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Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults

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Nephropathic cystinosis is a multisystem autosomal recessive disease caused by cystine accumulation, which is usually treated by oral cysteamine. In order to determine long-term effects of this therapy, we enrolled 86 adult patients (mean age 26.7 years) diagnosed with nephropathic cystinosis, 75 of whom received cysteamine. Therapy was initiated at a mean age of 9.9 years with a mean duration of 17.4 years. By last follow-up, 78 patients had end-stage renal disease (mean age 11.1 years), 62 had hypothyroidism (mean age 13.4), 48 developed diabetes (mean age 17.1 years), and 32 had neuromuscular disorders (mean age 23.3 years). Initiating cysteamine therapy before 5 years of age significantly decreased the incidence and delayed the onset of end-stage renal disease, and significantly delayed the onset of hypothyroidism, diabetes, and neuromuscular disorders. The development of diabetes and hypothyroidism was still significantly delayed, however, in patients in whom therapy was initiated after 5 years of age, compared with untreated patients. The life expectancy was significantly improved in cysteamine-treated versus untreated patients. Thus, cysteamine decreases and delays the onset of complications and improves life expectancy in cystinosis. Hence, cysteamine therapy should be introduced as early as possible during childhood and maintained lifelong.

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Cystinosis is a rare autosomal recessive disease caused by intracellular cystine accumulation,[1] which is estimated to occur in 1/100,000 live births.[2] The *CTNS* causative gene maps to chromosome 17p13 (ref. 3). More than 90 different *CTNS* mutations have been described. The 57-kb deletion is the most common mutation associated with cystinosis; it has been detected in ~75% of cystinotic patients of European origin.[4–6] The *CTNS* gene encodes cystinosin, which transports the cystine out of lysosomes into cytoplasm where it is reduced to cysteine. This transport process is defective in cystinosis, causing intralysosomal accumulation, crystal formation, and progressive organ damage.[7] This process is attenuated in some variants of cystinosis with residual activity.[8]

Nephropathic infantile cystinosis is the most common form of the disease. Early symptoms include Fanconi's syndrome, rickets, impaired growth, polyuria, and polydipsia at 6–12 months of age.[9] End-stage renal disease (ESRD) occurs at approximately 10 years of age in the absence of treatment.[10] Renal transplantation markedly improved the life span of cystinotic patients. However, cystine accumulation continued in non-renal organs.[11] The clinical course of cystinosis changed from that of a largely renal disease to a multisystem disorder that can encompass severe corneal and retinal damage,[12] distal myopathy,[13] decreased pulmonary function,[14] impairment of swallowing,[15] deterioration of the central nervous system,[16] endocrinopathies,[17] vascular calcifications,[18] nodular regenerating hyperplasia of the liver,[19] pancytopenia,[20] and male hypogonadism.[21]

Since 1987, therapy for nephropathic cystinosis has centered on the oral administration of cysteamine.[22] When compliance is consistent, cysteamine achieves leukocyte cystine depletion of up to 95%. However, because of inconvenient dosing requirements and barely tolerable side effects, cysteamine compliance is challenging.

Little has been known about the long-term progression of nephropathic cystinotic patients since cysteamine treatment became available. Gahl *et al.*[23] have recently described the natural history of nephropathic cystinosis in a cohort of 100 adults and demonstrated that long-term oral cysteamine therapy mitigates the effects of the disease. Outcome of 10 Dutch cystinotic adults has been studied[24] but no uniform treatment strategy was applied. In 1995, Broyer *et al.*[25] described a cohort of 33 cystinotic French adults, but only five patients were under treatment. In France, in 1999, out of 144 cystinotic patients, Cochat *et al.*[26] reported data from 115 individuals who received cysteamine, but the long-term effect of therapy could not be analyzed. After 10 years, we studied the clinical outcomes of a cohort of French adults with nephropathic cystinosis and the impact of long-term oral cysteamine administration.

RESULTS

Patient characteristics

A total of 86 adult cystinotic patients from 82 pedigrees were included (44 male, 42 female). Twelve patients were from consanguineous families. Mean age at diagnosis was 2.2 years (median 1.5; range 0.5–11.6). Mean age at last follow-up was 26.7 ± 7.0 years (median 25.9; range 15.2–50.1).

The mean age at first clinical symptoms was 11.1 months (median 9; range 3–48). The earliest clinical symptoms were polyuria–polydipsia for 82% of the patients, growth retardation for 63%, and rickets for 41%. All the children had Fanconi's syndrome. Cystine corneal deposits were described at diagnosis in 71% of the patients.

Final adult height was 152.1 cm (range 129–177) and 142.1 cm (range 105–164) for men and women, respectively. Growth hormone was administered to 28 patients (33%), starting at a mean age of 10.0 years (median 10.1; range 3.6–15.6) for a mean duration of 4.3 years (median 2.7; range 0.9–11.7). Among the 58 patients who did not receive growth hormone, 10 individuals (17%) were significantly shorter than the 48 patients (83%) treated with cysteamine (mean 127.8 cm, median 129.0, range 105–150 cm versus mean 147.6 cm, median 147.0, range 111–177; $P_{\text{Wilcoxon}} < 0.001$).

Cysteamine therapy was administered to 75 patients (75/86, 87%), starting at a mean age of 9.9 years (median 4.3; range 0.9–38.6) with a mean duration of 17.4 years (median 18.4; range 0.9–28.4). A total of 48 patients started cysteamine therapy before 8 years of age, one patient started between 8 and 15 years, and 27 patients started after 15 years (Figure 1). For the 75 treated patients, compliance was reported as good for 26 patients (34.6%) and quite good for 31 patients (41.3%). A total of 21 patients had extended periods without treatment (seven missing data). Mean leukocyte cystine level recorded in 78 patients during the overall follow-up was <2 nmol half-cystine/mg protein for 22 patients (28.2%; mean level 1.8), between 2 and 3 for 27 patients (34.6%; mean level 2.3), and >3 for 29 patients (37.2%; mean level 4.3).

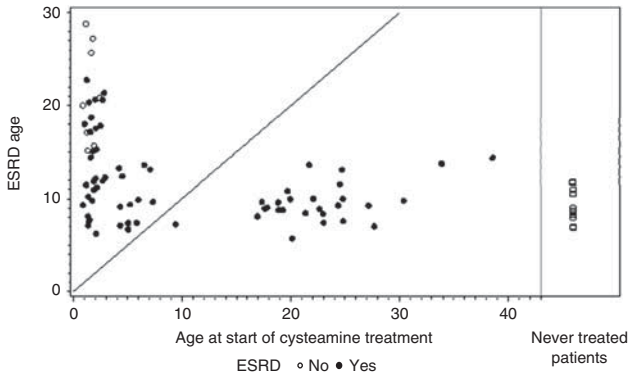

Figure 1 | The age at which end-stage renal disease (ESRD) developed according to the age at which cysteamine therapy was introduced. The $X = Y$ line separates the patients who started cysteamine before ESRD onset ($n = 40$), on the left, and, on the right, the patients who started cysteamine after ESRD onset ($n = 27$). The eight patients without ESRD are displayed with unfilled circle with their age at last follow-up. Patients who were never treated are displayed on the right part of the graph ($n = 11$).

Renal function

ESRD developed in 78 patients (91%) at a mean age of 11.1 years (median 9.9; range 5.7–22.7). A total of 65 patients had received one kidney transplant, 11 patients had received a second kidney graft, and 2 patients had undergone three transplants. The remaining eight patients (9%) who had functioning native kidneys had a mean age of 21.5 years (median 21.0; range 15.2–28.8). Of these, five, one, and two patients, respectively, had chronic kidney disease stages 1, 3, and 4 (ref. 27).

Extrarenal complications

Hypothyroidism was diagnosed in 62 patients (71%) at the mean age of 13.5 years (median 11.5; range 5.8–34.8). Diabetes developed in 48 patients (55.8%) at the mean age of 16.8 years (median 15.3; range 1.1–43.6) and occurred within the first year post transplant in 8/48 patients (16.7%). Neuromuscular disorders were reported in 32 patients (37.2%) at the mean age of 23.3 ± 6.3 years (median 25.9; range 7.0–35.4) and were categorized as follows: myopathy in 22 patients (68.8%), swallowing impairment in 17 (53.1%), paresis in 24 (75.0%), related to stroke in 9 patients (37.5%), mental function deterioration in 18 (56.3%), and seizures in 10 (31.3%). Cerebral imaging was performed in 38.4% of the patients (33/86). Of these, imaging was performed in response to symptoms of neurological disorders in 72.7% (24/33) of the cases, with the remaining 27.3% (9/33) performed systematically. Of the nine patients who underwent systematic imaging, results were normal in 33.3% of cases (3/9) and showed cortical atrophy in the other 66.7%. Tomodensitometry or magnetic resonance imaging performed to explore neurological symptoms were normal (13%) or showed cerebral calcifications (38%), cortical atrophy (33%), or ischemia (25%).

Eighteen patients (20.9%) underwent splenectomy during the period 1975–1997. Since 1997, no splenectomy has been performed. Hypogonadism was reported in 29.5% of the men (13/44). None of the men had children. Among the 42 women, 3 had children (one, one, and two children, respectively). Only four patients (5%) experienced pulmonary insufficiency. All patients exhibited cystine corneal deposits causing photophobia. In total, 12 patients (14%) had corneal erosions, 3 of whom required corneal replacement.

Effects of cysteamine therapy

Renal complications. Patients were separated into three groups: patients who started cysteamine therapy before 5 years of age ($n=40$, 46.5%), after 5 years of age ($n=8$, 9.3%), and those who were not treated before ESRD ($n=38$, 44.2%). The characteristics of those populations are presented in Table 1. The ESRD incidence is decreased in cysteamine-treated patients versus the absence of treatment (Table 2). However, starting cysteamine therapy after 5 years does not significantly decrease the incidence of ESRD in comparison with the absence of treatment. The age at ESRD was 13.4 ± 4.8 years (median 12.2) and 9.6 ± 2.6 years (median 9.5), in the before 5-years- and after 5-years-treated patient groups ($P<0.05$), respectively. Eight patients had chronic kidney disease but did not reach ESRD. All of them had been treated with cysteamine before 2.5 years of age (median 1.5, Figure 1).

Kaplan–Meier survival curves indicated that starting cysteamine therapy before the age of 5 years significantly delayed the ESRD onset (Figure 2a, $P<0.0001$). When cysteamine therapy is started after 5 years of age, ESRD is not significantly delayed in comparison with the absence of treatment (Figure 2a).

Renal survival was analyzed according to compliance to cysteamine therapy and impact of leukocyte cystine level (<3 and >3 nmol half-cystine/mg protein). Patients with good compliance had significantly delayed ESRD in comparison with patients with lower compliance or those not treated (log-rank $P<0.0001$). ESRD occurred significantly later in patients below 3 nmol half-cystine/mg protein than in patients with higher concentrations (Figure 2b, log-rank $P=0.004$).

Extrarenal complications. The influence of the age at cysteamine treatment introduction on the onset of hypothyroidism, diabetes, and neuromuscular disorders was assessed according to whether patients were treated before, after 5 years of age, or not treated before the event (Table 2). The incidence of hypothyroidism, diabetes, and neuromuscular disorders was significantly reduced when cysteamine was started before 5 years of age in comparison with the absence of treatment. Starting therapy after 5 years still decreases the incidence of hypothyroidism and diabetes when compared with no treatment.

Survival curves indicated that treatment started before 5 years of age was associated with significant delay, compared with untreated patients, in the occurrence of hypothyroidism, diabetes, and neuromuscular disorders (log-rank $P<0.001$, see Figures 2c–e). For diabetes and hypothyroidism, a statistical significant delay of the event was still noticed between patients who started treatment after the age of 5 years compared with the absence of treatment ($P<0.001$).

The total number of events among ESRD, hypothyroidism, diabetes, neuromuscular events, and death was significantly lower in the group treated before 5 years than in the other groups (median 2 versus 4; $P<0.001$, Table 1).

Only five patients (5%), with a mean age of 21.4 years (median 20.9, range 15.7–27.2), all treated with cysteamine before 2.5 years of age, did not develop any complications. We analyzed the sequence of onset of complications. Figure 3 shows the age at the first complication onset according to the age at the start of cysteamine treatment. All patients who had the first complication after 15 years of age were treated with cysteamine before 3 years of age. The first complication consisted in ESRD ($61/81=75.2\%$, median age 9.8 years), hypothyroidism ($16/61=19.8\%$, median age 8.7 years), diabetes ($2/81=2.5\%$ median age 4.8 years), and neuromuscular disorders ($2/81=2.5\%$ median age 9.0 years). The percentage of patients who had at least two, three, four, and five complications were 75.6% (median age 12.4 years), 62.8% (median age 17.9 years), 37.2% (median age 24.3 years), and 12.8% (median age 26.8 years), respectively. The most frequent complications were, in the chronological order, ESRD, hypothyroidism, and diabetes.

Educational and socioprofessional outcome. Educational level was set for each patient and categorized into the following four groups: primary school (10.5%), middle school (43.0%), high school (16.3%), and university (30.2%; Table 3). The mean age at the start of cysteamine treatment was 21.0 (median 21.4, range 7.3–33.9), 9.9 (median 4.3, range 1.2–30.4), 6.7 (median 2.6, range 0.9–24.5), and 9.1 (median 4.2, range 0.9–38.6) years, respectively. With regard to the socioprofessional outcome, 17.4% of the patients were not professionally integrated, 39.5% were students, 31.4% were technicians, and 11.6% were senior executives. Their mean age at cysteamine treatment introduction was 16.7 (median 19.3, range 1.2–33.9), 4.4 (median 1.9, range 0.9–19.9), 11.8 (median 5.2, 1.4–38.6), and 14.7 (median 19.9, range 1.2–27.7) years, respectively.

Death. Twenty-four patients died (27.9%): 29.2% (7/24) had never been treated, 8.3% (2/24) had been treated before 5 years of age, and 62.5% (15/24) had been treated after 5 years of age (Table 2).

Survival curves show that life expectancy is significantly improved in the patients treated before the age of 5 years when compared with the absence of treatment ($P=0.03$, Figure 2f). Starting cysteamine after 5 years of age still significantly improves the life expectancy in comparison with the untreated patients ($P<0.05$, Figure 2f).

Table 1 | Characteristics of cystinotic patients according to the age at start of cysteamine treatment

	0–<5 Years (*N*=40) (col.1)	5 Years and more (*N*=8) (col.2)	Untreated before ESRD (*N*=38) (col.3)	Total (*N*=86)	Overall *P*-value	*P*-value (col.1)-(col.2)	*P*-value (col.1)−(col.3)	*P*-value (col.2)-(col.3)
Age (years)								
n	40	8	38	86				
Mean ± s.d.	23.4 ± 4.4	28.0 ± 6.0	29.8 ± 8.0	26.7 ± 7.0	<0.001	NS	<0.001	NS
Min. ; Max.	15.2 ; 31.9	15.3 ; 32.8	15.3 ; 50.1	15.2 ; 50.1				
Median	23.0	30.7	29.3	25.9				
Q1 ; Q3	20.7 ; 26.8	25.1 ; 32.3	23.6 ; 36.6	21.8 ; 31.4				
Sex								
Men	20 (50.0%)	5 (62.5)	19 (50.0)	44 (51.2%)	0.900			
Women	20 (50.0%)	3 (37.5)	19 (50.0)	42 (48.8%)				
Age at diagnosis (years)								
n	40	8	38	86				
Mean ± s.d.	1.8 ± 1.8	2.5 ± 2.0	2.6 ± 2.5	2.2 ± 2.1	0.321			
Min. ; Max.	0.5 ; 11.5	0.6 ; 5.9	0.5 ; 11.6	0.5 ; 11.6				
Median	1.3	1.8	1.6	1.5				
Q1 ; Q3	1.0 ; 1.7	0.9 ; 4.0	1.1 ; 3.0	1.0 ; 2.3				
Leukocyte cystine level (nmol half-cystine/mg protein)								
<2	12 (30.0%)	0 (0.0)	10 (32.3)	22 (28.2%)	0.135			
2–3	17 (42.5%)	2 (28.6)	8 (25.8)	27 (34.6%)				
>3	11 (27.5%)	5 (71.4)	13 (41.9)	29 (37.2%)				
Not recorded	0	1	7	8				
Follow-up (years)								
n	40	8	38	86				
Mean ± s.d.	21.9 ± 4.5	25.5 ± 7.3	27.2 ± 8.0	24.6 ± 7.0	0.004	NS	0.003	NS
Min. ; Max.	13.8 ; 30.6	10.6 ; 31.8	10.0 ; 47.0	10.0 ; 47.0				
Median	21.3	29.2	26.6	23.6				
Q1 ; Q3	18.8 ; 25.1	21.5 ; 30.3	20.5 ; 32.9	19.7 ; 29.3				
Start of treatment with cysteamine (years)					[b]			
n	40	8	27	75[a]				
Mean ± s.d.	2.0 ± 0.9	6.0 ± 0.9	22.6 ± 5.7	9.9 ± 10.3				
Min. ; Max.	0.9 ; 4.5	5.0 ; 7.3	9.4 ; 38.6	0.9 ; 38.6				
Median	1.8	5.9	22.1	4.3				
Q1 ; Q3	1.4 ; 2.3	5.1 ; 6.8	18.9 ; 24.8	1.7 ; 19.7				
Overall number of complications[c] (mean)								
n	40	8	38	86				
Mean ± s.d.	1.8 ± 1.2	3.5 ± 0.8	3.8 ± 1.1	2.8 ± 1.5	<0.001	<0.001	<0.001	NS
Min. ; Max.	0.0 ; 5.0	2.0 ; 4.0	1.0 ; 5.0	0.0 ; 5.0				
Median	2.0	4.0	4.0	3.0				
Q1 ; Q3	1.0 ; 3.0	3.0 ; 4.0	3.0 ; 5.0	2.0 ; 4.0				

Table 1 | Continued

	0–<5 Years (N=40) (col.1)	5 Years and more (N=8) (col.2)	Untreated before ESRD (N=38) (col.3)	Total (N=86)	Overall P-value	P-value (col.1)-(col.2)	P-value (col.1)–(col.3)	P-value (col.2)-(col.3)
Overall number of complications (n, %)								
0	5 (12.5)	0 (0.0)	0 (0.0)	5 (5.8%)	<0.001[d]	0.001	<0.001	NS
1	14 (35.0)	0 (0.0)	2 (5.3)	16 (18.6%)				
2	9 (22.5)	1 (12.5)	1 (2.6)	11 (12.8%)				
3	9 (22.5)	2 (25.0)	11 (28.9)	22 (25.6%)				
4	2 (5.0)	5 (62.5)	14 (36.8)	21 (24.4%)				
5	1 (2.5)	0 (0.0)	10 (26.3)	11 (12.8%)				

Abbreviations: Col., column; ESRD, end-stage renal disease; Max., maximum; Min, minimum; NS, not significant; Q1: lower quartile (25%); Q3: upper quartile (75%); s.d., standard deviation.
[a]Eleven patients did not receive any treatment. No statistical test was performed for this parameter.
[b]No statistical test was performed as the parameter represents the groups' definition.
[c]Complications are: end-stage renal disease, hypothyroidism, diabetes, neuromuscular disorder, or death.
[d]Monte Carlo estimate (exact P-value could not be calculated because of a too large number of rows and columns).
The overall test used non-parametric test for quantitative parameters and Fisher's exact test for qualitative parameters. Two-by-two comparisons were performed using Hochberg adjusted test and are only displayed for statistically significant overall tests.

Causes of death were linked to cystinosis or related to renal failure. Patients treated before 5 years of age died from infection ($n=1$) and neurological reasons ($n=1$). In the group treated after 5 years of age, death occurred because of pulmonary edema ($n=2$), infections ($n=2$), neurological reasons ($n=4$), suicide ($n=1$), respiratory distress due to swallowing impairment ($n=4$), trauma ($n=1$), and for one patient the cause remained unknown. The non-treated patients died from pulmonary edema ($n=1$), infections ($n=2$), digestive hemorrhage ($n=1$), and neurological reasons ($n=3$).

CTNS mutation

Genetic screening data were available for 68 patients (79%). Results showed that 66 patients were homozygous or heterozygous for a severe *CTNS* mutation, as already described.[1,3,28] Among them, 28 patients were homozygous for the 57-kb *CTNS* deletion, 15 patients were compound heterozygous for that deletion and for a second mutation, and 23 patients were homozygous or heterozygous for another severe mutation. One patient was heterozygous carrying one severe mutation, whereas the second mutation could not be detected. One patient was homozygous for a mild mutation (splice site mutation, G110V).[29,30]

We compared the 28 patients homozygous for the 57-kb deletion with the other 40 patients. These two groups had similar mean age, 26.3 ± 6.5 (range, 15.7–39.9) and 27.4 ± 6.7 years (range, 15.1–41.1), respectively ($P=$ not significant). The mean age at the start of cysteamine treatment was 10.1 (range 1.2–30.4) years and 8.4 years (range 0.9–33.9; $P=$ not significant), respectively. Patient's survival was not different between the two groups. Occurrence of renal and extrarenal complications (hypothyroidism, diabetes, neuromuscular disorders) was not significantly different.

The patient with the mild mutation reached ESRD at 13.8 years. She neither had hypothyroidism nor had diabetes. Neuromuscular disorder set at 35.4 years of age and the patient died at 39.4 years of age.

DISCUSSION

The analysis of this cohort of 86 adults with nephropathic cystinosis shows that early treatment with cysteamine has a positive effect on the onset of renal and extrarenal complications.

That is a second description of a large cohort of cystinotic patients after National Institutes of Health cohort published by Gahl *et al.* in 2007 (ref. 23). A French cohort of infantile cystinosis was described by Cochat *et al.*[26] in 1999 as an epidemiological study. The novelty of our study relies on the early introduction of cysteamine and an extended follow-up until adulthood.

Our study suggests a mortality benefit from therapy, consistent with previous data from Gahl *et al.*[23] Mortality rate of cystinosis in adulthood approximates one-third and death occurs before 30 years of age. The causes of death in our population, which were mostly infections or events

Table 2 | Complications of cystinotic patients according to the age at start of cysteamine treatment

	0–<5 Years (col.1)	5 Years and more (col.2)	Untreated before event (col.3)	Total (*N*=86)	Overall *P*-value	*P*-value (col.1)-(col.2)	*P*-value (col.1)–(col.3)	*P*-value (col.2)–(col.3)
ESRD (Y/N)								
No	8 (20.0%)	0 (0.0%)	0 (0.0%)	8 (9.3%)	0.006	NS	0.001	NS
Yes	32 (80.0%)	8 (100.0%)	38 (100.0%)	78 (90.7%)				
Age at ESRD (years)								
n	32	8	38	78				
Mean ± s.d.	13.4 ± 4.8	9.6 ± 2.6	9.5 ± 2.0	11.1 ± 4.0	<0.001	0.048	<0.001	NS
Min. ; Max.	6.3 ; 22.8	6.7 ; 13.6	5.7 ; 14.4	5.7 ; 22.8				
Median	12.2	9.5	9.0	9.9				
Q1 ; Q3	9.6 ; 17.7	7.4 ; 11.5	8.3 ; 10.5	8.4 ; 13.1				
Hypothyroidism (Y/N)								
No	19 (47.5%)	4 (26.7%)	1 (3.2)	24 (27.9%)	<0.001	NS	<0.001	0.027
Yes	21 (52.5%)	11 (73.3)	30 (96.8)	62 (72.1%)				
Age at hypothyroidism (years)								
n	21	11	29	61				
Mean ± s.d	13.5 ± 4.7	17.9 ± 7.3	11.7 ± 5.9	13.5 ± 6.2	0.010	NS	NS	0.003
Min. ; Max.	6.1 ; 23.9	9.5 ; 29.2	5.8 ; 34.8	5.8 ; 34.8				
Median	12.7	14.5	10.4	11.5				
Q1 ; Q3	10.1 ; 16.9	10.9 ; 25.9	8.5 ; 13.7	9.1 ; 16.2				
Diabetes (Y/N)								
No	29 (72.5%)	6 (35.3)	3 (10.3)	38 (44.2%)	<0.001	0.010	<0.001	0.049
Yes	11 (27.5%)	11 (64.7)	26 (89.7)	48 (55.8%)				
Age at diabetes (years)								
n	11	11	26	48				
Mean ± s.d.	17.6 ± 6.1	21.6 ± 10.1	14.4 ± 5.3	16.8 ± 7.3	NS			
Min. ; Max.	9.1 ; 28.9	8.0 ; 43.6	1.1 ; 25.6	1.1 ; 43.6				
Median	16.6	21.1	13.7	15.3				
Q1 ; Q3	13.0 ; 21.2	14.2 ; 27.7	11.7 ; 18.2	11.9 ; 20.8				
Neuromuscular disorders (Y/N)								
No	34 (85.0%)	13 (46.4)	7 (38.9)	54 (62.8%)	<0.001	0.002	0.001	NS
Yes	6 (15.0%)	15 (53.6)	11 (61.1)	32 (37.2%)				
Age at neuromuscular disorders (years)								
n	6	15	11	32				
Mean ± s.d.	17.8 ± 5.2	26.6 ± 5.4	21.9 ± 5.5	23.3 ± 6.3	0.012	0.002	NS	NS
Min. ; Max.	11.0 ; 23.4	18.2 ; 35.4	7.0 ; 27.2	7.0 ; 35.4				
Median	19.6	26.7	24.0	23.7				
Q1 ; Q3	11.8 ; 21.4	22.5 ; 31.5	20.6 ; 25.1	20.0 ; 26.9				

Table 2 | Continued

	0–<5 Years (col.1)	5 Years and more (col.2)	Untreated before event (col.3)	Total (*N*=86)	Overall *P*-value	*P*-value (col.1)-(col.2)	*P*-value (col.1)-(col.3)	*P*-value (col.2)-(col.3)
Death (Y/N)								
No	38 (95.0%)	20 (57.1)	4 (36.4)	62 (72.1%)	<0.001	<0.001	<0.001	NS
Yes	2 (5.0%)	15 (42.9)	7 (63.6)	24 (27.9%)				
Age at death (years)								
n	2	15	7	24				
Mean ± s.d.	22.3 ± 1.2	29.7 ± 8.0	21.7 ± 5.0	26.8 ± 7.8	NS			
Min. ; Max.	21.4 ; 23.1	15.3 ; 40.0	15.3 ; 26.8	15.3 ; 40.0				
Median	22.3	29.4	23.2	26.0				
Q1 ; Q3	21.4 ; 23.1	22.8 ; 37.3	15.5 ; 26.3	21.1 ; 32.0				

Abbreviations: Col., column; ESRD, end-stage renal disease; Max, maximum; Min, minimum; N, no; NS, not significant; Q1, lower quartile (25%); Q3, upper quartile (75%); s.d., standard deviation; Y, yes.
The overall test used non-parametric test for quantitative parameters and Fisher's exact test for qualitative parameters. Two-by-two comparisons were performed using Hochberg adjusted test and are only displayed for statistically significant overall tests.

related to neuromuscular complications, were comparable to those identified by Gahl *et al.*[23] and to data from the ERA–EDTA registry.[31] The causes of death have evolved during recent decades. More than 20 years ago, patients died from uncontrolled water and electrolyte disturbances, as well as from uremia.[26,32]

Renal complications are improved by cysteamine. Cysteamine makes it possible to delay the occurrence of ESRD if therapy is introduced before the age of 5 years. In untreated patients, the mean age for ESRD is 9.6 years,[10] and the speed of renal loss is slower under treatment.[33] In the study by Cochat, patients reached ESRD at a mean age of 9.8 years, even though 83% had received treatment,[26] probably due to the late introduction of cysteamine (7.3 years). The mean age of ESRD in our study is 11.1 years (median 9.9). In Gahl's study,[23] 92% of the patients were kidney transplanted at the mean age of 12.3 years. In our study, and that of Gahl *et al.*,[23] 9% and 8% of patients, respectively, did not need renal replacement therapy at the age of 20 years. In our cohort, patients who did not develop ESRD started treatment at a mean age of 1.5 years. In the study by Gahl *et al.*,[23] the eight non-dialyzed patients were all considered by the authors to have been adequately treated; that is, treated for more than 8 years.

Extrarenal complications such as hypothyroidism, diabetes, and neuromuscular disorders are less frequent and delayed when cysteamine has been administered before 5 years of age. Starting therapy after 5 years of age still delays hypothyroidism and diabetes. Gahl *et al.*[23] reported that the incidence of diabetes, hypothyroidism, and myopathy increased with the duration of non-treatment and decreased with longer treatment. In most studies, hypothyroidism and diabetes mellitus have occurred in 75%[34,35] and 24–50%[23,35,36] of the cases, respectively. Hypothyroidism and diabetes were the earliest extrarenal complications to develop, as confirmed in our study. Development of diabetes after renal transplantation is more common in cystinotic patients than in patients transplanted for other causes;[36,37] however, cysteamine may ameliorate the diabetogenic impact of corticosteroids by delaying the age of renal transplantation and by a direct effect on cystine accumulation in the β-cells. Prognosis appears to be primarily related to neuromuscular complications. More than one-third of the patients developed a neuromuscular event at a mean age of 24 years. Gahl *et al.*[23] observed a 50% incidence of myopathy and 60% incidence of swallowing abnormalities. In our study, cerebral calcifications were observed during imaging in more than one-third of the patients with neurological symptoms, and atrophy in 20% of the patients. However, atrophy was also reported in two-thirds of the patients with no major clinical abnormality, as observed elsewhere.[38] Hepatosplenic complications became rare with routine use of cysteamine. In our cohort, 21% of the patients underwent splenectomy because of portal hypertension, but none was performed after 1997.

Lifelong cysteamine treatment should be taken in order to prevent renal and extrarenal complications of cystinosis.

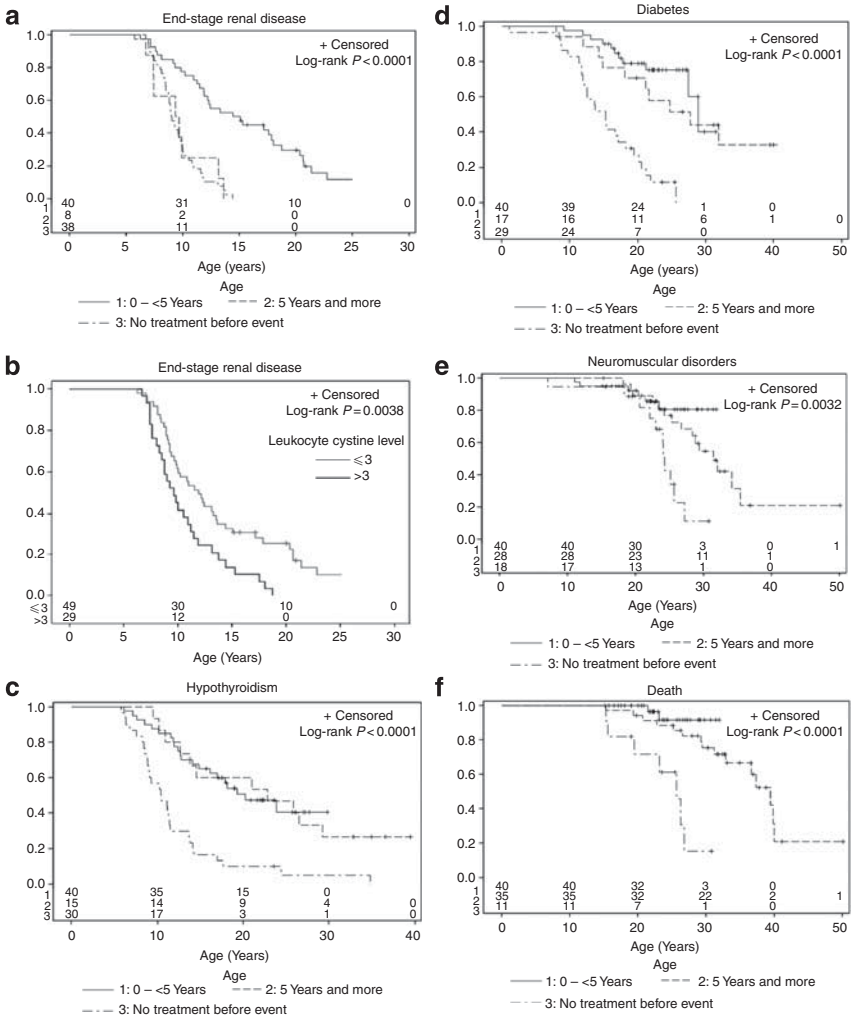

Figure 2 | Survival curves using Kaplan–Meier analysis ($n = 86$). (**a**) End-stage renal disease (ESRD) according to age at start of cysteamine treatment: patients were separated into three groups whether cysteamine was introduced before or after 5 years. The third group corresponds to the patients not treated before ESRD. (**b**) End-stage renal disease according to leukocyte cystine level (<3 or >3 nmol half-cystine/mg protein). Eight missing data. (**c**) Onset of hypothyroidism according to the age at start of cysteamine treatment (before or after 5 years, or not treated before hypothyroidism). (**d**) Onset of diabetes according to the age at start of cysteamine treatment (before and after 5 years, or not treated before diabetes). (**e**) Onset of neuromuscular disorder according to the age at start of cysteamine treatment (before or after 5 years, or not treated before neuromuscular disorder). (**f**) Death according to the age at start of cysteamine treatment (before or after 5 years, or not treated). The numbers below the curves are the number of patients at risk in the risk groups at different ages.

In the study of Gahl *et al.*,[23] adequate treatment considered as already substantial was fixed at 8 years of age. We showed that a treatment started before 5 years of age decreased the incidence of complications. Age at the start of treatment was not mentioned in the study carried out by Gahl *et al.*[23] In our historical cohort, the mean age of cysteamine introduction is 9.9 years. As the course of the disease was not yet described, cysteamine therapy was stopped at the time of renal transplantation. Furthermore, when extrarenal complications were found to be related to cystinosis, cysteamine was reintroduced. This may explain why only one patient from our study started cysteamine therapy between the age of 8 and 15 years. The treatment was prescribed continuously throughout life since 1995. Cysteamine should be introduced before 5 years of age. However, we still recommend starting cysteamine as early as possible after diagnosis.

The better outcome of the cystinotic patients during the last decade could also be caused by other medical and non-medical factors. Early recognition of cystinosis allowed starting an adequate supportive therapy quickly. Patients benefit from improvement of renal transplantation outcome and progresses in diabetes medications. Cystinotic patients' families profit by better social and psychological support. Thus, improvement in symptomatic treatment of extrarenal complications and outcomes following renal transplantation has potentially contributed to higher survival.

Adherence to cysteamine treatment is poor for two reasons. First, the pharmacokinetics of the drug imposes

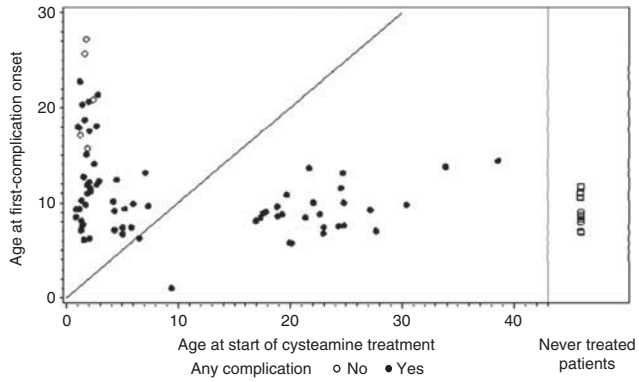

Figure 3 | The age at first complication onset (end-stage renal disease, hypothyroidism, diabetes, neuromuscular disorder, or death) according to the age at cysteamine treatment start. The $X = Y$ line separates the patients who started cysteamine before the onset of the first complication ($n = 42$), on the left, and, on the right, the patients who started cysteamine after any complication onset ($n = 28$). The five patients without complications are displayed with unfilled circle with their age. Patients who were never treated are displayed on the right part of the graph ($n = 11$).

Table 3 | Educational level and professional status with the age at start of cysteamine treatment

Educational level	Number of patients (percentage)	Age at start of treatment (in years)
Primary school	9 (11%)	21.0 [7.3–33.9]
Middle school	37 (43%)	9.9 [1.2–30.4]
High school	14 (16%)	6.7 [0.9–24.5]
University	26 (30%)	9.1 [0.9–38.6]
Professional status		
None	15 (18%)	16.7 [1.2–33.9]
Student	34 (39%)	4.4 [0.9–19.9]
Technician	27 (31%)	11.8 [1.4–38.6]
Senior executive	10 (12%)	14.7 [1.2–27.7]

Number, N (percentage). Mean [range].

the need for oral dosing every 6 h. Second, side effects such as nausea and halitosis are frequent. In the study by Cochat *et al.*,[26] the rate of non-adherence was estimated to be 62%. Evaluation of the compliance to cysteamine treatment throughout life is difficult as it changes from childhood, when parents look after their children, to puberty, when adherence is poor, and adulthood, when adherence is inconstant. In our study, the leukocyte cystine level was optimal in only 28% of the patients. Research is under way to develop a formulation that can be taken twice daily.[39] Interestingly, a recent experimental work showed that using hematopoietic stem cells is an efficient therapy to prevent cystine accumulation in cystinosis mice.[40] This new perspective of treatment needs further studies.

Although cysteamine treatment has improved the care and management of cystinotic patients over the past 20 years, the disease continues to disrupt the educational and professional life of patients. In 1999, Guest *et al.*[41] described the professional outcome of 36 cystinotic patients: 28% were handicapped, 39% were students, and 33% were employed. In our cohort, 17% were at home, 40% were students, and 43% were employed. We might expect a better professional outcome for cystinotic patients if optimized treatment could be achieved.

Our study has limitations. It is a retrospective study that included patients whose diagnosis of cystinosis was made between 1961 and 1995. There may be survivor bias, especially for the early diagnosed patients in the 1960s. Improvement in supportive treatment for renal and extra-renal complications could potentially contribute to higher survival among later patients.

In conclusion, this large series confirms the severe impact of cystinosis, both in clinical terms and in relation to socioprofessional outcomes. Our findings indicate that cysteamine reduces and delays the incidence of renal and extrarenal complications. On the basis of these results, we recommend that cysteamine treatment should be started as early as possible, at the time of diagnosis. Pediatric and adult clinicians must insist on adherence to the treatment regimen.

PATIENTS AND METHODS

Patients

Adult patients, at least 15 years old, in whom nephropathic cystinosis had been diagnosed between 1961 and 1995 in France were included. Patient's data were collected from historically referent hospitals (Lyon–Herriot and Paris–Necker Hospital). French pediatric and adult nephrologists were asked about their patients. Study conduct complied with the Declaration of Helsinki Principles.

Criteria for diagnosis and compliance

The diagnosis of cystinosis was based on evidence of cystine corneal deposits and/or elevated leukocyte cystine level >3 nmol half-cystine/mg protein.[42] Fanconi's syndrome diagnosis was based on standard clinical and biological criteria,[43] including polyuria–polydipsia, electrolyte imbalance, dehydration, rickets, and growth failure. Estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula[44] or the Schwartz equation.[45,46]

Compliance to cysteamine treatment was graded by the physician according to the patient questioning: good, quite good, or extended period without treatment. Leukocyte cystine level (expressed as nanomoles of half-cystine/mg protein, normal <0.15), measured before the cysteamine uptake, was determined using liquid chromatography–tandem mass spectroscopy (API 3000LC/MS/MS; Applied Biosystems/MDS Sciex, Foster City, CA).[47]

Hypothyroidism was diagnosed if a patient was receiving L-thyroxine replacement therapy. Diabetes mellitus was diagnosed when the patient was receiving insulin therapy. With regard to the neurological complications, myopathy was defined clinically by wasting of the distal muscles of the hand. Swallowing abnormalities were diagnosed on the basis of a

detailed examination showing impairment. Paresis is characterized by a partial loss of movement. Patients were described to have mental function deterioration when they had an obvious cognitive impairment. Hypogonadism was reported when a substitutive hormonal treatment had to be prescribed according to clinical examination and hormonal analysis.

CTNS mutations

Blood samples for DNA studies were drawn after obtaining informed consent from patients. Mutations were detected as described elsewhere.[3,5]

Statistical analysis

Data were collected in an Excel data sheet and transferred to SAS data sets. The quantitative variables were described by mean ± s.d., range (minimum, maximum), median, and quartiles, and compared when necessary, using a non-parametric Wilcoxon test for the overall comparison. The qualitative variables were presented by the number of observations and percentages. Binary variables were analyzed by the Fischer's exact test. If the overall test was statistically significant, multiple comparisons were made using Hochberg adjusted test (SAS 9.2 proc multtest option *ad hoc*) for quantitative variables after data ranking and for qualitative variables. Survival analysis was performed using Kaplan–Meier analysis with overall log-rank testing and Bonferroni method for two-by-two comparisons. SAS 9.2 was used for data management and all calculations. Statistical significance was set to 5%.

DISCLOSURE

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