Understanding Cystinosis, Clinical Characteristics and Hypothyroidism Prevalence in Iraqi Pediatric Patients

Khamees M. Al-Dulaimy [1], Zaynab Hameed Ibrahim [1], Bassim Mohammed Salman [1*]

Abstract

Background: Cystinosis, an autosomal recessive lysosomal storage disease, leads to the abnormal accumulation of cystine, primarily affecting the kidneys. Despite various treatments, including cysteamine therapy, renal replacement, and hormonal interventions, no curative treatment exists. Hypothyroidism is a common complication in cystinosis patients, but its prevalence and associations require further investigation. This study aimed to assess the prevalence of hypothyroidism in cystinosis patients and identify associated risk factors. Methods: A six-month cross-sectional study was conducted at Al-Ramadi Teaching Hospital, Iraq, involving 92 cystinosis patients. Data were collected from patient records, and thyroid dysfunction was defined by abnormal thyroid hormone levels. Results: Hypothyroidism prevalence among cystinosis patients was 40.2%. It significantly increased with patient age and age at cystinosis diagnosis, reaching 85.7% and 87.5% in patients over 10 years and diagnosed after 2 years of age, respectively. A positive family history of cystinosis correlated with higher hypothyroidism prevalence. Conclusion: Hypothyroidism is prevalent (40.2%) in cystinosis patients, particularly in older individuals with delayed diagnosis or cysteamine initiation, and those with a family history of the disease. Timely diagnosis, early cysteamine therapy initiation, and regular monitoring for hypothyroidism are essential for managing cystinosis-associated endocrine complications. Further research should explore additional factors influencing hypothyroidism in cystinosis patients to optimize treatment and outcomes.

Keywords: Cystinosis, Hypothyroidism, Cysteamine, Renal Dysfunction, Genetic Mutation (CTNS gene)

Significance | Understanding the genetic basis of cystinosis aids in early diagnosis, genetic counseling, and potential gene therapy approaches for disease management.

*Correspondence. Bassim Mohammed Salman, Al-Ramadi Teaching Hospital for Maternity and Childhood
E-mail: drkhameesmushrif@yahoo.com , basim.salman@meciq.edu.iq , phone: 009647700016459, 009647727126722

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Introduction

Cystinosis, a rare lysosomal storage disorder, has its etymological roots in the German term "Cystindiathese" or "hereditary cystine disease," coined by Emil Abderhalden in 1903. This term evolved through the English literature as "cystine disease" before settling on "cystinosis." This genetic disorder, inherited in an autosomal recessive pattern, is marked by the abnormal accumulation of cystine, an oxidized form of the amino acid cysteine, within lysosomes (Elmonem et al., 2016). Cystinosis is notably the most prevalent cause of Fanconi syndrome in pediatric populations (Nesterova et al., 2013).

The classification of cystinosis includes three types based on the age of onset and the degree of cystine accumulation: infantile, adolescent, and adult onset. Infantile nephropathic cystinosis manifests early in life and, if untreated, often leads to end-stage kidney disease by late childhood. Treatment options include

Author Affiliation.
[1] Al-Ramadi Teaching Hospital for Maternity and Childhood, Ramadi, Al Anbar Governorate, Iraq

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cystine-depleting agents like cysteamine, renal replacement therapies, and hormonal treatments, though a definitive cure remains elusive (Levtchenko et al., 2023).

Cystinosis arises from mutations in the CTNS gene, which encodes cystinosin, a lysosomal cystine transporter. This defect prevents the efflux of cystine from lysosomes, leading to its accumulation as crystals in various tissues (Levtchenko et al., 2014). The most common mutation, a 57-kb deletion, is prevalent in nearly half of the cases in North European and North American populations but is rare in other regions such as the Middle East. Severe or truncating mutations typically result in the infantile form of the disease, while milder mutations are associated with juvenile and ocular forms (Soliman et al., 2014).

Cystinosis has a reported birth prevalence of approximately 1 in 100,000 to 200,000 live births in North America, with around 400 affected individuals in the United States. Incidence rates in Europe vary, with France reporting 1 in 167,000 and Sweden 1 in 260,000 live births. Higher rates are observed in populations with founder mutations, such as in Brittany, France (1 in 26,000) and the Pakistani community in the West Midlands, UK (1 in 3,600) (Hult et al., 2014). While cystinosis predominantly affects individuals of European descent, it also occurs in other racial and ethnic groups globally. The male-to-female ratio in cystinotic children is approximately 1.4:1 (Nesterova et al., 2013).

Cystinosis presents in three clinical forms, differentiated by the age of onset and severity of renal involvement. Infantile nephropathic cystinosis, the most severe form, initially presents with renal Fanconi syndrome characterized by excessive losses of amino acids, glucose, phosphate, and other substances in the urine. This leads to symptoms such as failure to thrive, polyuria, polydipsia, dehydration, and electrolyte imbalances. Without treatment, patients progress to end-stage renal disease (ESRD) by late childhood (Besouw et al., 2010).

Late-onset forms, including adolescent and adult types, have milder renal symptoms. Adolescent cystinosis may present with isolated proteinuria or mild Fanconi syndrome without significant growth retardation. The adult, non-nephropathic form typically manifests with photophobia due to corneal cystine deposits and rarely affects renal function (Levtchenko et al., 2023).

Corneal cystine crystals are a hallmark of cystinosis, leading to photophobia and blepharospasm. Retinal complications can cause progressive vision loss (Tsilou et al., 2002). Hypophosphatemic rickets, characterized by bone deformities like genu varum and rachitic rosary, results from phosphate loss and vitamin D metabolism disturbances (Besouw et al., 2015). Cystine accumulation in the brain can impair cognitive function, particularly nonverbal learning skills. Early and continuous cysteamine treatment can mitigate some neurological symptoms (Pape et al., 2017). Hypothyroidism is common, with about 50-70% of cystinosis patients developing thyroid dysfunction by the second decade of life. Hypogonadism and diabetes mellitus are also observed, with male patients often experiencing infertility due to azoospermia (Pape et al., 2017).

Diagnosis relies on detecting elevated cystine levels in white blood cells and identifying mutations in the CTNS gene. Additional evaluations include electrolyte measurements, renal ultrasounds, and ophthalmologic examinations for corneal crystals (Elmonem et al., 2016).

Management of cystinosis involves symptomatic treatments to maintain fluid and electrolyte balance, nutritional support, and prevention of rickets and other complications. The cornerstone of treatment is cysteamine, which depletes cystine stores and delays the progression of renal disease and other complications (Emma et al., 2014). This includes electrolyte replacement, vitamin D supplementation, and the use of ACE inhibitors to manage proteinuria. Renal transplantation is an option for patients with ESRD (Ariceta et al., 2019). Oral cysteamine helps reduce cystine accumulation in tissues, and eye drops are used to treat corneal cystine crystals. Despite its effectiveness, cysteamine therapy has side effects such as gastrointestinal discomfort and requires strict adherence to dosing schedules (Gahl et al., 2002). Thyroid function is monitored, and hypothyroidism is treated with thyroxine. Male infertility remains a challenge, though assisted reproductive techniques have shown some success (Besouw et al., 2010).

Cystinosis is a complex disorder with significant renal and extra-renal manifestations. Early diagnosis and comprehensive management, including cysteamine therapy, are crucial for improving outcomes and quality of life for affected individuals. Continued research is essential to better understand the disease mechanisms and develop more effective treatments, ultimately aiming for a curative approach.

Materials and Methods

Study Design

This cross-sectional study was conducted in the Pediatric Department at Al-Ramadi Teaching Hospital for Maternity and Childhood over a six-month period from November 2021 to April 2022. The study focused on patients diagnosed with cystinosis and aimed to investigate the prevalence and associated factors of primary hypothyroidism among these patients. The study included data collection from archived files in the cystinosis unit, encompassing all patients diagnosed with cystinosis. The total number of patients included in the study was 92. This sample size was determined based on the total number of diagnosed cases available in the unit during the study period.

Ethical Approval

The study adhered to ethical standards and obtained necessary permissions. Institutional Approval was granted by the Pediatric

Department at Al-Ramadi Teaching Hospital for Maternity and Childhood to access and collect data from the archive files. All patient information was anonymized. Names were replaced with identification codes to maintain confidentiality. The data was stored securely on a password-protected laptop and was used exclusively for research purposes. Parental Informed consent was obtained from the parents or guardians of the patients for the use of the data in this study.

Data Collection

A structured data form was utilized to gather necessary information from each patient's file. The form included the following demographic and clinical information: Date of Birth and Gender, Consanguinity, Family History of Cystinosis, Age of Cystinosis Diagnosis, Age of Start of Cysteamine Intake, Age of Diagnosis of Hypothyroidism, Thyroid and Renal Function Tests, and Complications.

Diagnosis of Hypothyroidism

Hypothyroidism was diagnosed based on the levels of thyroid hormones (T3, T4) and thyroid-stimulating hormone (TSH) according to age-specific reference ranges. Thyroid dysfunction was defined when the patient's thyroid hormone levels fell outside the reference range, as detailed in Table 1 of the study. Both T4 and TSH measurements were conducted simultaneously as part of the screening method to ensure accurate diagnosis of hypothyroidism.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 26. The data were summarized using descriptive statistics: Continuous Variables and Categorical Variables. To compare continuous variables, the independent t-test (two-tailed) was employed. The chi-square test was used to assess associations between the prevalence of hypothyroidism and other demographic and clinical variables. A p-value of less than 0.05 was considered statistically significant, indicating a meaningful association between the variables studied.

Results

The study comprised ninety-two (92) patients, all diagnosed with cystinosis. General characteristics revealed a diverse age range (10 months to 18 years) with a mean of 5.71 years (± 3.7 years). The highest proportion fell between 5 – 10 years (46.7%), as depicted in Figure 1. Males constituted 55.4% compared to females (44.6%), indicating a male-to-female ratio of 1.24:1, as illustrated in Figure 2. Notably, 46.7% were diagnosed before their first year, with 50% exhibiting consanguinity and 25% having a positive family history of cystinosis. Clinical data in Table 3 displayed that 47.8% commenced Cysteamine treatment between 1 – 2 years, while 20.2% experienced renal failure, and 5.3% underwent renal transplantation. Hypothyroidism was diagnosed in 40.2% through screening (Figure 2), with all cases receiving thyroxine treatment, 54.1% of which were diagnosed post-sixth year (Table 4). Table 5 revealed a significant increase in hypothyroidism prevalence with age and cystinosis diagnosis age, notably reaching 85.7% and 87.5% in patients > 10 and > 2 years old, respectively, with the highest prevalence in those with a family history of cystinosis (60.9%, P=0.019). No statistical association was found between hypothyroidism and gender or consanguinity. Table 6 further explored associations between hypothyroidism prevalence and clinical factors, indicating significant increases with delayed Cysteamine treatment onset (> 2 years: 88.5%, P=0.001) and renal impairment (88.9%, P=0.001).

Discussion

In the current study, 92 were enrolled. All of them were diagnosed with cystinosis. The present work observed that 40.2% of cystinosis patients were diagnosed with hypothyroidism by screening. All patients with hypothyroidism received thyroxine treatment and 54.1% of them diagnosed as hypothyroidism after sixth year of age. In comparison to other studies, Hypothyroidism was reported in 20% of patients enrolled in Hussein et al study in 2018. Also, Azat et al study enrolled twenty-nine patients diagnosed with cystinosis, of which only one patient developed hypothyroidism (3.44%), at the age of 11 years (Azat et al, 2012). Moreover, Keser et al study in 2014 concluded that endocrinologic complications of cystinosis can be seen in pediatric population, as they found that 23.8% of patients had overt hypothyroidism and 23.8% had subclinical hypothyroidism with only elevated TSH levels (Levtchenko et al, 2022). A different results observed in Brodin-Sartorius et al study, in which a total of 86 cystinotic patients were enrolled, hypothyroidism was diagnosed in 62 patients (71%) at the mean age of 13.5 years (Keser et al, 2014).

In this study, 40.2% of cystinosis patients were diagnosed with hypothyroidism by screening as shown in Figure 2. All patients with hypothyroidism received thyroxine treatment and 54.1% of them diagnosed as hypothyroidism after sixth year of age as shown in Table 4.

The current study, Prevalence of hypothyroidism was significantly increasing with increasing in age of patients and age of diagnosis of cystinosis to reach 85.7% at ages > 10 and >2-years respectively. Highest prevalence of hypothyroidism was seen significantly in those with family history of cystinosis (P= 0.019). No significant association between hypothyroidism and both of gender and consanguinity (P ≥ 0.05).

Different results published in Hussein et al study in 2018, in which they found and a statistically very highly significant relationship between hypothyroidism and Kurdish ethnic group (P <0.001),

Table 1. Normal range of thyroid with age group

T3		**T4**		**TSH**	
Age (Years)	**N.R (nmol/l)**	**Age**	**N.R (nmol/l)**	**Age**	**N.R (mlU/l)**
1 – 5	1.54 – 4.0	**1 - 3**	88 – 174	**21 wk – 20 y**	0.7 – 6.4
6 - 10	1.39 – 3.7	**3 - 10**	71 – 165		
11 - 20	1.23 – 3.23	**> 10**	54 - 167		

Table 2. Distribution of study patients according to their general characteristics

Variable	**No. (n= 92)**	**Percentage (%)**
Age of diagnosis of cystinosis (Year)		
< 1	43	46.7
1 – 2	41	43.6
> 2	8	8.5
Consanguinity		
Yes	46	50.0
No	46	50.0
Family history of cystinosis		
Yes	23	25.0
No	69	75.0

Table 3. Distribution of study patients according to their clinical information

Variable	**No. (n= 92)**	**Percentage (%)**
Age of Cysteamine treatment start (Year)		
< 1	22	23.9
1 – 2	44	47.8
> 2	26	28.3
Renal failure		
Yes	19	20.2
No	73	79.8
Renal transplant		
Yes	5	5.3
No	87	94.7

Table 4. Distribution of study patients according their thyroid details

Variable	No. (n= 37)	Percentage (%)
Age of diagnosis of hypothyroidism (Year)		
≤ 6	17	45.9
> 6	20	54.1
Thyroxine treatment		
Yes	37	100.0

Table 5. Association between prevalence of hypothyroidism and general characteristics

General characteristics	Hypothyroidism		Total (%) n= 92	P - Value
	Yes (%) n= 37	No (%) n= 55		
Age (Year)				
< 5	2 (4.8)	40(95.2)	42 (45.7)	**0.001**
5 - 10	29 (67.4)	14 (32.6)	43 (46.7)	
> 10	6 (85.7)	1 (14.3)	7 (7.6)	
Gender				
Male	17 (33.3)	34 (66.7)	51 (55.4)	**0.09**
Female	20 (48.8)	21 (51.2)	41 (44.6)	
Age of diagnosis of cystinosis (Year)				
< 1	9 (20.9)	34 (79.1)	43 (46.7)	**0.001**
1 - 2	21 (51.2)	20 (48.8)	41 (44.6)	
> 2	7 (87.5)	1 (12.5)	8 (8.7)	
Consanguinity				
Yes	21 (45.7)	25 (54.3)	46 (50.0)	**0.287**
No	16 (34.8)	30 (65.2)	46 (50.0)	
Family history of cystinosis				
Yes	14 (60.9)	9 (39.1)	23 (25.0)	**0.019**
No	23 (33.3)	46 (66.7)	69 (75.0)	

Table 6. Association between prevalence of hypothyroidism and clinical characteristics

Clinical characteristics	Hypothyroidism		Total (%) n= 92	P - Value
	Yes (%) n= 37	No (%) n= 55		
Age of Cysteamine treatment start (Year)				
< 1	1 (4.5)	21 (95.5)	22 (23.9)	**0.001**
1 - 2	13 (29.5)	31 (70.5)	44 (47.8)	
> 2	23 (88.5)	3 (11.5)	26 (28.3)	
Renal failure				
Yes	16 (88.9)	2 (11.1)	18 (19.6)	**0.001**
No	21 (28)	53 (71.6)	74 (80.4)	

while no relation to age nor gender observed (P>0.05) (Hussein et al, 2018).

Moreover, current study observed that prevalence of hypothyroidism was significantly increasing with delay onset of starting Cysteamine treatment to reach 88.5% at age > 2 years (P<0.05). on the other hand, B. urea, S. creatinine, and TSH were significantly higher in those with hypothyroidism than those who didn't (P < 0.05).

As compared to Brodin-Sartorius et al study, different results noticed, in which hypothyroidism was significantly reduced as cysteamine was started before 5 years of age in comparison with the absence of treatment. Therapy after 5 years still reduce the incidence of hypothyroidism as compared without treatment (Brodin et al, 2012). On the other hand, Vaisbich et al study reported that early therapy initiation is significantly associated with a lower incidence of hypothyroidism and significant delays in the onset of these conditions. Furthermore, long-term (≥8 years) cysteamine therapy reduces the incidence of hypothyroidism in patients with cystinosis (Vaisbich et al, 2010). Also, Gahl et al study reported that the incidence of hypothyroidism increased significantly with the duration of non-treatment and decreased with longer treatment (P<0.05) (Gahl et al, 2007). Finally, Ariceta and colleagues in their study reported that early diagnosis of cystinosis and adequate life-long treatment with cysteamine are essential for preventing end-organ damage and improving the overall prognosis in these patients. They concluded that early treatment initiation and good compliance to therapy, significantly decreases frequency and severity of extra-renal complications (Ariceta et al,2019).

The explanation for the differences reported above can attributed mainly to the different sample size in each study, in addition it may related to the different duration of disease, severity, duration of drug onset and the type of intervention used in each study. Also, genetic factors play an essential role in that high incidence among patients with positive family history can be due to poor medical counseling, antenatal and postnatal screening tests. The delay in its diagnosis was due to atypical clinical presentation and unavailability of specific genetic tests. Also, early complications were due to inadequacy of specific medications.

In fact, pathogenesis of thyroid dysfunction appears to be more complex than merely thyroid gland destruction by lysosomal cystine. In early disease, accelerated thyrocyte turnover with increased cell proliferation plus enhanced apoptosis linked to endoplasmic reticulum stress yields impaired thyroglobulin production and altered endolysosomal trafficking and iodothyroglobulin processing as has been recently demonstrated in the knockout mouse model of cystinosis (Gaide et al, 2015). Given the strong evidence for cysteamine-associated benefits and longer life expectancy in most patients, there is increasing interest in improving patient care with regard to extra-renal disease manifestations, treatment adherence, and adult patient care (Ariceta et al,2019)

In general, not only does the systemic nature of cystinosis pose some challenges, but these effects often present during adolescence, creating further issues. Transition of adolescents from pediatric to adult services is often poor, particularly if there is limited knowledge of the disease, because of its low prevalence (Levtchenko et al, 2022).

This study revealed that 47.8% of study patients started Cysteamine treatment between 1 – 2 years of age. Renal failure was diagnosed in 20.2% of them and 5.3% of patients underwent renal transplantation.

In comparison to other studies, a different result observed in O'Connell et al study in 2022, as found that systemic cystine-depleting therapy was initiated at a median age of 16.5 months. In 71.6% of patients, cysteamine e therapy started within one-month after initial diagnosis. Moreover, 41.9% of patients underwent renal replacement therapy (either dialysis or pre-emptive kidney transplantation)(Cherqui, 2012). Differently, Brodin-Sartorius et al study reported that cysteamine therapy was administered to 75 of 86 patients (87%) received cysteamine, starting at a mean age of 9.9 years (0.9–38.6 years) with a mean duration of 17.4 years (range between 0.9–28.4 years). A total of 55.8% of patients started cysteamine therapy before eight-years, 1.1% started between eight and 15 years, and 31.3% of them started after 15 years (Brodin et al,2012). Furthermore, end-stage renal disease is one of the major complication that occurred in 12% of patients enrolled in Hussein et al (2018) study , which is close to that observed by Azat et al study, in which 41.3% of patients had chronic renal insufficiency, 27.5 % of them were on conservative treatment only and 13.79 % of the remaining patients were on dialysis (Azat et al, 2012).

One explanation to the differences may be due to that, in addition to the different sample size, most of them develop end-stage renal disease at 2nd or 3rd decades of their life (Gahl et al, 2000).

Early recognition of cystinosis allowed starting an adequate supportive therapy quickly. On the other hand, Adherence to cysteamine treatment is poor for two reasons. First, the pharmacokinetics of the drug imposes the need for oral dosing every 6 hours. Second, side effects such as nausea and halitosis are frequent ((Brodin et al,2012). Cysteamine, by allowing cystine to exit the lysosomes, overcomes the major function of the missing cystinosin but does not replace cystinosin. Even if the level of cystine in white blood cells is low. Moreover, the fact that cysteamine does not treat the proximal tubulopathy shows that the physiopathology of cystinosis is more complicated than expected, and cystinosin may have other functions still to be identified (Cherqui et al, 2012).

In this study, mean a standard deviation (SD) of age was 5.71 ± 3.7 years, ranging from 10 months to 18 years, with highest proportion was aged between 5 – 10 years (46.7%).

Regarding gender, proportion of males was higher than females (55.4% versus 44.6%) with a male to female ratio of 1.24:1. Moreover, 46.7% of patients were diagnosed with cystinosis before the first year of life, consanguinity was positive in 50% of them; and 25% of them had positive family history of cystinosis. In comparison to other studies, a total of 74 patients were included in O'Connell et al study in 2022. A sight male predominance was reported (52.7%), with male to female ratio was 1.1:1.

The mean and SD of age of patients was 11 ± 2.3 years (O'Connell et al, 2022). In a different manner, 50 patients with cystinosis were enrolled in Florenzano et al study in 2020. Of them, 29 individuals were male (58%), with male to female ratio was 1.3:1. Mean and SD of age was 14 ± 4.3 years, ranging from 2–28 years (Di Cosmo et al. 2010). In Hussein et al study in 2018, twenty-five patients with cystinosis were enrolled, the genders of them were 52% females, with female to male ratio was 1.08:1. The patients' age ranged from 1 to 12 years with a mean of 6.25 ± 4.3 years, 4%of them were 11 months, 32% between 13 months to 5 years, and 64% were older than 5 years. The results also showed a positive consanguinity for 80% of the patients. Moreover, there was a 76% positive family history (Hussein et al, 2018).

Differently, Brodin-Sartorius et al study, found that a total of 86 cystinotic patients were included, in which a nearly an equal percentage of the participants in regard to gender, as male represented 51.1%, with male to female ratio of 1.04:1. Twelve patients were from consanguineous families. Mean and SD of age at time of diagnosis was 2.2 ± 4.4 years (0.5–11.6 yr) (Brodin et al,2012).

Many factors determined the differences observed among above studies, of these factors related to the different sample size and study design, and other related to genetic or ethnic factors. The family history of the disease will increase the chances of occurrence of cystinosis as well as a positive parental consanguinity because the mode of inheritance is autosomal recessive. Moreover, other factors were educational level of participants and socioeconomic factors that determined the attendance for diagnosis and follow-up of the disease.

Conclusion

In conclusion, this study determined the high prevalence of hypothyroidism (40.2%) among patients with cystinosis, particularly in older individuals, those with a positive family history of the condition, and those experiencing renal impairment. Furthermore, the rate of hypothyroidism appears to increase with delays in both the diagnosis of cystinosis and the initiation of cysteamine treatment. To mitigate the burden of hypothyroidism in cystinosis patients, several recommendations are proposed. Firstly, there is a pressing need to educate primary healthcare providers, particularly those working in antenatal care units, to advocate for early neonatal screening, especially among individuals with a positive family history of cystinosis. Early detection through screening could significantly contribute to the prevention and management of hypothyroidism in cystinosis patients. Secondly, initiating treatment as early as possible is paramount in mitigating endocrine complications associated with cystinosis. Additionally, regular screening for hypothyroidism and prompt initiation of thyroxine treatment are strongly recommended to ensure timely management of this condition. Lastly, further extensive studies with larger sample sizes are recommended across various medical centers in Iraq to provide researchers and policymakers with a comprehensive understanding of the prevalence and impact of hypothyroidism in cystinosis within the country. These measures collectively aim to enhance the management and outcomes of cystinosis patients, particularly concerning the development of hypothyroidism.

Author contributions

K.M.A., Z.H.I. contributed to the developed the concept and the design of the study, analyzed the data, and wrote the draft of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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