Paediatrica Indonesiana

VOLUME 51 July • 2011 NUMBER 4

Original Article

Admission characteristics of pediatric chronic kidney disease

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Abstract

Background Chronic kidney disease (CKD) in children is a potentially fatal disease if left untreated. Early detection and treatment are important to slow progression to end-stage renal disease requiring dialysis.

Objective We aimed to find characteristics of CKD patients at admission and evaluate factors associated with end-stage CKD (stage 5).

Methods Our cross-sectional study was based on medical records of CKD patients aged less than 18 years in Cipto Mangunkusumo Hospital, Jakarta, from January 2007 to December 2009. Diagnosis and stages of CKD were based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) criteria. Data on disease etiology, symptoms, nutritional status and laboratory tests were collected. Bivariate and multivariate analyses were performed to examine the association between end-stage CKD and its possible risk factors.

Results Of the 142 cases eligible for analysis, 55% were boys. Subjects' median age was 73.5 months (interquartile range of 23.5-122.5 months). Edema and recurrent fever were the two most frequent symptoms of CKD if diagnosed at stages 2-4, while breathlessness was the most frequent symptom of CKD if diagnosed at stage 5. The most common etiologies were glomerulonephritis (49.3%) and anomalies of the kidney and urinary tract (32.4%). Of our CKD subjects, 21.8% were in stage 5. Independent predictors of stage 5 CKD at presentation were hypertension (OR 3.88; 95% CI 1.17 to 12.87; P=0.026), urea level > 60 mg/dL (OR 39.11; 95%CI 4.86 to 314.74; P<0.001) and non-glomerulonephritis as the etiology (OR 6.51; 95%CI 2.12 to 19.92; P<0.001).

Conclusion Glomerular disease was the most common cause of CKD in our study. Stage 5 CKD was present in 21.8% of subjects at admission and could be predicted by the presence of hypertension, high serum urea level, and non-glomerular disease as the etiology. **[Paediatr Indones. 2011;51:192-7]**.

Keyword: *pediatric chronic kidney disease, end-stage renal failure, risk factors*

Chronic kidney disease (CKD) is a major public health problem worldwide. Pediatric CKD comprises a small portion of total CKD population, but it has a substantial impact since the mortality rate of a child with end-stage renal disease (ESRD) requiring dialysis is estimated to be 30 times higher than that of the general pediatric population.[1] In early stages of pediatric CKD, therapeutic interventions may be targeted to change the course of the disease and avoid ESRD. Therefore, primary prevention, early detection and aggressive management should be emphasized for CKD patients. This requires a comprehensive knowledge of CKD epidemiology in children and its associated clinical risk factors.[2]

Data on the frequency of pediatric renal insufficiency at the community level is limited and is often based on patients who underwent dialysis therapy or kidney transplant. A prospective study in Italy, the Italkid Project, was conducted on pre-dialysis CKD patients. This study revealed that in patients aged < 20 years, the incidence of a glomerular

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filtration rate < 75 mL/minute/1.73m^2 body surface area (BSA) was 12.1 cases per year per 1 million children. The disease prevalence was reported to be 74.4 per 1 million population.[3] Using the same criteria, a Turkish study found an incidence rate of 10.9 cases per 1 million children.[4]

The burden of pediatric renal disease in Indonesian children is largely unknown due to the lack of a national reporting and recording system. As a developing country, the cost of renal replacement therapy would be too high for most patients. Therefore, early detection and adequate management is important to delay disease progression. This study is a preliminary report on CKD in Indonesian children. We aimed to define the characteristics of CKD patients at admission and evaluate factors associated with end-stage CKD.

Methods

A cross-sectional study was conducted on children with CKD aged < 18 years, admitted to Cipto Mangunkusumo Hospital, between 1 January 2007 and 31 December 2009. Data was retrieved from medical records and consisted of demographic characteristics, clinical signs and symptoms, and laboratory evaluation. Age was defined as the patient's age at the initial diagnosis of CKD. Informed consent was obtained in each case.

Diagnosis of CKD was based on the K/DOQI criteria.[5] CKD staging was defined according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines.[6] Briefly, the diagnosis of stage 1 CKD was based on kidney abnormalities found in the imaging test or in the composition of the blood or urine, persisting for 3 months or more, with a normal glomerular filtration rate (GFR). CKD in stages 2-5 was diagnosed if the patient had a GFR < 60 mL/min/1.73m^2 BSA, lasting for 3 months or more. GFR was calculated with the Schwartz formula: 0.55 x height (cm) / serum creatinine (mg/dL).[7] The only nephrotic syndrome patients we enrolled in this study were the steroid-resistant, steroid-dependent and congenital cases. Presumptive diagnoses of primary chronic glomerulonephritis were made by the presence of proteinuria and/or hematuria and hypertension. Other secondary glomerulonephritides, such as lupus nephritis or Henoch Schonlein purpura, were diagnosed accordingly. Renal tubular acidosis was diagnosed based on the presence of hyperchloremic metabolic acidosis and normal anion gap. Blood pressure was measured according to the recommendation of the Task Force on Blood Pressure in Children.[8]

Normally distributed data were presented as mean (standard deviation), while skewed data was presented as median and interquartile range. Factors associated with stage 5 CKD were analyzed by Chi-square test with a 95% confidence interval. Variables with a P value < 0.25 in bivariate analysis were included in the multivariate analysis. Predictors of stage 5 CKD were identified by applying binary logistic regression. All analyses were performed with SPSS for Windows PC version 13.0 (SPSS Inc., Chicago, Illinois, USA).

Results

During the three year period, 150 CKD pediatric cases were identified, with 142 of these having sufficient data to be eligible for further analysis. Boys comprised 55% of the subjects, with a male-to-female ratio of 1.2:1. Subjects' median age was 7 years (73.5 months) with an interquartile range of 23.5 to 122.5 months. Children with kidney and urinary tract anomalies presented at an earlier age than those with acquired disorders (median 26.5 *vs.* 96 months, respectively).

Subjects were classified according to their estimated GFR level at presentation. Distribution was almost equal across the CKD stages, except for stage 4 CKD. End-stage renal disease (ESRD or stage 5 CKD) was found in 31 (21.8%) cases. (**Table 1**) Among those with ESRD, 13 of 31 children (42%) had kidney and urinary tract anomalies as the etiology. Renal replacement therapy was initiated in 15 (48.4%), comprised of 5 undergoing peritoneal dialysis and 10 undergoing hemodialysis. The remaining 16 patients refused dialysis and they received conservative treatment.

The two most common causes of CKD were glomerulonephritis (GN) and kidney and urinary tract anomalies, together accounting for more than 80% of all cases. (**Table 2**) However, in GN patients,

Table 1. Characteristics of the study subjects (n=142)

Characteristics	N	%
Sex		
• Male	78	55
• Female	64	45
Age group		
• 0 – 5 years	66	46
• > 5 – 12 years	55	39
• > 12 years	21	15
Chief complaint at admission		
• Edema	39	28
• Recurrent fever	34	24
• Dyspnea	18	13
• Rash/ butterfly rash	15	11
• Seizures	12	9
• Failure-to-thrive	6	4
• Urine/micturation abnormalities	5	3
• Intrauterine screening	3	2
• Others	10	7
Nutritional status		
• Good	81	57
• Overweight	11	8
• Poor	50	35
Stage of CKD		
• Stage 1	41	29
• Stage 2	29	20
• Stage 3	29	20
• Stage 4	12	8
• Stage 5	31	22

Table 2. The etiologies of CKD in children (n=142)

Glomerulonephritis	70	49%
• Acquired nephrotic syndrome	37	
• Lupus nephritis	16	
• Primary chronic glomerulonephritis	7	
• Henoch-Schoenlein nephritis	7	
• Diabetic nephropathy	1	
• Congenital nephrotic syndrome	2	
Anomalies of kidney and urinary tract	46	32%
• Hydronephrosis/hydroureter	11	
• Neurogenic bladder	7	
• Pelvioureteral junction obstruction	6	
• Vesicoureteral junction obstruction	3	
• Posterior urethral valve	3	
• Ureterocele	2	
• Primary VUR	2	
• Unilateral renal hypoplasia/agenesis	4	
• Bilateral kidney hypoplasia	4	
• Others (polycystic kidney, obstructive megaureter, mega-kidney, post traumatic urethral stricture)	4	
Tubular disease	7	5%
Urinary tract stone	6	4%
Chronic pyelonephritis	5	3%
Malignancy	5	3%
• Wilm's tumor	2	
• Retinoblastoma	1	
• Chronic myeloid leukemia	1	
• Bladder rhabdomyosarcoma	1	
Unknown	1	1%

histopathological diagnoses were unavailable because kidney biopsies were not routinely performed.

Characteristics of the subjects were collected to determine their relationship with stage 5 CKD (ESRD), as shown in **Table 3**. ESRD presentation was significantly higher in children with poor nutritional status, hemoglobin level <10 g/dL, blood urea level > 60 mg/dL, dyspnea, and hypertension. However, ESRD was significantly lower in children with edema, skin rash, and recurrent fever.

After adjusting for potential confounders, we observed that the independent risk factors for stage 5 CKD or ESRD were hypertension, blood urea level > 60 mg/dL, and non-glomerulonephritis disease etiology. In contrast, children presenting with recurrent fever were less likely to present with ESRD. (**Table 4**)

Discussion

This is the first Indonesian study on CKD in children following the introduction of the CKD terminology by the K/DOQI in 2002. Our hospital is a national, tertiary, referral hospital which receives a substantial number of children with complex uronephrological problems. Therefore, patients' characteristics described here may not represent the true population of pediatric CKD nationwide. However, our study subjects may share common characteristics of pediatric CKD with other developing countries, where delayed diagnosis is often the cause of late-stage kidney dysfunction.

We found that about half of children with acquired disorders were diagnosed around 8 years of age, whereas children with kidney and urinary tract anomalies primarily due to congenital disorders were diagnosed at about 2 years of age. There were 3 referred neonates who were determined to have urological anomalies while in utero. In comparison, an epidemiological study on children with chronic renal failure in Sweden reported that children with congenital disorders were diagnosed at a median age of 3.3 years, while those with acquired disorders had a median age of 11.3 years at diagnosis.[9] In the ItalKid Project, the mean age at diagnosis was 6.9 years,[3] whereas in Turkey[4] and Sudan,[10] children were diagnosed at older ages, 8.0 and 9.8 years, respectively.

Table 3. Factors associated with end-stage chronic kidney disease at admission (n=142)

Variable	CKD Stage		Total	P value
	Stage 1-4	Stage 5		
Sex				
• Male	59 (75.6)	19 (24.4)	78 (100)	0.42
• Female	52 (81.3)	12 (18.8)	64 (100)	
Age group				
• 0 – 6 years	60 (83.3)	12 (16.7)	72 (100)	0.13
• > 6 years	51 (72.9)	19 (27.1)	70 (100)	
Etiology				
• Congenital disease	36 (72.0)	14 (28.0)	50 (100)	0.19
• Acquired disease	75 (82.4)	17 (17.6)	92 (100)	
Nutritional status				
• Good/ Overweight	77 (83.7)	15 (16.3)	92 (100)	**0.03**
• Poor	34 (68.0)	16 (32.0)	50 (100)	
Hemoglobin level				
• ≥ 10 g/dL	68 (93.2)	5 (6.8)	73 (100)	**<0.001**
• 10 g/dL	43 (62.3)	26 (37.7)	69 (100)	
Ureum level				
• ≤ 60 mg/dL	81 (98.8)	1 (1.2)	82 (100)	**<0.001**
• > 60 mg/dL	30 (50.0)	30 (50.0)	60 (100)	
Edema				
• No	75 (72.8)	28 (27.2)	103 (100)	**0.01**
• Yes	36 (92.3)	3 (7.7)	39 (100)	
Breathlessness				
• No	107 (86.3)	17 (13.7)	124 (100)	**<0.001**
• Yes	4 (22.2)	14 (77.8)	18 (100)	
Rash				
• No	96 (75.6)	31 (24.4)	127 (100)	**0.04**
• Yes	15 (100)	0	15 (100)	
Seizures				
• No	104 (80.0)	26 (20.0)	130 (100)	0.18
• Yes	7 (58.3)	5 (41.7)	12 (100)	
Recurrent infection				
• No	78 (72.2)	30 (27.8)	108 (100)	**0.002**
• Yes	33 (97.1)	1 (2.9)	34 (100)	
Hypertension				
• No	95 (84.8)	17 (15.2)	112 (100)	**<0.001**
• Yes	16 (53.3)	14 (46.7)	30 (100)	

Table 4. Multivariate analysis to predict end-stage CKD at admission

Variable	OR	95%CI	P
Hypertension	3.88	1.17 to 12.87	0.03
Recurrent fever	0.06	0.01 to 0.60	0.02
Blood urea >60 g/dL	39.11	4.86 to 314.74	<0.001
Etiology – non-glomerulonephritis	6.51	2.12 to 19.92	<0.001

Developmental abnormalities involving the kidney and urinary tract have been reported to be the most common causes of CKD in children.[3,4,11] In contrast, we found that glomerular disease was the more common etiology, comprising 49.3% of the cases. A study in Sudan reported similar findings, though to a lesser degree, in that chronic glomerulonephritis was identified as the main cause of chronic renal failure (25.4%).[10] It is possible that the higher prevalence of glomerulonephritis in our subjects was due the higher rate of patient referrals to our tertiary center, as patients with glomerulonephritis have more obvious

symptoms, such as edema, the most common symptom leading to kidney disease. Our results might also represent a failure in early diagnoses of congenital anomalies in the kidney and urinary tract cases before the occurrence of renal impairment, since the clinical manifestations of these cases were non-specific and some patients were even asymptomatic. Children with this abnormality usually came for urinary tract infections, but not all received proper work-ups to exclude underlying abnormalities of the kidney and urinary tract.

The most frequent etiologies of glomerulonephritis in our series of cases were idiopathic nephrotic syndrome and lupus nephritis. Nephrotic syndrome was also observed as the most common etiology of CKD in KwaZulu-Natal, South Africa, with 30.9% in children aged $\leq$ 5 years and 40.8% in children $>$ 5 years.[12]

The prevalence of ESRD at presentation in our study was 21.8%. This number is much lower than that found in the studies in Turkey (32.5%)[4] and Sudan (63%).[10] We found the highest percentage of ESRD in the group of children with kidney and urinary tract anomalies, while most available data has shown that progression towards ESRD in patients with congenital renal disorders is much slower than in patients with glomerular disease.[13,14] These findings emphasize the necessity of using recurrent UTIs as a precursor to search for kidney and urinary tract anomalies, such that if indicated, early correction or intervention can prevent declines in renal function. A substantial proportion of these ESRD patients (51.6%) refused to have dialysis, despite extensive discussions with parents, and none were willing to have kidney transplantation. Living in rural areas far from the dialysis center and poor family finances were the major reasons given.

We found correlations between ESRD at presentation and nutritional status, hemoglobin level, urea level, dyspnea and hypertension. More frequent and complicated co-morbidities were associated with advanced stages of CKD. Dyspnea may be due to metabolic acidosis or fluid overload, and we were unable to determine the etiology. Children with ESRD grow poorly, and the current challenge in clinical management of CKD is to optimize care based on factors affecting growth or to reverse growth retardation. These factors affecting growth may also affect progression to ESRD.[15-17] Anemia is also a complication of CKD, often developing in stage 3. Anemia is largely due to relatively inadequate production of erythropoietin. Anemia increases with increasing CKD stage and has been significantly associated with hospitalization risk.[4,18-20]

Among the clinical factors associated with ESRD, we found non-glomerular disease, hypertension and urea level of $>$ 60 g/dL to be independent predictors at admission. Therefore, any child presenting with hypertension and high urea levels, without an obvious acute cause, should be suspected of having end-stage renal failure. However, if the child also has a recent history of recurrent fever, the presence of stage 5 CKD would be less likely.

Systemic hypertension often accompanies CKD as a consequence of underlying renal disease and may also contribute to CKD progression.[18,21] A pediatric study found that as many as 54% of subjects had either systolic or diastolic BP $\geq$ 95th percentile, or a history of hypertension plus current antihypertensive use.[22] Therefore, the presence of hypertension in children should prompt the pediatric nephrologist to look further for underlying glomerulonephropathy. In the recent report of the National Institutes of Health (NIH) task force on research priorities in CKD in children, Chesney *et al*. pointed out the necessity of prevention research to identify risk factors for long-term kidney disease, including growth, anemia and hypertension.[23]

The prediction model of our study was limited by the study design. We used a cross-sectional design since there was no previous data on CKD and its clinical factors. A prospective study with the proportional hazard model would be more appropriate for identifying risk factors associated with disease progression to CKD stage 5. A recent study in Brazil showed that primary renal disease, CKD stage and proteinuria at admission were identified as significant predictors of disease progression to CKD stage 5.[14,17]

We found that glomerular disease was the most common cause of CKD in children. The most common presenting symptoms were edema and recurrent fever, except for stage 5 CKD patients who usually present with shortness of breath. ESRD was present in 21.8% of subjects at admission and may be predicted by the presence of hypertension, high

urea level and non-glomerular disease as the etiology. Further prospective study is needed to identify risk factors for disease progression in children with early stage CKD.

Acknowledgement

The author would like to thank Dr. Levina S. Pakasi for her valuable contribution in performing the statistical analysis.

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