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ORIGINAL ARTICLE

Infants with congenital nephrotic syndrome have comparable outcomes to infants with other renal diseases

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Abstract

Background Children with congenital nephrotic syndrome (CNS) commonly develop end stage renal failure in infancy and require dialysis, but little is known about the complications and outcomes of dialysis in these children.

Methods We conducted a retrospective case note review across members of the European Society for Pediatric Nephrology Dialysis Working Group to evaluate dialysis management, complications of dialysis, and outcomes in children with CNS.

Results Eighty children (50% male) with CNS were identified form 17 centers over a 6-year period. Chronic dialysis was started in 44 (55%) children at a median age of 8 (interquartile range 4–14) months. Of these, 17 (39%) were on dialysis by the age of 6 months, 30 (68%) by 1 year, and 40 (91%) by 2 years. Peritoneal dialysis (PD) was the modality of choice in 93%, but 34% switched to hemodialysis (HD), largely due to catheter malfunction ($n = 5$) or peritonitis ($n = 4$). The peritonitis rate was 0.77 per patient-year. Weight and height SDS remained static after 6 months on dialysis. In the overall cohort, at final follow-up, 29 children were transplanted, 18 were still on dialysis (15 PD, 3 HD), 19 were in pre-dialysis chronic kidney disease (CKD), and there were 14 deaths (8 on dialysis). Median time on chronic dialysis until transplantation was 9 (6–18) months, and the median age at transplantation was 22 (14–28) months.

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Conclusions Infants with CNS on dialysis have a comparable mortality, peritonitis rate, growth, and time to transplantation as infants with other primary renal diseases reported in international registry data.

Keywords Congenital nephrotic syndrome · Infant dialysis · Complications · Outcome

Introduction

Despite advances in pediatric dialysis therapy, dialysis in infants remains challenging with increased mortality, higher rate of infections, and poor growth compared to older children and adults [1, 2]. Children with congenital nephrotic syndrome (CNS) account for approximately 15% of infants who start dialysis at less than 1 year of age [3, 4]. They usually start dialysis in early infancy and may also be prone to complications secondary to hypoalbuminemia and low immunoglobulin levels, such as infections, thrombosis, impaired nutritional status, and growth [5, 6]. In a review across the European Society for Paediatric Nephrology (ESPN) dialysis working group, we have shown that in children with NPHS1 mutations, there is no clear genotype-phenotype correlation and the severity of the clinical presentation may vary. We therefore suggest that an individualized, stepwise approach with prolonged conservative management may be a reasonable alternative to early bilateral nephrectomies and dialysis in children with CNS due to NPHS1 mutations [7].

Due to the rarity of CNS, details of dialysis in infants with CNS are scarce and no recommendations are available [5, 8]. Recently, data on renal and patient survival in children with CNS were published by the French group [9] and data on dialysis and transplantation outcomes by the European Renal Association/European Dialysis and Transplantation Association (ERA/EDTA) registry [4]. However, specific information on the dialysis management and complications are not available from those studies.

We performed a retrospective case note review across all members of the ESPN dialysis working group in order to evaluate the current practice of dialysis management and the morbidity and outcomes of dialysis in children with CNS across Europe. Outcomes in the CNS patients were compared with international registry studies reporting on infants with other primary diseases who required dialysis.

Patients and methods

A retrospective case note review on the dialysis management of children with CNS was performed across all members of the ESPN Dialysis working group which includes 22 centers from 15 European countries. Together, these centers manage over 250 pediatric peritoneal dialysis (PD) and hemodialysis (HD) patients per year and perform about 180 renal transplants per year. Infants with a diagnosis of CNS between 01/01/2010 and 31/12/2015 were included. Infants with nephrotic syndrome of any other type, presentation after the first 3 months of life, or those where complete data could not be obtained were excluded.

Eighty-eight children with CNS were identified in the 6-year study period. Eight children had to be excluded as the diagnosis of CNS was unclear ($n = 4$), data was incomplete ($n = 3$), or consent was withdrawn ($n = 1$). The final dataset consisted of 80 children from 17 centers: 25 from Helsinki (Finland); 10 from London (UK); 8 each from Heidelberg (Germany) and Barcelona (Spain); 4 each from Padova (Italy) and Ankara (Turkey); 3 each from Bologna (Italy), Athens (Greece), Istanbul Marmara (Turkey), and Lyon (France); 2 each from Milan (Italy) and Malta (Malta); and 1 each from Genova (Italy), Istanbul Cerrahpasa (Turkey), Erciyes (Turkey), Adana (Turkey), and Gazi (Turkey). The following information was collected: demographics and presenting features, dialysis specific data: need for short (< 3 months) or chronic (≥ 3 months) dialysis, parameters at start of dialysis (age, weight, S-albumin, S-creatinine), dialysis modality at start, dialysis prescription, dialysis modality changes, complications (peritonitis, sepsis, line infections, thrombosis), growth on dialysis, and outcome. Molecular screening was performed in the local center according to the center-specific standards. Details on the genetic background of each patient are provided in Dufek et al. [7].

Data were pseudonymised and entered into an electronic database that was analyzed in a central unit (Great Ormond Street Hospital) and verified by email correspondence and at meetings of the group.

Statistical analysis

Most of the analyses are of a descriptive nature. Continuous variables are presented as median with interquartile range (IQR). Categorical variables are presented as number and percentage. For group comparison of continuous variables, the non-parametric Mann-Whitney *U* test was used, and for comparison of inter-individual changes, the Wilcoxon signed rank test. For group comparison of categorical variables, the Pearson Chi-square test or Fisher's exact *t* test was used. Kaplan-Meier curves were used to determine the renal survival time with start of dialysis or transplantation as endpoints. Censored were patients who died or reached end of follow-up. Statistics were calculated using SPSS Statistics 24.0 for Mac

(IBM Corporation). A p value of < 0.05 was considered significant.

Results

Demographic details

In total, 80 children (50% male, 90% Caucasian) with CNS were included. Demographic details and details at presentation are described in a previous study [7]. Briefly, children presented at a median age of 9 (2–45) days with a median S-albumin of 11 (8–16) g/L and S-creatinine of 27 (16–56, max 480) μmol/L. A genetic diagnosis was confirmed in 69 (86%) (*NPHS1* in 55 (69%), *WT1* in 9 (11%), *NPHS2* in 1 (1.3%), *LAMB2* in 2 (2.5%), *PLCE1* in 1 (1.3%) and in 1 (1.3%) a mutation in a new gene, *SGPL-1*, was found [10]). No mutation was found in 11 (14%) children [7].

Details of dialysis therapy

Fifty-five (69%) children received dialysis (both acute or chronic dialysis) during the study period at a median age of 8 (4–15) months. The infants who required dialysis first presented at an age of 6 (2–32) days with a median S-albumin of 11 (7–16) g/L and S-creatinine of 29 (17–84) μmol/L. When analyzed in sub-groups based on their underlying genetic diagnoses, dialysis was performed in 34 of 55 (62%) children with NPHS1, 1 (100%) child with NPHS2, all 9 (100%) children with WT1, and 11 of 15 (73%) children with other diagnoses. In the whole cohort, the median renal survival time (defined as the time from birth until dialysis or pre-emptive transplantation, whichever came first) was 13 (95% CI: 8.6–17.4) months (Fig. 1a). The median renal survival time was 15 (95% CI: 8.6–21.4) months for NPHS1, 30 months for NPHS2, 2 (95% CI: 0.6–3.4) months for WT1, and 10 (95% CI: 0.3–19.7) months for the others (Fig. 1b).

For further assessment, dialysis therapy was divided into short-term dialysis (< 3 months) and chronic dialysis ($\geq$ 3 months), with the focus on chronic dialysis.

Short-term dialysis

Eleven children (14%) received short-term dialysis. Three received acute renal replacement therapysecondary to acute fluid overload ($n = 2$) and acute kidney injury secondary to sepsis ($n = 1$). Of these three, one (age 40 months) recovered renal function (estimated glomerular filtration rate 25 ml/min/1.73 m^2) and 2 children died, 1 on PD secondary to severe prematurity (gestational age 27 weeks) and in the other withdrawal of care was decided while on dialysis. A further eight children received dialysis for < 3 months: four proceeded to transplantation, three were still within 3 months of dialysis by the termination of the study, and one died after 1 month on HD.

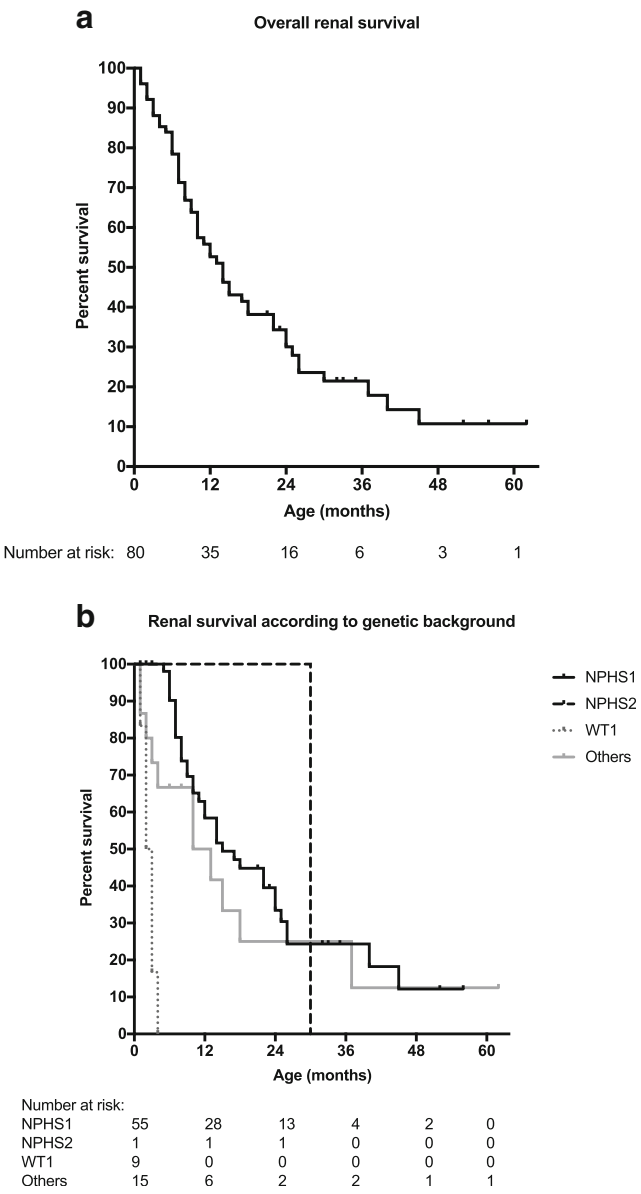

Fig. 1 **a** Kaplan-Meier curve for overall renal survival from birth until start of dialysis or transplantation. Total $n = 80$. **b** Kaplan-Meier curve for renal survival according to underlying diagnosis from birth until start of dialysis or transplantation. NPHS1 $n = 55$, NPHS1 $n = 1$, WT1 $n = 9$, others $n = 15$

Chronic dialysis

Chronic dialysis (defined as dialysis for ≥ 3 months) was performed in 44 (55%) children, of whom 25 had a diagnosis of NPHS1 mutation, 1 had a NPHS2 mutation, 7 had a WT1 mutation, and 11 had other diagnosis. Median age at the start of chronic dialysis was 8 (4–14) months, median weight 8.25 (5.8–9.25) kg, median serum creatinine 242 (175–291)

μmol/l, and median serum albumin 21 (17–28) g/L. Seventeen (39%) children required dialysis by the age of 6 months, 30 (68%) by 1 year, and 40 (91%) by 2 years. Twelve (29%) had residual urinary output.

Of these, 23 (52%) children had nephrectomies before commencing dialysis (18 bilateral nephrectomies, 2 unilateral nephrectomy with second kidney removed after start of dialysis, and 3 unilateral nephrectomy only), and 8 (18%) children had bilateral nephrectomies after commencing dialysis, while 13 (30%) did not have nephrectomies during the study period. Bilateral nephrectomies were performed in 19 (76%) children with NPHS1, in no child with NPHS2, in 6 (86%) children with WT1 (as 1 child died before second nephrectomy), and in 3 (27%) children with other diagnosis at a median age of 8 (6–14) months. The median S-creatinine just prior to performing bilateral nephrectomies was 19 (13–246) μmol/l.

Choice of chronic dialysis in children with CNS

Forty-one children (93%) initiated dialysis on PD. Continuous cycling PD (CCPD) with a day exchange or CCPD with a dry day were the commonest prescriptions with 13 (32%) each, followed by CCPD with a last bag fill in 8 (20%), continuous ambulatory PD in 6 (15%), and tidal PD in one (2%). Details of the PD prescriptions of patients on CCPD are given in Supplementary Table 1. Three (7%) children commenced dialysis on HD (one with hepatic fibrosis and extensive ascites, one due to social reasons, and one due to lack of chronic PD program in the dialysis center).

Fourteen (34%) children needed to switch to HD (4 transiently and 10 permanently). Reasons for switching to HD were PD catheter dysfunction or inadequate ultrafiltration ($n = 5$), peritonitis ($n = 4$), development of pleural effusion ($n = 2$), abdominal surgery ($n = 2$), and family preference ($n = 1$). No patient who initially commenced on HD switched to PD. Children who were started on PD were younger compared to those who were started on HD (7 vs 17 months, $p = 0.05$).

Infectious complications of chronic dialysis

Of the 41 children on chronic PD, 20 (49%) developed peritonitis during the study period, with a total of 40 peritonitis episodes in 675 patient months on PD, giving a peritonitis rate of 0.77 per year at risk. Ten (50%) patients who developed peritonitis started PD at an age less than 6 months and 16 of 20 (80%) at an age less than 1 year. There was no difference in children who underwent nephrectomies compared to those without nephrectomies (48% versus 50%, $p = 0.92$). The commonest organism was *Staphylococcus epidermidis* (33%).

During the study period, 17 children received HD at some point during the study; all were via a central venous line (CVL). Only one patient developed a CVL infection, but none had septic episodes.

Non-infectious complications of chronic dialysis

None of the children on PD developed thrombosis while on dialysis. One child on HD developed a CVL-related thrombosis in the right jugular vein that was treated with therapeutic anticoagulation with heparin. Ten (24%) children developed hernias after starting PD, with no difference in children who underwent nephrectomies compared to those without nephrectomies (28% versus 17%, $p = 0.46$): 7 were inguinal hernias (bilateral in 2 children), 1 was an abdominal wall hernia, and in 2 cases, the site of hernia was not specified. Three children (7%) had pleural effusions of which 2 were switched to HD.

Growth on chronic dialysis

Anthropometric data were collected every 6 months from birth (Fig. 2a, b). Using the dry weight based on clinical assessment, the median weight SDS at the start of dialysis was − 1 (− 2.22 to + 0.32) and showed a non-significant decrease to − 1.65 (− 2.80 to − 0.27) SDS after 6 months on dialysis ($p = 0.37$; intra-individual change − 0.78 (− 1.45 to + 1.40)). The median height SDS at the start of dialysis was − 1.13 (− 2.48 to − 0.21) and showed a non-significant change to − 1.33 (− 2.70 to − 0.19) after 6 months on dialysis ($p = 0.56$; intra-individual change + 0.05 (− 0.78 to + 0.41)) (Fig. 2c).

Final outcomes

At final follow-up, the median age of the overall cohort was 31 (14–49) months. Twenty-nine (36%) children were transplanted, 18 (23%) children were still on dialysis (15 PD, 3 HD), 19 (24%) were in pre-dialysis CKD, and there were 14 (18%) deaths.

Twenty-nine of 80 (36%) children received a transplant during the study period—24 of 44 (55%) children on chronic dialysis, 4 children after a short dialysis period of less than 3 months, and one child in pre-dialysis CKD. Fifteen transplants were living related. The median age at transplantation was 22 (14–28) months and the median time on chronic dialysis before transplantation was 9 (6–18) months.

Fourteen children (18%) died during the study period. Three children died within 3 months of dialysis onset, 5 on chronic dialysis. The latter (4 PD, 1 HD) died at a median age of 11 (5–51) months after a median dialysis time of 4 (3–31) months (Fig. 3). Causes of death in patients on dialysis were sepsis in 3 (1 HD, 2 PD), cardiac arrest in 2 (1 PD, 1 HD), severe prematurity in 1 (PD), and withdrawal of active treatment in 2 (1 PD, 1 CVVH).

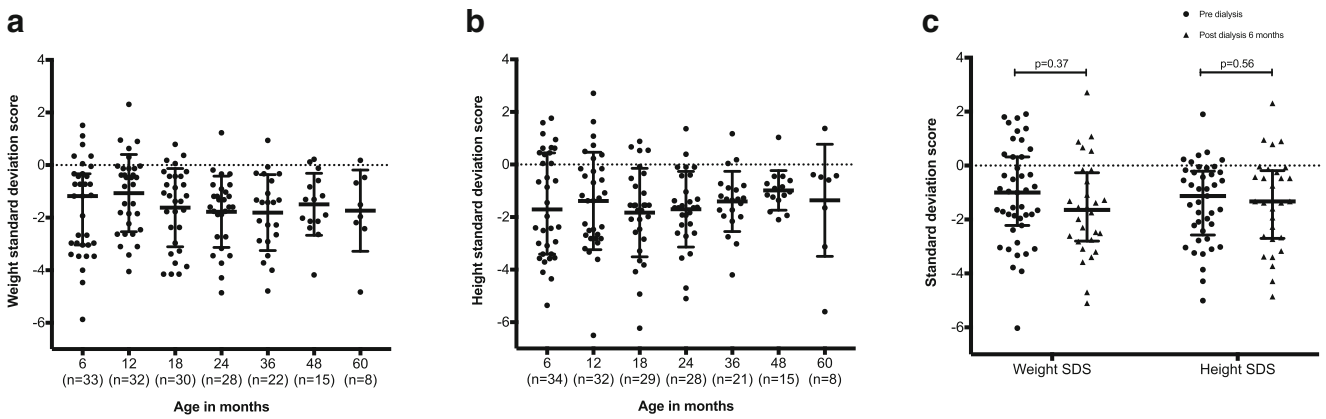

Fig. 2 **a** Weight SDS in 6 monthly steps until 2 years of age, then 12 monthly until 5 years of age. **b** Height SDS in 6 monthly steps until 2 years of age, then 12 monthly until 5 years of age. **c** Weight SDS and height SDS at the start of chronic dialysis and 6 months after. *P* values for Wilcoxon signed rank test displayed

Discussion

We describe a large multi-center series on children with CNS with a focus on the complications, growth, and outcomes on dialysis. Due to the rarity of CNS, the literature is generally scarce. Most studies, including transplant outcomes in a large North American registry report (NAPRTCS) of 132 CNS patients [11], were performed over two decades ago [12, 13]. A recent ERA/EDTA study reported on 170 children with CNS, comparing outcomes of dialysis and graft survival between children with NPHS1 and those with renal dysplasia, found a comparable 5-year patient survival on dialysis [4]. However, this registry focused on children with NPHS1 only and did not report on complications of dialysis. The French study with 55 CNS patients focuses on general management of CNS and gives insight in the overall patient and renal survival of children with CNS but details on dialysis and its complications are not elaborated [9].

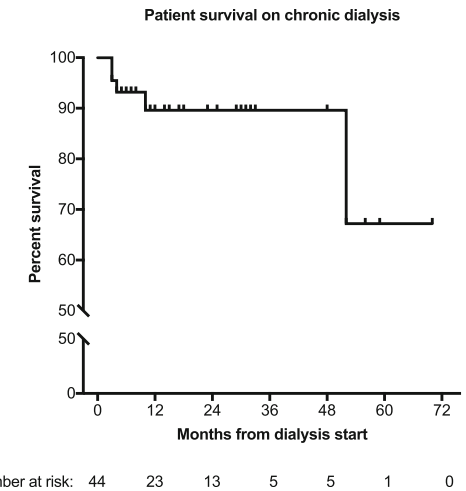

Fig. 3 Kaplan-Meier curve for patient survival on chronic (> 3 months) dialysis. Total $n = 44$

We report a cohort of 80 children with CNS, of which 86% had a confirmed underlying genetic diagnosis. This is similar to findings of the recent French study, where in 84% of the children, a causative mutation was identified [9]. In our cohort of 80 children with CNS, chronic dialysis was required in 55%, with nearly all children starting dialysis in the first 2 years of life. PD was clearly the modality of choice and was commenced in 93%. The percentage of CNS patients starting on PD is slightly higher compared to infants on dialysis with other primary renal diseases (PRD), where 57–86% are started on PD as first choice [4, 14–16]. HD as an alternative to PD in infants has been supported by recent studies, showing no difference in patient survival between the two modalities [14–16]. Although numbers are small, we did not find any difference in complication rate, growth, transplantation rate, or survival in CNS infants started on PD or HD, suggesting that although HD is not the modality of first choice, it is acceptable in infants with CNS. Importantly, one-third of infants in our study needed to switch modalities before eventual transplantation, mainly due to peritonitis or PD catheter-related problems. An ESPN/ERA-EDTA registry study [14] and the NAPRTCS registry [17] on infant dialysis due to other PRDs report similar frequencies and causes of modality change; 25% and 14%, respectively, with peritonitis and excessive infections being the main reasons for modality change from PD to HD [14, 17].

Infants with CNS on PD might be at higher risk of peritonitis, particularly in the first months of treatment, due to the low immunoglobulin levels and in some cases due to the impaired nutritional status, depending on the proteinuria levels. In our study, the peritonitis rate was 0.77 per patient year at risk which is above the current ISPD recommendation of 0.5 per patient year at risk [18]. However, compared to peritonitis rates reported in infants with different PRDs in developed countries, which vary from 0.58 episodes per patient-year in the Italian registry study [3], over 0.68 reported by NAPRTCS [19], 1.1 episodes per patient-year in a UK cohort [20],

and 1.7 episodes per patient-year in US cohorts [21], children in our study seem to have a comparable peritonitis rate compared to children with other PRDs on PD. Half of the children who developed peritonitis in our study started on dialysis at an age less than 6 months. This increased risk for peritonitis in younger children on PD has also been reported by NAPRTCS, where children less than 1 year had an annualized peritonitis rate of 0.79 per patient-year compared to an annualized rate of 0.67 per patient-year in children older than 1 year, and 0.57 per patient-year in those above 12 years of age [22].

Children with CNS on dialysis may be at higher risk of thrombosis secondary to hypoalbuminemia. However, reports on this complication are rare and expert opinions on use of antithrombotic treatment vary [23]. In our population, only one child (2%) developed a thrombus while on hemodialysis, which is even less than reported in some studies where 38% of children younger than 2 years on HD had central vein thrombosis [24].

The risk of poor growth might be higher in infants with CNS on dialysis due to the above mentioned factors. In our series, growth, expressed by both weight and height SDS, of children with CNS on dialysis remains unsatisfactory, but comparable to those reported in other studies of infants on dialysis with different PRDs. The recent ERA/EDTA registry showed catch up growth in non-Finnish *NPHS1* patients on dialysis, but static growth in CAKUT patients on dialysis [4]. In our population, the weight SDS tends to decrease further while on dialysis and the height SDS tend to remain static. The decrease in weight SDS may, at least in part, reflect the decrease in edema after starting dialysis, whereas the static height SDS is comparable to previous reports of stable growth in children with different PRDs after starting on dialysis [1, 20, 25].

The overall transplantation rate for children on chronic dialysis was 55% after a median time of 9 months on chronic dialysis, which is comparable to that of the Italian registry [3] (transplantation rate of 39% after a median time on dialysis of 29 months) and that of the ESPN/ERA-EDTA registry study on infant dialysis [14] (cumulative 5-year transplantation rate of 70%). In general, the overall patient and graft survival post-transplantation of children with CNS are comparable to CAKUT patients as investigated in detail by the ERA/EDTA registry study [4].

In our study, there were 15 deaths, of which 8 (15%) children died on dialysis, with sepsis and cardiovascular disease being the main causes of death. In the ERA/EDTA registry report, 13 of 157 (8.3%) children died while on dialysis, and mortality was comparable in children with *NPHS1* compared to those with dysplasia [4]. The Italian registry reports similar survival rates irrespective of the PRD: mortality rates were 10% at 1 year, 13.1% at 2 years, and 16.1% at 5 years with infections being the main cause of death, followed by cardiovascular disease [16].

Our study has some limitations which are mainly within the nature of a retrospective, descriptive analysis. Also, given that the study is multi-center, management is likely heterogeneous which can impact outcomes including the assessment of renal survival time, and since CNS is a rare disease with only a few patients per center, we are unable to correct for cofounders such as comorbidities, regional variations in practice, or nutritional status. With a high percentage of Caucasians in our study (90%), we are unable to comment on outcomes in other ethnic groups. However, in view of the rarity of CNS, no prospective studies exist, and this is the largest multi-center study providing extensive details on dialysis management, complications, and outcomes of dialysis in children with CNS. This report may help clinicians in their discussions with parents about the decision-making process regarding dialysis treatment and the short- and long-term prognosis of CNS children.

In summary, we report that by 2 years of age, 50% of surviving children with CNS require chronic dialysis. Importantly, in children with CNS, the overall complication rate, in particular the peritonitis rate and the need for changing dialysis modalities, as well as growth and transplantation rates are comparable to that reported in infants with other PRDs. Although PD remains the modality of choice, HD is an acceptable alternative with comparable outcomes in children with CNS.

Compliance with ethical standards

Ethical approval for retrospective case-note review was obtained at each center as per local requirements.

Conflict of interest The authors declare that they have no conflict of interest.

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