotype, phenotype, and long term outcomes in children with PH.

CONCLUSION

This brief survey revealed that at least 80 cases of genetically confirmed PH was detected, the majority of which were diagnosed after the age of ten at which they required transplantation. Four centers used family history, clinical presentation, imaging, and biochemical analysis to diagnose PH. All centers managed their patients conservatively upon diagnosis. No new methods of management are currently available in Iran. We recommend genetic screening in individuals suspected of having primary hyperoxaluria and those with unexplained end-stage kidney disease candidate for kidney transplant, recurrent multiple urolithiasis, and a family history of urolithiasis HOX.

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Metabolic Disorders in Iranian Children with Urolithiasis. Maedica (Bucur). 2019;14:270-73.

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