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ORIGINAL ARTICLE

Timing of renal replacement therapy does not influence survival and growth in children with congenital nephrotic syndrome caused by mutations in *NPHS1*: data from the ESPN/ERA-EDTA Registry

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Abstract

Background Congenital nephrotic syndrome (CNS) of the Finnish type, NPHS1, is the most severe form of CNS. Outcomes of renal replacement therapy (RRT) in NPHS1 patients in Europe were analysed using data from the ESPN/ERA-EDTA Registry. As NPHS1 is most prevalent in Finland and the therapeutic approach differs from that in many other countries, we compared outcomes in Finnish and other European patients.

Methods *NPHS1* mutations were confirmed in 170 children with CNS who initiated RRT (dialysis or renal transplantation) between 1991 and 2012. Finnish ($n = 66$) and non-Finnish NPHS1 patients ($n = 104$) were compared with respect to treatment policy, age at first RRT and renal transplantation (RTX), patient and graft survival, estimated glomerular filtration rate (eGFR) and growth. Age-matched patients with congenital anomalies of the kidney and urinary tract (CAKUT) served as controls.

Results Finnish NPHS1 patients were significantly younger than non-Finnish patients, both at the start of RRT and at the time of RTX. We found similar overall 5-year patient survival on RRT (91 %) and graft survival (89 %) in both NPHS1 groups and CAKUT controls. At the start of RRT, height standard deviation score (SDS) was higher in Finnish patients than in non-Finnish patients (mean [95 % CI]: −1.31 [−2.13 to −0.49] and −3.0 [−4.22 to −1.91], $p < 0.01$ respectively), but not at 5 years of age. At 5 years of age height and body mass index (BMI) SDS were similar to those of CAKUT controls.

Conclusions Overall, 5-year patient and graft survival of both Finnish and non-Finnish NPHS1 patients on RRT were excellent and comparable with CAKUT patients with equally early RRT onset and was independent of the timing of RRT initiation and RTX.

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Keywords Congenital nephrotic syndrome · NPHS1 · Kidney transplantation · Graft survival · Dialysis · Pediatrics

Introduction

Congenital nephrotic syndrome (CNS) is a rare kidney disease defined by heavy proteinuria starting within 3 months after birth. Most cases of CNS are caused by genetic defects in different components of the glomerular filtration barrier, especially mutations in *NPHS1* (nephrin) and *NPHS2* (podocin), *WT1*, *LamB2* and *PLCE1* genes [1–4]. *NPHS1* usually leads to a severe form of CNS, the so-called Finnish type (NPHS1), which is highly prevalent in Finland [3]. Worldwide, over 200 mutations have been identified in the *NPHS1* gene (http://www.ncbi.nlm.nih.gov/gene/4868) and most patients have individual mutations. However, in Finland two equally severe truncating nonsense mutations (Fin-major and Fin-minor) are present in over 90 % of the patients [3].

There is relatively limited phenotypic variation in NPHS1 in Finnish patients [5]. Most children are born prematurely after an uneventful pregnancy. The placental weight is more than 25 % of the weight of the newborn in almost all cases [5, 6]. Severe proteinuria begins mostly in utero and, without therapy, results in oliguria and severe oedema soon after birth. NPHS1 infants do not have extra-renal malformations, but muscular hypotonia and cardiac hypertrophy are common during the nephrotic stage.

Most "non-Finnish" mutations in *NPHS1* lead to a severe phenotype, with an early onset of nephrotic syndrome, similar to Finnish patients [7]. However, cases involving a milder course of disease and/or later onset (up to adulthood) of nephrotic syndrome have also been described [8–10]. The presence of at least one non-truncating, "mild" mutation explains the phenotype of these patients.

Patients with severe NPHS1 do not respond to captopril and indomethacin therapy for controlling proteinuria [3, 11]. In Finnish NPHS1 patients, timely bilateral nephrectomy and commencement of peritoneal dialysis (PD; when weight is approximately 7 kg) followed by renal transplantation (RTX) has been the therapeutic approach of choice for many years [3, 6]. In an attempt to delay dialysis and its inherent complications, Coulthard proposed an alternative strategy, with unilateral nephrectomy, which would lead to reduced protein losses and easier management of the patient [12, 13]. This management principle has been adopted in many centres during the past decade [11, 14]. Another approach has been to perform early pre-emptive RTX and remove the nephrotic kidneys. However, this strategy has been shown to predispose to thrombotic complications of the graft [15]. As detailed data on outcomes in this population are scarce, the optimal treatment strategy for this complex disease is unclear. Therefore, the objective of this study was to describe renal replacement therapy (RRT) outcomes of Finnish and non-Finnish NPHS1 patients who survived the nephrotic phase and initiated RRT, and to compare their outcomes with those of age-matched RRT patients with congenital anomalies of the kidney and urinary tract (CAKUT) registered in the ESPN/ERA-EDTA Registry.

Subjects and methods

Data collection

We included data on children with NPHS1 whose mutation was confirmed by their treating physician and who started RRT (dialysis or renal transplantation) between 1 January 1991 and 31 December 2012 collected within the framework of the European Society for Paediatric Nephrology/European Renal Association and the European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry. Details on neither the mutation nor the type of sequencing have been reported to the Registry. On an annual basis, the Registry collects individual patient data on date of birth, sex, treatment and date of first RRT, and on subsequent changes in treatment modalities for all European children with end-stage renal disease (ESRD) [16]. Furthermore, for most countries, anthropometric and biochemical data are available (77 % of the NPHS1 patients). We identified patients from the following countries: Austria, Belgium, Finland, France, Italy, the Netherlands, Norway, Russia, Spain, Sweden, Switzerland, Slovakia, Turkey and the UK. No NPHS1 patients were identified in the following countries: Czech Republic, Estonia, Lithuania and Slovenia.

Causes of death were grouped according to the ERA-EDTA coding system: cardiac failure and cardiac arrest/sudden death; other cause or unknown were combined as "cardiovascular mortality" [17].

Patients were divided into two groups: the NPHS1 patients from Finland and the NPHS1 patients from other countries. A group of CAKUT patients age-matched to the non-Finnish NPHS1 patients served as controls. Three control patients were selected for each NPHS1 patient.

Definition of variables

Height values were normalized to standard deviation scores (SDS) for chronological age, according to recent national growth charts or growth charts for Northern or Southern European countries [18]. Body mass index (BMI) was calculated as weight/height^2 and expressed according to chronological age (0–1 years) or height–age (≥2 years) [19]. Reference charts from the World

Health Organization were used to calculate SDS values for BMI [20, 21]. Estimated glomerular filtration rate (eGFR) was calculated according to the bedside Schwartz formula [22].

Statistical analyses

Baseline demographic and clinical characteristics were calculated as medians and interquartile ranges (IQRs; continuous variables) or proportions (categorical variables). To compare the groups, we used the Kruskal–Wallis test for continuous variables and the Chi-squared test for categorical variables. Patient survival was calculated from the time of initiation of RRT until death, loss to follow-up or the end of observation (31 December 2012), whichever came first. Graft survival was analysed both including and excluding death with functioning graft as a cause of graft failure. The Kaplan–Meier method was used for calculation of unadjusted patient and graft survival (including death), whereas a competing risk method was applied to estimate unadjusted death-censored graft survival and patient survival after transplantation [23]. Risk factors for mortality were analysed using Cox proportional hazard regression models, adjusted for potential confounders. Linear mixed models with both a random intercept and a random slope for chronological age were used to model the evolution of height and BMI SDS. An unstructured correlation matrix structure was assumed. Adjustments were made for treatment modality.

Statistical tests were two-tailed and were considered significant when $p < 0.05$. Data were analysed using SPSS version 20 (SPSS, Chicago, IL, USA) and SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 170 patients with CNS caused by *NPHS1* mutation were extracted from the ESPN/ERA-EDTA Registry. Sixty-six patients were from Finland and 104 from other countries. Median age at start of RRT was significantly lower in the Finnish (0.7 [IQR: 0.6–0.8] years) compared with non-Finnish NPHS1 patients (1.7 [IQR: 1.0–2.9] years; $p < 0.01$; Fig. 1, Table 1). Of the non-Finnish patients, 9.9 % received a pre-emptive RTX, 68.3 % initiated RRT while on PD and 21.8 % while on haemodialysis (HD). All Finnish patients initiated RRT while on PD and none underwent pre-emptive RTX (Table 1).

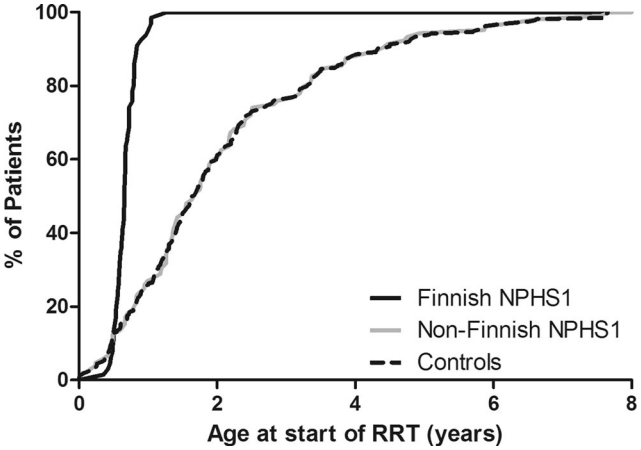

Fig. 1 Age at start of renal replacement therapy (*RRT*) for Finnish and non-Finnish NPHS1 patients and for age-matched congenital anomalies of kidney and urinary tract controls for the non-Finnish NPHS1 patients

Patient survival

Sixteen NPHS1 patients (6 Finnish [5 on dialysis] and 10 non-Finnish [7 on dialysis]) out of 170 died while on RRT at a median age of 1.4 (IQR: 1.0–2.0) and 2.9 (IQR: 1.1–5.0) years respectively, whereas 33 (22 on dialysis) out of 312 patients from the CAKUT control group died at a median age of 2.3 (IQR: 1.3–6.0) years. The cause of death was known for 63 % of patients (83.3 % Finnish NPHS1, 60 % non-Finnish NPHS1, 61 % CAKUT). Infection was the most common known cause of death in all groups and accounted for 50 %, 20 % and 21 % of the fatalities in Finnish NPHS1, non-Finnish NPHS1 and CAKUT patients, respectively.

The overall unadjusted 5-year patient survival on RRT was 91 % in both Finnish and non-Finnish NPHS1 and 90 % in CAKUT patients ($p = 0.83$; Fig. 2a). There was no difference among the groups with regard to unadjusted patient survival according to chronological age. After adjustment for age at the start of RRT and sex, the risks of death of Finnish (adjusted hazard ration [aHR]: 0.53, 95 % CI: 0.21–1.33) and non-Finnish NPHS1 patients (aHR: 0.84, 95 % CI: 0.40–1.80) were similar to that of CAKUT patients.

Five-year patient survival after first RTX was also similar in all three groups of patients: 98.4 % in Finnish NPHS1, 97.8 % in non-Finnish NPHS1, and 96.6 % among control patients ($p = 0.42$). The risk of death post-RTX remained similar to CAKUT controls after adjustment for age at RTX and sex (aHR: 0.32, 95 % CI: 0.04–2.86 for Finnish NPHS1 and aHR: 0.45, 95 % CI: 0.09–2.35 for non-Finnish NPHS1).

When comparing NPHS1 patients, Finnish patients had a similar risk of death as the non-Finnish ones after adjustment for age at RRT and sex (aHR: 0.79, 95 % CI: 0.25–2.48). NPHS1 patients who started RRT at below 1 year of age (aHR: 1.36, 95 % CI: 0.31–5.96) and patients who were aged 1 to 2.5 years (aHR: 0.54, 0.95 % CI: 0.11–2.70) had a similar risk of death as NPHS1 patients who were over 2.5 years of

Table 1 Characteristics of NPHS1 patients and congenital anomalies of kidney and urinary tract (*CAKUT*) controls at the time of RRT initiation. Values are given as median (IQR) or number (%)

Variable	Overall NPHS1 ($n = 170$)	Finnish NPHS1 ($n = 66$)	Non-Finnish NPHS1 ($n = 104$)	CAKUT controls ($n = 312$)
Age	0.9 (0.6-1.9)	0.7 (0.6-0.8)	1.7 (1.0-2.9)	1.7 (0.9-2.8)
Females	91 (53.3)	31 (47.0)	60 (57.7)	61 (19.6)
Initial RRT modality[a]				
PD	135 (80.8)	66 (100)	69 (68.3)	188 (60.3)
HD	22 (13.2)	0	22 (21.8)	38 (12.2)
RTX	10 (6.0)	0	10 (9.9)	66 (21.2)

RRT renal replacement therapy, *PD* peritoneal dialysis, *HD* haemodialysis, *RTX* renal transplantation

[a] Missing for three non-Finnish patients and 20 CAKUT controls

age when commencing RRT. Among transplanted patients, time to RTX was not associated with patient survival; aHR for each additional year was 0.04 (95 % CI: 0.00–1.47).

Renal transplantation and graft survival

The majority of patients (88.8 %) received a renal transplant during the observation period after a median dialysis time of 0.9 years (Table 2). The median interval between initiation of RRT and undergoing a transplant did not differ between Finnish (0.9 [IQR: 0.6–1.4] years) and non-Finnish NPHS1 patients (1.0 [IQR: 0.3–1.7] years; $p = 0.69$; Table 2). The median age at RTX was 1.6 (IQR: 1.2–2.1) years in Finnish and 3.0 (IQR: 1.7–4.4) years in non-Finnish patients respectively ($p < 0.01$).

The proportion of living donor RTX was similar in both groups (30 % vs 35 % in Finnish and non-Finnish NPHS1 patients respectively, $p = 0.52$).

The graft survival of the first RTX is shown in Fig. 2b. After a median follow-up of 8.5 years, 26 grafts (including 3 deaths) were lost, 11 (18 %) in Finnish and 15 (17 %) in non-Finnish NPHS1 patients. Graft survival did not differ between these two groups and was 89 % after 5 years of follow-up. The 5-year graft survival was comparable in the 10 subjects transplanted pre-emptively (80 %). Results were similar when considering death as a competing event (data not shown). Despite equal graft survival, median eGFR was significantly lower in Finnish NPHS1 patients than in non-Finnish NPHS1 patients at 5 years after RTX (Table 2). It should, however, be noticed that 5-year eGFR was available only for 24 % of non-Finnish and 64 % of Finnish NPHS1 patients.

Graft survival of NPHS1 patients did not differ compared with age-matched CAKUT patients (Fig. 2b) and remained similar after adjustment for age at RTX and sex (aHR Finnish NPHS1: 0.83, 95 % CI: 0.40–1.70; aHR non-Finnish NPHS1: 0.96, 95 % CI: 0.51–1.80).

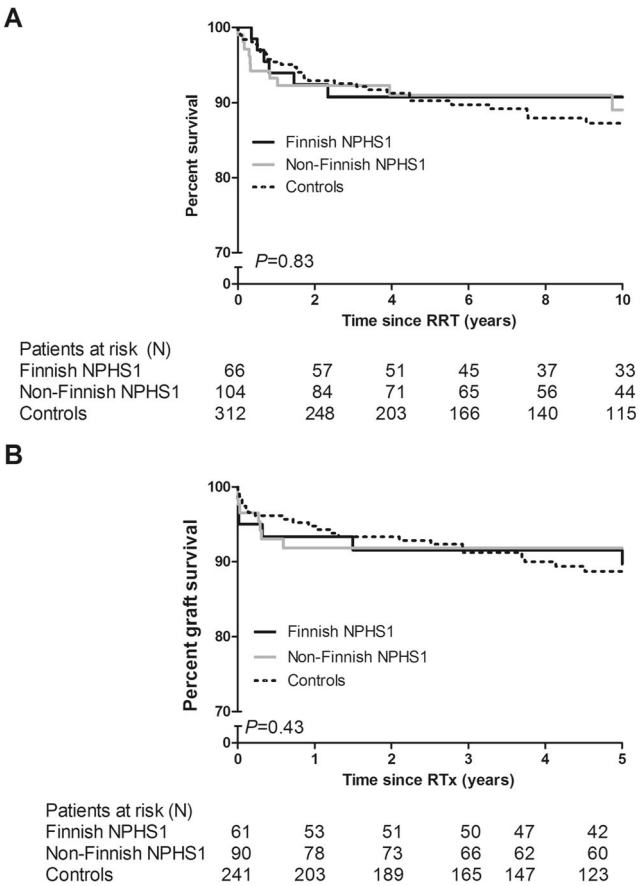

Fig. 2 **a** Patient survival since start of renal replacement therapy (RRT) and **b** 5-year graft survival (including death) for Finnish and non-Finnish NPHS1 patients and for age-matched congenital anomalies of kidney and urinary tract controls for the non-Finnish NPHS1 patients

Growth and BMI

Modelled patterns of height and BMI SDS are shown in Fig. 3. Height SDS at the start of RRT was higher in Finnish NPHS1 (−1.31; 95 % CI: −2.13 to −0.49) compared with non-Finnish NPHS1 (−3.0; 95 % CI: −4.22 to −1.81) or CAKUT patients (−2.22; 95 % CI: −2.83 to −1.61), and at the time of RTX. It should, however, be noted that Finnish NPHS1 patients were much younger when commencing RRT and when receiving their first renal graft. At the age of 5 years, there were no significant differences in height SDS between the groups. Data

Table 2 Transplantation characteristics by patient subgroups. Values are given as median (IQR) or number (%)

Variable	Overall ($n = 170$)	Finnish NPHS1 ($n = 66$)	non-Finnish NPHS1 ($n = 104$)	P value
Patients receiving transplant	151 (88.8)	61 (92.4)	90 (86.5)	0.24
Age at RTX (years)	2.1 (1.4–3.5)	1.6 (1.2–2.1)	3.0 (1.7–4.4)	<0.01
Dialysis time (years)	0.9 (0.6–1.7)	0.9 (0.6–1.4)	1.0 (0.3–1.7)	0.69
Patients with LRD RTX	47 (32.4) ($n = 145$)	18 (29.5) ($n = 61$)	29 (34.5) ($n = 84$)	0.52
eGFR at 1 year (ml/min/1.73 m^2)	58 (51–85) ($n = 76$)	57 (47–77) ($n = 52$)	71 (55–95) ($n = 24$)	0.08
eGFR at 5 years (ml/min/1.73 m^2)	61 (47–77) ($n = 67$)	54 (47–67) ($n = 42$)	69 (59–83) ($n = 25$)	<0.01

RTX renal transplantation, *eGFR* estimated glomerular filtration rate, *LRD* living related donor

on growth hormone (rhGH) use was available in all Finnish NPHS1 patients, in 55 non-Finnish NPHS1 patients (52.8 %) and in 55.4 % of CAKUT controls. The overall ever use of rhGH was lower in Finnish NPHS1 patients (10.6 %) compared with non-Finnish NPHS1 (30.9 %) and CAKUT patients (27.2 %).

Standard deviation scores for BMI showed different patterns between the start of RRT and the age of 5 years for the three groups of patients. At the start of RRT, mean BMI SDS was lowest among Finnish NPHS1 (0.30; 95 % CI: −0.39 to 0.98), followed by CAKUT patients (0.49; 95 % CI: −0.09 to 1.07) and non-Finnish NPHS1 patients (1.68; 95 % CI: 0.54 to

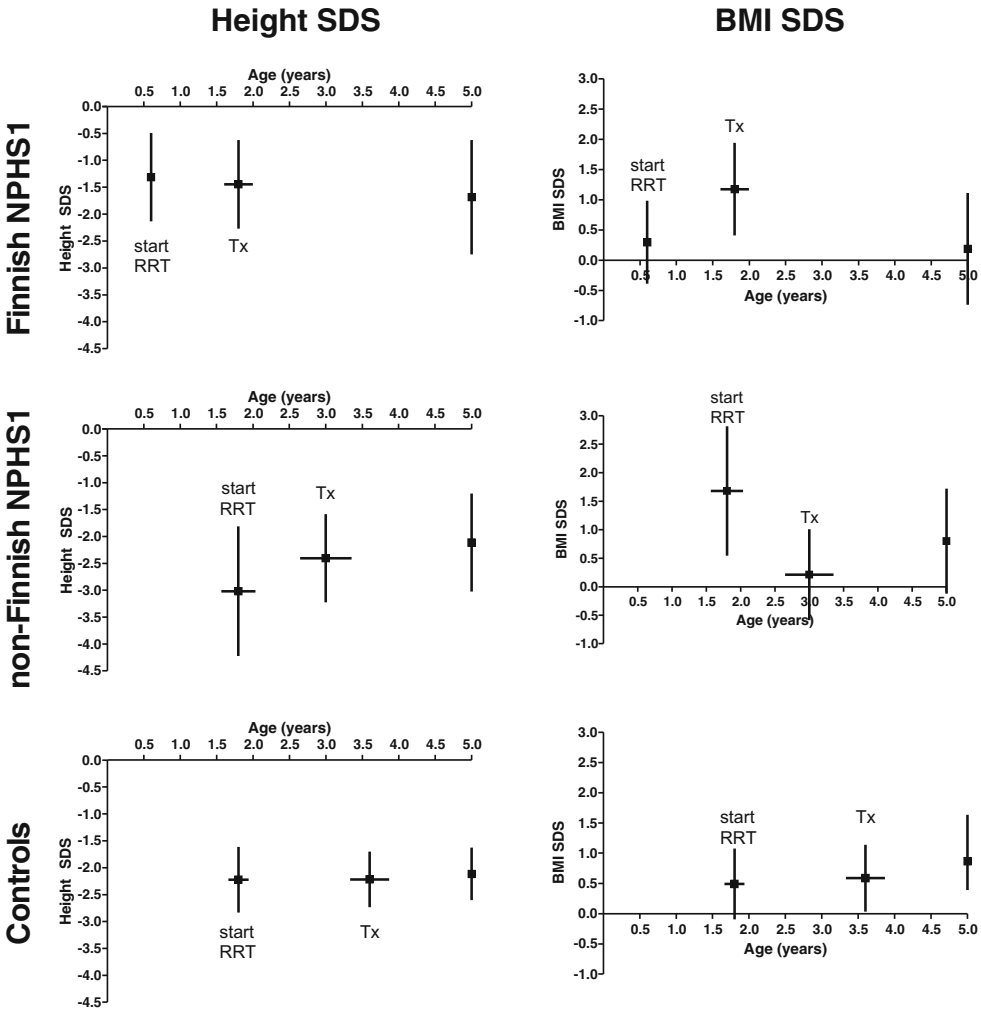

Fig. 3 Modelled evolution of height standard deviations score (SDS) and body mass index (BMI) SDS by chronological age in Finnish and non-Finnish NPHS1 patients compared with age-matched congenital anomalies of kidney and urinary tract controls. Adjustments were made for treatment modality. Data shown represent mean estimates at the time of entering renal replacement therapy (RRT), at the time of renal transplantation (RTX) and at the age of 5 years. Two-dimensional error bars indicate the mean age and SDS and their respective 95 % confidence intervals at the different time points

2.81). BMI SDS was significantly lower in Finnish than in non-Finnish NPHS1 patients ($p < 0.05$). Between the start of RRT and RTX, on average, BMI SDS increased slightly in Finnish NPHS1 and CAKUT patients, whereas it decreased in non-Finnish NPHS1 patients. However, at the age of 5 years, there were no significant differences in the mean BMI SDS among the three groups (Fig. 3).

Discussion

To our knowledge, this ESPN/ERA-EDTA Registry study on 170 children with NPHS1 is the largest outcome study on this very rare disease performed to date. Given the severe early course of the disease, we found good 5-year patient and graft survival periods in patients who entered an RRT program, which were comparable to age-matched RRT controls with CAKUT. Notably, we did not find any significant differences in outcomes between non-Finnish NPHS1 patients treated with variable protocols and Finnish NPHS1 patients treated with a uniform protocol involving early elective bilateral nephrectomy to minimize infectious and thrombotic complications and to send patients to home care. It should, however, be noted that Finnish NPHS1 patients may have had a more serious form of the disease, because of severe mutations in over 90 % of patients [3].

The literature on both CNS and NPHS1 is scarce. A single large-scale registry study compared transplant outcomes in 132 CNS patients with those of other patients [15], whereas other studies reported pooled outcomes of infants, including only a few CNS/NPHS1 patients commencing dialysis or RTX [24–28].

In general, children with ESRD up to 3–4 years of age have the highest mortality rates during dialysis [29–32] and after RTX [33], and the poorest graft survival [33]. However, we observed very good patient and graft survival after starting RRT in this challenging subgroup of NPHS1 infants, and no differences were found between patients from Finland and those from elsewhere in Europe. Patient and graft survival periods were also similar to those of CAKUT controls age-matched to the non-Finnish NPHS1 patients.

The 91 % 5-year patient survival in the present study was similar to the 4-year patient survival of 87 % observed across all ESRD patients aged 0–4 years in Europe in 2007–2011 [29]. Lower 5-year patient survival (75 %) has been reported in a study from the same time period of 87 infants entering RRT for different diseases in Canada, 57 of whom received RTX at a median age of 2.7 years [25]. Mortality was highest in the youngest patients [25]. In contrast to previous studies, we found equal patient survival in both NPHS1 groups and CAKUT controls, although the Finnish NPHS1 patients were significantly younger at the start of RRT and at RTX. The equal patient survival of Finnish and non-Finnish NPHS1, despite the age difference, may be explained by the fact that physicians have more experience in caring for infants on dialysis and RTX in Finland because the severe NPHS1 mutation is more prevalent in the Finnish population.

The 5-year graft survival of 89 % in the present study was slightly better than the survival observed in North American transplanted infants and toddlers reported to the USRDS database between 1995 and 2005 (70–81 % for deceased donor transplants and 88–92 % for living donor transplants) [34]. The graft failure rate was significantly higher in 132 CNS patients compared with other NAPRTCS Registry patients who underwent transplantation between 1987 and 1997 (33 % compared with 24 %) [15], which was explained by a higher rate of vascular thrombosis. Further, a recipient age of less than 2 years in CNS patients, according to the NAPRTCS report in the 1990s, was found to be a significant predictor for poor graft survival [15]. Approximately half of the CNS patients in this study were nephrectomised, and no difference in occurrence of thrombotic complications was found between those who had been nephrectomised and those who had not. A Finnish study from the early 1990s was more in concordance with our study. Laine et al. did not find a difference in graft survival by renal diagnosis in 39 young Finnish RTX patients (59 % NPHS1), nor did the authors report thrombotic vascular complications in NPHS1 patients [35]. The lack of thrombotic vascular complications, contrary to the NAPRTCS report of the 1990s, was explained by normalisation of the coagulation system after bilateral nephrectomy, which was performed at least 3 months before RTX. The difference in the occurrence of thrombotic vascular complications in nephrectomised children between these two studies may be associated with the timing of the nephrectomy, possibly also with use of anticoagulation. Kim et al. reported neither the timing of nephrectomy, nor the use of anticoagulation, whereas the latter has been part of the routine since the 1990s in the treatment of NPHS1 patients in Finland before nephrectomy [15, 36]. Recent studies have shown a significant improvement in the outcome of kidney transplantations in young children, which has been mainly attributed to better neonatal care, withdrawal of dialysis treatment from infants with very serious comorbidities [24] and a reduction of acute rejections owing to improvements in organ allocation policy, perioperative care and immunosuppressive medications [37]. Accordingly, excellent graft survival (75 % at 10 years) without any impact of age at RTX, has been reported in a single-centre study of 71 ESRD infants undergoing transplantation at a median age of 3.2 years [24].

Finnish NPHS1 patients were taller at the start of RRT and at the time of RTX compared with non-Finnish NPHS1 and CAKUT patients. However, this difference in height SDS disappeared at the age of 5 years. The Finnish NPHS1 patients differed from the others in respect of commencing dialysis at a much younger age and without uraemia, which may have had

an impact on height SDS at the start of RRT in the other groups. Although not reported for every patient, rhGH was used less frequently in Finnish compared with non-Finnish NPHS1 patients and CAKUT controls, which together with a lower BMI SDS, may partly explain the lack of catch-up growth during RRT course in the Finnish NPHS1 patients. The different evolution of BMI SDS in the Finnish and non-Finnish patient groups may reflect differences in nutritional management between countries [19]. Finnish children increased their BMI SDS while on dialysis, but not following RTX. This finding may reflect a particularly efficient enforcement of nutritional targets in dialysed infants. The non-Finnish NPHS1 patients underwent dialysis at ages when growth is less affected by nutrition, which could explain their catch-up growth, despite decreasing BMI SDS. In an International Pediatric Dialysis Network (IPPN) Registry report with 153 infants undergoing chronic PD in 2007–2009, the median age (0.9 years) and height SDS (−2.4) at study entry were comparable to our study [38]. The subgroup of European children ($n = 67$) significantly improved their BMI SDS while on dialysis; however, in contrast to NPHS1 patients from the present study, their BMI SDS stayed below zero. Mekahli et al. reported better growth in a single-centre study of 71 infants commencing dialysis and receiving RTX during the same time period as our patients [24]. The authors concluded that normal growth is possible in infants on dialysis and after RTX, but it is labour-intensive and heavily dependent on adequate renal dietician support. Compared with our study, a high percentage of infants also received pre-emptive RTX (44 %), which may have favoured catch-up growth [24].

The major strength of our study is the large number of NPHS1 patients followed, which is to our knowledge the largest cohort of this monogenic disease entity to date. Furthermore, we compared the outcome of non-Finnish NPHS1 patients with age-matched CAKUT patients. Contrary to the Finnish NPHS1 patients, non-Finnish ones seemed to enter RRT when they reach uraemia, but eGFR at the start of RRT was only available for a limited number of patients.

Some further limitations of our study need to be acknowledged. Results of the present study only apply to NPHS1 patients who survived the nephrotic period and entered into an RRT programme. The ESPN/ERA-EDTA Registry collects data from the start of RRT only, and, unfortunately, no information is available on pre-RRT treatment, the number of nephrectomies, or the number of patients dying before RRT. However, the Finnish patients commenced RRT within the first year of life, and in the non-Finnish NPHS1 and CAKUT controls there was a relatively short interval between birth and RRT. Furthermore, as no differences in outcomes were found, it is unlikely that pre-RRT management had had a large impact on the outcomes in our study population. As the ESPN/ERA-EDTA Registry includes only limited information on nutritional therapy, growth hormone use, albumin infusions and comorbidities (such as preterm birth), we were not able to study the factors affecting growth and BMI in more detail.

Management of NPHS1 patients is challenging, as there are only very few patients over a long time span in the majority of the centres, treatment protocols are variable, and hardly any data exist on outcomes. This study showed for the first time that it is worth treating these challenging patients: NPHS1 patients' outcomes are similar to those of CAKUT infants and toddlers who require RRT early in life. Both starting RRT early with elective bilateral nephrectomy while eGFR is still normal, and starting RRT later, after deterioration of the kidney function, are safe management options with regard to patient and graft survival and long-term growth outcomes.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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