Evaluation of Cystinosis Patients and Factors Associated with Chronic Kidney Disease

Begüm Avcı [1], Gönül Parmaksız [1]

1 Department of Pediatric Nephrology, Başkent University Faculty of Medicine, Adana, Türkiye

Abstract

Aim: Cystinosis is a rare genetic, lysosomal storage disorder, leading to kidney involvement and other organs. The most critical factor determining the prognosis is its impact on the kidneys especially nephropathic cystinosis. This study aimed to evaluate cystinosis patients and identify factors associated with chronic kidney disease (CKD).

Methods: The medical records of 18 nephropathic cystinosis patients were retrospectively reviewed. Demographic and clinical features, prognosis were evaluated. Patients were classified according to their estimated glomerular filtration rate (eGFR) at last visit as eGFR<60 ml/min/1.73 m^2 and eGFR>60 ml/min/1.73 m^2, and were compared for CKD related factors.

Results: The mean age at diagnosis was 46.61±50.42 months. The most common allele was c. 451A>G. Polyuria, polydipsia, vomiting, growth retardation, and renal osteodystrophy were typical presenting symptoms. At diagnosis, the mean eGFR was 72.94±21.69 ml/min/1.73 m^2. After an average follow-up of 68.28±60.18 months, the mean eGFR was 63.97±23.59 ml/min/1.73 m^2, and CKD was observed in 44.4% of patients, and 5 (27.8%) underwent kidney replacement therapy (KRT). In patients with GFR<60 ml/min/1.73 m^2, the initial cysteamine dose was found to be significantly lower (p=0.03), while consanguinity (p=0.04) and family history presence (p=0.01), presence of renal osteodystrophy at diagnosis and the development of rickets (p=0.02), were statistically significantly higher.

Conclusions: **Conclusion:** This study highlights the importance of effective cystinosis management, focusing on early diagnosis and optimal cysteamine treatment to prevent complications especially CKD. Consanguinity and family history, accompanying rickets emerged as notable risk factors for CKD, underscoring the significance of genetic counseling and bone health monitoring.

Keywords: *Cystinosis, Kidney, Children*

1. Introduction

Cystinosis is a systemic disorder caused by mutations in the *CTNS* gene, which encodes the lysosomal cystine transporter protein, leading to intracellular cystine accumulation primarily affecting the kidneys, causing progressive organ damage[1]. The incidence of autosomal recessive cystinosis disease is 0.5-1/100.000[2]. So far, over 140 mutations have been found in cystinosis patients. The most common one is a significant 57-kb deletion that impacts the initial 9 exons of *CTNS* and a portion of exon 10[2,3]. However, it's worth noting that a Turkish patient group studied by Topaloglu et al. did not exhibit this particular 57-kb deletion[4].

There are three clinical forms of cystinosis based on age of onset and kidney involvement: infantile, juvenile, and adult (ocular non-nephropathic). Infantile nephropathic cystinosis is severe, often leading to end-stage kidney disease (ESKD). Juvenile form is less common, with diagnosis after age 10. Adult form is rare, causing photophobia due to corneal cystine accumulation[5].

Infantile nephropathic cystinosis presents with Fanconi syndrome around 6 months accompanying polyuria, growth issues, vomiting, dehydratation, and rickets[5,6]. Glomerular function declines, usually resulting in ESKD by the first decade, treated with kidney replacement therapy (KRT) include hemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation. Since cystinosis patients do not experience recurrence after kidney transplantation, kidney transplantation is preferred for KRT[4]. However, early cysteamine therapy helps clear cystine, benefiting kidney function and delaying ESKD onset[7,8]. The prevention of progression to ESKD is of significant importance in terms of patients' prognosis and morbidity, as it enables the identification of other prognostic factors, in addition to the significance of early initiation and effectiveness of treatment. In a recent study, a high level of proteinuria at the time of diagnosis (spot urine protein/creatinine >6 mg/mg) was identified as a prognostic

* *Corresponding Author: Begüm Avcı*
e-mail: begumavcidr@gmail.com
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factor affecting kidney survival[9].
This study aims to assess cystinosis, a rare condition with significant multisystem impact and potential complications, particularly kidney failure. By investigating clinical features, disease progression, and prognosis, we also aim to identify the factors like early treatment that relate to chronic kidney disease (CKD) and ESKD outcomes.

2. Materials and methods

We conducted a retrospective review of the medical records of cystinosis patients who were diagnosed and followed up at the Department of Pediatric Nephrology, Başkent University Adana Application and Research Center, from 2006 to 2023.

The study included patients diagnosed with cystinosis based on clinical and laboratory findings. Patients with accessible medical records and a follow-up period of at least 6 months were included. Cystinosis diagnosis was confirmed through the observation of corneal cystine crystals in slit lamp examinations, elevated leukocyte cystine levels (> 2 nmol ½ cystine per mg protein), and/or the presence of mutations in the *CTNS* gene identified through genetic testing.

The medical records of patients' age at diagnosis, consanguinity and family history, age of onset of symptoms, duration of diagnosis and follow-up, presenting clinical findings, and laboratory values at diagnosis and at the end of follow-up, leukocyte cystine level (nmol ½ cystine mg protein), cysteamine dose and supportive treatments were evaluated retrospectively. The eGFR was calculated with the Schwartz formula.[10]

Cysteamine was initiated orally at a dose of 60–90 mg/kg/day, which was initiated at a low dose and gradually increased, for all patients upon diagnosis. Additionally, topical cysteamine eye drops were prescribed for all patients upon detection of eye involvement.

At the end of the follow-up period, the patients were classified into five stages of CKD 1,2,3,4 and 5 according to the KDIGO classification. Then the patients were categorized into two groups based on their stages: patients with stage 3, 4 and 5 grouped as eGFR<60 ml/min/1.73 m^2 and with stage 1, 2 and without CKD grouped as eGFR>60 ml/min/1.73 m^2. Then, demographic, clinical, and laboratory data, along with treatment and disease-related complications, were statistically compared between these two groups to identify factors associated with CKD.

This study was approved by Başkent University Instutional Review Board. (Project no: KA23/253).

2.2 Statistical Analysis

Statistical analyses for this observational, descriptive, retrospective study were conducted using IBM® SPSS© 24 software. Categorical variables were presented as numbers and percentages. Normality of numerical variables was assessed using analytical methods such as Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics for normally distributed numeric variables were reported as mean and standard deviation. To compare continuous variables between groups, we used either Student's t-test for parametric values or Mann-Whitney U test for non-parametric values. Categorical variables between groups were analyzed using the chi-square test or Fisher's exact test. The threshold for statistical significance was set at $p<0.05$.

3. Results

3.1. Demographic and Clinical Findings

A total of 18 cystinosis patients, 7 males and 11 females, were followed up at our center, with a mean age at diagnosis of 46.61±50.42 months. The patient with the older age at diagnosis, he was at 174 months and had a homozygous c.451A>G p.Arg151Gly mutation. The other four patients with older age at diagnosis (minimum 43 months-maximum 126 months) also had the same mutation. The patient diagnosed at 53 months had a heterozygous mutation of c.864_842del p.Val279_Tyr281del/c.1015G>A p.Gly339Arg. Among the patients diagnosed at an early age (minimum 7 months, maximum 17 months), 5 had a homozygous c.681G>A p.Glu227Glu mutation, and the other 3 had a homozygous/heterozygous c.18-21del p.Thr7Phefs*7 mutation. The genetic analysis of a total of 15 patients revealed that the homozygous c.451A>G p.Arg151Gly, which was detected in six patients, was the most frequently observed mutation in our study. The mean diagnosis period was 4.33±7.64 months.

All patients presented with polyuria and polydipsia as their chief complaints, while vomiting (44.4%) and growth retardation (33.3%) were other commonly observed symptoms. While proteinuria was present in 17 (94.4%) patients, fanconi syndrome was observed in 12 (66.7%) patients. Eleven patients (61.1%) exhibited acidosis, while alkalosis was present in 2 patients (11.1%). One patient had acute kidney injury at presentation, which improved during follow-up. At the time of diagnosis, the mean eGFR of the patients was 72.94±21.69 mL/min/1.73m^2, and the mean spot urine protein/creatinine (Spot Up/cr) was 2.20±1.88 mg/mg. The mean leukocyte cystine level in all patients was 5.51±4.63 nmol ½ cystine per mg protein, while the initial treatment doses averaged at 27.22±8.61 mg/kg.Table-1 summarizes the demographic and clinical characteristics of the patients at the time of presentation.

Table 1

Demographic, clinical characteristics, and findings of the cystinosis patients at presentation and diagnosis

	Patients (n= 18)
Male, n (%)	7 (38.9%)
Consanguinity, n (%)	14 (77.8%)
Family history of Cystinosis, n (%)	4 (22.2%)
Age of diagnosis, months (mean±SD)	46.61±50.42
Diagnosis period, months (mean±SD)	4.33±7.64
Symptoms	
• Polyuria, n (%)	18 (100%)
• Polydipsia, n (%)	18 (100%)
• Vomiting, n (%)	8 (44.4%)
• Growth retardation, n (%)	6 (33.3%)
• Photophobia, n (%)	1 (5.6%)
• Tetany, n (%)	1 (5.6%)
Other findings	
• Proteinuria, n (%)	17 (94.4%)
• Corneal involvement, n (%)	14 (77.8%)
• Fanconi, n (%)	12 (66.7%)
• Acidosis, n (%)	11 (61.1%)
• Anemia, n (%)	9 (50.0%)
• Renal osteodystrophy, n (%)	6 (33.3%)
eGFR at (ml/min/1.73m2), mean±SD	72.94±21.69
Spot Urine protein/creatinine (mg/mg), mean±SD	2.20±1.88
Leukocyte cystine level (nmol half-cystine/mg protein), mean±SD	5.51±4.63
Cysteamine dose (mg/kg/day), mean±SD	27.22±8.61

eGFR: estimated Glomerular Filtration Rate

3.2. Prognosis

During an avarage follow-up of 68.28±60.18 months, rickets were observed in 9 cases (50.0%). At their last visit, patients had a mean eGFR 63.97±23.59 mL/min/1.73m^2. Among them, with 44.4% (8 patients) had an eGFR below 60 mL/min/1.73m^2, and 5 (27.8%) underwent KRT with three of them receiving kidney transplantation. Currently, 10 cystinosis patients are being actively monitored, with two having undergone kidney transplantation and one continuing PD. The prognosis is summarized in Table 2.

Among the 8 patients with eGFR<60 mL/min/1.73 m^2, 4 had the homozygous c.681G>A mutation and 1 had the homozygous c.18-21delGACT p.T7Ffs7 mutation (early-onset diagnosis), while 3 had the c.451>G p.Arg151Gly mutation (late-onset diagnosis). The mean age of ESKD development in the 5 patients with ESKD was 12.8±6.05 (ranging from 7 to 20 years) years. Among these, 3 patients with the homozygous c.681G>A mutation and 1 patient with the homozygous c.18-21delGACT p.T7Ffs7 mutation (early-onset diagnosis) had a mean age of ESKD development at 8.67±2.89 years. In siblings with late-onset c.451>G p.Arg151Gly mutation, the age of ESKD was 18 and 20 years.

3.3 CKD with GFR<60 mL/min/1.73 m2 associated factors

In patients with eGFR<60 mL/min/1.73 m^2, the presence of consanguinity (8/8 patients vs. 6/10, *p=0.04*) and family history (4/8 patients vs. 0/10, *p=0.01*), the presence of renal osteodystrophy at presentation (5/8 patients vs. 1/10, *p=0.02*), and the development of rickets (7/8 patients vs. 2/10, *p=0.02*) were statistically significantly higher. The initial cysteamine dose was found to be statistically significantly lower in patients with eGFR<60 mL/min/1.73 m^2 (22.50±8.45 vs. 31.0±6.99; *p=0.03*). The comparison between patients with eGFR<60 mL/min/1.73 m^2 and >60 mL/min/1.73 m^2 is shown in Table 3.

Table 2

Prognosis of the cystinosis patients

	Patients (n= 18)
eGFR at last visit (mL/min/1.73m2), mean±SD	63.97±23.59
Spot Urine protein/creatinine at last visit (mg/mg), mean±SD	2.59±2.32
Leukocyte cystine level at last visit (nmol half-cystine/mg protein), mean±SD	3.35±3.32
Cysteamine dose at last visit (mg/kg/day), mean±SD	53.3±14.45
Systemic findings	
• Rickets, n (%)	9 (50.0%)
• Hypothyroidism, n (%)	2 (11.1%)
• Gastrointestinal involvement, n (%)	2 (11.1%)
Chronic Kidney Disease with eGFR<60 mL/min/1.73m2, n (%)	8 (44.4%)
Kidney Replacement Therapy, n (%)	5 (27.8%)
• Kidney Transplantation, n (%)	3 (16.7%)
• Peritoneal Dialysis, n (%)	2 (11.1%)
Follow-up period (months), mean±SD	68.28±60.18
Follow-up situation at last visit	
• Follow-up	10 (55.6 %)
• Follow-up by adult	4 (22.2%)
• Unfollowed	4 (22.2%)

eGFR: estimated Glomerular Filtration Rate

Table 3

Demographic, clinical characteristics, and prognosis differences between cystinosis patients with eGFR<60 mL/min/1.73m^2 and eGFR>60 mL/min/1.73m^2

	eGFR<60	eGFR>60	p value
Number of patients, n (%)	8	10	
Gender (Male/Female)	5/3	2/8	0.06
Consanguinity, n	8	6	0.04
Family history of Cystinosis, n	4	-	0.01
Age of diagnosis, month (mean±SD)	42.13±50.24	50.20±52.97	0.74
Diagnosis period, month (mean±SD)	2.75±2.49	5.60±10.07	0.45
Growth retardation at diagnosis, n	2	4	0.50
Symptoms at diagnosis			
• Growth retardation, n	2	4	0.50
• Photophobia, n	0	1	0.36
• Vomiting, n	5	3	0.17
• Tetany, n	1	-	0.25
Other findings			
• Proteinuria, n	8	9	0.36
• Fanconi, n	6	6	0.50
• Renal osteodystrophy, n	5	1	0.02
• Acidosis, n	5	6	0.91
• Anemia, n	3	6	0.34
eGFR (ml/min/1.73m2) at diagnosis, mean±SD	80.13±23.47	67.94±19.43	0.22
Spot Urine protein/creatinin (mg/mg) at diagnosis, mean±SD	2.41±1.95	2.03±1.91	0.68
Leukocyte cystine level (nmol half-cystine/mg protein) at diagnosis, mean±SD	6.58±5.65	4.66±3.72	0.39
Initial dose of Cysteamine (mg/kg), mean±SD	22.50±8.45	31.0±6.99	0.03
Systemic findings			
• Rickets, n	7	2	0.02
• Hypothyroidism, n	2	-	0.09
• Gastrointestinal involvement, n	1	1	0.87
• Corneal involvement, n	7	7	0.38

Bold shows that p value is statistically significant, eGFR: estimated Glomerular Filtration Rate

4. Discussion

Cystinosis is a rare, autosomal recessive, multisystemic, lysosomal storage disorder. Although cysteamine treatment significantly improves the disease course, allowing for more widespread use of KRT, the development of ESKD and systemic symptoms are still commonly observed, particularly due to ongoing challenges in drug procurement and other social and economic difficulties in our country. Therefore, we evaluated cystinosis patients followed up at our center in terms of clinical manifestations, disease progression, and kidney involvement, aiming to identify factors associated with CKD and the development of ESKD.

In autosomal recessive hereditary diseases, consanguineous marriages increase the risk of being affected, and in our study, consanguineous marriage was found in 77.8% of cases, while family history was present in 22.2%. Similar rates have been reported in other studies conducted in our country, where the rate of consanguineous marriages is generally high in the general population[4,9,11,12]. In contrast to our population, Greco et al. reported the rate of consanguineous marriages as 8.6%[13]. Cystinosis, although considered a rare disease, is important in our country due to its relatively higher occurrence resulting from consanguineous marriages. Therefore, raising awareness about the condition is crucial to facilitate early diagnosis.

In our study, the average age at diagnosis (46.61±50.42 months)

was found to be higher compared to previous studies.[4,8,14] Among the patients with late-onset disease, six had the homozygous c.451A>G p.Arg151Gly mutation. On the other hand, among the patients diagnosed at an early age, five had the homozygous c.681G>A p.Glu227Glu mutation, and the other three had the homozygous/heterozygous c.18-21del p.Thr7Phefs*7 mutation. Likewise, a recent extensive cohort study conducted in Turkey revealed that the prevailing mutations were c.681G>A p.Glu227Glu and c.18-21del p.Thr7Phefs*7, both linked to early-onset disease and a more severe clinical progression.[4] In the study by Atmış et al[9], it was reported that patients with the c.451A>G mutation had older ages at diagnosis and longer follow-up periods compared to patients with other mutations. In our study, similar to the previously reported findings from the same region in our country, the homozygous c.451A>G p.Arg151Gly mutation was also found to be prevalent[9,15]. The higher proportion of patients with the homozygous c.451A>G p.Arg151Gly mutation, which was the initial description was provided by Topaloglu et al. in Turkey[16], in our study might have contributed to the higher average age at diagnosis compared to previous studies. Although we observed fewer patients with mutations detected at a young age, we would have expected a longer diagnosis period due to factors such as non-specific evaluation of symptoms in younger patients, insufficient awareness of the disease among primary care physicians, limited diagnostic methods, and the presence of corneal cystine crystals in examinations before the age of 1.5 years. However, the diagnosis period in our study was not very long. This may be attributed to pediatric physicians promptly referring suspicious patients to the nephrology department.

Consistent with previous research, our study also found that the most frequent initial symptoms were polyuria and polydipsia, followed by vomiting, growth retardation, and renal osteodystrophy.[4,8] At the time of diagnosis, renal osteodystrophy was observed in 33.3% of patients. Previous studies by Brodin et al.[8] and Topaloglu et al.[4] reported the occurrence of rickets in 41% and 44% of cases, respectively. Patients with rickets were found to have a younger age at diagnosis and to have the c.681G>A p.Glu227Glu and c.18-21del p.Thr7Phefs*7 mutations. Nevertheless, the research conducted by Topaloglu et al.[4] reported no notable distinction concerning the occurrence of rickets between individuals with these frequently observed mutations and those with other genetic mutations. While typical clinical presentation in cystinosis involves proximal renal tubular acidosis, our study and the others reported cases where patients presented with a hypokalemic, hypochloremic metabolic alkalosis pattern, resembling Bartter syndrome[12,17-20]. The exact cause of metabolic alkalosis is not fully understood. Nonetheless, it has been proposed that an abnormality in sodium-dependent transtubular transport contributes to heightened sodium reabsorption, leading to the depletion of potassium and hydrogen ions. Consequently, this process culminates in the development of metabolic alkalosis[18-20].

At the time of admission, the average eGFR of the patients was 72.94±21.69 ml/min/1.73 m2. One patient had acute kidney injury due to dehydration, with an eGFR of 32 ml/min/1.73 m2, which later improved to above 90 ml/min/1.73 m2 during follow-up. After an average follow-up of 68.28±60.18 months, the mean eGFR was 63.97±23.59 ml/min/1.73 m2, similar to the findings reported by Atmış et al.[9] with the most common C.451A>G mutation. At the end of the follow-up period, the prevalence of CKD (eGFR<60 mL/min/1.73m2) was 44.4%, and the rate of KRT was 27.8%. In a large-scale cohort study conducted in our country, the rate of KRT was reported as 36%,[4] while in the study by Atmis et al.[9], where the C.451A>G mutation was most commonly identified, the rate was 16.6%. Our study, in which the mean age of ESKD development was found to be 12.8 years, is consistent with a similar study where the most common C.451A>G mutation was identified, reporting an mean ESKD age of 122 months[9]. On the other hand, in a large cohort study by Topaloglu et al.[4], where the c.681G>A p.Glu227Glu and c.18-21del p.Thr7Phefs7 mutations were more prevalent, the average ESKD age was reported as 11 years. The later onset of ESKD in the study with a higher frequency of these mutations, which are more common and have a more severe course at a young age diagnosed, was attributed to the early initiation of cysteamine therapy (<2 years). In our study, cysteamine treatment was started before the age of 2 in patients, who developed ESKD, with the c.681G>A p.Glu227Glu and c.18-21del p.Thr7Phefs7 mutations.

In cystinosis patients, various factors affecting prognosis, such as the timing of cysteamine treatment initiation, and treatment dose, patient adherence to therapy, leukocyte cystine levels, and spot urine protein/creatinine ratios, have been evaluated in previous studies. It has been suggested that starting cysteamine treatment before the age of 2 delays the onset of ESKD[4,8,13], and that patient adherence and proper dosage usage also delay ESKD development.[8] Furthermore, it has been observed that patients with lower leukocyte cystine levels develop ESKD at a later stage,[8] and those with spot urine protein/creatinine ratios lower than 6 mg/mg have a better prognosis[9].

In our study, there were no significant differences in the age of cysteamine treatment initiation, leukocyte cystine levels, and spot urine protein/creatinine ratio between patients with eGFR<60 ml/min/1.73 m^2 and eGFR>60 ml/min/1.73 m^2. However, it was observed that the initial cysteamine treatment dose was lower in patients with eGFR<60 ml/min/1.73 m^2. This result is consistent with the poor adherence to cysteamine treatment is associated with early onset of ESKD detected in the previous studies[8]. Also, the most significant contributing factor to this situation in our country is the difficulties patients experience in obtaining drugs. These results are emphasizing the importance of starting treatment with higher doses or increasing doses promptly to ensure treatment adherence and achieve optimal outcomes. Compliance with medication and regular intake of prescribed drugs are of critical importance for cystinosis patients[21].

In our study, there was a statistically significant higher in consanguinity and family history among patients with CKD. Consanguinity and family history should be considered as risk factors for CKD development. In our country, where consanguineous marriages are observed at a high rate, patients should be evaluated for their family history and receive genetic counseling. Close monitoring, family education, and early diagnosis are crucial, and sibling screening is highly important for cystinosis patients.

In our study, the presence of renal osteodystrophy or the development of rickets during follow-up period was found to be significantly associated with CKD. Rickets, being a factor associated with ESKD, can have negative effects on patients' growth and bone health. Therefore, regular monitoring of bone health in cystinosis patients and the appropriate and adequate treatments, especially cysteamine and other supportive therapies, are crucial, as emphasized once again in this study.

The limitations of our study include its retrospective nature, small sample size, short follow-up period, and the lack of molecular genetic analysis performed in all patients. However, considering the importance of identifying factors that can impact the prognosis of this rare and preventable condition, the findings of this and other studies may be beneficial in planning larger-scale prospective studies in the future.

5. Conclusions

In conclusion, our study highlights crucial aspects of managing cysti-

nosis, including early diagnosis and appropriate treatment dosing to prevent complications and enhance patients' quality of life. Consanguinity and family history emerged as significant risk factors for CKD in cystinosis patients, underscoring the importance of assessing family history and providing genetic counseling, especially in regions with prevalent consanguineous marriages such as our country. The presence of renal osteodystrophy or rickets during follow-up was strongly linked to CKD, stressing the need for regular bone health monitoring and timely, suitable cysteamine therapy. Despite the study's limitations, these findings underscore the significance of further research involving larger patient cohorts to better comprehend cystinosis and CKD-related factors. This knowledge will ultimately lead to improved patient outcomes and a deeper understanding of the disease.

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Statement of ethics

This study was approved by was approved by Başkent University Instutional Review Board. (Project no: KA23/253).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

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