Hemodialysis in Children
Eleven Years in a Single Center in Egypt

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Introduction. The objective of this study was to report the clinical characteristics and outcomes of children with end-stage renal disease under regular hemodialysis in a dialysis unit in Egypt.
Materials and Methods. Ninety children with end-stage renal disease were included in this study and their charts over the past 11 years (from January 2001 to January 2012) were reviewed.
Results. The mean age of the patients at the start of hemodialysis was 5.6 ± 1.4 years. The main causes of end-stage renal disease were glomerular diseases (35.6%), unknown etiology (33.3%), and urological problems (17.8%). Hospital admissions were due to hypertensive attacks, cardiac problems, arteriovenous shunt complications, and infections. Only 3 children received a kidney transplant and 24 (26.7%) died during the 11-year follow-up. Eight patients died of heart failure, 5 due to sepsis, and 4 due to unexplained causes.
Conclusions. Maintaining an appropriate care for children with end-stage renal disease is quite difficult in developing countries due to factors such as late referral, poor medical service utilization, limitation of financial resources, and limitations to transplantation. As a result, maintaining on hemodialysis for long periods imposes a high risk of complications.

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INTRODUCTION

The incidence rate of end-stage renal disease (ESRD) in the United States is 11 to 14 per million population for individuals under 20 years of age.[1] The ESRD incidence was age-dependent, from 13.0 per million population in 12 year-old persons to 32.6 per million population for 19 year-old persons in countries with active pediatric transplant programs.[2] However, hemodialysis is not used as the 1st choice of chronic renal replacement therapy, as most pediatric nephrologists would aim for preemptive transplants for their patients.[1] Hemodialysis procedures have become increasingly sophisticated, however, and many of the theoretical and technological advances studied previously in adult patients have been applied to children receiving hemodialysis.

Provision of optimal pediatric hemodialysis requires a specialized and integrated healthcare team to manage the medical, nursing, nutritional, developmental, and psychological aspects of care for the pediatric patients with ESRD. Continued advances in acute and chronic hemodialysis treatment in children require accurate data on treatments and their outcomes. Improvement in hemodialysis techniques over the last 20 years has come from lessons learned in adults, results of single-center trials or surveys, and registry studies. The number of pediatric patients even in the largest pediatric centers is not large enough to provide sufficient data to optimally advance the practice of hemodialysis in children.[3]

More than 40% of patients are on hemodialysis at the initiation of ESRD,[1] and the majority of patients with ESRD for 24 months or longer receive a kidney transplant; thus, the pediatric ESRD population is small and moving from dialysis to kidney transplant some of them back to chronic kidney disease and dialysis or transplant again, making prospective studies on patients on any single modality difficult. This limitation is coupled with the fact that the incidence rates of hard outcomes such as mortality are relatively low when compared with adult ESRD patients,[4] and although mortality and hospitalization rates remain unacceptably high in pediatric hemodialysis patients compared with the general pediatric population, death and hospitalization are infrequent events in pediatric hemodialysis patients compared with adult hemodialysis patients.[5]

The aim of this study was to review cases of pediatric ESRD on maintenance hemodialysis at the nephrodialysis unit of Zagazig University Hospital over the past 11 years in terms of patients' characteristics, complications, and outcomes.

MATERIALS AND METHODS

Ninety children with ESRD were studied by reviewing their charts from January 2001 to January 2012. The following data were collected for all of the patients: anthropometric measurements, age of onset of ESRD, etiology of the disease, duration of ESRD, duration of dialysis, and sign and symptoms on clinical examination, history of any complication and its management laboratory investigations (complete blood count, blood urea, serum creatinine, serum iron, serum ferritin, serum calcium, serum phosphorus, and intact parathyroid hormone). Data on blood culture, Doppler ultrasonography for arteriovenous fistula (AVF), and echocardiography were collected in selected patients.

The dialysis prescription was as follows three times per week, 3 to 5 hours per session. Blood flow was 300 mL\min, with target urea reduction ratio greater than 65%, as calculated as follows:

Urea reduction ratio (predialysis urea – postdialysis urea)/predialysis urea

Dialysis had been performed with Fresenius 2008K machines and hollow fiber polysulfone dialysis filters (Fresenius, Bad Homburg, Germany), using standard citrate dialysis solution.

RESULTS

Patients

Clinical charts of 90 children on hemodialysis during the studied period were reviewed. They were 53 girls and 37 boys. Characteristics of the patients and their mean laboratory study values are presented in Table 1.

Hospital Admissions

Overall, 1267 hospitalizations had been recorded for these patients (Table 2). The most responsible diagnosis for hospital admissions were as follows:

Uncontrolled blood pressure. There were 400 hospital admissions for controlling high blood pressure with a mean of 4.4 times per patient. The most common cause of these episodes of hypertension (50%) was hypervolemia and fluid overload corrected by correction of dry weight, followed by noncompliance with the treatment (30%).

Table 1. Demographic and Clinical Characteristic of Pediatric Patients on Hemodialysis

Characteristic	Value
Age at onset, y	5.6 ± 1.4 (1 to 15)
Body weight, kg	17.0 ± 2.7 (8 to 50)
Duration of disease before initiating dialysis, mo	41 ± 7 (0 to 93)
Duration of dialysis, mo	42 ± 8 (1 to 107)
Cause of end-stage renal disease	
Glomerulonephritis	32 (35.5)
Steroid-resistant nephrotic syndrome	22 (24.4)
Systemic lupus	3 (3.3)
Hereditary nephropathy	3 (3.3)
Hemolytic uremic syndrome	3 (3.3)
Antiphospholipid syndrome	1 (1.1)
Unknown	30 (33.3)
Urological malformations	16 (17.8)
Familial interstitial nephritis	2 (2.2)
Dysplasia	3 (3.3)
Amyloidosis	1 (1.1)
Hypoxic nephropathy	3 (3.3)
Shunt nephritis	3 (3.3)
Laboratory Measurements	
Urea reduction ratio, %	62.1 ± 4.0 (50 to 65)
Hemoglobin, g/dL	8.0 ± 1.3 (6.5 to 11.3)
Serum ferritin, µg/L	1200 ± 500 (80 to 9000)
Serum iron ng/dL	76 ± 14 (26 to 170)
Serum calcium, mg/dL	7.9 ± 1.3 (5.9 to 14)
Serum phosphorus, mg/dL	6.0 ± 2.3 (3.8 to 9.5)
Parathyroid hormone, pg/mL	300 ± 40 (9 to 1300)
Serum albumin mg/L	3.4 ± 0.3 (2.6 to 4.2)

*Values are calculated as mean ± standard deviation of the mean values for each patient.

Table 2. Number of Hospital Admissions by Etiology

Etiology	Number of Admissions	Mean Length of Stay, d	Percentage of All Admissions
Uncontrolled blood pressure	400	3 ± 2	31.6
Vascular complication	281	6 ± 2	22.2
Heart failure	209	4 ± 1	16.5
Pneumonia and infections	200	9 ± 1	15.8
Bleeding	107	3 ± 1	8.4
Others	70	3 ± 1	5.5

Vascular access complications. There were 281 admissions because of vascular access complications with a median 3.1 admissions per patient. The main complication was thrombosis followed by infections and steel phenomenon. The least common was rupture in 5 arteriovenous fistulas.

Heart failure. Two hundred and nine admissions were because of heart failure (2.3 times per patient), and the main causes were cardiomyopathy and anemic heart failure. These admissions did not include those with hypertensive heart failure or overload as it was counted in admissions for uncontrolled hypertension.

Pneumonia and infections. The patients had been admitted because of respiratory problems 200 times (2.2 times per patients). The main cause was lobar pneumonia, followed by bronchopneumonia and pleural effusion, while the least frequent cause of admission was wheezy chest. For pneumonia the main organisms isolated were *Streptococcus pneumoniae, Pseudomonas, Klebssila,* and *Staphylococcus aureous*. One-fourth of the cases responded to treatment for *atypical organisms* with ordinary negative cultures. We concluded that they were *Mycoplasma* or *Chlamydia* responding to azithromycin. The least frequent cause was fungal infection responding to fluconazole. There were 4 attacks of chest infection with vancomycin-resistant *Staphylococcus aureous*, responding only to teicoplanin. Seven admissions were diagnosed with encephalitis and treated by acyclovir, vancomycin, and 3rd generation cephalosporins.

Hemorrhage. We had 107 admissions because of hemorrhage, 92 of which were because of vascular access bleeding, either due to local infection of the access; overdose of heparin, or hepatic disease (38 patients were positive for hepatitis C virus). The remaining 15 admissions were because of bleeding from other sites, such as gastrointestinal tract, pulmonary system, or to epistaxis.

Mortality

Only 3 children received a kidney transplant. A total of 24 children (26.7%) died while being on dialysis treatment. The main cause of death was heart failure (8 of 24), including hypertensive heart failure secondary to chest infection, arrhythmia, or dilated cardiomyopathy; sepsis in 5; unexplained cause of death in 4; pulmonary embolism in 2; acute fulminate hepatic failure in 2; encephalitis in 1; and acute abdomen due to rupture of splenic cyst in 1 (Table 3).

DISCUSSION

Despite all the improvement that have taken place over the years, such as more biocompatible high-flux dialysis membranes and ultrafiltration-controlled machines, along with better understanding of the management of nutrition, anemia, and chronic kidney disease, and metabolic bone disease, mortality in adults on dialysis has shown no signs of improvement. In children on dialysis, mortality is markedly lower than in adult patients, but it is still 30 times higher than that of the age-matched healthy population.[1]

In Egypt, there is no regional registry collecting data on end-stage renal disease and its outcome, so we tried to find out the outcome of patients treated with hemodialysis in our unit over 11 years. Taking into consideration that we might have a poor prognosis due to late referral, lack of transplantation, and high cost of replacement therapy, our results are similar to those of many other countries.

In children, the incidence and etiology of kidney failure are age-dependent and vary according to geography and nationality, reflecting the changing nature of the pediatric service.[6] We reported age of onset of our patient 5.6 year, and this matched age onset in some countries, as in a previous study of Turkish children, the mean age was 9.5 years,[7] but we found this younger than age of onset in

Table 3. Clinical Data of Pediatric Patients on Hemodialysis Who Died

Patient	Age at Disease Onset, y	Duration of Disease, mo	Duration of Dialysis, mo	Primary Renal Disease	Cause of Death
1	13	24	6	Systemic lupus erythematosus	Pulmonary embolism
2	10	16	12	Unknown	Unexplained
3	14	30	9	Antiphospholipid syndrome	Pulmonary embolism
4	9	11	7	Fabry with glomerular disease	Acute heart failure
5	8	87	8	Focal segmental glomerulosclerosis	Arteriovenous fistula thrombosis, amputation, and sepsis
6	9	44	13	Steroid-resistant nephrotic syndrome	Ventricular fibrillation, heart failure
7	5	10	10	Unknown	Encephalitis
8	4	31	6	Steroid-resistant nephrotic syndrome	Sepsis
9	7	97	83	Steroid-resistant nephrotic syndrome	Acute abdomen, rupture of splenic cyst
10	3	32	7	Urological disorder	Unexplained
11	5	112	100	FSGS	Fulminate hepatic failure (while on treatment for tuberculosis)
12	4	8	8	Unknown	Sepsis
13	7	76	60	Urological disorder	Hypertensive crisis, heart failure
14	4.5	8	8	Unknown	Unexplained
15	9	74	74	Unknown	Acute heart failure
16	8	21	11	Steroid-resistant nephrotic syndrome	Unexplained
17	2.5	55	38	Congenital nephrotic syndrome	Heart failure during pneumonia
18	8	120	120	Interstitial nephrites	Acute hepatic failure (while on amphotericin B therapy for fungal infection)
19	4	28	16	Urological problem	Heart failure
20	11	120	96	Systemic lupus erythematosus	Sepsis
21	1.5	18	2	Urological disorder	Heart failure
22	9.5	87	9	Steroid-resistant nephrotic syndrome	Sepsis
23	6	31	31	Unknown	Pneumonia and heart failure
24	6.6	19	12	Shunt nephritis	Encephalitis

countries like India, as the median age of those patients was 13 years and only 6.25% of patients were under 5 years of age.[8] Other Indian centers reported 33% of there patients were under 5 years of age.[9] This proves the geographic variability in age of onset.

In our study, glomerulonephritis was the most common cause of ESRD (35.5%). As the 1st most common cause of ESRD, this seems to be close to the Indian data, which presented that the most common causes of ESRD in Indian children were glomerulonephritis (36%),[9] and in other studies, the most common cause was glomerulonephritis (37.5%).[10] Our finding matches also data from Thailand as another developing country with 34.7% of ESRDs due to chronic glomerular diseases.[10] In our study, the 2nd cause of ESRD was unknown 33.3%, and this relatively high percentage reflects one of our problems of medical staff awareness and suspicions, especially of vague symptoms like failure to thrive, refractory anemia, recurrent unexplained fever or other symptoms which in systematic reviewing centers may point to possibility of renal problem. This may agree with some other countries with the same socioeconomic status as the Egyptian citizens, especially those our university hospital is covering, which is a mixed community of urban and rural people. This comes close to other Egyptian data published in the textbook of *Pediatric Nephrology*, 6th edition, that glomerular diseases present 26% of causes of chronic kidney disease; unknown etiology, 28%; urinary obstruction, 31%; and reflux nephropathy, 15%.[1]

The third most common cause of ESRD in our patients was represented by hereditary urological

malformations, similar to what is reported on Swedish and Tunisian children,[2] which describe glomerular diseases as the leading cause of ESRD, followed by urological malformation,[11,12] while in Turkey, estimation of urological problems such as vesicoureteral reflux, which accounts around 18.5% of cases of ESRD, is close to our percentage, but it is the 1st cause of ESRD in their study.[13] Our rate of 17.8% is much lower than 52% in Indian children,[8] and the Italian project which estimated the leading causes of chronic kidney disease to be urinary tract malformations (53.6%) and isolated hypodysplasia (13.9%), whereas glomerular disease accounted for as few as 6.8%.[14]

By revising our laboratory data we found our patients' mean hemoglobin level was lower than the target hemoglobin for those patients, which is 11 g/dL to 13 g/dL (hematocrit, 33% to 36%), according to the Kidney Disease Outcomes Quality Initiative guidelines for management of anemia in pediatric dialysis patients.[15] This low hemoglobin level may be explained by inadequate recombinant erythropoietin dosage or frequency of administration due to financial restrictions and hyporesponsiveness to given recombinant erythropoietin due to iron deficiency, which is the most common cause of this hyporesponsiveness. Causes underlying this pathology and the subsequent contribution of absolute or functional iron deficiency to renal anemia include inadequate intake of dietary iron, blood loss during the extracorporeal procedure in hemodialysis patients, blood loss from the gastrointestinal tract, too frequent diagnostic blood tests, inadequate intestinal iron absorption and inhibition of iron release from macrophages (anemia of chronic disease), and lastly, increased iron requirements during therapy with erythropoiesis-stimulating agents.[16] Our patients had a combination of these factors leading to low hemoglobin level in them.

In our study, also we found a high level of ferritin (1200 µg/L), while the upper ferritin level recommended for adults and children with chronic kidney disease is 500 µg/L.[15] This might be explained by shortage of recombinant erythropoietin that leads to more frequent blood transfusion, intravenous administration of iron when needed to maintain target hemoglobin levels,[17] chronic inflammatory conditions accompanying chronic kidney disease, raising serum ferritin as one of acute phase reactants, and abnormal iron trafficking by abnormal hepcidine, the regulator of iron status, which may lead to iron deficiency with high serum ferritin.

Our results show that the main cause of hospital admission was uncontrolled hypertension. Mitsnefes and colleagues[18] showed that 57% of children on long-term dialysis had blood pressure above the age-, sex-, and height-specific 95th centile, and this could be explained by changes in patients' dry weight, salty food and bad food habits, and relatively poor treatment compliance with much medication and long duration of therapy.

Vascular access complications represented by thrombosis, infection, or malfunction. This finding is similar to the data of a 20-year retrospective review of 304 vascular access procedures performed in children, reporting a median survival of arteriovenous fistula of 3.1 years.[19]

The third common cause of admission was heart failure and cardiovascular morbidity, which agrees with standard reports of morbidity in cases with ESRD.[20] Mortality in our 11-year follow-up was 26.7%, mainly due to heart disease, that makes us conclude that ESRD has a poor prognosis in our unit, which is higher than 4% to 8% in North America,[21,22] but close to 16% in India,[8] 18% in Kingdom of Saudi Arabia,[23] and 14% as reported by Offner and coworkers.[24] A high death rate can be explained by long duration of dialysis due to lacking transplantation and it is well established that the longer the duration on dialysis the higher the mortality rate. The mortality rates were 30-times higher than for children without chronic kidney disease.[25,26] Dialysis treatment was also associated with a mortality risk more than 4-times higher than for children who had received a transplant, younger age at the start as a risk factor. Our transplantation law restrictions come from restricting donors to living related ones only.

Life span is reduced by 40 to 60 years in children on dialysis, with 50% of deaths due to cardiovascular diseases.[1] The main cause of death in our patients was cardiac (35%), this agrees with Tim and colleagues who reported that a 1000-fold increased risk of cardiovascular mortality in young adults (25 to 29 years of age) treated for ESRD,[27] also this goes with most of similar studies which described the cardiovascular disease as the single most common cause of death in their

chronic kidney disease patients.[28] Causes of death specified are, cardiopulmonary disease was the reason cited most often, at 21.5% overall and for each specific age group. While the Dutch Registry data attributes 41% of deaths to cardiovascular disease,[29] Rukshana and colleagues reported that cardiovascular disease accounted for 57% of deaths in children on hemodialysis.[30] By analyzing the underlying disease and mortality rate we found no relation between these. This matches the United States Renal Data System 2006 report, which cites primary diagnosis as an independent determinant of mortality for children on dialysis.[31]

CONCLUSIONS

Maintaining an appropriate care for children with ESRD in developing countries is quite difficult due to many factors including late referral of children with chronic kidney failure, poor acceptance of parents to ask medical service, limitation of financial resources to supply high-cost medication for replacement therapy, and poor logistic and availability of transplantation with the limitation of laws that restrict transplantation to living related donors and complexity of pediatric transplantation in such condition. Since our ESRD children have to be treated with hemodialysis for long periods, they are exposed to a high risk of complications. We found that the most common cause of ESRD was glomerular disease in our pediatric patients, followed by urological problems. The main reason for hospital admission was uncontrolled blood pressure, followed by arteriovenous fistula complications, while the main cause of death was cardiac disease, accounting for one-third of deaths.

CONFLICT OF INTEREST

None declared.

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