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Prevalence Of Hypothyroidism In Cystinosis In Al-Ramadi Teaching Hospital For Maternity And Children

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Abstract

The endocrine organs are frequently affected in cystinosis, and these are often the organs of the patient under good care with cysteamine. Thyroid disease happens after kidney disease, and manifests in about half (50%) of untreated children by the age of 5-10 years old. The exact causative link between cystinosis and hypothyroidism remains unexplained. The aim of our study to estimate the prevalence of hypothyroidism in patients diagnosed with cystinosis and to find the possible associated factors that increase the possibility of hypothyroidism in patients with cystinosis. Our subjects and Method this was a cross sectional study that was conducted in Pediatric Department at Al-Ramadi Teaching Hospital for maternity and childhood in Iraq during a period of six months from November 2021 till the end of April 2022. It included 92 patients who diagnosed with cystinosis and collected from the archive files. Thyroid dysfunction was considered if patient's thyroid hormones is out of reference. Main results in this study, forty-point two percent (40.2%) of cystinosis patients were diagnosed with hypothyroidism. Prevalence of hypothyroidism was significantly increasing with increasing in age of patients and age of diagnosis of cystinosis to reach eighty-five-point seven percent (85.7%) and eighty-seven-point five percent (87.5%) at ages > 10 and > 2 years respectively. Higher prevalence of hypothyroidism was seen significantly in those with family history of cystinosis. The conclusion Prevalence of hypothyroidism is high forty-point two percent (40.2%) in patients with cystinosis. Hypothyroidism happens more frequently in older cystinosis patients, in those with positive family history of cystinosis and in those suffering from renal impairment. Rate of hypothyroidism is increased in case of delay in diagnosis of cystinosis or delay in cysteamine intake.

Keywords: *Cystinosis, hypothyroidism, prevalence, pediatrics, west of Iraq.*

INTRODUCTION

It's now termed "cystinosis", which was derived from the German "Cystindiathese" or "hereditary cystine disease" which, at first in 1903, Emil Abderhalden applied to it (it became "cystine disease" and later "cystinosis" in English). Cystinosis is a lysosomal storage disease with an autosomally recessive inheritance that manifests as a chronic excess of cystine, the oxidised doublet of the amino acid cysteine (1). Cystinosis is the most frequent cause of Fanconi syndrome in children (2).

They've identified three types of cystinosis depending on the age at diagnosis and the extent of cellular cystine build-up: infantile, teenage and adult. Patients with infantile nephropathic cystinosis become symptomatic early in life, and end-stage kidney failure occurs by late childhood, if left untreated. There are

many treatments for cystinosis, such as the cystine depleting drug cysteamine, kidney replacement therapy, hormone therapy and so on, but no curative remedy is known (3).

Etiology and Pathophysiology

Obscured protein travels to the lysosome, where acid hydrolases reduce it into its components amino acids such as cysteine. Cysteine is easily oxidised to cystine in the lysosome. In healthy patients, cystine and cysteine are both normal carriers into the cytoplasm where cystine is converted rapidly to cysteine by the reducing enzyme glutathione. Due to a cystinosin defect, cystine is not allowed out of the lysosomes, but accumulates there as birefringent, hexagonal or rectangular crystals in cells of all organ systems. The nephropathic infantile variant of cystinosis, where cystine crystals settle in the cells of the proximal tubules and manifest as Fanconi syndrome at 6-12 months of age, involves the kidney being destroyed early in life. Cystinosis arises from bi-allelic changes in the CTNS gene (systinosin,lysosomal cystine transporter 17p13.2) that encodes cystinosin, a lysosomal cystine-proton co-transporter. As a result, cystine accumulates in the lysosomes of diseased cells and crystallises under low lysosomal pH (6). The most frequent pathogenic mutation is a 57-kb deletion that occurs in nearly 50 per cent of CTNS mutant alleles in patients of North European and North American descent, but outside these regions the mutation is virtually nonexistent, particularly in the Middle East. Strong or truncating mutations in either of the two alleles are generally associated with infantile severe disease, and juvenile and ocular cystinosis are usually associated with at least one mild mutation (7, 8).

Epidemiology

In the country, birth prevalence data for cystinosis are available only in small groups. The infantile rate of nephropathic cystinosis in North America is 1 per 100,000-200,000 live births (9); there are approximately 400 people with cystinosis in the United States. Around 15 cases of cystinosis are diagnosed each year in the United States. The combined incidence rates for France, Australia, Germany, Denmark and Sweden were 1: 167,000, 1: 192,000, 1: 179,000, 1: 115,000 and 1: 260,000 live births, respectively (10). It is at higher incidence in selected populations with founder mutations identified than in Brittany, France (1: 26,000 live births). Our severance rate was the lowest ever recorded, among Pakistanis in the UK's West Midlands (1: 3,600). It has often been said that cytostinosis is the illness of Europeans with fair skin, but it has also been found in blacks, Hispanics and other races around the world. Male-to-female ratio of cystinotic children was 1.4:1(3). Because cystinosis is autosomal recessive, its prevalence should depend on how much consanguinity exists in the population. Unfortunately, we do not have reliable statistics on the prevalence of cystinosis in high consanguinity countries including the Middle East and North Africa (11).

Clinical presentation

I. Renal manifestations

- Three different clinical syndromes of cystinosis can be differentiated according to the age at diagnosis and severity of renal disease. The neonatal nephropathic cystinosis shows renal Fanconi syndrome and progressive glomerular loss, culminating in end-stage renal failure. Asymptomatic aminoaciduria is the first symptom of renal Fanconi syndrome in humans, where the urinary loss of amino acids is 6 to 16 times greater than normal (6).
- Infants arrive with failure to thrive, polyuria, polydipsia, episodes of dehydration and electrolyte loss, vomiting, constipation, and occasionally vitamin D resistant rickets. – Hypokalemia, metabolic acidosis, hypophosphatemia, hypocalcemia, low carnitine and, less commonly, hyponatremia can be present in the lab. But metabolic alkalosis, in the event of a Bartter-like syndrome, has also been observed (12).

- At birth, patients have normal birth length and weight. By 6–12 months, height declines to the third per centile, and more growth is constrained to fewer than 60 per cent of average (13). Calcium / phosphaturia along with phosphate, calcium, vitamin D and alkalinizing agents supplementation in some patients may lead to medullary nephrocalcinosis and nephrolithiasis. Glomerular proteinuria: This starts early and is defined by high-albumin and high-molecular-weight proteins that accumulate in the urine to the nephrotic threshold (14).
- Late onset cystinosis patients (late teenage years) can have a varied spectrum, from single asymptomatic proteinuria, a mild renal Fanconi syndrome to an overt nephrotic syndrome, and typically do not exhibit significant growth retardation.
- Adult, non-nephropathic ocular cystinosis is a light-sensitive condition characterised only by corneal cystine crystallisation, rarely developing before adulthood (3, 14).

II. Extra-renal manifestations

1. Eye

Corneal cystine build-up with crystal formation is the first extra-renal abnormality in all cystinosis patients. It can cause photophobia and blepharospasm generally from midchildhood through early adolescence. Despite superficial punctate and filamentary keratopathy occurring predominantly in adolescents and adults, band keratopathy, peripheral corneal neovascularisation and posterior synechiae causing thickening of the iris occur mainly in the elderly (15). Pulsatile retinal depigmentation by pigment epithelial mottling is a common posterior segment complication. Retinopathy causes retinal blindness in 10–15 per cent of patients (16, 17).

Bone and Muscle

Increased urine loss of phosphate, calcium and deficiencies in the biochemistry of vitamin D lead to hypophosphatemic rickets in cystinosis. Genua vara, bossing, rachitic rosary, and metaphyseal widening on skeletal X-rays are clinical symptoms (18).

2. Neurology

Neurocognitive decline is caused by the accumulation of cystine crystals in the brain. In the first traces of brain involvement, we find a pattern of nonverbal learning deficits with weak executive functioning, while verbal and general intelligence levels are average (19).

Cysteamine can also cross the blood–brain barrier. By reducing cysteamine loss treatment can improve neurological function in pre-symptomatic patients but visual-motor function is impaired even when cysteamine was administered before the neurologic symptoms were apparent (20).

Endocrinology

Slowly accruing cystine and crystals in the follicular cells leads to fibrosis and atrophy of the thyroid and ultimately primary hypothyroidism in most cystinosis patients (50–70 %) during their second decade of life(19). Previous thyroid modifications involving thyroglobulin production and iodo-thyroglobulin processing may explain subclinical hypothyroidism with elevated TSH and normal T3 and T4 levels in the blood (21). Hypogonadism is another common finding. Male cystinosis patients are likely to become infertile due to azoospermia despite taking cysteamine from an early age. We have already discovered that testicular spermatogenesis is possible without disruption. What actually works is not yet understood (22). Recently a successful conception via percutaneous epididymal sperm aspiration with intracytoplasmic sperm injection was

described (23). Female cystinosis patients can conceive, and several healthy pregnancies have been reported. Other endocrine organs affected are exocrine and endocrine pancreas which causes diabetes mellitus in 5% of all patients (18). Possible symptoms and disease presentations of nephropathic cystinosis are presented in the figure below (4).

Diagnosis

Laboratory studies

The gold standard now is elevated cystine in white blood cells, which is extremely sensitive and specific to the disease.

Molecular detection of the rather microscopic CTNS gene is also a well-known method for discovering 95 % of disease causing mutations (1).

Blood gas and serum electrolyte evaluations detect acidosis and severe hypokalemia, hyponatremia, hypophosphatemia, low bicarbonate level in patients with cystinosis (24).

Other studies in diagnosis of patients with suspected cystinosis: (3, 24)

• Slit-lamp exam of the eyes: Corneal and conjunctival crystals (pathognomonic).

• Funduscopic examination: Potential presence of peripheral retinopathy that is more severe on the temporal side than the nasal side.

• Kidney biopsies and histological examination: Variability is dependent on stage of disease.

Imaging studies: [25]

• Renal ultrasonography: performed in patients with elevated urine calcium excretion to rule out nephrocalcinosis.

• Renal, Urterine, Bladder imaging: Diagnosis of possible urinary tract calcification in hypercalciuria or edema due to abdominal discomfort.

• Computed tomography and magnetic resonance imaging: Evaluation of adult infantile nephropathic cystinosis with central nervous system symptoms in infantile nephropathic cystinosis.

Management

Best-practice symptomatic control of renal Fanconi syndrome and extra-renal complications with cystamine, the targeted cystine-depleting therapy, is the cornerstone of cystinosis therapy. An early diagnosis is critical for the prevention of cystinosis, because the introduction of appropriate therapy allows for faster growth and avoids ESRD and most additional renal problems (26).

Symptomatic treatment

- Symptomatic, prophylactic treatment for cystinosis will ensure sufficient fluid- and electrolyte substitution and maintain acid–base balance, nutrition support, rickets avoidance, and adequate replacement of needed hormones (1).

Electrolyte replacement is achieved through oral administration of sodium bicarbonate or sodium/potassium citrate. Replace with sodium or potassium phosphate and 1–25-(OH)2 cholecalciferol beginning from infancy to correct the phosphate imbalance and avoid rickets in those with a low GFR (27).

ACE inhibitors are a popular drug to decrease glomerular origin proteinuria and prevent slowing down of glomerular filtration rate in chronic renal failure, For renal failure, the only effective therapy

is renal transplantation (28).

Ophthalmologic diseases are asymptomatic and induced with cystine-sucking drugs:

Photophobia involves crystallisation, inflammatory cell invasion, and nerve inflammation within the cornea. It is managed by avoiding the sun, wearing dark sunglasses, and moisturizing the eyes with over-the-counter eye drops (17).

If untreated with eye drops, patients will occasionally experience corneal ulceration and need a corneal transplant. A topical treatment is needed even following corneal transplantation since cystinosin-resistant host cells can repopulate the transplanted cornea (4).

Systemic Depletion Therapy

Cysteine-depleting therapy using cysteamine first was reported in 1976 and is the gold standard for cystinosis therapy to this day (19). Continually and faithfully administering cysteamine helps to prevent or delay ESRD and hypothyroidism, promotes growth, and depletes muscle parenchyma of cystine (30).

We should begin cysteamine therapy as soon as possible after diagnosis to facilitate kidney development and the acquisition (not elimination) of renal function (31).

Cysteamine is administered every 6 hours at 60 to 90 mg free base per kg per day (1.3 to 1.95 g/m2/day). But for children and adults the dose is lowered to keep leukocyte cystine (measured 5-6 hours after a dose) below 1.0 nmol half-cystine/mg protein (31) as low as possible (optional).

Procysbi (cysteamine bitartrate) is a delayed-release capsule designed for patients six years and over. You take a dose of Procysbi every 12 hours. Procysbi was no better than Cysteamine at lowering cystine levels (by blood tests) (32).

Nasal and vomiting are side effects of the cysteamine medication, partially due to the unpleasant odour and taste. Cysteamine stimulates gastrin production and gastric acid production. Oral cysteamine treatment could be improved with omenprazole (31).

Despite the best efforts of oral cysteamine therapy, 0.34% cysteamine hydrochloride eye drops or (cysteamine ophthalmic solution) are necessary to achieve adequate tissue concentration to remove corneal crystals. Cysteamine eye drops are administered 10 to 12 times a day as 0.55% solution with benzalkonium chloride 0.01% used as a preservative.

Hypothyroidism in cystinosis

Endocrine organs are frequently affected in cystinosis, particularly in those patients who don't receive adequate cysteamine therapy. Thyroid illness is chronologically related to kidney disease, and manifests in half of untreated children by 5-10 years of age (33). In 1970, Chan et al reported first-degree primary hypothyroidism in cystinosis, and histologically analysed the thyroid gland for cystine crystals and fibrosis. Biochemically, hypothyroidism generally presents with high TSH but normal T4 (subclinical disease) and can become progressively severe hypothyroidism over years, where thyroxin supplementation is advised (33). It appears that the cause of thyroid dysfunction is a little more complicated than thyroid gland destruction by lysosomal cystine. Notably, cysteamine therapy prevents hypothyroidism in most cystinosis patients, indicating that cystine accumulation plays a critical role in thyroid disease (33, 34).

Mechanisms for thyroid alterations in infantile Cystinosis

Cystinosin is a 7-transmembrane protein of 367 amino acids with two major lysosomal targeting reasons, and is the only lysosomal membrane cystine exporter that has been shown to act via coupled proton efflux

(35). Cystine is a mandatory end-degradation byproduct of disulfide-containing proteins. Cysteine exported from lysosomes gets quickly converted into cystine by cytosolic reducing machinery. Cysteine and glutamate cooperate to form glutathione, and so, regulate redox homeostasis in cells. This lysosomal cystine build-up is corrected in cystinosis with substrate depletion therapy consisting of oral cysteamine, but the regimen is extremely gruelling. Cysteamine and cystine symbiose in lysosomes to form a mixed disulfide that flows out through the lysine transporter (36).

The precise causal relationship between cystinosis and hypothyroidism is unknown. With respect to the kidneys, impaired thyroid was once explained by pathognomonic cystine crystals atrophy. Yet, crystals are not pathogenic, and early impairment of proteolysis in cystinotic lysosomes has also been observed and suggested to be due to lysosomal redox imbalance (21). Thyroid hormones (THs) are secreted in lysosomes through proteolytic degradation of the phagocytic thyroglobulin (Tg), though protease may also begin within the follicular lumen. Tg is an oligomer of monomers (330-kDa), which assume a tightly packed globular shape surrounded by vastly increased amounts of disulfide bonds (>100/monomer). Tg is dimerised in the ER, and then collapsible in the follicular lumen via intermolecular disulfide cross-linking into insoluble thyroid globules for maximum storage (38). Extrinsic [secreted protein disulfide isomerase (PDI)] and intrinsic disulfide bond exchange [through conserved thioredoxin motivations] account for luminal compactness. The degree of luminal Tg cross-linking is varying from species to species and is dependent on age and follicle activation state (38). Tg folding through disulfide bond reduction by lysosomal reducing substitutes therefore seems to be needed to reveal secret peptides for lysosomal proteases. Stepwise Tg proteolytic reactions depend on co-dependent endo- and then exopeptidases, such as the aspartyl protease, cathepsin D, and the cysteine proteases (cathepsin B), and even the cysteine proteases need a reductative state. Such demands would predict that Tg unfolding and cysteine protease attack were suppressed when lysosomal cystine loading led to redox imbalance (21). In the absence of TSH, basal TH production is also aided by Tg endocytosis out of the colloid via small endocytic pits. This is controlled through expression and activation of tandem rate-limiting GTPase catalysers, Rab5 and Rab7, together coordinating vesicular transport to lysosomes (39). Interestingly, in mice, acute stimulation at a high TSH dose results in micrometric colloid uptake via actin-dependent lamellipodia projection followed by micropinocytosis, or phagocytosis: large amounts of Tg being transferred to lysosomes in colloid droplets. How released THs cross the lysosomal membrane isn't known. This process might include a transporter analogous to monocarboxylate transporter-8 (Mct-8) at the basolateral membrane, for secretion into blood capillaries. But a Mct-8 defect is unlikely in a monogenic disease like cystinosis (21, 40).

Aim of study

1) To estimate prevalence of primary hypothyroidism in patients diagnosed with cystinosis.

2) To find the possible associated factors that increase the possibility of hypothyroidism in patients diagnosed with cystinosis.

PATIENTS AND METHODS

Study Design, setting and data collection time

This was a cross sectional study that was conducted in Pediatric Department at Al-Ramadi Teaching Hospital for maternity and childhood during a period of six months from November 2021 till the end of April 2022.

Study patients and sample size

The study included collection of data from the archive files in cysteine unit involving all patients who were diagnosed with cystinosis. The total number of patients included in this study was 92.

Data collection tool

A data form had been applied to all study patients to collect needed information. It included questions to gather demographic information such as:

- ✓ 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.
- ✓ Complications (Hypothyroidism and renal failure).

Diagnosis of hypothyroidism

The normal level of T3, T4, and TSH was determines according to age. Thyroid dysfunction was considered if patient's thyroid hormones is out of reference range as shown in table (2.1):
Simultaneous T4 and TSH measurements was done for screening method to diagnose hypothyroidism.

Table 2.1: Normal range of thyroid function tests by age [41]

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		

Ethical approval

• Pediatric department Al-Ramadi Teaching Hospital for Maternity and Child Development granted the permission to obtain necessary data from the archive files. None of the information's was anonymous. Identities replaced the names with codes. All data stored confidentially in a password protected laptop and used for the sole purpose of the research.
• Written informed consent was obtained from parents for study purposes.

Statistical analysis

Data was analysed by SPSS version 26. Data as mean, standard deviation and range. Frequency and percentage of categories data. A two-tailed independent t-test was used to evaluate the continuous variables accordingly. The association between prevalence of hypothyroidism and some of the information was tested using the chi square test. P – value less than 0.05 was deemed significant.

RESULTS

The total number of study patients was ninety-two (92). All of them were diagnosed with cystinosis.

General characteristics

The studied patients' ages ranged from 10 months to 18 years, with a mean of 5.71 years and a standard deviation of ± 3.7 years. The highest proportion of study patients was aged between 5 – 10 years (46.7%). (Figure 3.1) Regarding gender, the proportion of males was higher than females (55.4% versus 44.6%) with a male-to-female ratio of 1.24:1. (Figure 3.2)

In this study, 46.7% of patients were diagnosed with cystinosis before the first year of life, 50% of them had consanguinity, and 25% had a positive family history of cystinosis.

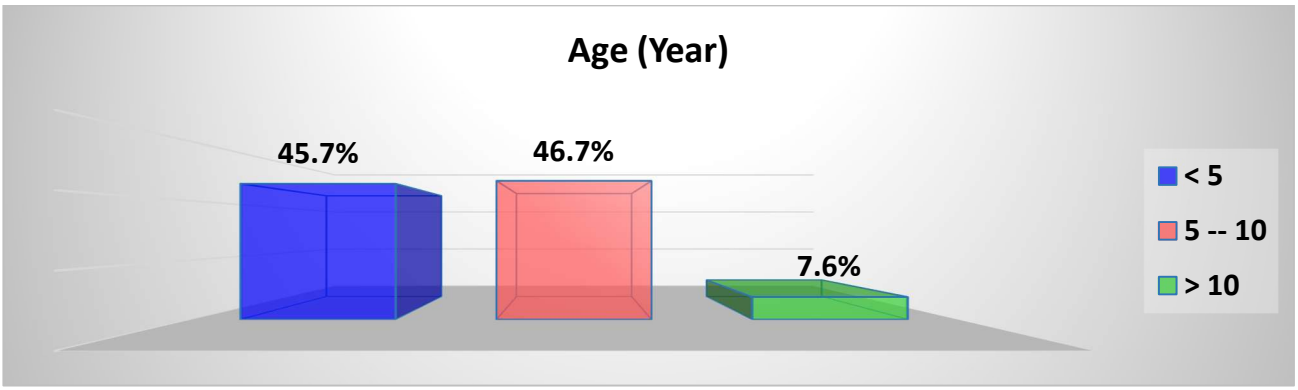

Figure 3.1: Distribution of study patients by age

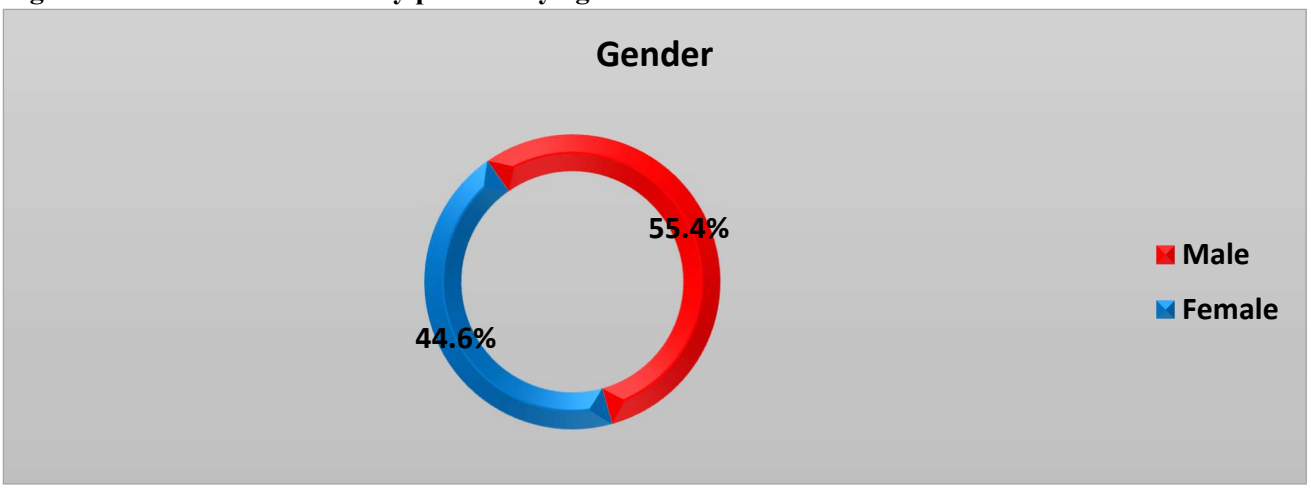

Figure 3.2: Distribution of study patients by gender

Table 3.1: Distribution of study patients according 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

Clinical information

Table 3.2 shows the distribution of study patients by clinical information. We noticed 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.

Table 3.2: Distribution of study patients according 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

Hypothyroidism

In this study, 40.2% of cystinosis patients were diagnosed with hypothyroidism by screening as shown in figure (3.2).

All patients with hypothyroidism received thyroxine treatment and 54.1% of them diagnosed as hypothyroidism after sixth year of age as shown in table (3.3).

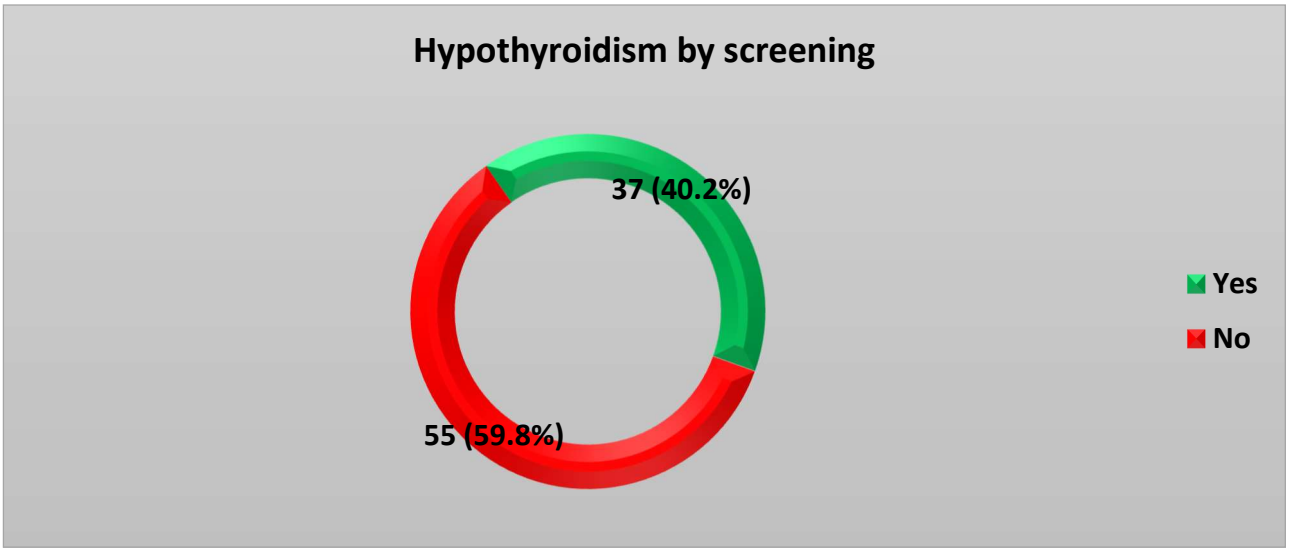

Figure 3.3: Prevalence of hypothyroidism among cystinosis patient

Table 3.3: 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 3.4 shows the association between the prevalence of hypothyroidism and general characteristics. The prevalence of hypothyroidism significantly increased with increasing age of patients and age of diagnosis of cystinosis, reaching 85.7% and 87.5% at ages > 10 and > 2 years, respectively. The highest prevalence of hypothyroidism was seen significantly in those with a family history of cystinosis (60.9%, P= 0.019).
No statistically significant association was detected (P ≥ 0.05) between hypothyroidism and both gender and kinship.

Table 3.4: 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 3.5 shows the association between the prevalence of hypothyroidism and clinical characteristics. The prevalence of hypothyroidism significantly increased with the delay in starting Cysteamine one treatment, reaching 88.5% at age > two years (P= 0.001) and increased with renal impairment (88.9%, P= 0.001).

Table 3.5: 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)	

DISCUSSION

The current study enrolled 92 patients, all of whom 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 were diagnosed with hypothyroidism after six years of age.

In comparison to other studies, Hypothyroidism was reported in 20% of patients enrolled in the Hussein et al. study in 2018 [42]. 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 [43]. Moreover, Keser et al. study in 2014 concluded that endocrinologic complications of cystinosis can be seen in the pediatric population, as they found that 23.8% of patients had overt hypothyroidism and 23.8% had subclinical hypothyroidism with only elevated TSH levels [44]. A different result was observed in the 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 [45].

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

Different results were published in the Hussein et al. study in 2018, in which they found a statistically very highly significant relationship between hypothyroidism and the Kurdish ethnic group (P <0.001), while no relation to age or gender was observed (P>0.05) [42].

Moreover, the current study observed that the prevalence of hypothyroidism was significantly increasing with delayed 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).

Different findings were observed than Brodin-Sartorius et al.'s study, with hypothyroidism significantly reduced when cysteamine was initiated before age five compared to no intervention. Even 5-year treatment significantly lowers hypothyroidism rates compared with untreated (45). In contrast, Vaisbich et al. observed that initial therapy was significantly correlated with lower rates of hypothyroidism and increased delay in these conditions. Additionally, chronic (8 years) cysteamine therapy prevents the development of hypothyroidism in cystinosis patients (46). Also, Gahl et al. reported the rate of hypothyroidism went up significantly over time without treatment and down considerably with treatment (P0.05) (29). At last, in their review, Ariceta and colleagues stated that prompt diagnosis of cystinosis and proper lifetime administration of cysteamine were needed to prevent end-organ damage and increase the overall prognosis for these patients. They determined that a prompt start to therapy and high compliance with treatment significantly reduce the incidence and severity of extra-renal complications (47).

The explanation for the differences reported above can be attributed mainly to the different sample sizes in each study; it may also relate to the various durations of disease, severity, duration of drug onset, and the type of intervention used in each study. Genetic factors are also significant because low rates among patients with a good family history may result from inadequate medical counseling and antenatal and postnatal screening tests. It didn't become diagnosed until too late because of its unusual symptomatology and the absence of diagnostic tests based on genetics. Also, there were earliest issues owing to deficiencies in specific drugs.
Thyroid dysfunction is a little more intricate than thyroid cancer, which is caused by lysosomal cystine. Rapid thyrocyte turnover accompanied by cell growth plus increased apoptosis under endoplasmic reticulum stress leads to decreased TH production and reduced endolysosomal trafficking and iodoflouroglum processing in early disease, as recently observed in the knockout mouse model of cystinosis (48). As evidence for cysteamine benefits and increased life expectancy for most patients has mounted, there is a rising interest in optimizing patient care regarding extra-renal disease manifestation, medication compliance, and adult care (47).

Overall, however, not only is the systemic aspect of cystinosis problematic, but it usually occurs in adolescence, making things worse. The transition of adolescents from child to adult care is poor, primarily if the disease is poorly understood, as it's rare (49).

Clinical information

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.

Compared to other studies, a different result was observed in the O'Connell et al. study 2022, which 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) [50]. Differently, the Brodin-Sartorius et al. study reported that cysteamine therapy was administered to 75 of 86 patients (87%) who 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). 55.8% of patients started cysteamine therapy before eight years, 1.1% began between eight and 15 years, and 31.3% started after 15 years [45]. Furthermore, end-stage renal disease is one of the significant complications that occurred in 12% of patients enrolled in the Hussein et al. study [51], which is close to that observed by the 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 [43].

One explanation for the differences may be that, in addition to the different sample sizes, most of them develop end-stage renal disease in their second or third decades of life [52].

A rapid diagnosis of cystinosis provided early access to a well-rounded, supportive treatment. In contrast, Treatment compliance with cysteamine is shoddy for two reasons. First, oral doses must be given every 6 hours due to the drug's pharmacokinetics. Second, nausea and halitosis are common side effects (45). By releasing cystine from the lysosomes, cysteamine succeeds in the leading role played by missing cystinosis but doesn't substitute for cystinosis. Even if cystine levels in white blood cells are low. Further, the fact that cysteamine fails to alleviate the proximal tubulopathy indicates that the physiopathology of cystinosis is not as simple as one might imagine and that cystinosis has other functions that remain to be determined (53).

General characteristics

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

Regarding gender, the 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 a positive family history of cystinosis. Compared to other studies, 74 patients were included in the O'Connell et al. study in 2022. A sight male predominance (52.7%) was reported, with a male-to-female ratio of 1.1:1.

The age of patients varied by the mean and SD between them: 11 2.3 years (50). By way of illustration, 50 cystinosis patients in the Florenzano et al. study in 2020 were 29 men (58%), with a 1.3:1 male to female ratio, with a median and SD of age of 14 4.3 years range 2–28 years (37). In the Hussein et al. (2018) study, they enrolled 25 cystinosis patients; 52% of them were female, and the ratio of female to male was 1.08:1; patients' ages ranged from 1 to 12 years with mean 6.25 4.3 years; 4 percent 11 months; 32% 13 months-5 years; and 64 percent over five years. 80% of patients also had positive consanguinity. Additionally, there was an overall 76% good family background (51).

However, Brodin-Sartorius et al. reported that: Of the 86 cystinotic patients, nearly an equal percentage were males (51.1%), males to females (1.04:1), with 12 patients in consanguineous families—average and mean age

at diagnosis: 2.2 4.4 (0.5–11.6 yr) (45)

Most of the variation between the above studies was due to several factors, including sampling and study design and some genetic or ethnic. The disease's family background will likely make cystinosis also occur, together with positive parental consanguinity, since inheritance is autosomal recessive. Among other variables were the subjects' education level and the participants' socioeconomic status, which controlled their attendance at diagnosis and follow-up for the disease.

CONCLUSION AND RECOMMENDATIONS

Conclusions

- ❖ Prevalence of hypothyroidism is high (40%.2) in patients with cystinosis.
- ❖ Hypothyroidism happens more frequently in older cystinosis patients, in those with a positive family history of cystinosis, and those suffering from renal impairment.
- ❖ Rate of hypothyroidism is increased in case of delay in diagnosis of cystinosis or delay in cysteamine intake.

Recommendations

1. Primary health care physicians (especially those who work in ANC units) should be encouraged to advise attendants on early neonatal screening for the risk of cystinosis, especially for those with a positive family history. This can help prevent and control hypothyroidism in cystinosis.
2. We recommend starting treatment early to decrease endocrine complications.
3. Regular screening for hypothyroidism and early start of treatment with thyroxine is highly recommended.
4. more extensive studies with larger sample sizes are recommended for other centers in Iraq to give researchers and policymakers a general idea about the magnitude of this problem in Iraq.

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