World Journal of Nephrology

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DOI: 10.5527/wjn.v5.i2.213

World J Nephrol 2016 March 6; 5(2): 213-219
ISSN 2220-6124 (online)

ORIGINAL ARTICLE

Observational Study

Chronic kidney disease in children and adolescents in Brunei Darussalam

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Institutional review board statement: The study was reviewed and approved by the Medical Health Research and Ethics Committee and the Ministry of Health, Brunei Darussalam.

Informed consent statement: The authors confirmed that informed consent from patients is not needed for this study. The data were pooled and anonymized and would not reveal identities of any patients.

Conflict-of-interest statement: The authors confirmed that there is no conflict of interest.

Data sharing statement: The authors gave informed consent for data sharing.

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Received: June 8, 2015
Peer-review started: June 10, 2015
First decision: September 17, 2015
Revised: December 9, 2015
Accepted: December 29, 2015
Article in press: January 4, 2016
Published online: March 6, 2016

Abstract

AIM: To determine epidemiology of Bruneian paediatric chronic kidney disease (CKD) patients and factors that affect growth and progression of disease.

METHODS: A cross-sectional study conducted on all children below 18 years old who were diagnosed with CKD over a ten year period (2004 to 2013). The reference population was all children (< 18 years old) suffering from CKD and attending the tertiary paediatric nephrology clinic in Brunei Darussalam. Demographic (current age, age of diagnosis, gender, ethnicity), anthropometric (weight and height), diagnosis, laboratory data (serum creatinine and haemoglobin, urinalysis) and blood pressure were extracted from the patients' clinical case notes and recorded using a data collection form.

RESULTS: The study revealed a high national prevalence [736 per million child population (pmcp)] and incidence (91 pcmp) of CKD. If CKD was defined at Stage 1, 2, 3, 4 or 5, the associated prevalence figures were 736, 132, 83, 50 and 33 pmcp. Glomerulonephritis accounted for 69% of all prevalent cases, followed by congenital abnormalities of kidney and urinary tract (20%) and tubulointerstitial diseases (8%). Minimal change disease being the most common histological diagnosis. The median age of diagnosis was 4.5 years, with congenital disease patients experiencing an earlier onset of diagnosis. A large

proportion of patients were below the 5% percentile for height and weight. Non-glomerular diseases, adolescent and female patients were significantly associated with poor growth, but not glomerular filtration rate, age of diagnosis or steroid usage.

CONCLUSION: Brunei has a high prevalence of chronic kidney disease in the paediatric population with glomerulonephritis being the most common disease.

Key words: Brunei; Children; Adolsecent; Chronic kidney disease; Epidemiology

Core tip: This study provides demographic data for chronic kidney disease (CKD) in children and adolescents in Brunei Darussalam. Due to the small population, referral pattern and healthcare infrastructure of the country, the authors believe that the research has enabled a closer estimate of national prevalence and incidence of all stages of CKD than most countries. To our knowledge, this study is the first of its kind to report on epidemiology of CKD from the earliest stages.

Tan SY, Naing L, Han A, Khalil MAM, Chong VH, Tan J. Chronic kidney disease in children and adolescents in Brunei Darussalam. *World J Nephrol* 2016; 5(2): 213-219 Available from: URL: http://www.wjgnet.com/2220-6124/full/v5/i2/213.htm DOI: http://dx.doi.org/10.5527/wjn.v5.i2.213

INTRODUCTION

Chronic kidney disease (CKD) affects almost 500 in 1 million people per year, among which 1%-2% are in the paediatric age range (0-17 years old)[1]. Childhood and adolescent CKD, particularly in later stages, are associated with serious cardiovascular, neurologic, metabolic and other clinical complications. Further understanding in the epidemiology of CKD plays a fundamental role in identifying populations at risk as well to evaluate the interventions undertaken. Existing paediatric epidemiological data on incidence and prevalence are flawed by methodological differences between the various data sources in characterising age groups, degree of renal insufficiency and disease classifications[2]. Most of the robust and available CKD data are extrapolated from national registries with adult ESRD cohorts in developed countries. To date, there are scarce epidemiological data on paediatric patients with earlier stages of CKD, especially in developing Asian countries where there are limited procedures and activities to collect and publish valid epidemiological data.

In Brunei Darussalam, there has been no published or collated information for this group of patients. Therefore, this study serves to determine the epidemiological characteristics and clinical factors [gender, diagnosis, glomerular filtration rate (GFR), steroid usage] affecting growth and progression of kidney disease in the Bruneian paediatric CKD population. Additionally, comparisons were also made with data from pub-med listed literature on demographics and characteristics of international paediatric CKD patients.

MATERIALS AND METHODS

This was a cross-sectional study conducted on all children below 18 years old who were diagnosed with CKD over a ten year period (2004 to 2013). The reference population was all children (< 18 years old) suffering from CKD and attending the tertiary paediatric nephrology clinic in Brunei Darussalam. All available cases were included without sampling. Demographic (current age, age of diagnosis, gender, ethnicity), anthropometric (weight and height), diagnosis, laboratory data (serum creatinine and haemoglobin, urinalysis) and blood pressure were extracted from the patients' clinical case notes and recorded using a data collection form.

Weight and height retardation were defined as less than fifth percentile on the Disease Control and Prevention (CDC) growth charts[3]. CKD was defined as GFR < 60 mL/min per 1.73 m^2 or the presence of kidney damage (structural or functional abnormalities other than decreased GFR) for more than three months[4]. GFR was estimated by Schwartz's formula when height was recorded[5]. The value of *k* varied with age and gender, being 0.33 in preterm infants (< 1 year old), 0.45 in full-term infants (< 1 year old), 0.55 in children (< 13 years old) and adolescent girls (≥ 13 years old), and 0.70 in adolescent boys (≥ 13 years old)[5]. For children without height records (n = 3), eGFR-Pottel's formula was used[6,7]. Anaemia was defined by the Clinical Practice Guidelines of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI guidelines) as haemoglobin level less than a specific threshold which varied with children's age and gender[3]. Blood pressure readings were compared with blood pressure tables for children and adolescents, which were dependent on age and height. The diagnosis and classification of hypertension were accorded with National Heart, Lung, and Blood Institute (NHLBI)'s guidelines[8].

RESULTS

The male to female gender ratio was 1.3:1. Socio-demographic characteristics and aetiological diseases of the study sample are shown in Table 1. The most common aetiology was glomerular diseases (n = 61) followed by congenital abnormalities of kidney and urinary tract (CAKUT) and tubulointerstitial diseases. Nine out of 61 cases were biopsied with minimal change disease (n = 4) being the most common histological diagnosis. The median age of diagnosis (data skewed to the right) was 4.5 (IQR = 6.0) years, with congenital disease patients

Table 1 Socio-demographic characteristics of study sample (89 patients)

Variable	*n* (%)	Mean (SD)
Current age (yr)		11.3 (4.12)
1-4	1 (1.1)	
5-9	30 (33.7)	
10-14	36 (40.4)	
15-18	22 (24.7)	
Gender		
Male	51 (57.3)	
Female	38 (42.7)	
Race		
Malay	76 (85.4)	
Chinese	9 (10.1)	
Others	4 (4.5)	
Aetiology		
Glomerular	61 (68.5)	
CAKUT	20 (22.5)	
Tubulointerstitial	8 (9.0)	

CAKUT: Congenital abnormalities of kidney and urinary tract.

Table 2 Anthropometric, clinical and laboratory characteristics of the study sample

Variable	*n*	*n* (%)	Mean (SD)	Median (IQR)
Weight in kilogram	87		-	29.90 (23.60)[1]
< 5th percentile		22 (25.3)		
⩾ 5th percentile		65 (74.7)		
Height in cm	74		-	123.70 (27.60)[2]
< 5th percentile		23 (31.1)		
⩾ 5th percentile		51 (68.9)		
Systolic blood pressure (mmHg)	79		111.8 (13.86)	-
Diastolic blood pressure (mmHg)	79		70.9 (10.40)	-
Normal		40 (50.6)		
Pre-hypertensive		12 (15.2)		
Stage 1 hypertension		21 (26.6)		
Stage 2 hypertension		6 (7.6)		
Haemoglobin level (g/dL)	82		12.7 (1.65)	-
Normal		63 (76.8)		
Anaemia		19 (23.2)		
eGFR (mL/min per 1.73 m^2)	86		124.6 (52.99)	-
Stage 1 (> 90)		70 (81.4)		
Stage 2 (60-89)		6 (7.0)		
Stage 3 (30-59)		4 (4.7)		
Stage 4 (15-29)		2 (2.3)		
Stage 5 (< 15)		4 (4.7)		
Proteinuria	82		-	-
Yes		42 (51.2)		
No		40 (48.8)		
Haematuria	82		-	-
Yes		21 (25.6)		
No		61 (74.4)		

[1]The distribution is skewed to the right; [2]The distribution is skewed to the left. eGFR: Estimated glomerular filtration rate; IQR: Interquartile range.

experiencing an earlier onset of diagnosis.

Twenty-five point three percent and thirty-one point one percent of patients were under the 5% percentile for weight and height respectively. Patients with non-glomerular disease were found to be statistically most likely to have growth hindrance (P = 0.001 and P = 0.003 for weight and height respectively). A significant proportion of patients were hypertensive (34.2%) and anaemic (23.2%). Proteinuria and haematuria were present in 51.2% and 25.6% of patients respectively. The majority of patients were in Stage 1 CKD (81.4%) but 4 patients (4.7%) had end stage renal disease (on peritoneal dialysis). The anthropometric, clinical and laboratory characteristics of the study sample are shown in Table 2. The study found that there was no significant correlation between GFR and age of diagnosis with weight and height (Table 3). Steroid usage was not associated with growth attenuation (P = 0.111 and P = 0.579 for weight and height respectively) in patients with glomerular disease. However female, adolescent and non-glomerular patients were statistically more likely to experience growth attenuation. Details are shown in Tables 3 and 4.

Table 3 Correlation between glomerular filtration rate, current age and age of diagnosis with weight and height

		Weight	Height
GFR	Correlation coefficient	0.168[1]	0.176[1]
	P value	0.125	0.140
	n	85	72
Current age	Correlation coefficient	0.609[1]	0.541[2]
	P value	0.001	0.001
	n	87	74
Age at diagnosis	Correlation coefficient	0.450[1]	0.368[2]
	P value	< 0.001	0.002
	n	84	71

[1]Spearman's rank correlation; [2]Pearson's correlation. GFR: Glomerular filtration rate.

Based on population statistics for children of Brunei Darussalam, the age adjusted annual incidence of CKD over the 10 year range (2004-2013) is shown in Figure 1. The cumulative incidence and prevalence of all stages of CKD in 2013 were 91 and 736 per million child population (pmcp) respectively.

DISCUSSION

There is limited literature on the epidemiology of CKD in the paediatric population. Most paediatric patients with mild CKD are not represented in national registries, due to the asymptomatic nature of the condition. From our local experience, diseases with a more "dramatic" presentation like glomerulonephritis were more likely to be picked up and followed up by nephrologists. "Silent disease" may be missed especially in developing countries where screening, diagnosis and awareness of diseases may not be as extensive and comprehensive. The major difficulty in comparing studies is the inconsistent criteria used to define CKD. Our interpretation of the literature revealed that it is commonplace to disregard CKD stage

Table 4 Relationship between gender and aetiology with weight and height

	Weight		χ^2 statistic (*df*)	*P* value[1]	Height		χ^2 statistic (*df*)	*P* value[1]
	< 5th percentile *n* (%)	⩾ 5th percentile *n* (%)			< 5th percentile *n* (%)	⩾ 5th percentile *n* (%)		
Gender								
Male	9 (17.6)	42 (82.4)	3.81	0.051	10 (21.7)	36 (78.3)	4.95	0.026
Female	13 (36.1)	23 (63.9)	(1)		13 (46.4)	15 (53.6)	(1)	
Aetiology								
Glomerular	9 (15.0)	51 (85.0)	10.83	0.001	10 (20.0)	40 (80.0)	8.84	0.003
Non-glomerular	13 (48.1)	14 (51.9)	(1)		13 (54.2)	11 (45.8)	(1)	

[1]χ^2 test for independence.

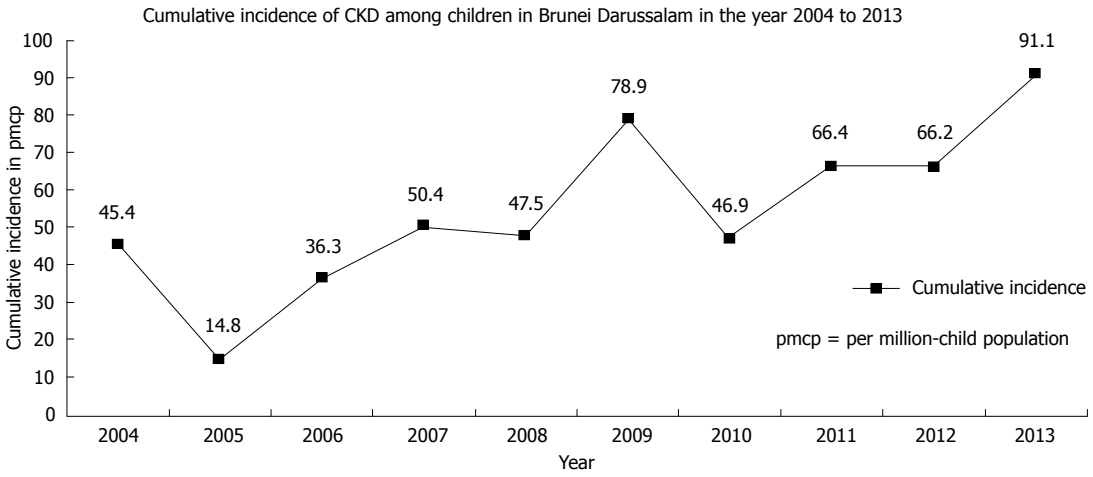

Figure 1 Cumulative incidence of chronic kidney disease among children in Brunei Darussalam in the year.

1 due to the lack of tangible physical and serological evidence of kidney impairment. However one can argue that such paediatric patients (*e.g.*, nephrotic syndrome in remission) are debatably at higher risk of future kidney damage than their GFR-matched adult counterparts (with age related deterioration) due to the inherent reduced threshold for renal injuries and longer lifelong exposure to renal insults. For this research, we have made a conscious effort to include patients with all stages of CKD in an attempt to elucidate the true estimate for CKD prevalence and incidence in our population.

Our research revealed an estimated incidence and prevalence that is higher than most countries. However, if CKD definitions were set at Stage 1, 2, 3, 4 and 5, then the calculated prevalence would be 736, 132, 83, 50 and 33 pmcp respectively. The incidence of CKD in Brunei has shown progressive increments in the ten year period from 2004 to 2013, consistent with trends in the adult population[9]. Local data from the Brunei Dialysis and Transplant Registry revealed a prevalence of 75 pmp in the young adult ESRD (CKD stage 5D) population (age 19-30), with a similar trend of increment over the last ten years[10]. If only CKD stage III or lower patients are to be considered, our prevalence of 83 pmcp is on par with data from European studies with similar CKD profiles like Italy (74.7 pmcp)[11], Belgium (56 pmcp)[12] and Spain (71.1 pmcp)[13]. The prevalence of paediatric ESRD (33 pmcp) was also consistent with trends from developed Western and affluent Asian countries[14]. Data from other developing Asian countries were available but direct comparisons on incidence and prevalence were difficult because of the difference in patients' population. Table 5 compares Bruneian data with PubMed listed literature (from the past 15 years) on prevalence, incidence and other demographic data from other countries.

There were some important differences between the aetiology of kidney diseases in our cohort with the local adult population and the international paediatric literature. The spectrum of disease differed markedly from our adult population, where diabetes mellitus and hypertension were the main aetiological diseases[9]. There appeared to be a progression of importance for diabetes mellitus as an aetiological cause with increasing age. Glomerulonephritis (52%), diabetes mellitus (23%) and CAKUT (15%) were the three main causes of ESRD in our young adult population (age 19-30)[10]. Globally, congenital causes (CAKUT) accounted for the most common aetiology among paediatric CKD[2]; this was reported in developed countries including United States[15], United Kingdom[23] and Italy[11]. However, only twenty patients (22.5%) were diagnosed with congenital anomaly in this study. On the contrary,

Table 5 Comparisons of paediatric epidemiological data from different countries from 1990-2015

	Period	No. of patients	Main aetiology	Male/female ratio	Mean age at diagnosis	GFR/CKD stage	Incidence	Prevalence
Brunei	2004-2013	89	GN (69%)	1.3	4.5	Mainly CKD 1 (81%)	91	736 (CKD1) 132 (CKD2 and above) 83 (CKD3 and above) 50 (CKD4 and above) 33 (CKD5)
Italy[10]	1990-2000	1197	CAKUT (58%)	2.0	6.9	GFR 42 (mean)	12.1	75
Belgium[11]	2001-2005	143	CAKUT (59%)	1.3	3.0	Mainly CKD 3 (67%)	11.9	56
Spain[12]	2007-2008	605		1.9	3.9	GFR 52 (mean)	8.7	71
United States[15]	1994-2007	7037	CAKUT (48%)					
Kuwait[16]	1996-2003	171	CAKUT 62%	2.7	33 mo	30% of patient reached ESRD within 18 mo of diagnosis	38-55	
Vietnam[17]	2001-2005	152		1.7	11.3	65% received RRT		5.1
Sudan[18]	2001-2006	205	GN 25%	1.7	9.8	63% of cohort reached ESRD during the follow up period		
Turkey[19]	2005	282	"Urological problem" 44.3%	1.3	8.0	CKD2-5	11.9	
Thailand[20]	1982-2005	101	GN 35%	1.6			Not rare	Double in last 6 yr of research
Jordan[21]	1988-2001	202	CAKUT 42%	1.3	7.5	59/202 patients require RRT	10.7	51
China[22]	1990-2002	1658	GN 52%	1.5	8.18	Mean serum creatinine 594.7 mmol/L		

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; CAKUT: Congenital abnormalities of kidney and urinary tract; GN: Glomerulonephritis; ESRD: End stage renal disease.

there was a high prevalence of glomerular diseases (68.5%), comparable to published data from developing countries like Vietnam[17], Sudan[18], Thailand[20] and Malaysia[24]. It has been postulated that high proportions of glomerulonephritis may be related to high prevalence of bacterial, viral and parasitic infections that commonly affect the kidneys in developing countries[14]. Furthermore, many paediatric CKD patients with CAKUT may have been referred directly to surgeons, with no subsequent follow up by nephrologists. As many of these patients do not have overt clinical symptoms, there may have been a delay in presentation of renal disease. This may have led to the patients being missed by this research leading to an underestimate of the prevalence of this disease.

Our study reports a male preponderance of 1.3. This is universally consistent with all the published studies in the literature which reported a range between 1.3 and 2.7. This gender disproportionality can be explained by the higher incidence of congenital disorders (obstructive uropathy, renal dysplasia and prune belly syndrome) in boys[9]. Even after excluding these congenital defects, boys were still more likely to be affected by CKD[11]. The median age of diagnosis (4.5 years) was similar to developed European countries (range of 3.3-6.9 years) but lower than developing Asian countries (range of 7.5 to 13 years). We suspect that this is related to healthcare infrastructure and health seeking behaviours of the population rather than the intrinsic characteristics of the disease in the population.

Poor growth in children with CKD is associated with increased morbidity and mortality[25]. A significant proportion of our patients were below the 5th percentile for weight (25.3%) and height (31.1%). This is not unusual for children with CKD due to congenital predisposition, electrolyte imbalances, malnutrition, bone disease and medications[26]. Hamasaki *et al*[27] revealed that Asian CKD patients with congenital anomalies, lower GFR, being small for date and asphyxia at birth are more likely to have growth impairment. Our research showed that female and adolescent patients are more likely to experience growth attenuation. Adolescent patients usually experience growth spurts in their teenage years and it is not surprising to find that growth attenuation is maximal during this period. We observed other studies[28,29] also derived similar results with females being more antropometrically challenged than males, likely from a difference in age when they experience their growth spurts. Consistent with some literature reports[30,31], this study did not find an association with steroid usage and growth attenuation in patients with glomerular disease. This suggests that GN diseases were predominantly steroid responsive and steroid regime was consistently kept to a minimum. This study also showed that there was no correlation between GFR and growth (weight and height), which corresponded with some reports from the literatures[32,33]. We were not able to find an association between clinical and epidemiological factors linked with progression of renal disease.

We acknowledge that the sample size of this study is small and this may have affected the statistical evaluation of clinical and demographic factors, particularly in

association with growth. Since this is a retrospective study, there were some incomplete datasets from patients that were lost on follow up. We would also have like to scour paediatric, urological and general practitioner clinics for unreferred CKD patients but this would have gone beyond the realms of the ethical agreement set for the study.

This study is the first to describe the epidemiology of CKD among children and adolescents in Brunei Darussalam. The spectrum of disease is dissimilar to that in our adult population. We reported a higher incidence and prevalence than most countries because we were able to capture patients at earlier stages of their diseases. Our clinic is a one-stop referral centre for all cases of paediatric CKD in the country and we believe that it enables us to capture most of the symptomatic CKD patients in the country, regardless of stages of disease. We believe that this is unique as it allows us to predict the true scale of paediatric CKD and provide a closer estimate of national prevalence and incidence of CKD than most other countries. Furthermore, this study has heightened our awareness of growth attenuation and highlighted the need for early involvement of dieticians, nutritionists and social workers to improve the nutrition, education and social welfare of future paediatric CKD patients in our clinics.

COMMENTS

Background

Demographic data on paediatric patients with chronic kidney disease (CKD) are limited. This is especially true for patients with earlier stages of CKD and from developing countries. This study provided epidemiological characteristics of Bruneian patients from all five stages of CKD. In addition, analysis was done to elucidate factors that may have affected growth of patients and progression of renal disease. The study revealed a high national prevalence [736 per million child population (pcmp)] and incidence (91 pcmp) of CKD. If CKD was defined at Stage 1, 2, 3, 4 or 5, the associated prevalence figures were 736, 132, 83, 50 and 33 pcmp. Glomerulonephritis accounted for 69% of all prevalent cases. A large proportion of patients were below the 5% percentile for height and weight. Non-glomerular diseases, adolescent and female patients were significantly associated with poor growth, but not glomerular filtration rate, age of diagnosis or steroid usage.

Research frontiers

In comparison with other studies, the authors believe that we have a closer national estimate of CKD in the paediatric population due to our ability to capture CKD patients through our one-stop tertiary clinic and the relative small population in the country. Additionally, the authors identified that a significant proportion of the patients have attenuated growth, prompting us to advocate early interventions by nutritionists, dieticians and social workers to supplement treatment options by physicians to augment and intensify growth and physical development.

Innovations and breakthroughs

The authors believe that the authors are one of very few studies to predict the prevalence and incidence of CKD in the paediatric population, particularly for the earlier stages of diseases where patients may remain asymptomatic. More studies will be needed to evaluate this further.

Applications

Knowledge of national prevalence and incidence of CKD in the paediatric population can help service providers plan future population needs for renal replacement therapy and can help public health promotion exercises to identify early disease and to delay progression to irreversible end stage renal disease.

Terminology

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; KDOQI: National Kidney Foundation's Kidney Disease Outcomes Quality Initiative; CAKUT: Congenital abnormalities of kidney and urinary tract; GN: Glomerulonephritis; ESRD: End stage renal disease; Pmcp: Per million child population.

Peer-review

A reasonable first analysis of congenital pediatric renal disease in a previously unstudied population with findings in the range of what might has been predicted.

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