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EDITORIAL COMMENTARY

J. W. Groothoff

Long-term outcomes of children with end-stage renal disease

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Abstract Long-term survival of children with end-stage renal disease (ESRD) has increased in the last 20 years, but the mortality rate remains high. Cardiovascular disease accounts for 40 to 50% of all deaths, infectious disease for about 20%. A prolonged period of dialysis versus having a renal graft and persistent hypertension are mortality risk factors. The prevalence of the various morbidities is high among those who have reached adulthood. Nearly 50% of all these patients suffer from left ventricular hypertrophy and life-threatening vascular changes; nearly one third has clinical signs of metabolic bone disease. This accounts for both dialysis and transplant recipients. The chance of getting cancer is increased ten times compared to the general population; skin cancer and non-Hodgkin lymphomas are most commonly reported. A long period of dialysis at childhood is associated with impairment of both cognitive and educational attainment. However, despite all these negative outcomes, the health perception of young adults with childhood onset ESRD is positive. Research and therapy in children with ESRD should focus not only on prevention of graft failure, but also on prevention of co-morbidity, especially cardiovascular disease, life-threatening infections and malignancies. Early transplantation, more extended forms of frequent hemodialysis in those who can not be transplanted, a more rigorous treatment of hypertension, avoidance or at least dosage reduction of calcium-containing phosphate binders, reduction of the chronic inflammatory state, and tailor made anti-rejection therapy after transplantation may all be targets to improve the outcome in future patients.

Keywords End-stage renal disease · Long-term survival · Mortality rate

J. W. Groothoff (✉)
Department of Pediatric Nephrology,
Emma Children's Hospital AMC, University of Amsterdam,
P.O. Box 22700, 1100 DE Amsterdam, The Netherlands
e-mail: jwgroothoff@amc.uva.nl

Introduction

"The patient remained unconscious during dialysis, showing cramps from time to time...suddenly he vomited, showing massive gingival bleeding...after 13 h the patient started shaking after a piece of wood had been placed in the device against the spatter of dialysate...an example of a smooth dialysis session". These intriguing notes come from Willem Kolffs thesis in which he describes his first dialysis experiences [1]. He performed them during World War II in a small town in the Nazi-occupied Netherlands. Although only one patient survived the treatment, these sessions provided the basis for modern hemodialysis. However, it would take until the end of the 1960s before chronic renal replacement therapy (RRT) became applicable on a routine basis in children with end-stage renal disease (ESRD). Improvement of the dialysis technique and supportive therapy during the 70s and 80s gradually placed chronic RRT in children beyond controversy. In particular, better nutrition, the introduction of bicarbonate-buffer replacing acetate in hemodialysis, the introduction of continuous cycling peritoneal dialysis, the use of recombinant human erythropoietin and of growth hormone therapy, and the introduction of cyclosporine after transplantation contributed to a marked decrease in morbidity and mortality.

Yet, until the mid 1980s, RRT in children remained controversial, and the concerns about its outcome were great. Once dialysis and kidney transplantation had become technically feasible in children, the hope existed that RRT would offer these children the possibility of a normal life. The complications had rapidly tempered the original enthusiasm. In 1979, Cyril Chantler expressed the then general view among physicians on the prospects of children with ESRD by writing: "...we cannot escape the question whether children with end-stage renal failure should be treated or helped to die peacefully...", "...treating children under the age of 5...we do not always recommend..." [2]. Dialysis was still a means to survive in the short term, and very few speculations on long-term outcomes were made. In the same article, Chantler stated

that the current treatment..."justified the hope that a substantial number of patients should survive 10–20 years and live a useful life" [2].

As the first generation of patients surviving childhood had emerged at the turn of the millennium, the question arose of what indeed had become of these patients in terms of physical and psychosocial condition. Until recently, very few data existed on the consequences of childhood ESRD into adulthood, apart from less reliable registry data. Over the last half decade the first studies on this issue have emerged, and it is time for reflection on what has been learned and how we might further improve the prospects for our patients.

Mortality and causes of death

The survival rates of children on chronic renal replacement therapy vary from 79 to 82% at 10 years and from 66 to 79% at 20 years [3, 4, 5]. The overall mortality rate is about 30 times as high as expected for age [3, 4]. All studies show a substantial decrease in mortality over the last 25 years, especially in the very young age groups. However, this trend toward improvement of survival has also slowed dramatically during the last 25 years [3, 4, 5]. Taking into account the experimental nature of renal replacement therapy among children during the 1st years, it is disappointing to notice that in both McDonald's study and ours no increase in survival was seen after 1983 [3]. To some extent, selection bias might have influenced this outcome. Data on the referral and selection of patients for chronic RRT do not exist at this time. Since there has been an increasing tendency over time toward treating sicker children, the observed improvement in survival might be an underestimation for the average patient. However, it is beyond discussion that the more or less stable mortality rate over the last 20 years, which remains between 25 and 30 times as high as expected, is unacceptably high [3, 4, 5].

Cerebrovascular accidents as a result of malignant hypertension at young age and cardiac death at older age are the most prominent causes of death, followed by infection, malignancies and deliberate cessation of treatment. Cardiovascular causes account for 35 to over 50% of all deaths [3, 4, 5, 6, 7]. Although one has to be cautious in interpreting "cardiac death" as a genuine cause of death, these figures indeed reflect the excess risk of cardiovascular disease in children with ESRD. Prolonged hypertension has been shown to be independently associated with increased morality [4]. Other recent studies show that left ventricular hypertrophy (LVH) occurs early in children with ESRD and that it is strongly associated with hypertension [8, 9, 10]. Mitsnefes et al. found that 69% of all children already had LVH at the onset of dialysis therapy, that it persisted for 2 years after transplantation in 56% and that regression of the LVH could be induced by controlling systolic blood pressure [11, 12]. These data emphasize the pivotal role of blood pressure in both dialysis and transplanted children. Prolonged stay on dialysis seems to be the most important mortality risk factor. Patients on dialysis, who are not transplanted have a four-times increased risk of death as compared to transplant recipients; in patients who have remained longer on dialysis than on a renal graft, mortality rates are seven times higher [3, 4]. However, this does not take into account the relatively short stay on dialysis before transplantation. No differences are found in survival between preemptively transplanted recipients and those with dialysis periods of up to 24 months before transplantation [3, 13]. Therefore, it is beyond discussion that early transplantation remains the most important therapeutic aim in ESRD in children. However, at the same time, although preemptive transplantation is in many ways the best option for these children, no data on patient survival exist that support this strategy. A younger age at onset of RRT was found to be a considerable mortality risk factor in all studies [3, 4, 5]. However, it is encouraging to notice that the survival of the very young patients has improved over time. Taking into account the fact that more infants have been accepted for chronic RRT during the last 20 years, it seems that we indeed have overcome a great deal of the specific technical problems concerning delivering RRT to very young children, at least in terms of survival.

Morbidity

Asymptomatic cardiovascular disease, which might induce sudden death, appears to be highly prevalent in both transplanted and dialysis patients [7, 14, 15]. Nearly 50% of all living male and 40% of all female patients aged between 20 and 42 years were found to have a moderate to severe left ventricular hypertrophy (LVH), 75% being transplanted at the time of investigation [14]. Like LVH, cardiac valve calcification and arterial wall stiffening as a result of media proliferation and secondary calcification are highly prevalent in young adults with childhood ESRD, both in dialysis and transplant recipients [7, 14, 15]. All these abnormalities are associated with an increased risk of death.

Coronary ischemia and cardiac conduction defects due to myocardial calcification are the most probable links between aortic valve calcification and mortality. Aortic valve calcification in ESRD patients reflects a more generalized artery disease with calcification of the coronary arteries and the myocardium, as has been shown by Braun et al. [16]. Vascular calcification appears to already start at a young age. Eifinger et al. described coronary calcifications in 16-year-old dialysis patients, while Oh et al. found coronary calcification in 92% of 39 adults, aged 19–39 years, with childhood ESRD [7, 17].

Chronic hypertension, a high calcium phosphate product and a chronic state of inflammation are among the most important potential determinants of cardiovascular disease in ESRD.

Whereas cardiovascular disease and infections have proven to be the most life-threatening co-morbidities,

chronic fatigue in dialysis patients and disabilities as a result of metabolic bone disease are the most frequently reported daily problems of young adults with childhood ESRD [18, 19].

As expected, in a cohort of patients that has grown up in the pre-growth hormone era, more than two-thirds of the LERIC patients were severely growth retarded [18]. A more surprising and more worrisome finding was the extent and severity of clinically manifest metabolic bone disease that we found in the LERIC patients. More than one-third had daily complaints or disabilities related to metabolic bone disease. About 18% was disabled as a result of bone disease [18]. Very few data exist on this evidently underexposed problem. Although conclusive evidence is lacking, most of these problems seem to be related to chronic inactivity, a high burden of corticosteroids and an increased total duration of renal replacement therapy. Bone mineral densities (BMD) are found to be lower than –2.5 SDS in over 50% of adult patients with childhood ESRD [18, 20]. However, the relevance of BMD values, measured by DEXA, with respect to an increased risk of atraumatic fractures is speculative in patients with childhood ESRD, and further follow-up is warranted [21].

Malignancy is seen about ten times more frequently than expected for age [19, 22]. The most prevalent forms of malignancies seen are non-Hodgkin lymphomas and, above all, skin cancer at older age. In our study, we found that the cumulative dose of more than 20 mg/kg of cyclophosphamide at youth was associated with an increased risk of cancer [22]. As mentioned earlier, there are indications that the outbreak of malignancies and life-threatening infections in this group of patients might become a far more prevalent problem in the next few years than it already is today. Physicians who tend to use more potent immunosuppressive therapy in transplanted children should be aware of this potential hazard. Regular screening of the skin is of utmost importance in order to reduce mortality in this group of patients.

Psychosocial consequences

Cognitive and learning impairment is more prevalent in young adult patients with childhood ESRD than in the age-matched population [23, 24]. Mean IQ scores in young adults with childhood ESRD are on average ten points lower than in controls, which is in line with the result of recent IQ studies performed in children [23, 25]. Impaired schooling and cognition appear to be induced by a long period of dialysis during youth. In our study, we found no difference in intellectual performance between patients who were on dialysis and those who were transplanted by the time of investigation. In theory, chronic aluminum intoxication as a result of chronic use of aluminum-containing phosphate binders could have influenced the cognitive development of our patients. However, we found no evidence for this. On the contrary, the compatible results of recent IQ studies in ESRD children indicate that abandoning aluminum-containing phosphate binders has not shown beneficial effects on intellectual development [23, 25]. Most deficits are found in tasks requiring concentration, memory and most of all general knowledge [23]. Consequently, early educational intervention in young patients on dialysis might prevent most of these impairments.

Compared to age-matched individuals, adult patients with childhood ESRD are significantly more often involuntarily unemployed. Unemployment has recently been reported to be as high as 18.3% in the Netherlands [26] and 25.1% in France, which is about twice as high as in the age-matched population in both countries [24]. Data from the early 1990s show that these percentages may vary considerably from country to country [27]. However, the frequency of unemployment of dialysis patients with childhood onset of ESRD appears to be much lower than those found in age-matched patients with adult onset of ESRD, which varies from 49 to 77% [28, 29]. The LERIC study found that unemployment was related to a low subjective health perception, an apparent failure to adjust to their disease, rather than to their objective physical condition, or to whether they were transplanted or on dialysis. Patients with disabilities tend to remain living with their parents [24, 26]. Men appear to have problems finding a life-partner more often than women [26].

Taking into account all the physical problems, the overall subjective health perception in young adult patients with childhood ESRD appears surprisingly good [30]. On average, transplant recipients report a normal physical health perception; dialysis patients, as expected, report on average impaired physical and social functioning, induced by physical impairment. However, both transplanted and dialysis patients report a normal mental health perception, in sharp contrast to age-matched dialysis patients with adult onset of disease. This concurs with the differences in employment state between patients with adult onset and those with childhood disease onset. It seems that the latter group has adapted better to the disease state than patients with adult onset of disease.

Transplantation versus dialysis

All late outcome studies favor early transplantation in children with ESRD, which appears to have a beneficial effect on overall mortality, morbidity and psychosocial development. However, it has also become clear that transplantation is associated with its own considerable late morbidity. Disabling co-morbidity was reported by 40% of all our transplant recipients. Apart from clinical bone disease, most reported disabling problems; severe daily headaches, tremors and severe itching have been directly related to the transplanted state.

Malignancies, infection, hypertension-related LVH and arterial wall stiffening are the most life-threatening problems after transplantation. Although, current insight shows a much lower mortality in transplant recipients

with childhood ESRD than in patients who stay on dialysis, with the passage of time the dark side of Camelot becomes more lucid. We found a sharp increase in the number of malignancies after only 15 years of follow-up. A large German long-term follow-up study of transplanted children with a mean follow-up of 13 years showed a relatively low percentage of malignancies of 2.6%, as compared to the 8.4% found in the LERIC study, which had a mean follow up of 18 years. Bartosh et al. found 12% malignancies after only 13 years of follow-up in renal transplanted children [6, 19, 22]. As of yet unpublished data of our 5-year follow-up study of the original cohort show a further increase in both life-threatening infections and malignancies, each being responsible for 23% of the new casualties between 1999 and 2004. Taking into account the current trend towards the use of more potent and, consequently, more immune-suppressive and potentially carcinogenic anti-rejection therapy in transplantation, this could emerge as a problem in the near future.

Where to from here?

The first generation of adults with renal replacement therapy since childhood has survived at the cost of a considerable co-morbidity. At the same time, despite this and despite the limitations brought on by a lack of sufficient educational achievement, these patients report a relatively good overall quality of life and appear to be far better adapted to their illness than patients with ESRD of adult onset. The technical improvements of renal replacement therapy over the last 20 years have reduced some of the reported late effects in the new generation, such as stunted growth. However, with respect to the determinants of the most life-threatening problems in ESRD, i.e., cardiovascular disease, infections and malignancies, only little advancement has been seen over the last 30 years, and in some respects, we might even currently be performing worse. Future research should therefore be focused on the prevention of cardiovascular disease, metabolic bone disease, life-threatening infections, malignancies and impaired learning. Transition programs should focus on the stimulation of independency, and they should better prepare adolescents for a professional life. A reduction of all potential cardiovascular risk factors through a more intensive treatment of hypertension and avoidance of calcium-containing phosphate binders in order to prevent a high calcium phosphate product as well as prevention of a chronic inflammatory state are potential targets for treatment. Apart from early transplantation, high frequency and overnight hemodialysis in those who cannot be transplanted might increase the prospects for these children. Finally, a modification of the immunosuppressive regime tailored to the individual using new, less toxic and more specific anti-rejection therapy are warranted in order to reduce life-threatening infections and malignancies.

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