



## Gastrointestinal Manifestations of Adult Cystinosis in Iran: A Descriptive Study

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Received: 25 Jul 2021

Published: 28 Feb 2022

### Abstract

**Background:** Cystinosis is a multisystemic disease caused by the accumulation of cystine crystals in the kidney and many other organs. This disease most often involves children. Recent developments in the treatment procedures have improved the chance of patients surviving as long as puberty. This study discusses the importance of immediate diagnosis and early treatment of the disease with cystagon, which reduces gastrointestinal complications in such patients.

**Methods:** This descriptive study was performed on 19 adult patients (over 18 years old) with cystinosis who were observed by nephrologists from medical universities throughout Iran. Gastrointestinal complications were studied in the patients. Data were analyzed using SPSS Version 22.

**Results:** The mean age of patients at the time of enrollment was  $23.89 \pm 5.06$  years. Seventeen (89.4%) patients of this group had received renal replacement therapy (3 dialysis, 14 renal transplantation) due to end-stage renal disease and 2 (10.5%) of them were in stages 2 and 3 of chronic kidney disease. Three patients (15.7%) had hepatomegaly and splenomegaly; liver enzymes were normal in all patients. One patient (5.2%) had increased portal vein flow velocities, 2 of the patients (10.5%) underwent percutaneous endoscopic gastrostomy implantation due to severe dysphagia and eventually died. Most gastrointestinal symptoms in patients were nausea and abdominal pain.

**Conclusion:** Early diagnosis and treatment with the proper dose of cystagon can increase life expectancy, reduce complications, and improve the patient's quality of life.

**Keywords:** Cystinosis, Gastrointestinal Complications, Adults, Chronic Kidney Disease

**Conflicts of Interest:** None declared

**Funding:** The study was supported by the Deputy of Research of Iran University of Medical Sciences, Tehran, Iran.

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**Cite this article as:** Nakhaie Sh, Sharif AS, Hosseini Shamsabadi R, Otukesh H, Hashemipour M, Mohammadi Sh. Gastrointestinal Manifestations of Adult Cystinosis in Iran: A Descriptive Study. *Med J Islam Repub Iran.* 2022 (28 Feb);36:15. <https://doi.org/10.47176/mjiri.36.15>

### Introduction

Cystinosis is a rare autosomal recessive lysosomal storage disorder. This disorder is characterized by inadequate excretion of cystine from the lysosome into the cytoplasm, resulting in the accumulation of cystine crystals in various organs of the body (1). One in 100,000 to 1 in 200,000

people are affected by the afore mentioned disease. Globally, the disease affects every ethnic group (2).

Three types of cystinosis have been found: the most severe form is nephropathic or classic infantile cystinosis. As a result, the kidneys fail in the first decade of life and

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#### ↑What is “already known” in this topic:

Cystinosis is a multisystemic disease caused by the accumulation of cystine crystals in the kidney and many other organs. This disease most often involves children. The most severe form is nephropathic or classic infantile cystinosis. Cysteamine reduces intracellular cystine contents by 90%, which delays the loss of renal function.

#### →What this article adds:

This study showed the importance of immediate diagnosis and early treatment of the disease with cystagon, which reduces gastrointestinal complications in such patients.

are the major cause of renal Fanconi syndrome in children who have already been diagnosed (3). The second type is the intermediate form, which has all the same symptoms as the nephropathic type, but usually develops during adolescence. There is a third type of cystinosis that is nonnephropathic. This type is characterized only by corneal crystals and photophobia. About 95% of patients involved by cystinosis have the nephropathic form (3). Cystine transporter cystinosin is encoded by the CTNS gene (4), so all 3 forms result from bi-allelic mutations in this gene (5-7).

The pathogenesis of tissue damage in cystinosis involves cellular mitochondrial oxidative stress, cell dysfunction, and death followed by replacement with fibrosis tissue (8, 9). Successful treatment of cystinosis highly depends on early diagnosis and effective treatment. Supportive therapy and cysteamine-specific therapy are involved (1, 6). Cysteamine reduces intracellular cystine content by up to 90%, delays renal failure, and promotes growth (10-13).

In general, cysteamine is usually taken divided every 6 hours at a dosage of 60 to 90 mg/kg or 1.35-1.90 g/m<sup>2</sup> (14). Patients with cystinosis suffer from various gastrointestinal complications. A study by Rizantoploglober et al. on these patients revealed that even in childhood, in addition to renal dysfunctions, extrarenal organs might be involved by cystine accumulation, especially in patients who are incompliant to treatment. This can result in complications such as swallowing difficulties, hepatomegaly, and portal hypertension (15).

The causes of the above-mentioned gastrointestinal complications are as follows: (1) About 50% of patients experience oromotor dysfunction and dysphagia due to cystine accumulation in the lamina propria and muscles (16); (2) cystagon itself has gastrointestinal side effects that are not serious but are common and include unpleasant taste, nausea, and other digestive issues (11); (3) in children aged 6 to 12 months, untreated NC can cause the proximal tubular Fanconi syndrome. It leads to polyuria so that even in children with creatinine clearance less than 30 mL/min/1.73 m<sup>2</sup>, the urinary volume of 3 L is seen that if not compensated, it will cause dehydration. Therefore, these children have a strong tendency to drink water, which causes abdominal distention and a feeling of premature satiety, nausea, vomiting, and loss of appetite (8); (4) these patients also need replacement therapy for salts lost through the kidneys, including citrate, phosphate, calcium, phosphorus, and vitamin D, and their gastrointestinal side effects include nausea, vomiting, abdominal pain, and mild or occasional diarrhea (17); (5) some patients suffer from tubular and later glomerular proteinuria of nephropathic severity. Glomerular function gradually declines, resulting in renal failure between ages 7 and 10 years; however, the rate of the progression of end-stage renal disease (ESRD) differs. Some children reach a plateau in renal function, while others rapidly deteriorate (18). Eventually, due to ESRD, patients require alternative therapy (dialysis or transplantation). Peritoneal dialysis is associated with a variety of complications, including reflux oesophagitis, hernias, bowel erosions from catheter pres-

sure, and sclerosing peritonitis. Complications related to hemodialysis include nausea, vomiting, anxiety, hunger, intestinal ischemia due to hypotension, digestive system bleeding from heparin, and pancreatitis induced by accidental hemolysis (19-21); (6) about 20% of patients develop gastrointestinal complications after renal transplantation (RT). Other manifestations are directly related to the use of antibiotics during infection, while others are associated with immunosuppressive therapy, such as mycophenolate mofetil and steroids. The most common clinical symptoms are nausea, vomiting, and abdominal pain. However, esophageal infections by candida, herpes or cytomegalovirus, ulcerous peptic disease, diarrhea, and perforation in the colon or digestive bleeding have also been reported (22); and (7) there is a common finding of hepatomegaly in the gastrointestinal system, usually without liver dysfunction (23, 24). Accumulation of cystine crystal activates Kupffer cells and secreted vasoactive substances cause vasoconstriction in microcirculation which results in portal hypertension (23, 25).

Since the prevalence of cystinosis is very low and there are only 218 patients in Iran, limited studies have been done in this field, especially in the adult population and no gastrointestinal complications have been studied in this age group in Iran. In a study by Elenberg et al. about the complications of nephropathic cystinosis in adults, the most common gastrointestinal manifestations reported are periods of nausea and vomiting (26); other reported symptoms include appetite, constipation, diarrhea, abdominal pain, swallowing dysfunction, and gastroesophageal reflux (26, 27). In a study conducted in Iran on gastrointestinal complications of children with cystinosis, the mean age of patients was 5.99 ± 0.50 years, and the most common gastrointestinal complication of vomiting was observed in about 70% of these patients (28).

Regarding the causes of gastrointestinal complications mentioned in these patients, the case that is under our control and through which gastrointestinal complications can be greatly reduced is the drug treatment of cystagon. Therefore, this study aimed to investigate the importance of early diagnosis and treatment with the appropriate dose of cystagon, which can delay the course of the disease and increase the life expectancy of patients and reduce complications, including gastrointestinal complications.

## Methods

This was a descriptive study. Out of 218 cystinosis patients in Iran, 19 adults patients (over the age of 18) were included in the study. The studied patients underwent additional studies through clinical findings with suspected cystinosis. Cystinosis was diagnosed based on the presence of cystine crystals in the cornea or bone marrow, evaluation of leukocyte cystine levels, or genetic testing.

After that, all patients were treated with cystagon. Demographic findings of patients, including sex, the current age of the patient, age at the time of diagnosis, clinical manifestations at the time of diagnosis, way of diagnosing the disease, the family ratio of parents, the daily dose of cystagon, age at the time of renal failure, type of kidney replacement therapy (dialysis or transplant), gastrointesti-

nal signs and symptoms, including abdominal pain, nausea, vomiting, diarrhea, reflux, dysphagia, and constipation, ultrasound findings for organomegaly and Doppler ultrasound of the portal system, laboratory findings, including blood creatinine level and liver function tests, were collected.

Data were analyzed using SPSS Version 22. Quantitative variables were presented by central indexes (mean and standard deviation) and qualitative variables were presented by frequency tables.

## Results

### Demographic Characteristics

Nineteen patients (11 women) with a mean age of  $23.89 \pm 5.06$  years were studied. Eighteen patients were of the classic form and 11 of whom were diagnosed before the age of 1. Only 1 patient was in the juvenile form. Fifteen patients had assigned parents. The most common way to diagnose the disease was to observe cystine crystals in the cornea. The most common clinical manifestations at the diagnosis were growth retardation, and other common symptoms were polyuria, polydipsia, vomiting, and fever.

### Renal Functions

At the time of the study, 17 patients had received renal replacement therapy (3 dialysis, 14 RT) due to ESRD ( $\text{GFR} < 15 \text{ mL/min/1.73 m}^2$ ), and 2 patients were in stages 2 and 3 of chronic kidney disease (CKD). Only 1 patient had experienced transplant rejection due to the improper use of immunosuppressive drugs. The mean age of ESRD in patients with the classic form diagnosed at less than 1 year old was  $11.89 \pm 1.96$  years. In other classic form patients, it was  $8 \pm 1$  years.

### Gastrointestinal System Findings

Abdominal ultrasonography was performed in 19 patients and portal vein Doppler ultrasonography was performed in 18 patients. Three patients had hepatomegaly and splenomegaly, and Liver enzymes were normal in all patients. One patient had increased portal vein minimum and maximum flow velocities (minimum 19-35 cm/sec, maximum 35-51 c). Two patients underwent percutaneous endoscopic gastrostomy (PEG).

Most gastrointestinal symptoms in patients were nausea and abdominal pain, which was observed in 11 patients, and all of them were undergoing dialysis or transplantation due to ESRD. Seven out of these 11 patients were diagnosed after 1 year old, 4 of whom did not receive the proper dose of cystagon and 2 of whom eventually died (Table 1).

## Discussion

The results showed that the majority of patients were diagnosed at less than 1 year old, which is the age at which the disease manifests itself for the first time. Early detection of the disease is highly important in improving the quality of life of patients with cystinosis and increase the life expectancy and reduce the involvement of various systems. As in our study, 11 classic form patients diag-

nosed at less than 1 year old, all received cystagon at the appropriate dose, and 2 patients were in stages 2 and 3 of CKD and did not need any alternative treatment. The mean age of ESRD in the other 9 patients was higher than 7 classic form patients who had been diagnosed over 1 year old. Because there is a significant amount of glomerular damage at the time of diagnosis of cystinosis, treatment with cystagon cannot completely stop the progression of kidney failure, but it can delay it and can also reduce the frequency of complications, such as diabetes, myopathy, hypothyroidism (29).

Apart from the importance of early detection of the disease, the proper dose of cystagon is also of high importance. Because of this gene defect, the deposition of cystine crystals in various tissues continues even after kidney replacement therapy and patients suffer from various complications, including in the gastrointestinal tract. As in our study, 2 patients suffered from severe gastrointestinal complications, including dysphagia and recurrent pneumonia aspiration because of not receiving the drug, so they eventually needed to have a PEG implant and died. One of them had organomegaly and increased port pressure. In a study by Sonies and colleagues, 43 patients with cystinosis aged 3 to 31 years were found to have abnormal barium swallowing in one-third to three-quarters of the patients. They believed that the treatment with cystagon could reduce dysphagia but found no measurable benefit in the patients, probably because of the short duration of the treatment (30).

Because long-term oral therapy appears to limit the accumulation of cystine in the kidney, it may do the same in the muscle tissue responsible for swallowing, thus, it is best to observe the patients for long periods. Among the remaining patients studied, the most common gastrointestinal complication was nausea and abdominal pain, which was more common among patients who were diagnosed later. According to Topaloglu et al., a study performed on patients with cystinosis revealed that the mean age at last visit was  $11.3 \pm 6.5$  years, and that complications, such as hepatomegaly, swallowing difficulty, and portal hypertension, were found (15). Two previous studies were performed on patients who did not take cystagon regularly, and this may make the result different from our study.

In a study conducted by Nakhaei, the most frequent gastrointestinal manifestation was vomiting and the second was diarrhea. In general, there were no significant differences between those with and without end-stage renal disease in terms of gastrointestinal symptoms (28). The reason for this difference with our study can be due to different populations. This study was performed on children with cystinosis, while our study was performed on adults.

## Conclusion

Inadequate treatment of cystinosis can lead to multisystem involvement and even death. However, long-term cystamine treatment, if started early and used in appropriate doses, can significantly improve renal and extrarenal outcomes and can increase patient life expectancy and improve their quality of life.

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## Gastrointestinal Manifestations of Adult Cystinosis

**Table 1. Demographic, Clinical, and Paraclinical Findings of Adult Cystinosis Patients in Iran**

No	Sex	Current age (Year)	Age of diagnosis	Attributed parents	Cystinosis diagnostic methods	Signs at presentation	Cystinosis type	Proper dose of daily Cystagon	Age at ERSD (Year)	Kidney replacement therapy	Serum creatinine level	Abdominal ultrasound	Portal vein doppler ultrasound	Gastro intestinal symptoms	LFT
1	M	18	6M	+	leukocyte cystine levels	Polyuria Fever FTT	Classic	+	Stage 2 CKD	-	1.3	NL	NL	-	NL
2	M	20	6M	+	Corneal cystine crystal	polyuria polydipsia FTT	Classic	+	12	Dialysis	7.5	NL	NL	Nausea Abdominal pain Reflux Diarrhea	NL
3	M	26	21Y	-	Corneal cystine crystal	Photophobia malaise renal failure	Juvenile	-	23	Transplantation	1.1	NL	NL	-	NL
4	F	22	7M	+	leukocyte cystine levels	Polyuria Fever FTT	Classic	+	10	Dialysis	5.4	NL	NL	-	NL
5	F	34	3Y	+	Corneal cystine crystal	Polyuria Polydipsia FTT Fever	Classic	+	8	Transplantation	1	Hepatosplenomegaly	NL	Nausea Abdominal pain	NL
6	M	28	5M	+	Corneal cystine crystal	Photophobia Polyuria FTT	Classic	+	12	Transplantation	1.4	NL	NL	Nausea Abdominal pain	NL
7	F	23	9M	+	leukocyte cystine levels	Polyuria Polydipsia anemia FTT proteinuria glucosuria	Classic	+	16	Transplantation	0.9	NL	NL	-	NL
8	M	18	5.5Y	+	Bone marrow	FTT muscle spasm	Classic	+	10	Transplantation	0.6	NL	NL	Reflux Diarrhea Abdominal pain	NL
9	F	21	7M	+	Bone marrow	FTT vomiting	Classic	+	10	Dialysis	6	Hepatosplenomegaly	NL	Nausea Abdominal pain	NL
10	M	18	7M	+	Corneal cystine crystal	Polyuria Polydipsia	Classic	+	Staege 3 CKD	-	3.7	NL	NL	-	NL

Sex: Male (M), Female (F); Age of diagnosis: Year (Y), Month (M); Attributed parents: Parents are attributed (+), Parents are not attributed (-); Proper dose of daily Cystagon (cysteamine dosage 60–90 mg/kg/day or 1.35–1.90 g/m<sup>2</sup>/day): Take enough medicine (+), Do not take enough medicine (-); Normal (NL); Failure To Thrive (FTT); Portal vein doppler ultrasound: Not done (-); Gastro intestinal symptoms: No symptom (-).

**Table 2.** Demographic, Clinical, and Paraclinical Findings of Adult Cystinosis Patients in Iran

No	Sex	Current age (Year)	Age of diagnosis	Attributed parents	Cystinosis diagnostic methods	Signs at presentation	Cystinosis type	Proper dose of daily Cystagon	Age at ERSD (Year)	Kidney replacement therapy	Serum creatinine level	Abdominal ultrasound	Portal vein doppler ultrasound	Gastro intestinal symptoms	LFT
11	F	30	3.5Y	+	Corneal cystine crystal	Osteodystrophy	Classic	+	7	Transplantation	1.4	NL	NL	Nausea Abdominal pain	NL
12	F	20	9M	+	leukocyte cystine levels	proteinuria polyuria FTT fever	Classic	+	13	Transplantation	1.3	NL	NL	Nausea Abdominal pain	NL
13	F	22	7M	+	Genetic	Polyuria FTT Polydipsia	Classic	+	11	Transplantation	1.2	Hepatosplenomegaly	NL	-	NL
14	F	18	6M	+	leukocyte cystine levels	Proteinuria glucosuria	Classic	+	10	Transplantation	0.7	NL	NL	-	NL
15	M	30	5Y	+	Corneal cystine crystal	FTT Polyuria Polydipsia	Classic	-	8	Transplantation	1.3	NL	NL	Nausea	NL
16	F	22	2.5Y	-	Corneal cystine crystal	FTT Polydipsia	Classic	-	8	Transplantation	1.2	NL	NL	Nausea Abdominal pain Reflux	NL
17	M	24	6M	-	leukocyte cystine levels	Fever FTT	Classic	+	13	Transplantation	1	NL	NL	-	NL
18	F	30	4Y	+	Corneal cystine crystal	Fever FTT	Classic	-	7	Transplantation	1.6	Hepatosplenomegaly	Increased	Sever swallowing disorder	NL
19	F	30	5Y	-	Corneal cystine crystal	FTT	Classic	-	8	Transplantation	1.8	NL	-	Sever swallowing disorder	NL

Sex: Male (M), Female (F); Age of diagnosis: Year (Y), Month (M); Attributed parents: Parents are attributed (+), Parents are not attributed (-); Proper dose of daily Cystagon (cysteamine dosage 60–90 mg/kg/day or 1.35–1.90 g/m<sup>2</sup>/day): Take enough medicine (+), Do not take enough medicine (-); Normal (NL); Failure To Thrive (FTT); Portal vein doppler ultrasound: Not done (-); Gastro intestinal symptoms: No symptom (-).

Health care professionals, patients, and support groups should make fundamental efforts to maintain and enhance long-term cystamine therapy.

### Acknowledgement

Hereby, the authors extend their gratitude to Ali-Asghar clinical research development center for statistical/search assistance and all pediatric nephrologists throughout the country who participated in this study and made their best efforts.

### Research Involving Human Participants and/or Animals

The study was performed in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and Ethical approval was elicited from the Ethical Committee at Iran University of Medical Sciences, Iran, and patients' parents gave informed consent.

### Informed Consent

Informed written consent was obtained from all individual participants included in the study.

### Conflict of Interests

The authors declare that they have no competing interests.

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