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Regular Article

Beneficial effects of starting oral cysteamine treatment in the first 2 months of life on glomerular and tubular kidney function in infantile nephropathic cystinosis

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ABSTRACT

Nephropathic cystinosis is a rare lysosomal storage disease whose basic defect, impaired transport of cystine out of lysosomes, results in intracellular cystine storage. Affected individuals exhibit renal Fanconi Syndrome in infancy, end-stage kidney disease at approximately 10 years of age, and many other systemic complications. Oral cysteamine therapy mitigates the detrimental effects on glomerular function and prevents most of the late complications of the disease but has not shown benefit with respect to the early tubular damage of cystinosis. This is because cystinosis is generally diagnosed in the second year of life, after the damage to kidney tubular function has already occurred. We longitudinally evaluated 6 infants diagnosed and treated with cysteamine from before 2 months of age. The 4 infants with good compliance with cysteamine and consistently low leucocyte cystine levels maintained normal eGFR values, exhibited only minor degrees of renal Fanconi Syndrome, and maintained normal serum levels of potassium, bicarbonate, phosphate, and calcium without electrolyte or mineral supplementation through 2, 4, 10 and 16 years of age. Thus, renal Fanconi syndrome can be attenuated by early administration of cysteamine and renew the call for molecular-based newborn screening for cystinosis.

1. Introduction

Cystinosis (OMIM 219800) is an autosomal recessive lysosomal storage disease due to impaired transport of cystine out of lysosomes [1,2]. The causative gene, *CTNS*, encodes a lysosomal transmembrane carrier protein called cystinosin [3]. In classic nephropathic cystinosis, the lysosomal accumulation of cystine damages cells and tissues beginning in the first year of life. The initial organs affected are the kidneys, with generalized proximal tubular dysfunction (renal Fanconi syndrome) presenting at approximately 6 months of age with failure to thrive, polyuria, polydipsia, dehydration, acidosis, hypokalemia, hypophosphatemic rickets, and hypocalcemia [4]. These are treated with replacement of water, bicarbonate or citrate, potassium, sodium, phosphate, and calcium [5].

Renal glomerular function deteriorates inexorably in cystinosis, leading to end-stage kidney disease (ESKD) at approximately 10 years of age [4,6] and requiring kidney replacement therapy, i.e., dialysis and/or kidney transplantation. The use of oral cysteamine has attenuated this glomerular damage by depleting intracellular cystine stores

Abbreviations: eGFR, estimated glomerular filtartion rate; $eGFR_{cr}$, creatinine-based estimated glomerular filtartion rate; ESKD, end-stage kidney disease; FSI, Fanconi syndrome index.

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[7,8]. Cysteamine therapy, which is monitored by measurement of leukocyte cystine levels [4], delays ESKD, allows for improved growth [9,10], and attenuates hypothyroidism of cystinosis [11]. It also prevents many of the late complications of cystinosis, which include distal vacuolar myopathy [12], swallowing difficulty [13], restrictive lung disease [14], idiopathic intracranial hypertension [15], neurological symptoms [16], and impairment of various other organs [17–20]. Cysteamine eyedrops also dissolve the corneal crystals of cystinosis, which occur by 16 months of age [21–23].

The full benefits of cysteamine treatment, however, are masked by the relatively late age of diagnosis for children with cystinosis, which generally occurs in the second year of life [4]. By this time, renal tubular function is usually irreversibly impaired, and some glomerular damage has already occurred. Over the past 10 years, we had the opportunity to follow 6 children who were diagnosed with cystinosis and treated with oral cysteamine within 2 months of birth. Four of the 6 were compliant with the treatment and had excellent leucocyte cystine depletion for 2.7–16.7 years. We present their outcomes, demonstrating maintenance of kidney tubular and glomerular function.

2. Methods

2.1. Patients

Six children were diagnosed with cystinosis within 2 months after birth because of either an affected sibling (5 infants) or newborn screening (1 infant). The diagnosis of cystinosis was based upon an elevated leukocytic cystine level and/or molecular confirmation of biallelic pathogenic mutations in *CTNS*. The 6 patients were followed annually in an interdisciplinary cystinosis clinic staffed by a multidisciplinary team performing evaluations in a standardized manner [24,25]. Longitudinal data included age, height, weight, cysteamine dosage, leukocyte cystine levels, and kidney data such as serum and urine measures of tubular function, dietary supplements for renal losses, and serum creatinine levels. Recent clinical visits (in 2021 and 2022) for the 6 patients provided additional data on tubular and glomerular kidney function. Note that some of the data on patients # 5 and # 8, including date of birth, start of cysteamine treatment, date of last visit before 2017, and genotype, have been reported [26].

2.2. Determination of leukocyte cystine

Cystine levels were determined almost exclusively in the metabolic laboratory in Muenster [27], where the cystine measurement was carried out by the method described by Spackman et al. [28]. For patients seen in the interdisciplinary cystinosis clinic, leukocytes were prepared on site, and the frozen leukocyte pellets were sent to Muenster for analysis. When assessing the extent of leucocyte cystine depletion associated with cysteamine therapy, values obtained within 2 months of the initiation of therapy were discarded, because incremental dosing at the start of treatment achieved only minimal cystine depletion.

2.3. $eGFR_{cr}$ determination

Estimated glomerular filtration rate ($eGFR_{cr}$) was calculated based on age and sex-specific formulas, i.e., the most recent Schwartz formula for individuals up to the age of 18 and the formula of Levey et al. for adults [29,30].

2.4. Fanconi Syndrome Index (FSI)

The FSI provides a measure of renal tubular reabsorption of amino acids. It is calculated as the sum of the amounts of 20 specific amino acids excreted in the urine in 24 h [31]. The units are μmol/kg/day; normal values are 94 +/− 45 (SD) while Fanconi syndrome patients have FSIs of 1085 +/− 725 (SD) [31,32]. The FSI has the advantage of being independent of electrolyte and mineral supplementation.

2.5. Study approval

The study was approved by the ethics committee of the Bavarian Medical Association (internal No: 2015–030). Written informed consent was obtained from all parents/guardians, with assent from patients when appropriate for their age.

3. Results

3.1. Patients

The 5/6 cystinosis infants diagnosed early in life had baseline, untreated leucocyte cystine levels ranging from 2.2 to 3.1 nmol/mg protein (Table 1), confirming the diagnosis of cystinosis. One patient (#74) was diagnosed prenatally; the initial postpartum cystine level was not available. Cystinosis patients not receiving oral cysteamine have leucocyte cystine levels between 1.5 and 10 nmol/mg protein [4,5]. The infants began oral cysteamine between 0.2 and 1.6 months of age and were between 2.8 and 18.8 years old at the time of their latest evaluation (Table 1).

3.2. Compliance and $eGFR_{cr}$

Recommended doses of cysteamine are 60–90 mg/kg/day [4,5]. Mean cysteamine doses for the 6 patients ranged from 48 to 71 mg/kg/day, but there was considerable intra- and inter-patient variability in the doses of cysteamine received by the 6 children over the course of their lives (Fig. 1A). The target range of leucocyte cystine levels for cysteamine-treated patients is <0.5 nmol/mg protein. The 6 early-treated cystinosis patients had mean leucocyte cystine levels ranging from 0.34 to 0.73 nmol/mg protein (Table 1) but, again, these values varied widely over the course of therapy (Fig. 1B). At the time of their last evaluation, 5 of the 6 early-treated cystinosis patients had maintained an $eGFR_{cr} > 90$ ml/min/1.73 m^2 (Table 1). Each patient's $eGFR_{cr}$ values, however, fluctuated over time (Fig. 1C).

All 6 patients displayed reasonable compliance with acceptable doses of oral cysteamine and maintained kidney glomerular function that vastly exceeded levels for untreated patients the same age (Fig. 1C) [10]. However, two patients, #5 and #8, were followed long enough (16 and 18 years) to illustrate the relationship of cystine depletion and maintenance of $eGFR_{cr}$. Patient #5 maintained a high per kg cysteamine dose (Fig. 1A), consistently achieved good cystine depletion (Fig. 1B), and maintained excellent estimated glomerular function (Fig. 1C). In contrast, patient #8 did not tolerate cysteamine early in life because of extensive vomiting; he required a PEG tube early in life and tolerated only a relatively low dose of cysteamine, especially during adolescence (Fig. 1B). His leukocyte cystine levels were relatively high during the first 3 years of life and during adolescence, and his $eGFR_{cr}$ declined after 10 years of age, averaging approximately 60–70 ml/min/1.73 m^2 (Fig. 1C).

3.3. Systemic effects of early cysteamine treatment (Table 2)

At the time of their latest evaluations at 2–18 years of age, all the patients had heights in the 20^{th} to 63^{rd} percentiles; only patient #8 had received treatment with recombinant human growth hormone. Weight was in the 6^{th} to 87^{th} percentiles. Serum creatinine and Cystatin C levels were within the normal ranges. Patient #8 also received thyroid replacement, but in the remaining 5 patients normal serum TSH and T4 concentrations reflected preservation of thyroid function.

3.4. Maintenance of tubular function

Several parameters were employed to gauge renal tubular function in the 6 patients treated with cysteamine before 2 months of age. Four of the 6 individuals never required potassium, bicarbonate, citrate, or

Table 1
Adherence with cysteamine therapy and $eGFR_{cr}$ values for 6 cystinosis patients treated within 2 months of birth.

Patient #	105	88	5	74	8	99
Age at start of cysteamine (mo)	1.6	0.9	0.4	0.2	0.4	0.7
Age at last visit (y-mo)	2-7	4-2	16-7	10-9	18-7	6-5
Cysteamine Dose (mg/kg/day)						
Mean (SD)	71 (10)	70 (3)	66 (14)	48 (8)	48 (16)	63 (9)
Median (min, max)	73 (47, 82)	70 (57, 74)	68 (42, 91)	48(31,66)	45 (16, 80)	60 (50, 76)
Leukocyte cystine (nmol/mg)						
Initial value	2.2	2.82	3.1	NA[a]	2.28	2.2
Mean (SD)	0.73 (0.79)	0.35 (0.12)	0.49 (0.23)	0.34 (0.25)	0.67 (0.46)	0.52 (0.30)
Median (min, max)	0.51 , (0.16,2.63)	0.36 (0.21,0.55)	0.47 (0,14,1.14)	0.3 (0,0.94)	0.56 (0.07, 2.16)	0.44 (0.23, 1.4)
$eGFR_{cr}$ at last visit (mL/min/1.73 m^2)	136	106	115	93	79	126

[a] NA, Not available; prenatally diagnosed; no postnatal cystine level.

phosphate supplements, and they still had normal serum potassium, bicarbonate, and phosphate levels (Table 3). Five of the 6 never received oral calcium repletion; all 5 had normal serum calcium levels. In addition, only 1 of the 6 was significantly polyuric (Table 3). Urine low molecular weight protein was in the normal range for patient #88; patients #105, #74, and #8 showed moderate and patients #5 and #99 had elevated levels for α_1-microglobulin. Tubular reabsorption of phosphate was in the normal range for 3 of the patients and near

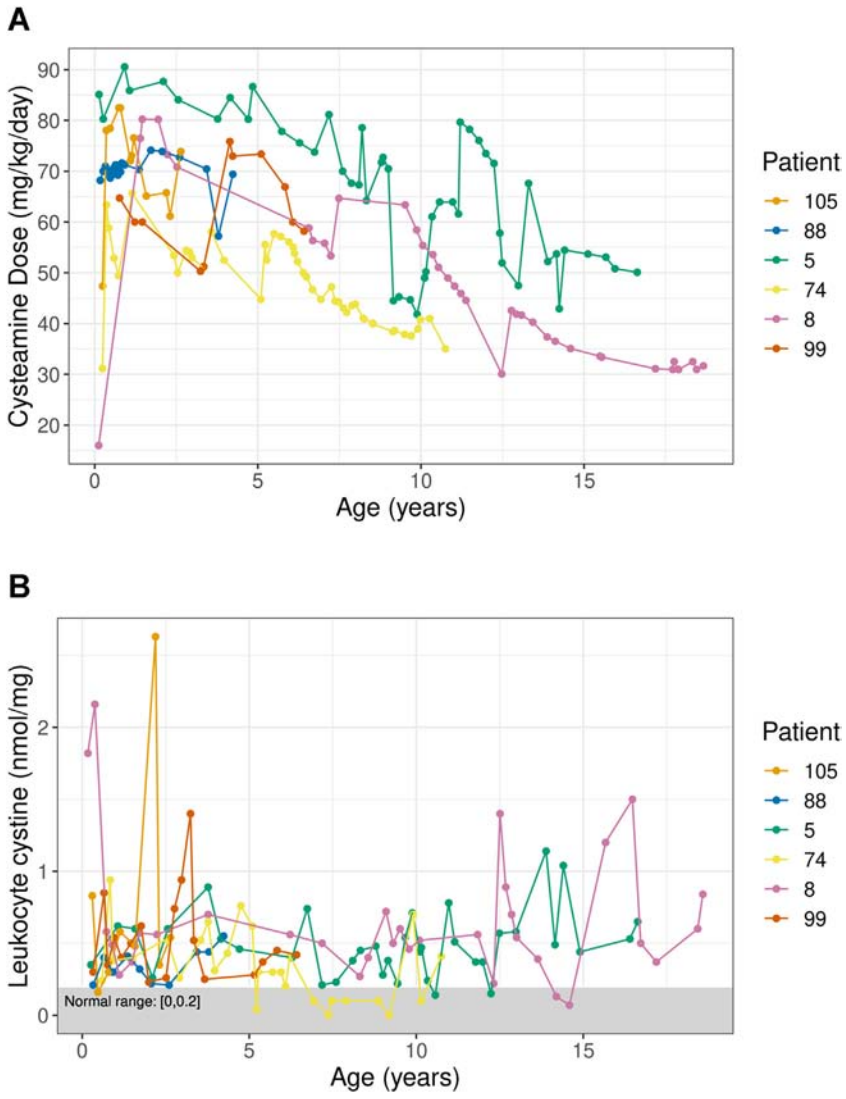

Fig. 1. Age-related values for 6 children with cystinosis treated with oral cysteamine prior to 2 months of age.
A. Daily cysteamine dosage.
B. Leukocyte cystine levels.
C. $eGFR_{cr}$.

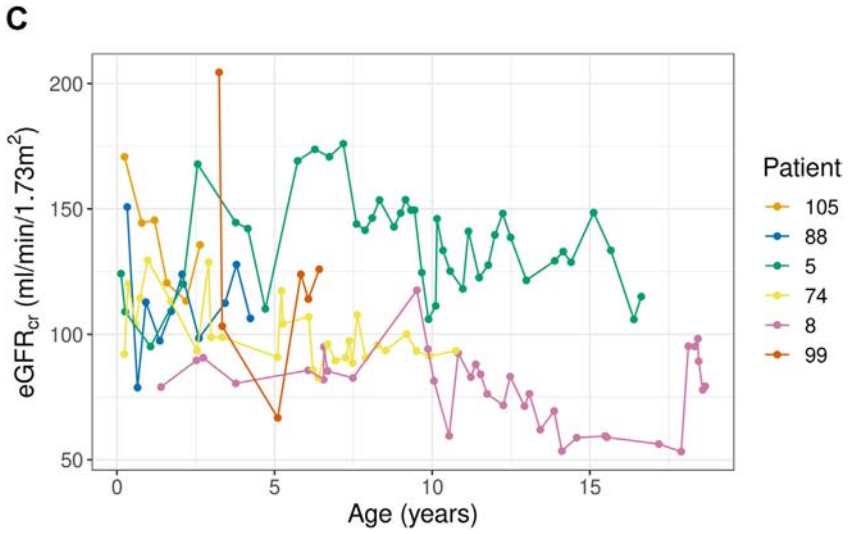

Fig. 1 (*continued*).

normal in 2 others (Table 3) [33–35]. The FSI, which is generally 10-fold elevated in Fanconi syndrome patients, was only up to 4-fold elevated in 5 of the 6 patients [31,32]. None of the 6 patients had glucosuria.

Patient #8, who was less compliant with cysteamine than the other individuals, frequently had serum potassium, bicarbonate, phosphate, and calcium levels outside of the normal range (Fig. 2A–D), was polyuric, and excreted large amounts of amino acids and protein (Table 3).

Patient #99 did not tolerate cysteamine for the first 3 years of life because of vomiting, but her parents refused a PEG tube. She had a very difficult course at the age of 3 years, with a serum potassium of 1.9 mEq/L and admission to the intensive care unit. The child was considered to have received only a small number of the cysteamine doses prescribed.

4. Discussion

Newborns with cystinosis are normal in weight and size and are clinically unremarkable. Affected infants usually manifest renal tubular Fanconi syndrome at 6–18 months of age, with poor growth starting as early as 6–9 months, accompanied by polydipsia, polyuria and episodes of dehydration [4,5]. Laboratory findings include hypokalemia, metabolic acidosis, and hypophosphatemia, with rickets delaying the age at ambulation. The glomerular disease of untreated nephropathic cystinosis progresses inexorably to ESKD by approximately 10 years of age [4,6], although serum creatinine levels are generally not elevated until approximately 5 years of age because of the extensive functional reserve of the kidney.

Cysteamine treatment preserves kidney function and delays progression to renal failure [9,10], especially if begun early in life [36,37]. Oral cysteamine therapy also allows for a normal growth rate [10],

Table 2
Systemic characteristics of patients treated with cysteamine within 2 months of birth.

Patient #	105	88	5	74	8[a]	99	Normal range
Age (y-mo)	2-7	4-2	16-7	10-9	18-7	06-5	
Somatic parameters							
Height (Percentile)	90	27	52	58	(173 cm)	49	3-97
Weight (Percentile)	86	14	14	88		59	3-97
Weight (kg)	15.7	15.1	49.9	47.1	62.7	23.2	Variable
Serum values							
Creatinine (mg/dL)	0.3	0.4	0.6	0.65	1.3	0.4	Variable
Cystatin C (mg/L)	0.72	0.86	0.93	0.91	1.05	0.66	0.62–1.11
TSH (μLU/ml)	3.1	3.11	2.33	0.85	3.14	4.46	Variable
T4 (ng/dL)	1.09	1.3	0.95	1.34	0.91	1.3	Variable

[a] Received growth hormone and thyroid hormone.

Table 3
Parameters of kidney tubular function in patients treated with cysteamine within 2 months of birth.

Patient #	105	88	5	74	8	99	Normal range
Age (y-mo)	2-7	4-2	16-7	10-9	18-7	6-5	
Oral replacement							
Potassium	No	No	No	No	Yes	Yes	
Bicarbonate	No	No	No	No	Yes	Yes	
Citrate	No	No	No	No	No	Yes	
Phosphate	No	No	No	No	Yes	Yes	
Calcium	No	No	No	No	No	Yes	
Serum values							
Potassium (mmol/l)	4.3	3.9	3.8	3.6	3.5	4.4	3.5–5.0
Bicarbonate (mmol/l)	23.1	21.2	21	24.2	22.4	21.3	21–26
Phosphate (mmol/l)	1.64	1.52	1.23	1.15	0.74[a]	1.58	0.9–1.95
Calcium (mmol/l)	2.42	2.38	2.24	2.34	2.46	2.26	2.15–2.62
Alkaline Phos (U/l)	229	273	111	348	194	267	Variable
PTH (pg/mL)	41.5	18.6	18.4	24.4	15.2	14.6	15.0–65
Spot urine values							
Creatinine (g/l)	0.61	0.54	0.96	0.7	0.26	0.29	Variable
Albumin (mg/l)	12.5	5.9	95.8	8.1	58.3	111.6	<20
mg/g Creatinine	21	11	100	12	224	385	<20
IgG (mg/l)	4.3	<4.0	30.8	11.4	12.7	18.1	<14
mg/g Creatinine	7	<7.4	32.1	16.3	48.8	62.4	<10
α_1-Microglobulin[b] (mg/l)	27.5	7.5	153	23	44	107	<20
mg/g Creatinine	45	14	158	33	169	367	<10
α_2_Macroglobulin (mg/l)	<4.0	<4.0	<4.0	<2.41	<4.0	<4.0	<20
mg/g Creatinine	<6.6	<7.4	<4.2	<2.4	<15.4	<13.8	<10
Urine values							
Volume (mL/24 h)	600	700	2000	1600	7400	1300	
TRP (%)	84	91	88	84	45	72	82–90
FSI (μmole/kg/day)	318	176	425	208	1236	560	49–139[c]
TmP/GFR (mg/dl)	4.6	1.8	2.7	3.9	0.9	3.5	

[a] Normal range, 0.81–1.45.
[b] Normal ranges: <12.0 mg/l; 14 mg/gCrea.
[c] Range based on mean +/− one SD.

delays or prevents the requirement for thyroid hormone replacement [11], and reduces the frequency of myopathy, swallowing difficulties, pulmonary restrictive disease, and death [19]. In general, proximal tubular dysfunction was not reversible by cysteamine therapy begun at the typical time of diagnosis [37].

Despite oral cysteamine treatment, all cystinosis patients eventually require kidney replacement therapy by dialysis or transplantation. In 1993, Markello et al. [10] demonstrated the importance of early initiation of cysteamine therapy, strict adherence to the drug regimen, and adequate dosing for cystine depletion. However, none of the patients in that or other large studies had begun cysteamine treatment prior to 1 year of age [26], so the full benefit of early initiation of cystine-depletion could not be ascertained. In the current study, when cysteamine treatment was begun prior to 2 months of age with good compliance, 5 patients with cystinosis maintained an $eGFR_{cr}$ >90 ml/min/1.73 m^2 at ages 2–16 years of age.

Early initiation of oral cysteamine treatment also had beneficial effects on renal tubular function. Four of the 6 patients who started cysteamine prior to 2 months of age tolerated the therapy well and had good adherence. They exhibited normal growth, only mild proteinuria and aminoaciduria, and normal serum electrolyte and mineral concentrations without supplementation at ages ranging from 2 to 16 years; only patient #8 was polyuric. Even the two early-treated cystinosis patients with poor adherence to cysteamine therapy maintained a modicum of tubular function. A previous study of renal tubular function in cystinosis did not reveal a beneficial effect of long-term adherence with cysteamine therapy [37], but that report dealt only with patients starting cysteamine treatment at the usual age of diagnosis, i.e., after tubular damage had already occurred.

Early treatment of cystinosis with cysteamine has a substantial impact on the kidney. For the glomeruli, it raises the prospect of long-term preservation of filtration function. For the tubules, early cysteamine treatment offers the possibility to avoid renal Fanconi syndrome and its requirements for electrolyte and mineral supplementation (Table 3).

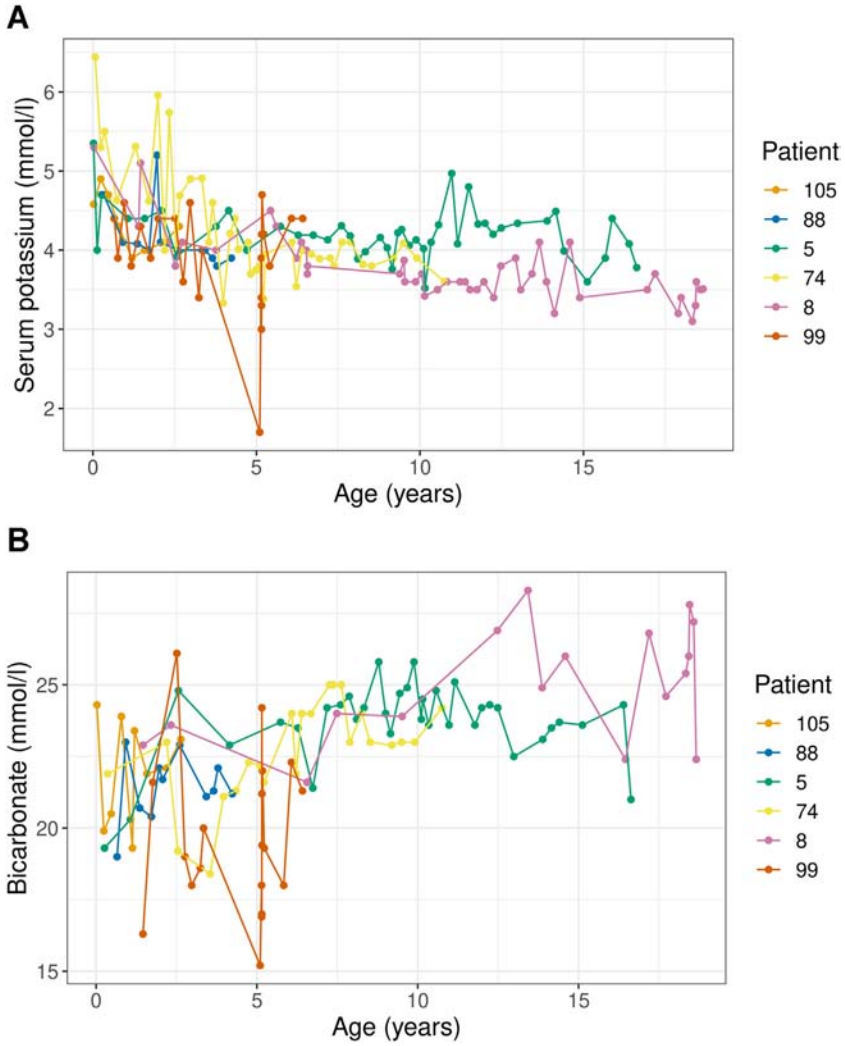

Fig. 2. Age-related serum electrolyte and mineral values for 6 children with cystinosis treated with oral cysteamine prior to 2 months of age.
A. Potassium
B. Bicarbonate
C. Phosphate
D. Calcium

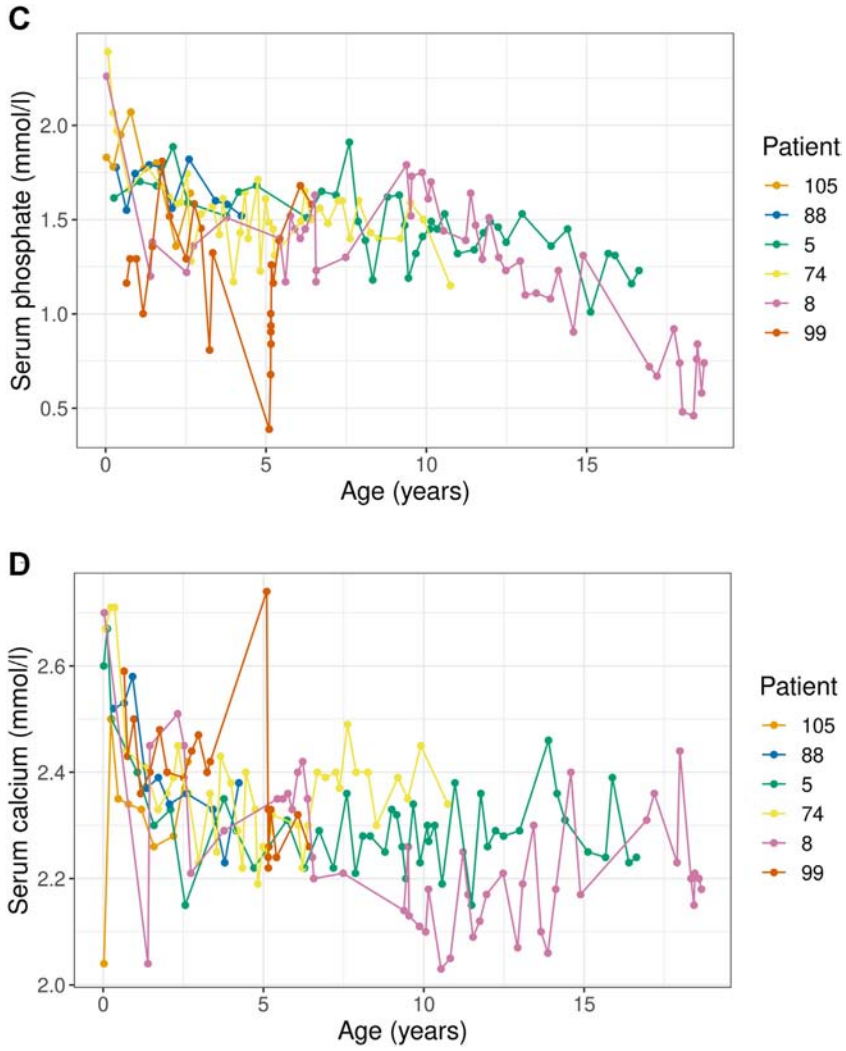

Fig. 2 (*continued*).

5. Conclusion

The implications of these findings are enormous. First, it is possible that neonates diagnosed and treated from birth can avoid kidney replacement therapy altogether. Second, the finding that initiating cysteamine treatment at 1–2 years of age appears to be too late to ultimately rescue either glomerular or tubular function means that other treatments, including gene therapy, must be initiated shortly after birth. Finally, these results bring urgency to the implementation of newborn screening for cystinosis, already proven to be feasible using molecular-based screens [24,38]. In Germany (with 800,000 live births annually) and in the United States (with 3.75 million live births annually), 4–8 and 19–38 babies, respectively, are born each year with cystinosis. In just these two countries, every year that the introduction of newborn screening for cystinosis is delayed means that 23–46 more individuals will lose their kidney function due to cystinosis.

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Data availability statement

The clinical data as well as laboratory values and anamnestic data are documented in the patient files non-anonymized with the treating physicians in Rosenheim and cannot be shared freely.

Authors' contributions

KH established the database and provided the clinical data. WAG and KH wrote the manuscript. CN provided the graphs. All authors edited the draft manuscript and approved the final manuscript.

Conflicts of interest

KH, CN, CO, KP, KPS, SW, WAG, declared no competing interests.

JO has received consulting fees. JO, DH received payment or honoraria for lectures or presentations from Recordati GmbH and Chiesi GmbH.

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