CHRONIC RENAL FAILURE IN CHILDREN

-psychological implications for development and family-

G.M. Hulstijn-Dirkmaat

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Voor de patiëntjes en hun ouders die hebben bijgedragen aan mijn kennis en ervaring, meer en anders dan de in dit proefschrift vermelde wetenschappelijke wijsheid

CONTENTS

Abbreviations

BUN	=	blood urea nitrogen
CAPD	=	continuous ambulatory peritoneal dialysis
CCPD	=	continuous cycling peritoneal dialysis
CNS	=	central nervous system
CRF	=	chronic renal failure
CSF	=	cerebrospinal fluid
CT	=	computer tomography
DI	=	developmental index
EDTA	=	European Dialysis and Transplantation Association
EEG	=	electro-encephalography
ESRD	=	end-stage renal disease
GFR	=	glomerular filtration rate
GH	=	growth hormone
HD	=	haemodialysis
IQ	=	intelligence quotient
NMR	=	nuclear magnetic resonance
NIPD	=	nightly intermittent peritoneal dialysis
RRT	=	renal replacement therapy
SD	=	standard deviation
SEM	=	standard error of the mean
UV	=	ultraviolet

Chapter 1

GENERAL INTRODUCTION

This thesis addresses a number of aspects of chronic renal failure (CRF) and dialysis treatment in children and its implications for a child's development and family functioning.

Until twenty years ago, chronic renal failure in children which led to end stage renal disease (ESRD) could not be treated. Since then, life-saving techniques - haemodialysis (HD) and transplantation - became also suitable for children, at first in the U.S.A., later in western Europe. Right from the start, particularly paediatricians paid a great deal of attention to the psychosocial implications of these far-reaching forms of treatment [1], mainly as a result of experience with adult dialysis patients and study findings of especially Abram and Kaplan-De Nour [2,3]. A number of publications appeared in the early nineteen seventies which aimed to evaluate the heavy emotional burden for the child and his/her family, and the psychological processes resulting from adaptation to haemodialysis and transplantation [4-10]. Further progress in the medical-technical field and the development of new techniques, such as continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD), meant that the accent shifted from research on behavioural and emotional aspects, to the effects of chronic renal failure on the development of the child and improvement of the quality of life, also in the longer-term [11-18].

The first part of this thesis (Chapters 1, 2, and 3) forms the introduction to the research section that is described in Chapters 4 to 9. Chapter 2 deals with the medical aspects of chronic renal failure and renal-replacement techniques in as far as they are relevant to a good understanding of the study. Chapter 3 provides an overview of the implications of a chronic disease in general, as well as the specific consequences of renal disease, for both the child and the family. The majority of psychological aspects of chronic renal disease in childhood, as far as mentioned in the literature, are dealt with in this chapter, so that together these chapters form the theoretical framework of the two types of studies which were performed.

The background of the studies described were generated by the application of CAPD/CCPD techniques at the beginning of the nineteen eighties at paediatric dialysis centres where children younger than five year of age could receive long-term dialysis treatment [19,20]. In view of the lower age limit for dialysis treatment and the consequential increase in life expectancy, it appeared to be necessary to perform a systematic investigation on the influence of renal function disorders and dialysis treatment on the psycho-motor growth and development of children with CRF.

The general overview by Biasioli et al. [21], and other publications on children with renal disease [16-18], brought forward the alarming fact that young renal patients could suffer from developmental disorders and progressive encephalopathy in the pre-dialysis phase. These findings partly agreed with our experience with young renal patients. Psychological examination performed on a small number of patients with developmental retardation showed that their development improved significantly after the start of CAPD. This resulted in the question as to whether the early application of renal replacement therapy would offer this group of children better developmental chances. Chapters 4, 5, and 6 present the results of prospective research into the neurological, motor, and cognitive development of young patients with ESRD in both the pre-dialysis phase and the dialysis phase. Also the effect of starting dialysis treatment and the influence of other medical and psychological factors were evaluated. Chapter 7 describes the effects of transplantation on the cognitive functioning of older children.

During the first few years of applying CAPD treatment to young children at our centre, we found that the shift from haemodialysis (centre dialysis) to CAPD treatment (home dialysis) and the delegation of medical responsibility to the parents, also had implications for family functioning [22]. Particularly the parents of young patients appeared to be burdened heavily. Evaluation of the most optimal time to start CAPD treatment in young children should therefore not only consider the importance of an early start of renal replacement therapy in order to prevent developmental disorders, but also whether a family and the parents can sustain the treatment.

To be able to make reliable and systematic assessments of the amount of burden dialysis treatment has on a family and to monitor risk factors in relation

to family functioning, it was necessary to develop specific measurement instruments [23,24]. Chapters 8 and 9 describe the development of these instruments and the results of a study on family burden in relation to HD and CAPD treatment.

The research findings are discussed and summarized with a number of recommendations in Chapter 10.

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Chapter 2

MEDICAL ASPECTS OF CHRONIC RENAL FAILURE IN CHILDREN

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2.1. Function of the kidneys and the consequences of renal failure

The kidneys are two organs localized retroperitoneally in the upper abdomen. Their main function is the control of the fluid and electrolyte homeostasis in the body, as well as the elimination of metabolites from the body. Other functional contributions relate to the control of blood pressure (renin), bone metabolism (vitamin D), and red blood cell formation (erythropoietin). For these functions, each kidney contains about 1,000,000 glomeruli (Figure 2.1).

A glomerulus is a small filter unit which filters water and electrolytes from the blood. Most of the filtrate is re-absorbed in the tubules, where under the control of hormones, the fluid and electrolyte balance is maintained. Finally, the urine leaves the tubular system by the collecting ducts and flows into the renal pelvis.

The excretory function of the kidneys is commonly calculated as clearance, i.e., the amount of bloodplasma which is fully cleared of a metabolite within a certain period of time. A number of substances are suitable for clearance studies. In clinical practice, the most widely used marker is creatinine. Creatinine clearance is expressed as ml/min/1.73m^2 body surface and can be calculated from data obtained by the collection of a 24-hour urinary specimen and a blood sample. If no 24-hour urinary collection is available, creatinine clearance can be estimated from the serum creatinine concentration and the height of the patient [1]. Normal values beyond two years are 100-156ml/min/1.73m^2.

Renal function has a great reserve. A loss of up to 50% of functional renal tissue will have no consequences on the patient. If less than 50% of functioning renal tissue is present, therapeutic measures (see below) are indicated. A patient can survive, however, with a renal function as low as 10%, without renal replacement therapy. If the renal function drops below 10% (end stage renal disease) dialysis therapy or renal transplantation will be necessary.

Symptoms of renal failure generally occur if renal function drops to below 25%. Initial symptoms are decreased growth and poor weight gain [2].

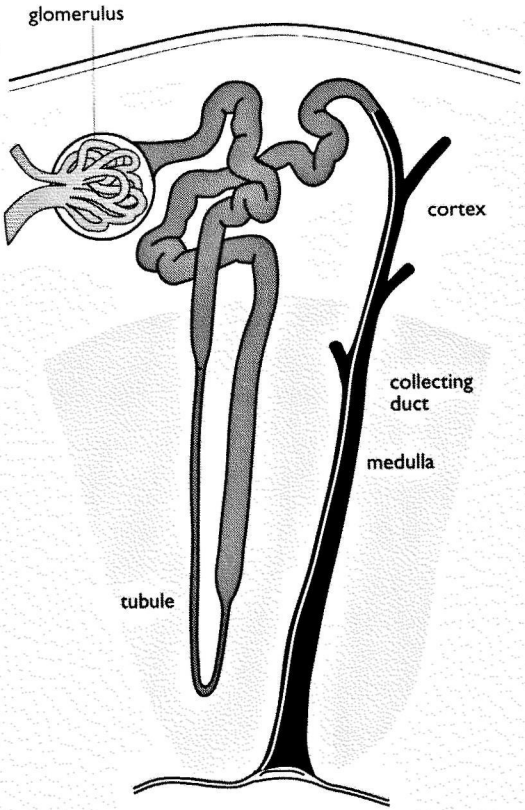

Figure 2.1. Schematic drawing of the anatomy of the functional unit of the kidney, the nephron. (from Junquiera LD, Corneiro J, Kelly RO. Functionele Histologie. Utrecht, Wet. uitg. Bunge, 1990. With permission).

At a later stage acidosis, renal osteodystrophy, hypertension, and anaemia are common. In the absence of therapy, the combination of anaemia, acidosis, and azotemia leads to increasing clinical disability and establishes the multisymptom complex known as uraemia. In this phase avitality, loss of appetite, nausea, and vomiting are common symptoms. In this phase also the so-called uraemic encephalopathy may occur.

Uraemic encephalopathy is one of the most serious complications of chronic renal failure. Several excellent reviews have been published on this topic [3-8]. Uraemia has damaging effects on cerebral function, although all neurotoxic substances responsible have not yet been fully identified. Uraemic encephalopathy is characterized by mental status abnormalities, headaches, disturbances of sleep

and vegetative functions, and polyneuropathy. Lethargy, general malaise, and easy fatigue of mental activity are common in adult dialysis patients. In children disturbances of brain maturation have been reported using spectral electroencephalography [9]. The use of aluminium as a phosphate binding agent contributes to the occurrence of toxic encephalopathic symptoms [10].

2.2. Incidence and aetiology of chronic renal failure in childhood

End-stage renal disease in childhood is a rare condition. Frequency rates vary regionally. The most recent data from the European Dialysis and Transplantation Association (EDTA) show a mean number of 3 new paediatric cases per million child population (0-15 years) in Europe in 1991, with a variation of <1 (Algeria, Malta, Romania, Turkey) to 14 (Iceland) [11]. For the United States similar figures have been reported. The incidence was 11 per million child population (0-19 years) in the period 1989-1991 [12]. It should, however, be noted that the incidence in the older age group (15-19 years) was relatively high in this population. In the Dutch population of 3,027,573 children younger than 15 years (mean value for 1979 to 1986) 18 new patients per year were admitted to one of the four paediatric dialysis programmes [13]. In 1994, 22 patients below the age of 15 years were admitted to a paediatric dialysis programme. The total number of paediatric dialysis patients treated at the four centres was 61 on January 1, 1995 [14].

The aetiology of end-stage renal disease in the Dutch paediatric population is given in Table 2.1. Comparisons between the findings of different studies are complicated by the use of different classification systems and different upper-age limits. It is clear, however, that in paediatric programmes hereditary and urological causes of end-stage renal disease are relatively frequent, compared to adult programmes, whereas diabetes mellitus is almost completely absent.

2.3. Comorbidity and mortality

Recent publications draw attention to the remarkable high proportion of other and multiple disorders in children with chronic renal failure (one third of the patients) [15,16].

Table 2.1. Causes of ESRD in 167 children in the Netherlands, 1979-1986 (modified from [13]).

Diagnosis	Number	%
Glomerulonephritis	43	25.7
focal segmental glomerulosclerosis	22	
other	21	
Hereditary diseases	33	19.8
nephronophtisis	11	
other	22	
Pyelonephritis	32	19.2
urological pathology	26	
other	6	
Congenital hypoplasia/dysplasia	23	13.8
Systemic disorders	20	12.0
haemolytic uraemic syndrome	16	
other	4	
Other	8	4.8
Unknown	8	4.8

This is over thirty times the incidence in the normal population [15]. Twenty percent of the patients has one other abnormality, while twelve percent has two or more [17,18].

Comorbidity may be related to the original disease (for example in syndromal diseases), or may be acquired during the period of chronic renal failure or dialysis treatment. According to the data of the EDTA registry (1992) the severity of the abnormalities generally was considered to be mild [11]; the abnormalities varied from motor disturbances, visual, and auditory impairment to mental handicaps. Visual and auditory pathology was generally irreversible, but motor abnormalities showed amelioration after successful transplantation in only 39% of the patients [18]. In 18% of the study population mental handicaps were noted at the beginning of treatment, but in the opinion of the dialysis physician, an improvement occurred during renal replacement therapy in 38% of the children [18]. Comorbidity and its severity did not correlate with the duration of renal replacement therapy.

With respect to mortality again the EDTA data can be used. Five-year patient

survival after start of renal replacement therapy is 85% [11]. Similar rates are derived from the American Medicare data [12]. These studies report that the youngest children have the poorest survival.

2.4. Renal replacement therapy

Dialysis and renal transplantation are generally considered to be acceptable treatment modalities for children with end-stage renal disease. Selection criteria, that have been applied in the past - mainly with respect to the exclusion of children with severe mental retardation -, are no longer valid at almost all centres [13]. Especially in the youngest age group, - the newborns and young infants -, the opinion of the parents plays an important role in the decision of whether to treat the child or not. It is not an obvious choice to dialyse a newborn, because major medical complications may occur, particularly in this age group. Complications can have an important impact on quality of life and even lead to death. It can not be the goal of renal replacement therapy to extend the suffering of a patient. However, also newborns have good chances for survival if the parents and the dialysis team are highly motivated and have a positive attitude towards dialysis treatment. Excellent results have been reported for peritoneal dialysis in children younger than two years [19-21]. Even renal transplantation is feasible in this age group, although a high mortality (about 25%) has to be accepted [22-24].

Dialysis treatment in childhood should always be considered as a temporary measure to bridge the gap between end-stage renal disease and renal transplantation. This period may be relatively long (several years) for a number of reasons:

- shortage of donor kidneys [14]
- technical problems with transplantation in infants and toddlers
- presence of HLA-antibodies in some patients, especially after a previous transplantation.

So-called pre-emptive transplantation also deserves attention. This is a transplantation which is performed before end-stage renal disease has been reached, just before dialysis therapy needs to be started. Mostly, this form of transplantation is applied using a kidney donated by one of the parents. There is no

unanimous opinion whether it is desirable to promote this kind of transplantation.

An important advantage of pre-emptive transplantation is that negative consequences such as malnutrition, a decrease in growth, renal osteodystrophy, anaemia, hypertension, avitality, and long-term dialytic therapy, can be avoided. Psychosocial benefits for the patient and the family are: alleviation of the fear of death, of feelings of powerlessness, and of loss of control. Also the concept of body-image and self-esteem can improve because suffering from profound illness with concomitant physical symptoms, deterioration of school performance, cognitive impairment, and social isolation are prevented. Family life improves as well if dialysis treatment is not necessary: less frequent visits to the doctor and hospitalization resulting in less absenteeism from work and less financial strain, more equal care for the siblings, more time for leisure activities and holidays.

A major disadvantage of pre-emptive transplantation is that, if the transplant fails, the patient and the family are inadequately prepared for dialysis treatment. No assessments will have been made of coping skills, motivation, and the support system [25].

It is commonly considered to be an injustice to put a patient on the waiting-list for a pre-emptive transplantation, while there is still a shortage of donor kidneys. Therefore at most paediatric centres, a pre-emptive transplantation is only performed if there are strong medical or psychosocial indications or if a kidney is donated by a family member.

2.4.1. Conservative treatment

In the early phases of chronic renal insufficiency (renal function between 25 and 50%) vitamin D metabolism will be impaired, necessitating the administration of active vitamin D metabolites to prevent renal osteodystrophy.

With progression of renal disease, the patient's dietary protein intake will have to be restricted to prevent uraemic symptoms. Whereas in adult patients a protein intake of 0.6g/kg body weight/day can maintain adequate nutrition as well as neutral nitrogen balance, children require a higher protein intake. The theory that early protein restriction in the diet would conserve renal function for a longer period, has - although proven in the rat - not been confirmed in human

studies [26,27].

As a consequence of the relatively high protein intake in children with renal failure, especially in infants, hyperphosphataemia is a common finding. The administration of phosphate-binding agents such as calciumcarbonate or calciumacetate is therefore generally necessary. Aluminium-containing phosphate-binding agents were used in former days on a regular basis, but these are now avoided because of the risk of aluminium encephalopathy [28].

As renal function deteriorates, it is generally indicated to restrict potassium in the diet and to administer potassium-binding resins, such as calciumpolystyrenesulphonate. These drugs are very unpleasant to use, but sometimes pretreatment of drinks with these drugs can significantly lower the potassium content [29].

If diuresis decreases, dietary fluid restriction will be necessary. Sodium-restriction is not generally required. In the case of acidosis, additional sodium bicarbonate must be administered.

In summary, a child who is approaching end-stage renal disease will be treated with a complicated and very restrictive diet, as well as with a large number of medications, which impairs the quality of life considerably.

Two methods of dialysis can be applied: haemodialysis and peritoneal dialysis. Generally, also dietary restrictions (potassium, protein, fluid) and a strict medication regimen are required with both treatment modalities.

In the Netherlands chronic paediatric dialysis is always performed at one of the four paediatric dialysis centres which form part of a university hospital (Amsterdam, Nijmegen, Rotterdam, and Utrecht).

2.4.2. Haemodialysis

Intermittent chronic haemodialysis in childhood is performed thrice weekly for an average duration of 4 hours per session; it is always performed at a hospital. The blood is purified by an artificial dialyser, which is placed in a dialysis machine. The treatment is based on the principle of the filter properties of a semi-permeable membrane: the blood flows on one side of this membrane while dialysis fluid flows on the other side (Figure 2.2).

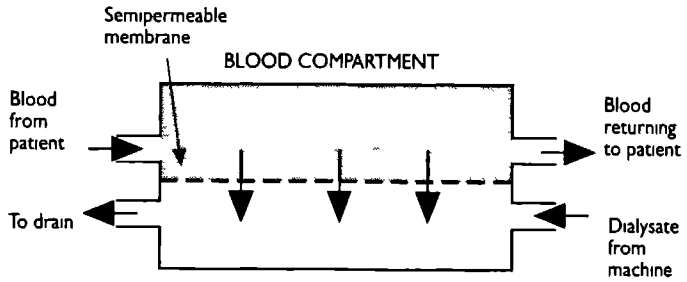

Figure 2.2. A diagram of a dialyser. The vertical arrows represent waste products diffusing, and water ultrafiltrating from blood. (From Gabriel R. A patient's guide to dialysis and transplantation. Dordrecht, Kluwer Academic Publishers, 1990. With permission).

This dialysis fluid removes toxic metabolites by diffusion and excessive fluid from the body by ultrafiltration. Blood is circulated through the dialyser using a pump. The blood is obtained from an arteriovenous fistula (Figure 2.3), which is surgically created 6-8 weeks before dialysis is started. During this operation a connection is made between an artery and a superficial vein, generally in the forearm. For each dialysis session it is necessary to puncture this fistula with one or two needles. During dialysis and sometimes shortly afterwards, alterations in fluid and electrolytes, as well as a rapid decrease in the blood urea concentration, may cause symptoms of low blood pressure, nausea, and headaches ("dialysis disequilibrium"). Recent developments in dialysis fluid composition (bicarbonate- instead of acetate-dialysis) have decreased the incidence of these complications.

Contra-indications for haemodialysis generally have a medical-technical background. Especially in young children it may be difficult to create a suitable arteriovenous fistula, which allows sufficient blood flow. Psychosocial factors may also form contra-indications for haemodialysis: extreme fear of injections and needles, geographic distance between home and the dialysis centre, as well as the absence of specific teaching facilities (particularly for vocational training) at the hospital school.

2.4.3. Peritoneal dialysis

The technique of continuous ambulatory peritoneal dialysis (CAPD) was

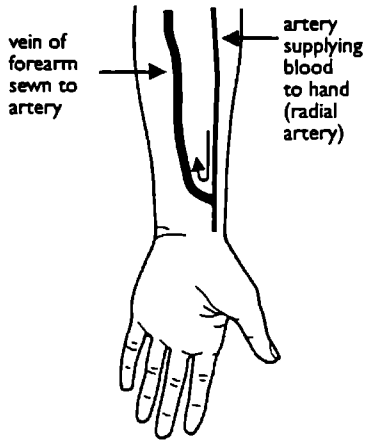

Figure 2.3. A Cimino fistula. The hand receives an adequate amount of blood because another artery runs down the opposite side of the arm to the radial artery. From Gabriel R. A patient's guide to dialysis and transplantation. Dordrecht, Kluwer Academic Publishers, 1990 (With permission).

developed in the second half of the seventies and has been applied to children in the Netherlands since 1980 [30]. This treatment modality is particularly suitable for children under the age of six years. EDTA data over the period 1980-1986 show a gradual increase in the application of CAPD as a renal replacement therapy, but there are large regional differences between European countries [31]. Treatment is performed on an ambulatory basis i.e., the parents perform the treatment at home. If the child is old enough (12-14 yrs.), and has sufficient knowledge, self-reliance, and responsibility, he/she can perform the treatment him/herself. Not only chronological age, but also developmental and emotional maturity and stability are determining factors.

The principle of peritoneal dialysis is based on the usage of the peritoneal membrane as a semi-permeable membrane. After a catheter is surgically inserted into the abdominal cavity, sterile dialysis fluid is infused. Because of the membrane properties of the peritoneum toxic metabolites are withdrawn from the peritoneal blood vessels into the dialysate. Excessive fluid can be removed from the body by increasing the osmolarity of the dialysis fluid. Osmolarity can be increased by adding extra glucose to the dialysis fluid.

The dialysate is exchanged four times a day; it drains by gravity (Figure 2.4). Because of an open connection with the abdominal cavity there is a risk of

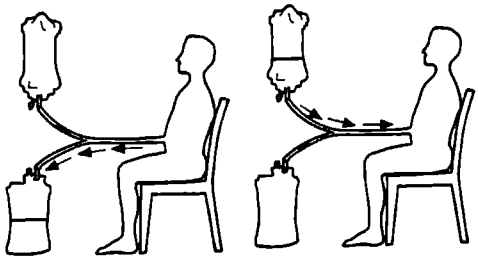

Figure 2.4. Principle of CAPD-technique. From Khanna R, Nolph KD, Oreopoulos DG. The essentials of peritoneal dialysis. Dordrecht, Kluwer Academic Publishers, 1993. (With permission).

bacterial contamination from outside. This can lead to one of the most feared complications of peritoneal dialysis: peritonitis. To prevent this complication, many efforts have been made to improve the safety of the exchange procedure. Innovations in the equipment have considerably reduced the incidence of peritonitis in recent years [32]. At the paediatric dialysis centre in Nijmegen exchanges are performed using the ultraviolet (UV) light method. During the exchange procedure, the connecting parts of the dialysis system are irradiated and sterilized by UV light [33-35]. Unfortunately, the semi-closed, so-called twin-bag system, is not suitable for paediatric patients [36].

It is common practice at Dutch paediatric centres that both parents (or other care-providers) are trained and prepared to perform the dialysis treatment in the home situation. They have to perform the dialysate exchange itself and properly record and interpret the fluid balance, body weight, and blood pressure. Peritoneal dialysis patients have monthly check-ups at the hospital on an outpatient basis.

There are other, "automated", forms of peritoneal dialysis. Continuous cycling peritoneal dialysis (CCPD), based on the same principle, is the most widely-applied method. Dialysis is not performed manually, but automatically by a machine (cycler), several times during the night. If the abdomen is left empty during the daytime, this method is called nightly intermittent peritoneal dialysis (NIPD), a preferred treatment modality in children. An important advantage is that the child has more freedom of movement during the daytime and theoretically will have better motor development. A disadvantage is that the dialysis equipment may produce alarms at night if the child is restless during

sleep. This can lead to sleeping disturbances in the child and/or parents. NIPD is particularly indicated in children with serious feeding complications, caused by the sensation of a filled abdomen and the high glucose content of the dialysis fluid and in children with a limited ultrafiltration capacity [37].

For children, peritoneal dialysis has a number of medical and psychosocial advantages over haemodialysis. As peritoneal dialysis is a long-term process (i.e., 24 hours per day for CAPD and CCPD, 8-12 hours at night for NIPD) body fluid composition and volume will change slowly and result in a near steady state. Children on peritoneal dialysis do not suffer from the disequilibrium syndrome, as some children do during haemodialysis. The psychosocial advantages of peritoneal dialysis largely relate to less dependence on the hospital, better school attendance, continuity in the parent-child and family relationship, and less need for invasive procedures [38]. There are, however, obvious medical and psychosocial contra-indications for peritoneal dialysis, such as severe adhesions in the peritoneal cavity due to previous operative procedures or infections, negative psychosocial circumstances like other diseases in the family, parental mental and/or emotional restrictions, and a pathological family structure (see Chapter 3). Furthermore, peritoneal dialysis may be contra-indicated in adolescents, because of the risk of noncompliance and the risk of developing negative self-esteem because of the unsightly appearance of the catheter in the abdomen and a strong dependency on the parents (see Chapter 3).

The final choice between the two treatment modalities is generally made in close cooperation with the parents and the child. On January 1 1994, 20 children (30.5%) below the age of 15 years were being treated with haemodialysis, and 41 (69.5%) with peritoneal dialysis in the Netherlands [39].

2.4.4. Renal transplantation

Renal transplantation is the therapy of choice for patients with end-stage renal failure. All the physical signs of a disturbed renal function disappear after a successful transplantation. This is accompanied in most cases by psychosocial rehabilitation, predominantly with respect to motor and cognitive functioning [16,38,40,41].

Preparation for transplantation includes tissue typing. Data are collected by

the Eurotransplant Foundation (Leiden), which coordinates cadaveric transplantation for a number of Western European countries. The large majority (over 90%) of transplantations in the Netherlands are performed with kidneys obtained postmortally. Only a small proportion (8.4% in 1991 [14]) of transplantations are performed with a living donor kidney. In children, the living donor will mostly be one of the parents, because law prescribes a minimum donor age of 18 years, so the sibs will generally be too young. Living donor transplantation is not promoted on a large scale in Western Europe. A parent-child transplantation can increase the vulnerability of a family with mostly young children. Psychological and ethical arguments may also impair a more positive attitude towards family transplantations.

Psychological contraindications for (especially) a parent-child transplantation are a pathological family structure, e.g., serious marital conflicts or a symbiotic relationship between one of the parents and child. Also, psychological instability or psychiatric illness of the donor are considered to be negative factors in the decision of using a kidney from a living donor. Unfavourable consequences of a living kidney donor include an increased pressure on the parent and child, and dependency between them. Problems can also arise if the transplant fails, and the removal of the graft is necessary. Irrealistic expectations and fantasies that the incorporation of a physical organ will result in the transfer of personal characteristics of the donor can form a psychological obstacle for a parent-child transplantation. Particularly in adolescents, strong identification with the donor may impair the development of autonomy which can be an unfavourable outcome [42].

Ethical conflicts can arise in consideration of the interests of the donor against those of the recipient. It is complicated to prevent moral or emotional pressure on the potential donor because any information given or even withheld is always selective and, moreover, is not always identical to previously received information. Wolff [42] has argued in favour of the obligation to inform families about all treatment modalities at an early stage, so that more time is available to reflect on donation. The physician has to respect the donor's dignity and autonomy in his/her decision.

Experience has shown, that using a kidney from a living donor leads to better medical results than cadaveric transplantation [14,43]. Three-year graft survival

is 65% after cadaveric transplantation and 80% after living donor transplantation [11]. Moreover the majority of kidney donors and patients show satisfactory physical and psychological rehabilitation and remain positive, even after transplant failure [42,44].

After renal transplantation, immunosuppressive medication is necessary to prevent rejection of the allograft. Nevertheless, rejection episodes arise frequently, sometimes leading to loss of the allograft. In a large number of cases, hypertension occurs after renal transplantation; this may be difficult to regulate. Some renal diseases tend to recur in the allograft (e.g., focal glomerulosclerosis), and lead to graft loss.

Most paediatric centres do not perform transplantation on infants for technical reasons, but prefer to postpone the transplantation until a minimum body size (generally 10-12 kg) has been reached. It is known that a young age of the recipient as well as a young age of the donor have negative influence on the transplantation results [45,46]. Surgical complications (thrombosis) occur more frequently.

2.5. Specific non-psychological problems related to end-stage renal disease

2.5.1. Growth [47]

Formerly, it had to be accepted that children with chronic renal failure (CRF) would suffer from (severe) growth retardation. Successful treatment of long-standing end-stage renal disease (ESRD) led to an acceptable renal function after transplantation, but also resulted in small stature of most of our patients also in adulthood. In the early years of continuous ambulatory peritoneal dialysis (CAPD) there were a few optimistic reports about a better growth in children on CAPD than those on haemodialysis [48]. More recent studies, however, could not find any support for this optimism: growth was equally disappointing in both groups of patients [49]. Renal transplantation allowed subsequent normal growth, as long as the graft was functioning well, but catch-up growth rarely occurred [50-53].

The severity of growth retardation depends on several factors. The most important is the age of onset of CRF. A child who develops renal failure at an older age will have had more opportunity for normal growth than a child who

has had renal failure from birth.

Small adult stature is an important cause for concern in adolescents and young adults who have been treated for ESRD in childhood. Several studies have been performed on the outcome of treatment for ESRD in children [54-56]. Items that rank high in papers on psychosocial aspects of this treatment are unemployment, dependence on others, fear of graft loss, fear of cancer, sexual problems, and small stature. Concern about height was reported with average frequency among these items. It should be emphasized, however, that these studies were performed on the whole group of persons, regardless of the severity of growth retardation. In this context it is more worthwhile to refer to the numerous studies on adult patients with growth hormone deficiency, which have indicated that it is a great concern to be too short. These people had low scores for positive well-being and high scores for anxiety and depressed mood. They felt socially isolated, slept poorly, and had difficulty with physical mobility. The group was also characterized by having few hobbies, an impaired sex life, high unemployment, and a tendency to live at home with their parents [57].

For a few years it has been possible to treat growth-retarded children with ESRD with rhGH. Growth hormone is not new as a medication. Growth hormone deficiency, mentioned above, is a well-known disease entity in paediatrics. Children with this deficiency have been treated successfully with human growth hormone which was extracted in small amounts from human hypophyses at obduction. Using modern DNA techniques it is now possible to produce recombinant human growth hormone - rhGH - in relatively large quantities. It has proven to be effective not only in growth hormone deficient children, but also in normal children and in children suffering from Turner syndrome. In normal small children, a growth velocity increase of up to 4 times that in a control group was observed [58]. This means that the growth rate of children with normal endogenous growth hormone production can be stimulated by the administration of additional growth hormone. As this became evident, it was clear that a therapeutic effect was likely in children with renal failure. Presently, studies on the effects of rhGH on children in all stages of renal failure are in progress in many hospitals. In children in the pre-dialysis phase it has been found that mean growth velocity increased from 5.0 to 8.5 cm per year in the first year of treatment and remained that high in the second and

Table 2.2. Influence of treatment with recombinant human growth hormone in 9 children with chronic renal failure (pre-dialysis) [59].

	Growth velocity (cm/year)			
	before treatment	after 1 year	after 2 years	after 3 years
mean	5.0	8.5	8.2	8.1
SD	1.4	1.3	1.6	1.8

third years of the study (Table 2.2) [59].

In children treated with dialysis, a 3-4 fold increase in growth velocity was observed during the treatment period [60]. Finally, in transplanted children who had acceptable graft function but nevertheless poor growth, growth velocity doubled in the year of therapy (Table 2.3) [61].

These data show clearly that the results of rhGH therapy in ESRD are very encouraging. Although the results of treatment have not yet been recorded over a very long period, it should be emphasized that every centimetre won is of great importance to the patients, with a potentially great impact on their (future) psychosocial functioning.

2.5.2. Anaemia [47]

Anaemia is a common complication of end-stage renal disease. It is mainly caused by a deficiency of erythropoietin (EPO), a hormone stimulating red blood cell formation, and which is produced by the normal kidney. Until recently, frequent blood transfusions were common practice at all dialysis units. The development of recombinant DNA techniques has enabled the production of biosynthetic erythropoietin on a large scale. Nowadays, all patients with renal anaemia in the Netherlands are treated with erythropoietin.

A number of excellent reviews have been published on the positive therapeutic effects and the side-effects of EPO [59-64]. It is generally known that EPO is the optimal treatment for renal anaemia in all patients with CRF, by improving their general condition and well-being. Most of the side-effects, such as hypertension and thrombosis of the arteriovenous fistula, are directly related to this therapeutic effect.

Table 2.3. Influence of treatment with recombinant human growth hormone in 9 children after renal transplantation [61].

	Growth velocity (cm/year)	
	before treatment	after 1 year
mean	2.5	5.7
SD	2.1	2.7

A major disadvantage of this drug is the fact that it has to be administered by the parenteral route. Subcutaneous and intravenous application are the best known; subcutaneous administration has proven to be the most cost-effective, which is important, because EPO is a very expensive drug. To children, especially the younger ones, these modes of administration are unattractive. The threat of a needle can cause considerable distress in these children and lead to conflicts between the patient and the person who has to administer the drug. In CAPD patients parents generally perform the treatment, which may cause unacceptable situations. Therefore, other modalities to administer EPO to children have been evaluated. In those treated with haemodialysis intravenous application three times a week at the end of dialysis is the preferred method, although a somewhat higher (approximately 25%) dose is required. In children treated with CAPD, we studied the resorption of EPO from the peritoneal cavity [65]. Until now over 30 CAPD patients have been treated with EPO intraperitoneally. Similar therapeutic effects were observed as those obtained with intravenous or subcutaneous administration. The dosage, however, was about 25-50% higher than that needed for subcutaneous application, which was a real disadvantage cost-wise. Nevertheless, the reduction in family stress and the prevention of burn-out outweigh the higher cost, in our opinion. Intraperitoneal administration does not necessarily lead to a higher frequency of peritonitis if the parents are trained carefully [66].

Some large multi-centre studies have been performed, in which the quality of life was measured in large groups of adult patients using multiple scoring systems [67,68]. Patients treated with EPO had significantly higher scores than those not treated with EPO in all categories. Using treadmill studies, EPO improved the exercise tolerance of both adults and children [69,70]. An impor-

tant improvement of quality of life has been reported [71]. The results with respect to the cognitive functioning are more conflicting. In a group of adult haemodialysis patients intelligence test scores improved by about 10 points after treatment with EPO [72-74]. In one study on children, correction of anaemia with EPO was also associated with an improvement in cognitive performance [75]; in our own patient group, however, we did not observe any significant improvement (Chapter 5; this dissertation).

2.5.3. Renal osteodystrophy

Bone abnormalities in renal osteodystrophy are determined by hyperparathyroidism and disturbed bone mineralization [76-78]. In advanced renal failure, phosphate retention occurs due to a decrease in phosphate excretion. This phenomenon leads to hypocalcaemia, which in turn may cause hyperparathyroidism. The kidney also plays an important role in the activation of vitamin D. In renal failure, activation is impaired. If this condition is not treated, clinical signs of osteodystrophy will appear. Major symptoms are bone pain and fractures, but extra-osseous calcifications, muscle weakness, and pruritus may also occur. In children, skeletal deformities and growth disturbances are prominent.

Therapy is based on the lowering of the blood phosphate concentration and the administration of sufficient amounts of active vitamin D metabolites. Blood phosphate concentration can be lowered by administration of phosphate binding agents orally. Nowadays, mostly calcium salts such as calciumcarbonate or calciumacetate are prescribed. These drugs did not become available until a few years ago. Prior to this, phosphate was bound in the gut by aluminium salts, but major absorption of aluminium often gave rise to aluminium encephalopathy. Nowadays, compounds containing aluminium have almost completely been abandoned.

The combined use of calcium containing phosphate binding agents and active vitamin D metabolites has meant that severe renal osteodystrophy is seldom encountered in modern dialysis clinics. Only in rare cases autonomous therapy-resistant hyperparathyroidism occurs, requiring surgical treatment (parathyroidectomy) [79,80].

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Chapter 3

PSYCHOLOGICAL ASPECTS OF CHRONIC RENAL FAILURE IN CHILDREN

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3.1. Implications of a chronic disease for the child and the family

A child is more vulnerable to the physical, psychological, and social consequences of a chronic disease than an adult, since a child is in development and dependant on adults in material, emotional, and social respects. The family in which a child grows up plays a central role, and as Eiser [1] put it, chronic disease in a child is a diagnosis that affects and influences the whole family. Optimal development requires accomplishing age-specific developmental tasks within a safe and stable upbringing climate [2,3]. Long-term physical limitations and psychological burden resulting from chronic disease can cause stagnation or retardation in development and have negative influences on completing developmental tasks [4-7].

Over the past twenty-five years, many studies have been performed on the relationship between chronic disease or physical handicap and psychopathology in the child or family. The results vary strongly and depend on the nature, stage, and severity of the disease [8-12]. For example, in children with asthma, diabetes, epilepsy, and cystic fibrosis, a high percentage of psychological problems were detected, also in the parents, particularly if the child was mentally retarded or had a cerebral dysfunction [8,13-15]. Other studies, however, conducted on children with cystic fibrosis, could not demonstrate an increased risk of psychological disturbances [16,17]. Stein and Jessop [18] stated that psychological adaptation is determined just as much by demographic factors as by disease-specific factors.

A growing number of reports, mainly published over the past ten years, have indicated that a chronic disease can have a positive and growth-stimulating influence on the child and his/her family [19-24]. If the demands made by the chronic disease can be met, and the problems associated with the disease can be overcome, then this can enhance the self-respect, self-esteem, and mutual solidarity of the child and other family members.

Table 3.1. Factors that determine how and to what extent the disease interferes with development and family functioning.

Disease-specific factors	- severity, chronicity, life-threatening character - demands, limitations resulting from the disease - abnormal appearance, iatrogenic effects - past medical history
Intrapersonal factors	- age, developmental level of the child - socio-adaptive capacities - personality characteristics
Environmental factors	- attitude, coping behaviour of the parents - social support - other factors that form a burden - brothers and sisters

Therefore the question remains: what factors, besides the disease, are (jointly) responsible for the problems, and how can these problems be prevented? [25]. Variables that determine how and to what extent the disease interferes with development and family functioning, can be divided into three categories [1,26,27] (Table 3.1).

Disease-specific factors, such as the severity of the disease, the chronicity, and prognosis are of great importance in the adaptation process: whether or not the disease has a life-threatening character, uncertainty about the course of the disease, and whether or not the disease has a congenital origin [12,18-23,28,29]. Other specific consequences that also play a role include the limitations caused by the disease, the demands made by the treatment, possible iatrogenic effects, and the visibility of the disease [1,23,24,27]. The medical anamnesis in terms of frequency and duration of hospitalization is also of importance [29,30].

Intrapersonal factors include the age of the child and his/her developmental level, the age at which the diagnosis was made, the intellectual and social-adaptive capacities of the child, and personality characteristics.

Environmental factors also determine the way in which a chronic disease influences the development of a child. In the literature, besides the well-known factors such as the socio-economic status of the family, the educational level of the parents, family structure, the geographical living situation [29], a number of other relevant variables are also mentioned [1,20,23,24,26,27,30].

Attitude of the parents

The attitude of the parents, the way in which they accept and cope with the disease, to a large extent determines the upbringing behaviour and consequently the interaction between the parents and child [27]. This attitude can vary from a positive accepting, over-involved, indulgent, and over-protective attitude at one end of the scale, to a negative, hostile, rejecting attitude at the other end of the scale [1,31]. In general, an over-protective attitude of the parents is considered to be a risk factor with regard to optimal development. However, recent research by Veldhuizen & Meyer has shown that an over-protective upbringing attitude, as long as it is combined with warmth and care, can have a positive and protective effect on the emotional adaptation of children with cancer in certain stressful phases of the disease [32].

Social support

Another important environmental factor is the extent to which social support is available and accepted [23,33-36]. The quality of the medical and psychological care forms an essential part of the support, not only in a practical and informative respect, but also in an emotional one [23,24,35,37-39]. Parents, but in particular the mothers of children with a severe illness, often feel socially isolated because friends and family are unable to understand the full extent of the burden and consequences of the illness. A study by Morrow et al. [36] showed that support and understanding from professionals - particularly from the treating physician - offer compensation for feelings of loneliness and isolation.

Other factors which affect the burden

Besides a chronic disease of a child, other pre-existing factors in a family can influence the development of a child. Serious life events, such as illness and bereavement among other (close) family members, dismissal and unemployment, financial problems, serious relational problems and divorce, determine the weight of the burden that a family can carry and its flexibility.

Brothers and sisters

The role of brothers and sisters in a family with a sick child deserves special attention. Brothers and sisters of a sick child often miss actual and emotional care from their parents, but also from grandparents and other family members. Parents, particularly mothers, mention that they often have the feeling that they give inadequate attention and love to their healthy children; school and behavioural problems can be attributed to this. Data in the literature on this subject are not univocal. A number of authors observed an increased risk of learning, emotional, and behavioural problems [40-43], while others found that healthy brothers and sisters were functioning reasonably well [17,24,44,45]. Brothers, particularly younger brothers, were found to be more vulnerable to behavioural disturbances than sisters [24,44,45]. Moreover, it is of importance whether the illness is visible externally: people often react differently to a "visibly" sick child than to healthy brothers and sisters. In addition, more emotional problems, such as feelings of guilt and suicidal fantasies, have been observed in the brothers and sisters of children with a life-threatening disease [1,27]. In younger children, extreme feelings of jealousy and over-demanding behaviour can be displayed [40], while in older children over-adaptation or withdrawal can indicate the wish to spare and protect the parents from any further distress [46]. Research has also shown that siblings not only suffer from or react to receiving inadequate attention from their parents, but also suffer from or react to the sometimes disrupting, demanding, and dominant behaviour of their sick brother or sister [40].

Before dealing with the specific consequences of chronic renal failure in the next section, this paragraph will summarize the problems which can arise (also on the grounds of the above-mentioned risk factors) in a chronically sick child and in its family [1,6,7,9,11,13,20,24-27,30,36-38,40,41,47]. Most frequently discussed in the literature are:

- Disorders or retardation in psychomotor and cognitive development resulting directly from the effects of the disease (e.g., cerebral disorders), the limitations these impose (e.g., pain, physical, or sensory handicaps), and the treatment (e.g., side-effects of medication) [48];
- Learning and school problems as a secondary effect of cognitive defects,

concentration, and tempo problems, lack of vitality, school absenteeism;
- Emotional problems resulting from anxiety and uncertainty about mutilating interventions, death and the effects of medication, admissions to hospital and frequent separation from the parents;
- Social problems resulting from feelings of isolation, not being able to join in, having a different appearance and inferiority complex;
- Behavioural problems resulting from pedagogical deprivation, over-indulgence, and over-protection;
- Specifically in the adolescent phase: problems with coping and accepting an abnormal appearance, worries about the longterm perspectives, being accepted by peers and difficulties starting relationships and friendships, acquiring independence and autonomy, doubts about school and career choice, problems with intimacy and sexuality [24];
- Family problems resulting from fixation on the disease and the extra burden imposed by the treatment, manifesting itself in: tension and conflicts between the parents, social isolation, limitation of leisure-time activities and relaxation, extra financial burden, problems at work owing to hospital visits, check-ups, problems with the healthy brothers and sisters and worries about the future of the sick child. If the child has a life-threatening disease, anxiety about losing the child and anticipated grief can put heavy pressure on the parents [28,29-49].

3.2. Specific consequences of chronic renal failure on the psychosocial functioning of the child

3.2.1. Neurological, motor, and cognitive development

In 1986, Biasioli et al. [50] published an overview of the neurological complications of uraemia by listing the clinical symptoms, the difficulties involved with various diagnosis techniques and the pathophysiology of uraemic encephalopathy. The article is based on studies performed since the early nineteen sixties on adult patients with progressive renal failure [51-53]. Even in the very early stages of renal insufficiency, there can be changes in mental functions, the level of consciousness, and hormone balance, as well as neurological and motor disturbances. Various diagnostic techniques can be used to evaluate uraemic

encephalopathy and its consequences: EEG, evoked potentials, neuropsychological tests, cerebrospinal fluid (CSF) examination, brain density (CT) scanning, and nuclear magnetic resonance (NMR).

Cerebral maturation occurs mainly in the first twelve months of life. Therefore children with congenital renal failure are vulnerable to the consequences of uraemic toxicity. Rotundo et al. [55] published alarming results on 23 infants with renal disease up to the age of one year. In 20 out of the 23 cases, serious neurological abnormalities were found, which manifested themselves in developmental retardation, microcephaly, hypotonia, convulsions, dyskinesia, and EEG abnormalities. None of the children were on dialysis treatment. It should be mentioned that this was a retrospective study, so it is possible that infants with less severe anomalies had been excluded from the sample. One year later, Schnaper et al. [56] published a study on 15 children with ESRD; using CT scanning, 8 of them were found to have cerebral cortical atrophy and 2 ventricular dilatation. The age of these patients ranged between 3.5 and 20 years. A multifactorial explanation was given for the findings: high doses of steroids combined with specific biochemical and hormonal abnormalities resulting from uraemia, as well as the duration of haemodialysis (HD). In 1985 another report was published by McGraw et al. [57] on the neurological, motor, and cognitive development of 12 children who had been suffering from severe renal failure since infancy. These children were found to have neurological abnormalities: 7 of them had first been on dialysis and later received a kidney transplant; 9 of them had convulsions, and 8 had mild to moderate cortical atrophy. Eight out of the 10 children showed a retarded fine motor and cognitive development; in 5 cases retardation was reported to be mild. Improvement after the start of renal-replacement therapy (dialysis/transplantation) was only seen in one of these patients. The authors also gave a multifactorial explanation for their findings: long-term hospitalization, sensory deprivation, malnutrition, in some cases renal osteodystrophy resulting from hyperparathyroidism and the use of aluminium containing phosphate binders. However, in young patients with other serious abnormalities, such as congenital cardiac malfunction or malabsorption disturbances, who also had a history of malnutrition and frequent admissions to hospital, no irreversible motor or mental retardation was observed. Therefore, particularly the toxic

effects of uraemia during the first 12 months of life seem to have a decisive influence on both motor and cognitive development. Some authors have drawn attention to abnormal plasma amino acid concentrations in patients with uraemia [50,58] which can influence the development of the CNS. These notions are shared by a number of other authors who published studies on infants with severe renal insufficiency during the same period [58-62]. However, the study designs were heterogeneous with regard to selection and the number of patients, the clinical condition, the severity of renal disease, medication, and diagnostic techniques. Consequently, Geary et al. [63] performed a prospective longitudinal study on a fairly large group of patients (n=33) who had been suffering from mild to severe renal failure since infancy (GFR 31 ± 29ml/min/1.73m^2). Seventeen young patients developed ESRD during the course of the study. At the last measurement, 10 children had mild to moderate developmental retardation; 7 of them had ESRD. Of the 16 children with moderate renal function, only three were mildly retarded. The conclusion drawn from this study and from the studies by Kleinknecht et al. [64] and Elzouki et al. [65] was that the developmental chances of children who had been suffering from chronic renal failure (CRF) since infancy were more favourable than had been reported previously. This was thought to be the result of changed insights regarding treatment, discontinuation of the use of aluminium containing phosphate binders and a stringent, aggressive regimen (by means of tube feeding) to improve nutritional state.

This conclusion led to accentuated controversy about the optimal time for kidney transplantation. To prevent the negative toxic effects of renal failure during the critical period of cerebral maturation, a number of (mainly American) authors argued in favour of performing a kidney transplant at a very young age with, if possible, a kidney from a living donor [55,66-69]. A more reluctant policy was recommended by authors of the opinion that it is justified to postpone transplantation until the child is older owing to the increased risk of technical complications during renal transplantation in infants, improvements in treatment techniques, and a more favourable developmental prognosis [58,63-66,70-72].

Therefore the question remains - a question which dominates recent literature -: can developmental disorders resulting from chronic renal failure be pre-

vented and what are the determining factors? Although a few authors have suggested that starting dialysis at an early stage can contribute to the optimal growth and development of young children, little is known about the consequences of this policy on the ultimate developmental course [72,73]. Moreover, it has not always been possible to demonstrate a direct relationship between changes in biochemical parameters, such as creatinine clearance and blood urea nitrogen (BUN), and developmental parameters [63,74,75]. In addition, children with existing CNS disturbances were excluded from some samples, while it was not always clear whether or not these disturbances had been caused by chronic renal failure [63,69]. And finally, no longitudinal data are available on the effects of treatment modalities [62,63,69].

The effects of the dialysis modality and transplantation

Little research has been conducted into the effects of the *dialysis modality* on the cognitive function of children. CAPD/CCPD appear to be more favourable for young as well as older children than HD [62,76-78]. These findings have been confirmed in studies on adolescents and adults [79-81]. The explanation for the improvement in cognitive performance particularly in the fields of attention, vigilance, and rate of information processing, can partly be found in the so-called dialysis disequilibrium that does occur during HD but not during PD.

After successful transplantation, various publications have reported considerable improvement in growth, development, physical well-being, quality of life, and cognitive functioning [66,70,74,82-85]. There appears to be a certain amount of "catching up" of cognitive development, particularly on a number of non-verbal skills that can be measured using so-called performal subtests of an intelligence test [74,82,83]. Interesting results were published by Davis et al. [69] and Fennell et al. [83] who showed that the increase in IQ and intelligence profile after transplantation was significantly correlated with the IQ and profile before transplantation. In addition, children who still demonstrated mental retardation after transplantation had been suffering from CRF since birth. Rasbury et al. [74] therefore concluded that CRF during infancy reduces the cognitive potential significantly and permanently. In a longitudinal study, Fennell et al. [83] observed that one month after transplantation there was a

significant improvement in IQ, but this effect had disappeared one year later. It was concluded that the effect of ESRD on cognitive functioning could not be compensated for by a transplantation, but further deterioration was prevented. This discussion is interesting in the light of conflicting findings regarding the cognitive status of older children with CRF in general and of young dialysis patients in particular. Various studies have demonstrated that the cognitive performance of children with ESRD was not significantly different from that of healthy children [86-88], whereas other studies have reported that a number of cognitive functions were affected. The latter included poorer problem-solving capacity, arithmetic, memory, concentration, verbal reasoning, and visual-motor coordination [74,83,89,90]. In these non-transplanted patients, once again those who had been suffering from CRF since birth were the most vulnerable. Generally, factors such as socio-economic status, primary renal disease, and the effects of chronic illness, were found to be of little importance [86,88,89,91].

In a recent longitudinal and carefully executed neuropsychological study, Fennell et al. postulated that as opposed to the case in adults, the consequences of CRF are not so-called state-like effects (i.e., dependent on the state of the patient) and thus reversible, but that young children with ESRD have a predisposition towards permanent CNS dysfunction [86,92]. According to Fennell et al. [92] state-like effects can be defined as direct effects of renal function on test performance (c.q. cognitive tasks). In other words, after the start of dialysis treatment or after a transplantation, the scores obtained by patients with ESRD on neuropsychological tests improve because of the reduction in uraemic toxicity. These state-like effects could not be demonstrated using global intelligence tests [75], contrary to the results of more refined neuropsychological methods.

Although in most studies, if not all, conducted over the past 10 years, the emphasis was focused on possible cognitive defects in children with CRF, it ultimately appeared that the majority of these patients were functioning on a normal cognitive level. This can be derived indirectly from a number of follow-up studies conducted over the past few years on adolescents and young adults who had been on dialysis or had undergone transplantation in childhood [79,93,94]. A considerable percentage of these patients had completed primary, and a minor percentage secondary, education. The educational outcome of the

patients with a successful transplant was more favourable than that of the patients on dialysis. In a next paragraph the long-term effects of CRF will be discussed extensively.

Summarizing

The neurological, motor, and cognitive development of young children who had renal insufficiency in infancy has found to be more retarded than that of children with other chronic diseases [55-62]. A distinction should be made between children with ESRD (who need RRT) and children with less serious renal failure who can be treated conservatively. The latter group has a better developmental perspective [63,64]. Although the detrimental influence of uraemic neurotoxicity on the development of the maturing CNS is recognised as being the most important determining factor, other factors also appear to exert an influence: nutritional state, negative effects of anaemia, phosphate binders containing aluminium, hyperparathyroidism, long-term hospitalization, and psychosocial factors [57,63-65,95].

There is no consensus about the reversibility of developmental disturbances. According to some authors [66-68] (primary) transplantation in infancy will prevent mental retardation in the long-term. Other studies have demonstrated that even after transplantation, developmental disturbances, and mental retardation were irreversible in children who had been suffering from ESRD since infancy [55,58-63,83,92].

The effects of CRF on the cognitive functioning of older children generally seem to be less negative and even reversible after transplantation [74,82,83,86-88]. Specific problems can occur, particularly in HD patients on tasks related to attention, concentration, problem-solving capacity, short-term auditory memory, and visual-motor coordination. The implications for on psychosocial adaptation are discussed in the next paragraphs.

3.2.2. Psychological adaptation of children and adolescents on dialysis treatment and after transplantation

The way in which children and adolescents adapt themselves psychologically and socially to chronic renal disease chiefly depends on a number of non-disease-specific factors, such as age, developmental phase, personality, and

family variables, as was mentioned above. In addition, a number of factors specifically related to renal disease play a role in the adaptation process.

A child with renal disease, who requires dialysis and transplantation, is confronted with acute phases in the disease which are associated with invasive interventions, hospitalization, stress, pain, and great uncertainty. These phases alternate with periods of comparative rest and stability. This has implications for the evaluation of the psychological adaptation of young kidney patients [8,15]. Study results can be seriously distorted if insufficient attention is paid to the phase of disease or treatment of an individual patient. Over the past few years, there has been growing interest in the long-term consequences of dialysis and transplantation in childhood [79,93,94,96].

A characteristic of chronic renal disease even after a successful transplantation, is the life-long dependence on medical check-ups, medication associated with anxiety and uncertainty about possible rejection of the kidney.

Although the mortality rate of kidney patients is higher than that associated with a number of other chronic diseases, the life-threatening character of the disease has gradually been losing significance over the past twenty years. However, not only older patients, but also younger ones are aware of life-long dependence on dialysis or on a well-functioning transplant [1,87]. Nevertheless, despite the drastic medical treatment, the majority of young kidney patients adapt reasonably well psychosocially and do not distinguish themselves from children with other chronic diseases [91,97-99]. Severe psychological problems and psychopathology, which occur during the acute phase of the disease, are generally reversible [8,97]. However, this global conclusion does require some amount of nuancing.

A number of factors can have a negative influence on ultimate psychosocial rehabilitation, such as dialysis treatment during early childhood, the duration of the disease, the complexity of the medical history, as well as the above-mentioned factors, such as lack of social support, premorbid personality problems, and negative family circumstances [98,100]. Moreover, adolescence has proven to be a critical period [91,97,100]. In addition there has also been increasing interest in the influence of the treatment modality (HD-CAPD) and transplantation. Research has shown that kidney transplantation is the most favourable mode of treatment also in relation to psychosocial adaptation [70,79,93,97-102].

Not only the patients' physical condition improves after transplantation, but also self-confidence, social contacts, and mood. However, Reynolds et al. [97] reported an increase in slight behavioural problems after transplantation. They attributed this to the need for a patient to learn to deal with the transition from *being ill* to a situation of *being healthy*.

In the more recent literature, CAPD treatment has taken preference over HD treatment. PD patients showed more self-confidence [99], were more socially competent, had fewer practical problems with the treatment, had lower depression scores and displayed fewer behavioural disorders [84]. A major explanation for this is the fact that with CAPD, the patient makes a more active contribution, has more control and command (internal locus of control) of the treatment and consequently of the disease process, which, in general, is considered to be a positive factor for adequate coping behaviour [84,99]. Although no systematic research has been conducted, there is some clinical evidence that HD takes preference for adolescents: physical growth and psycho-sexual maturation can interfere with a negative body image resulting from the abdominal CAPD catheter which is sometimes regarded as mutilating to the appearance, as well as the feeling of being "too fat" because of the dialysis fluid in the abdomen [103]. Comparative studies on adults, on the contrary, have generally shown positive results with regard to the psychological well-being of CAPD patients in comparison with HD patients [80].

A number of authors have shown greater reservation regarding the psychosocial adaptation of chronic kidney patients and have argued in favour of structural psychosocial counselling, even after successful transplantation, to prevent social dysfunctioning and the onset of mental disorders [101,104-107]. Garralda et al. [8] concluded that the children with more severe renal failure (on HD) tended to have more psychiatric disturbance than the children who had been treated conservatively.

The combined ill group (HD and non-dialysis patients) showed disorders in 23% of the cases against 13% in the healthy controls. Korsch et al. [85] also found a comparable percentage of emotional problems and psychopathology (22%) in children who had been on HD or had undergone transplantation.

Table 3.2. Renal-disease-specific factors that influence psychosocial adaptation.

- feeding and nutritional problems during infancy
- tiredness, lack of vitality
- diet, medication, fluid restriction
- abnormal appearance, growth retardation, retarded sexual maturation
- frequent and/or long-term hospitalization
- invasive interventions, frequent (vena) puncture
- unsuccessful transplantation

Table 3.2 gives an overview of the specific factors of renal disease which can influence psychosocial adaptation. These effects are described separately below.

Nutritional problems

Nutritional problems in infants with congenital renal anomalies are caused by metabolic disturbances, the strict diet, lack of vitality, lack of "normal" taste patterns, not feeling hungry, nausea from the urea and, if CAPD is being applied, the continuous impression of "feeling full" owing to the dialysis fluid in the abdomen. Gastro-oesophageal reflux is a frequent complaint in CAPD patients [108]. The result is often refusal of food, vomiting, and consequently, malnutrition. This together with the possible need for naso-gastric tube feeding, can lead to so many aversion stimuli in relation to food that serious and sometimes permanent eating disorders arise. Another serious consequence is that the mother-child interaction can be charged with so much tension that the formation of biological regulation, basic safety, and an effective bonding relationship, essential to accomplishing developmental tasks in the first few years of life, are difficult or impossible [109,110].

Effects of tiredness and lack of vitality

The physical complaints associated with chronic renal failure, such as tiredness, lack of appetite, lack of vitality, and general malaise, differ strongly in severity and duration from one patient to another. Tiredness is very common in HD patients, especially after dialysis. This can have serious effects on development and behaviour, such as decreasing or completely suppressing an infant's or pre-school child's initiative to explore and experiment in his/her environment. The result will be stagnation in cognitive development, impairment of the child's

growth to independence, and disruption of contact with other children [110,111]. In children of school age and during adolescence, particularly aspects such as education, identity formation, and social contact with children of the same age, weigh heavily. Not only more frequent absenteeism from school, but also defects in cognitive functions, such as attention, concentration, and memory in dialysis patients, can cause problems at school [76,89,92,112]. Although there are hospital schools in the Netherlands which can partly compensate for regular absenteeism, studies have shown that dialysis patients cannot always keep up with the tempo of classmates (93,112).

School problems often lead to social problems. Through the lack of vitality and regular absenteeism from school, it will be difficult to develop social skills and experiment with them. Moreover, owing to their specific circumstances, i.e., learning to cope with uncertainty, illness, limitations, and painful interventions, young kidney patients appear to be more emotionally mature than their peers, but on the other hand this can also form the reason why they have difficulty making adequate contact.

Diet, medication, fluid restriction, and compliance

A strict diet with low protein and low potassium (e.g., no or very small quantities of dairy products, meat, meat products, bread, fruit, vegetables, crisps, chocolate, etc.) isolates both younger and older ESRD children from daily social reality: they form an exception in the family, at school and at birthday parties. Large quantities of various types of medication in addition to strict fluid limitation (in some cases 1 litre or less per day) have sometimes been found to lead to serious ritual and obsessive behaviour. Irreversible compulsive, neurotic disturbances can result from very long-term dialysis.

Compliance with the prescribed regimen has been a frequent study subject among children and adults with ESRD. Korsch & Fine [113] reported that non-compliance, particularly with taking immune-suppressive agents after transplantation, is an important causative factor of morbidity and mortality. This finding could not be confirmed by other authors, but in an overview paper, Wolcott et al. [114] mentioned a non-compliance rate of between 20% and 78% in adult HD patients. Psychological variables chiefly determine non-compliance. These include lack of knowledge and understanding of the purpose and effect of the

various types of medication, negative family factors such as lack of support, poor doctor-patient relationship, an external locus of control, low frustration tolerance, anxiety about side-effects and changes in physical appearance, depression, or anger/hostility regarding the illness and problems with coping after a failed transplant [114,115]. Reichwald-Klugger et al. [105] concluded that the main cause of non-compliance was the double controversial role of the parents. They are responsible for the child's upbringing and the continuity of the dialysis treatment, which can be conflicting for both the parent and the child, particularly if there is strict fluid limitation. A recent study on 32 transplanted children aged between 6 and 21 years, focused on the influence of social support and family factors on compliance [99]. The conclusion was that no clear relation was found with parental support or family factors. The authors could not confirm the notion that adolescents are more at risk for non-compliance [113,114]. However, from the point of view of developmental theories, it is obvious that adolescents are likely to display more non-compliance behaviour, because they are at the stage of experimenting with limits in a tension field of dependence-independence and oriented towards body image and physical appearance. Wolff [116] justifiably focused attention on the paradox of expecting even a child with CRF to develop as normally and psychologically autonomously as possible, while at the same time demanding that the child - as a patient - behaves with as much compliance as possible. This dilemma should not only form a problem for the child and parents, but also for the health care workers treating the patient.

In the case of non-compliance, particularly in adolescents, it is important to evaluate whether this is due to "normal" adolescent behaviour: protest against having to obey rules, overstepping margins, or whether non-compliance is a symptom of underlying psychological problems: of (masked) depression to the conscious or unconscious wish to commit suicide.

Abnormal physical appearance, growth retardation (short stature), and retarded sexual maturation

Sooner or later, all children with renal disease will be confronted by temporary or permanent physical changes and an abnormal physical appearance. These can arise as a direct effect of the renal disease, or owing to side-effects of medica-

tion, such as a "Cushing" face after large doses of prednisone, hirsutism due to cyclosporin, obesity, and scarring from drains, fistulae, and operations. Possible psychological consequences include a negative body-image and self-esteem, lack of self-confidence with social contacts and social isolation [97,101, 111,113]. Reynolds et al. [97,98] found, however, that after a successful transplant, children were aware of "looking different" but did not suffer as a result, or experienced it as a handicap.

The psychological consequences of growth retardation have been described extensively in various groups of patients, such as children with growth hormone deficiency, Turner's syndrome, and idiopathic short stature. An overview article by Kelnar [117] deals with the biological, social, psychological, and societal effects. One of the conclusions is that the emotional and social environment (parents, school) determine the way in which a child with short stature sees and feels about himself. This interaction effect, or so-called silhouette effect, in which a person is addressed, treated or regarded according to his/her stature, can be responsible for retardation in social-emotional development (too childish behaviour), lack of independence, and a sombre view of the future. Growth retardation in combination with retarded sexual maturation is a major stress factor, particularly for adolescents. Being small and remaining small, not having secondary sexual characteristics (development of breasts, fat deposits, and body hair) have also appeared to inhibit stable friendships and sexual relationships, even in the long-term and after transplantation [93,97,98,101,111,116].

Through the development and administration of growth hormone (GH) treatment, which has already proved successful [118], it can be expected that the negative psychological consequences of short stature will disappear. An - as yet short - follow-up study on the psychological effects of GH treatment in adolescents, has offered leads for positive changes in self-confidence, anxiety, and depression [119].

The influence of frequent and long admissions to hospital

In 1976, Quinton & Rutten [120] clearly demonstrated a correlation between admissions to hospital at a young age and behavioural disturbances later in life. However, the majority of more recent studies on the cognitive and socio-emotional development of children with CRF were unable to establish an

influence of hospital admission [18,90,121]. Improvements in the care of sick children and the opportunity for parental participation form positive and important explanations for these changes [8]. In clinical practice, however, young children, particularly between 6 months and 4 years of age, show a negative reaction to frequent admissions to hospital. This is manifested in clinging behaviour, separation anxiety, eating and sleeping disturbances, protest and crying fits, apathy, withdrawal, and shyness.

The influence of invasive interventions and frequent (vena) puncture

Throughout the literature, invasive interventions and frequent (vena) punctures, such as those associated with HD in particular, are considered to have a negative influence on the psychological development of a child. Especially young children are vulnerable, and they are inclined to relate (vena) puncture and interventions with punishment and guilt [1]. The more positive outcomes in relation to the psycho-social adaptation of young CAPD patients, can be ascribed in part to relatively infrequent exposure to painful and threatening procedures. As yet, little is known about the psychological effects of daily injections of GH, although in recent Dutch studies, compliance was found to be satisfactory [119], while Smith et al. mentioned that 50% of the 118 patients had problems with the treatment [122].

The influence of a failed transplant

A failed transplant, especially if the organ was from a living donor, is a very drastic event, which, as is the case with other comparable life events, evokes reactions of anger, rebellion, disbelief, and sadness from both the child and the parents [123-128]. Some studies have reported that particularly denial of, for instance, sadness and disappointment, is a frequent reaction pattern after a failed transplant [99,123,124,127]. Sinnema [24] emphasized that denial as a defense mechanism in stressful situations should not always be viewed as inadequate coping behaviour, but that it may have adaptive and functional value to minimize and control the stress and intimidation. Although a failed transplant is generally regarded as a stressful factor in the treatment of renal patients and is referred to as such in the literature, no systematic research has been conducted into its effects on psychosocial development in the long-term [97].

3.3. Specific consequences of chronic renal failure on the family

Section 3.1. describes the implication of chronic disease in general on family functioning. In the case of a chronic renal disease, the above-mentioned variables: disease-specific factors, intrapersonal factors, and environmental factors, are of importance for the way in which parents and other family members deal with renal disease in a child. According to Reynolds et al. [107] the effects of renal disease on a family can be divided into problems which are directly related to the *physical condition* of the child, *practical problems*, and the *psychological burden*. Moreover, specific problems also arise in the various phases in the course of renal disease, i.e., the *pre-dialysis phase* in which renal function gradually deteriorates, the *dialysis phase*, the *transplantation phase*, and the *post-transplantation phase* [70,79,84,85,91,93,97,98,105,111,124,129-133).

In the *pre-dialysis phase*, particularly deterioration of the physical condition of the child, expressed as tiredness, lack of vitality, and eating disturbances, form a considerable burden for the child, the parents and brothers and sisters. As this phase of chronic renal failure can encompass many years, continual confrontation with a sick child can lead to strong fixation of the family on the disease and consequently on illness-related behaviour. Healthy aspects in the behaviour of the sick child (such as a young child's need to explore, an older child's pleasure in going to school, and an adolescent's growth towards independence) are ignored or neglected. The result is pedagogical deprivation, behavioural problems, and often the child develops an egocentric attitude.

Practical problems in this phase are mainly concerned with supervising the (strict) diet and administering (many different) medications. Eating disturbances and problems with toilet training are also common in this phase. These factors cause an increase in the psychological burden of the parents, which is reinforced by uncertainty about future dialysis treatment and transplantation.

In the *dialysis phase*, besides care for the child in relation to the necessary surgical interventions (creating a fistula or inserting a CAPD catheter), practical problems place a particularly heavy burden on the family. In relation to HD, these problems can include a long distance between home and the dialysis

centre, organising transport by taxi, arranging baby-sitters for the other children if the parents have to accompany the sick child. In the case of CAPD/CCPD, the parents carry great medical responsibility for the dialysis procedure, taking care of the catheter, recording the child's weight and fluid balance, measuring the blood pressure, and administering medication. An ambivalent attitude is often the result (being a parent and doctor at the same time), in addition to fixation on the ever-returning need to perform the dialysis procedure [105,124,-132]. Studies have shown that 77% of the parents of dialysis patients, as opposed to 31% of the parents of pre-dialysis patients [124], report that the daily programme and life-style of the whole family, including work and leisure-time activities, often have to be adapted to the intensive treatment of the CAPD/CCPD patient [129]. Particularly the parents of young children who require a great deal of care and are not yet ready for a transplant because they have not reached the target weight, experience a heavy burden [132,134].

Owing to the considerable time investment in PD treatment, the other children in the family, unintentionally, receive too little attention. As was mentioned above [46,107], this can be expressed as over-adaptive behaviour and/or withdrawal behaviour to spare the parents, or as acting-out behaviour, particularly at school, or as jealousy from brothers and sisters [124]. The mother's and/or father's job(s) also suffer under the treatment of the child: absenteeism, lack of concentration, impossibility of combining work with the care of a sick child (especially for mothers), lack of understanding from the employer and colleagues, are often mentioned by parents [107]. Financial problems are also common in this period [107,124,129]. The study by Reynolds et al. [124] showed that 65% of dialysis parents reported that the treatment was having a negative influence on their marriage, as opposed to 27% of pre-dialysis parents. They also found that this did not always lead to an increase in divorce and this finding was confirmed by Brownbridge et al. [84]. Psychological problems were found to be particularly common in the parents of HD patients, more than in the parents of PD patients [84]. But similar observations were reported in relation to episodes of peritonitis by the parents of PD patients [134].

The time-consuming treatment as well as mental preoccupation of the parents with their sick child sometimes results in social isolation. Relationships with

friends and acquaintances trail off, family members show too little understanding for the parent's burden. It often appears difficult to accept support and help, but it contributes to an adequate way of coping with the disease [26,34,121].

Besides negative consequences of dialysis treatment on the family, the literature also mentions positive aspects. After an anxious period during deterioration of renal function and the adaptation period to dialysis treatment, the daily structure of HD or PD offers the parents and family a certain grip on life and more certainty. It is often found that after the start of dialysis treatment, there is a "honeymoon" period of 3 to 6 months duration [131,134]. Keeping up the treatment after this period is a heavy task and uncertainty returns about a future transplantation. Symptoms of burn-out arise after a long period of treatment [134].

Being able to carry out PD treatment adequately on their child leads to more self-respect and a more positive self-image in a number of parents, even in those who did not meet criteria such as normal cognitive function and economic, psychological, and social stability [132]. Moreover, home treatment offers the parents more control and the feeling of being independent of the hospital.

In the *transplantation phase* and the period directly afterwards, there are always many worries. Except in the case of family organ donation, a new kidney generally comes unexpectedly, even after the family members have been waiting months for that "special" telephone call. It means that a number of practical measures have to be taken care of quickly, concerning work, baby-sitters for the other children, admission to hospital and particularly support and care for the sick child. The psychological burden, however, is even heavier: uncertainty about how the operation will go, possible vascular complications and rejection sometimes prevail over happiness and relief. In an overview article on the psychological aspects of organ transplantation, Gold et al. [123] described this phase as a "cease-fire period". In addition, some parents might feel saddened by the thought that the kidney came from another child or adult who died. Although parents are generally well-prepared for possible complications, they experience symptoms of rejection or infection as unexpected disappointments. Loss of control of the disease and feelings of powerlessness often cause more stress than the dialysis phase [84,97,106,113,123]. Nevertheless, after a successful transplant, improvements are seen in the parent's mood, social

life, health, and in family functioning in general [84,97]. It is also common for the majority of parents and the other children to maintain their fixation on the health of the kidney patient, all the more if he or she is displaying behavioural problems in the post-transplant period. Temporary or permanent changes in appearance (Cushing face, hirsutism, and short stature) contribute to this situation [97,101,113,128]. Reynolds et al. [97] have therefore argued in favour of providing support and counselling for parents in the period after transplantation.

The effect of a failed transplant on family functioning has never been studied systematically [97]. Streltzer et al. [127] and Gold et al. [123] described the process of denial and grief that follows a failed transplant in psychological terms. On the other hand, as was mentioned above, denial can be an adequate form of coping behaviour that protects the child and parents from the reality of having to restart dialysis treatment, which might have to be continued for many months or even years [24]. Lack of short-term perspective and loss of faith in medical technology are the heaviest burdens.

Conclusion: the way in which parents and family experience and contend with all phases of the disease, depend strongly on personality characteristics, coping abilities of the parents, family structure, and external factors, such as those described in Section 3.1.

3.4. Long-term effects of dialysis treatment and renal transplantation on psychosocial functioning

Over the past ten years, great progress has been made with renal replacement therapy, even for very young children: dialysis techniques have improved, erythropoietin and growth hormone became available, and transplant results have been more promising improved. The mortality and morbidity rates as a result of ESRD in children have dropped considerably. Therefore the question of quality of life in relation to psychological, social and societal functioning in the long-term, has become steadily more relevant. Since 1988, a number of large-scale studies have been performed in the USA and Europe. The results were encouraging, although there were many differences in emphasis between the American and European studies. In three publications in 1991, American research groups sketched an optimistic picture of the psychosocial and societal

rehabilitation of patients who underwent dialysis and transplantation in childhood: in studies with respectively 118, 57, and 37 patients the large majority received an adequate education, albeit with some amount of delay (135-137). Physical condition was considered to be good or normal in 66.7%, 91%, and 100%, respectively. Also social contacts, work, and family life were satisfactory after a successful transplant.

Recent unpublished research at Dutch and Belgian centres showed that nearly all of the 43 kidney patients completed primary education; a large proportion completed secondary education, but only a small percentage completed vocational training [138]. Delay of an average of two to three years was also observed, as a result of having to repeat classes and/or school years. These percentages are more favourable than those reported in comparable studies performed in Manchester and Germany [98,94]. In Manchester, two thirds of the - by then - adult renal patients (n=45) had obtained a school diploma as opposed to 90% in the healthy control group [98]. In the German study on a large sample of patients (n=276), 74% had not completed (secondary) vocational training (Hauptschule). The dialysis patients were at a disadvantage compared to the transplanted patients: 95% versus 58% had not completed their education. The data provided by the EDTA were even less favourable: 41% (of 617 young adults) had never been to secondary school or had not completed secondary education [94]. Comparison is difficult, because in this situation not only West European countries were included, but also South European countries. In the German study, the number of students who had received a special form of education (owing to mental, physical, and sensory handicaps) was five times higher than in the total German population [93].

These data show that although the education situation in the Netherlands seems to be slightly more favourable than in neighbouring countries, children with renal failure are clearly at a disadvantage compared to their healthy peers and that a deficient education or delayed completion decrease the chance of social rehabilitation, especially in periods with high unemployment figures.

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Chapter 4

DELAYED MOTOR AND COGNITIVE DEVELOPMENT OF YOUNG CHILDREN WITH MAJOR NEPHROPATHY

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Summary

Objective: medical technical advances in the development of far-reaching techniques, such as continuous ambulatory peritoneal dialysis (CAPD) and haemodialysis (HD), have made it possible to treat young children with chronic renal insufficiency. The aim of the study was to evaluate whether chronic renal disease has a detrimental effect on motor and cognitive development.

Setting: paediatric Dialysis Centres at the University Hospitals in Nijmegen, Utrecht, and Rotterdam.

Design: prospective study.

Methods: 18 children (mean age 37 months) who had been suffering from chronic renal disease since the first months of life, and 18 healthy children (mean age 35 months) underwent tests to evaluate their cognitive development; during the tests their behaviour was also monitored. The motor development of 9 children with renal disease was compared to that of a control group of 17 children.

Results: significant retardation (>1 SD) was found in the cognitive and motor development of the patients. Within this group, there was a considerable difference in cognitive development between the children being treated conservatively (n=8; developmental index = 92.0) and the children on CAPD or HD treatment (n=10; developmental index = 72.4).

Conclusion: dialysis patients have an increased risk of developmental retardation. Regular screening of the development of this vulnerable group and intensive counselling of the parents are strongly recommended.

4.1. Introduction

In the Netherlands, 20 to 25 children per year become candidates for renal replacement therapy: haemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD) or continuous cycling peritoneal dialysis (CCPD), as a result of chronic renal failure. Before these treatments can be instigated, there is usually a short-term or long-term period of severe renal failure, which requires strict diet and medication regimens (so-called conservative treatment). Dialysis treatment in children should be regarded as a temporary solution, because a kidney transplantation is the ultimate goal. Owing to the increasing shortage of donor kidneys, HD or CAPD may have to be continued for many years - precious years, in which stagnation in growth and development can have serious implications for the quality of life, as has been demonstrated by research over the past 10 years [1-7].

Young children (<5 years) and especially those who develop renal disease before the age of one year, are at the greatest risk of suffering severe consequences [4,8-14]. During the phase of cerebral ripening, not only the toxic effects of uraemia, but also anaemia and a poor nutritional condition are likely to have a detrimental influence on neurological, motor, and later cognitive performance. Research has shown that a kidney transplantation has a favourable effect on motor and cognitive development [4,12,15-18]. Further studies have also been conducted on the influence of other treatment modalities on the development of children [11,19].

However, the findings were ambiguous. Data were obtained in retrospect, patient populations were heterogeneous (regarding age, size, and type of treatment), and various study designs were used. In addition, it was not always clearly specified whether the patients had been suffering from chronic renal disease since infancy (with the exception of a few studies [16-18]).

Therefore a prospective study was conducted in cooperation with three Dutch paediatric dialysis centres. Over a period of three years, an inventory was made of the development of young children (<5 years) with severe renal failure (renal function <20%). This longitudinal study formed part of a prospective study and aimed particularly at evaluating the motor and cognitive development of play group/nursery school age children (1.6 to 4 years of age) with chronic renal failure, in comparison with healthy children of the same age.

Table 4.1. Population in a study on motor and cognitive development of young children with severe renal failure.

	Renal patients	Control group
cognitive development		
total number	18	18
boys	10	7
girls	8	11
conservative treatment	8	
CAPD	8	
HD	2	
mean age in months (range)	37 (21-35)	35 (27-45)
motor development		
total number	9	17
boys	5	7
girls	4	10
conservative treatment	3	
CAPD	6	
HD	0	
mean age in months (range)	38.6 (27-51)	35 (28-45)

We also investigated whether there was a difference in motor and cognitive functioning between the patients on conservative treatment and those on dialysis. Close observation was made of the children's behaviour during the tests.

4.2. Patients and methods

In the longitudinal study, there were 31 consecutive patients who met the selection criteria for age (0.4-5 years) and renal function (<20% of the normal value). To measure renal function, the endogenous creatinine clearance was used. A number of the patients were being treated conservatively, while the rest were on CAPD or HD. The paediatric dialysis centres in Nijmegen, Utrecht, and Rotterdam participated in the study. From the original group of 31 patients, 18 were selected who were of "play group/nursery school" age (mean age 37 months). The performance of these children was compared to that of 18 healthy play group/nursery school children (mean 35 months) of a similar age and socio-economic status (Table 4.1).

Table 4.2. Overview of the diagnoses in the group of 18 patients with severe renal failure.

Diagnosis	number of patients
renal dysplasia	4
polycystic kidneys	3
urethral valves	3
congenital nephrotic syndrome	2
prune-belly syndrome	2
branchio-oto-renal syndrome	1
haemolytic-uraemic syndrome	1
Bartter's syndrome	1
renal hypoperfusion	1

The age range in the control group was slightly wider than in the patient group. Evaluation of motor development was only conducted in Nijmegen; 9 of the patients participated, and there was a control group of 17 children.

Table 4.2 shows an overview of the diagnoses of the renal patients. With the exception of one, all the children had been suffering from renal failure since birth. Mean treatment duration (CAPD or HD) was 21.4 months (range 9-35). The children in the control group were attending a play group in Nijmegen for several half days a week. The patients were tested at hospital after an outpatient follow-up visit, while the control children were tested at play group in a separate area. The same researcher administered the psychological tests to both groups of children and observed their behaviour.

Motor development

The Hoskins and Squires test was used for testing motor performance (revised by Jansen, Duyghuizen, and Worm) [20]. Motor development was expressed as a motor quotient (age on the basis of the result of the motor test divided by the calendar age of the child). To make separate assessments of fine and gross motor performance, the so-called Van Wiechen scheme was used [21]. During the tests, motor behaviour was observed, and any striking characteristics were recorded and evaluated in retrospect.

Cognitive development

For all the children younger than 2.6 years, Bayley's Developmental Scales was

used [22]. The children's performance was expressed as a mental development index (DI score, norm: mean = 100; SD = 16), which gave an indication of the mental development level in comparison with the norm group of age-matched controls.

For all the children older than 2.6 years, the McCarthy Developmental Scales was used [23]. Performance on the McCarthy was expressed as a "general cognitive test score" (GCT score, norm: mean = 100; SD = 16). This test differentiates between various cognitive functions, represented by the following subscales: verbal understanding, perceptual-performal tasks, quantities (understanding of numbers), and memory. In our opinion, reliable comparisons could be made between the total scores obtained with the Bayley and McCarthy because in our longitudinal study, regular measurements on the same child as he/she grew older, did not reveal any influence of the cross-over from Bayley to McCarthy.

Statistical analysis

The effect of the factor "treatment" (CAPD/HD, conservative treatment, no treatment (control)) on cognitive development was tested with a non-parametric analysis of variance (according to Kruskall & Wallis). Differences between two groups were also tested with a non-parametric analysis, the Mann-Whitney U test; χ-square tests were used to analyze behaviour. Differences were considered to be significant at $p \leq 0.05$.

4.3. Results

Motor development

Table 4.3 shows that the motor quotient in the patient group was significantly lower than that in the control group (Mann-Whitney U value = 22; $p<0.005$). In addition, the gross motor function in the patient group was significantly lower than that in the control group, whereas no difference could be found between the two groups for fine motor function.

In the observations of motor behaviour using the subscales "strength", "tonus", "walking", and "running", no anomalies were recorded for the control children, whereas there were deviations in the scores of the patients.

Table 4.3. Level of motor development in the children with severe renal failure.

	Average score (SD) in the		U; p*
	patients (n=9)	**controls (n=17)**	
motor quotient according to Hoskins & Squires	76.4(18.6)	99.7(11.9)	22;<0.005
gross motor (Van Wiechen schema)	83.3(20.9)	127.8(14.5)	9;<0.0005
fine motor (Van Wiechen schema)	103.2(22.2)	108.0(17.4)	74;<0.05

U = Mann-Whitney-value
*p = value of patients compared to controls

It was striking that only 2 out of the 9 children in the patient group crouched down spontaneously, whereas this was the case in 14 out of the 17 control children. Moreover, 8 out of the 9 patients displayed signs of pes valgus. In 5 of them there was slight flat-foot, while in 3 the condition was more pronounced. None of the children in the control group had clear signs of pes valgus or pes planus, but 6 of them had slight flat-foot and tilting in accordance with their age.

Cognitive development

Within the group of patients, a distinction was made between the children on conservative therapy and those on dialysis. Table 4.4 shows that the mean developmental indexes in both patient groups were significantly lower than the mean index in the control group. The difference between the two patient groups was significant in favour of the children on conservative treatment ($U = 96.5$; $p<0.02$). The difference in development between the children on conservative treatment and the control children was also significant ($U = 30$; $p<0.01$). There were significant differences between the three groups ($\chi^2 = 19.25$; $df = 2$; $p<0.001$). The groups were also compared on the various subtests of the McCarthy Scales which was administered to the children of older than 2.6 years. On all four subtests, the patients had significantly lower scores than the controls ($p<0.05$). The test profile was harmonic for both groups.

Analysis of the children's behaviour showed that the patients deviated negatively from the controls on a number of variables.

Table 4.4. Level of cognitive development of the children with severe renal failure.

	conservative treatment	CAPD/HD treatment	controls
number of children	8	10	18
mean cogn. developmental index	92.0	72.4	102.4
Mann-Whitney U test	13.7	19.2	7.2

Significant differences ($p<0.05$) were found for the factors "concentration", "cooperation", and "contact" with the researcher; strongly significant differences ($p<0.001$) were found for the factors "task orientation", "testability", and "lateralisation". In relation to the item "lateralisation", it should be mentioned that in the control group, significantly more preference was displayed for a particular hand, i.e., the hand used to perform the various tasks.

4.4. Discussion

The central question in this study was: to what extent do the motor and cognitive performances of young (pre-school age) children with a chronic renal disease differ from those of a group of healthy age-matched controls? The results showed that in agreement with recent reports in the literature [8-14] young renal patients are at increased risk for cognitive and motor developmental delay or retardation.

It was striking that the delay in motor development lay exclusively in the gross motor evaluations. These delays may be explained by the direct effects of renal disease: anaemia, poor nutritional condition, and uraemia. In addition, the dialysis fluid in the abdomen of the children on CAPD (6 out of the 9 patients) had a limiting effect on mobility, which may have also had a negative influence.

Compared to the control group, there was a delay in the cognitive development of the renal patients. The delay in the 10 dialysis patients was much larger than that in the 8 patients on conservative treatment (cognitive developmental indexes: 72.4 and 92, respectively). These findings partly confirm the results of other recent investigations in which slight developmental delay was reported in patients on conservative treatment [10,11,13,14].

These literature data were often contradictory and offered little in the way of clear answers about the developmental chances of young patients on dialysis treatment. None of the studies confirmed our results that children on dialysis have significantly lower scores than children on conservative treatment. Salusky et al. mentioned that after the start of CAPD treatment, three out of the four patients were able to catch up some of their delay in development [19]. However, these measurements were performed on a very small number of patients.

What can be the explanation for the differences observed between the patients on conservative treatment and those on dialysis? The not inconsiderable delay in development in the dialysis patients can partly be explained by the fact that four out of the ten patients in our group also had multiple congenital anomalies, which had a negative influence on the total score. All four patients scored >2 SD below the norm average. When these scores were omitted from the analysis, the dialysis group had a higher mean developmental index (83 instead of 72), but it remained lower (non-significant) than the score of the conservative treatment group (92). Moreover, it is possible that the remaining renal function in the patients on conservative treatment had a positive effect on their cerebral functions.

The results of our observations also suggest that behavioural factors may have had an influence on the retardation or delay in development of the total patient group. The parents of these patients and particularly the parents of the dialysis patients (10 out of the 18 patients) were carrying a great deal of responsibility for the medical condition of their child, because they were performing the treatment themselves. It is known that fixation on the disease, concern, and anxiety can lead to overprotection and pedagogical deprivation [2,3,7,18].

4.5. Conclusion

Young children with chronic renal failure are at increased risk for developmental retardation. Children on conservative treatment seem to run less risk of developmental retardation than dialysis patients. The delay in motor and cognitive development of young dialysis patients can be attributed to an

interaction between direct effects of renal failure and behavioural factors.
In children of younger than 5 years of age with chronic renal failure, it is recommended to conduct systematic tests on the motor and cognitive development. The early detection of developmental delay or disorders, offers the opportunity to apply a specific approach or treatment. In addition, structured counselling should be offered to the parents of young children who are participating in a dialysis programme, which not only provides information, but also pays attention to pedagogical aspects.

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Chapter 5

THE COGNITIVE DEVELOPMENT OF PRE-SCHOOL CHILDREN TREATED FOR CHRONIC RENAL FAILURE

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Summary

Chronic renal failure in young children is associated with impaired cognitive development, but recent studies present a more optimistic perspective. An important question is whether the earlier initiation of renal replacement therapy (RRT) might prevent the reported developmental retardation. The cognitive development of 31 patients (age <5 years with a serum creatinine clearance of <20% of normal) undergoing different treatment modalities was monitored by repeated measurements during a prospective 3-year study. Fifteen patients received conservative treatment and 16 patients were on dialysis treatment at the start of the project. We were able to evaluate the effect of the onset of RRT on 12 patients who were transferred from conservative treatment to dialysis. At the beginning of the study, the cognitive development of the total group was significantly delayed (mean developmental index = 78.5, SD = 19.5) compared with a normal population. Patients undergoing conservative treatment scored significantly higher ($p<0.01$) than those on dialysis. The effect of starting dialysis treatment appeared to be positive, but only a significant short-term improvement was observed. Follow-up evaluation of 7 patients on conservative treatment and of 9 dialysis patients over a 2-year period did not show any significant change in a positive or negative direction.

The present study revealed that pre-school dialysis patients are at risk with respect to their cognitive development. This is particularly true for the group with concomitant disorders. Less severe disease in the group on conservative treatment may be assumed to be a positive contributing factor to the more normal performance of these patients. No evidence was found to support the hypothesis that the earlier initiation of dialysis treatment will have a beneficial effect on development.

Key words: Chronic renal failure - conservative treatment - dialysis treatment - cognitive development - children

5.1. Introduction

During the past decade, a number of reports have been published on the neurological, motor, and cognitive development of infants and young children with chronic renal disease (CRF). The results of these largely retrospective studies are heterogeneous and sometimes contradictory, but generally lead to the conclusion that young children with CRF are seriously retarded in their development [1-9]. However, recent studies have presented a more optimistic view in terms of improvement in developmental progress due to better medication and nutrition, treatment modality (conservative versus dialysis), or early transplantation [6-8,10-14]. Geary and Haka-Ikse [11] concluded that generally the developmental prospects of young renal patients are better than was previously assumed, but others stated that very young children in a critical period of cerebral growth may suffer more from the toxic effects of uraemia, anaemia, and a poor nutritional state [8]. Early transplantation in young children may reverse these effects [7,12-14], but these findings are still controversial [11,15,16].

Therefore, an important question is: what is the optimal time to start renal replacement therapy (RRT), or in other words: will the course of development of young renal patients benefit from starting dialysis treatment at an early stage? The best approach to find answers to these questions is to monitor prospectively the developmental course of infants and young children with advanced renal failure who are undergoing either conservative treatment or dialysis, and to investigate the effects of dialysis on children who were previously treated conservatively.

The present study reports the results of a longitudinal project which investigated the neurological, motor, and cognitive status and development of 31 young renal patients under 5 years of age, whose renal function was <20% of normal. A group of patients on conservative treatment was followed as well as a group of dialysis patients. The effect of changing from conservative treatment to dialysis was assessed in 12 patients. In addition, the developmental scores were related to factors which are known to be associated with a negative outcome, such as biochemical parameters, presence of multiple congenital diseases, and psychosocial variables.

Table 5.1. Primary renal disease in all 31 patients.

Diagnosis	No. of patients
Dysplasia/hypoplasia	7
Urethral valves	7
Congenital nephrotic syndrome	3
Renal hypoperfusion	3
Polycystic kidneys	2
Glomerulosclerosis	2
Prune-belly syndrome	2
Unknown	2
Branchio-oto-renal syndrome	1
Haemolytic uraemic syndrome	1
Bartter syndrome	1

5.2. Patients and methods

Patients

Thirty-five patients treated at three Dutch paediatric nephrology units participated in the project between 1988 and 1991. Inclusion criteria were defined by age (<5 years) and by creatinine clearance, calculated from serum creatinine (<20% of normal renal function for age). During the project, new patients were admitted, and patients over 5 years of age and patients who received a kidney transplant dropped-out after a limited follow-up assessment. The mean duration of follow-up was 25.8 months (range 6-41 months). The data on 4 patients could not be used in the analysis (2 patients underwent only one assessment, 1 patient did not co-operate in any session and 1 patient proved to have central nervous system disturbances as a result of serious cerebral complications (spastic tetraplegia and mental retardation after septic shock) and was unable to be examined by the appropriate method. The head circumference of all children except 3 (missing values) was lower than the 50th percentile. Nutritional status was generally satisfactory; in the youngest age group forced tube-feeding was necessary in most patients. Aluminium-containing phosphate-binding agents had been used in 5 children. Parathyroid hormone was normal at the time of study in all children.

The study group comprised 31 patients (13 girls, 18 boys) aged 0.3-5.0 (mean 2.5) years at the first assessment. Their primary renal diseases are listed in Table 5.1.

Table 5.2. Concomitant disorders in 10 patients.

Pat. no	Primary disease	Develop-mental disorder	Cerebral com-plication	Visual disorder	Deaf-ness	Cong. heart disease
2	branchio-oto-renal syndrome	X			X	
8	dysplasia	X		X		
10	haemolytic uraemic syndrome		X[a)]			
14	dysplasia	X				
22	Prune-belly	X				
26	congenital nephrotic syndrome	X				
29	glomerulosclerosis	X	X[b)]			
31	unknown	X				
32	renal hypoperfusion					X
35	renal hypoperfusion		X[c)]			

a) Varicella encephalitis
b) Cerebral hypoperfusion during artificial ventilation for septicaemia
c) Meningoencephalitis

All but 5 patients had been suffering from chronic renal insufficiency from infancy. Ten patients proved to have multiple (congenital) diseases or concomitant disorders (Table 5.2).

Of these 10 patients, 7 had an "early developmental disorder" at the time they were admitted to the paediatric nephrology unit. These developmental disorders, which included serious developmental delay, were diagnosed by a paediatrician as not being the result of their renal insufficiency, but due to either an event resulting in cerebral and renal complications or to unexplained cerebral impairment. Five children had started receiving RRT during infancy; in 16 children RRT was initiated after the 1st year of life.

For the dialysis patients, the duration of dialysis was calculated from the onset until the first assessment: mean 30.1 months, range 4.4-54.4 months.

The research population of 31 patients was divided into two groups: patients treated conservatively, i.e., they were receiving standard medical management for CRF (n=15, mean age 29.2 months, SD = 19.0) and patients who were on dialysis (n=16, mean age 31.0 months, SD = 17.8). Twelve patients changed from conservative treatment to dialysis during the project because of end-stage renal disease (creatinine clearance <5-10ml/min per 1.73 m^2) (Figure 5.1).

There were only small differences in socio-economic class according to the occupation of both parents (6 categories). The majority of children were living in a rural area.

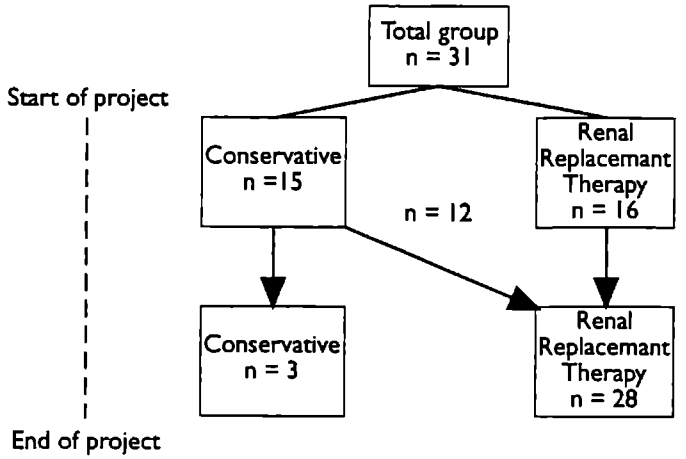

Figure 5.1. Distribution of patients between conservative treatment and renal replacement therapy throughout the project.

All the children over 2.5 years were attending a (sometimes specialised) day nursery or school. The study was approved by the ethics committees of the University Hospitals. Informed consent was obtained from the parents. The treatment in the three centres was essentially similar.

Methods

The cognitive development of the 16 children under 2.6 years and the 15 children over 2.6 years was assessed by the Bayley Developmental Scales (mental scale only) [17] and the McCarthy Developmental Scales (verbal perceptual-performance and quantitative scales, respectively) [18]. These scales provided respectively a developmental index and a general cognitive index, based on raw scores, corrected for chronological age. Therefore in the repeated measurement design that was used, time effects such as maturation could be controlled. The mean score in the normal population is 100, with a SD of 16. The effect of the transition from one method (Bayley) to the other (McCarthy) was assessed: no significant differences were observed between the Bayley scales and the McCarthy scales during the course of the project (paired t-test, p=0.96). Behavioural observations and interviews with the parents about the child's condition, child-rearing practices, and special circumstances complemented the assessments. The children were examined once every 6 months. The test/retest reliabilities of the two methods were 76.4 (percentage of agreement

[17] and 0.91, respectively [18]. The examinations, including medical screening, were carried out by the same health care professionals at each follow-up visit at the outpatient clinic. Blood urea, creatinine, and haemoglobin concentrations were determined each time, as well as height, weight, and head circumference.

Statistical analysis

The influence of the presence or absence of multiple disorders on the developmental index was assessed by Student's t-test. Fisher's exact test (two-tailed) was used to test the difference in the proportions of children with multiple disease in the two treatment groups. Two-way analysis of variance (ANOVA) was used to analyze differences in the developmental index between the two treatment groups and between the patients with and without multiple diseases. The developmental course over a 2-year period of the two treatment groups (conservative versus dialysis) was analyzed by repeated measurement ANOVAs. The effect of the change from conservative treatment to dialysis on the patients who were transferred was analyzed using a paired Student's t-test. Pearson's correlation coefficient was used to examine the correlation between the development index and the various medical, biochemical, and psychological parameters.

Because age at initiation of treatment is critical, this factor was entered as a covariate in the ANOVAs to examine if there was an age/treatment interaction.

5.3. Results

Overall developmental level

The cognitive development of the total patient group was delayed (Table 5.3). The mean developmental index based on the original values of each patient was significantly lower (mean = 78.5, SD = 19.5) than that of the normal population.

Only 2 patients (6.5%) scored above the mean of the normal population (normal distribution 50%), while the scores of 29% were more than 2 SDs lower (normal distribution 2.3%). The low mean score in the total group might have been caused by the patients with concomitant disorders (10/31), most of whom had an early developmental disorder.

*Table 5.3. Cognitive development of patients undergoing different treatment modalities with and without multiple diseases**

	Patients with and without multiple diseases (total)			Patients without multiple diseases			Patients with multiple diseases		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Total	31	78.5	19.5	21	86.7	15.5	10	61.4	15.6
Conservative	15	90.3	14.3	12	93.3	13.2	3	78.0	14.0
CAPD/HD	16	67.6	17.3	9	77.9	14.5	7	54.3	10.1

CAPD, Continuous ambulatory peritoneal dialysis; HD, haemodialysis

* Two way analysis of variance: treatment (p=0.001), multiple diseases (p=0.001) and interaction between treatment and multiple diseases, as well as interaction between treatment and age at initiation of treatment

Therefore, the influence of the presence of multiple disorders on the cognitive score of the total group was tested and proved to be significant ($p<0.0001$). There were also differences in the mean developmental index of the patients in the two treatment groups. A significant difference was found between the developmental index and the treatment modality ($p=0.001$) and between the developmental index and multiple diseases ($p=0.001$). No interaction was found between the treatment modality and multiple diseases, which meant that the difference in the developmental index between the two treatment groups was not significant for the patients with and without multiple diseases. The proportion of patients with multiple diseases in the dialysis group was however larger, but not significantly so.

Developmental course during treatment for CRF

A complicated methodological problem in this longitudinal project was the uncontrolled selection of the study sample, as a result of the clinical need to transfer patients from conservative treatment to dialysis. Consequently, the treatment groups did not remain stable over a period of 3 years. However, it did prove possible to compare the treatment groups with regard to progression or retardation in development by monitoring the developmental course of 16 of the 31 patients over a period of 24 months, with a minimum of five measurements.

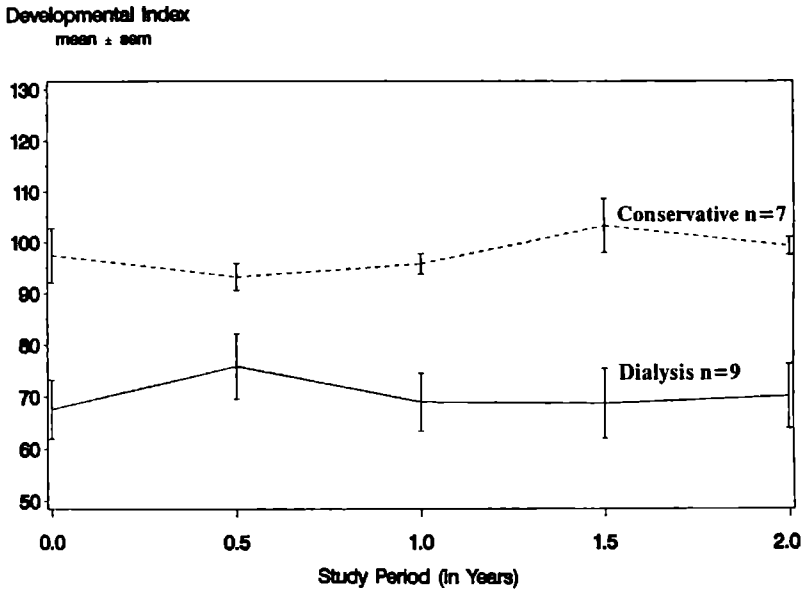

Figure 5.2a. Cognitive development over time (mean +/- SEM) of a group of 7 patients treated conservatively and of a group of 9 patients treated by continuous ambulatory peritoneal dialysis/haemodialysis.

The remaining 15 patients were excluded from the analysis over a longer period because of a kidney transplant or a change from one treatment group to the other within the 2-year study period. Figure 5.2a presents the developmental course of the group of 7 patients who received only conservative treatment and of the group of 9 patients who were only treated with dialysis over a 2-year period. Figure 5.2b shows on an individual basis an increase or decrease in developmental quotients between the initial and last evaluation. Apparently, the significant difference between the two treatment groups was maintained over time (repeated measurement ANOVAs).

The effect of starting dialysis treatment

The effect of initiating dialysis treatment could be investigated in 12 children, all of whom transferred from conservative to continuous ambulatory peritoneal dialysis (CAPD) treatment. These changes occurred at random in the 6-month interval between successive measurements. Therefore, we could not measure short-term (2-6 months) and long-term (8-16 months) effects on all 12 patients.

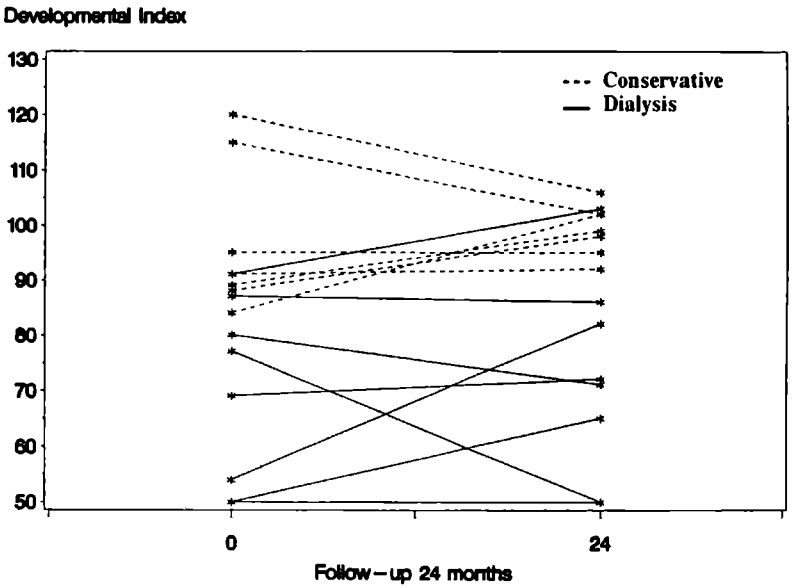

Figure 5.2b. Cognitive development over time of 7 individual patients treated conservatively and of 9 individual patients treated with CAPD/HD.

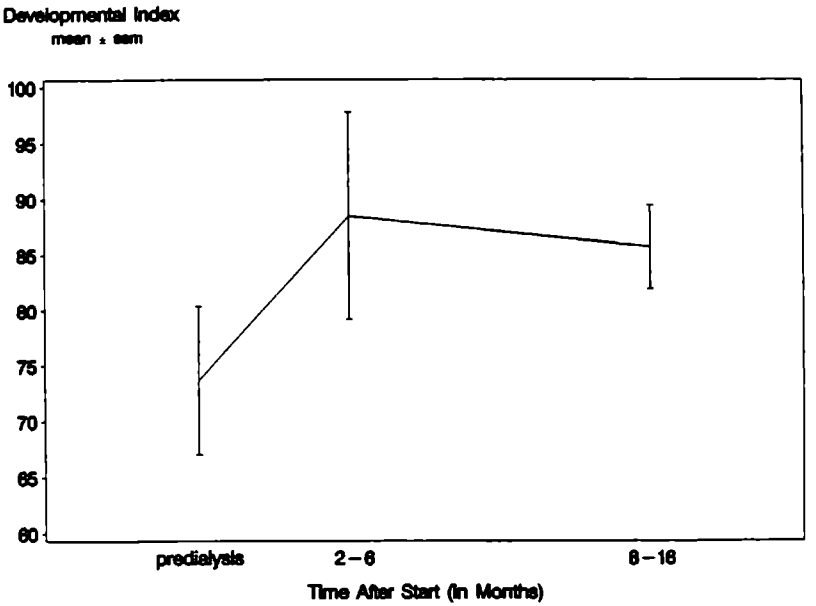

Figure 5.3. Short-term and long-term effects of the initiation of dialysis treatment on the cognitive development of 6 patients.

All the patients had a pre-dialysis score (<2 months before starting dialysis); for 6 patients there were both short-term and long-term measurements (Figure 5.3); 2 others only had short-term scores, while 4 other patients only had long-term scores. The short-term effect of dialysis treatment, which could be assessed in 8 patients, was significant (p=0.029). In Figure 5.3, which is based on the 6 patients for whom both short-term and long-term scores were available, a significant improvement was noticed after 2-6 months (p=0.017). At a later phase, after 8-16 months, the developmental index had deteriorated slightly, but the overall improvement remained significant (p=0.026). However, the long-term effect assessed in all 10 patients with long-term scores was not significant (p=0.29).

The contribution of biochemical and psychosocial variables to cognitive development.

A relationship between changes in renal function (blood urea, creatinine clearance, and haemoglobin) and improvement or deterioration in cognitive functioning was anticipated, but no significant correlations could be established.

The effect of erythropoietin treatment was evaluated on 11 dialysis patients after 2-7 months, but no influence could be demonstrated. Age (under or over 2.5 years), CRF since birth, onset of dialysis treatment during infancy, age at initiation of treatment, duration of dialysis treatment, and medical complications (frequency and duration of admissions to hospital) did not contribute significantly to the developmental indices. There was no relationship with socio-economic class or with attending day nursery or school.

5.4. Discussion

This study longitudinally assessed the developmental progress of young children with severe CRF who were undergoing different treatment modalities. Consistent with other studies [1-9], our data supported the conclusion that the cognitive development of infants and young children with CRF is impaired. This statement is an oversimplification, because there were two groups: a group treated conservatively, who scored at a nearly normal developmental level, and a group on dialysis treatment, who scored slightly more than 2 SDs below

average. These findings are in partial agreement with the results of some studies [2-4,11], but contradict others [1,8,10,19]. Comparison was difficult, however, because age, sample, methods, renal function, and inclusion criteria were different. In only one study young renal patients were investigated prospectively [11]. In addition, our sample was not assigned at random to different treatment conditions, because clinical indications for one modality or another precluded the use of a strictly experimental design. The potential impact of using non-random assignment would not be easy to assess, but in any case involves the uncontrolled selection of treatment groups and as a consequence, unpredictable effects. Nevertheless the striking difference in cognitive functioning between the conservatively treated group and the dialysis group in our study cannot be explained purely by the effects of selection.

In studies on the implications of various modes of therapy on the developmental progress of children, adolescents, and adults, impaired cognitive functioning was found to be particularly associated with severe renal insufficiency and the need for RRT [10,11,20-22]. It has also been stated that children on dialysis treatment have lower performance levels for cognitive tasks. Some authors have emphasised the benefit of relieving uraemia [10], which suggests that changing from conservative treatment to dialysis might improve the cognitive functioning of advanced renal failure patients [20,21]. In the present study, the expected benefit of a lower blood urea level was not demonstrated. This is in contrast to the study of Geary and Haka-Ikse [11] in which the glomerular filtration rate was 31 (± 29) at the initiation and 29 (± 30) at the final evaluation. In our study all patients had a renal function of <20%. Consequently, differences were too small to reach statistical significance. Possibly, the less-severe nature of the disease and residual renal function were favourable contributing factors to the better cognitive performance of patients undergoing conservative management.

Other relevant variables which might be related to developmental delay were also investigated. No evidence was found for significant correlations with age and the presence of CRF since birth. These findings are at variance with the results of other studies [1-9], but it should be borne in mind that our sample consisted of patients under 5 years of age and that all but 5 patients had had CRF since birth. There was very little variance in factors such as the onset of

dialysis treatment during infancy and the duration of dialysis treatment. Also expected hospitalisation effects [2], (medical complications as well as the frequency and duration of admissions to hospital) were lacking. Surprisingly, we did not find that erythropoietin had a positive effect as was found in recent studies on cognitive functioning and neuropsychological tests in adults and children [23-27], perhaps because the long-term effects could not be measured in the present study. The relatively young age of our subjects may have contributed to the inconsistency between our results and those reported in the literature [23-27]. In this age group cognitive functioning and intelligence are relatively unstable, but increasing stability can be expected over time at school age [10, 38]. No evidence was found for a relationship between the developmental index and psychosocial factors such as socio-economic class, attending a day-nursery or school, and admissions to hospital; this was probably due to the small variance in our sample.

It is noteworthy that there was a large number of patients with multiple diseases or concomitant disorders in our sample, particularly in the dialysis group, and these patients were not excluded, as in other studies [9,20,29], because they account for one-third of a paediatric renal sample, and the 32% in our study was consistent with other studies [10,30]. Although the scores of these patients had a negative influence on the mean developmental index of the total group, the difference between the two treatment groups remained significant even after they had been excluded. Additional evidence of a difference between the two treatment groups can probably be found in the interaction of psychological factors with biochemical and clinical factors. Fixation on the disease and overprotection, resulting in educational and social deprivation, particularly in the dialysis group, might have had a negative influence on the cognitive development of the young, mainly CAPD patients [2,31-34].

The hypothesis that initiating dialysis treatment at an earlier stage will improve a child's developmental course was not confirmed, although the mean developmental index of 6 of 12 patients advanced significantly after starting CAPD, particularly in the period shortly afterwards. There was probably a short-term catching-up effect which disappeared later. An explanation might be that the start of dialysis treatment was strongly indicated because of biochemical findings and the clinical condition of the patient. The amelioration of this

state may temporarily improve cognitive functioning, whereas the long-term effects of uraemia remain. This outcome was also consistent with another interesting finding, and in accordance with Geary and Haka-Ikse [11], that patients treated conservatively over a 2-year period and patients on dialysis over a similar period maintained their developmental level, as no significant differences were found between the first and the last measurements (Figure 5.2a). These results emphasise the need for longitudinal studies in young patients. It is clear that we need to gain greater insight into the developmental course from sensorimotor functioning to more differentiated cognitive functioning on a higher cortical level [10,29]. Moreover, any misleading short-term effect of changing the mode of therapy can then be put into proper perspective in relation to development over a longer period of time.

It might be argued that the striking differences between the group treated conservatively and the dialysis patients existed right from the start. This might mean that the children who need RRT at a very early age and over a long period (≥2.5 years) are more vulnerable not only with respect to their renal function but also to neurodevelopmental variables [29]. Fennell et al. [20,29] investigated neuropsychological functioning in patients aged 6-18 years, but excluded children who were clinically retarded or had overt neurological disease, hence a comparison with the present study can hardly be made. However, their hypothesis that impaired development of renal patients is a trait-like effect, which is probably caused by as yet unidentified congenital factors, rather than a state mainly determined by compromised renal function, might be valid for the neurodevelopmental course of young patients. Prospective research into this issue is required, with the ultimate goal of preventing cognitive retardation. Possible promoting features might include systematic developmental screening of this vulnerable patient group and the implementation of appropriate therapeutic interventions, such as sensorimotor training, speech therapy, advising the parents on educational matters and, if necessary, referral to a specialised day-nursery.

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Chapter 6

EVOKED POTENTIALS IN CHILDREN WITH CHRONIC RENAL FAILURE, TREATED CONSERVATIVELY OR BY CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

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Summary

Children with chronic renal failure (CRF) show developmental intellectual and motor disturbances. It is questionable if an early start of renal replacement therapy may prevent or delay these disturbances. We studied the neurological and intellectual development of children <5 years suffering from CRF (creati-nine clearance <20% of normal) prospectively, over a period of 3 years. As part of the neurological study brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SSEP) were recorded. Measurements were performed in a group of 22 children every 6 months. In 18 of these children CRF was present from birth. Sufficient data were available for analysis in 19 (BAEP) and 22 (SSEP), respectively. A delay of peak I of BAEP gave indications for peripheral conduction disturbances, possibly due to cochlear dysfunction. Brainstem conduction was normal. There were no differences between the children treated conservatively (n=9) and those treated with continuous ambulatory peritoneal dialysis (CAPD) (n=10). In children <2.5 years SSEPs showed a delayed thalamocortical conduction, which was not observed in older children. This might indicate a delayed myelination in young children with CRF. No differences were found between the children treated conservatively (n=10) and those treated with CAPD (n=12).

Keywords: Chronic renal failure - Continuous ambulatory peritoneal dialysis - Evoked potentials

6.1. Introduction

It has long been recognised that end-stage renal failure in adults is associated with neurological complications [1,2]. Developmental disturbances and encephalopathy have also been reported in children with chronic renal failure (CRF) [3-6]. Intellectual and motor development of young children with CRF is delayed compared with healthy children [7-11]. The investigation of cerebrospinal fluid has also shown abnormalities in purine/pyrimidine metabolism [12]. The young, maturing central nervous system seems to be affected in children suffering from CRF. It may be hypothesised that an early start of renal replacement therapy may prevent these disturbances.

The neurological and cognitive development of children <5 years suffering from CRF (creatinine clearance <20% of normal) was studied prospectively, over a period of 3 years. As part of the evaluation of the neurological status of these patients, brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SSEP) were measured. Since peripheral nerve conduction may be delayed in uraemia, decreased latencies in evoked potentials can be expected.

6.2. Patients and methods

BAEP and SSEP were measured every six months in a group of 22 children (8 girls, 14 boys). All children were <5 years and had a creatinine clearance <20% of normal, calculated with the serum creatinine using the Schwartz formula [13]. The children were divided in two subgroups. Group I was treated conservatively (n=9 for BAEP, n=12 for SSEP), group II with continuous ambulatory peritoneal dialysis (CAPD) (n=10 for both investigations). The mean creatinine clearance was 15ml/min per 1.73m^2 (range 6-20). Renal replacement therapy was started at a creatinine clearance <5-10ml/min per 1.73m^2.

In 18 children CRF was present from birth. The aetiology of CRF is given in Table 6.1; 8 patients had disorders affecting the nervous system (mental retardation (n=6), deafness (n=2), and motor retardation (n=1)). The BAEP of the two deaf children were excluded from the study.

Table 6.1. Aetiology of chronic renal failure (CRF) in the study group.

Urethral valves	7
Renal dysplasia	5
Polycystic kidney disease	2
Focal glomerulosclerosis	2
Branchio-oto-renal syndrome	1
Congenital nephrotic syndrome	1
Haemolytic-uraemic syndrome	1
Jeune syndrome	1
Bartter syndrome	1
Unknown	2

In group I the last recording before the start of dialysis was evaluated, in group II a recording at least 6 months after the start of dialysis. No recordings from the same patients were compared. For group I the mean age at performance of BAEP was 37 months and SSEP 40 months. In group II these ages were 43 and 36 months, respectively.

Potentially ototoxic drugs had been taken previously by some children: 3 were treated with frusemide, and 5 (CAPD) patients had been treated with aminoglycosides for a short period for peritonitis. Aluminium-containing phosphate-binding agents had been taken by 5 children in the past. The parathyroid hormone level was normal at the time of investigation in all children. All evoked potential recordings were obtained with a standard evoked potential device (Nicolet CA 1000). The children were in the supine position. Sedation or anaesthetics were not used.

Brainstem auditory evoked potentials

Tin electrodes were attached to the prepared skin of the skull according to the international 10-20 system [14]. First the right and then the left ear was stimulated. Each test was performed twice in order to establish reproducibility. Each test was performed by delivering at least 1000 rarefaction clicks (0.1ms duration), at a regular rate of 11.1/sec and an intensity of 80dB. The results were analyzed, using a Nicolet Pathfinder II. The BAEP components were determined by visual analysis. Latencies of waves I, II, III, and V ipsilateral to stimulation and IIc, IIIc, and Vc contralateral to stimulation were measured. Furthermore the interpeak latencies I-III, I-V, III-V, IIc-Vc, and IIIc-Vc were calculated. All values were compared with

normative values published by Thivierge and Cote [15].

Somatosensory evoked potentials

The right median nerve was stimulated at the wrist at a regular stimulus rate of 3.3/sec, with the stimulus intensity adjusted to produce a minimal thumb twitch. Each average contained between 100 and 1000 artefact-free sweeps, and the test was performed twice in order to establish reproducibility. At the spinous process of the seventh cervical vertebra (C7) the cervical responses, N13 and P16, were measured. From the contralateral somatosensory cortex (C3') peak P15 and the cortical responses N20, P22, P27, and P45 were determined. P15 is the first consistent wave form observed in scalp recordings. It is generated between the medulla and the thalamus in the medial lemniscus or in the ventroposterolateral nucleus of the thalamus [16,17]. N20 is a cortical response generated in the posterior wall of the central sulcus, and P22 is also cortical, generated in the crown of the posterior central sulcus [16,18]. Interpeak latencies N13-P16, N13-P15, N13-N20, and N20-P22 were then derived from their corresponding peak latencies. Our data were compared with normative values published by Taylor and Fagan [18].

Statistical analysis

Because there were no latency differences in BAEP dependent on the side of stimulation we used the mean value of the measurements obtained on the right and left ears. The two-tailed probability test of Wilcoxon (Kruskal-Wallis) was used for the comparison of the CAPD and the conservatively treated group. A p-value <0.05 was considered to be statistically significant. After comparing peaks and interpeak latencies with the normal range, the significance of the number of children having a delayed peak or interpeak latency was assessed by binominal testing. For SSEP a t-test was applied at a significance level of $p<0.05$.

Table 6.2. Brainstem auditory evoked potentials (BAEP) peak latencies and inter peak latencies (IPL) in children treated with CAPD (n=10) and those treated conservatively (n=9).

	CAPD n=10		Conservatively n=9		Normal range [8]
Peak/IPL	Mean (ms)	SD	Mean (ms)	SD	1st - 99th percentile
I	1.93	0.20	1.91	0.27	1.40 - 1.96
II	2.90	0.29	2.82	0.27	2.36 - 3.26
III	3.99	0.25	3.98	0.26	3.28 - 4.12
V	5.88	0.35	5.78	0.34	5.00 - 6.16
I-III	2.06	0.19	2.09	0.22	1.68 - 2.48
I-V	3.95	0.31	3.89	0.24	3.28 - 4.68
III-V	1.89	0.18	1.80	0.14	1.41 - 2.34
IIc-Vc	3.05	0 29	3.04	0.36	---
IIIc-Vc	2.17	0.21	2.16	0.15	---

6.3. Results

Brainstem auditory evoked potentials

The BAEP latencies were not different between children treated with CAPD and those treated conservatively (Table 6.2).

In 9 of 19 patients peak I was significantly delayed, although the mean value of peak I latency was in the normal range. Of these 9 children, 4 were treated conservatively and 5 received CAPD. No age difference was found between children with normal peak I latency and those with delayed peak I latency. The latencies of peak II were delayed in 3 children, peak III in 7 children, and peak V in 8 children. There was no correlation between the use of potentially ototoxic drugs and these delayed latencies. Interpeak latencies were all within normal limits. This indicates a normal central conduction time (IPL I-V), from the acoustic nerve across the brainstem to the inferior colliculus.

Somatosensory evoked potentials

In view of the age dependency of SSEP latencies, we divided our group into children <2.5 years of age (n=10) and those between 2.5 and 5 years (n=12). In both age groups there were no significant differences between the conservatively treated children and those who were treated with CAPD (Table 6.3).

Table 6.3. Somatosensory evoked potentials latencies/IPL in the children on CAPD and treated conservatively subdivided into < and > than 2.5 years.

	Children <2.5 years				**Children >2.5 years**			
	CAPD n=4		**Cons. n=6**		**CAPD n=6**		**Cons. n=6**	
Peak/IPL	**Mean (ms)**	**SD**	**Mean (ms)**	**SD**	**Mean (ms)**	**SD**	**Mean (ms)**	**SD**
N13	8.2	0.6	7.9	0.7	8.1	1.1	9.0	0.6
P16	12.1	1.0	11.6	0.6	12.8	1.0	13.0	1.3
N13-N16	3.9	1.0	3.7	1.1	4.7	1.1	4.0	1.2
P15	12.0	1.4	11.1	1.0	10.5	1.1	11.2	0.4
N20	17.1	1.1	16.4	1.8	15.4	1.3	16.1	0.5
P22	21.5	1.9	22.5	1.5	20.9	2.7	22.5	1.7
P27	24.7	1.9	26.8	1.0	26.2	3.9	27.2	2.8
P45	40.0	6.2	42.1	4.7	41.6	4.2	41.3	7.9
N13-P15	3.8	1.3	3.2	0.3	2.4	0.4	2.2	0.3
N13-N20	8.9	1.1	8.5	0.7	7.0	0.8	7.1	0.8
N20-P22	4.4	1.4	6.1	1.7	5.5	2.7	6.4	1.6
Age (months)	22	5	18	9	50	8	54	12

Therefore, further analyses were performed on the total group of 22 children. The latencies of components P15, N20, and P22 were delayed compared with normative values for children <2.5 years, and interpeak latency N13-N20 was significantly increased (Table 6.4). The latency of peak N13, a post-synaptic response in the dorsal column/cuneate nucleus, was not delayed. This implies that the conduction between the cervical myelum via the medial lemniscus and the thalamus to the somatosensory cortex is delayed in these young children. In the children between 2.5 and 5 years only P22 and N20-P22 were delayed. The central conduction between the cervical myelum and the cortex (N13-N20) was not delayed.

Table 6.4. Comparison of the SSEP data of the whole group of children with CRF with normal values [11].

	Children >2.5 years				Children >2.5 years			
	CRF n=12		Normal n=11		CRF n=12		Normal n=16	
Peak/IPL	Mean (ms)	SD	Mean (ms)	SD	Mean (ms)	SD	Mean (ms)	SD
N13	8.1	0.6	7.8	0.3	8.5	1.0	8.6	0.5
P15	11.6	1.3*	10.1	0.5	10.8	0.9	10.8	0.5
N20	16.8	1.1*	15.4	0.6	15.7	1 0	15.3	0.6
P22	21.9	1.8**	20 4	0.9	21.7	2.3*	19.1	0.6
N13-N20	8 8	0.9*	7.8	0.4	7.0	0.8	6.7	0.5
N20-P22	5.1	1 7	4.7	0.7	5.9	2.1*	3.9	0.7

* = $p<0.01$
** = $p<0.05$

6.4. Discussion

In adults with end-stage renal disease polyneuropathy, demonstrated by the delay of peripheral conduction velocity, is frequently present [19-22]. The central conduction is also decreased, as measured by BAEP [23-25] and SSEP [22,24]. However, reports are rather scarce in children. De Beaufort et al. found normal peroneal nerve conduction in 12 children (mean age 11, range 5-17 years) treated with haemodialysis [26]. More recently, Suppiej et al. measured median nerve SSEP in 10 children (median age 14, range 9-19 years) treated by haemodialysis and reported no abnormalities [27]. Since the children in their group were significantly growth retarded, they corrected their data for arm length and found a significantly delayed peripheral conduction. These children were considerably older than those in the present study. No evoked potentials are available for children with CRF from infancy. In 18 of the 23 children we investigated, CRF was present from birth. In our study, the delayed peak I latency of the BAEP in a large number of patients suggests the presence of a hearing disorder. Wave I represents activity of the acoustic nerve [28]. Stimulus intensity has significant effects on the latency of auditory brainstem potentials. A decrease in stimulus intensity is accompanied by an increase in BAEP latencies. The delayed latency of peak I may be the result of inner ear dysfunction, either anatomical or functional; a hair cell loss in Corti's organ has been supposed in a study of adult patients [28,29]. Using a click

stimulus, our study is not designed to detect frequency dependent dysfunctions. None of the children had clinically evident middle ear effusions during the investigation. It is known that drugs such as aminoglycosides and frusemide are potentially ototoxic [30-33]. Many children with renal failure have been treated with frusemide in the pre-terminal phase. Aminoglycosides were only used in some of the children treated with CAPD, and always for a short period, in the case of a peritonitis episode. Ototoxicity, although unlikely, can not be ruled out as an additional etiological factor of the disturbances observed in these children. Routine audiographies showed no abnormalities in our patients, in contrast to recently published data [33]. This study reported no abnormalities in BAEP. In our patient group ultra-high pure-tone testing was not performed. The normal interpeak latencies indicate that brainstem conduction in the auditory pathway was normal in both groups. There were no differences between the children who were treated conservatively and those who were treated with CAPD.

No differences between children treated conservatively and children treated with CAPD were observed for SSEP or BAEP. This suggests that the start of CAPD has no influence on the SSEP of young children suffering from CRF. We should, however, take into account the fact that the start of CAPD could have prevented a deterioration of SSEP and BAEP; this cannot be tested. The significantly increased interpeak latency N13-N20 in the younger age group indicates a delayed thalamocortical conduction in these children. There was no relationship between the abnormalities in SSEP and in BAEP in individual patients. This delayed conduction was not observed in the older age group. This may be due to a delayed myelination and/or synaptogenesis in the somatosensory pathway in young children with CRF. Of the sensory systems, the somatosensory is the most immature at birth. During growth and development there are variations in the rates of maturation of different aspects of neural pathways [16,34-36]. Pathological conditions occurring in the maturing human brain may cause retarded maturation of myelin sheath. CRF might be such a pathological condition.

BAEP and SSEP were not different between children treated conservatively and those treated with CAPD. Short latency evoked potentials do not measure cognition and motor control function. In the same patient group investigations on the motor and cognitive development showed significant differences between the conservatively treated children and the children in whom CAPD treatment was

established. The children who were treated with CAPD proved to be more at risk of impaired motor and cognitive development (Chapter 5, this dissertation).

In conclusion, the study of BAEP and SSEP offers no arguments for an early start of renal replacement therapy in young children with CRF, although it cannot be excluded that evoked potentials would have deteriorated as start of dialysis would be postponed. The somewhat better renal function in the group treated conservatively should be considered in the interpretation of the data.

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Chapter 7

EFFECTS OF A KIDNEY TRANSPLANTATION ON THE COGNITIVE FUNCTIONING OF CHILDREN

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Summary

Cognitive functioning of 20 children (aged 4-14 years) with end stage renal disease (ESRD) was assessed before and after a kidney transplantation using an intelligence test (WISC-R or WPPSI). Research questions were: 1. Do the test scores of children with ESRD obtained before transplantation deviate significantly from those of the norm group? 2. Do the test scores of children with ESRD increase significantly from pre- to post-transplantation? 3. After transplantation, do the test scores of children with ESRD deviate significantly from those of the norm group?

The pre-transplantation scores showed that the performance of children with ESRD was significantly poorer than that of the norm group on the verbal part of the WISC-R. After transplantation, significant progress was observed in their general cognitive functioning, which was primarily due to a significant improvement in performance on the verbal part of the test. However, kidney transplantation did not lead to complete recovery of cognitive functioning: after transplantation, the ESRD children still showed significantly lower scores for several of the tests (e.g., tasks involving concentration) than the children in the norm group.

7.1. Introduction

Children with end stage renal disease (ESRD) form a small proportion of the total population of children with chronic diseases. In the Netherlands, 20 to 25 children per year develop ESRD. After renal function has dropped to about 5%, it is necessary to start therapy to replace the function of the kidneys. Continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis are suitable treatment modalities until a kidney transplantation can be performed. Owing to the fact that the chances of survival of children with ESRD have increased, the question of quality of life is being raised more and more often. Studies on this topic have usually led to the same conclusion: chronic renal failure can form a serious threat to the cognitive and socio-emotional development of the child [1-7].

Since 1979, several reports have appeared in the literature about the effects of end stage renal disease on the cognitive functioning of children. The results were heterogeneous. In various studies, the performance of the children with ESRD who were being treated with dialysis did not differ significantly from that of healthy children [8,9]. On the basis of these results, the authors concluded that the toxic effects of uraemia on cognitive functioning can be kept to a minimum by performing haemodialysis regularly. However, other studies on children undergoing dialysis treatment have shown a detrimental effect on a number of cognitive skills. These children obtained significantly lower scores for total IQ, i.e., on both the verbal and performal tasks of an intelligence test (Wechsler intelligence scale for children-revised (WISC-R)). More specifically, this applied to their problem-solving capacity, arithmetic skills, memory, abstract reasoning, visual-motor coordination and concentration [10-13].

In addition, several factors were found to be related to possible differences in cognitive functioning between children with ESRD. The age at onset of ESRD appeared to influence the course of mental development of the child. Early onset (i.e., before the age of 1 year) of chronic renal failure was found to have a permanent and significant detrimental effect on cognitive performance [3,14-16]. The level of cognitive functioning also appeared to be related to whether or not the child was on dialysis (improvement in functioning after treatment was started) [17], the age at which dialysis became imperative (better functioning if treatment could be started later in life) [13], and the duration of

renal disease (more damaging effects with longer duration) [3]. Various medical parameters were also mentioned (positive correlation between performance on neuro-psychological tasks and blood pressure) [10]. Psychosocial factors which can have a negative influence on cognitive functioning include social isolation from children of the same age, depression, attitude of family members towards the child (including overprotection), decrease in feeling of general well-being, and an increase in school absenteeism. It is not uncommon for the parents and the medical team to concentrate (too) strongly on the physical condition of the child, with the risk that too little attention is paid to cognitive development.

Contrary to the research findings regarding the cognitive functioning of children with ESRD, the study results on the effects of a kidney transplantation on intellectual development are unequivocal [2,3,12]. A kidney transplantation was generally found to lead to significant improvement in cognitive functioning. This improvement was specific for a number of nonverbal tasks measured with the performal subtests of the WISC-R.

Up till now, no research has been performed in the Netherlands into the effects of a kidney transplantation on the cognitive functioning of children. In this study, the first inventory was made of the problems encountered in children with ESRD at a Dutch university hospital clinic. The aim was to perform a longitudinal study on the cognitive functioning of children before and after a kidney transplantation. It was considered to be of great clinical relevance not only to follow individual children during the treatment so that problems could be detected at an early stage and solved if necessary, but also to be able to attempt to prevent problems from occurring on the basis of the data obtained.

In this study, the three central questions were:

1. Do the intelligence test scores of children with ESRD obtained at the start of dialysis treatment deviate significantly from those of the norm group?
2. After a kidney transplantation, do the children obtain higher scores on an intelligence test than they did at the start of dialysis treatment?
3. Does a kidney transplantation compensate for a possible delay in development at the start of dialysis so that the functioning of the transplanted child becomes adequate for his/her age?

Table 7.1. Overview of the diagnoses of the patient population.

Diagnosis	No. of patients
Renal hypoplasia/dysplasia	5
Reflux uropathy/nephropathy	4
Congenital hydronephrosis	2
Nephrotic syndrome	4
Glomerulosclerosis	2
Glomerulonephritis	2
Alport's syndrome	1
Haemolytic uraemic syndrome	1
Nephronophtisis	1

7.2. Patients and methods

The study population comprised 20 children with ESRD (10 boys and 10 girls) who were being treated by CAPD or haemodialysis. They formed part of a total group of 29 children (17 boys and 12 girls) who, in the period 1979 to 1987, had undergone psycho-diagnostic investigation before and after renal transplantation. A prospective study design was used. The data obtained from nine children could not be used in the analyses. These children had not completed the tests, or there were no comparable test instruments available for use in their case. There were various reasons for this, such as the use of a non-verbal test for allochtonous or hearing impaired patients and noncompletion owing to fatigue or time factors. Any possible effects of selection were probably excluded in this way. At the start of the study, the age of the patients varied between 4.3 and 14.7 years. Table 7.1 shows an overview of the diagnoses of the study population.

Three children also had other disorders, which comprised hearing impairment, orthopaedic abnormalities, and hydrocephalus, respectively. The renal function of all the children was less than 5%, so they had to rely on CAPD (n=5) or haemodialysis (n=15) prior to transplantation.

To establish the intelligence quotient of each child, the Wechsler preschool and primary scale (WPPSI) [18] was used for the children younger than 6 years at the time of testing, whereas the Wechsler intelligence scale for children (revised version, WISC-R) [19] was used for the children older than 6 years at the time of testing. The two intelligence tests were designed with the same scale

construction, which enabled reliable comparison of the different IQ scores. Both tests could be used to obtain a total IQ score and two separate scores for the verbal and performal tasks (mean = 100, SD = 15 for each age group). On the basis of the raw score, it was also possible to calculate a standard score for each subtest (mean = 10, SD = 3) [20]. These standard scores could be used to calculated a score for seven combinations of tasks (each measuring a specific skill): concept formation, spatial ability, sequencing, perceptual organisation, concentration, verbal understanding, and visual-motor coordination (mean = 10, SD = 3) [21].

The intelligence tests were administered to the patients at two different times. The first measurement took place before or shortly after commencement of CAPD or haemodialysis treatment (mean 4 weeks before starting; range 7 months before to 13 weeks after). Particularly medical factors caused the variations in time. During the first measurement, the age of the children varied from 4.3 years to 14.7 years (mean 9.5 years).

The second measurement took place as soon as the child was sufficiently recuperated and in a stable medical condition after the kidney transplantation (mean 1.7 years after transplantation; range 5 to 47 months). During the second measurement, the age of the children varied from 8.2 to 17.6 years (mean 12.6 years). There was wide variation in the intervals between the first and second measurements, ranging from 8 months to 68 months (mean 3 years). The length of the interval depended on various factors, such as the amount of time that a patient had to wait for a donor kidney, the number of unsuccessful transplantations (e.g., because of rejection), and the duration of recovery after a successful transplantation.

7.3. Results

The data were analyzed using an univariate analysis of variance (SPSS-X programme MANOVA).

Cognitive performance at the start of haemodialysis treatment

The mean IQ scores of the children with ESRD during the first measurement were 97 (SD = 16.6) for the total test, 90 (SD = 16.4) for the verbal tasks and

Table 7.2. Average scores and standard deviations of children with ESRD before and after transplantation#

	Before transplantation		After transplantation		F-value of the difference
	X	SD	X	SD	
Total IQ	96.65	16.65	101.90	16.46	7.85*
Verbal IQ	90.35@	16.43	96.85	15.68	12.79**
general knowledge	7.85@@	3.13	8.70@	2.68	2.90
similarities	8.15@@	2.50	8.40@	3.03	0.31
arithmetic	9.55	3.50	11.15	3.28	6.81*
vocabulary	7.70	3.54	9.25	3.19	7.31*
comprehension	9.30	3.51	9.50	3.25	0.14
digit span	7.12@@	2.09	6.60@@	2.06	2.72
Performal IQ	103.70	15.89	108.35	17.71	2.51
picture completion	9.70	2.70	9.95	3.14	0.17
pict. arrangement	11.00	3.02	11.75	3.37	1.13
block design	11.65	3.53	12.25	2.63	1.50
object assembly	10.18	2.43	11.95	3.22	12.72**
codes	9.40	3.02	10.15	4.15	0.80
mazes	11.11	2.96	10.95	3.20	0.03
Comprehension	8.29@	2.89	9.05	2.93	1.79
Sequencing	8.33@	2.29	9.30	2.41	6.77*
Spatial ability	10.26	2.42	11.38	2.52	6.11*
Perceptual organisation	10.74	2.71	12.10	2.62	8.13*
Concentration	8.12@@	2.44	8.88@	2.11	6.52*
Verbal comprehension	8.07@	2.81	8.96	2.50	7.20*
Visual-motor coord.	10.18	2.32	11.45	2.81	8.61*

\# n=20, owing to incompletion of a number of subtests of the WPPSI, n=17 for the first measurement and for the difference scores for "digit span", "picture arrangement", "object assembly", and all the factors.
* significant difference before and after transplantation ($p<0.05$)
** significant difference before and after transplantation ($p<0.01$)
@ significant difference from the norm group ($p<0.05$)
@@ significant difference from the norm group ($p<0.01$)

104 (SD = 15.0) for the performal tasks. Comparison of these scores to the norm scores showed that the total IQ score did not deviate significantly, whereas the scores of the ESRD patients for the verbal part of the test were significantly lower than those of the norm group ($p<0.05$) (see Table 7.2).
This applied particularly to the following subtests of the verbal tasks: general knowledge, similarities (verbal reasoning), vocabulary, and digit span (short-term memory, concentration). The scores of the ESRD children for the perfor-

mal tasks were very similar to those of healthy children.

The scores obtained by the children with ESRD for the factors related to "concept formation", "sequencing", "concentration", and "verbal comprehension", were below average for their age. Nearly all of these factors consisted of verbal subtests, which contributed to this significant discrepancy.

Analyses were also performed on the data obtained at the first measurement to evaluate whether there were any significant differences between the cognitive performance of:

- children who developed renal failure before the age of 2 years (n=6) and children who developed ESRD after the age of 2 years (n=14);
- children who were already having dialysis treatment at the time of the first measurement (n=10) and children who had not yet started treatment (n=10);
- children in whom it had been imperative to start dialysis at a young age (<12.0 years) (n=14) and children who had started dialysis later in life (n=6);

There were no significant differences between the scores obtained at the first measurement for any of these three variables.

Differences between cognitive performance before and after transplantation

The scores for total IQ on the Wechsler scale increased significantly after kidney transplantation. This increase was mainly due to a significant increase in the scores for the verbal tasks (Table 7.2). Significant improvement in performance was observed for the verbal subtests "arithmetic" and "vocabulary" and for the performal subtest "object assembly". No significant differences were found for any of the other tasks between the first and second measurements.

After renal transplantation, there was a significant improvement in performance for the tasks which involved "sequencing", "spatial ability", "perceptual organisation", "concentration", "verbal comprehension", and "visual-motor coordination". However, there was no improvement for "concept formation".

Cognitive performance after the transplantation

After transplantation, the children obtained the following scores for the TIQ, VIQ, and PIQ: 102 (SD = 16.5), 97 (SD = 15.7), and 108 (SD = 17.7) and were therefore functioning at an average intelligence level. The retardation observed during the first measurement for the verbal IQ, the subtest "vocabulary" and the

factors "concept formation", "sequencing", and "verbal comprehension" were no longer visible after the transplantation. The transplanted children were therefore functioning adequately for their age on these (parts of the) tests, contrary to the situation prior to transplantation.

However, the children obtained significantly lower scores than those of the norm group for the subtests "similarities", "digit span", and the factor concentration even after transplantation (Table 7.2).

7.4. Discussion

The main objective of this study was to evaluate the effect of a kidney transplantation on the cognitive functioning of children with chronic renal insufficiency. For this purpose, comparisons were made between pretransplantation and posttransplantation scores. We also investigated whether the cognitive performance of the ESRD children before and after transplantation was significantly different from that of age-matched children in the norm group.

During the first measurement, the performance of the children with chronic renal insufficiency was significantly poorer than that of age-matched children in the norm group for the verbal parts of the test (VIQ) and for the tasks which involved concept formation, sequencing, and concentration. Poor performance on the verbal tasks was mainly due to scores which were significantly below average for a number of subtests of the WISC-R: "general knowledge", "similarities", "vocabulary", and "digit span". This verbal retardation can be explained to a large extent by repeated absenteeism from school; poor physical condition, fatigue, and little motivation, hindered the children from following a normal education programme. Another explanation was that if the children had emotional problems, these were very likely to influence verbal functioning [23]. It may be assumed that these children will have been carrying a heavy emotional burden just before starting dialysis treatment or during the early stages of treatment. It was in this period that we performed the first measurement.

When the scores of the first and second measurements were compared, it appeared that the general cognitive functioning of the children with ESRD improved significantly after renal transplantation. This finding is in agreement with other research results [2,3,12]. The increase in total IQ was mainly caused by a significant improvement in performance on the verbal parts of the tests,

particularly for the subtests "vocabulary" and "arithmetic". The strong increase in the scores for "general knowledge" was probably due to less absenteeism from school; during haemodialysis treatment, the children received individual tuition from the hospital school. After transplantation, they were able to resume their normal education programme. On the basis of the above-mentioned assumption that emotional problems can influence verbal functioning, the improvement in verbal skills can be explained by a decrease in the emotional burden after transplantation.

At the first measurement, there was no significant retardation in performal IQ, which was probably why there was no significant improvement in performance on these parts of the tests after transplantation. However, there was one exception: the subtest "object assembly". This subtest is more strongly affected by test-retest bias than any of the other subtests; familiarity with the puzzles which the child had to complete, will have increased his or her chances of being successful at a second measurement.

The findings related to the seven factors which each measured a specific skill, contributed little to the interpretation of the test results.

In this study, we also investigated whether the performance of the children at the first measurement was influenced by three independent variables: "age of onset of renal function disorder", "treatment already started during the first measurement", and "age at which dialysis was started". None of these variables had any major effect.

It is of importance to find out whether ESRD has a permanent and deleterious effect on a number of specific cognitive functions. As mentioned above, the study results showed that part of the retardation which the children displayed before transplantation, in comparison with the age-matched norm group, was neutralized after the transplantation. However, the scores of the ESRD children for the subtests "general knowledge", "similarities", "digit span", and the factor concentration, were significantly lower than average for their age. These findings indicate that children with ESRD are more likely to obtain significantly lower scores before and after transplantation for tasks which involve memory and concentration than the normal peer group.

7.5. Conclusions

Part of the retardation (compared to the normal peer group) encountered in the ESRD children at the start of dialysis could be caught up after transplantation. This was partly thanks to directed coaching (including schooling).

Further longitudinal research is strongly recommended to evaluate the cognitive development of children with ESRD, in which attention is paid to factors which might have a detrimental effect (e.g., social-emotional problems).

Moreover it is imperative to follow the course of development of children with chronic renal disease so that retardation can be detected at an early stage and possibly even prevented.

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Chapter 8

A RETROSPECTIVE STUDY ON DIALYSIS TREATMENT IN CHILDREN AND THE BURDEN FOR THE FAMILY:

-design of a family stress questionnaire-.

Chapter 8

A RETROSPECTIVE STUDY ON DIALYSIS TREATMENT IN CHILDREN AND THE BURDEN FOR THE FAMILY:

-design of a family stress questionnaire-.

8.1. A retrospective study

Introduction

This chapter is divided in two parts. The first one describes a retrospective study focused on the assessment of the burden placed on a family with a child on CAPD or HD. The underlying question was how parents experience the disease and the treatment of their child. Since no disease-specific methods were available two preliminary questionnaires were designed: one for parents with a child on CAPD treatment and one for parents with a child on HD treatment. The contents of these checklists were based on interviews and clinical experiences with parents of renal patients, as well as on literature on the impact of chronic diseases on the family (see Chapter 3.3). The preliminary results, conclusions, and a comparison between the two modes of therapy are reported in this first part.

The second part of this chapter presents a methodological account for the construction of the final questionnaire, which is designed for prospective investigations and for repeated measurements. The ultimate goal of the use of this method is a systematic monitoring of possible stressing factors during the dialysis treatment of a child in order to prevent so-called "parent-fatigue" or burn out [1,2].

Patients and methods

Table 8.1 presents data of patients and parents who participated in the retrospective study.

Table 8.1. Demographic data of 17 CAPD patients and 21 HD patients and their parents.

CAPD			HD		
patients					
n=17	boys	n=11	n=21	boys	n=14
	girls	n= 6		girls	n= 7
age:	<5 yrs old	n=13	age:	<5 yrs old	n= 0
	>5 yrs old	n= 4		>5 yrs old	n=21
mean age:	6.2 years		mean age:	15.4 years	
range:	1.2 - 11.1		range:	9.4 - 21.1	
parents					
n=32			n=39		
	15 pairs of parents			18 pairs of parents	
	1 father only				
	1 mother only			3 mothers only	
refused participation: n=2			refused participation n=1		

All parents of patients who were treated during the last 5 years with renal replacement therapy at the paediatric dialysis unit of the Nijmegen University Hospital were asked to enter the study. In the CAPD study two couples of parents refused participation and in the HD study one pair of parents. After written information and a short introductory talk with the parents in which the aim of the study was explained, they were asked to answer a questionnaire consisting of two parts: a checklist of 27 (CAPD) or 30 (HD) items related to the medical and psychological aspects of the treatment. The question "which of the following factors do you find difficult or cause a great burden" could be answered by yes or no; comments were encouraged (see Appendix 8.1 and 8.2). These yes/no questions were followed by 8 open questions relating to the subjective feelings of the parents towards CAPD or HD treatment of their child. Examples of these questions are: "what was the most difficult or most stressful experience", "what turned out better or worse than you expected", "who gave you support".

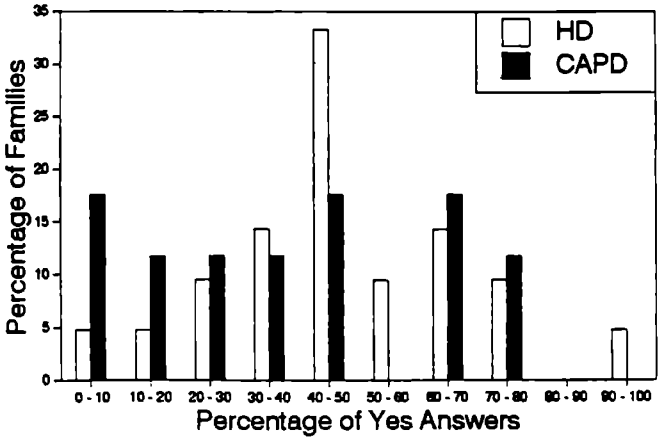

Figure 8.1. Frequency distribution of percentage of yes-answers on Questionnaires Family Stress HD- and CAPD treatment.

The final question encouraged the parents to give their own comments.

Statistical analysis: the difference between the mean percentages of the amount of experienced stress in CAPD-parents and HD-parents and between fathers and mothers in the total sample, as well as in the treatment groups separately, was tested by a Mann-Whitney U-test. Spearman correlation coefficients were calculated in order to assess the agreement between fathers and mothers, as well as to test the relation between the stress-score and a number of variables: sex and age of the patient, socio-economic status of the family, geographic distance home-hospital, episodes of peritonitis, duration of hospitalization (in days), other complications, and duration of the dialysis treatment (in months). The results were considered to be statistically significant if $p<0.05$.

Results

Figure 8.1 presents the frequency distribution of the percentage of yes-answers on the checklist, averaged over both parents of children on CAPD (black bars) or HD (white bars). This figure shows clearly that parents differ in the way in which they experience the treatment of their child as stressful. Table 8.2 shows the mean percentages of yes-answers on both checklists (CAPD/HD) of the mothers, the fathers, and of the total group. No significant differences were noticed between fathers and mothers in both groups.

Table 8.2. Mean percentages of yes-answers on two Questionnaires on CAPD treatment and HD treatment.

	fathers	mothers	total
CAPD	37.5	43.1	38.3
HD	50.6	43.2	45.7

Table 8.3. Questionnaire on CAPD treatment and Family Stress. The items are presented in order of percentage of yes-answers.

	Total %	Mother	Father
1. Admissions to hospital	69	69	69
2. Eating problems	59	69	50
3. Hygienic limitations	59	69	50
4. Diet or medication rules	56	63	50
5. Fear of peritonitis	56	56	56
6. Distance home-hospital	56	56	56
7. Family recreation	53	56	50
8. Uncertainty about transplantation	50	56	44
9. No prospect of transplantation	44	50	38
10. Changing rules, habits	44	44	44
11. Lack of social contacts parents	44	44	44
12. Lack of contact with peers	41	38	44
13. Late dialysis at 23:00	41	38	44
14. Frequency of changing the dialysate	38	38	38
15. Financial problems	38	38	38
16. Fixation on the disease	37	50	25
17. Drain into the abdomen	31	31	31
18. Household problems	31	38	25
19. Sustaining the treatment	28	50	19
20. Behavioural problems due to the treatment	25	31	19
21. Responsibility for the treatment	25	31	19
22. Baby-sitting arrangements	25	31	19
23. CAPD check-ups	22	25	19
24. Problems with the sibling	22	25	19
25. Absenteeism (work)	19	0	38
26. Talks with the doctor	19	25	13
27. Care of the exit site	9	19	0

The correlation between fathers and mothers was 0.80. It was hypothesised that the CAPD-parents would score higher on the list than the HD group, because of the considerable practical burden and the medical responsibility related to CAPD-treatment. There was, however, no significant difference between both

CAPD-treatment. There was, however, no significant difference between both groups. Also the mean stress-scores of CAPD-parents and HD-parents on the 18 items, that were non-specific for the treatment and therefore similar in both questionnaires, were not significantly different. No significant correlations were found, within each of the two treatment groups, between the amount of the experienced stress and sex, age of the patient, socio-economic status of the family, distance to and from the hospital, episodes of peritonitis, days of hospitalization, and the duration of the treatment. The last factor reached a borderline significance in the CAPD-group ($p=0.05$).

Table 8.3 shows the 27 items of the first part of the CAPD-questionnaire ordered on the total percentage of yes-answers. Not the practical aspects directly related to the execution of the treatment (e.g., changing the dialysate, check-ups) were experienced as a burden, but the - unexpected - complications like peritonitis and admissions at hospital. Together with a number of factors related to the medical responsibility (e.g., eating problems, diet, and medication) this can induce feelings of uncertainty resulting in an increase of psychological stress.

Table 8.4 presents the 30 items of the HD-questionnaire. Remarkable is that the psychological aspects, more than the medical aspects, were rated most frequently, especially 'concern about the future', developmental aspects (e.g., growth, school, and social contacts), and 'uncertainty about transplantation'.

A few striking differences between the responses of fathers and mothers on the items of the separate checklists were demonstrated: CAPD-fathers scored higher than mothers on only 3 items and HD-fathers on more than 18 items. This finding reveals that the mothers of the CAPD patients were burdened with the practical execution of the treatment, whereas the fathers of the HD patients were involved and stressed by the psychological, financial, and employment consequences.

A synopsis of the content of the responses on the 8 open questions of the CAPD-parents and HD-parents is outlined in Table 8.5. The answers showed a wide diversity, and many parents mentioned more than one aspect. Only responses that were given by more than 10% of the parents are included in Table 8.5.

Table 8.4. Questionnaire on HD treatment and Family stress. The items are presented in order of percentage of yes-answers.

	Total %	Mother	Father
1. Concern about the future	90	86	94
2. Feeling ill during dialysis	74	71	78
3. Growth problems	69	67	72
4. School absenteeism	67	67	67
5. Lack of social contacts peers	67	67	67
6. Fixation on the disease	67	67	67
7. Uncertainty transplantation time	64	62	67
8. Being connected to the dialyser	62	57	67
9. Admissions to hospital	59	48	72
10. Family recreation	59	52	67
11. Being dependant on the dialyser	56	62	50
12. Distance home-hospital	54	48	61
13. Administering diet and medication	54	48	61
14. Behavioural problems	51	52	50
15. Fistula/shunt operation	49	52	44
16. Problems with siblings	49	43	56
17. Sustaining the treatment	49	48	50
18. Eating/feeding problems	44	48	39
19. Immobility during dialysis	41	43	39
20. Responsibility diet and medication	33	33	33
21. Transport to and from hospital	31	38	22
22. Work absenteeism	31	19	44
23. Outpatients' clinic visits	28	19	39
24. Financial problems	28	29	28
25. Social isolation	28	24	33
26. Changing rules/habits	26	24	28
27. Talks with the doctor	18	24	11
28. Baby-sitting arrangements	15	14	17
29. Problems householding activities	10	10	11
30. Care of fistula/shunt	8	5	11

A few answers were very detailed, sometimes several pages long, which provided insight into the specific problems of each treatment modality and which contributed considerably to the clinical experience of the team members of the dialysis unit. The responses of the CAPD-parents indicated that those aspects of the treatment which made explicit demands on the feeling of responsibility were experienced as most stressful (e.g., eating problems, diet, and drug therapy including home treatment of peritonitis).

Table 8.5. Responses in percentages of parents on 8 open questions of the Questionnaires on CAPD and HD treatment and Family Stress.

	CAPD	HD
1. What was (is) most difficult for you?		
- Eating problems	22%	-
- Diet/Medicine/fluid limitations	19%	-
- Frequency of changing the dialysate	16%	-
- Peritonitis	13%	-
- Uncertainty/stress about transplantation	-	28%
- Lack of child's capacity to cope with medical problems	-	26%
- Lack of child's capacity to cope with psychological problems	-	21%
- Uncertainty	-	13%
2. What did you fear the most when the treatment started?		
- Changing the dialysate: carrying out the procedure	19%	-
- Uncertainty	19%	23%
- Child's capacity to cope	19%	46%
- Everything	13%	-
- Distance home - hospital	-	18%
3. What is/has been the most difficult/stressful for your child?		
- Admissions to hospital	22%	38%
- CAPD check-ups	19%	-
- Hygienic limitations (no baths/swimming)	19%	-
- Diet/medicine	16%	-
- Lack of contact with peers	13%	13%
- Medical complications due to transplantation	-	18%
- Psychological stress	-	18%
4. What turned out worse than you had expected?		
- Admissions to hospital	19%	-
- Peritonitis	19%	-
- Eating problems	13%	-
- Diet/medicine/fluid limitations	13%	-
- Complications	13%	13%
- Nothing	13%	8%
- Complications due to transplantation	-	21%
5. What turned out better than you expected?		
- The child's capacity to cope	19%	28%
- CAPD: carrying out the procedure	13%	-
- Support from hospital	-	18%
- Waiting time kidney	-	10%
6. What do you think of this mode of treatment?		
- Good	50%	18%
- Reasonable, but difficult if complications arise	16%	18%
- Stressful	13%	25%
7. Are you able to sustain the treatment?		
- Yes, without help	50%	26%
- Yes, with help	38%	13%
- Very difficult, no	6%	13%
- No choice	-	26%
8. Who gave you support?		
- Partner/family	66%	49%
- Friends/neighbours	16%	21%
- Hospital/G.P./district nurse	29%	38%

Some parents made a distinction between what was seen as a burden to themselves and what they perceived as stress for the child (hospitalizations, blood drawing). Six parents felt that their child was able to cope better with the CAPD-situation than expected. Half of the parents considered CAPD an acceptable form of treatment notwithstanding the stress involved. Fifty percent was able to continue CAPD treatment without support and 38% indicated to need support. The question "who gave you support" elicited in 82% of the cases that support came from family and friends, and in particular from the grandparents. The medical sector scored rather low with 29%. One parent commented "from nobody".

Table 8.5 reveals that the responses of the HD-parents were also very diverse, but the content differed considerably from the responses of the CAPD-parents. Most stressing for these parents was the uncertainty regarding several aspects of transplantation and the lack of the child's capacity to cope with the medical and psychological aspects of the treatment (54%). However, other parents (28%) commented that the child's stress tolerance turned out better than expected.

Discussion

The data gathered in this retrospective survey provide insight into the specific problems with which parents have to cope when their child is on dialysis treatment. The following tentative conclusions and recommendations can be made:

- parents in both treatment groups differ extremely in the way they experience the therapy of their child as stressful. Particularly in the HD-group, these differences can be attributed more to psychological than to medical factors, which has obviously to do with the age (mean 15.4 years) of the patients. Concern about the future and feelings of uncertainty regarding transplantation, as well as the child's inability to cope with the treatment, were frequently mentioned as stressing in this group. Feeding problems and medication rules, as well as the responsibility for the treatment, contribute considerably to the stress experienced by the CAPD-parents. If parents are unable to cope with eating problems serious disturbances in the parent-child relationship may result, leading to negative feelings in parents and child. The consequences for the functioning of the whole family, e.g., with regard to the siblings, recre-

ational activities and the need to change habits and rules, were mentioned very often and therefore the risk of fixation on the disease is considerable [3]. Attention needs to be paid to preventive measures by the paediatric renal team early in the course of the treatment.

- mothers and fathers in both treatment groups differ very little in the stress they experience. This is probably due to the fact that both parents are drawn into the treatment schedule right from the start and were advised to take turns. The mothers however were particularly stressed by problems related to the direct daily care, whereas the fathers were concerned about the influence of the disease on their job situation [4] (see Table 8.4).
- social support, especially by family and friends, proved to be a positive factor, which is in accordance with the literature on stress and coping [5-7].
- no significant correlation was found between the stress scores of the parents and a number of demographic and clinical parameters. Only the length of CAPD seemed to have some influence. Repeated measurements during the course of the treatment may offer more insight into the influence of the duration of the therapy on family stress.
- the hypothesis that the parents of CAPD patients would be more burdened than HD-parents, because of their medical responsibility and the time consuming daily care, was not confirmed. No significant differences were established between the two treatment groups.

These conclusions have to be interpreted with caution, since the two samples of patients and parents were different on a number of variables which affected the results.

- The data of the HD-group were more retrospective than those of the CAPD-group since some patients were transplanted a few years before, which might have distorted the results.
- Another factor, which was already mentioned, was the difference in age in the two samples: the mean age of the CAPD patients was 6.2 years and the mean age of the HD patients was 15.4 years. Parents of young children encounter other problems than parents of schoolchildren and adolescents who are more confronted with the long-term consequences of the disease. Therefore a reliable comparison between family stress related to CAPD- or HD treatment itself can not be made on these data.

- The HD-parents frequently reported their concern about transplantation, which was not the case in the CAPD-group. Because the majority of the CAPD patients was under 5 years of age and transplantation was possible at a minimum weight of 12 kg (see Chapter 2), this topic was less relevant for these parents.

Notwithstanding the different samples, these results give insight into the specific problems of each treatment modality.

In conclusion it can be stated that prospective research, with repeated evaluations of the same questionnaires with a treatment specific part, is needed in order to follow and improve patient care with more efficient and goal oriented interventions.

8.2. Design of the revised version of the Family Stress Questionnaire

In order to assess family stress due to dialysis treatment in a child, two separate questionnaires were developed: one focusing on CAPD and one on HD. The items were based on the literature on this topic [1-4,8,9] and on clinical interviews with all parents by the psychologist and social worker who were involved in the psychosocial care of paediatric renal patients in the University Hospital Nijmegen. The CAPD-scale consisted of a checklist of 27 yes/no (dichotomized) questions and 8 open questions. The HD-scale contained 30 dichotomized items, partly different from the CAPD-list, and the same 8 open questions (see Appendix 8.1 and 8.2). By means of a retrospective investigation in CAPD-parents as well as HD-parents the construction of a treatment specific questionnaire was pursued, applicable in the two dialysis groups and suitable for repeated measurements during the course of the treatment.

In order to compare modalities of dialysis treatment in families with a renal patient, an instrument designed specifically for these families is necessary, since the practical and psychosocial stress is quite different from those with other diseases or with other problems. The advantage of disease specific methods is that the responsiveness to changes due to e.g., alterations in modes of therapy is higher than that of global measures. They also are better accepted by patients who perceive them to be relevant to their particular problems [10,11]. Furthermore the questionnaire should meet criteria as brevity, ease of understanding by

parents, simplicity of administration, and amenability to statistical analysis [10].

The initial versions, those used in the study described in the first part of this chapter are given in Appendix 8.1 and 8.2; the revised versions are presented in Appendix 8.3 and 8.4.

Scale construction

Thirty-two fathers and mothers of 17 CAPD patients and 39 fathers and mothers of 21 HD patients filled in the questionnaires (see par. 8.1).

Missing responses - only 3.7% in the CAPD-group and 2.6% in the HD group - were found in nearly all items and in fathers and mothers as well. Relatively many missings in both scales were found in the items "asking days off from work" and "problems with siblings" (Appendix 8.1 and 8.2). Probably parents did not answer these questions because they were unemployed (the majority of the mothers) or they did not have other children. This finding resulted in an adapted instruction in which "no" has to be answered if a question does not apply.

The internal consistency (homogeneity) of both scales was analyzed by the SPSSX program RELIABILITY. Cronbach's α [12] of the CAPD scale was 0.87, which means that the internal consistency was high. The item-total correlations of 24 items were moderate to high-positive (= very good). The items 4, 11, and 19 (Appendix 8.1) were respectively negative and <0.10. After having omitted these items the α increased to 0.89. The internal consistency of the HD scale was also very good (α=0.89). The items 2, 20, and 22 (Appendix 8.2) showed a low (<0.10) item-total correlation. After deletion of these items α increased to 0.90.

The responses on the 8 open questions were rated by two psychologists, independent from each other, and, after interpreting the individual answers, classified into a number of question specific categories (see Table 8.5). Those answers which met a frequency >10% (more than 10% of the parents mentioned this topic) as well as an inter-rater agreement of 1.00, were added to the revised version of the checklist.

The item-selection can be accounted for as follows (for item numbers see Appendix 8.1 and 8.2): cancelled due to low (<0.10) item-total correlation:

CAPD

4: care of the exit site

15: no prospect of transplantation (does not longer apply since transplantation is also possible in younger children)

19: baby sitting arrangements

HD

2: care of fistula or shunt

20: baby sitting arrangements

Maintained despite the low item-total correlation, but because of the high value in the other scale:

CAPD

11: outpatient's clinic visits and check-ups: see item 14 revised questionnaire

HD

22: financial problems: see item 24 revised questionnaire

Added to revised CAPD-questionnaire because of high value in HD-scale or responses on open questions (Appendix 8.3 and 8.4):

CAPD/HD

10: responsibility diet and medication

30: problems growth retardation

31: school absenteeism

32: concern about the future

Added to final CAPD/HD questionnaire because of frequency (>10%) in open questions:

CAPD/HD

9: fluid restriction

18: to be available for transplantation

19: waiting period transplantation

20: uncertainty result transplantation

33: physical handicaps/limitations (fatigue)

34: coming to terms/acceptance

35: counselling and education

36: lack of information

37: unexpected medical complications

After item-analysis and the extension with new items based on responses on the open questions a revised questionnaire (see Appendix 8.3 and 8.4 and Chapter 9, Table 9.2) was devised with:

- unique items [1-6] for either the CAPD/CCPD-parents or the HD-parents
- common items to compare family stress in both treatment groups [7-37].

The internal consistency of this revised checklist (see Chapter 9) was high (Cronbach's α=0.87).

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Appendix 8.1. Questionnaire on CAPD treatment and Family stress

Child's name: .....

I. The statements below are associated with .....'s CAPD treatment. Which of them have you found difficult, or a burden?

	Yes	No	Remarks
1. The regularity of changing the dialysate (4 times per day, every day)			
2. Late dialysis at 11 or 12 pm			
3. The catheter in ..... 's abdomen			
4. Taking care of the exit site			
5. The diet/administering medication			
6. Possible eating disturbances related to the treatment			
7. Limitations related to hygiene (no baths, no swimming)			
8. Possible behavioural problems associated with the treatment			
9. The responsibility you have for carrying out the treatment at home			
10. Anxiety/uncertainty about possible peritonitis			
11. The regular visits to hospital and check-ups			
12. The distance from home to the hospital			
13. The regular admissions to hospital			
14. Consultations with the doctor about .....'s condition			
15. No prospect of there being a transplant in the near future, because your child is still too young			
16. Uncertainty about when the transplant will take place			
17. Possible problems with brothers and sisters			
18. Possible problems with daily household activities			
19. Having to arrange a baby-sitter for the other children if you have to go to hospital			
20. Often having to ask for time off work			

	Yes	No	Remarks
21. Possible financial problems resulting from the illness and treatment of			
22. Having to keep up the treatment			
23. Spending your family's leisure time (e.g. going on holiday, going out for the evening)			
24. Always being occupied with or talking about .....'s illness and/or treatment			
25. Rules and habits which had to be changed in your family because of .....'s treatment			
26. Missing contact with friends of the same age as			
27. Becoming isolated/missing contact with your family and friends			

II.

1.	What has been the most difficult or the heaviest burden in ..... 's treatment up to now?
2.	What did you dread the most when the treatment was started?
3.	What has turned out worse than you expected?
4.	What has turned out better than you expected?
5.	What do you think about the treatment now?
6.	Are you able to keep up the treatment? With help - Without help -
7.	Who gives you a great deal of support?
8.	In your opinion, what is the most difficult or the greatest burden for .....?
9.	Do you wish to make any further comments?

Appendix 8.2. Questionnaire on Haemodialysis treatment and Family stress

Child's name: .....

I. The statements below are associated with .....'s haemodialysis treatment. Which of them have you found difficult, or a burden?

	Yes	No	Remarks
1. Creating the fistula/shunt in ..... 's arm			
2. Taking care of the fistula/shunt			
3. The distance from home to the hospital			
4. Travelling (alone) in the taxi to and from haemodialysis			
5. Being connected up to the machine (vena puncture)			
6. Having to be connected to the machine and being dependent on it			
7. Having to lie still for several hours			
8. The idea that ..... has to keep up the treatment			
9. The diet/administering medication			
10. The responsibility of having to administer the medication and stick to the strict diet			
11. Possible eating problems associated with the treatment			
12. If ..... does not feel well on dialysis day (e.g., headaches, nausea) or after treatment			
13. Possible behavioural problems associated with the treatment			
14. The regular visits to hospital and check-ups			
15. The regular admissions to the hospital			
16. Consultations with the doctor about .....'s condition			
17. Uncertainty about when the transplant will take place			
18. Possible problems with brothers and sisters			
19. Possible problems with daily household activities			
20. Having to arrange a baby-sitter for the other children if you have to go to the hospital			

	Yes	No	Remarks
21. Often having to ask for time off work			
22. Possible financial problems resulting from the illness and treatment of			
23. Spending your family's leisure time (e.g. going on holiday, going out for the evening)			
24. Always being occupied with or talking about .....'s illness and/or treatment			
25. Rules and habits which had to be changed in your family because of .....'s treatment			
26. Missing contact with friends of the same age as			
27. Becoming isolated/missing contact with your family and friends			

II.

1.	What has been the most difficult or the heaviest burden in ..... 's treatment up to now?
2.	What did you dread the most when the treatment was started?
3.	What has turned out worse than you expected?
4.	What has turned out better than you expected?
5.	What do you think about the treatment now?
6.	Are you able to keep up the treatment? With help - Without help -
7.	Who gives you a great deal of support?
8.	In your opinion, what is the most difficult or the greatest burden for .....?
9.	Do you wish to make any further comments?

Appendix 8.3. Questionnaire on CAPD treatment and Family stress
(revised version)

Date: .....

Concerning: mother/father of: .....

This questionnaire comprises a number of issues associated with the CAPD treatment of ..... Please indicate which of these issues you find difficult, or a burden for yourself or your child. The questions should be answered with yes or no. Give only one answer per question. If an issue is sometimes stressing and sometimes not, choose the answer which describes the situation which occurs most frequently. It is very important that you answer all of the questions with yes or no. If an issue does not apply to you or your child, answer with no.

	Yes	No	Remarks
1. The regularity of changing the dialysate (4 times per day, every day)			
2. Late dialysis at 11 or 12 pm			
3. The catheter in .....'s abdomen			
4. Limitations related to hygiene (no baths, no swimming)			
5. Carrying the responsibility for the dialysis, being afraid of doing it wrong			
6. Anxiety/uncertainty about possible peritonitis			
6a. If applicable, administering growth hormone			
7. Possible eating disorders related to the treatment			
8. The diet/administering medication			
9. Limiting the quantity of fluid ..... may drink			
10. The responsibility of administering the medication and keeping to the strict diet			
11. Distance from home to the hospital			
12. Keeping up the treatment			
13. Possible behavioural problems associated with the treatment			
14. The (regular) hospital visits and check-ups			
15. The regular admissions to hospital			

	Yes	No	Remarks
16. Consultations with the doctor about .....'s condition			
17. Uncertainty about when the transplant will take place			
18. Always having to make sure that you can be reached because of the transplant			
19. Being on the waiting-list for a transplant for too long			
20. Uncertainty about the outcome of the transplant			
21. Possible problems with .....'s brothers and sisters			
22. Possible problems with daily household activities			
23. Often having to ask for time off work			
24. Possible financial problems resulting from the illness and treatment of			
25. Spending your family's leisure time (e.g. going on holiday, going out for the evening)			
26. Always being occupied with or talking about ..... 's illness and/or treatment			
27. Rules and habits which had to be changed in your family because of .....'s treatment			
28. Becoming isolated/missing contact with your family and friends			
29. Missing contact with friends of the same age as			
30. .....'s possible growth problems			
31. .....'s regular absenteeism from school			
32. Anxiety about .....'s future in relation to:			
a. medical condition			
b. education			
c. social contacts with boy/girl friends			
d. choice of career			
33. .....'s tiredness of physical limitations			

	Yes	No	Remarks
34. .....'s coping and acceptation of the treatment			
35. Counselling and taking care of			
36. Lack of adequate information and counselling about the illness and treatment			
37. Extra interventions, unexpected admissions to hospital and other treatment complications			

Appendix 8.4. Questionnaire on Haemodialysis treatment and Family stress
(revised version)

Date: .....

Concerning: mother/father of: .....

This questionnaire comprises a number of issues associated with the CAPD treatment of ..... Please indicate which of these issues you find difficult, or a burden for yourself or your child. The questions should be answered with yes or no. Give only one answer per question. If an issue is sometimes a burden and sometimes not, choose the answer which describes the situation which occurs most frequently. It is very important that you answer all of the questions with yes or no. If an issue does not apply to you or your child, answer with no.

	Yes	No	Remarks
1. Creating the fistula/shunt in .....'s arm			
2. If ..... does not feel well on dialysis day (e.g. head-aches, nausea) or after treatment			
3. Travelling alone in the taxi to and from haemodialysis			
4. Being connected up to the machine (vena puncture)			
5. Having to be connected to the machine and being dependent on it			
6. Having to lie still for several hours			
6a. If applicable, administering growth hormone			
7. Possible eating disorders related to the treatment			
8. The diet/administering medication			
9. Limiting the quantity of fluid ..... may drink			
10. The responsibility of administering the medication and keeping to the strict diet			
11. Distance from home to hospital			
12. Keeping up the treatment			
13. Possible behavioural problems associated with the treatment			
14. The (regular) hospital visits and check-ups			
15. The regular admissions to hospital			
16. Consultations with the doctor about .....'s condition			

	Yes	No	Remarks
17. Uncertainty about when the transplant will take place			
18. Always having to make sure that you can be reached because of the transplant			
19. Being on the waiting-list for a transplant for too long			
20. Uncertainty about the outcome of the transplant			
21. Possible problems with .....'s brothers and sisters			
22. Possible problems with daily household activities			
23. Often having to ask for time off work			
24. Possible financial problems resulting from the illness and treatment of			
25. Spending your family's leisure time (e.g. going on holiday, going out for the evening)			
26. Always being occupied with or talking about ..... 's illness and/or treatment			
27. Rules and habits which had to be changed in your family because of .....'s treatment			
28. Becoming isolated/missing contact with your family and friends			
29. Missing contact with friends of the same age as			
30. .....'s possible growth problems			
31. .....'s regular absenteeism from school			
32. Anxiety about .....'s future in relation to:			
a. medical condition			
b. education			
c. social contacts with boy/girl friends			
d. choice of career			
33. .....'s tiredness of physical limitations			
34. .....'s coping and acceptation of the treatment			
35. Counselling and taking care of			

	Yes	No	Remarks
36. Lack of adequate information and counselling about the illness and treatment			
37. Extra interventions, unexpected admissions to hospital and other treatment complications			

Chapter 9

PERITONEAL DIALYSIS TREATMENT IN CHILDREN AND PARENTAL STRESS

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Summary

The burden placed on the parents of a child in dialysis treatment can induce negative effects on the medical treatment and on the psychological development of the child. To identify which families are at risk, both parents of 14 out of 16 eligible patients in continuous ambulatory peritoneal dialysis (CAPD) answered an extensive questionnaire three times during one year. Large differences were found between the families with regard to the amount of stress experienced. Parents of older children (>5 years) (and particular parents of children with a failed transplantation) experienced significantly more stress. The nature of the stress was determined more by the psychological aspects than by the medical aspects of the treatment. Concern about the future contributed most to the stress experienced. Therefore, emotional support as well as practical help for families at risk is recommended.

Keywords: Chronic renal disease - Children - Peritoneal dialysis - Family stress.

9.1. Introduction

Children with end-stage renal disease (ESRD) can be treated by haemodialysis (HD) or by continuous ambulatory peritoneal dialysis (CAPD) and continuous cyclic peritoneal dialysis (CCPD) until a kidney is available for transplantation. HD usually takes place in hospital, whereas CAPD and CCPD are carried out at home by the parents. Both methods have advantages and disadvantages, and it may be assumed that medical factors alone are not decisive for successful treatment.

Children with a chronic disease requiring intensive medical treatment such as dialysis, are more vulnerable than adults to the negative impact of the disease, because a child is still developing and is strongly dependent on his family, both physically and psychologically [1]. Parental coping behaviour is of great influence, not only on the course of the medical treatment, but also on the psychological development of the child [2].

Previous reports on hospital versus home HD and on CAPD treatment have shown that the burden of responsibility for the physical well-being of their child is very stressful for the parents. A possible consequence is an ambivalent attitude: being both doctor and parent. In this respect "parent-fatigue" is a well-known phenomenon [3-7]. Problems, such as concern about growth, medical prognosis, other siblings at home, finances, and risk of marital breakdown are reported frequently [8-10].

In order to obtain a balanced view of the psychological impact of CAPD-treatment, we have performed a study on the specific burden placed on the family, i.e., on the parents of a CAPD patient. The initial purpose of the present study was to determine the amount of stress that parents experienced as a result of their child's treatment and if this stress increased or decreased during the course of treatment. Second, we were interested in the differences between fathers and mothers, and the influence of factors such as age of the patient, failed transplantation, duration of the illness and dialysis treatment, patients' school attendance and socio-economic class, on the amount of stress. The third issue was the specific nature of stress due to the treatment (what is stressful and what is not?).

In order to evaluate and to measure the parental stress due to CAPD treatment, it was necessary to develop a specific method for investigation. This

method had to be appropriate for prospective goals and for repeated measurements in order to monitor the process of coming to terms with the treatment, management of the disease, and to highlight potential burn out. A questionnaire based on the material of a previous retrospective study [7] was therefore designed.

9.2. Patients and methods

Patients

Both parents (n=28) of 14 of the 19 CAPD patients in the paediatric dialysis unit at the Nijmegen University Hospital were included in the study. Two sets of parents refused cooperation, and 3 couples were unable to cooperate: 2 couples were too stressed because of major complications due to encephalitis following transplantation in 1 child and a long-term period of artificial ventilation in the other. In 1 family, cooperation was not possible because of serious psychological problems unrelated to the treatment (child abuse). No single-parent families participated in the study, which is not normal for the Dutch population in general, but is probably related to the fact that the majority of the families were living in rural, non-urbanized areas. At the start of the study, 4 out of 14 patients had undergone a failed transplantation; none was less than 5 years of age. The mean age of the patients was 5.6 years (range 0.8-14.0 years). Mean duration of the underlying illness was 4.5 years (range 0.8-13.8 years). Mean duration of CAPD treatment was computed from the onset of CAPD until the first measurement: mean 1.8 years (range 0.2-7.0 years). During the study period, 1 child was successfully transplanted and 1 child was transferred from CAPD to conservative treatment.

Methods

After receiving written information and an introduction explaining the aim of the study, each parent was asked to answer a standardized questionnaire three times during 1 year. Parents of patients who changed from dialysis to conservative management, or who underwent a kidney transplant were followed-up by one measurement after 4 months. The items of the questionnaire were based on findings in the literature [1,3-5,8-10] and on extensive previous interviews,

which were held as part of the normal routine at the start of dialysis treatment with the parents of patients with renal disorders. By means of "yes" and "no" answers to the question: "which of the following aspects of the dialysis treatment of your child do you find difficult or causes you great burden?" the parents could report what was stressful during the preceding period. The method was based on the results and item analysis of a previous, retrospective study on 32 parents of 17 children [7]. Short descriptions of the items are given in Table 9.2. The first item "concern about the future", was subdivided into "concern of medical, social, educational, or occupational nature".

The questionnaire consisted of 37 items. The internal consistency (homogeneity) of the checklist was high. (Cronbach's $\alpha = 0.87$) [11].

Statistical analyses

The amount of family stress experienced by a particular family was expressed as the total percentage of yes answers on the questionnaires at all three assessments. A mean score was computed for the total study population, for the fathers and the mothers separately, and for the successive assessments.

Wilcoxon matched-pairs signed ranks test was used to test differences in amount of stress between the successive assessments and between fathers and mothers. Spearman correlation coefficients were calculated in order to assess the agreement between fathers and mothers. Mann-Whitney U-tests were used to test differences in amount of stress due to the following variables: transplantation (not versus failed), age (<5 years versus >5 years), duration of illness (<5 years versus >5 years), duration of CAPD treatment (<1 year versus >1 year), socio-economic class (working class versus middle/upper class), and school attendance of the patient (yes versus no). The results were considered to be statistically significant if $p<0.05$. A conservative level of significance ($p<0.01$) is elected for testing the differences at the item level concerning the nature of stress between parents with children <5 yrs and >5 yrs by Mann-Whitney U-test as well.

Table 9.1. The amount of stress averaged over 3 measurements during 1 year, influenced by 6 factors.

	n	Amount of stress	Mann-Whitney U	p - value
Transplantation (Tx)			4.0	0.0003
without	10	27.4		
failed	4	45.5		
Age			7.0	0.026
<5 years	7	23.2 [1]		
>5 years	7	42.1		
(without Tx)	(3)	(37.5)[1][2]		
(failed Tx)	(4)	(45.5)[2]		
Duration Illness			7.0	0.029
<5 years	8	24.8		
>5 years	6	42.9		
Duration CAPD treatment				ns
<1 year	5	28.2		
>1 year	9	35.0		
Socio-economic status				ns
working	7	36.4		
middle/upper	6[3]	22.5		
School attendance				ns
yes	11	33.6		
no	3	28.2		

[1] Significantly different (U=2, n=7,3, p=0.033).
[2] Not significantly different (U=3, n=3,4, p=0.20).
[3] One missing.

9.3. Results

Amount of stress experienced

Considerable differences in the stress experienced were found between individual families, ranging from 5.4% to 67.6%. The average amount of stress over the three assessments for the total research population was 32.6% (31.7-33.3%). In order to monitor the amount of stress during the research period of 1 year, comparisons were made between the scores of assessment 1 with assessment 2 and 3, respectively. No significant differences were found between these assessments: the amount of stress neither increased nor decreased essentially

during the period studied.

No significant differences were found in the amount of stress experienced between fathers and mothers on any of the three measurements; the mean of the amount of stress experienced over these assessments was 33.8% for mothers and 31.8% for fathers; the mean Spearman correlation coefficient was 0.72 ($p<0.002$) and therefore the following analyses were executed on so-called family scores, i.e., the average of the two parents.

It was hypothesized that according to the literature and clinical experience, a number of variables could influence the amount of stress experienced. Table 9.1 presents the results and obviously only age (>5 years versus >5 years), and related to age, a failed transplantation and duration of the illness (>5 years) show significant differences in amount of stress.

Nature of the stress experienced

Table 9.2 presents the frequency distribution of the items in the questionnaire, ordered according to the percentage of yes answers. The first column shows the total percentage, averaged for fathers and mothers together, over three assessments, since no significant differences were found between fathers and mothers and between the three assessments with regard to the overall amount of stress. At item level, however, comparisons between fathers and mothers concerning the nature of the stress revealed that mothers felt a significantly greater burden than fathers due to the behavioural problems of their child ($p=0.028$). The items "requesting time off work" and "drain in the abdomen" were significantly more stressful for the fathers ($p=0.008$ and $p=0.043$, respectively). The majority of both parents were stressed by "concern about the future", particularly with regard to the medical and educational prognosis.

The most striking differences at item level with regard to the nature of the stress were found between parents of an older child (>5 years) and parents of a younger child (<5 years) (Table 9.2). A remarkable finding was that 5 out of the 6 significant items were concerned with the psychological (particularly with uncertainty about transplantation) and not with the medical aspects of treatment, although both categories were equally represented in the total scale.

Table 9.2. Frequency distribution of the Questionnaire Family Stress CAPD Treatment for the total group, and split up between parents with childeren <5 years and >5 years. P-values for the differences between these two subgroups are given. The items are rank ordered according to the percentage of yes answers of the total group.

Items	Total group n=14	<5 years n=7	>5 years n=7	P values
Concern about the future*	73 1	50.0	92.9	
Unexpected medical complications	66.1	48 8	83 3	
Distance home-hospital	65.5	61 9	69 0	
Family recreation	60.1	45.2	75 0	
Eating/feeding problems	54 8	60.7	48 8	
Admissions to hospital	54 2	46 4	61 9	
Uncertainty result transplantation	51.2	9 5	92 9	0 001
Hygienic limitations	47.6	48.8	46.4	
Problems growth retardation	45 8	16 7	75 0	0 004
Physical handicaps/limitations	45.2	26 2	64.3	
Uncertainty transplantation time	44.0	17.9	70.2	
Fear of peritonitis	41 7	26.2	57.1	
Visits outpatient clinic	41 7	47 6	35 7	
Late dialysis at 23 00	37.8	41.7	33.3	
Financial problems	37.5	26.2	48 8	
School absenteeism	34.5	7.1	61.9	0.002
Waiting period transplantation	33.9	0.0	67.9	0 003
To be available for transplantation	32.7	0 0	65.5	0.003
Social isolation	30.4	26.2	34.5	
Frequency of changing the dialysate	28.2	26.2	30.6	
Behavioural problems	28.0	25.5	31.0	
Fixation on the disease	25.6	16.7	34.5	
Work absenteeism	22.6	25.0	20.2	
Changing rules, habits	21.4	20.2	22 6	
Problems with siblings	20.2	14.3	26.2	
Sustaining the treatment	19.0	8.3	29.8	
Lack of social contacts peers	17.9	11.9	23 8	
Problems household activities	17.9	23.8	11.9	
Coming to terms, acceptance	16.7	11.9	21.4	
Administering diet and medication	16.1	16.7	15.5	
Counselling and education	16.1	7.1	25.0	
Fluid restriction	13.7	0.0	27.4	
Drain into the abdomen	11.3	11.9	10.7	
Talks with the doctor	7.1	0.0	14.3	
Lack of information	7.1	0.0	14.3	
Responsibility for the treatment	7.1	9.5	4.8	
Responsibility diet and medication	4.2	2.4	6.0	
* Concern about the future				
- medical	66.7	41.7	88.1	
- educational	42.9	16 7	65.5	
- social	25.6	20.8	29.8	
- occupational	24.4	0.0	45.2	0 014

Discussion

Parents of dialysis patients differed greatly in the degree to which they experienced their child's treatment as a burden. A previous study of parents of CAPD-patients [7] produced similar findings, but the process of dealing with the treatment over a longer period was not investigated. The results of the present study showed that the amount of stress did not increase or decrease over a 1-year period of treatment, either at an individual level or in the total group. Nor did the duration of treatment (prior to the period studied) influence the amount of stress experienced. It might have been more convincing if the questionnaire had been administered from the start of the dialysis treatment. Nevertheless, it may be concluded that parental burn-out is not simply determined by being obliged to sustain the treatment, which is frequently assumed in clinical practice. Maybe the process of adaptation, the practical routine of dialysis treatment, and the personal control and involvement [10] offer a kind of structure and clarity in the daily life of a family with a chronically ill child [1,9,12,13].

The effect of the duration of the illness must be interpreted with caution, because all but three children had renal disease from the time of birth. Consequently, age and duration of illness are highly interrelated variables.

No differences were found in the amount of stress between fathers and mothers, except for some specific items; this is probably due to the fact that at the start of renal replacement therapy, both fathers and mothers were equally involved and instructed in the management of the treatment.

The parents of the older children (>5 years) experienced more stress than the parents of the younger ones, which seems to be the main explanation for the great variety in parental stress. It was hypothesized that families of younger renal patients were, in particular, more at risk of burn-out [5,7] because of the practical burden, the higher incidence of medical complications and the specific vulnerability of young children to developmental delay and emotional disorders [5,13,14]. With older children, however, parents are confronted with problems at school (absenteeism), growth retardation, and concern about medical, educational, and occupational perspectives, all of which are considered to be obstacles, impeding the normal development of the child, because of the risk of feelings of dependency and lack of self esteem and autonomy, especially during

adolescence. This finding of higher stress in the parents of older children is in accord with the study of Reynolds et al. [9] in which over half of the children were of secondary school age.

Another major factor contributing to the amount of experienced stress in parents is failed transplantation. In our population however this factor was related with age, since all four children who had a failed transplantation were older than 5 years. Nevertheless, the parents of children not yet transplanted in both age groups were able to deal with the disease and treatment with the comforting cognition that all problems and stress would be solved by a successful transplantation. Although they know that transplantation can fail and that many medical complications can arise, selective perception and even distortion of reality are part of adequate coping behaviour which was oriented towards a healthy future and a positive prospect for their child [12,15,16]. After a failed transplantation, however, the shattered positive expectations, the re-initiation of the straining treatment and the confrontation with a probably longer waiting time caused a higher level of stress in the family.

Socio-economic class, which can influence the cognitive and medical management of the treatment, did not appear to contribute essentially to the amount of stress experienced. This finding is in accordance with the outcome of other studies [7,10]. The expectation that the patients' day nursery or school attendance could reduce the parents' practical burden of everyday life was not confirmed, since no significant effect was found. These findings have to be interpreted with care, however, since the sample size was rather small.

In the present study, the nature of the stress experienced differed partly from that in previous studies [5,7,8]. The results of these studies revealed a strong fixation on the medical and practical aspects of treatment (complications, household activities, feeding problems, frequency of changing the dialysate). In contrast, the present study made it clear that parents were strained mainly by psychological aspects. In particular, uncertainty and lack of confidence in the future were prominent contributing factors to the stress experienced.

An explanation for the shift from medical to psychological aspects of treatment may be found in the fact that, since CAPD-treatment is widely accepted and has improved technically, and since experience with this treatment modality has increased, the medical staff places less emphasis on strict rules

concerning hygiene and practical management. As a result, parents are less focused on their medical responsibility and are more open-minded to the psychosocial implications of their childs' disease.

From a psychological point of view, it has to be considered positive that parental stress is not only determined by medical and practical care, which includes the risk of fixation and overprotection resulting in impairment of the childs' development [13]. Concern about the psychological impact implies coming to terms with, as well as accepting, the disease and considering the consequences for the future [1,12,17,18].

In conclusion, this study revealed that parents of children of school age and parents of children who have undergone a failed transplantation are particularly at risk. Chronic illness in a child challenges the family at three levels: cognitive, emotional, and the behavioural [1]. Medical and psychosocial care in a paediatric dialysis unit is usually oriented towards practical and behavioural support. Particularly for the above-mentioned families at risk, not only should adequate and repeated information be available, but also structural emotional support in order to help them to deal with the undermining and stressing feelings of uncertainty.

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Chapter 10

GENERAL DISCUSSION

10.1. Cognitive development

The first part of this thesis describes research which focused on the cognitive development of children with chronic renal disease. The main topics of interest were the neurological, motor, and cognitive development of young children (<5 years) with serious renal function disorders (<20%). The hypothesis that starting renal replacement therapy at an early stage would improve a child's developmental chances, could not be confirmed on the basis of neurological (Chapter 6) or developmental psychological parameters (Chapter 5). Nevertheless longitudinal research revealed several important findings. It was expected that especially the children on conservative treatment with poor (or rapidly deteriorating) renal function whose motor and cognitive development were at risk. Contrary to this assumption, however, the dialysis patients scored more than one standard deviation below the average score of the norm group. Moreover the longitudinal design of the study made it possible to demonstrate that the effect of starting dialysis treatment was only temporary and did not lead to any long-term improvement.

These results seem to contradict those reported in an important study by Geary et al. on the same subject and with a similar number of patients [1]. However, it was not possible to make any direct comparisons between the results, because the methods used by Geary et al. differed considerably from ours, in particular regarding the test method (Revised Yale Developmental Schedule), a less differentiated method, and the calculation of the level of the renal function (in Geary et al. the mean GFR was 31 ± 29, without the usual correction for age).

The explanation of the striking discrepancy between the patients on conservative treatment and those on dialysis, should not only be sought in the positive effects of the remaining renal function on a child's cognitive capacity (as described in Chapters 4 and 5), but also in other, as yet undetermined, factors as well [5,6].

So-called uraemic toxins are a group of poorly-defined substances, which

have not all been fully identified. It is unlikely that a single substance can be incriminated. Over one hundred solutes have been distinguished that accumulate in higher than normal levels in the body fluids of patients with advanced renal failure [7]. The best-known of these is urea. Many investigators have shown that urea has little toxicity at the concentrations commonly found in the body fluids of uraemic patients, especially in dialysis patients [8]. Similarly, the infusion of large concentrations of creatinine into dogs has not been found to produce any neurological symptoms [9]. Several guanidines have been implicated as causal elements of the uraemic syndrome. However, due to nonspecific measurement methods, this has not been proven yet [10].

The brain's metabolism of amino acids is altered in uraemia and this may also produce neurotransmitter imbalance. It has been demonstrated that the transport of most amino acids is impaired at the level of neurons and/or glial cells [11]. A high gamma-amino-butyric acid level is thought to indicate a specific disturbance of glutamine/glutamate metabolism and to lead to the delivery of abnormal substrates to brain cells [11]. Studies on purine and pyrimidine metabolism in young children with chronic renal failure have shown a marked increase in pseudouridine and cytidine in cerebrospinal fluid, as well as the presence of a high concentration of a compound which has not yet been identified [12].

The neurotoxic potential of parathyroid hormone has been evaluated extensively and it is the only substance which has been causally related to clinical findings [13]. However, hyperparathyrodism can be carefully and effectively prevented by the administration of active vitamin D components; this was the case in our patients as well as in most other study groups.

The above-mentioned findings may be closely related to the high percentage of comorbidity, not only in our sample, but also in other study populations of children with renal failure [14]. The fact that the number of children with multiple disorders (n=10) was over-represented in our sample of dialysis patients, should not be considered a coincidence.

In this study, we did not evaluate the extent to which the efficacy of dialysis played a role in the difference in cognitive functioning between the two treatment groups and why this difference did not manifest itself in the neurophysiological parameters (Chapter 6).

To judge the adequacy of dialysis, urea kinetics can be used. Within the limitations of the correlation between the blood urea concentration and the uraemic syndrome, the quantity of urea removed from the body by dialysis can be used as a means to measure the adequacy and efficiency of treatment. The concept of KT/V was developed for this purpose; K is the dialyser clearance, T the time of dialysis and V the patient's distribution volume of urea [15]. A positive correlation was found between the KT/V urea concentration and mortality and morbidity in adult haemodialysis patients [16,17]. Surveys have also been performed on adult peritoneal dialysis patients [18-20], and a small number of studies are presently available on paediatric peritoneal dialysis [21-23]. Further and more extensive studies are needed.

In this study insufficient proof has been found for the conjecture that psychological factors influenced the difference between the two treatment groups. However, significant differences were found on a number of behavioural variables between the group of kidney patients (n=18) and a group of healthy controls (n=18) (see Chapter 4). The method used (behavioural observations during testing sessions according to a structured checklist, partially derived from Bayley [24]) and performed by the same researcher) was insufficiently standardized and therefore not reliable enough. In this part of the study, no significant difference was found in behavioural factors between the patients on conservative treatment (n=8) and those on dialysis (n=10), but the samples were too small to draw reliable conclusions. However, evidence has been found by other researchers [14,25-28] who have recently performed studies on the psychosocial adaptation, schooling and rehabilitation of chronic renal patients (including CAPD/HD patients) and transplanted patients. The results showed that the psychosocial adaptation and psychological well-being of (particularly) the children on dialysis *and* of their parents, differed in a negative sense from the predialysis and transplanted patients. Earlier reports in the literature have also demonstrated that psychosocial factors, such as social isolation from peers, depression, the attitude of the parents and an increase in school absenteeism, may have a negative influence on cognitive functioning. In addition, the parents and the medical team as well can be strongly fixated on the physical condition of the child, particularly during the dialysis phase, which carries the risk that too little attention is paid to cognitive development [29,32]. In the introductory

chapter on the psychosocial consequences of chronic renal disease in children (Chapter 3), these aspects are dealt with extensively (see Sections 3.2, 3.3, and 3.4).

The research results described in Chapter 7 show that:

- a group of 20 children with ESRD aged 4 to 14 years at the start of dialysis treatment (an average of 4 weeks before) had significantly lower scores on the verbal part of an intelligence test than their normal peers, but that the total IQ was not significantly different from the norm group;
- after a successful transplantation, the total IQ showed a significant increase. However, the scores for general knowledge, similarities and concentration, were significantly lower than those of the norm group, both before and after transplantation.

These findings are in general agreement with those of other studies [33-35], but seem to disagree with the conclusion drawn in the studies described in Chapters 4 and 5: cognitive development, particularly in dialysis patients, was retarded by more than one standard deviation below the norm mean. This gives rise to the question of whether or not the cognitive functioning of young dialysis patients is at risk in the long-term, i.e., as they grow older and/or have a transplant. In the approach to this question, it is important to incorporate various methods, namely developmental tests versus intelligence tests.

Recent Dutch research [35] has revealed that the Bayley scale, when applied to children of 2 years, can make a predictive distinction between low risk and high risk for developmental disorders at the age of 5 years. In addition, developmental tests used at a young age have proven their worth in intra-individual longitudinal research, for example to evaluate the effect of starting a particular treatment. Predictions about intellectual functioning made on the basis of developmental research, measured by intelligence tests which call upon higher cortical functions, can only provide a global indication, or aim at the detection of risks [36,37].

In the light of these remarks, the discrepancy between the outcomes of the studies described in Chapters 4 and 5 and the relatively positive results reported in Chapter 7, can be explained as follows:

1. None of the patients who participated in the study on the effects of transplantation on cognitive functioning (Chapter 7), except for one (4.3 years), reached the stage of ESRD before the age of 5 years. This sample cannot be considered to belong to the risk group of renal patients who need to start dialysis treatment at a very young age (Chapters 4 and 5).
2. Although, particularly after transplantation, the general cognitive status of the patients in this group hardly differed from the norm mean, these children had a number of irreversible function disorders (on e.g., memory and concentration tasks), which was also demonstrated by Fennell et al. [34,38] in a longitudinal study. This explains why renal patients, despite having mental capacities which seem normal, often have problems at school or have difficulty completing their education [14,39].
3. The effects of transplantation on cognitive functioning could not be evaluated sufficiently in a number of young patients during the study period, because they had not yet reached the target weight for a transplant. Therefore the question whether the developmental potential of this group is permanently reduced, could not be answered.

Evaluation of the described research into the neurological, motor, and cognitive development of children with severe renal disease, leads to the following recommendations:

1. Further studies on the pathogenesis of uraemic encephalopathy are necessary to gain more insight into a possible relationship between congenital renal disease and early developmental disorders.
2. Longitudinal screening of motor and cognitive development has turned out to be worthwhile, because treatment interventions and counselling of the parents can be initiated at an early stage, in order to compensate for any further delay or retardation. For reliable motor screening, more standardised screening methods are required than those applied in this study. We are currently pursuing new designs.
3. The influence of psychological factors on the difference between the conservative treatment group and the dialysis patients (Chapters 4 and 5) deserves further attention, with more objective observation methods and a controlled design.

4. In view of the specific failure of cognitive functions, even after a successful transplantation in children of school age, further neuropsychological diagnostic assessment is indicated in this group, along with contiguous schooling focused on the individual and the specific problems. The results of (particularly European) large-scale studies have shown that the schooling of (ex)-renal patients is unsatisfactory and reduces the chance of social integration [14,27,39]. It is therefore fortunate that a multicentre project aimed at the schooling of dialysis patients has been started recently in the Netherlands.
5. Finally, establishing guidelines for improving the adequacy of dialysis treatment is strongly recommended.

10.2. Family stress

The chapters in the second part of this thesis deal with the level and nature of the daily and psychological burden on the family, particularly the parents, resulting from their child's dialysis treatment. At the start of the study, there was the feeling that especially the parents of young CAPD patients would be heavily burdened by having to carry out their child's treatment. This assumption was based on experience of paediatricians, nurses, psychologists and social workers. At that time, little or no systematic research had been conducted into the family burden of dialysis treatment and in addition, no disease-specific instruments were available to measure the burden. Owing to the fact that the central question in the study on cognitive development was whether starting renal replacement therapy at an early stage would improve a young child's developmental chances, a second question arose, namely whether the parents would be able to keep up with the (long-term) treatment of their child. In other words: can the risk of burn-out be foreseen *and* prevented? It was therefore considered necessary to make an inventory of the parents experience of their child's treatment and how much of a burden dialysis treatment was in general and per family (Chapter 8). On the basis of this inventory, a disease-specific questionnaire was constructed, the Family Stress Questionnaire, which was applied in a prospective study on parental stress (Chapter 9).

The hypothesis that the parents of young CAPD patients would be heavily burdened by the practical aspects of the treatment and by the delegated medical

responsibility, was confirmed in the retrospective study, whereas in the prospective study, we found that these aspects were of minor importance compared to the psychological burden of the treatment. Particularly the factors associated with uncertainty about the disease, treatment, transplantation and the child's future, were consistently mentioned by the parents as being a heavy burden. An explanation for the difference between the two studies may be found in the time factor, as described in Chapter 9: the retrospective study on CAPD patients was conducted in the early phase of CAPD in young children. The emphasis at that time was lying on meticulousness, hygiene, the lack of aids (e.g., UV device), the risk of peritonitis and was inducing a certain amount of fixation on the medical aspects of the treatment to the parents. The prospective study, on the other hand, showed that the aspects of treatment that were within the parents' control, even if they required considerable time investment over a long period, were ultimately less of a burden than the aspects that were beyond their control. These findings are not only in agreement with current theories about stress and coping behaviour in relation to a chronic disease [40-43], but also with the results of recent studies in which the parents of CAPD patients experienced fewer psychological problems than the parents of haemodialysis patients [25,26,44].

Unfortunately, we could not demonstrate the difference in the degree of burden between CAPD parents and HD parents reliably, because only four HD patients and their parents participated in the study. The mean score for stress in this small, non-representative group was higher than that of the CAPD parents (60% versus 34%, respectively).

The hypothesis that the parents of young children in particular, would be at risk for burn-out could not be confirmed. On the contrary, the results of the retrospective and prospective studies showed that the parents of children of school age experienced the heaviest burden. Concern about their child's future played a major role.

The fact that an unsuccessful transplant made a considerable contribution to the severity of the burden, was not a surprise in itself. The long waiting time until a kidney becomes available for a re-transplant and a structural shortage of donor kidneys emphasizes the importance of societal activities and of government intervention for providing more information about organ donation and donor

recruitment.

The level and the nature of stress resulting from the dialysis treatment of a child are not determined by the duration of the disease or treatment, nor by the socio-economic status, nor by whether or not the child attends (nursery) school which gives the family a break, but by a number of the above-mentioned factors *and* by the way in which a family copes with the disease and the treatment (Chapter 3, Sections 3.1 and 3.3).

A start was made with a study, expected to be important, to evaluate the coping behaviour of the parents and specific family characteristics. For this purpose, a disease-specific method (Family Characteristics Checklist) [45] was developed to enable paediatricians to detect risk factors resulting from inadequate coping behaviour and negative family characteristics. However, this method requires further validation, with criteria such as non-compliance of the child and parents, and the frequency and nature of the requests for help.

Recommendations which arise from the results of these studies on family stress, focus on:

1. Further research to determine risk factors for inadequate disease management and for parental burn-out by means of validation of the measurement methods.
2. Systematic and serial application of both methods at the paediatric dialysis centres in order to identify problems in the treatment and symptoms of potential burn-out, so that practical support and, if necessary, therapeutic help can be offered.

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SUMMARY

Recent progress in the medical treatment of children with chronic renal failure has led to a longer life expectancy and, in many respects, also to a better quality of life. Studies have shown, however, that radical replacement therapies, such as haemodialysis, peritoneal dialysis, and transplantation, have serious consequences on a child's development - particularly on that of young children - and on the psychological functioning of the child and its family. This thesis describes the psychological consequences of end-stage renal disease in children in the light of a number of studies. These studies focused on the question of whether the neurological, motor, and cognitive developmental disorders and retardation, as reported in the literature published in the nineteen eighties, could be prevented by the early initiation of renal replacement therapy. An integral part of this question was also to evaluate whether and how much a family and especially the parents were burdened by the treatment and by having to keep it up.

Chapters 1, 2, and 3 form an introduction to the six studies we performed. They offer an overview of the medical and the psychological aspects of chronic renal disease and treatment in children, based on the literature.

In Chapters 4, 5, 6, and 7, four studies are described that focused on the effects of chronic renal failure and transplantation on the neurological, motor, and cognitive development of young children.

Chapter 4 describes a prospective study on 18 renal patients of preschool age and on 18 healthy peers. Motor and cognitive development were assessed by developmental screening methods and additionally the behaviour by means of observation. Significant retardation was found in motor and cognitive development in the patient group. Moreover, there was a considerable difference in cognitive functioning between the patients on so-called conservative (pre-dialysis) treatment and those on dialysis treatment. It was concluded that dialysis patients are at increased risk for developmental retardation.

Chapter 5 deals with a multicentre study on the cognitive development of 31 patients younger than 5 years who had a renal function of <20%. The study had

a duration of three years. At the start of the project, 15 children were on conservative treatment and 16 were on dialysis. In this study, the effect of starting dialysis treatment was evaluated in 12 patients. The cognitive development of the total group at the start of the study was retarded (M = 78.5, SD = 19.5). The patients on conservative treatment had significantly higher scores than the dialysis patients; particularly the children with multiple diseases were at risk. Starting dialysis treatment had a positive effect, but only for a short period. Follow-up evaluation of 7 children on conservative treatment and of 9 dialysis patients over a period of two years did not reveal any significant amelioration or deterioration in the two groups. It was concluded (as in Chapter 4) that dialysis patients are at risk for developmental retardation and that this is particularly the case in patients with comorbidity. The hypothesis that starting dialysis treatment at an early stage would improve the developmental chances of young children with ESRD was not confirmed.

Chapter 6 presents a monograph of a longitudinal project aimed at the neurological development of 23 young kidney patients younger than 5 years of age and with a creatinine clearance of <20% of the age-related norm. Brain stem auditory evoked potentials (BAEPs) showed delay of peak I of the BAEP, indicative of peripheral conduction disturbances, possibly resulting from cochlear dysfunction. In children younger than 2.5 years (but not in older children) disturbances were found in thalamocortical conduction on the basis of somatosensory evoked potentials (SSEPs). This finding is an indication of delayed myelination in young children with chronic renal failure. No differences were found between the children who received conservative treatment and those on dialysis.

Chapter 7 describes a follow-up study on the effects of a kidney transplantation on 20 (predominantly) older patients of school age. Cognitive function was evaluated with intelligence tests before and after transplantation. The results showed that the performance of the renal patients on the verbal part of the test was significantly poorer than that of a norm group. However, after a successful transplantation, the patients showed great progress in their general cognitive functioning as a result of an improvement of the scores on the verbal subtests. The transplanted patients had significantly lower scores than normal children of

the same age, particularly on concentration tasks. It was concluded that this group of patients are still at risk of falling behind at school, also in the long-term.

Chapters 8 and 9 describe studies on family stress. For this purpose, questionnaires had to be developed because no disease-specific instruments were available, and very little research had been performed on the burden caused by dialysis treatment. It was our aim to design questionnaires which are easy to administer and suitable for serial measurements. The central theme was the stress as experienced by the parents of renal patients undergoing CAPD/CCPD and HD. Based on experience in the early years of PD, it was hypothesized that the parents of young CAPD patients would be the most heavily burdened and at the greatest risk of burn-out.

Chapter 8 reports on a retrospective study on the parents of CAPD patients and of HD patients. The results provided a great deal of insight into the specific burden as experienced by these parents, and showed that the amount of stress varied considerably from one parent to another. The parents of the CAPD patients experienced eating problems as a particular burden, whereas the parents of the HD children expressed most concern about their child's future. The considerable difference in age between the two groups played a role in this finding. In totality, psychological factors were found to contribute more to the stress than medical and practical factors. Contrary to the hypothesis, no significant differences were found in the amount of stress between the mothers and the fathers or between the CAPD parents and the HD parents. In the second part of Chapter 8, a methodological account is given of the construction of the final versions of the family stress questionnaires, which were developed for prospective research and for use at a paediatric dialysis centre.

Chapter 9 describes a prospective study on the burden, as experienced by the parents of 14 CAPD patients. Three measurements were performed over a period of one year. Once again, considerable differences were found in the amount of stress reported by the parents. Contrary to the hypothesis, the parents of the older children (>5 years) felt more burdened than the parents of the younger patients. Especially the parents of the children who had undergone an unsuccessful transplantation reported a high degree of stress. There were no

significant increases or decreases in the amount of stress measured at the three intervals during the one-year study period. The nature of the stress was determined more by psychological factors than by the medical aspects of the treatment. Support was found for our previous findings that concern about the future and factors associated with uncertainty made the greatest contribution to the burden. Emotional support for those parents with the highest scores on the questionnaires was therefore recommended.

Chapter 10 presents the General Discussion in which comparisons are made between the results in the above-mentioned studies and those of various other recent surveys and in which shortcomings of the research are discussed. A summary is given of the most important conclusions and recommendations are made for further research.

SAMENVATTING

De recente vooruitgang in de medische behandeling van kinderen met een chronische nierinsufficiëntie heeft geleid tot een verlengd levensperspectief, en in velerlei opzicht ook tot een verbeterde kwaliteit van leven. Ingrijpende nierfunctievervangende technieken zoals hemodialyse, peritoneaal dialyse en transplantatie bleken echter ook ingrijpende gevolgen te hebben voor de ontwikkeling van met name jonge kinderen en voor het psychisch functioneren van kind en gezin. Dit proefschrift beschrijft de psychologische gevolgen van terminaal nierlijden bij kinderen aan de hand van een aantal studies. Deze onderzoeken waren gericht op de vraag of de, in de jaren '80 in de literatuur, geconstateerde stoornissen en retardatie in de neurologische, motorische en cognitieve ontwikkeling van jonge kinderen voorkomen zouden kunnen worden door vroegtijdig te starten met nierfunctievervangende therapie. Met deze vraag diende ook een afweging gemaakt te worden of en in hoeverre een gezin en vooral de ouders belast zouden worden met de uitvoering van de behandeling en of zij deze zouden kunnen volhouden.

De hoofdstukken 1, 2 en 3 vormen een inleiding op de zes uitgevoerde studies en bieden een overzicht van zowel de medische als de psychologische aspecten van een chronische nierziekte en de behandeling daarvan bij kinderen, aan de hand van de literatuur.

In de hoofdstukken 4, 5, 6 en 7 wordt een viertal studies beschreven die gericht waren op de effecten van een terminale nierinsufficiëntie en transplantatie op met name de cognitieve ontwikkeling. De studies waren prospectief en longitudinaal van aard.

In hoofdstuk 4 wordt een prospectief onderzoek beschreven bij 18 nierpatientjes in de peuter/kleuterleeftijd en bij 18 gezonde leeftijdsgenootjes. Onderzocht werden de motorische en cognitieve ontwikkeling, alsmede het gedrag aan de hand van observaties. Er werd een significante achterstand gevonden in zowel de motorische als cognitieve ontwikkeling van de patiëntengroep. Bovendien werd een groot verschil geconstateerd in het cognitieve functioneren tussen patiëntjes in zg. conservatieve behandeling en patiëntjes die in dialysebehandeling waren. Geconcludeerd werd dat dialysepatiëntjes een vergrote kans op een ontwikkelingsachterstand hebben.

Hoofdstuk 5 behandelt een multi-centre onderzoek naar de cognitieve ontwikkeling van 31 patiëntjes <5 jaar en met een nierfunctie van <20% gedurende een looptijd van drie jaar. Vijftien patiëntjes werden bij de start van het project conservatief behandeld en 16 patiënten waren in dialysebehandeling. In dit onderzoek werd het effect van de aanvang van dialysebehandeling geëvalueerd bij 12 patiënten. De cognitieve ontwikkeling van de totale groep bleek bij aanvang van de studie vertraagd (M = 78.5, SD = 19.5). Patiëntjes die conservatief behandeld werden scoorden significant hoger dan de dialysepatiëntjes, waarbij met name de kinderen met multipele afwijkingen een verhoogd risico hadden. Het effect van starten met dialysebehandeling leek positief, echter alleen op korte termijn. Follow-up evaluatie van 7 conservatief behandelde en 9 dialysepatiënten over een periode van twee jaar bracht geen significante verschillen aan het licht. Geconcludeerd werd dat, evenals in hoofdstuk 4, dialysepatiëntjes een risico hebben op ontwikkelingsretardatie en dat dit met name geldt voor de patiënten met comorbiditeit. De hypothese dat een vroegtijdige start van dialysebehandeling de ontwikkelingskansen van jonge patiëntjes met een terminale nierinsufficiëntie zou kunnen verbeteren, werd niet bevestigd.

Hoofdstuk 6 beschrijft een deelstudie van een longitudinaal project gericht op de neurologische ontwikkeling van 23 nierpatiëntjes beneden de 5 jaar en met een creatinineklaring van <20% van de leeftijdsnorm. Brainstem auditory evoked potentials (BAEP) onderzoek liet een vertraging zien in peak I van de BAEP, hetgeen indicaties geeft voor perifere geleidingsstoornissen, mogelijk tengevolge van een cochleaire dysfunctie. Bij kinderen <2.5 jaar, maar niet bij oudere kinderen werden stoornissen in de thalamocorticale geleiding gevonden op basis van somatosensory evoked potentials (SSEP) onderzoek. Deze bevinding biedt aanwijzingen voor een vertraagde myelinisatie bij jonge kinderen met een chronische nierinsufficiëntie. Er werden geen verschillen gevonden tussen de conservatief behandelde kinderen en de kinderen in dialysebehandeling.

Hoofdstuk 7 beschrijft een follow-up studie naar de effecten van een niertransplantatie bij 20, overwegend oudere, patiënten in de schoolleeftijd. Het cognitief functioneren werd onderzocht aan de hand van intelligentietests voor en na transplantatie. Uit de resultaten van het onderzoek bleek dat nierpatiëntjes in vergelijking met de normgroep op het verbale gedeelte van de test lager

presteerden, maar dat zij na een geslaagde niertransplantatie significant vooruitgingen in het algemeen cognitief functioneren als gevolg van een stijging in scores op de verbale subtests. De getransplanteerde patiënten echter scoorden significant lager dan normale leeftijdsgenoten op met name concentratietaken. De conclusie is dat deze groep patiënten ook op langere termijn een achterstand op school kan ontwikkelen.

De hoofdstukken 8 en 9 zijn gericht op het onderzoek naar de gezinsbelasting. Omdat er geen ziekte- of behandelingsspecifieke methode voorhanden was en er nog nauwelijks onderzoek naar de belasting tengevolge van dialysebehandeling was verricht, werd er een vragenlijst ontwikkeld die gemakkelijk toepasbaar en voor herhaalde metingen geschikt moest zijn. Uitgangspunt was de belasting tengevolge van CAPD/CCPD en HD, zoals ouders deze zelf ervaarden. Op grond van ervaringen in de beginjaren van PD was de hypothese dat ouders van jonge CAPD-patiënten het meest belast zouden zijn en een verhoogd risico hadden voor burn-out.

Hoofdstuk 8 behelst een verslag van een retrospectief onderzoek bij ouders van zowel CAPD-patiënten als HD-patiënten. De resultaten bieden een goed inzicht in de specifieke belasting die ouders ondervinden. Ouders verschilden aanzienlijk in de mate waarin zij de belasting ten gevolge van de behandeling van hun kind ervaarden. Voor de CAPD-ouders bleken vooral eetproblemen en problemen rond dieet en medicatie bij te dragen aan de ervaren belasting, terwijl dit voor de ouders van HD-kinderen vooral de zorgen voor de toekomst betrof. Het aanzienlijke leeftijdsverschil tussen beide groepen speelde hierbij een rol. In totaliteit bleken psychologische factoren meer bij te dragen aan de ervaren belasting dan medische en practische factoren. Er werden geen significante verschillen gevonden in de ervaren belasting tussen vaders en moeders en, dit in tegenstelling tot de hypothese, tussen de CAPD-ouders en de HD-ouders. De tweede paragraaf van hoofdstuk 8 geeft een methodologische verantwoording van de constructie van de definitieve Gezinsbelastings-vragenlijsten die voor prospectieve doeleinden en voor gebruik in het kinderdialysecentrum ontwikkeld werden.

In hoofdstuk 9 wordt een prospectief onderzoek beschreven naar de belasting van ouders van 14 CAPD-patiënten gedurende een jaar, waarin drie metingen

werden verricht. Opnieuw werden er grote verschillen in de ervaren stress tussen ouders geconstateerd. De ouders van oudere kinderen (>5 jaar), voelden zich, ook weer in strijd met de hypothese, meer belast dan de ouders van de jongere kinderen. Van deze ouders rapporteerden vooral de ouders van kinderen die een mislukte transplantatie hadden ondergaan een hoge mate van stress. De belasting gemeten op drie tijdstippen gedurende een jaar nam wederom niet significant toe of af. De aard van de belasting werd meer bepaald door psychologische factoren dan door de medische aspecten van de behandeling. Ook in deze studie bleken zorg over de toekomst, alsmede factoren die samenhingen met onzekerheid, het meest bij te dragen aan de ervaren belasting. Emotionele ondersteuning van ouders die hoog scoorden op de checklist werd dan ook aanbevolen.

Hoofdstuk 10 tenslotte geeft een slotbeschouwing, waarin de uitkomsten van de verschillende studies worden vergeleken met recent verrichte andere onderzoeken, waarin tekortkomingen van het onderzoek worden bediscussieerd en waarin een samenvatting wordt gegeven van de belangrijkste conclusies en aanbevelingen voor verder onderzoek.

Veel mensen ben ik dank verschuldigd voor hun eigen en specifieke bijdrage aan de totstandkoming van dit proefschrift.

Allereerst wil ik alle patiëntjes en hun ouders danken voor hun medewerking aan de halfjaarlijkse onderzoeken en aan het invullen van de vragenlijsten - het fundament voor dit boekje werd door hen gelegd.

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Ook Els Hammes, maatschappelijk werkende op de afdeling Kinderdialyse heeft een wezenlijke bijdrage geleverd in het meedenken over de inhoud en de conclusies van het onderzoek.

Dr. R. Donckerwolcke, Wilhelminakinderziekenhuis te Utrecht en Dr. E. Wolff, Sophiakinderziekenhuis te Rotterdam, beiden kindernefroloog, wil ik van harte bedanken voor hun medewerking bij de multi-centre opzet van het onderzoek en voor hun organisatorische inzet bij het testen van hun patiëntjes.

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Mijn collega's van de afdeling Medische Psychologie, van de Afdeling Kindergeneeskunde en vooral natuurlijk de medewerkers van Kinderpsychologie zijn door hun belangstelling, geduld, collegialiteit en meedenken tot grote steun geweest en hebben op de juiste momenten voor de goede afleiding gezorgd.

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Gerdine Marijke Hulstijn-Dirkmaat werd op 1 april 1943 geboren te Amsterdam. Na het behalen van de diploma's H.B.S.- A in 1960 en Pedagogische Academie in 1962, was zij als leerkracht werkzaam op een basisschool in Amsterdam gedurende een tweetal jaren. In 1964 werkte zij als vrijwilliger in een kibboets in Israël. In 1965 werd aangevangen met de studie Psychologie aan de Vrije Universiteit te Amsterdam. Gedurende de kandidaatsstudie was zij incidenteel werkzaam als vervangende leerkracht in het speciaal onderwijs. Na het kandidaatsexamen in 1968 vervolgde zij haar studie aan de Katholieke Universiteit te Nijmegen met als afstudeerrichting Ontwikkelingspsychologie (Prof. Dr. F.J. Mönks). Van 1969-1970 was zij student-assistent bij de vakgroep Ontwikkelingspsychologie. In 1971 volgde een aanstelling als adjunct-wetenschappelijk ambtenaar bij de afdeling Medische Psychologie (waarnemend hoofd Drs. Th. Gijsbers) en was zij gedetacheerd werkzaam bij de afdeling Kindergeneeskunde van het Sint Radboudziekenhuis (Prof. Dr. E.D.A.M. Schretlen) tot januari 1973. In 1974 werd de studie afgesloten met het behalen van het doctoraal examen Psychologie. Van 1973-1975 werkte zij als psycholoog bij het Medisch Kleuterdagverblijf "Maria Christina" te Nijmegen en van 1975-1978 in de toelatingscommissie van de L.O.M.-school te Cuijk en tevens als schoolpsycholoog ten behoeve van het basisonderwijs in de Gemeente Cuijk. Vanaf 1978 tot heden is zij als psycholoog en de laatste jaren als universitair docent verbonden aan de afdeling Medische Psychologie (hoofd Prof. Dr. P.B. Bierkens) en voor de patiëntenzorg gedetacheerd werkzaam bij de afdeling Kindergeneeskunde (achtereenvolgens Prof. Dr. E.D.A.M. Schretlen, Prof. Dr. G.B.A. Stoelinga en Prof. Dr. R.C.A. Sengers) van het Academisch Ziekenhuis Nijmegen. Aandachtsgebieden binnen de patiëntenzorg zijn Kinder-cardiologie/hartchirurgie en Kindernefrologie/dialyse. Sinds 1990 is zij coördinator patiëntenzorg cluster Kinderen binnen de afdeling Medische Psychologie.

STELLINGEN

behorende bij het proefschrift

CHRONIC RENAL FAILURE IN CHILDREN

- psychological implications for development and family -

In het openbaar te verdedigen
op vrijdag 20 oktober 1995
des namiddags om 3.30 uur

door

G.M. Hulstijn-Dirkmaat

I. Uit een inventariserend onderzoek in het kader van het Onderwijsproject Kinderdialyse Nederland blijkt dat van de dialysepatiënten in de leeftijd van 4 - 16 jaar meer dan 50% is aangewezen op het speciaal onderwijs. Voor de totale Nederlandse leerlingenpopulatie ligt dit percentage tussen 4 en 7.6%. De extra financiële inspanning die momenteel wordt opgebracht ten behoeve van het zojuist gestarte project kan dan ook allerminst als een luxe worden beschouwd.

II. De bevinding dat vaders zich in gelijke mate belast voelen door de ziekte en de behandeling van hun kind als moeders lijkt zo vanzelfsprekend, dat in de literatuur hiervan niet eerder melding is gemaakt.

(dit proefschrift)

III. Thrombose van de donornier is de belangrijkste vroege complicatie van een niertransplantatie op de kinderleeftijd. Het is te hopen dat profylaxe met anti-stolling deze complicatie zal doen verdwijnen.

(AF van Lieburg et al, J Pediatr Surg 30:616-619, 1995)

IV. De prevalentie van mentale retardatie onder patiënten met erfelijke diabetes insipidus is minder uitgesproken dan in de literatuur wordt gesuggereerd.

(JA Hoekstra et al., Human Genetics, in press)

V. Gezien het algemeen publiek belang dient de bevordering van orgaandonatie niet alleen een zaak en een taak van particuliere instellingen te zijn, maar ook van de overheid, waarbij in voorlichtingscampagnes de psychologische, ethische en juridische aspecten belicht dienen te worden.

VI. Psychologische contraindicaties bij een ouder-kind transplantatie dienen in een vroeg stadium van de besluitvorming met de ouders besproken en gewogen te worden.

VII. Indien therapieontrouw wordt vermoed bij dialyse- en getransplanteerde patiënten in de adolescentiefase, is het van groot belang na te gaan of dit een symptoom is van (psychisch) gezond adolescentengedrag, dan wel van onderliggende psychische problematiek, zoals een (gemaskeerde) depressie met al dan niet bewuste suïcidale componenten.

(dit proefschrift)

VIII. Uitgangspunt bij de start van de nog steeds belastende behandeling van kinderen met groeihormoon dient te zijn dat méér centimeters zonder meerwaarde van geen waarde zijn.

(BJ Otten, MCWJ de Jong, GM Hulstijn-Dirkmaat)

IX. De psychologische voorbereiding van kinderen op invasief onderzoek en operaties is alleen dan effectief indien deze is afgestemd op de specifieke ingreep en op het individuele leeftijds- en ontwikkelingsniveau van het kind. Bij een collectieve voorbereiding middels folders, boekjes en videofilms ontbreekt de mogelijkheid in te gaan op de emoties en (ir)reële voorstellingen en fantasieën van het individuele kind.

X. Bij de conservatieve of palliatieve behandeling van kinderen met een ernstige congenitale hartafwijking en een beperkte levensverwachting is de inbreng van een medisch psycholoog gewenst vanwege de vragen en problemen van ouders rond ontwikkeling en opvoeding die samenhangen met het begrensde perspectief van het kind.

XI. Gezien het toenemende aantal allochtone patiëntjes dat een complexe behandeling ondergaat, verdient het aanbeveling om naast het inschakelen van tolken ook allochtone consulenten met een medische en/of verpleegkundige deskundigheid aan te stellen, ter voorkoming van andere dan alleen taalkundige communicatieproblemen.

XII. Dat pijn nooit went, wordt in het professioneel enthousiasme over verbeterde behandelingsresultaten bij chronisch zieke kinderen nogal eens vergeten.

XIII. Le voyage est une expérience, comme l'immobilité sur un coin de terre est une expérience, comme l'amitié, la contemplation, l'amour, le travail, la maladie, sinon le jardinage ou la cuisine, sont des expériences. Pourquoi discriminer entre elles? *(Marguerite Yourcenar in "Les Yeux Ouverts")*

XIV. Die hele volmaakte wereld die er moet zijn - het volmaakt onvindbare antwoord op de vraag welke wereld dat is.

(Rutger Kopland in "Voor het verdwijnt en daarna")

Heumen, 20 oktober 1995