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The cognitive development of pre-school children treated for chronic renal failure

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Abstract. 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

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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

Table 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

biochemical parameters, presence of multiple congenital diseases and psychosocial variables.

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 1. 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 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,

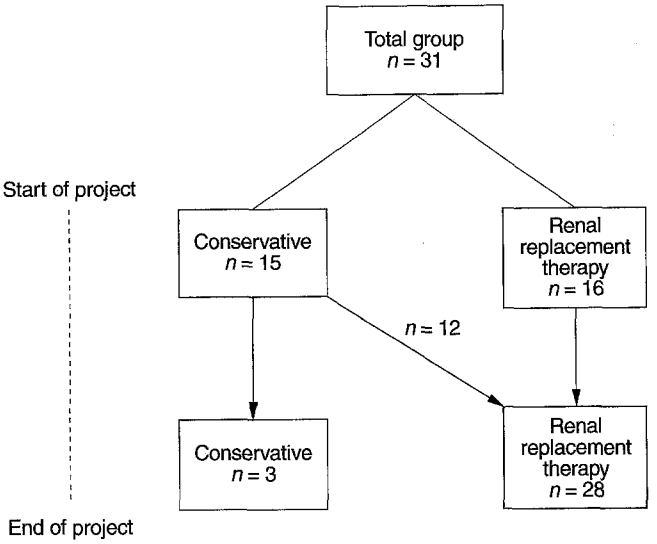

Fig. 1. Distribution of patients between conservative treatment and renal replacement therapy throughout the project

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 < 5–10 ml/min per 1.73 m^2) (Fig. 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. 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

Table 2. Concomitant disorders in 10 patients

Patient no.	Primary disease	Developmental disorder	Cerebral complication	Visual disorder	Deafness	Congenital 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

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 (stability coefficient), 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 analyse 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 vs. dialysis) was analysed by repeated measurement ANOVAs. The effect of the change from conservative treatment to dialysis on the patients who were transferred was analysed 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 iniation of treatment is critical, this factor was entered as a covariate in the ANOVAs to examine if there was a age/treatment interaction.

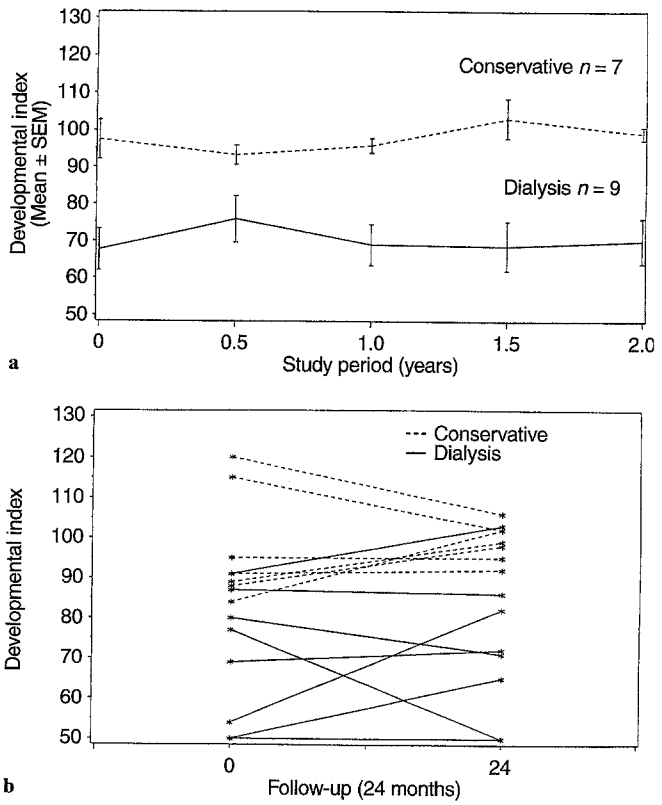

Fig. 2. a Cognitive development over time (mean ± SEM) of a group of 7 patients treated conservatively and of a group of 9 patients treated by continuous ambulatory peritoneal dialysis/haemodialysis (CAPD/HD). **b** Cognitive development over time of 7 individual patients treated conservatively and of 9 individual patients treated with CAPD/HD

Results

Overall developmental level

The cognitive development of the total patient group was delayed (Table 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. 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.

Table 3. Cognitive development of patients undergoing different treatment modalities with and without multiple diseases

	Total group (with and without multiple diseases)			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

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. 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 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 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. 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 (Fig. 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 Fig. 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.

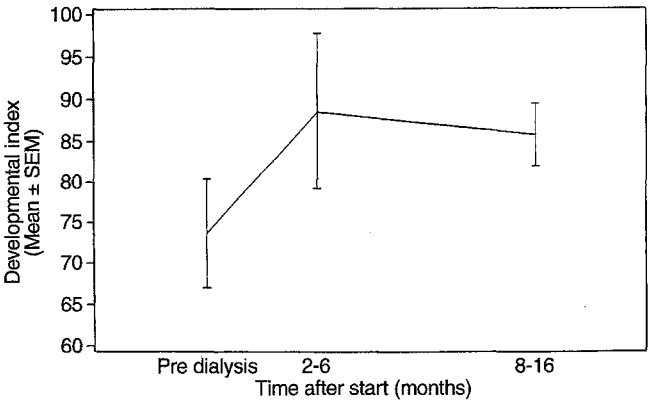

Fig. 3. Short-term and long-term effects of the initiation of dialysis treatment on the cognitive development of 6 patients

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 were young renal patients 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, 28]. 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 (Fig. 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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