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ORIGINAL ARTICLE

Management of children with congenital nephrotic syndrome: challenging treatment paradigms

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ABSTRACT

Background. Management of children with congenital nephrotic syndrome (CNS) is challenging. Bilateral nephrectomies followed by dialysis and transplantation are practiced in most centres, but conservative treatment may also be effective.

Methods. We conducted a 6-year review across members of the European Society for Paediatric Nephrology Dialysis Working Group to compare management strategies and their outcomes in children with CNS.

Results. Eighty children (50% male) across 17 tertiary nephrology units in Europe were included (mutations in *NPHS1*, $n = 55$; *NPHS2*, $n = 1$; *WT1*, $n = 9$; others, $n = 15$). Excluding patients with mutations in *WT1*, antiproteinuric treatment was given in 42 (59%) with an increase in S-albumin in 70% by median 6 (interquartile range: 3–8) g/L ($P < 0.001$). Following unilateral nephrectomy, S-albumin increased by 4 (1–8) g/L ($P = 0.03$) with a reduction in albumin infusion dose by 5 (2–9) g/kg/week ($P = 0.02$). Median age at bilateral nephrectomies ($n = 29$) was 9 (7–16) months. Outcomes were compared between two groups of *NPHS1* patients: those who underwent bilateral nephrectomies ($n = 25$) versus those on conservative management ($n = 17$). The number of septic or thrombotic episodes and growth were comparable between the groups. The response to antiproteinuric treatment, as well as renal and patient survival, was independent of *NPHS1* mutation type. At final follow-up (median age 34 months) 20 (80%) children in the nephrectomy group were transplanted and 1 died. In the conservative group, 9 (53%) remained without dialysis, 4 (24%; $P < 0.001$) were transplanted and 2 died.

Conclusion. An individualized, stepwise approach with prolonged conservative management may be a reasonable alternative to early bilateral nephrectomies and dialysis in children with CNS and *NPHS1* mutations. Further prospective studies are needed to define indications for unilateral nephrectomy.

Keywords: bilateral nephrectomies, congenital nephrotic syndrome, genotype–phenotype correlation, management approach, *NPHS1*

INTRODUCTION

Congenital nephrotic syndrome (CNS) is one of the most challenging conditions within the field of paediatric nephrology, with high morbidity and mortality [1]. Children present within the first 3 months of life with severe proteinuria, hypoalbuminaemia and oedema. They usually are treated with frequent albumin infusions and may suffer from severe complications related to hypoalbuminaemia such as recurrent infection, thrombosis and impaired growth [2]. In many centres, including developed countries, active treatment was not offered until the 1980s.

CNS is primarily caused by mutations within the *NPHS1* gene that encodes nephrin [3]. The two most common mutations within *NPHS1* are Fin-major and Fin-minor, which are highly enriched in the Finnish population [4]. Further, mutations in other genes including *NPHS2*, *PLCE1*, *WT1*, *LAMB2*, *PDSS2* and *COQ2* can cause CNS, associated with a clinically heterogeneous disease [5–11]. However, there are few data that provide insight into the genotype–phenotype relationship in CNS [5, 12].

The currently recommended treatment approach, as established by the Finnish group two decades ago, is to give daily albumin infusions, perform elective bilateral nephrectomies at a weight of ∼7 kg with start of peritoneal dialysis (PD) and aim for early transplantation at a weight of ∼10 kg [2, 13]. Alternatively, some centres follow a more conservative approach, which combines antiproteinuric treatment and/or unilateral nephrectomy in order to reduce protein loss and delay dialysis and transplantation [14–16]. However, the rarity and heterogeneity of CNS make it extremely difficult to develop clinical trials, and therefore comparative studies do not exist.

We performed a retrospective case-note review across all members of the European Society of Pediatric Nephrology (ESPN) Dialysis Working Group in order to evaluate (i) the response to antiproteinuric treatment and unilateral nephrectomy with regards to S-albumin, albumin infusion requirement and complication rates in children with CNS depending on detailed underlying genetic diagnosis, (ii) outcomes of bilateral nephrectomies and early dialysis versus conservative management (no nephrectomy) in children with *NPHS1* mutations with regards to complications (sepsis, thrombosis), growth, renal and patient survival and (iii) outcomes based on *NPHS1* mutation type to assess for possible genotype–phenotype correlations.

MATERIALS AND METHODS

We performed a retrospective case-note review across 22 centres in 15 European countries, who are members of the ESPN Dialysis Working Group, enquiring about the management of children diagnosed with CNS. We included all children who were diagnosed with CNS between 1 January 2010 and 31 December 2015, including those in whom care was withdrawn. Children with any other type of nephrotic syndrome and those presenting after the first 3 months of life were excluded.

These centres represent the key tertiary nephrology units across Europe and cover ∼105 paediatric PD and 105 paediatric haemodialysis (HD) patients per year and perform ∼180 paediatric renal transplants per year. A total of 88 children met the inclusion criteria. Eight children were excluded due to congenital cytomegalovirus ($n = 3$), transient CNS due to anti-neutral endopeptidase antibodies ($n = 1$), incomplete data ($n = 3$) or withdrawal of consent ($n = 1$). Eighty children were included in the final analysis across 17 centres: 25 from Helsinki (Finland); 10 from London (UK); 8 each from Heidelberg (Germany) and Barcelona (Spain); 4 each from Padua (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).

Detailed anonymized information on each child with CNS, including patient demographics, presenting features, management approach, antiproteinuric treatment and albumin infusions, nephrectomies, specifics of dialysis therapy and outcome, were collected. S-albumin and weekly dose of albumin infusion were recorded at distinct time points [for S-albumin: at presentation, at start of albumin infusion, pre- and 4 weeks post-antiproteinuric treatment, pre- and 4 weeks after unilateral nephrectomy, pre- and 4 weeks post-bilateral nephrectomies; for albumin infusion dose: at start of albumin infusion treatment (considered as baseline), 4 weeks after antiproteinuric treatment and 4 weeks after unilateral nephrectomy].

Available genetic information is presented in Supplementary data, Table S1. Genetic testing was performed by the local centre according to centre-specific standards. For some patients, a formal genetic report was not available as results were obtained on a research basis only, without confirmation from a clinical genetic laboratory, and details were provided by the contributing clinicians to the best of their knowledge. Thus, data need to be interpreted with caution.

In children with *NPHS1* mutations, the severity of the mutation was determined to enable assessment for a potential genotype–phenotype correlation. A genotype with homozygous or compound heterozygous nonsense mutations in both alleles (frameshift, stop codon, splice site) was considered as 'severe', whereas a genotype with homozygous or compound heterozygous missense mutations in one or both alleles was considered as 'milder' as described previously [17, 18].

For the genotype–phenotype analysis, children with biallelic severe mutations were compared with children with at least one milder mutation. Parameters compared were gestational age, birthweight, age at presentation, S-albumin and S-creatinine at presentation, response to angiotensin-converting enzyme inhibitors (ACEis) treatment and outcome parameters (dialysis, transplantation and survival).

Data were analysed in a central unit (Great Ormond Street Hospital) and verified by email correspondence and at meetings of the group. Ethical approval for fully anonymized retrospective case-note review was obtained as per local requirements.

Statistical analysis

The data were tested for normality using the Kolmogorov–Smirnov test. Since most data were non-parametric, results are presented as median with interquartile range. The Mann–Whitney test was used for group comparisons where appropriate. The Wilcoxon signed-rank test was used for comparison of inter-individual changes. Categorical/dichotomous variables are expressed as percentages and were tested using the Pearson Chi-square test. Kaplan–Meier curves were used to determine the time to start of dialysis and survival across groups.

SPSS Statistics 24.0 for Mac (IBM Corporation) was used for the analysis. Statistical tests were two-tailed and $P < 0.05$ were considered significant.

RESULTS

Cohort structure and first presentation

Eighty children (50% male) with CNS from 17 tertiary paediatric dialysis units in 9 countries across Europe were included. This total cohort included 90% Caucasian and 10% Asian with 6% Arabic. Underlying genetic diagnoses were mutations in the genes *NPHS1* in 55 (69%), *WT1* in 9 (11%), *NPHS2* in 1 (1.3%), *LAMB2* in 2 (2.5%) and *PLCE1* in 1 (1.3%). In one (1.3%), a mutation in a new gene, sphingosine-1-phosphate lyase (*SGPL-1*) was found [19]. No causal mutations were found in 11 (14%), of which 3 had diffuse mesangial sclerosis (DMS) (3.8%) and 2 focal segmental glomerulosclerosis (FSGS) (2.5%) on biopsy, 1 each had clinical diagnoses of Galloway–Mowat syndrome and Pierson syndrome. One patient had a variant of uncertain significance in the *NPHS1* gene and another, a variant in the *WT1* gene, which is likely not pathogenic. Details are given in Supplementary data, Table S1.

The median gestational age was 37 (35–38) weeks with a birth weight of 2635 (2268–3033) g. At the time of presentation to a dialysis centre, the median age was 9 (2–45) days with S-albumin 11 (8–16) g/L and S-creatinine 27 (16–56, max 480) μmol/L; 19 (24%) children had S-creatinine >50 μmol/L at presentation and 9 (11%) had S-creatinine >100 μmol/L.

Management of children with *WT1* mutations

Since conservative management is clearly not recommended in children with *WT1* mutations, they are briefly described here and excluded from all further analysis. Nine patients had *WT1* mutations (Supplementary data, Table S1). Four out of nine (44%) developed Wilms tumour during the study period at a median age of 5 (range 0–11) months. Six (66%) had bilateral nephrectomies at median age of 10 (5–16) months and three (33%) died before bilateral nephrectomies at the age of 0, 3 and 11 months, respectively.

Management of CNS patients without *WT1* mutations albumin infusion and anti-proteinuric treatment

Albumin infusions were given in 68 of 71 children (96%) starting at a median age of 9 (3–47) days and S-albumin of 10 (8–13) g/L with a median dose of 2 (1–3) g/kg/dose and 7 (4–7) sessions per week (1 with Galloway–Mowat syndrome and 2 with DMS did not receive albumin infusions). A total of 14 (20%) children from five centres received albumin infusions at home.

Forty-two (59%) children received ACEis starting at a median age of 57 (28–81) days with corresponding S-albumin level of 13 (10–20) g/L. Seven of 42 (17%) children were on ACEis and indomethacin. Details on S-albumin levels pre- and 4 weeks post-ACEi treatment were available in 33 of 42 (79%) children. Of these, 23 (70%) had an increase in their S-albumin by median 6 (3–8) g/L ($P < 0.001$) with an intra-individual reduction of weekly albumin infusion dose by 1 (0–4) g/kg/week ($P = 0.03$). In the remaining 10 children, S-albumin stayed stable in 5 and decreased in 5, while the albumin infusion dose remained unchanged in 8 and was reduced in 2. There was no difference between children on ACEis only compared with those on additional indomethacin ($P = 0.3$).

Increase in S-albumin in genetic subgroups was: *NPHS1* 67% (14 of 21), *NPHS2* 100% (1 of 1) and all others 73% (8 of 11) (Figure 1A), with change in weekly albumin dose shown in Figure 1B.

Anti-thrombotic treatment

Routine anti-thrombotic prophylaxis was used in 10 (59%) centres as part of their policy for CNS management. A total of 45 (63%) children received prophylactic antithrombotic medication. Nine (13%) children developed thrombosis: 4 children of 26 (15%) not on prophylaxis versus 5 children of 45 (11%) on anti-thrombotic prophylaxis ($P = 0.60$) (warfarin in 3, heparin in 1 and aspirin in 1). The median age at thrombosis was 2 (20 days to 8 months) months. At the time of thrombosis, median S-albumin was 15 (10–22) g/L; one child was on dialysis (HD). In five (56%), the thrombus formation was at the site of a central line with two having a line infection. All children received therapeutic anticoagulation, with heparin in six (67%) or warfarin in three (33%). One child received additional thrombolysis with alteplase 2 mg/kg.

Nephrectomy and outcome

Nephrectomy was performed in 33 (47%) children (29 with *NPHS1* and 4 without confirmed genetic cause). Unilateral nephrectomy only was performed in 4 (12%), bilateral in two steps in 6 (18%) and bilateral in one step in 23 (70%) children. Respective ages were 6 (4–11) months for unilateral nephrectomy or first kidney removal and 9 (7–16) months for bilateral nephrectomies or second kidney removal.

Ten children underwent unilateral nephrectomy (six as part of a stepwise approach to bilateral nephrectomy), of which one was on dialysis already and one had his second nephrectomy within 3 weeks. The response in S-albumin and albumin infusion dose was assessed in the remaining eight (six with *NPHS1* mutations): S-albumin increased by 4 (1–8) g/L ($P = 0.03$) (Figure 2) and weekly albumin dose decreased by 5 (2–9) g/kg/week from baseline ($P = 0.02$). In the same patients, S-creatinine increased from median 21 (10–35) μmol/L before unilateral nephrectomy to median 45 (10–84) μmol/L, 4 weeks after unilateral nephrectomy. Six progressed to dialysis at median 7 (0–14) months post-unilateral nephrectomy due to deterioration in renal function in the solitary kidney. Two did

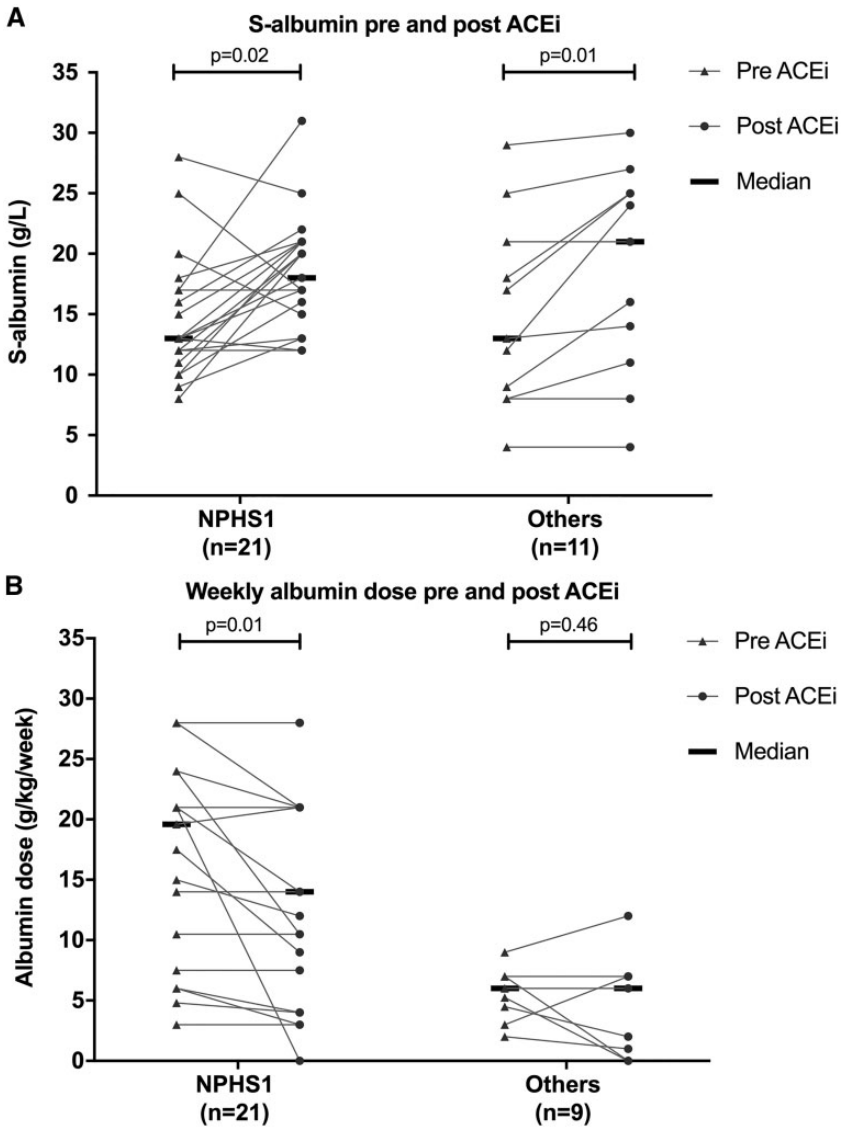

FIGURE 1: (**A**) S-albumin levels pre- and 4 weeks post-treatment with ACEi according to underlying genetic type. (**B**) Weekly albumin infusion dose g/kg/week pre- and 4 weeks post-treatment with ACEi according to underlying genetic type. The figure shows a scatterplot of intra-individual change pre- and post-treatment with ACEi. The bold line represents the group median. P-values for Wilcoxon signed-rank test displayed. Only one child had *NPHS2* mutation, which is not shown in the figure.

not require dialysis during the study period (aged 33 and 35 months, respectively).

Eleven of 71 (16%) children died at a median age of 8 (4–33) months. Survival of the whole cohort (including WT1) grouped by underlying diagnosis is shown in Figure 3.

Comparison: bilateral nephrectomies versus conservative management

In the following part of the study, we compared the outcome of bilateral nephrectomies (performed in one or two steps) versus conservative management (no nephrectomy) (Table 1). In order to get comparable study groups, we only included children with *NPHS1* mutations ($n = 55$).

In addition, 3 children with unilateral nephrectomy only and 10 children with follow-up of <1 year were excluded (as the median age for bilateral nephrectomies was 9 months). Out of the three with unilateral nephrectomy, all are alive with one on PD and two without renal replacement therapy. Out of the 10 children with follow-up <1 year, 6 are alive, of which 1 had bilateral nephrectomy and is on dialysis. Four children died with none having bilateral nephrectomies.

Nephrectomized children ($n = 25$) presented earlier (2 versus 29 days; $P = 0.01$), but with similar S-albumin (8 versus 10 g/L, $P = 0.29$) and S-creatinine (20 versus 20 µmol/L, $P = 0.27$) compared with conservatively managed children ($n = 17$). Nephrectomized children were less likely to receive ACEis (28% versus 94%; $P < 0.001$) prior to nephrectomies. All nephrectomized and six conservatively managed children required dialysis ($P < 0.001$) because of progression to end-stage kidney disease at the median age of 8 versus 25 months ($P = 0.001$). The median renal survival time was 8 [95% confidence interval (CI): 6–10] months versus 45 (95% CI: 26–64) months.

The nephrectomized and conservative groups were followed from birth until a median age of 35 (22–49) and 33 (22–54)

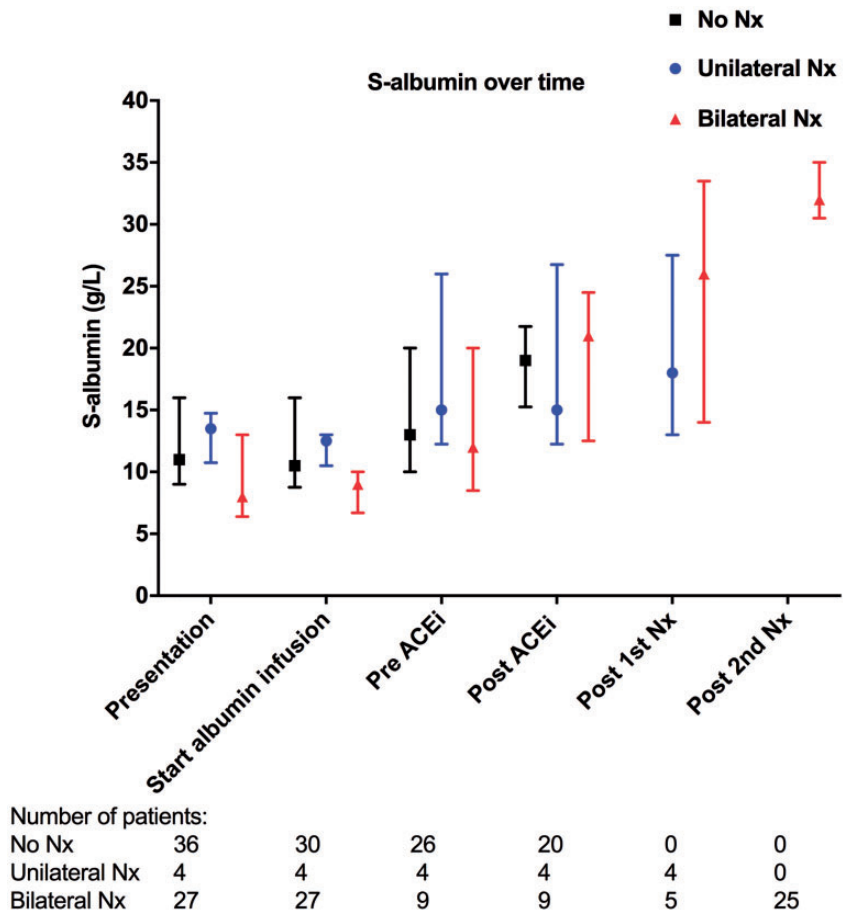

FIGURE 2: Change in S-albumin over time in patients with no nephrectomy, unilateral nephrectomy or bilateral nephrectomies. The level of S-albumin at different time points shown for three different groups: patients with no nephrectomy ($n = 38$), with unilateral nephrectomy ($n = 4$) and with bilateral nephrectomies ($n = 29$). *Y*-axis: median S-albumin and interquartile range (g/L). Nx, nephrectomy.

months, respectively, and compared for complications during the observation period. There was no statistically significant difference in the number of children who developed peritonitis (32% versus 13%; P = 0.16), central line infections (48% versus 47%; P = 0.95), septic episodes (54% versus 53%; P = 0.94) or thrombotic events (16% versus 12%; P = 0.70) between the groups (Table 1). The median weight standard deviation score (SDS) was significantly higher in nephrectomized children at 12 months of age (−0.69 versus −1.49; P = 0.04) but with no statistically significant difference in height SDS (−0.47 versus −1.15; P = 0.29). However, there was no difference in growth at age 18, 24 and 36 months between the groups (Table 1).

Final outcomes of bilateral nephrectomies versus conservative management

In the final follow-up in the nephrectomy group, one patient died at the age of 13 months versus two in the conservative group at 33 and 49 months, all from cardiovascular causes (survival 96% versus 88%; P = 0.34; Table 1). A significantly higher number were transplanted in the nephrectomy group (80% versus 24%; P < 0.001) at a younger age (17 versus 33 months; P = 0.005) and four were still on dialysis (three PD, one HD) versus two in the conservative group (two PD). In the conservative group, nine (53%) children did not require renal replacement therapy during study period at median 23 (21–44) months of age. Out of the 24 children receiving a renal transplant in both groups, all children were alive. Four had a recurrence of nephrotic syndrome post-transplantation, one from the conservative group and three from the nephrectomy group.

In addition, a Kaplan–Meier analysis for renal survival was performed on all children with *NPHS1* including those with follow-up <1 year or unilateral nephrectomy only (Figure 4).

Outcomes based on *NPHS1* mutation type

In the conservative group, 8 of 17 children had homozygous or compound heterozygous mutations classified as 'severe' and 9 had at least one mutation classified as 'milder'. Details are provided in Table 2. Although numbers are small, baseline parameters were comparable between children with 'severe' and children with 'milder' mutations (gestational age 37 versus 36 weeks, P = 0.45; birthweight 2720 versus 2500 g, P = 0.27; age at presentation 34.5 versus 28 days, P = 1.0; S-albumin at presentation 9 versus 10 g/L, P = 0.71; S-creatinine at presentation 19 versus 20 µmol/L, P = 0.72). A comparable percentage of children in both groups showed an increase in S-albumin with ACEi therapy (75% versus 80%; P = 0.86). Renal survival (no need for dialysis in 63% versus 44%; P = 0.46 and start of dialysis at 19 versus 26 months; P = 0.17) and patient survival

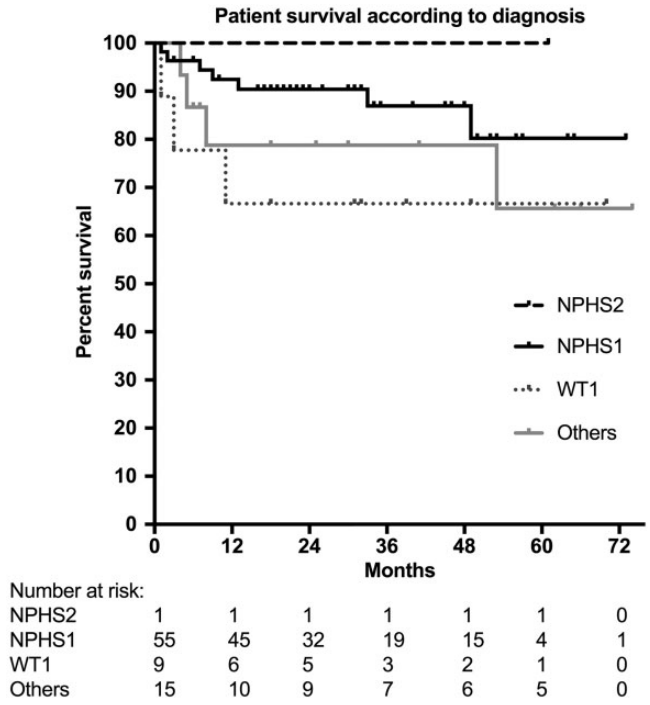

FIGURE 3: Kaplan–Maier curve for patient survival according to underlying genetic diagnosis. Others: mutation in *LAMB2* ($n = 2$), mutation in *PLCE1* ($n = 1$), mutation in *SGPL-1* ($n = 1$), no mutation found but DMS ($n = 3$), FSGS ($n = 2$), Galloway–Mowat syndrome ($n = 1$), Pierson syndrome ($n = 1$) and no other association ($n = 4$).

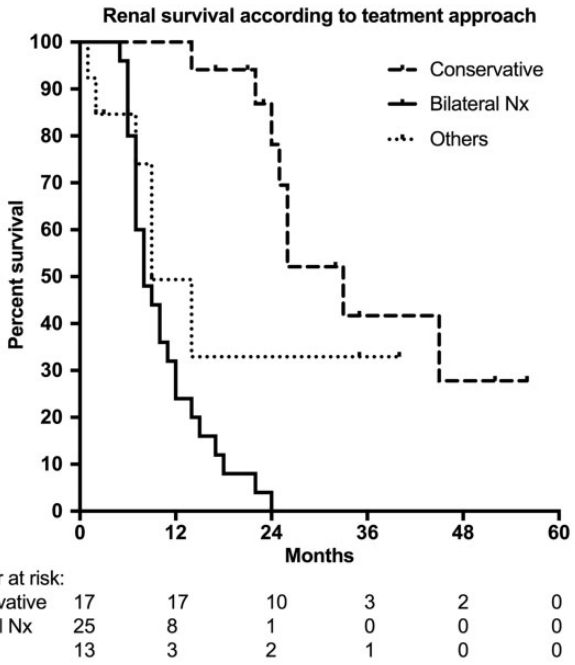

FIGURE 4: Kaplan–Maier curve for renal survival of children with *NPHS1* according to management approach ($n = 55$). Conservative management ($n = 17$); bilateral nephrectomies ($n = 25$); others: inlcudes children with unilateral nephrectomy only ($n = 3$) and children with follow-up <1 year ($n = 10$).

Table 1. Comparison of children with *NPHS1* and follow-up >1 year: bilateral nephrectomies versus conservative management

Parameters	B/l nephrectomies $n = 25$	Conservative management $n = 17$	P-value
Gestational age (weeks)	37 (34–38)	36 (35–38)	0.85
Birth weight (g)	2498 (2170–2891)	2510 (2468–2853)	0.64
Parameters at presentation			
Age (days)	2 (1–7)	29 (7–51)	0.01
Creatinine (μmol/L)	20 (16–40)	20 (9–26)	0.27
Albumin (g/L)	8 (7–12)	10 (7–11)	0.29
ACEis	7 (28)	16 (94)	<0.001
Maintenance dialysis	25 (100)	6 (35)	<0.001
Age at start (months)	8 (7–13)	25 (20–31)	0.001
Complications			
Peritonitis	8 (32)	2 (13)	0.16
Central line infections	12 (48)	8 (47)	0.95
Septic episodes	13 (54)	9 (53)	0.94
Thrombus formation	4 (16)	2 (12)	0.70
Transplantation	20 (80)	4 (24)	<0.001
Living related donor	12	0	
Age at Tx (months)	17 (12–24)	33 (27–45)	0.005
Time on dialysis before Tx (months)	6 (4–10)	11 (4–25)	0.31
Weight SDS/height SDS			
12 months	−0.69/−0.47	−1.49/−1.15	0.04/0.29
18 months	−1.27/−1.38	−1.00/−0.75	0.71/0.70
24 months	−1.65/−1.60	−1.43/−1.32	0.98/0.58
3 years	−1.19/−1.38	−2.17/−1.33	0.19/1.00
Survival (%)	24 (96)	15 (88)	0.34
Time of follow-up (months)	35 (22–49)	33 (22–54)	0.87

Values represented as median (interquartile range) or percentage.
B/l, bilateral; Tx, transplantation.

Table 2. Genotype–phenotype correlation in children with *NPHS1* and conservative treatment ($n = 17$)

Pt ID	Gender	Type of mutation	Outcome	Age at final follow-up (months)
	Milder mutations			
1	F	Homozygous missense	Alive—transplanted	65
2	M	Homozygous missense	Alive—transplanted	34
3	M	Homozygous missense	Alive—no RRT	21
4	M	Homozygous missense	Alive—no RRT	35
5	F	Homozygous missense	Dead—PD	49
6	M	Compound heterozygous missense/nonsense	Alive—no RRT	23
7	M	Compound heterozygous missense/nonsense	Alive—no RRT	17
8	M	Compound heterozygous missense/nonsense	Alive—transplanted	73
9	M	Compound heterozygous missense/nonsense	Alive—PD	26
	Severe mutations			
10	M	Homozygous nonsense	Alive—PD	18
11	M	Homozygous nonsense	Alive—no RRT	21
12	F	Homozygous nonsense	Alive—transplanted	57
13	F	Homozygous nonsense	Dead—no RRT	33
14	F	Homozygous nonsense	Alive—no RRT	23
15	F	Homozygous nonsense	Alive—no RRT	32
16	F	Compound heterozygous nonsense/nonsense	Alive—no RRT	56
17	F	Homozygous nonsense	Alive—no RRT	52

Pt ID, patient ID; F, female; M, male; RRT, renal replacement therapy.

(88% versus 89%; P = 0.93) were comparable between children with 'severe' and children with 'milder' mutations.

DISCUSSION

In this study, we compare management strategies and their outcomes in children with CNS. With 80 children from 17 tertiary centres in Europe, this is the largest multicentre study comparing management approaches in this rare disease cohort. Our data suggest that an individualized, stepwise approach, with prolonged conservative management may be a reasonable alternative to early bilateral nephrectomies in some children with CNS and *NPHS1* mutation. A trial of ACEi should be considered to reduce proteinuria with preservation of renal function. Furthermore, prospective studies are needed to define indications for unilateral nephrectomy. It is likely that there is a poor genotype–phenotype correlation even in children with *NPHS1* mutations, which in turn causes differences in the severity of the disease and makes it difficult to apply the same treatment regimen to all.

In 1996, Holmberg *et al.* [13], published a successful therapy for the infants with Finnish-type CNS: early bilateral nephrectomies with start of PD when the child weighed ∼7 kg. Whereas previously, virtually all patients died, this approach allowed the vast majority to survive and has been used by the Finnish team as well as in many other centres [13, 20]. However, PD in infants and transplantation in very young children can be challenging and may not be offered at all nephrology centres [21]. Recently, a shift in management of CNS towards a more conservative approach without surgical intervention has been reported by Reynolds *et al.* [22]. Two children in this series received a nephrectomy, but five, three of whom had *NPHS1* mutation, could be managed without any surgical intervention [22].

This raises the question, whether some patients with CNS have a milder form of the disease that can be managed conservatively, or whether improvements in the supportive treatment, such as timely administration of albumin and antibiotics during acute illnesses, could allow all patients with CNS to be treated conservatively. Since our study is retrospective, no definitive answer can be provided, but within the captured data, we tried to assess for differences in disease severity. First, we looked at the genetic data, as the predominant presence of the two nonsense mutations in the Finnish population could suggest a more severe phenotype. Yet, 'severe' and 'mild' mutations were equally common in the conservatively managed group, with no significant difference in outcome based on the mutation type. Indeed, that mutation does not necessarily influence the severity of the disease is demonstrated by the mutation most commonly seen in Malta (R1160X), which also introduces a premature stop codon and causes CNS, but can be associated with spontaneous improvement [12]. Further, *in vitro* studies showed that missense mutations in *NPHS1* most commonly lead to retention of protein in the cytoplasm [23]. Thus, mutations classified here as 'milder' may lead to just as severe loss-of-function of *NPHS1* as the ones classified as 'severe'.

Next, we assessed whether there were clinical indicators for more severe diseases, such as differences in S-albumin or S-creatinine at start, response to ACEi treatment or renal and patient survival. However, there was no indication that children with 'severe' mutations had a more severe phenotype than children with 'milder' mutations.

We also compared baseline parameters between children receiving nephrectomies or conservative management. There was a significant difference in the age at presentation between the two groups, but it is likely that Finnish patients, who make up 80% of the cases treated with bilateral nephrectomies, were diagnosed and referred to specialist centres earlier. However, three centres had patients in both groups, which make a bias towards the individual centres unlikely. Otherwise, baseline parameters were comparable between the two groups. Nearly all children not undergoing nephrectomy were treated with ACEi to control proteinuria, and only 35% proceeded to dialysis

and one had a pre-emptive transplant. More than half of the children within this group did not require renal replacement therapy and were alive at final observation. The PodoNet Registry reports similar findings with 57% of children with CNS Finnish-type developing end-stage renal disease at median follow-up time of 3.7 years [24]. Further, our results show that dialysis in the conservative group could be delayed to almost 2 years of age. Even in children with severe homozygous or compound heterozygous mutations, dialysis was required in only 25%. This suggests that a strong genotype–phenotype correlation may not exist and an individualized approach depending on a child's clinical response to treatment might be considered.

The benefit of ACEi in children with CNS has been controversial, but all studies are small and single-centre. Licht *et al.* [15] reported an increase in S-albumin in all five children with CNS (100%) treated with captopril and indomethacin with a maximum effect after 6 weeks, and Wong *et al.* [25] showed a response rate of 60% to combination therapy of indomethacin and ACEi. Poorer response to ACEi treatment is reported in children with *NPHS1* mutations [2, 4]. In our study, 67% of children with *NPHS1* mutations showed an increase in S-albumin and a significant reduction in albumin infusion requirement. While this is based on retrospective data, which may be biased by confounders, the overall response rate may still justify a trial of antiproteinuric treatment in all *NPHS1* patients.

One might argue that the complication rate secondary to ongoing nephrosis is higher in children not undergoing nephrectomy and dialysis. In our study, the rate of complications was similar in both groups. There was no increase in CNS-related complications (infections, thrombosis) with conservative treatment and also an even lower percentage of peritonitis, although not statistically significant. Also, growth in both groups was comparable. Similar results were observed by the recent ESPN/ERA-EDTA Registry study, which reported no significant differences in outcomes regarding infections and thrombotic events between Finnish patients with mutations in the *NPHS1* gene treated with bilateral nephrectomy and early dialysis versus non-Finnish patients with mutations in the *NPHS1* gene treated with different approaches [1].

The main limitation of our study is that it is a retrospective case-note review. This could have affected the quality and completeness of data collection; however, data were verified via email and meetings of the group. We therefore are only able to state percentages and not rates of complications. However, since the groups were followed for similar amounts of time, the percentage is most likely reflecting the rate of complications. It remains difficult to establish clinical trials in children with CNS, as the disease is not only rare but also the phenotype varies significantly between different genetic groups of CNS [5–11]. We are not able to provide clinical practice recommendations for the treatment of children with CNS.

In conclusion, in the children with CNS caused by *NPHS1* mutations, the specific genotype appears to provide only limited prognostic information and should not influence management decisions. Our data suggest that it may be possible to manage at least a subset of these children using a conservative approach and thereby prolonging the time-off dialysis. We suggest that in children with CNS, an individualized, stepwise approach may be appropriate, including a trial of ACEi treatment to reduce proteinuria but preserve renal function. Whether unilateral nephrectomy is of benefit to those patients who remain severely symptomatic, or whether such children should proceed to bilateral nephrectomies requires further investigation.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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