**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 is practiced in most centers, 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:** 80 children (50% male) across 17 tertiary nephrology units in Europe were included (NPHS1 n=55; NPHS2 n=1, WT1 n=9, others n=15). Excluding patients with 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 2 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 were 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. Further prospective studies are needed to define indications for unilateral nephrectomy.

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

**Introduction**

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

CNS is primarily caused by mutations within the NPHS1 gene that encodes for 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 is little data into the insight of 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 about 7 kg with start of peritoneal dialysis and aim for early transplantation at a weight around 10 kg 2,13. Alternatively, some centers 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 ESPN dialysis working group in order to evaluate a) 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 and b) 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 c) outcomes based on NPHS1 mutation type to assess for possible genotype-phenotype correlations.

**Material and Methods**

We performed a retrospective case-note review across 22 centers in 15 European countries who are members of the European Society of Pediatric Nephrology 17 dialysis working group enquiring about the management of children diagnosed with CNS. We included all children who were diagnosed with CNS between 01/01/2010 and 31/12/2015, 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 centers represent the key tertiary nephrology units across Europe and cover approximately 105 pediatric PD and 105 pediatric HD patients per year and perform around 180 pediatric renal transplants per year. A total of 88 children met the inclusion criteria. Eight children were excluded due to congenital CMV (n=3), transient CNS due to anti-neutral endopeptidase antibodies (n=1), incomplete data (n=3) or withdrawal of consent (n=1). 80 children were included in the final analysis across 17 centers: 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), 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 dose of weekly albumin infusion were recorded at distinct time points (for S-albumin: at presentation, at start of albumin infusion, pre- and 4 weeks after antiproteinuric treatment, pre- and 4 weeks after unilateral nephrectomy, pre- and 4 weeks after 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 table 1. Genetic testing was performed by the local center according to center specific standards. For some patients, a formal genetic report was not available as results were obtained on a research basis only, without confirmation in 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 mutation in one or both alleles was considered as “milder” as described previously 18,19.

For the genotype-phenotype analysis children with bi-allelic severe mutations were compared to 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 ACEi treatment and outcome parameters (dialysis, transplantation and survival).

Data were analyzed 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 values <0.05 were considered significant.

**Results**

***Cohort structure and first presentation***

80 children (50% male) with CNS from 17 tertiary pediatric dialysis units in 9 countries across Europe were included. 90% were Caucasian and 10% Asian with 6% Arabic of this total cohort. Underlying genetic diagnoses were 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 1 (1.3%) a mutation in a new gene, SGPL-1, was found 20. 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 one a variant in the WT1 gene which is likely not pathogenic. Details are given in supplementary table 1.

The median gestational age was 37 (35-38) weeks with a birth weight of 2635 (2268-3033) grams. At the time of presentation to a dialysis center, 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 a S-creatinine >50 μmol/L at presentation and 9 (11%) > 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 table 1). Four out of 9 (44%) developed Wilms tumor 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 antiproteinuric 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). 14 (20%) children from 5 centres received albumin infusions at home.

42 (59%) children received angiotensin converting enzyme inhibitors (ACEi) starting at a median age of 57 (28-81) days with corresponding S-albumin level of 13 (10-20) g/L. 7 of 42 (17%) children were on ACEi 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 whilst the albumin infusion dose remained unchanged in 8 and was reduced in 2. There was no difference between children on ACEi only compared to 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.

***Antithrombotic treatment***

Routine antithrombotic 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. 9 (13%) children developed thrombosis: 4 children of 26 (15%) not on prophylaxis versus 5 children of 45 (11%) on antithrombotic prophylaxis (p=0.60); (Warfarin in 3, Heparin in 1 and Aspirin in 1). The median age at thrombosis was 2 (20 days – 8 months) months. At time of thrombosis, median S-albumin was 15 (10 – 22) g/L; one child was on dialysis (HD). In 5 (56%) the thrombus formation was at the site of a central line with 2 having a line infection. All children received therapeutic anticoagulation with heparin in 6 (67%) or warfarin in 3 (33%). One child received additional thrombolysis with alteplase 2mg/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 2 steps in 6 (18%) and bilateral in 1 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.

10 children underwent unilateral nephrectomy (6 as part of a stepwise approach to bilateral nephrectomy), of which 1 was on dialysis already and 1 had his second nephrectomy within 3 weeks. The response in S-albumin and albumin infusion dose was assessed in the remaining 8 (6 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. 6 progressed to dialysis at median 7 (0-14) months post unilateral nephrectomy due to deterioration in renal function in the solitary kidney. Two did not require dialysis during the study period (age of 33 and 35 months).

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 1 or 2 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 less than 1 year were excluded (as the median age for bilateral nephrectomies was 9 months). Out of the 3 with unilateral nephrectomy, all are alive with 1 on PD and 2 without renal replacement therapy. Out of the 10 children with follow up less than 1 year, 6 are alive of which one had bilateral nephrectomies and is on dialysis. Four children died with none having had bilateral nephrectomies.

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

The nephrectomised and conservative groups were followed from birth until a median age of 35 (22 – 49) and 33 (22 – 54) 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% vs 13%; p=0.16), central line infections (48% vs 47%; p=0.95), septic episodes (54% vs 53%; p = 0.94) or thrombotic events (16% vs 12%; p = 0.70) between the groups; Table 1. The median weight SDS was significantly higher in nephrectomised children at 12 months of age (-0.69 vs -1.49, p=0.04) but with no statistically significant difference in height SDS (-0.47 vs -1.15; p=0.29). However, there was no difference in growth at 18, 24 and 36 months between the groups; Table 1.

***Final outcomes of bilateral nephrectomies versus conservative management***

At final follow up in the nephrectomy group 1 patient died at the age of 13 months versus 2 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 vs 33 months; p=0.005) and 4 were still on dialysis (3 PD, 1 HD) versus 2 in the conservative group (2 PD). In the conservative group 9 (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 are alive. Four had a recurrence of nephrotic syndrome post transplantation, 1 of the conservative group and 3 of the nephrectomy group.

In addition, a Kaplan Meier analysis for renal survival was performed on all children with NPHS1 including those with follow up less than 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 vs 36 weeks, p=0.45; birthweight 2720 vs 2500g, p=0.27; age at presentation 34.5 vs 28 days, p=1.0; S-albumin at presentation 9 vs 10 g/L, p=0.71; S-creatinine at presentation 19 vs 20 μmol/L, p=0.72). A comparable percentage of children in both groups showed an increase in S-albumin with ACEi therapy (75% vs 80%; p=0.86). Renal survival (no need for dialysis in 63% vs 44%; p=0.46 and start of dialysis at 19 vs 26 months; p=0.17) and patient survival (88% vs 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 centers in Europe this is the largest multicenter 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. Further 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 that 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 established a successful therapy for their infants with Finnish-type CNS: early bilateral nephrectomies with start of peritoneal dialysis when the child weighed approximately 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 centers 13,21. However, PD in infants and transplantation in very young children can be challenging and may not be offered in all nephrology centers 22. Recently, a shift in management of CNS towards a more conservative approach without surgical intervention has been reported by Reynolds et al. 23. Two children in this series received a nephrectomy, but five, three of whom had NPHS1 mutation, could be managed without any surgical intervention 23.

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 2 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 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 the protein in the cytoplasm 24. 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 disease, 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 centers earlier. However, 3 centers had patients in both groups, which makes a bias towards the individual centers 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 are alive at final observation. The PodoNet Registry reports similar findings with 57% of children with CNS Finnish-type developing ESRD at median follow up time of 3.7 years 25. 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-center. Licht et al. 15 reported an increase in S-albumin in all 5 children with CNS (100%) treated with Captopril and Indomethacin with a maximum effect after 6 weeks and Wong et al. 26 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. Whilst this is based on retrospective data, which may be biased by confounders, this 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, that reported no significant differences in outcomes regarding infections and thrombotic events between Finnish patients with NPHS1 treated with bilateral nephrectomy and early dialysis versus non-Finnish patients with NPHS1 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 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 in those patients who remain severely symptomatic or whether such children should proceed to bilateral nephrectomies requires further investigation.

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**Conflict of Interest**

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

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**Tables**

Table 1: Comparison of children with NPHS1 and follow up more than 1 year: bilateral nephrectomies versus conservative management.

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

Legend: Median and 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 |

Legend: Pt ID: patient ID; f: female; m: male; RRT: renal replacement therapy; PD: peritoneal dialysis

**Figures**

Figure 1a: S-albumin levels pre and 4 weeks post treatment with ACEi according to underlying genetic type.

Figure 1b: Weekly albumin infusion dose g/kg/week pre and 4 weeks post treatment with ACEi according to underlying genetic type.

Legend figure 1a and 1b: 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 1 child had NPHS2 mutation and is not shown in the figure.

Figure 2: Change in S-albumin over time in patients with no nephrectomy, unilateral nephrectomy or bilateral nephrectomies.

Legend figure 2: The level of S-albumin at different time points shown for 3 different groups: patients with no nephrectomy (total n=38), with unilateral nephrectomy (total n=4) and with bilateral nephrectomies (total n=29). Y-Axis: Median S-albumin and interquartile range (g/L). ACEi: ACE Inhibitor; Nx: nephrectomy

Figure 3: Kaplan-Maier curve for patient survival according to underlying genetic diagnosis.

Legend figure 3: 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).

Legend figure 4: Conservative management (n=17), bilateral nephrectomies (n=25); Others: children with unilateral nephrectomy only (n=3) and children with follow up less than 1 year (n=10).