Pediatr Nephrol (1995) 9: 87–93

Pediatric Nephrology

Practical pediatric nephrology

Management of congenital nephrotic syndrome of the Finnish type

Christer Holmberg, Marjatta Antikainen, Kai Rönnholm, Marja Ala-Houhala, and Hannu Jalanko

Division of Paediatric Nephrology, Children's Hospital, University of Helsinki, Stenbäckinkatu 11, SF-00290, Helsinki, Finland

Received July 25, 1994; received in revised form August 19, 1994; accepted September 2, 1994

Abstract. Congenital nephrotic syndrome of the Finnish type (CNF) is a rare autosomal recessively inherited disease characterised by intrauterine onset of massive urinary loss of proteins, 90% of which is albumin. The CNF gene has been localised to the long arm of chromosome 19, but the pathogenesis remains unclear. Historically, all CNF patients died, usually within the first 6 months of life. Today, a normal life can be achieved for a child with CNF by correcting the protein deficiency and normalising nutrition. This is accomplished by early intravenous albumin supplementation, nutritional support, aggressive treatment of complications and early renal transplantation, after bilateral nephrectomy and peritoneal dialysis. In the present article current treatment strategies are reviewed, and our own experience with 43 CNF patients during the last 10 years is presented.

Key words: Nephrotic syndrome – Congenital – Finnish type – Therapy

Introduction

Congenital nephrotic syndrome (CNS) has traditionally been considered as one entity and differentiated mainly from "infantile nephrotic syndrome" which manifests later in life and has a more favourable prognosis [1–3]. Historically, most children with CNS had an extremely poor prognosis with death occurring usually within the first 6 months of life [1, 2]. However, with improvement in protein supplementation, nutritional support, continuous cycling peritoneal dialysis (CCPD) and renal transplantation in infancy, a close to normal life can today be guaranteed to these patients [4–8]. There are many problems in the treatment of these small children in the different stages of the disease, and only optimal medical and nutritional support lead to an acceptable result. The aim of the present article is to review treatment strategies from different centres and to report our own experience with 43 patients with CNS of the Finnish type (CNF) during the last 10 years. We will restrict our presentation to this clearly defined disease. However, patients with other types of CNS can often be treated according to similar guidelines.

Correspondence to: C. Holmberg

Congenital nephrotic syndrome of the Finnish type

CNF is an autosomal recessively inherited disease seen in 1:8,000 newborns in Finland [9–11], but the disease has been described worldwide [1, 2]. CNF maps to the long arm of chromosome 19 in the immediate vicinity of the markers D19S224 and D19S220 [12]. Although the gene has been localised, the pathogenesis of CNF is still unclear. In CNS altered incorporation of anionic components, especially heparan sulphate proteoglycan, into the glomerular basement membrane (GBM) has been suggested [13–16]. In CNF we have not found any major qualitative changes of GBM components in CNF kidneys [17, 18], anionic sites of the GBM are not reduced [19] and urinary heparan sulphate excretion is normal [20]. Also an association with the Pax-2 gene has been excluded [21] as well as defects in the genes coding for the α1(IV), α2(IV), α3(IV) and α4(IV) chains of type IV collagen, the B1e, B2e and B2t chains of laminin and the heparan sulphate proteoglycan core protein [22].

Clinically, the diagnosis of CNF is based on a positive family history, severe proteinuria of intrauterine onset (serum albumin < 10 g/l at presentation and urinary protein concentration > 20 g/l when serum albumin is corrected to > 15 g/l), a large placenta ($> 25\%$ of birth weight), exclusion of other causes of CNS and normal glomerular filtration rate (GFR) during the first 6 months of life. The diagnosis can, if necessary, be further strengthened by a typical renal histology after the first 3–6 months of life (Fig. 1), suspected prenatally on the basis of an increased amniotic fluid α-fetoprotein concentration [23] and verified with a

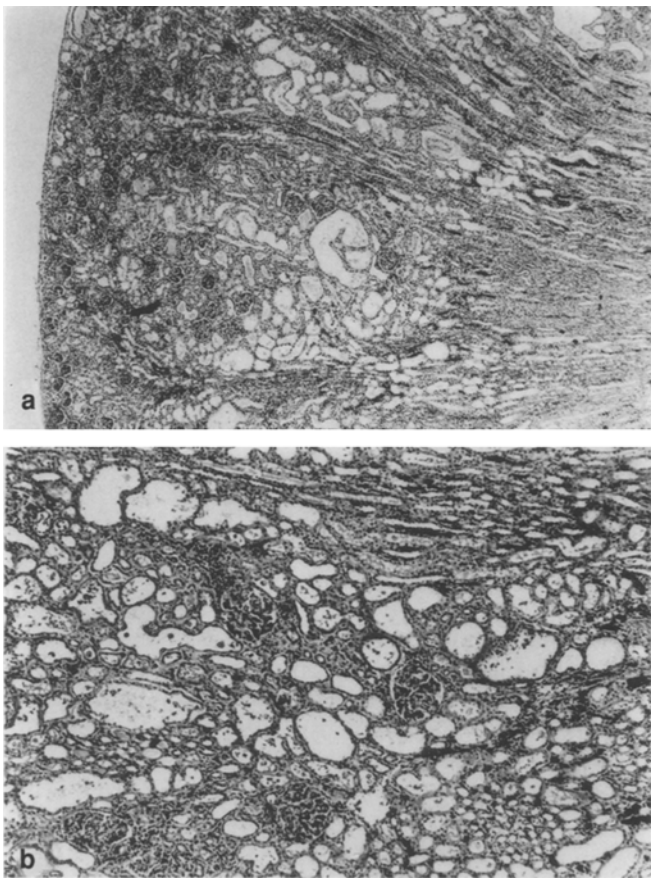

Fig. 1. Renal histology of a 6-month-old child with congenital nephrotic syndrome of the Finnish type (CNF) with typical tubular cysts, haematoxylin and eosin. **a** × 40, **b** × 100, courtesy of Juhani Rapola, MD

DNA method using informative markers in families with a previous CNF child [12].

Differential diagnosis

Even if one is faced with the typical clinical picture outlined above, combined with all secondary symptoms of hypoproteinaemia (oedema, ascites, hyperlipidaemia, susceptibility to thromboembolic events and bacterial infections), one has to exclude other causes of CNS [1–3, 24]. These include neonatal infections, renal diseases which can exceptionally occur in early infancy [minimal change NS, lupus erythematosus, haemolytic uraemic syndrome, diffuse mesangial sclerosis (DMS)] and, most importantly, many syndromes that can be combined with CNS and have a renal histology of DMS. The latter group includes the Drash syndrome and certain congenital brain malformations [3, 24–28]. It is thus of utmost importance to document renal function (faster deterioration in diseases with a DMS- or interstitial nephritis-type histology), the magnitude of proteinuria (always >20 g/l in CNF when serum albumin has been corrected to >15 g/l) and the neurological and malformation status of the infant. One has to remember that increased amniotic fluid α-fetoprotein concentration from the renal point of view only is a marker of intrauterine proteinuria due to any cause, and renal histology in a CNF child may during the first months of life be indistinguishable from the early picture in a DMS patient. After the first 3–6 months renal histology becomes typical of CNF (expansion of the mesangial area, fusion of the podocyte foot processes and presence of typical tubular cysts, Fig. 1).

Management during nephrosis

In infants with CNF the goal of all therapeutic decisions should be eventual renal transplantation, which is currently the only curative therapy [5–7, 29]. The goals of medical therapy are to provide good nutrition, to control oedema by parenteral protein supplementation and to prevent infections and thrombosis, allowing the child to reach a weight and body size consistent with a successful renal transplantation [2, 29].

Albumin substitution

The basic problem in these children is urinary loss of proteins, 90% of which is albumin. This loss leads to protein malnutrition, reduced growth and secondary symptoms of hypoproteinaemia [11]. Mahan et al. [5] reported good results in CNS with a high-energy (120 kcal/kg per day), high-protein (3–4 g/kg per day) and low-sodium diet. Diuretics and prophylactic penicillin were given daily and i.v. albumin occasionally. Although this treatment substantially improved outcome, many patients still had problems. Developmental delay and/or neurological abnormalities were observed in 93% of the children at transplantation and all exhibited growth retardation; mean standard deviation score (SDS) for height was –4.7 before transplantation and weight did not exceed the 3rd percentile in any patient. Broyer et al. [30] demonstrated substantial catch-up growth with aggressive tube feeding in CNS, but their patients never reached the 4% level in growth.

During the last 7 years we have adopted a more aggressive approach; i.v. albumin infusions are started at birth with a dose of 3–4 g albumin/kg per day i.v., and through an indwelling deep vein catheter from the age of 4 weeks. Albumin is given together with i.v. frusemide (0.5 mg/kg) as a 20% solution divided into three of four doses given over 2 h in the beginning, and as one i.v. infusion (over 6–8 h), usually during the night, from about 1 month of age. With this i.v. albumin substitution the serum albumin concentration is around 15 g/l, the patients do not have substantial oedema and growth is normal (Fig. 2) [31]. If one increases the i.v. albumin dose it only leads to more urinary loss and a vicious circle, with increased oedema, fluid overload and cardiac insufficiency.

Nutrition

Our patients received 130 kcal of energy and 4 g protein/kg per day per os (in addition to i.v. albumin substitution), resulting in 10%–14% protein, 40%–50% fat and 40%–50% carbohydrate energy; 10–15 ml of rape seed oil

Table 1. Treatment recommendations for congenital nephrotic syndrome of the Finnish type (CNF) patients during their 1st year of life

Albumin substitution	
	3–4 g/kg per day i.v. with frusemide 0.5 mg/kg (in four 2-h infusions during the 1st month and in one 6 to 8-h infusion later)
Nutrition	
	130 kcal of energy and 4 g protein/kg per day (in addition to i.v. albumin substitution) (10%–14% protein, 40%–50% fat and 40%–50% carbohydrate energy)
	15 ml rape seed oil and 2 ml fish oil
	fluids 100–130 ml/kg per day
	vitamin D_2 (2,000 IU/day), water-soluble vitamins (according to RDA), magnesium (40–60 mg/day) and calcium (500 mg <6, 750 mg 6–12 and 1,000 mg >12 months of age)
Additional medication	
	thyroxine (from birth, adjusted according to TSH)
	sodium warfarin (to keep PTT at 20%–30% of normal) (AT III 50 IU/kg i.v. 1 h before surgical or vascular procedures)
	prompt antibiotic therapy for septic infections

RDA, Recommended dietary allowance; TSH, thyroid-stimulating hormone; PTT, partial thromboplastin time; AT III, antithrombin III

and 2 ml of fish oil are added daily to increase the ratio of monounsaturated and polyunsaturated fatty acids and the P/S ratio of the diet. The excess protein is given as a casein-based protein product and additional energy as glucose polymers. In the beginning substantial water restriction was attempted to reduce GFR. This often led to osmotic diarrhoea, and today 100–130 ml/kg per day is given. Many patients need a nasogastric tube to guarantee their energy intake. All patients also receive vitamin D_2 (2,000 IU/day), vitamin E from the rape seed oil (2.5–3.0 mg/day) and water-soluble vitamins, according to the recommended dietary allowance (RDA) for healthy children of the same age. Supplementary magnesium (40–60 mg/day) and calcium (500 mg/day <6 months, 750 mg/day 6–12 months and 1,000 mg/day >12 months of age) are also given (Table 1).

Additional medication

The main problem in CNF is loss of proteins. In addition to albumin, IgG, transferrin, apoproteins, lipoprotein lipase, antithrombin III (AT III), ceruloplasmin and many others are lost into the urine [2, 29]. For example the mean concentration of vitamin D binding protein in 24-h urine is 48 mg/l in CNF (normal = 0) and the mean serum concentration only 81 mg/l (normal = 300–500 mg/l). Most of the problems encountered in CNF are caused by lack of these proteins and the present additional medication aims at correcting disturbances caused by the deficiencies.

Patients with NS mostly have low serum thyroid-binding globulin and low serum thyroid hormone concentrations [32]. McLean et al. [33] reported increase in thyroid-stimulating hormone (TSH) in four of five patients with CNS and a positive response to thyroxine substitution. We have a similar experience in CNF. Serum thyroxine concentration is always low, TSH may be normal in the beginning, but increases in most patients during the first months. Thus, we have adopted a policy of routinely substituting with thyroxine from birth, adjusting the dose according to TSH.

Urinary excretion of plasminogen and AT III results in plasma deficiencies, and compensatory protein synthesis may result in increased levels of macroglobulins, fibrinogen, thromboplastin and factors II, V, VII, VIII, X, and XIII, contributing to hypercoagulopathy [1, 34]. In one Minnesota series, 21 of 27 CNS infants had an abnormal partial thromboplastin time (PTT), often accompanied by a prolonged thrombine time [5]. Renal vein thrombosis has been reported in CNS children [35] and severe clinical coagulation problems occurred in 4 of 41 infants reported by Mahan et al. [5], with one episode each of radial artery, brachial artery, femoral artery and superior sagittal sinus thrombosis. They recommended low-dose acetosalicylate and dipyramidole therapy for children with laboratory evidence of hypercoagulability or clinical manifestations of thrombosis. We documented severe vascular complications in 5 of 17 children with CNF between 1985 and 1989, causing neurological sequelae in 4 [6]. After 1989 all CNF patients have been on sodium warfarin from 3–4 weeks of age, and no thrombotic complications have been documented. PTT is kept at 20%–30% of normal. Before surgical or vascular procedures, warfarin therapy is stopped and 50 IU/kg of AT III is given i.v. 1 h before the procedure to temporarily correct the AT III deficiency.

Infections are a major problem in infants with CNF. Mahan et al. [5] reported that 35 of 41 children with CNS suffered from severe bacterial infections, and one-third of all CNF children born in Finland from 1965 to 1973 died of infections [11]. Because of urinary losses of gamma globulin and complement factors B and D, nephrotic children are reported to be especially prone to infections caused by capsular bacteria such as pneumococci, and prophylactic use of penicillin has been recommended [5].

We have studied the incidence, type and aetiology of infections in 21 CNF infants during the nephrotic stage (Table 2) [36]. The effect of immunoglobulin and antibiotic prophylaxis was also analysed. The patients suffered from an average of five verified or suspected septic episodes per year mainly caused by staphylococci and coliforms. The incidence of focal bacterial, viral and fungal infections was normal. In retrospective analysis antimicrobial prophylaxis did not affect the incidence of septic infections and in our experience prophylactic antibiotics are not indicated. Also, prophylactic use of immunoglobulin is not indicated. The infused immunoglobulin is rapidly lost into urine (half-life of serum IgG is 10–12 h) and the commercial immunoglobulin preparations contain low IgG titres against bacteria mainly responsible for the septic episodes. Clinically, a high degree of suspicion for septic infections is warranted. The symptoms are often vague and masked by signs of focal infections occurring at the same time. Leucocytosis and an elevated C-reactive protein concentration were observed in only 50% and 85% of the septic episodes, respectively. Antibiotic therapy should be started promptly on suspicion and should cover the major hospital strains of bacteria. Response to treatment is usually excellent. Due to the in-

Table 2. Clinical characteristics and complications during nephrosis and continuous cycling peritoneal dialysis (CCPD) and after renal transplantation in 43 Finnish CNF patients seen during the last 10 years (1985–1994)

	Nephrosis (n = 43)	CCPD (n = 36)	Transplantation (n = 32)
Infections			
sepsis	2.5[a]	–	0.05[a]
suspected sepsis	2.5[a]	–	–
peritonitis	–	1.0[a]	–
Vascular complications	5	–	–
Neurological complications	4	–	–
Death	3	1	1
Growth	+	2+	3+
Quality of life	+	+	3+
Post-transplant nephrosis	–	–	6

+, Tolerable; 2+, fair; 3+, good

[a] Infections per patient per year, n = 21 for nephrotic patients studied for infections

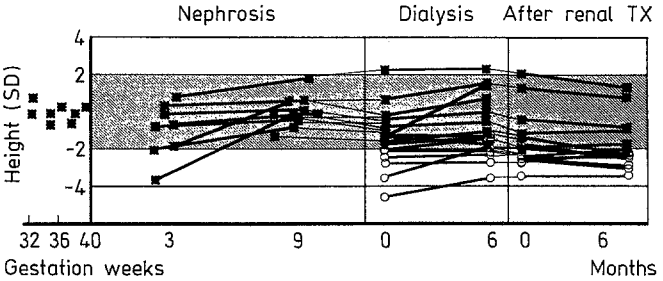

Fig. 2. Height (SD) during nephrosis, peritoneal dialysis and after renal transplantation (*TX*) in 16 children with CNF. *Black marks* represent children treated aggressively from birth and *open circles* older children with less nutritional support during nephrosis. The *hatched areas* represent normal Finnish values (±2 SD) [29]

creased risk of infection, and the questionable benefit, no vaccinations are given during nephrosis.

With the treatment outlined above (Table 1), growth and development are normal in CNF children from birth (Fig. 2) [31]. During the first years of more active treatment 3 infants succumbed [6], but since 1987 no child has died during nephrosis. Motor development is reduced because of muscular hypotonia. Most children also have a dilated heart on X-ray, probably due to the protein malnutrition. Some patients need digoxin during nephrosis and CCPD, but it can be stopped after renal transplantation, when the cardiac status normalises. After the first months, the patients spend their days at home and get their albumin infusions in hospital during the night. Some parents want to have their child at home and these children get their albumin during the daytime.

Some centres have adopted a routine of performing unilateral nephrectomy to reduce the protein loss and make substitution easier [37, 38]. We have not adopted this approach. Unilateral nephrectomy does not eliminate the need for aggressive nutritional support and i.v. albumin substitution. Also uraemia develops faster [37], which in our experience is accompanied with a fall off in growth [39]. Thus, we aim at aggressive treatment from birth to make bilateral nephrectomy, CCPD and renal transplantation possible at an early age. Prolonged nephrosis is also accompanied by a pathological lipid status, progressing with time and leading to vascular changes by 1 year of age [40]. This can be corrected only by early renal transplantation [29] which also, for the first time, introduces the child and the family to normal life.

The treatment outlined above is necessary only for a CNS child with severe protein loss, as in CNF. Other patients with CNS might lose less protein and in these protein substitution and other therapeutic measures have to be modified. It is quite clear that giving a patient with a less severe protein loss 3–4 g albumin kg/day i.v. may lead to volume overload and cardiac failure. One has, on an individual basis, to find the substitution needed to guarantee normal growth and a serum albumin concentration of 15–20 g/l. In CNS patients who develop uraemia, early aggressive treatment of uraemia is obligatory and has to be combined with substitution for renal protein loss and its secondary symptoms.

Management of CCPD after nephrectomy

Though normal growth can be achieved with the previously described therapy (Fig. 2), CNF children are still malnourished and have hypoproteinaemia [31]. To optimise treatment, we perform bilateral nephrectomy and start CCPD when a weight of 7 kg has been reached. The aims of this therapy are to end the proteinuria and correct the protein and lipid status prior to renal transplantation and to further improve the child's nutritional state. Thus, the conditions for successful renal transplantation will be met.

Dialysis

Two weeks prior to nephrectomy a curled Tenckhoff catheter with one peritoneal cuff is placed. Possible inguinal or other hernias are corrected under the same anaesthesia. The catheter is flushed every 4 h with 50–80 ml of heparinised dialysate (500 IU heparin/l dialysate) until the fluid is clear, and subsequently once a week. After 2 weeks without dialysis, CCPD is started with increasing volumes of dialysate to 20–30 ml/kg, and bilateral nephrectomy is performed when one knows that dialysis works. CCPD is continued according to a normal infant schedule [41]. We perform eight to ten 30–40 ml/kg exchanges during the night and two additional manual exchanges in the late afternoon and evening, to avoid hypervolaemia and hypertension. Heparin is always added to dialysate (250–500 IU/l), to avoid clotting of the catheter. In small nephrectomised children, variation in volaemia is seen if only three dextrose concentrations for CCPD are used. To reach optimal individual prescription of dialysis solution we mix different dextrose concentrations during CCPD (a different dextrose solution in the filling bags and the bag going to the patient). Hypervolaemia is avoided during blood transfusion by performing continuous ambulatory peritoneal dialysis every hour.

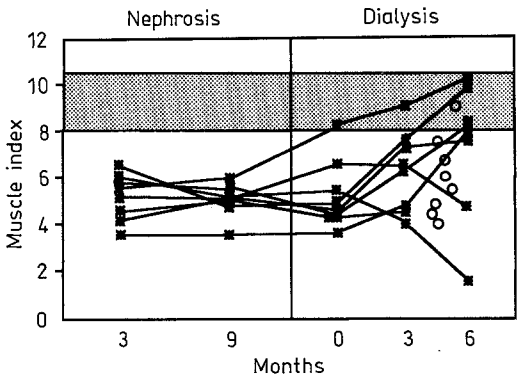

Fig. 3. Femoral quadriceps muscle index as measured by ultrasound. Muscle index = QM^2/S where QM = quadriceps muscle thickness (cm) and S = body surface area (m^2). *Black marks* represent children with CNF treated aggressively from birth and *open circles* older children with less nutritional support during nephrosis, and whose muscle index was measured only once during peritoneal dialysis [29]. The *shaded area* represents reference limits

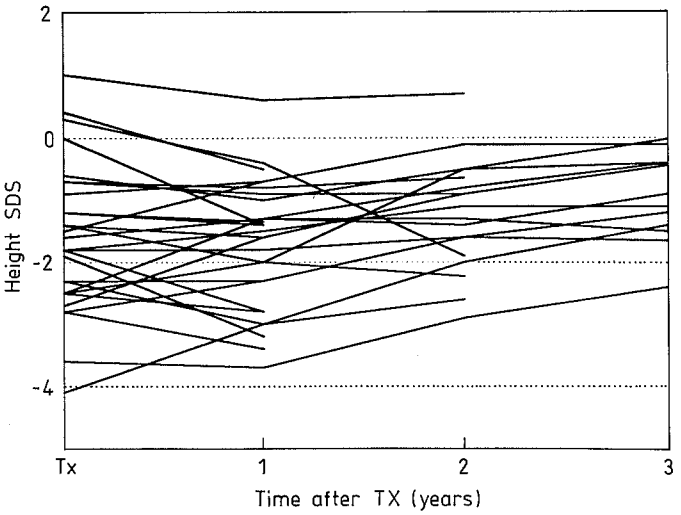

Fig. 4. Height standard deviation score (*SDS*) in CNF patients followed for more than 1 year after successful renal TX

Nutrition

Most patients are fed by a nasogastric tube. The diet is mainly based on the infant milk and cereal formulae, supplemented with a casein-based protein product and glucose polymers to reach a daily energy intake of 110% of the RDA for healthy children of the same age. Mean protein intake has been 2.5 g/kg per day (140% of the RDA). Rape seed oil (15 ml/day) and fish oil (2 ml/day) are added to the diet and water-soluble vitamins are given.

Additional medication

Over the last few years all patients have received recombinant human erythropoietin starting with 50 IU/kg three times weekly and later adjusted according to response [42]. Alphacalcidol pulse therapy has been used with great success to avoid hyperparathyroidism, and calcium carbonate as phosphate binder [43]. Sodium polystyrene sulphonate resin is given if needed for hyperkalaemia. When on CCPD all necessary vaccinations are given, according to Finnish recommendations.

After 1985 36 CNF patients have been treated with bilateral nephrectomy and CCPD. Mean age at nephrectomy was 1.2 years (range 0.6–4.0 years), and mean time on CCPD before renal transplantation 10 months (range 3–25 months). However, with improved nutritional support, the last 10 patients have been nephrectomised at a mean age of only 0.7 years (range 0.6–1.0 years). CCPD is performed at home, with visits to the clinic every 3rd week. After bilateral nephrectomy, on CCPD the general condition and hypoproteinaemia dramatically improve [44]. Muscle mass increases if no severe infections are present (Fig. 3) [44], and children with suboptimal growth during nephrosis show catch-up growth [6, 44]. Improvement in nutritional status is seen over 3–4 months, subsequently these children are similar to other children with end-stage renal disease. A weight compatible with renal transplantation with extraperitoneal placement of the graft (9 kg) was reached after 3–4 months on CCPD [6, 44]. Mean height SDS for all children at nephrectomy was –2.2, and –1.8 at transplantation (Fig. 4).

One patient died with hypervolaemia during a blood transfusion and infection. The most common complication during dialysis was peritonitis, with one episode per 11 months of CCPD (Table 2). The major pathogens were staphylococci, which usually responded to intraperitoneal vancomycin and netilmicin within a few days. Most patients had hypertension, mainly caused by hypervolaemia, and antihypertensive medication was used (nifedipine, labetalol, hydralazine and in a few patients minoxidil).

Renal transplantation

Although the first report of successful renal transplantation in CNS dates back to 1973 [4], it was the excellent long-term results after renal transplantation in CNS presented by Mahan et al. [5] in 1984 which changed the the treatment strategy for CNF [2, 6]. After 1987 we have performed renal transplantations in 32 patients with CNF, all nephrectomised and on CCPD for at least 3 months. Our overall results have recently been reported [8, 45–47]. Mean follow-up time is currently 3.7 years (range 0.1–7.1 years), 19 patients have been followed for over 3 years. Mean age at transplantation was 2.2 years (range 1.2–7.2 years). Patient survival is 97%; only 1 patient has been lost after transplantation because of hypertensive crisis after post-transplant nephrosis, chronic rejection and graft loss [48]. Graft survival is 94%, 81% and 81% after 1, 3 and 5 years, respectively. Renal function is excellent with a mean GFR of 73.7 and 75.3 ml/min per 1.73 m^2 1 and 3 years after transplantation [8, 45]. Growth has also been satisfactory (Fig. 4). Many of the older patients who not were treated according to the recommendations outlined above had reduced growth prior to transplantation (6), and 6 children have received growth hormone therapy. All other patients have either been growing normally from the beginning (Fig. 2) [29, 31] or shown growth spurt after renal transplantation (Fig. 4).

Mean height SDS for all patients was −1.85 at transplantation, −1.73 1 and −1.42 3 years after transplantation. After transplantation, 6 septic episodes, 3 pneumonias, 4 urinary tract infections (1 candida), 1 Epstein-Barr virus, 2 varicella and 6 cytomegalovirus infections have been documented. The 10 oldest children have reached school age, 9 are attending school and the 10th will start 1 year later, also in a normal class.

Post-transplant NS

Although no recurrence of the basic disease has been reported, post-transplant NS seems to be a special problem in these children. It has occurred in nine CNF patients after renal transplantation [48–51]. The episodes have usually been preceded by viral infections, and five patients have lost their grafts [48, 49]. In two patients the proteinuria responded to steroid treatment [49, 50]. Otherwise, only patients treated early with steroids and cyclophosphamide have responded with total remission [48, 51], and subsequently been switched to standard immunosuppression. In two patients post-transplant nephrosis has reappeared in a second graft, but responded to steroid and cyclophosphamide therapy ([48], Hansson, personal communication).

At our institution between 1987 and 1992, 24% of all grafts transplanted to CNF patients, but none of a similar number transplanted to patients with other diseases, developed a NS [48]. In our patients, a cytomegalovirus or Epstein-Barr virus infection preceded the insult. Three patients who immediately received cyclophosphamide treatment have subsequently had normal renal function without proteinuria with standard immunosuppression, and during the last 2 years no further episodes have been observed in our patients. Endothelial swelling of the glomerular capillaries resembling transplant glomerulopathy (TG) was seen on light and electron microscopy examination, but unlike TG the GBM was normal. All CNF patients with post-transplant nephrosis had one DR mismatch.

Psychosocial aspects

In the early days the treatment put a severe stress on the child and its family. The first years of life had to be spent in hospital, often complicated by septic episodes. The introduction of nightly i.v. albumin through a deep vein catheter and aggressive nutrition has, however, led to practically normal psychomotor development from birth, and most of the daytime can be spent at home, unless the family lives far from a hospital. While on CCPD most of the time is spent at home, feeding being the main problem. In families with a child without major complications things go smoothly, especially as the families know from the beginning that nephrectomy is going to be performed when a sufficient weight is reached and renal transplantation after 3 months on CCPD. Thus, early nephrectomy and transplantation after optimal nutrition is the best way to normal development for the child and puts strain on the parents for the shortest time. In addition, treatment costs that are high during the first 12–18 months of life are minimised with early transplantation.

Conclusion

CNF is an autosomal recessively inherited disease characterised by massive proteinuria of intrauterine onset. Historically, all children died, usually within the first 6 months of life, and the clinical picture of untreated children has been described in detail [1, 2, 11]. Today, early i.v. substitution of renal albumin loss, nutritional support and prophylactic treatment of secondary complications caused by deficiency of other, mainly low-molecular weight proteins lost in the urine makes normal growth and development possible during the 1st year of life. Bilateral nephrectomy at an age of 6–10 months and CCPD for 3–4 months corrects the protein deficiency and further improves nutrition. Subsequently, successful renal transplantation at an age of 1–2 years normalises life and the long-term results are very good [2, 8, 45–47], with post-transplant nephrosis being a special problem in only a few patients [48]. Although the CNF gene has been localised, alternative therapy, for example gene therapy, tried in other congenital diseases [52] is still some way off.

Acknowledgements. The authors wish to thank Olli Koskimies MD, Pentti Lautala MD, Niilo-Pekka Huttunen MD and the staff on the paediatric wards caring for these patients for their valuable contribution to the practical fulfilment of therapy. This study has been supported by the Children's Research Foundation and the Sigrid Juselius Foundation, Helsinki, Finland.

References

1. Rapola J, Huttunen N-P, Hallman N (1992) Congenital and infantile nephrotic syndrome. In: Edelman CM (ed) Pediatric kidney diseases, 2nd edn. Little Brown, Boston, pp 1291–1305
2. Mauch TJ, Vernier RL, Burke BA, Nevins TE (1994) Nephrotic syndrome in the first year of life. In: Holliday MA, Barratt TM, Avner ED (eds) Pediatric nephrology, 2nd edn. Williams and Wilkins, Baltimore, pp 788–802
3. Habib R (1993) Nephrotic syndrome in the first year of life. Pediatr Nephrol 7: 347–353
4. Hoyer JR, Kjellstrand CM, Simmons RL, Najarian JS, Mauer SM, Buselmeier TJ, Michael AF, Vernier RL (1973) Successful renal transplantation in three children with congenital nephrotic syndrome. Lancet i: 1410–1412
5. Mahan JD, Mauer SM, Sibley RK, Vernier RL (1984) Congenital nephrotic syndrome: evolution of medical management and results of renal transplantation. J Pediatr 105: 549–557
6. Holmberg C, Jalanko H, Koskimies O, Leijala M, Salmela K, Eklund B, Ahonen J (1991) Renal transplantation in small children with congenital nephrotic syndrome of the Finnish type. Transplant Proc 23: 1378–1379
7. Fasola CG, Gillingham KJ, Troppmann C, Gruessner RWG, Gores PF, Dunn DL, Payne WD, Sutherland DER, Matas AJ, Najarian JS (1994) Kidney transplant or retransplant can effectively treat congenital nephrotic syndrome: a single-center experience. Transplant Proc 26: 9
8. Laine J, Leijala M, Salmela K, Jalanko H, Sairanen H, Peltola K, Rönnholm K, Eklund B, Wikström S, Holmberg C (1994) Renal transplantation in children under 5 years of age. Transplant Proc 26: 106–109
9. Hallman N, Hjelt L, Ahvenainen EK (1956) Nephrotic syndrome in newborns and young infants. Ann Paediatr Fenn 2: 227–241
10. Norio R (1966) Heredity in the congenital nephrotic syndrome. Ann Paediatr Fenn 12 [Suppl 27]: 1–94
11. Huttunen N-P (1976) Congenital nephrotic syndrome of the Finnish type. Study of 75 patients. Arch Dis Child 51: 344–348

12. Kestilä M, Männikkö M, Holmberg C, Gyapay G, Weissenbach J, Savolainen E-R, Peltonen L, Tryggvasson K (1994) Congenital nephrotic syndrome of the Finnish type maps to the long arm of chromosome 19. Am J Hum Genet 54: 757–764
13. Vernier RL, Klein DJ, Oegema TR, Michael AF, Brown DM (1983) Heparan sulfate-rich anionic sites in human glomerular basement membrane. Decreased concentration in congenital nephrotic syndrome. N Engl J Med 309: 1001–1009
14. Vermeylen C, Levin M, Mossman J, Barratt TM (1989) Glomerular and urinary heparan sulphate in congenital nephrotic syndrome. Pediatr Nephrol 3: 122–129
15. Mahan JD, Sisson-Ross SS, Vernier RL (1989) Anionic sites in the human kidney: ex vivo perfusion studies. Mod Pathol 2: 117–124
16. Jadresic LP, Filler G, Barratt TM (1991) Urine glycosaminoglycans in congenital and acquired nephrotic syndrome. Kidney Int 40: 280–284
17. Ljungberg P, Jalanko H, Holmberg C, Holthöfer H (1993) Congenital nephrosis of the Finnish type (CNF): matrix components of the glomerular basement membranes and of cultured mesangial cells. Histochem J 25: 606–612
18. Van den Heuvel LPWJ, Van den Born J, Jalanko H, Schröder CH, Veerkamp JH, Assmann KJM, Berden JHM, Holmberg C, Rapola J, Monnens LAH (1992) The glycosaminoglycan content of renal basement membranes in the congenital nephrotic syndrome of the Finnish type. Pediatr Nephrol 6: 10–15
19. Jalanko H, Holmberg C, Ljungberg P, Rapola J, Koskimies O, Holthöfer H (1990) Glomerular basement membrane in congenital nephrotic syndrome of the Finnish type. Pediatr Nephrol 4: C52
20. Ljungberg P (1994) Glycosaminoglycans in urine and amniotic fluid in congenital nephrotic syndrome of the Finnish type. Pediatr Nephrol 8: 531–536
21. Kestilä M, Männikkö M, Holmberg C, Tryggvasson K, Peltonen L (1994) Congenital nephrotic syndrome of the Finnish type is not associated with the Pax-2 gene despite the promising transgenic animal model. Genomics 19: 570–572
22. Kestilä M, Männikkö M, Holmberg C, Korpela K, Savolainen E-R, Peltonen L, Tryggvasson K (1993) Exclusion of eight genes as mutated loci in congenital nephrotic syndrome of the Finnish type. Kidney Int 45: 986–990
23. Aula P, Rapola J, Karjalainen O, Lindgren J, Hartikainen AL, Seppälä M (1978) Prenatal diagnosis of congenital nephrosis in 23 high-risk families. Am J Dis Child 132: 984–987
24. Koskimies O (1990) Genetics of congenital and early infantile nephrotic syndromes. In: Spitzer A, Avner ED (eds) Inheritance of kidney and urinary tract diseases, Kluwer, Boston/Dordrecht/London, pp 131–138
25. Drash A, Sherman F, Hartman WH, Blizzard RM (1970) A syndrome of pseudohermaphroditism, Wilms' tumor, hypertension and degenerative renal disease. J Pediatr 76: 585–593
26. Galloway WH, Mowat AP (1968) Congenital microcephaly with hiatus hernia and nephrotic syndrome in two sibs. J Med Genet 5: 319–326
27. Palm L, Hägerstrand I, Kristoffersson U, Blennow G, Brun A, Jörgensen C (1986) Nephrosis and disturbances of neuronal migration in male siblings – a new hereditary disorder? Arch Dis Child 61: 545–548
28. Koskimies O, Sariola H, Holmberg C, Rapola J (1991) Clinical quiz. Congenital nephrotic syndrome, microcephaly, brain malformations and diaphragmatic abnormality associated with histological features of diffuse mesangial sclerosis. Pediatr Nephrol 5: 433–435
29. Antikainen M (1994) Growth, nutrition and lipoprotein abnormalities in children with congenital nephrotic syndrome of the Finnish type. Academic dissertation. University of Helsinki, Yliopistopaino, Helsinki
30. Broyer M, Narcy P, Rault G, Dartois A-M, Ricour C (1988) Nutritional therapy in nephropathic children. Contrib Infus Ther Clin Nutr 19: 61–75
31. Antikainen M, Holmberg C, Taskinen M-R (1992) Growth, serum lipoproteins and apoproteins in infants with congenital nephrosis. Clin Nephrol 38: 254–263
32. Gavin LA, McMahon FA, Castle IN, Cavalieri RR (1978) Alterations in serum thyroid hormones and thyroxine-binding globulin in patients with nephrosis. J Clin Endocrinol Metab 46: 125–130
33. McLean RH, Kennedy TL, Rosoulpour M, Ratzan SK, Siegel NJ, Kauschansky A, Genel M (1982) Hypothyroidism in the congenital nephrotic syndrome. J Pediatr 101: 72–75
34. Panicucci F, Sagripanti A, Vispi M, Pinori E, Lecchini L, Barsotti G, Giovanetti S (1983) Comprehensive study of haemostasis in nephrotic syndrome. Nephron 33: 9–13
35. Llach F, Papper S, Massry SG (1980) The clinical spectrum of renal vein thrombosis: acute and chronic. Am J Med 69: 819–827
36. Jalanko H, Ljungberg P, Holmberg C, Seppälä I, Repo H, Hurme M, Koskimies O (1989) Infections and immunological status of children with congenital nephrotic syndrome of the Finnish type (CNF). Pediatr Nephrol 3: C162
37. Coulthard MG (1989) Management of Finnish congenital nephrotic syndrome by unilateral nephrectomy. Pediatr Nephrol 3: 451–453
38. Mattoo TK, Al-Sowailem AM, Al-Harbi MS, Mahmood MA, Katawee Y, Hassab MH (1992) Nephrotic syndrome in 1st year of life and the role of unilateral nephrectomy. Pediatr Nephrol 6: 16–18
39. Holmberg C, Jalanko H, Koskimies O, Leijala M, Salmela K, Eklund B, Ahonen J (1990) Renal transplantation in children with congenital nephrotic syndrome of the Finnish type. Transplant Proc 22: 158–159
40. Antikainen M, Sariola H, Rapola J, Taskinen M-R, Holthöfer H, Holmberg C (1994) Pathology of renal arteries of dyslipidemic children with congenital nephrosis. APMIS 102: 129–134
41. Latta K, Offner G, Brodehl J (1992) Continuous peritoneal dialysis in children. Adv Perit Dial 8: 406–409
42. Siimes MA, Rönnholm KAR, Antikainen M, Holmberg C (1992) Factors limiting the erythropoietin response in rapidly growing infants with congenital nephrosis on peritoneal dialyses regimen after nephrectomy. J Pediatr 120: 44–48
43. Ala-Houhala M, Rönnholm K, Holmberg C, Antikainen M, Koskimies O (1993) Oral alphacalcidol pulse therapy in bone disease due to elevated PTH. Pediatr Nephrol 7: C52
44. Antikainen M (1993) Protein and lipid metabolism in nephrotic infants on peritoneal dialysis after nephrectomy. Pediatr Nephrol 7: 428–433
45. Laine J, Holmberg C, Salmela K, Jalanko H, Sairanen H, Peltola K, Rönnholm K, Eklund B, Wikström S, Leijala M (1994) Renal transplantation in children with emphasis on young patients. Pediatr Nephrol 8: 313–319
46. Laine J, Fyhrquist F, Holmberg C (1994) Effect of donor source on renal allograft function in children on triple immunosuppression. Nephrol Dial Transplant 9: 1468–1473
47. Laine J, Krogerus L, Jalanko H, Rönnholm K, Holmberg C (1994) Renal allograft histology and correlation with function in children on triple therapy. Nephrol Dial Transplant (in press)
48. Laine J, Jalanko H, Holthöfer H, Krogerus L, Rapola J, Willebrand E von, Lautenschlager I, Salmela K, Holmberg C (1993) Post-transplantation nephrosis in congenital nephrotic syndrome of the Finnish type. Kidney Int 44: 867–874
49. Sigström L, Hansson S, Jodal U (1989) Long-term survival of a girl with congenital nephrotic syndrome and recurrence of proteinuria after transplantation. Pediatr Nephrol 3: C169
50. Lane PH, Schnapper HW, Vernier RL, Bunchman TE (1991) Steroid-dependent nephrotic syndrome following renal transplantation for congenital nephrotic syndrome. Pediatr Nephrol 5: 300–303
51. Flynn JT, Schulman SL, deChadarevian J-P, Dunn SP, Kaiser BA, Polinsky MS, Baluarte HJ (1992) Treatment of steroid-resistant post-transplant nephrotic syndrome with cyclophosphamide in a child with congenital nephrotic syndrome. Pediatr Nephrol 6: 535–555
52. Grossman M, Raper SE, Kozarsky K, Stein EA, Engelhardt JF, Muller D, Lupien PJ, Wilson JM (1994) Successful ex vivo gene therapy directed to liver in a patient with familial hypercholesterolemia. Nat Gen 6: 335–341