Analysis of Factors Associated with Renal Function in Chinese Adults with Congenital Solitary Kidney

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Abstract

Background Patients with congenital solitary kidney have an increased risk of developing hypertension, proteinuria and renal insufficiency. However, the specific factors associated with the progression of renal function in adults with congenital solitary kidney remain still unclear. The purpose of this study was to identify factors that are independently associated with renal function progression in patients with congenital solitary kidney.

Methods Sixty-five Chinese adults with congenital solitary kidney (48 patients with unilateral renal agenesis and 17 with severe unilateral renal dysplasia) were recruited into our study retrospectively. Clinical data were analyzed.

Results Of sixty-five patients with congenital solitary kidney, the prevalence of hypertension, proteinuria and renal insufficiency was 36.9%, 35.4% and 38.5%, respectively. There was no significant difference in the glomerular filtration rate (GFR) between patients with and without hypertension, whereas GFR in patients with proteinuria was significantly lower than in those without proteinuria ($p < 0.05$). While there was no statistically significant difference in prevalence of hypertension between patients with and without renal insufficiency, the prevalence of proteinuria in patients with renal insufficiency was significantly higher than in those without renal insufficiency ($p < 0.05$). Logistic regression analysis revealed that kidney length and proteinuria were independently associated with the progression of renal function (OR=0.20, 95%CI 0.05-0.79, and OR=8.30, 95%CI 2.30-29.96, respectively).

Conclusion Hypertension, proteinuria or renal insufficiency was present in approximately one-third of adults with congenital solitary kidney. Those with a kidney length of less than 120 mm or proteinuria had a much higher risk of renal insufficiency.

Key words: congenital solitary kidney, renal function, unilateral renal agenesis, unilateral renal dysplasia

(Inter Med 49: 2203-2209, 2010)

(DOI: 10.2169/internalmedicine.49.3742)

Introduction

Congenital solitary kidney, at least including unilateral renal agenesis (URA) and severe unilateral renal dysplasia (URD), is one of the most common variations of congenital anomalies of the kidney and urinary tract (CAKUT), which account for a significant portion of morbidity and mortality, collectively representing a significant cause of chronic kidney disease (CKD) in children and young adults (1-4). A patient with congenital renal mass reduction does not mean a significantly reduced number of nephrons. It is possible

that a single functioning kidney could have extra nephrons as a consequence of intrauterine adaptation of nephrogenesis. Maluf (5) demonstrated that the congenital solitary kidney has twice as many nephrons and is 1.8-fold heavier than the normal kidney. Animal experiments and investigations in human beings also showed such evidence (6, 7). It is believed that the changes are beneficial. However, once beyond a certain limit compensatory adaptation results in a gradual decline in renal function and focal segmental sclerosis of glomeruli due to glomerular hyperperfusion, hyperfiltration, and hypertension (8, 9).

From the point of view of auxology, both URA and URD

result from aberrant outgrowth of the primary ureteric bud and/or disturbed interactions of the bud with metanephric mesenchyme (10, 11). As a condition of congenital severe renal mass reduction, children with URA or URD have a predisposition to hypertension, proteinuria and impaired renal function. Mei-Zahav et al (12) and Dursun et al (13) evaluated blood pressure in children with solitary kidney by ambulatory blood pressure monitoring, and found that the URA children had an elevated mean 24 hours systolic blood pressure, which had an inverse correlation with renal size. In one study, Schreuder et al (14) found that 50% children with congenital solitary kidney were hypertensive, using antihypertensive agents and/or had microalbuminuria. Seeman et al (15) found hypertension and reduced renal function in 57% and 43% of the URA children with abnormal contralateral kidneys respectively. González et al (16) studied children with chronic renal failure secondary to renal dysplasia, and found that both albuminuria and hypertension were related to deterioration of renal function.

Children with reduced nephron mass could have a predisposition to adult-onset diseases such as hypertension and chronic renal failure (17). In one long-term follow-up of renal functional reserve capacity after unilateral nephrectomy in childhood, although blood pressure and urinary albumin excretion increased with an interval of more than 25 years, renal function was well maintained at approximately 75% of the reported normal two-kidney value (18). Unlike adult patients suffering from a unilateral nephrectomy, adults with congenital solitary kidney frequently developed proteinuria and renal insufficiency. Wikstad et al (19) demonstrated that significant microalbuminuria occurred in 47% of the patients and was more frequent with a longer follow-up period, however neither hypertension nor renal insufficiency was found. In one retrospective study (20), proteinuria, hypertension and impaired renal function were found in 19%, 47% and 13% of patients respectively. Gonzalez et al (21), in a follow-up of adults with unilateral renal agenesis and remnant kidney, demonstrated that 63% of them had proteinuria and renal insufficiency with a higher blood pressure and body mass index at presentation, and during the follow-up, 9 patients developed proteinuria and renal insufficiency.

To date, although proteinuria, hypertension and impaired renal function occur in patients with congenital severe renal mass reduction, factors associated with progression of renal function in adults with congenital solitary kidney remain still unclear. In the present study, we retrospectively reviewed Chinese URA adults with URD, to identify factors that are independently associated with renal function progression.

Methods

Study subjects

Sixty-five Chinese adults (48 patients with URA and 17 with URD) were recruited through a retrospective review of

disease history data from 2006 to 2009 collected at Department of Nephrology, Ruijin Hospital affiliated to Shanghai Jiao Tong University. All of the patients were scanned by renal ultrasonography and ^{99m}Tc -diethylene triamine pentaacetic acid (DTPA) renoscintigraphy. The 48 patients with URA showed a single kidney without a history of nephrectomy. The 17 patients with severe URD showed a nonfunctioning kidney without cysts that atrophied in volume at least 50% of its parenchyma. Secondary causes of the small kidney such as chronic pyelonephritis, renal tuberculosis and renal artery stenosis were excluded from this study. Careful family history investigation and physical examination were performed for every patient.

Data collection

Demographic, clinical and laboratory data were collected from medical charts at Department of Nephrology, Ruijin Hospital affiliated with Shanghai Jiao Tong University. Body Mass Index (BMI) was calculated by dividing weight (kg) by height (m) squared. Blood pressure was recorded as the average of 3 measurements at the visit. Hypertension was defined as: 1) systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, or 2) on antihypertensive medications including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and calcium channel blockers (CCB).

Location and length of the solitary kidney were assessed by ultrasonography with the adult in the supine position. Glomerular filtration rate (GFR) was calculated accurately by ^{99m}Tc -DTPA renoscintigraphy. The GFR value in the patient with URD was represented only by the functioning kidney. Renal insufficiency was defined as a GFR less than 60 mL/min/1.73 m².

Serum creatinine and uric acid concentrations were determined by picric kinetic method and enzymatic method, respectively. Patients were considered to have proteinuria if the urinary albumin-creatinine ratio (ACR) in milligrams per millimole (mg/mmol) was higher than 10 mg/mmol at least in 3 consecutive measurements. Some patients were being treated with drugs that reduce the amount of urinary protein, thus we considered those patients as positive proteinuria.

Statistics

Parameters with a normal distribution were expressed as mean and standard deviation, and analyzed using the Student's t-test. Parameters that did not have a normal distribution were expressed as median and interquartile range, and analyzed using the Mann-Whitney test. The chi-square test was used for comparing proportions. Backward elimination logistic regression analysis was performed to identify factors that were independently associated with renal insufficiency. Those variables that ceased to make significant contribution to the model were eliminated in a stage-wise manner, yielding a final model. SPSS version 13.0 (SPSS Inc., Chicago, IL) statistics programs were used for statistical calculations. $p < 0.05$ was considered statistically significant in all analy-

Table 1. Clinical Characteristics of Adults with Congenital Solitary Kidney

	URA ^a (n=48)	URD ^b (n=17)	P
Age at diagnosis(years)*	28.9±10.2	35.6±9.9	0.022
Gender(M/F)	30/18	6/11	>0.05
Kidney location (L/R)	23/25	10/7	>0.05
Height at follow-up(mm)*	169.3±6.2	167.8±5.8	>0.05
Weight at follow-up(kg)*	63.3±7.0	62.8±3.2	>0.05
Family history of CAKUT ^c	4(8.3%)	2(11.8%)	>0.05
Family history of hypertension	3(6.3%)	1(5.9%)	>0.05
Genital tract anomaly	4(8.3%)	1(5.9%)	>0.05

Results are presented as *mean ±SD.

a: unilateral renal agenesis. b: unilateral renal dysplasia.

c: congenital anomalies of the kidney and urinary tract.

Table 2. Parameter Comparisons between Patients with and without Hypertension

	With hypertension (n=24)	Without hypertension (n=41)	P
Age (years)*	41.5±13.4	33.9±12.2	0.022
Gender(M/F)	16/8	20/21	>0.05
Kidney location(L/R)	13/11	20/21	>0.05
BMI ^a (kg/m ²)*	22.3±1.4	22.1±1.9	>0.05
Kidney length (mm)*	116.2±16.2	119.2±13.3	>0.05
Creatinine(umol/L) [‡]	106.2(44.3)	91(31.7)	0.028
Uric acid(umol/L)*	408.4± 76.9	348.1± 98.5	0.012
Proteinuria (%)	54.2	24.4	0.015
24h urinary protein(mg) [‡]	777.5(1573.0)	94.0(137.0)	0.023
GFR ^b (mL/min)*	54.2±24.5	63.3±22.7	>0.05

Results are presented as *mean ±SD or #median (interquartile range).

a: body mass index. b: glomerular filtration rate using ^{99m}Tc-DTPA renoscintigraphy.

ses.

Results

Of the 65 patients with congenital solitary kidney, 48 were diagnosed as having URA and 17 as URD (Table 1). On average, the diagnosis of URA was made at an earlier age. Both patients with URA and URD were found to have family histories of CAKUT. Extrarenal anomalies were only presented as genital tract anomalies (four female URA patients with didelphic uterus and oblique vaginal septum, one male URD patient with verumontanum cysts). Diabetes mellitus was found in one male patient with URA. None of the patients had a history of vesicoureteral reflux, or dysfunction of eyesight, audition and olfactus.

When this study was being carried out, the mean age of the patients with congenital solitary kidney was (36.7±13.1) years. Twenty-five (38.5%) patients developed renal insufficiency, and two started chronic dialysis. Twenty-four (36.9%) patients were found to have hypertension in which ten (15.4%) were using antihypertensive agents. Twenty-three (35.4%) patients had proteinuria and eight (12.3%) were treating with protein reduction medicines. The number of patients with both hypertension and proteinuria was 13 (20.0%), and 31 (47.7%) of them had neither hypertension nor proteinuria.

Based on hypertension, the patients were divided into two groups. The patients without hypertension were younger than those with hypertension ($p<0.05$). Although there was no difference in kidney length or GFR between patients with and without hypertension, the comparisons of several other parameters showed significant differences (Table 2).

Comparisons of parameters between the patients with and without proteinuria are shown in Table 3. The mean age in the patients with proteinuria was older ($p<0.05$). Both kidney length and GFR were lower in the patients with proteinuria than in those without proteinuria ($p<0.05$, respectively), whereas creatinine level, uric acid level, and the prevalence of hypertension were higher ($p<0.05$, respectively).

The patients with renal insufficiency had a shorter kidney length, higher levels of serum creatinine and uric acid level (Table 4). Both the prevalence of proteinuria and the amount of twenty-four hour urinary protein were significantly higher in patients with renal insufficiency as well. However, the comparisons of age, BMI and prevalence of hypertension between groups showed no statistically significant differences.

By univariate analysis, kidney length as well as ACR, were the only factors statistically associated with the risk for renal failure progression among the 65 patients. By multivariate analysis, both kidney length (OR=0.20, 95%CI 0.05-0.79, $p=0.02$) and ACR (OR=8.30, 95%CI 2.30-29.96, $p=$

Table 3. Parameter Comparisons between Patients with and without Proteinuria

	With proteinuria (n=23)	Without proteinuria (n=42)	p
Age (years)*	41.7±12.9	34.0±12.5	0.022
Gender(M/F)	13/10	23/19	>0.05
Kidney location(L/R)	16/7	17/25	0.025
BMI ^a (kg/m ²)*	22.2±1.5	22.1±1.8	>0.05
Kidney length (mm)*	106.7±15.5	124.3±9.1	<0.001
Creatinine(umol/L) [#]	128.0(79.0)	85.0(21.5)	<0.001
Uric acid(umol/L)*	433.1±81.7	336.0±84.4	<0.001
Hypertension (%)	56.5	26.2	0.015
GFR ^b (mL/min)*	41.7±24.2	69.9±16.2	<0.001

Results are presented as *mean ±SD or #median (interquartile range).

a: body mass index. b: glomerular filtration rate using ^{99m}Tc-DTPA renoscintigraphy.

Table 4. Parameter Comparisons between Patients with and without Renal Insufficiency

	With renal insufficiency (n=25)	Without renal insufficiency (n=40)	p
Age (years)*	39.5±13.4	35.0±12.7	>0.05
Gender(M/F)	14/11	22/18	>0.05
Kidney location(L/R)	12/13	21/19	>0.05
BMI ^a (kg/m ²)*	22.0±1.5	22.2±1.8	>0.05
Kidney length (mm)*	106.1±14.9	125.6±7.3	<0.001
Creatinine(umol/L) [#]	122.0(78.5)	85.5(20.8)	<0.001
Uric acid(umol/L)*	404.6±101.4	349.0±85.4	0.021
Hypertension (%)	48.0	30.0	>0.05
Proteinuria (%)	64.0	17.5	<0.001
24h urinary protein(mg) [#]	900.0(1546.0)	93.0(73.3)	<0.001

Results are presented as * mean ±SD or #median (interquartile range).

a: body mass index.

Table 5. Variables Influencing the Progression of Renal Insufficiency

Variable	Univariate analysis			Multivariate analysis		
	p value	Odds ratio	95% CI	p value	Odds ratio	95% CI
Age (years)	0.175					
Gender	0.937					
Kidney location	0.724					
BMI	0.572					
Kidney length≥120mm	<0.001	0.06	0.02-0.23	0.02	0.20	0.05-0.79
Hypertension	0.147					
ACR≥10mg/mmol	<0.001	8.38	2.64-26.58	0.001	8.30	2.30-29.96

0.001) remained as statistically significant risk factors (Table 5).

Discussion

Our data showed that the prevalence of hypertension, proteinuria and renal insufficiency, in Chinese population at a mean age of 37 years, was 36.9%, 35.4% and 38.5%, respectively. Patients with kidney length less than 120 mm or proteinuria had much higher risk of renal insufficiency.

Evaluation methods of renal function varied considerably in the previous studies, from creatinine clearance (Ccr) or inulin clearance to estimation by Schwartz formula. Inulin

clearance is an accurate method of measuring GFR, but in clinical practice this method is seldom performed in our country. Although the other two methods were operated conveniently, there are problems of evaluating renal function in patients with one functioning kidney by these methods. Both Ccr and Schwartz formula depend on creatinine level. However, creatinine is not a sensitive factor at an earlier stage of renal failure. Moreover, due to renal tubular excretion of creatinine and limited functional compensation of one kidney (5, 18), there would be a big deviation between the estimated value and the true value. Therefore, we measured GFR by ^{99m}Tc-DTPA renoscintigraphy, which is quite accurate in patients with URA. Additionally, the ^{99m}Tc-DTPA

renoscintigraphy could calculate the GFR of the individual kidney in patients with URD, in whom the GFR of the functioning kidney represented the true value without the interference of the nonfunctioning kidney. In the available literature we found no reports on the use of ^{99m}Tc -DTPA renoscintigraphy to measure GFR in congenital solitary kidney patients.

In several studies the term of renal insufficiency in patients with URA was defined as several criteria including creatinine clearance with a percentile rank less than 2.5% of published age- and sex-specific lower limits (20), serum creatinine concentration higher than 1.4 mg/dL in men and 1.3 mg/dL in women together with Ccr lower than 60 mL/min/1.73 m² (21), GFR lower than 90 mL/min/1.73 m² determined by Schwartz formula (13) and GFR less than 70 mL/min/1.73 m² measured with EDTA (16). In our study we used 60 mL/min/1.73 m² GFR measured by ^{99m}Tc -DTPA plasma clearance as a cut-point for patients stratification, which was consistent with the definition of CKD in Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (22). According to this classification we found 38.5% of patients with GFR of lower than 60 mL/min. Compared with data in other studies, this percentage of patients who developed renal insufficiency was lower than 43% (15) and 66.7% (36 of 54 patients) (21), but higher than 13% (20) and 15% (23).

Patients with congenital solitary kidney often had a larger kidney than normal (7, 24). Hill et al (7) studied renal length in fetuses with solitary kidney, and found that as early as 22 weeks' gestation the lengths of the solitary functioning kidney were increased in 44% of cases assessed by ultrasound. In one histological report (5) the congenital solitary kidney contained more nephrons. After unilateral nephrectomy during the period of normal nephrogenesis in the ovine fetus, final glomerular numbers in the single kidney proliferated strikingly to 70% of that in two normal kidneys (6). It is suggested that failure to undergo compensatory overgrowth usually indicates contralateral renal dysplasia and may predict progressive renal insufficiency. Thus, the short kidney length could be a predictor of kidney insufficiency and proteinuria. In our study, since there was no difference of BMI between groups, we used the length of solitary kidney as measurement of renal size. In our hospital the average renal length in normal kidney function with two-kidney is 10 cm-12 cm, and the width is 5 cm-6 cm. We found that the kidney length was significantly shorter in the patients with proteinuria or renal insufficiency, and the patients with a kidney length of less than 120 mm had a 5-fold higher risk of renal insufficiency.

Proteinuria and hypertension were the most common symptoms in patients with a solitary kidney. In children, Schreuder et al (14) found that 23% of children with congenital solitary kidney had microalbuminuria without hypertension, 50% of them were hypertensive, using antihypertensive agents and/or had microalbuminuria. In children with renal dysplasia, González et al (16) studied the progression

of chronic renal failure in children with dysplasia kidneys, and found deterioration of renal function was related to albuminuria, eGFR (estimated GFR) at onset of deterioration, hypertension, number of febrile urinary tract infections and puberty. Wasilewska et al (24) did not find a significant difference in blood pressure and urinary protein level between children with congenital solitary kidney and controls, however, serum cystatin C levels in the patients was significantly increased.

With the improvement of medical conditions, more and more children with congenital renal disease have been surviving to adulthood. Patients with URA or URD, a condition of congenital severe renal mass reduction, have a predisposition to hypertension, proteinuria and impaired renal function in adulthood. Argueso et al (20) found that 19% of 37 patients with URA developed proteinuria, 47% of 47 patients had hypertension and 13% of 32 patients had impaired renal function at a mean age of 37 years. Based on data from five studies, Oldrizzi et al (23) demonstrated prevalence rates of 40% for hypertension, 46% for proteinuria and 15% for impaired renal function in 39 subjects of mean age 33 years with URA. Our data showed that hypertension was found in 36.9% of the patients, proteinuria in 35.4%, both hypertension and proteinuria in 20.0%, at a mean age of 37 years.

This study revealed that in patients with congenital solitary kidney patients, having proteinuria was associated with a nearly 8-fold higher risk of renal insufficiency, which was compatible with previous findings in adults with two kidneys (25, 26) and children with dysplastic nephropathy (16, 27). Hypertension is another well-known risk factor in adults (25) and children (16, 28). However in our study, patients with hypertension did not show a significant difference in kidney length or GFR, and patients with renal insufficiency did not exhibit a statistically higher prevalence of hypertension either. Moreover in logistical regression analysis, hypertension was not independently associated with the progression of renal function. It is possible that different regulation pathways for water, ions and vasoactive hormones in solitary kidney patients may result in these disparities. A larger sample size needs to be performed in the future.

Sub-clinical defects of the solitary kidney were considered to be responsible for a poorer prognosis compared to more benign forms of CAKUT (29). In our study only four patients were found to be accompanied with genital tract anomalies, most of the patients had an isolated single kidney.

BMI probably was a factor associated with progression of renal function in patients with solitary kidney, as was shown in a retrospective study (21). However, repetitious comparisons of BMI in our study between groups did not show any differences.

Puberty was found to be related to deterioration of kidney function in children with dysplastic kidneys (16). In adults, Gonzalez et al (21) did not find a difference of mean age between the patients with a favorable evolution and those

who developed proteinuria or renal insufficiency, and between the patients with a stable clinical course and those with progressive renal insufficiency. In our patients, the mean age in patients with hypertension or proteinuria was older, however this phenomenon was not observed in patients with renal insufficiency. Additionally, age was not a factor associated with deterioration of renal function in the regression analysis. It probably suggested the individual variation of functional compensation of a single kidney, and intrinsic defects in the remaining nephrons during embryogenesis, like renal dysplasia (30) in some patients even with a normal profile.

In conclusion, adults with a congenital solitary kidney had a risk of developing hypertension, proteinuria and renal insufficiency. Those with a kidney length of less than 120 mm or proteinuria had a much higher risk of renal insufficiency, which warranted a careful evaluation of these factors.

Acknowledgement

We would like to thank all of the patients recruited in our study, and professor Lai Shenghan for statistical analysis in Johns Hopkins Hospital, School of Medicine, Baltimore, MD, USA.

Grants information: This research was supported by the Key Project of Shanghai Science and Technology Committee (No. 07JC14037), and the Major Project of Shanghai Science and Technology Committee (No. 08dz1900502).

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