Improvement in the Renal Prognosis in Nephropathic Cystinosis

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Summary

Background and objectives Nephropathic cystinosis (NC) is an autosomal recessive disorder occurring in one to two per 100,000 newborns. Because of the rarity of NC, long-term outcome data are scarce.

Design, setting, participants, & measurements 245 NC patients from 18 countries provided data to the ESPN/ERA-EDTA registry. We matched NC patients on renal replacement therapy (RRT) to non-NC children on RRT.

Results Between 1979 and 2008, mean age at the start of RRT among NC children increased by 0.15 year per calendar year (95% confidence interval, 0.10 to 0.21) from 8.8 to 12.7 years, whereas we did not observe this in non-NC children. Five-year survival after the start of RRT improved in NC patients from 86.1% (before 1990) to 100% (since 2000) as compared with the control population (89.6% and 94.0%). NC patients received a renal allograft more often (relative risk, 1.09; 95% confidence interval, 1.00 to 1.17) as compared with matched RRT children, and 5-year graft survival was better (94.0% *versus* 84.0%). NC dialysis patients were less often hypertensive than non-NC children matched for age, country, and dialysis modality (42.7% *versus* 51.7%) and had lower parathyroid hormone levels (median, 56 *versus* 140 pg/ml). Although height at start of RRT slightly improved during the past decade, children with NC remained significantly shorter than non-NC children at the start of RRT.

Conclusions We demonstrated improved survival of the renal function as well as better patient and graft survival after the start of RRT in a large European cohort of NC patients over the last two decades.

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Introduction

Cystinosis is a rare autosomal recessive disorder of lysosomal cystine transporter cystinosin encoded by the CTNS gene (17p13) (1). The disease affects approximately one to two in 100,000 newborns with a higher incidence in some North European regions such as Nord Pas de Calais and Bretagne in France (2). On the basis of the severity of the disease, cystinosis is subdivided in the most frequent and severe infantile form, a juvenile form that is characterized by less severe renal disease, and a benign form with primarily ocular symptoms. Infantile and juvenile forms are termed nephropathic cystinosis (NC). During early childhood, kidneys represent the primarily affected organs in NC, and nearly all patients develop renal Fanconi syndrome during the first year of life and without treatment progress to ESRD before the age of 10 years (3).

Cysteamine was first introduced as a potential treatment for NC in 1976 (4) but was only used on a broader scale at the end of the 1980s when its efficiency in preserving renal function was demonstrated (5,6). Because of the rarity of the disorder, long-term outcome data are scarce, and they are usually unadjusted for general improvements in renal care. Some studies indicate improved prognosis of patients treated with cysteamine (6–8). Unfortunately, this drug has little or no effect on the Fanconi syndrome, and it delays but does not prevent progression to ESRD in the majority of patients. Furthermore, treatment needs to be continued after the start of renal replacement therapy (RRT) for protecting extrarenal organs (3).

Partial treatment with cysteamine is not very effective in retarding the progression of ESRD (6,8). "Adequate" therapy includes an early diagnosis, thereby early initiation of cysteamine, possibly before 2 years of age, a strict 6-hour schedule, and regular monitoring of intraleukocyte cystine levels to adapt the daily dose (9). Patients who have been "adequately" treated have grown up to adulthood in recent years, allowing analysis of the effect of cysteamine treatment on renal outcome in NC. In addition, poor compliance is a recurrent problem of cysteamine treatment, particularly in adolescents, because of the stringent treatment schedule and foul odor; the effect of noncom-

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pliance is often underestimated in clinical trial settings. Furthermore, long-term data collected in single centers of excellence having extensive experience in treating NC patient may not reflect those in the NC population as a whole. To estimate long-term outcome of NC patients on a larger scale, we analyzed data from European Society for Paediatric Nephrology (ESPN)/European Renal Association and European Dialysis and Transplant Association (ERA-EDTA) registry collected between 1979 and 2008.

Materials and Methods

Data Collection

Within the framework of the ESPN/ERA-EDTA registry, information was available on a total of 245 patients with NC from Austria, Belgium, Denmark, France, Hungary, Iceland, Italy (dialysis patients only), the Netherlands, Norway, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom, whereas there were no patients reported in another 13 countries. The data included at least the following information: date of birth, gender, initial treatment modality on RRT (hemodialysis [HD], peritoneal dialysis [PD], or preemptive transplantation), changes in RRT modality during follow-up, and the underlying renal disease (10). We identified NC patients using codes for renal diseases according to the ERA-EDTA coding system (11). For a subset of the patients, more extensive data on clinical and biologic indicators such as height, weight, BP, antihypertensive medication (yes/no), albumin, hemoglobin, phosphate, and parathyroid hormone (PTH) levels were collected.

Data Analyses

Height and BP were expressed as SD scores (SDS). SDS for height was calculated using the Centers for Disease Control and Prevention growth charts (12). SDS for systolic and diastolic BP, adjusted for age, gender, and height (heights below −3 SDS were set to −3 SDS) (13) were computed according to the National High Blood Pressure Education Program Fourth Report (14). Hypertension was defined as systolic and/or diastolic BP SDS ≥1.64. PTH failed to pass normality tests and was log-transformed in the analyses.

Statistical Analyses

We created three different matched-control cohorts to control for relevant confounding factors that we identified by preliminary data analysis; matching criteria are summarized in Table 1. To detect possible "transition points" in the relationship between mean age at the initiation of RRT and calendar year, we developed a linear-splines model. We determined 5-year patient and graft survival by performing Kaplan–Meier analysis, thereby censoring follow-up time when a patient reached the age of 20 years, the end of the study, or 5 of years follow-up, whichever came first. Analyses on treatment modality were performed using logistic regression analyses, and relative risks were calculated. To avoid a biased patient sample, we imputed missing clinical parameters as recommended by the STROBE guidelines (15). Analyses were adjusted for age, gender, treatment modality, calendar year of initiation of RRT, and duration of RRT. As measurements within patients are correlated, analyses were performed using linear and logistic mixed model analyses. Furthermore, weighted analyses, on the basis of the number of measurements per patient were performed to determine the percentage of patients treated with antihypertensive medication. All of the analyses were performed in SAS 9.2.

Table 1. Characteristics of the different cohorts used in the analyses, matching criteria, and inclusion criteria

	Cohort 1 (Analyzes Age at Start)	Cohort 2 (Characteristics)	Cohort 3 (Clinical Analyses)
Controls serving to...	Study differences in mean age of start of RRT	Study treatment modality at start of RRT and during follow-up	Study clinical parameters in dialysis patients
Number of controls for each NC patient	2	2	3
Country	MC	MC	MC
Calendar year start RRT	MC	MC (2-year intervals)	
Age at start RRT		MC (2-year intervals)	MC (2-year intervals)
Gender	MC		
Treatment modality			MC
year of start RRT	1979 to 2008	1995 to 2008	1995 to 2008
inclusion criteria	Data collection over 18 years		
countries included	Austria, Denmark, Iceland, Italy, Spain, Sweden, Switzerland, the Netherlands, and the United Kingdom	Austria, Belgium, Denmark, France, Hungary, Iceland, Italy, the Netherlands, Norway, Poland, Portugal, Russia, Serbia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom	Belgium, Denmark, France Italy, Norway, Poland, Portugal, Serbia, Slovenia Spain, and the United Kingdom

MC, matching criterion was used to identify control subjects; NC, nephropathic cystinosis; RRT, renal replacement therapy.

Results

Age at Start of RRT and Survival on RRT

Between 1979 and 2008, 185 NC patients started RRT in countries that were able to provide a complete follow-up. Over this period, there was a progressive improvement (*e.g.,* increase) in the age distribution at the start of RRT in patients with cystinosis (Figure 1). The median age of initiation of RRT was 8.8 years in the cohort of 1979 to 1984 and 8.7 years in the cohort of 1985 to 1990. The linear splines model identified two time points at which the mean age seemed to increase more rapidly, namely in 1990 and 1996. Between 1990 and 1996, the mean increase in age was 0.14 years per calendar year (95% confidence interval [CI], −0.41 to 0.68; $P = 0.63$), whereas it increased by 0.29 years (95% CI, 0.11 to 0.48; $P = 0.002$) from 1996 onwards. The increase in mean age was not observed in the control cohort 1, *i.e.,* the matched cohort of non-NC pediatric RRT patients.

Patient survival after the start of RRT improved over time. Among NC patients who started RRT before 1990 the 5-year survival was 86.1%; it increased to 96.9% for those who started between 1990 and 1999 and was 100% in those who started RRT thereafter. The improvement was less prominent in the control population, where it increased from 89.6% before 1990 to 95.9% and 94.0% in the later periods. However, differences in survival between the groups were not statistically significant.

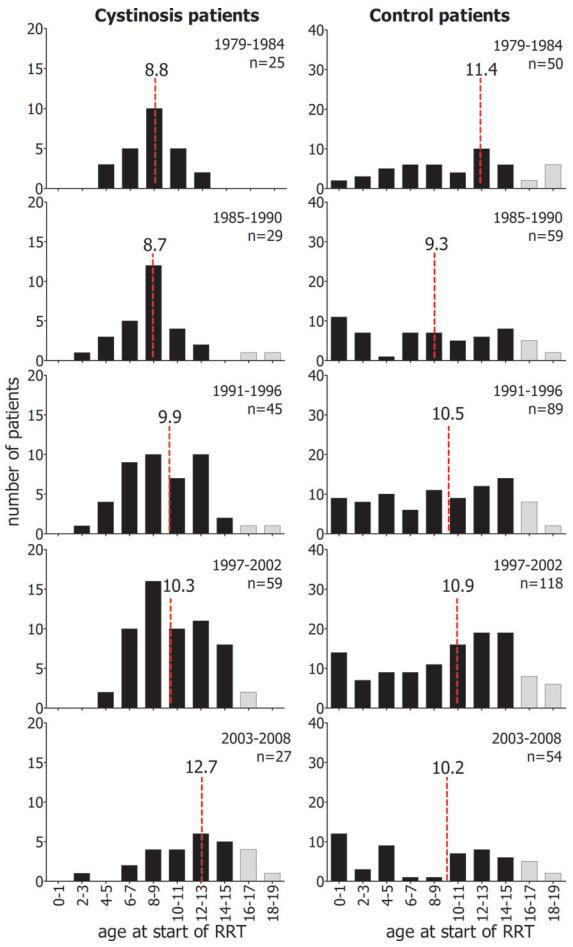

Figure 1. | Age distribution of patients starting renal replacement therapy (RRT) in different eras. Median age at start is indicated with the red dotted line. Because the data of patients over 15 years of age are likely to be incomplete and therefore an underrepresentation of the true numbers, they are indicated with the gray bars.

General Patient Characteristics and RRT Modality

NC patients were compared with the general pediatric RRT population—*i.e.,* control cohort 2—among those who started RRT after 1994 and were matched on age at start of RRT (mean age was 10.8 for NC patients and 10.7 for control patients) and country and calendar year (Table 1). The duration of follow-up (2.8 years in both groups) and gender distribution were similar, with a slight predominance of male patients (Table 2). The frequency of PD treatment as the first treatment modality was similar in both groups, but patients with NC were somewhat less likely to initiate HD, although not significantly (odds ratio [OR], 0.58; 95% CI, 0.33 to 1.02; $P = 0.06$), and had higher rates of preemptive transplantation (OR, 2.1; 95% CI, 1.3 to 3.6; $P = 0.03$) than non-NC patients. We did not observe significant differences in the source of the renal allografts (living donor graft: 23 out of 47 preemptive transplants [48.9%] in NC patients as compared with 28 out of 46 [61.4%] in controls; $P = 0.39$). During the observation period on dialysis, 64 (0.55 per patient) and 151 (0.66 per patient) additional transplants were performed in NC and control patients, respectively. At transplantation, after a period of dialysis in 21.4% of the NC and in 24.5% of the control patients, the organ was from a living donor. Four NC patients (3%) and 18 control subjects (6.7%) received a second transplant, whereas two control subjects received three transplants. At the last data collection, nearly 85% of NC patients had a renal allograft, as compared with 69% of patients in the control cohort ($P = 0.02$). Overall, patients with NC had a higher chance of receiving a renal transplant (relative risk, 1.09; 95% CI, 1.00 to 1.17; $P = 0.04$). NC patients had a significantly better 5-year graft survival (94.0%) than non-NC patients (84.0%, $P = 0.02$) (Figure 2).

Clinical Indicators

NC patients were significantly shorter ($P = 0.002$) at the start of RRT (−2.61 SDS) compared with their peers matched on country, age at start, and treatment modality (cohort 3, −1.65 SDS) (Table 3). A similar difference was observed after transplantation. Both NC and non-NC patients who started RRT in the period between 1995 and 1999 were slightly shorter (−2.8 and −1.8 SDS at the start of RRT, respectively) than those who started RRT after 1999 (−2.5 and −1.6 SDS at start of RRT, respectively); the P value for interaction was 0.33. The difference seemed much larger in children who started RRT before the age of 13 years (adjusted difference, 0.97; 95% CI, −1.74 to −0.19) but was no longer significant in children who started RRT after the age of 13 years (difference, 0.24; 95% CI, −1.4 to 0.90); however, the P value for interaction was NS ($P = 0.82$).

There were no differences between NC and non-NC patients with respect to hemoglobin, albumin, or phosphate levels. PTH levels were significantly lower in NC patients ($P = 0.003$) and were within the normal range

Table 2. General characteristics of nephropathic cystinosis patients compared with an age-matched cohort of pediatric RRT patients

	Nephropathic Cystinosis Patients (n = 134)	Matched Pediatric RRT Population (n = 268)
Age at start of RRT (years)	10.8	10.7
Duration of follow-up (years)	2.8 years	2.8 years
Gender		
female, n (%)	59 (44.0%)	119 (44.0%)
male, n (%)	75 (56.0%)	149 (55.6%)
RRT treatment at start		
HD, n (%)	24 (17.9%)	86 (32.2%)
PD, n (%)	53 (39.6%)	112 (41.8%)
Tx, n (%)	47 (35.1%)	46 (17.1%)
unknown, n (%)	10 (7.5%)	24 (9.0%)
Last known RRT treatment (missing in 7% of control subjects)		
HD, n (%)	8 (6.0%)	32 (11.9%)
PD, n (%)	11 (8.2%)	35 (13.1%)
Tx, n (%)	114 (85.1%)	184 (68.7%)
death, n (%)	1 (0.8%)	10 (3.7%)

All of the patients started RRT after the calendar year 1995. The patients were matched on calendar year of the start of RRT (2-year intervals) and age at the start of RRT (2-year intervals). RRT, renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; Tx, transplantation.

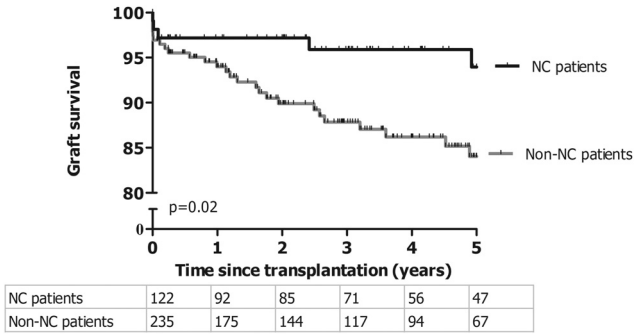

Figure 2. | Five-year graft survival of patients with nephropathic cystinosis (NC) and non-NC patients.

(median, 59 pg/ml; 95% CI, 34 to 91), whereas this was 140 pg/ml among their matched counterparts (95% CI, 101 to 189). Finally, NC patients were less often hypertensive (P = 0.04).

Discussion

In this paper, we provide an analysis of children with NC on RRT and compared them with a matched cohort of non-NC children on RRT from a large European pediatric database in the period 1979 to 2009. In NC patients, the mean age at the start of RRT increased, whereas it remained similar or showed a slight decrease in their matched counterparts. NC patients more often received a renal allograft, were less hypertensive, and had lower, close to normal PTH levels. Furthermore, although their height at start of RRT improved over time, it remained significantly shorter than in other children on RRT. Five-year patient and renal graft survival was better in the NC patients as compared with the non-NC pediatric RRT patients.

Increased Age at Start of RRT in NC Patients

We showed that in the period of 2003 to 2008, patients with NC started RRT more than 4 years later compared with 20 years earlier. We did not observe this increase in mean age at the start of RRT in patients suffering from other causes of renal failure and even noted a slight decrease in the 1980s. This was due to the more frequent treatment of infants with RRT, because the percent of children starting RRT younger than the age of 2 years increased from 4% before 1984 to 10% to 20% in the later periods (16).

The increase in mean age in NC patients commenced from 1990 onwards, with an even sharper increase starting from 1999. These findings are in contrast to those from a data analysis of the European NC patient cohort treated with RRT between 1964 and 1994, which was not yet able to demonstrate a change in age at the initiation of RRT (17). Although the exact information on cysteamine treatment was not registered, cysteamine was introduced on a wide scale in Europe starting in the late 1980s/early 1990s, and we believe that the better preservation of renal function in NC patients is most likely a consequence of cysteamine use. In 1976, Thoene *et al.* (4) demonstrated its efficiency to reduce lysosomal cystine accumulation in cystinotic fibroblasts and white blood cells and *in vivo* in white blood cell granules isolated after intravenous administration of the drug. Several studies demonstrated that cysteamine postponed the deterioration of renal function in patients with NC (5–7,18), stimulating its wide use in most of the developed countries. How cystine depletion by cysteamine can be translated into the preservation of the GFR is not fully understood. Apart from cystine depletion, the anti-oxidant properties and anti-apoptotic effects of cysteamine might play a role in renoprotection (4,19–23).

Because we did not have information on the use and availability of cysteamine in eastern European countries,

Table 3. Clinical course in nephropathic cystinosis dialysis patients *versus* the matched dialysis population

	Nephropathic cystnosis Patients (n = 57)	Matched Pediatric RRT Population (n = 171)	Unadjusted P Value/Adjusted P Value[a]
Median height SDS at start of RRT (95% CI)	−2.61 (−3.28 to −1.94)	−1.62 (−2.13 to −1.67)	0.009/0.002
between 1995 and 2000	−2.81 (−3.81 to −1.81)	−1.85 (−2.41 to −1.30)	0.05
between 2001 and 2009	−2.46 (−3.27 to −1.64)	−1.55 (−2.16 to −0.95)	0.03
Laboratory values	n = 60	n = 180	
albumin g/L, mean (95% CI)	36.7 (32.7 to 40.9)	37.3 (36.1 to 38.4)	0.73/0.88
Hb g/dl, mean (95% CI)	10.4 (9.1 to 11.7)	10.7 (10.2 to 11.2)	0.37/0.33
phosphate mmol/L, mean (95% CI)	1.84 (1.42 to 2.26)	1.83 (1.72 to 1.95)	0.89/0.83
PTH pg/ml, median (95% CI)	56 (34 to 91)	140 (101 to 189)	0.001/0.003
Blood pressure			
% hypertensive	42.3%	51.7%	0.06/0.04
SDS systolic blood pressure, mean (95% CI)	1.13 (0.64 to 1.56)	1.55 (1.13 to 1.97)	0.27/0.28
SDS diastolic blood pressure, mean (95% CI)	0.78 (0.11 to 1.44)	0.95 (0.44 to 1.46)	0.53/0.51

SDS, standard deviation score; PTH, parathyroid hormone; RRT, renal replacement therapy; CI, confidence interval; Hb, hemoglobin.
[a]Adjusted for age, sex, calendar year of start of RRT, duration of RRT, and dialysis modality.

we performed this analysis among western European countries only, where NC children have had access to cysteamine since early childhood. Nonetheless, we found high numbers of NC patients reaching RRT before the age of 18 years. These results are rather disappointing compared with the vast improvements expected from the pioneering studies (6,7). The observed difference can be attributed to less adequate treatment of NC patients on a large scale because of annoying side effects of the drug (24,25) and difficult dose regimen, leading to poor compliance (9). Furthermore, the rarity of NC might not allow physicians to have enough experience for the optimal monitoring of cysteamine treatment.

We used median age at the start of RRT as a proxy for renal survival in NC patients. We cannot exclude the possibility that our study underestimated renal function survival in NC patients over the last two decades, because our registry does not include NC pediatric patients who have not reached RRT (yet). Furthermore, in some countries, data collection came from pediatric centers and registries only, and therefore the number of patients who started RRT between the ages of 16 to 20 years may be incomplete because of referral to adult centers. Finally, no information was available on those starting RRT beyond the age of 20 years. Nevertheless, the mean age of onset of RRT in our cohort (12.8 years) was slightly higher compared with that recently reported from Australia and New Zealand (12.3 years in 2008) (26) and was comparable with that recently reported from a single center in Italy (8).

In addition to the use of cysteamine, also other changes in therapy during the past decades may have played a role in the improvement of renal survival. A recent observational study from Italy suggested a positive effect of angiotensin-converting enzyme (ACE) inhibitors on renal function survival in patients with NC (8). Unfortunately, we could not evaluate the role of ACE inhibitors or any other supportive therapies because these data were not available. However, because we did not observe a similar increase in median age at start of RRT in non-NC patients on RRT (many of whom were also treated with ACE inhibitors), we believe that the beneficial effects are mainly due to factors specific for NC treatment.

RRT Modality

At the start of RRT, the most frequent modality in NC was PD (39.6%) followed by renal transplantation (35%). Although NC patients had a double rate preemptive transplantation as compared with the control population, the frequency of hemodialysis was twice as low. Most NC patients are in renal care for a very long period before the start of RRT, which could explain the high rate of preemptive transplantation. The reason why HD was less frequently used in NC compared with a control population remains unclear; however, because NC patients usually remain polyuric, they might be relatively easy to manage on PD.

Clinical Characteristics at Start of RRT

Growth retardation is a major clinical feature of NC (3). While having normal length and weight at birth, most of the patients develop deviated growth during the first year of life. The majority of NC patients remain very short, as was confirmed in this study. Although height at start of RRT slightly improved over time in NC patients, this was also observed in control patients, resulting in a persisting difference between NC and non-NC patients. This improvement of height in NC patients could be caused by increased use of recombinant growth hormone before start of RRT (27), as well as by a growth promoting effect of cysteamine (8,28,29).

Among biochemical parameters, PTH levels were elevated in non-NC children on RRT, whereas they were nearly normal in NC patients. This observation suggests that persisting phosphaturia in NC patients on dialysis protects them from hyperparathyroidism. Although the similarity of plasma phosphate levels does not support this idea, these levels can probably be explained by rigorous use of phosphate-binding agents in non-NC patients that might mask the expected differences caused by persistent Fanconi syndrome in NC. NC patients were also less hy-

pertensive compared with the other children on RRT, possibly because of continued sodium wasting and preserved diuresis (3). Unfortunately, too limited data on the presence of comorbid conditions like diabetes and parathyroidectomy were available to allow for a solid overview.

Conclusions

In this large observational registry study in Europe, we demonstrated improved renal function survival and better patient survival in NC after the start of RRT over the last two decades. Short stature remains a severe complication of NC, arguing for prompt utilization of growth hormone treatment.

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Disclosures

None.

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