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ORIGINAL ARTICLE

Early kidney transplantation improves neurocognitive outcome in patients with severe congenital chronic kidney disease

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Keywords
chronic kidney disease, dialysis, infant, kidney transplantation, outcome.

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Summary

Renal replacement therapy has become available for the majority of patients suffering from severe congenital chronic kidney disease (CKD). Data on the long-term neurocognitive outcome and the impact of early kidney transplantation (KTx) in this setting is unclear. Neurocognitive outcomes in 15 patients (11 male) with isolated congenital CKD (stage 3–5) requiring KTx at a mean age of 2.8 ± 1.3 were assessed at a mean age of 8.3 ± 1.4 years. Patients underwent neurological examination and testing for neuromotor and neurocognitive function using three independent tests. Pre-emptive KTx was performed in six patients, and nine patients were dialyzed prior to KTx for a mean period of 11.1 ± 8.6 months. Neuromotor function was abnormal in 8/15 patients. HAWIK-III showed a global intelligence quotient (IQ) of 93.5 ± 11.4 ($P = 0.05$) due to a significantly reduced performance IQ of 89.1 ± 11.3 ($P < 0.01$). In three patients, the global IQ was clinically significantly reduced by >1 SD to <85. In patients with neuromotor dysfunction, performance IQ was lower than in patients with normal neuromotor function (83.8 ± 10.2 vs. 96.2 ± 9.0, $P = 0.04$). Time on dialysis was inversely correlated to verbal IQ ($r = 0.78$, $P = 0.02$). Pre-emptive KTx and duration of dialysis treatment <3 months was associated with superior neurocognitive outcome. Early (pre-emptive) KTx results in superior long-term neurocognitive outcome in children with severe congenital CKD.

Introduction

Until recently, renal replacement therapy (RRT) for neonates and infants with severe chronic kidney disease (CKD) was considered experimental. Clinical studies in the 1980s described a high incidence of encephalopathy and microcephaly in patients undergoing RRT in the first year of life [1]. This resulted in a reluctance of neonatologists to perform RRT in very young patients, which was highlighted in a survey in 1998 indicating that only 40% of pediatric nephrologists supported RRT in newborns and only 50% before the end of the first year of life [2]. Besides the awareness of an increased risk of surgical complications and of the difficult pre-operative as well as postoperative management, this may reflect doubts about the developmental prognosis of patients undergoing RRT. With technical improvements and improved immunosuppressive therapies, dialysis and kidney transplantation (KTx) have become standard of care today [3–5]. A recent analysis of a single-center series concluded that in spite of generally excellent long-term outcomes, specific problems such as adolescent adherence, malignancies, growth, and social outcome can affect quality of life and deserve priority research [6].

There is still little information on the cognitive and neuromotor development of children requiring RRT. Young age at manifestation of CKD and lengthy dialysis has been shown to be associated with neurodevelopmental deficits

[7–10]. However, most former studies have concentrated on older patients with CKD. Only few studies have explicitly looked at infants and at congenital kidney disease leading to severe renal failure specifically in early infancy [11–13]. Also, some previous studies were biased by including patients with underlying syndromes or neurological comorbidities possibly independently affecting neurodevelopment in infants with severe CKD [11].

Here, we investigated neurodevelopmental outcome of severe congenital CKD and the impact of early KTx in school age patients without underlying syndromal disorders.

Material and methods

Patients

Between 1997 and 2003, 49 patients were treated at our institution due to severe congenital CKD (CKD stage 3–5). Data on the nephrological outcome of these patients were published elsewhere [3]. Thirty four of 49 survived into school age by the time of the study. Figure 1 illustrates the inclusion criteria and exclusion criteria of the study. Fifteen patients could be included in the analysis. Demographic data of patients are summarized in Table 1. KTx was performed in all patients at a mean age of 2.3 ± 1.3 years. In 6/15, transplant was pre-emptive, and 9/15 underwent dialysis up from a mean age of 5.3 ± 4.2 months (range 0.26–11.1) for a mean duration of 11.1 ± 8.6 months (range 1.6–23.9). For statistical analysis, patients who underwent pre-emptive KTx and patients who underwent dialysis for <90 days prior to KTx were grouped together (n = 9) and compared with patients who required dialysis for more than 90 days (n = 6). Until 2003, standard immunosuppression following KTx consisted of basiliximab induction, Cyclosporin A, and prednisolone. From 2003 onward, mycophenolate mofetil was added. In case of acute rejection, the calcineurin inhibitor was changed to tacrolimus, and in case of CNI toxicity in renal biopsy, CNI dose was reduced and an mTOR-inhibitor (Sirolimus or Everolimus) was added. Prednisolone was discontinued in stable patients 6–12 months after transplantation.

Table 1. Demographic data for the 15 patients.

Gender	
Male	11
Female	4
Underlying renal disease	
Renal dysplasia	8
Obstructive uropathy	4
Congenital nephrotic syndrome	3
Prenatal diagnosis	7
Neonatal risk factors	
Prematurity	7 (mean gestational age 34.9 ± 1.8 weeks, range 31–37)
Need for mechanical ventilation	6
Neonatal seizures	2
Kidney transplantation (KTx)	
Pre-emptive KTx	6 (including 3 from living related donors)
KTx following dialysis	9 (including 5 from living related donors)

Methods

The study was approved by the local ethics committee, and written informed consent was obtained from parents of all

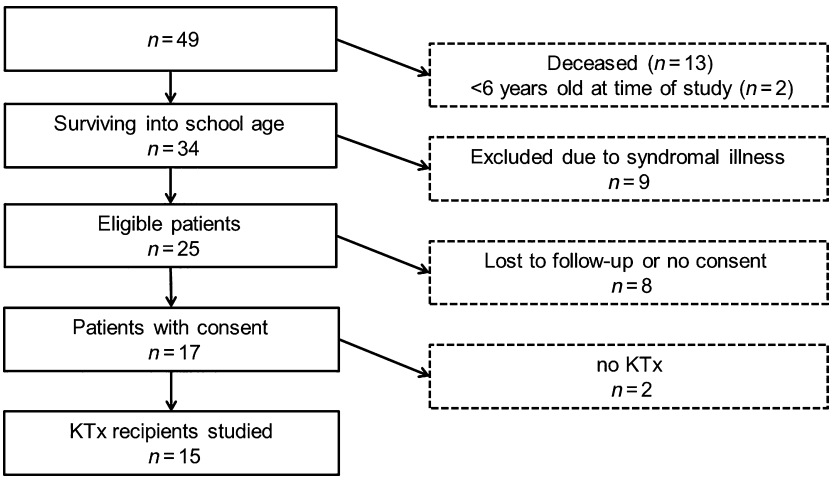

Figure 1 Flow-chart illustrating inclusion criteria and patient numbers. Of 49 patients treated at our institution because of severe congenital CKD (CKD stage 3–5) between 1997 and 2003, 15 could be included in our study: 9/34 were excluded due to underlying syndromal disorders possibly affecting neurodevelopmental outcome. In 4, families did not consent, and four were lost to follow-up. In one child, each with congenital kidney hypoplasia and obstructive uropathy, renal function improved to CDK stage II following conservative treatment. The other 15 (11 m and 4 f) required KTx due to end-stage renal disease and were included in this study.

patients. A standardized questionnaire was applied to obtain information about the medical history and socioeconomic status of patients. A socioeconomic status (SES) score was calculated according to the method suggested by Largo *et al.* [14]. The SES score is based upon parental education and professional status, with two being the lowest and 12 the highest score. Hospital notes were reviewed with regard to etiology of renal failure, age at initiation and duration of dialysis, age at KTx, and current renal function. Estimated glomerular filtration rate (eGFR) was assessed by the bedside CKiD equation (GFR (ml/min/1.73 m^2) = 0.413*body height (cm)/serum creatinine (mg/dl)) [15]. Patients were examined at a mean age of 8.3 ± 1.4 years (range 6.3–10.8). General medical examination included measurement of body height, weight, head circumference, and blood pressure. Individual values were transformed into standard deviation scores (SDS) [16,17]. Independent examiners performed the neurological and neuromotor examination (HH) and psychometric tests (NH). Neurological examination followed a standardized protocol including cranial nerves, muscle strength, tendon reflexes, polysynaptic reflexes, superficial and vibration sensory function, and proprioception. Additional postural tremor was assessed applying the raised-arm test and ataxia applying the finger–nose test and Romberg's test.

Neuromotor examination was performed using items from the "Zürcher Neuromotorik" test as described by Largo *et al.* in 2001. Patients were asked to perform pure motor tasks (repetitive finger, hand and feet movements, alternating hand and feet movements, and sequential finger movements), static balance, and stress gaits. Degree of associated movements for contralateral and ipsilateral extremity, face, head, and body was scored. In stress gaits, associated arm posture and movements were scored selectively [18]. The degree of associated movements was expressed using a 4-point scoring system: 0 = no associated movements, 1 = barely visible associated movements, 2 = moderately expressed associated movements, and 3 = markedly expressed associated movements. Similarly, postural change during stress gaits was assessed as 0 = normal, 1 = increased over one joint, 2 = increased over two joints, and 3 = increased tone involving the arm and shoulder. Because of the age dependency of physiological associated movements and postural changes, neuromotor dysfunction was only diagnosed if the child's associated movements and/or postural changes were rated as three in at least one task. No measurement of timed performance was taken.

Neurocognitive assessment was performed with two independent tests. The Hamburg-Wechsler-Intelligence scale for children, 3rd edition (HAWIK-III, Huber Verlag, Bern (Switzerland), 1999), was applied to assess global intelligence quotient (IQ), performance IQ, and verbal IQ. As one child was not a German native speaker, only 14/15 patients could be tested using the HAWIK-III. Additionally, patients were tested with the Culture Fair Intelligence Test (CFT) which is based on Cattell's model of fluid and crystallized intelligence [19]. CFT—Scale 1 (CFT 1, Hogrefe Verlag, Göttingen (Germany), 1997) could be applied to all patients younger than 9.5 years (n = 12) and Culture Fair Intelligence Test—Scale 20-R (CFT 20-R, Hogrefe Verlag, Göttingen (Germany), 2008) to all patients with an age equal or above 9.5 years (n = 3). CFT 1 allows the calculation of three sums: sum 1 (overall performance on the test), sum 2, and sum 3. According to Cattell′s model of intelligence, sum 2 includes a speed component and is indicative of culture and milieu-dependent performances, while sum 3 reflects general fluid ability. Results obtained by CFT 20-R are comparable to the results of sum 3 of the CFT 1 in younger children. Therefore, for statistical analysis, results of CFT 1 (sum 3) and CFT 20-R were grouped. By definition, in both the HAWIK-III and the CFT, the mean result is 100, with a standard deviation of 15.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Corp. Ehningen, Germany) software. Patients' IQ values were compared with the normative samples. The association between potential risk factors and neurodevelopment was assessed by applying Pearson's correlation coefficient for continuous variables (HAWIK-III and CFT) and logistic regression for categories (neuromotor assessment). Values were expressed as means, difference of means and 95% confidence intervals unless stated otherwise. Comparison of differences of the mean between categories was performed by the two-tailed t-test for independent samples. Independency of variables was tested by the chi-square test. A difference between groups was termed significant if $P < 0.05$.

Results

Fifteen patients (11 male, four female) were studied at a mean age of 8.3 ± 1.4 years. Socioeconomic status of the families was 5.7 ± 1.6, with a range of 2–8. Standardized body height and weight were reduced in comparison with the normative sample (Table 2), whereas SDS for body mass index and head circumference was not significantly different. Age and gender related systolic and diastolic blood pressure were increased (Table 2). Mean eGFR according to bedside CKiD equation was 55 ± 20 ml/min/1.73 m², with a range of 31–112. In all patients, standardized neurological examination was performed. Additionally, neuromotor function was assessed. Two patients showed abnormalities on standardized neurological examination (one presenting with increased tendon reflexes and

Table 2. Anthropometric data for the 15 patients.

Parameter	Mean ± SD	Range	95% CI	*P*-value
Anthropometric data				
Body height (SDS)	−1.14 ± 1.17	−3.03 to 1.31	−1.79, −0.49	<0.01*
Weight (SDS)	−0.60 ± 1.01	−2.55 to 1.39	−1.17, −0.43	0.04*
Body mass index (SDS)	−0.08 ± 0.91	−1.43 to 1.89	−0.42, 0.59	0.72
Head circumference (SDS)	−0.34 ± 1.39	−3.45 to 1.67	−1.11, 0.43	0.37
Systolic blood pressure (SDS)	2.12 ± 1.27	0.01 to 4.83	1.42, 2.82	<0.01*
Diastolic blood pressure (SDS)	0.88 ± 0.90	−0.47 to 2.37	0.38, 1.38	<0.01*
Psychometric data				
HAWIK global intelligence quotient (IQ) (n = 14) (a)	93.5 ± 11.4	74 to 116	−13.1, 0.1	0.05
HAWIK verbal IQ, (n = 14) (a)	99.1 ± 11.0	82 to 126	−7.2, 5.5	0.78
HAWIK performance IQ (n = 14) (a)	89.1 ± 11.3	68 to 109	−17.5, −4.4	≤0.01*
CFT 1, sum 1 (n = 12)	94.5 ± 12.2	73 to 115	−13.3, 2.3	0.15
CFT 1, sum 2 (n = 12)	96.3 ± 14.8	76 to 118	−13.1, 5.8	0.41
CFT 1, sum 3 or CFT 20-R (n = 15) (b)	98.3 ± 11.1	76 to 212	−7.9, 4.4	0.56

Data of patients with congenital CKD are compared with age, sex, and/or body height related normative samples (SDS, standard deviation score), and psychometric data to age related normative sample. ((CFT, Culture Fair Intelligence Test). (a): In one patient, HAWIK-III could not be performed due to insufficient fluency in German language. Depending on age, CFT 1 was performed in 12 and CFT 20-R in 3 patients. (b): The results of all 15 patients either in sum 3 of CFT 1 or of CFT 20-R, respectively, were grouped. Significant differences ($P < 0.05$) are marked with '*'.

one with postural tremor), eight presented neuromotor dysfunction (including both patients with abnormal neurological examination): four demonstrated increased associated movements when performing simple movements involving arms, hands, or fingers, five when performing simple movements involving legs or feet, 3/15 exhibited inadequate postural changes during test of static balance, and 5/15 during stress gaits. Psychometric testing revealed that HAWIK-III global IQ was within one standard deviation of the mean (85–115) in 11/14 patients tested. Verbal IQ and performance IQ were within the average range for 13/14 and 9/14 participants, respectively. A clinically relevant reduction of global IQ (<85) was observed in 3/14. Mean performance IQ was reduced in comparison with the normative sample, and there was a strong trend toward a reduced global IQ (Table 2). Verbal IQ was not significantly different. CFT showed no significant difference of mean global IQ in comparison with the normative sample (Table 2). In 2/15 patients, a reduced global IQ of <85 was found by the CFT 1 (sum 3)/CFT 20-R.

In patients with motor dysfunction, HAWIK-III performance IQ was significantly reduced (83.8 ± 10.2 vs. 96.2 ± 9.0, 95% CI −23.8 to −0.99, $P = 0.04$), and there was a trend toward lower HAWIK-III global IQ (89.0 ± 12.2 vs. 99.5 ± 7.1, 95% CI −22.8 to 1.8, $P = 0.09$) (Fig. 2). HAWIK-III verbal IQ was not different for patients with or without motor dysfunction (96.4 ± 13.4 vs. 102.8 ± 5.6, 95% CI −19.3 to 6.4, $P = 0.29$). CFT sum 1 and 2 showed a strong trend to reduced values in patients with motor dysfunction, and there was no difference regarding CFT 1 (sum 3)/CFT 20-R.

In the next step, potential modulating factors for cognitive function were evaluated. Socioeconomic status was not

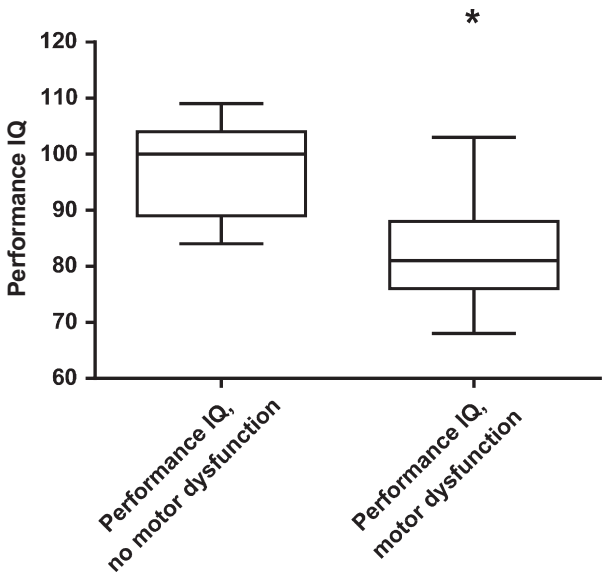

Figure 2 Performance IQ and motor dysfunction. HAWIK-III performance intelligence quotient in CKD patients without motor dysfunction (n = 6) and patients with motor dysfunction (n = 8), $P = 0.04$. As in one patient HAWIK-III could not be performed due to insufficient knowledge of German language, only 14 patients could be included in the analysis.

correlated with results of psychometric tests (results not shown). Prematurity and need for mechanical ventilation in the neonatal period were not associated with impaired cognitive function (Table 3). In the nine patients who underwent dialysis prior to KTx, duration of dialysis was inversely correlated with HAWIK-III verbal IQ ($r = 0.78$, $P = 0.02$, Fig. 3b), and there was a trend toward reduced

Table 3. Psychometric data for the 15 patients.

Modulating factor	Test	Present (*n*)	Mean ± SD	Absent (*n*)	Mean ± SD	95% CI	*P*-value
Prematurity	HAWIK global IQ*	7	96.0 ± 8.2	7	91.0 ± 14.1	−18.4, 8.4	0.43
	HAWIK verbal IQ*	7	100.7 ± 5.2	7	97.6 ± 15.1	−10.0, 16.3	0.61
	HAWIK performance IQ	7	92.4 ± 10.7	7	85.7 ± 11.6	−6.3, 19.8	0.28
	CFT 1, sum 3 or CFT 20-R	7	105.4 ± 9.2	8	92.0 ± 8.8	3.4, 23.5	0.01*
Neonatal mechanical ventilation	HAWIK global IQ*	6	92.0 ± 11.2	8	94.6 ± 12.9	−16.2, 11.5	0.69
	HAWIK verbal IQ*	6	89.7 ± 14.0	8	101.2 ± 12.7	−3.5, 27.7	0.12
	HAWIK performance IQ	6	95.7 ± 7.8	8	88.6 ± 9.8	−17.7, 3.6	0.17
	CFT 1, sum 3 or CFT 20-R	6	102.0 ± 9.9	9	95.8 ± 11.7	−18.8, 6.3	0.30
Prenatal diagnosis	HAWIK global IQ*	7	92.7 ± 8.1	7	94.1 ± 14.6	−12.5, 15.0	0.84
	HAWIK verbal IQ*	7	97.0 ± 5.8	7	101.3 ± 14.7	−8.7, 17.3	0.49
	HAWIK performance IQ	7	90.7 ± 10.4	7	87.4 ± 12.7	−16.8, 10.3	0.61
	CFT 1, sum 3 or CFT 20-R	7	101.1 ± 12.6	8	95.8 ± 9.8	−17.9, 7.0	0.37
Kidney transplantation (KTx) from living related donor	HAWIK global IQ*	8	96.0 ± 8.0	6	90.2 ± 14.9	−19.3, 7.6	0.36
	HAWIK verbal IQ*	8	101.8 ± 5.6	6	95.7 ± 15.6	−6.8, 19.0	0.32
	HAWIK performance IQ (	8	91.3 ± 9.5	6	86.2 ± 13.7	−8.4, 18.6	0.43
	CFT 1, sum 3 or CFT20-R	8	104.5 ± 8.9	7	91.1 ± 9.1	−23.4, −3.3	0.01*
Pre-emptive KTx	HAWIK global IQ*	6	98.0 ± 12.1	8	90.1 ± 10.2	−20.9, 5.1	0.21
	HAWIK verbal IQ*	6	102.8 ± 12.5	8	96.4 ± 9.6	−19.3, 6.4	0.29
	HAWIK performance IQ	6	93.8 ± 11.7	8	85.5 ± 10.3	−8.3, 5.9	0.18
	CFT 1, sum 3 or CFT 20-R	6	102.5 ± 9.8	9	95.4 ± 11.5	−19.5, 5.4	0.24
Dialysis > 90 days prior to KTx	HAWIK global IQ*	5	84.8 ± 7.0	9	98.3 ± 10.6	−25.1, −1.9	0.03*
	HAWIK verbal IQ*	5	90.4 ± 5.5	9	104.0 ± 10.3	−24.5, −2.7	0.02*
	HAWIK performance IQ	5	81.6 ± 9.0	9	93.2 ± 10.6	−23.9, 0.7	0.06
	CFT 1, sum 3 or CFT 20-R	6	90.0 ± 9.4	9	103.8 ± 8.6	−24.0, −3.6	0.01*

Results of psychometric tests in patients with congenital CKD were analyzed with regard to possibly modulating factors. *T*-tests and 95% confidence intervals are displayed. IQ= intelligence quotient. In one patient, HAWIK-III could not be performed due to insufficient fluency in German language. Culture Fair Intelligence Test (CFT) was performed in all 15 patients. Depending on age, CFT 1 was performed in 12 and CFT 20-R in three patients. Results of CFT 1 (sum 3) and CFT 20-R were grouped. Significant differences ($P < 0.05$) are marked with '*'.

HAWIK-III global IQ ($r = 0.71$, $P = 0.05$, Fig. 3a) and performance IQ ($r = 0.60$, $P = 0.11$). A similar trend was observed for CFT sum 2 ($r = 0.70$, $P = 0.05$). Furthermore, patients who never required dialysis (pre-emptive KTx) or received a renal transplant within 3 months following initiation of dialysis ($n = 9$) showed significantly better performance than those who underwent dialysis for more than 3 months ($n = 6$) in both the HAWIK-III (Table 3, Fig. 4) and the CFT (Table 3). The eight patients who received transplant organs from living related donors achieved significantly higher scores at the CFT 1 (sum 3)/CFT 20-R (Table 3). Patients with a history of prematurity were more likely to receive a transplant organ from a living related donor (6 vs. 1, $P = 0.02$). Blood pressure values, serum urea levels, and eGFR at time of study did not significantly correlate with neurocognitive outcome (results not shown).

Discussion

Few studies have examined neuromotor and cognitive development of children with severe CKD in the first year of life. Neuromotor dysfunction was observed in half of our patients. Even though most patients we examined achieved an IQ within the average range, it was below one

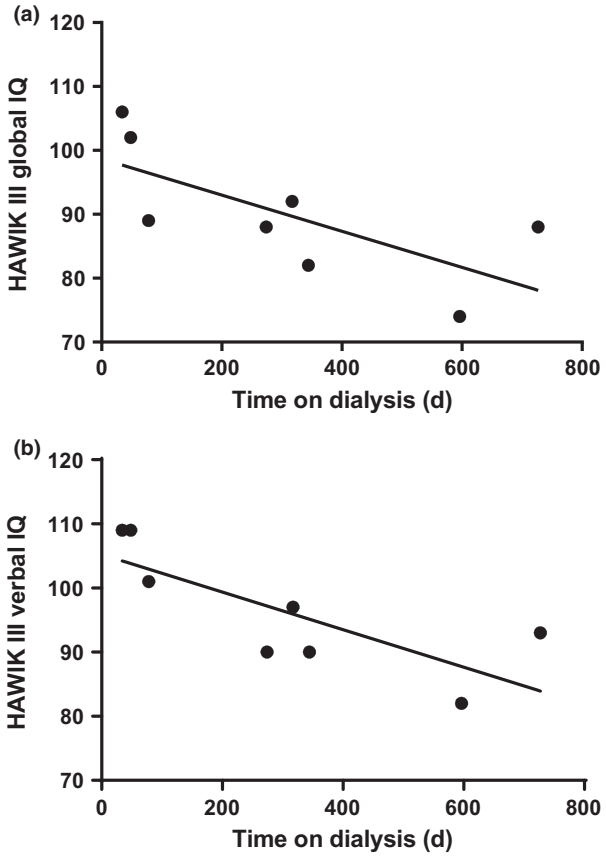

Figure 3 Influence of time on dialysis on HAWIK III results. (a) Correlation of HAWIK-III global intelligence quotient (IQ) to time on dialysis. $n = 8$, $R = -0.71$, p = 0.05, (b) correlation of HAWIK-III verbal IQ to time on dialysis. $n = 8$, $R = 0.78$, $P = 0.02$. As in one patient HAWIK-III could not be performed due to insufficient knowledge of German language, only eight patients could be included in the analysis.

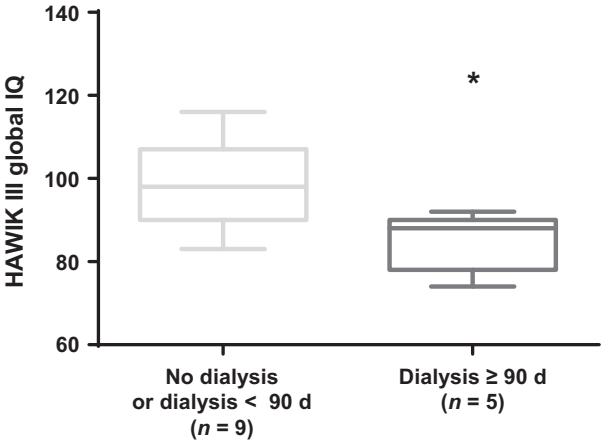

Figure 4 Favorable developmental outcome of patients undergoing pre-emptive KTx, or requiring dialysis for <90 days. HAWIK-III global intelligence quotient in patients requiring dialysis for over 90 days was significantly lower in comparison with patients requiring no dialysis or dialysis for <90 days ($P = 0.03$). As in one patient HAWIK-III could not be performed due to insufficient knowledge of German language, only 14 patients could be included in the analysis.

standard deviation in 3. Furthermore, the mean performance IQ was reduced. Time on dialysis was inversely correlated to verbal IQ. Likewise, pre-emptive KTx and duration of dialysis treatment <3 months was associated with superior overall neurocognitive outcome.

Falger *et al.* [11] also found reduced HAWIK-III global IQ and performance IQ in 27 patients with renal transplants. Similarly to our results, this was primarily due to reduced performance IQ. They also found reduced motor performance (Zürich Neuromotor Assessment). However, 10/28 patients whom they examined had syndromes possibly affecting cognitive and motor development, and 5/28 had pre-existing neurological comorbidity. Following exclusion of these 5, the association of performance IQ with motor performance was not significant in that study. In a recent retrospective analysis on the survival of children starting RRT in the neonatal period, concomitant neurological disorders were associated with a fivefold risk of death [5]. Therefore, in the present study, patients with syndromes possibly affecting cognitive and motor development were excluded. Seven of 15 patients whom we examined had a history of prematurity, but a neurological complication during the neonatal period with neonatal seizures was only observed in 2. In our study, patients with a history of prematurity surprisingly achieved significantly better results at the CFT 1 (sum 3)/CFT 20-R. However, patients with a history of prematurity were more likely to receive a transplant organ from a living related donor, and results were not consistent with the HAWIK-III. We therefore consider this finding coincidental. None of our patients had evidence of a persistent neurological disorder. Nevertheless, we observed a high frequency of motor dysfunction (8/15) and an association of motor dysfunction with reduced performance IQ in our patients with congenital CKD. Similar findings have been reported in prematurely born infants [20], but not yet in patients with CKD. The high number of patients with motor dysfunction in association with reduced performance IQ shows that severe CKD in the first year of life has negative effects on the further neuromotor and cognitive development of patients.

Whether early KTx may improve motor and cognitive development of infants with end-stage renal disease is not known. Whereas in some studies, no association between global IQ and type of RRT could be demonstrated [21,22], and differences in specific categories have repeatedly been shown. Lawry *et al.* [21] described better school performance in reading, writing, and algebra in patients who underwent KTx in comparison with patients on dialysis. A 12-point increase in intellectual functioning from the borderline range to the low average range in a small group of

six patients with CKD receiving transplant was described by Icard *et al.* [23]. In another study, an increase of performance IQ within 1 year following KTx was found [22], and additionally, an increase of head circumference and developmental quotient has been described [24]. These conflicting results might be explained by different ages at time of development of CKD and performance of KTx. In children with end-stage renal disease during infancy, Johnson *et al.* noted a correlation between younger age at KTx and higher scores in processing speed [13]. Similarly to others [8,9,25], we clearly observed a negative correlation between duration of dialysis and cognitive performance, and a reduction of global IQ by 1 SD in children requiring dialysis for more than 90 days. These data strongly support the concept of early/pre-emptive transplantation to avoid long-term dialysis. Our study is limited by a small sample size of 15 patients and cross-sectional nature. Due to the former, multivariate statistical analysis was implausible and results obtained are less definitive. However, our data support and extend previous studies showing superior outcome with respect to cardiovascular comorbidity and longitudinal growth in children undergoing early (pre-emptive) KTx in comparison with patients undergoing long-term dialysis [26–29]. A further prospective multicenter study is warranted to confirm our results.

In conclusion, overall outcome of patients with severe congenital CKD requiring RRT during infancy has improved greatly with better treatment. The results of this study suggest potential for normal or near-normal neurodevelopment, which may be further improved by early (pre-emptive) KTx.

Authorship

HH, KB, JHHE and LP: designed the study. NH and HH: performed the study. CV: did the biometric analysis. MW and AMD: as were involved in patient recruitment and care. DH: significantly contributed to the manuscript.

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