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Difficulties in the Diagnosis and Management of Nephropathic Cystinosis

Nefropatik Sistinozis Olgularında Tanı ve Tedavide Karşılaşılan Zorluklar

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ABSTRACT

Objective: Nephropathic cystinosis is the most severe form of cystinosis and usually leads to end stage renal disease in late childhood. We aimed to investigate the clinical and laboratory findings, therapeutic and diagnostic difficulties and prognosis of patients with nephropathic cystinosis.

Material and Methods: The medical records of fifteen patients who were diagnosed as cystinosis between 1996 and 2012 were retrospectively evaluated.

Results: The mean age of the patients was 31.8±35.9 months (6-144 months). 11 (73.3 %) had parental consanguinity. Polyuria, polydipsia and failure to thrive were the most common features. Mean glomerular filtration rate (GFR) was 47.6±29.9 ml/min/1.73 m2 (6.30-100) at admission. Corneal cystine crystals were detected in 12 (80 %) of the patients. We measured leukocyte cysteine levels in only three patients and found it above normal limits. During follow up, 10 patients developed chronic kidney disease (CKD) and three of them reached end-stage renal disease (ESRD). Two of the patients were lost to follow up.

Conclusion: There are still many technical and financial problems in the diagnosis and management of cystinosis in our country. Efforts should therefore be directed towards the avoidance of consanguineous marriages to decrease the incidence of the disease.

Key Words: Children, Chronic kidney disease, Cystinosis

ÖZET

Amaç: Nefropatik sistinozis, sistinozisin en ağır formudur ve genellikle geç çocukluk çağında son dönem böbrek hastalığı ile sonuçlanır. Çalışmada nefropatik sistinozis tanısı ile izlenen hastaların klinik ve laboratuvar özellikleri, tanı ve tedavide karşılaşılan güçlükler ve prognozunun değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Kliniğimizde 1996-2012 yılları arasında nefropatik sistinozis tanısı ile izlenmiş olan 15 hastanın dosyaları geriye dönük olarak incelendi.

Bulgular: Hastaların yaş ortalaması 31.8 ± 35.9 ay (6-144 ay)'dı. 11 (% 73.3) hastada akraba evliliği saptandı. Poliüri polidipsi ve gelişme geriliği, en sık görülen bulgulardı. Başvuruda ortalama glomerüler filtrasyon hızı (GFH) 47.6 ± 29.9 ml / dak / 1.73 m2 (6.30-100) idi. Korneal sistin kristalleri hastaların 12(% 80)'sinde vardı. Üç hastada lökosit içi sistin düzeyine bakıldı ve üçünde de yüksek saptandı. Takip sırasında 10 hastada kronik böbrek hastalığı (KBH) gelişti ve bunların da üçünde son dönem böbrek hastalığı (SDBH) gelişti. İki hasta ise takipten çıktı.

Sonuç: Nefropatik sistinozis tanı ve tedavisinde ülkemizde halen teknik, sosyal ve finansal problemler mevcuttur. Bu nedenle özellikle de hastalığın ortaya çıkışını azaltabilmek amacıyla akraba evliliklerinin önlenmesine yönelik çaba sarfetmek gerekmektedir.

Anahtar Sözcükler: Çocukluk çağı, Kronik böbrek hastalığı, Sistinozis

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INTRODUCTION

Cystinosis is a rare autosomal recessive disorder due to impaired transport of cystine out of cellular lysosomes. The responsible gene CTNS is located on the short arm of chromosome 17 and it encodes the lysosomal cystine carrier cystinosin (1). There are three different clinical forms of cystinosis depending on the severity of the disease and age at presentation: the nephropathic infantile form is the most severe and common form and usually leads to end-stage renal disease; the nephropathic juvenile form is diagnosed in the minority of the patients and most of the patients are diagnosed older than 10 years; and the adult or ocular nonnephropathic form manifests only with photophobia due to cystine accumulation in the cornea (1).

Infantile nephropathic cystinosis (NC) usually presents in the first year of life with early-onset Fanconi syndrome (2). Polyuria, polydipsia, failure to thrive, growth retardation, periods of dehydration and rickets are the most common clinical findings in these patients. Hypokalemia, hypophosphatemia, metabolic acidosis, low serum uric acid, low carnitine and hyponatremia are the characteristic biochemical features of the disease (1). The glomerular filtration rate (GFR) usually remains normal up to 2 years and then progressively decreases and end-stage renal disease (ESRD) develops at the end of the first decade (3). Both haemodialysis (HD) and peritoneal dialysis (PD) are suitable for renal replacement therapy (1). As cystinosis does not recur in the grafted organ,transplantation is the treatment of choice for patients with ESRD (4).

In this retrospective study we reviewed the outcome of 15 patients with NC who had been followed in our nephrology clinic between 1996 and 2012. We evaluated the clinical and laboratory findings and prognosis and we tried to detect the difficulties in the diagnosis, management and follow up. Although the prognosis of NC has improved due to introduction of treatment with cysteamine, a drug tht allows cystine clearance from the lysosomes (5, 6), there are still many problems including technical, social and financial difficulties in the diagnosis and management.

MATERIAL and METHODS

We retrospectively analysed the medical records of 15 children who were diagnosed as cystinosis between January 1996 and January 2012 at the Department of Pediatric Nephrology, Dr Sami Ulus Childrens' and Maternity Hospital. Clinical and laboratory data, treatment strategies, prognosis and complications related to NC were obtained from the hospital charts. The diagnosis of cystinosis was based on clinical findings and detecting cystine crystals on ophthalmological examination or bone marrow aspiration. We were able to measure intraleukocyte cystine (ILC) levels in only three of our patients. As soon as the diagnosis was established, specific treatment with systemic cysteamine and topical eye drops containing cysteamine and supportive treatment with potassium citrate, vitamin D preparations, and phosphate solution were started. Oral cysteamine was started at a dose of 1.3 g/m^2 and then increased during four weeks to a maximum dose of 1.9 g/m^2 when necessary. Eye drops containing cysteamine were used 12 times daily.

GFR was calculated by the Schwartz formula. Chronic Kidney Disease (CKD) was defined as structural or functional abnormalities of the kidney with or without decreased GFR indicated by one of the following: abnormalities in kidney biopsy or imaging tests or the composition of the blood and/or urine; or GFR <60 ml/min/1.73 m^2 for ≥3 months (7); and end -stage renal disease (ESRD) was defined as GFR <15 ml/min/1.73 m^2 and the need for renal replacement therapy.

Statistical Analysis

We analyzed the data with the SPSS for Windows 11.5 software package program (Chicago, IL) and expressed data as mean ± standard deviation.

RESULTS

Clinical and Demographical Findings

Fifteen patients consisting of 7 females and 8 males were enrolled in the study. The mean age of the patients at the time of diagnosis was 31.8±35.9 months (minimum 6 months and maximum 144 months). Duration between symptoms and diagnosis was 12.43 months (minimum 0.5 months and maximum 48 months). 11 (73.3 %) of the patients had parental consanguinity. Four of these patients were siblings. One of them was born to a brother of our patient who had already been diagnosed as cystinosis. The other siblings were diagnosed simultaneously while under investigation for failure to thrive, polyuria and polydipsia.

The most common symptoms before diagnosis were polyuria, polydipsia, vomiting and failure to thrive. Growth retardation was observed in 14 (93.3 %) and findings of chronic kidney disease in 2 of the 15 (20 %) patients at admission. None of the patients had goiter on first examination. Corneal cystine deposition was detected in 12 of the patients (80 %).

Laboratory Findings

The most common laboratory findings were hypokalemia, hypophosphatemia, metabolic acidosis, hypocalcemia and hypouricemia that represented Fanconi syndrome. Increased phosphate levels and hyperuricemia were observed in patients with decreased GFR (hyperphosphatemia was observed in patients I, II, VI, IX, X and hyperuricemia was observed in patients I, II, X). Eleven of the patients had radiological signs of rickets and increased echogenicity was detected on ultrasonographic examination in all of the patients. Laboratory parameters at first presentation are summarized in Table I.

Treatment Strategies

Symptomatic treatment with potassium citrate was administered to 13 of the patients. Potassium chloride was used in two of the patients because of metabolic alkalosis as were treated as Bartter syndrome erroneously at first. All of the patients received vitamin D supplementation. Seven patients received phosphate solution. All of the patients were administered oral cysteamine and cysteamine eye drops as soon as diagnosis was established. Specific treatment was started before 2 years of age in 8 patients.

Hypothyroidism was observed in one of the patients during follow up and he was treated with L-thyroxine.

Prognosis

During follow-up, 8 of the 15 patients progressed to different stages of CKD.

Two of the patients (patient V and IX) were lost to follow up. One of these patients was in stage IV and the other one was in stage II CKD.

Patient II had been lost to follow up for five years after being misdiagnosed as Bartter syndrome because of metabolic alkalosis and normal ophthalmological and bone marrow examinations. At his second admission after five years, he had already developed CKD. He was transferred to the adult system during follow-up.

Patient VI, who developed CKD during follow -up was incompliant with treatment both because of financial problems of the social security system and also familial neglect. This patient died during follow-up because of severe pulmonary infection. Two of the patients (VII and VIII) also developed CKD because of familial neglect and incompliance with treatment.

Patient XII was under investigation for failure to thrive and she developed CKD during follow-up because of the delay in diagnosis and treatment.

Two of the patients (I, X) were already at end-stage renal disease at the time of diagnosis due to late admission because of social and financial problems. They were started on continuous ambulatory peritoneal dialysis (CAPD). Patient I continued on dialysis during follow-up and patient X was transplanted after 7 years on dialysis.

Patient XV was incompliant with the treatment. He was lost to follow–up for four years and when he returned to our clinic he was at CKD stage III. He reached ESRD during follow–up and he underwent preemptive living-donor renal transplantation.

The remaining five patients (patient III, IV, XI, XIII, XIV) were followed up with normal renal functions. Patient III was first diagnosed as Bartter syndrome because of metabolic alkalosis and normal ophthalmological examination. During follow-up she was reevaluated and the diagnosis of cystinosis was made. Patient XI was the brother of patient VI and patient XIII was the brother of patient XII. Both of the parents had consanguineous marriages. While patient XI was born as a sibling of our patient who was already diagnosed as cystinosis, patient XIII was diagnosed as cystinosis with his elderly sister simultaneously. The prognosis of the patients is summarized in Table II.

DISCUSSION

Nephropathic cystinosis is characterized by lysosomal accumulation of cystine leading to widespread tissue and organ damage (1). In the past, treatment of cystinosis was

Table I: Laboratory parameters of the patients at first presentation.

	Ca (mg/dl)	P (mg/dl)	Na (meQ/L)	K (meQ/L)	UA (mg/dl)	PH	HCO_3
I	4.7	16.5	129	4.67	15.8	7.38	12.2
II	6.7	7.2	136	3.1	8.1	7.37	11
III	11	4.17	121	3.19	2.87	7.51	26
IV	13.1	2.5	127	3.05	1.9	7.32	8.1
V	11.1	2	131	1.87	2.6	7.26	11.3
VI	6.72	11	128	3.47	1.08	7.39	15.8
VII	9.9	1.2	127	2.52	2.14	7.22	5
VIII	7.6	4.3	113.9	1.9	3.3	7.30	6.6
IX	6.99	11.9	127	4.93	3.2	7.15	6
X	7.7	7.29	135	2.91	7.63	7.41	16
XI	9.5	1.9	129	2.61	2	7.29	11.7
XII	6.1	3.6	135	3.94	4.1	7.26	11.6
XIII	9	1.6	135	3.65	1.7	7.24	10.1
XIV	9.47	2.59	132	2.56	1.55	7.24	16
XV	9.5	2	131	3.4	3.02	7.35	16.8

Ca: *Calcium,* ***P:*** *Phosphorus,* ***Na:*** *Sodium,* ***K:*** *Potassium,* ***UA:*** *Uric acid.*

Table II: Prognosis of the patients.

Patient number	Creatinine at admission (mg/dl)	GFR at first visit ml/min/1.73m²	GFR at last visit ml/min/1.73m²	CKD stage at last visit	Prognosis
I	7.35	6.3	6	V	Followed up in CAPD
II	1.86	60	35	III	Adult nephrology
III	0.68	94	90	-	Regularly followed up
IV	0.51	78	97	-	Regularly followed up
V	0.64	86	75	II	Lost to follow up
VI	0.8	65	25	IV	Died because of severe pulmonary infection
VII	0.7	85	40	III	Incompliance with treatment
VIII	2.23	40	24	IV	Incompliance with treatment
IX	3.1	30	25	IV	Lost to follow up
X	11.4	7	7	V	Transplanted from cadaveric donor after 7 years of CAPD
XI	0.23	86	95	-	Regularly followed up
XII	1	37.4	75	II	Regularly followed up
XIII	0.24	100	110	-	Regularly followed up
XIV	0.51	74	95	-	Regularly followed up
XV	0.8	80	10	V	Transplanted from living related donor

CKD: *Chronic kidney disease,* ***GFR:*** *Glomerular filtration rate,* ***CAPD:*** *Continuous ambulatory peritoneal dialysis.*

limited to treatment of metabolic acidosis and replacement of electrolytes lost in the urine. Today, the wide availability of an effective drug, cysteamine, and kidney replacement therapy with transplantation has dramatically improved the outlook for patients (8). Despite these advances in the treatment of nephropathic cystinosis, there are still many problems in the diagnosis and management of patients with cystinosis in our population including technical, social and financial difficulties.

The most important factor to improve renal functions in cystinosis is early diagnosis and treatment. Starting treatment with cysteamine before the age of 2 years is crucial for preventing deterioration of renal functions (8, 9) . One of the main problems for the management of cystinosis in our patient population is the delay in diagnosis and treatment. This may be related to lack of awareness of cystinosis among general physicians and to lack of diagnostic facilities. Duration between symptom and diagnosis was 12.43 months in our study. The mean age of our patients at the time of diagnosis is higher than the mean age of the patients in the study of Greco et al. (9) (31.8±35.9 months versus 21 months). Delay in diagnosis and treatment leads to the emergence of CKD earlier than expected as seen in two of our patients (patients I and X).

Cystinosis is an inherited autosomal recessive disorder so consanguineous marriages may increase the risk of affected children. Eleven of our patients (73.3%) were born to consanguineous marriages and the rate of affected siblings was 26. 6 %. The parental consanguinity rate in the general population in our country is reported to be around 20.9 % (10). Topaloglu et al. (11) reported the consanguinity rate as 72% and rate of affected siblings as 28.5% in a multicentric study for hereditary renal tubular disorders in Turkey. In contrast to our country, Greco et al. (9) reported that only two of 23 patients with cystinosis had parental consanguinity (8.6%).

Cystinosis is the most common hereditary cause of renal Fanconi syndrome and it must always be suspected when children present with polyuria, polydipsia, failure to thrive, vomiting and constipation (4). Mild albuminuria, overt glucosuria and low specific gravity are observed in the urine dipstick test. Diagnosis of cystinosis can be confirmed by performing these tests: measurement of leukocyte cystine levels, demonstration of corneal or conjunctival cystine crystals on slit lamp examination and genetic analysis of the CTNS gene (4). Diagnosis in our patient population was based upon clinical findings and demonstration of corneal cystine crystals. Because corneal cystine crystals may not be present until the age of one year, this might cause delay in diagnosis as observed in our study (1). Although measuring elevated leukocyte cystine levels is the cornerstone of diagnosis, we were able to measure intraleukocyte cystine levels in only three of our patients because of financial difficulties due to the social security system in our country (1, 4, 9). This was an important and challenging issue both for establishing the diagnosis and monitoring the treatment in our population. We could not perform genetic analysis in our study because genetic analysis of the CTNS gene was only available in our country after the year 2012 and all of our patients were diagnosed before this date (12).

In most patients with cystinosis, the glomerular filtration rate remains normal for up to 2 years (1). Renal function begins to decline after this age and without treatment ESRD develops at the beginning of first decade (4). Two of our patients (III and XIII) (13.3%) had a GFR above 90 ml/min/1.73 m^2. Both of these patients and three patients who had a GFR below 90 ml/min/1.73 m^2 at presentation had a normal GFR at their last visit. We attributed the low GFR in these three patients at their first presentation to dehydration. Two of our patients were at ESRD on admission and CAPD was started for renal replacement therapy. They were 7 years 5 months and 10 years 6 months old respectively. Diagnosis and treatment were delayed in both of these patients because of social problems and financial difficulties in the social security system. During follow-up, 8 patients also developed different stages of CKD and one of these also reached ESRD at the age of 14 years 3 months. This patient was incompliant with treatment and he did not come to his visits regularly.

Cystinosis remains a severe disease and ESRD cannot be prevented in most patients although it may be postponed to the second or third decade of life as presented in the study of Greco et al (9). They followed up their patients for a mean follow-up time of 17.6 years (6.3 -27.8 years) and they detected that most of the patients reached CKD stage III by the age of 10 years and > 80 % initiated dialysis by the age of 14 years. The age of two of our children who started renal replacement therapy (RRT) was younger than the patients in the study of Greco et al. (9) but the European Dialysis and Transplant Association Registry found that the median age of children starting renal replacement therapy for cystinosis was 9.5 years, ranging between 1 and 20 years (13). In a recent study of Van Stralen et al. (14), the authors detected that patients with nephropathic cystinosis started RRT more than 4 years later in the period of 2003 to 2008 when compared with 20 years earlier. They attributed this increased age for starting RRT to the introduction of cysteamine on a wide scale in Europe as stated in other studies (3, 5, 15).

Although the treatment of choice is renal transplantation, both hemodialysis and peritoneal dialysis are suitable for RRT in cystinosis patients (1, 4, 8). In the study of Van Stralen (14), the most frequent modality of RRT was PD (39.6 %) followed by renal transplantation (35 %). In concordance with this report, 16 of the 23 patients were transplanted in the study of Greco et al (9). Although the number of patients with ESRD is only three in our study, the modality of RRT is similar to the previous reports. The rate of preemptive transplantation is high in patients with cystinosis, and the authors attributed this issue to the long-term follow-up (14).

CONCLUSION

Considering the fact that early and diligent treatment with cysteamine delays renal deterioration, enhances growth and also prevent non-renal complications of cystinosis, we have to emphasize the importance of the prompt diagnosis and therapy, and also for our country, more efforts should be directed towards the prevention of the disease especially with avoidance of consanguineous marriages.

REFERENCES

1. Wilmer JM M, Schoeber JP, van den Heuvel LP, Levtchenko E. Cystinosis: Practical tools for diagnosis and treatment. Ped Nephrol 2011;26:205-15.
2. Gahl WA, Thoene JG, Schneider JA. Cystinosis. N Engl J Med 2002;347:111-21.
3. Markello TC, Bernardini IM, Gahl WA. Improved renal function in children with cystinosis treated with cysteamine. N Engl J Med 1993;328:1157-62.
4. Emma F, Nesterova G, Langman C, Labbe A, Cherqui S, Goodyer P. Nephropathic cystinosis: An international consensus document. Nephrol Dial Transplant 2014;29:87-94.
5. Gahl WA, Reed GF, Thoene JG, Schulman JD, Rizzo WB, Jonas AJ, et al. Cysteamine therapy for children with nephropathic cystinosis. N Engl J Med 1987;316:971-7.
6. Schneider JA, Clark KF, Greene AA, Reisch JS, Markello TC, Gahl WA. Recent advances in the treatment of cystinosis. J Inherit Metab Dis 1995;18:387-97.
7. Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines in children and adolescents: evaluation, classification and stratification. Pediatrics 2003;111:1416-21.
8. Nesterova G, Gahl W. Nephropathic cystinosis: Late complications of a multisystemic disease. Pediatr Nephrol 2008;23:863-78.
9. Greco M, Brugnara M, Zaffanello M, Taranta A, Pastore A, Emma F. Long-term outcome of nephropathic cystinosis: A 20-year single-center experience. Pediatr Nephrol 2010;25:2459-67.
10. Aile Yapısı Araştırma T.C. Başbakanlık Aile ve Sosyal Araştırmalar Genel Müdürlüğü ve T.C.Başbakanlık Türkiye İstatistik Kurumu 2006; sayfa 8. Erişim tarihi: 21 Ocak 2008. Available from: http//www.aile.gov.tr/images/arastırmalar/Aile yapısı.pdf.
11. Topaloglu R, Baskın E, Bahat E, Kavukcu S, Cakar N, Donmez O et al. Hereditary renal tubular disorders in Turkey: Demographic, clinical and laboratory features. Clin Exp Nephrol 2011;15:108-13.
12. Topaloglu R, Vilboux T, Coskun T, Ozaltın F, Tinloy B, Gunay-Aygun M, et al. Genetic basis of cystinosis in Turkish patients: A single-center experience. Pediatr Nephrol 2012;27:115-21.
13. Manz F, Gretz N. Progression of chronic renal failure in a historical group of patients with nephropathic cystinosis. European Collaborative Study on Cystinosis. Pediatr Nephrol 1994;8:466-71.
14. Van Stralen KJ, Emma F, Jager KJ, Verrina E, Schaefer F, Laube GF, et al. Improvement in the renal prognosis in nephropathic cystinosis. Clin J Am Soc Nephrol 2011;6:2485-91.
15. van't Hoff WG, Gretz N. The treatment of cystinosis with cysteamine and phosphocysteamine in the United Kingdom and Eire. Pediatr Nephrol 1995;9:685-9.