The Incidence and Durability of Compensatory Hypertrophy in Pediatric Patients with Solitary Kidneys

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OBJECTIVE
To evaluate the incidence and durability of compensatory hypertrophy with solitary kidneys in the setting of those with multicystic dysplastic kidney (MCDK) or Wilms tumor (WT) status postnephrectomy.

PATIENTS AND METHODS
We conducted a retrospective cohort study of patients with MCDK and WT. MCDK patients were verified by sonographic findings prenatally. WT patients entered our study at time of nephrectomy. We compared the natural history of hypertrophy between the 2 cohorts via renal length measurement. We performed linear regression to predict creatinine clearance from renal length after adjusting for age and cohort status (MCDK versus WT).

RESULTS
Fifty-two patients (56%) were diagnosed with WT, and 71 patients (44%) with MCDK patients met study criteria with a median age of postnatal ultrasound at 1.6 months (interquartile range 0.5-3.6). The median (IQR) follow-up time was 7.5 years. At the time of nephrectomy, 25/52 (48%) of Wilms patients had contralateral hypertrophy, while at diagnosis 22/71 (31%) of MCDK patients had contralateral hypertrophy, \(P = .03\). Contralateral hypertrophy was a consistent finding throughout follow-up. As renal length increases by 1 cm, glomerular filtration rate increased by 7.8 mL/min/m\(^2\) (95% confidence interval 1.8-13.8, \(P = .01\)).

CONCLUSION
Contralateral hypertrophy appears to be a compensatory mechanism for unilateral kidney pathology as demonstrated by MCDK and WT patients. Hypertrophy often occurs at the time of diagnosis and appears to be a permanent finding as children reach their teenage years. Additionally, in nonhydronephrotic kidneys, increases in renal length correlate with improvement in glomerular filtration rate. Overall, the majority of children with solitary kidneys demonstrate compensatory hypertrophy.

In patients with a single kidney, the kidney can undergo compensatory hypertrophy to preserve glomerular filtration rate (GFR). This has been well documented in patients undergoing living related donor nephrectomy and those undergoing nephrectomy for tumor removal.\(^{1,3}\) In adults, it has been shown that renal length (as measured by ultrasound) correlates well with GFR.\(^{4,5}\) In children, however, this correlation has not been established. Children may have a solitary kidney for a variety of reasons, including congenital causes such as multicystic dysplastic kidney (MCDK) and acquired causes such as nephrectomy for Wilms tumor (WT).

In children with a solitary kidney, we sought to determine the natural history of compensatory hypertrophy by asking 3 specific research questions: (1) Does compensatory hypertrophy occur invariably in children? While there is previous literature looking into this question in MCDK, the results are conflicting, with 1 study reporting a higher prevalence of compensatory hypertrophy and another study reporting a lower prevalence.\(^{5,7}\) (2) Does compensatory hypertrophy persist into late childhood/early adolescence? (3) Does renal length in kidneys without hydronephrosis correlate with renal function in children? We hypothesize that hypertrophy occurs in the vast majority of children with a functional solitary kidney and will persist into late childhood/early adolescence. Additionally, we hypothesize that renal length in normal solitary kidneys correlate with renal function (GFR). This study seeks to answer these 3 questions using a retrospective chart review of children with MCDK and WT.
SUBJECTS AND METHODS

Study sample

Institutional Review Board committee approval at University of California San Francisco Benioff Children’s Hospitals at Mission Bay and Oakland was obtained for this retrospective cohort study. The patients were identified by searching the radiology report database for 1 of 2 possible phrases: “dysplastic kidney” or “Wilms tumor” to identify any patient with the potential diagnosis of MCDK or a child with WT. The time frame of the search was from 1997 to 2016, which was the longest time frame possible. All cases of MCDK were confirmed via review of sonograms. Eight patients with segmental dysplasia, bilateral cystic disease, and cystic dysplasia associated with ureteroceles or duplicated systems were excluded from analysis. For the WT group, the diagnosis of WT was confirmed with the pathologic report. Only patients who underwent a unilateral nephrectomy with normal contralateral kidney, without hydronephrosis or other genitourinary abnormalities were included in the WT cohort. None of the WT cohort included had hemihypertrophy or genetic syndrome associated with diagnosis. Exclusion criteria included duplicate entries, abnormal contralateral kidney, and MCDK patients with less than 7 years follow-up in order to match follow-up in the WT cohort. Patients were included regardless of presence or absence of creatinine lab draw.

Multiple clinical variables were recorded including: baseline age, sex, affected kidney side, height, weight, blood pressure, and creatinine, where available. We collected contralateral kidney length (cm) in all ultrasound reports available in our records. Although multiple providers completed the ultrasound measurements, renal length has been shown to be a reliable measurement as interobserver ICC’s have ranged from 0.9 to 0.99. Contralateral hypertrophy was defined as 2 standard deviations above the mean kidney length by age. We present hypertrophy in 3 categories: 2 standard deviations above the mean (hypertrophy [2 SD]), 1 standard deviation above the mean (hypertrophy [1 SD]), and below 1 standard deviation above the mean [No hypertrophy]). This was to present our outcome in a more granular fashion. We subsequently compared the natural history of compensatory hypertrophy between the 2 cohorts. We calculated GFR using the Beside Schwartz equation in a subcohort of patients with creatinine measurements. The equation used was GFR = 0.413 × (height/Scr), where height is measured in centimeters and Scr is the serum creatinine. We used the latest creatinine available in our records, and for the correlation analysis (see below), we used the closest renal length measurement to this creatinine draw. Creatinine was available in 32 WT patients and 42 MCDK patients (67% versus 59%, P = .41).

Statistical analysis

All data analysis was performed using Stata v. 13.0 (StataCorp, College Station, TX). We used descriptive statistics to evaluate baseline clinical characteristics by cohort status. We visually inspected the natural history of contralateral hypertrophy starting from time of diagnosis to determine whether or not hypertrophy was a consistent finding over time by collecting data from ultrasonography reports for contralateral renal length. We repeated this analysis in patients in whom we had creatinine clearance. We evaluated the correlation between contralateral kidney length and GFR. We then performed a sensitivity analysis and performed linear regression adjusting for age only and then age and cohort status (Wilms versus MCDK). All P values less than .05 were considered statistically significant, and all tests were 2-sided.

RESULTS

Demographics

During the 20-year study period, there were 685 radiology reports that included the search terms “dysplastic kidney” or “Wilms tumor.” After exclusion criteria were applied, there were 71 MCDK patients (none had nephrectomy for the MCDK kidney) and 52 patients identified with unilateral nephrectomy for WT. None of the WT cohort had bilateral disease or associated genetic syndromes. None of the WT patients had radiation to the nonaffected kidney with 57% undergoing localized radiation to the surgical bed on the side of the nephrectomy. All the WT patients received chemotherapy. Table 1 shows the demographic and clinical characteristics of these 2 groups of patients.

Incidence and persistence of compensatory hypertrophy

For the MCDK patients, 31% already had compensatory hypertrophy of the contralateral kidney at the time of the first postnatal ultrasound. For the WT patients, 48% had compensatory hypertrophy at the time of nephrectomy. After 9 years, 82% of the MCDK patients and 100% of WT patients had persistent compensatory hypertrophy of the unaffected kidney (Fig. 1).

Figure 1 demonstrates the natural history of contralateral hypertrophy in both the MCDK and WT cohort. Contralateral hypertrophy appears to be a consistent finding during follow-up in both cohorts. Similarly, Figure 2 shows both MCDK and WT patients’ renal length by age. Nearly all patient renal lengths were above the 2 standard deviation threshold.

Table 1. Demographic and clinical characteristics of included patients stratified by cohort status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCDK (n = 71)</th>
<th>Wilms (n = 48)</th>
</tr>
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<tbody>
<tr>
<td>Baseline age, median years (IQR)</td>
<td>0.1 (0.04-0.4)</td>
<td>2.7 (1.7-5.6)</td>
</tr>
<tr>
<td>Follow-up time, median years (IQR)</td>
<td>7.8 (4.1-10.0)</td>
<td>7.6 (4.3-10.1)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37 (52)</td>
<td>28 (58)</td>
</tr>
<tr>
<td>Affected kidney, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Left</td>
<td>35 (49)</td>
<td>22 (46)</td>
</tr>
<tr>
<td>Hypertrophy at diagnosis, n (%)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>22 (32)</td>
<td>25 (52)</td>
</tr>
<tr>
<td>Glomerular filtration rate at latest follow-up, median (IQR)</td>
<td>97 (75-115)</td>
<td>104 (95-117)</td>
</tr>
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</table>
GFR and blood pressure
GFR was calculated in 74 patients (32 WT and 42 MCDK). The median GFR was 99 mL/min/1.73 m² (interquartile range [IQR] 84-117). After accounting for age, renal length (cm) had a positive correlation with GFR (β-coefficient = 8.2, 95% confidence interval, 2.1-14.3, P = .009, Table 2). This positive correlation remained significant after adjusting for cohort status. Blood pressure data was collected on both cohorts at time of diagnosis and at time of follow-up. Median systolic blood pressure for patients with MCDK at time of diagnosis and follow-up were 100 mmHg (IQR 90-111) and 106 mmHg (IQR 99-113), respectively. Similarly, for our WT cohort, systolic blood pressures were 116 mmHg (IQR 105-122) at diagnosis and 113 mmHg (IQR 99-123) at follow-up.

DISCUSSION
This study sought to characterize the natural history and clinical significance of compensatory renal hypertrophy in children. By comparing renal ultrasound reports with clinical data in MCDK and WT patients, we were able to answer the 3 questions that we proposed in the affirmative.
Compensatory hypertrophy is a phenomenon known to occur in adult patients who have undergone transplant nephrectomy for renal donation. Studies demonstrate that compensatory hypertrophy occurs in 79.3% of patients with a mean volume increase in the remaining renal unit of 22.4%. Similar results have been shown in adults who have undergone radical nephrectomy for the presence of a renal mass. Contralateral renal hypertrophy up to 13% was noted and did not vary based on age or gender of the patient. Additionally, the median GFR change in the remaining hypertrophied kidney improved by 21.1% after radical nephrectomy. Both studies demonstrated a trend that hypertrophic response was blunted as age at nephrectomy increases. Children and neonates on the other hand, show a robust hypertrophic response and this has been replicated in rat models. Young rats underwent a 407% increase in renal volume after unilateral nephrectomy as opposed to their comparative adult model in which renal volume improved by only 81%.

Contralateral renal hypertrophy could be a safety mechanism for the remaining kidney to filter blood and excrete urine. Two main theories of compensatory renal hypertrophy have been proposed. (1) Increased glomerular filtration activity by the remaining kidney leading to hypertrophy and (2) Release of a kidney specific factor in response to the absence kidney and/or unilateral nephrectomy that signals the remaining kidney to under compensatory renal hypertrophy. Multiple growth factors such as hypoxia inducible factor and pathways such as the mTORC pathway have been implicated as the putative molecular mechanism of compensatory hypertrophy. Irregardless of our lack of understanding of the exact mechanism of compensatory hypertrophy our bodies appear to have an inherent signaling mechanism that initiates growth of the contralateral kidney when its mate is threatened with either absent function, such as MCDK or imaging, and (3) correlates positively with renal function. Additionally, the time to compensatory hypertrophy has been debated. Alaygut et al reported that solitary kidneys secondary to contralateral MCDK should complete compensatory hypertrophy by 17.5 months, and the subsequent renal growth after this parallels normal growth. From our MCDK cohort we were able to determine that 31% of infants presented with compensatory hypertrophy at birth, while by 2.5 years nearly 55% of had demonstrated contralateral renal growth above 2 standard deviations from normal. Persistent hypertrophy 1 or 2 standard deviations above the mean was noted in 85% of patients in late childhood/early adolescence (Fig. 2). Limited studies have been done following children with solitary kidneys into adulthood to evaluate for persistent renal hypertrophy. Aslam demonstrates that at 10 years follow-up 81% of patients with a solitary kidney secondary to MCDK had compensatory hypertrophy. Similarly, at our institution another study was performed on over 400 children with MCDK to evaluate for the natural history of contralateral renal length and despite following children over 10 years, not all children developed compensatory hypertrophy. The trends we observe for our MCDK cohort represent those found in other studies.

Surprisingly, 48% of patients presenting at time of WT surgery demonstrated compensatory hypertrophy in standard deviations above the expected mean renal length. This persisted into late childhood/adolescence for all children that had follow-up in to age 8.7-14 years with 100% demonstrating compensatory hypertrophy (Fig. 2). Similar rates of compensatory hypertrophy are observed in other studies, with rates of up to 68% noted and renal volume ranging from 112% to 140% of normal but this does not always portend to renal health. A recent prospective study examined WT patients after mean 24.8 years of follow-up from surgery, chemotherapy, and ± radiation therapy and identified that 83.3% had ultrasound detected compensatory hypertrophy. Despite this, 55.9% of these patients had lower GFR estimates than the norm for their age group. Contributing factors towards lower GFR estimates include bilateral disease in 2% of patients, while 100% of patients received chemotherapy with some receiving nephrotoxic regimens and 59.5% received radiation treatment, similar to our cohort in which 100% of patients received chemotherapy and 57% received radiation therapy (albeit not to remaining nonaffected kidney).

Table 2. Correlation of renal length and glomerular filtration rate in patients with solitary kidneys

<table>
<thead>
<tr>
<th>Renal length (by 1 cm increase)</th>
<th>All Patients</th>
<th>Age Adjusted</th>
<th>Cohort and Age Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>β-coefficient (95% CI)</td>
<td>β-coefficient (95% CI)</td>
<td>β-coefficient (95% CI)</td>
</tr>
<tr>
<td>P value</td>
<td>0.5 (−2.9 to 3.9)</td>
<td>8.2 (2.1-14.3)</td>
<td>7.8 (1.8-13.8)</td>
</tr>
</tbody>
</table>

showing that (1) prevalence of compensatory hypertrophy is high occurring in the majority of patients, (2) compensatory hypertrophy persists into late childhood/early adolescence, and (3) correlates positively with renal function.
not have normal renal function and therefore do not undergo compensatory hypertrophy (~4% of patients in our recently published series). A possible explanation is that a MCDK in a small majority of patients maybe a sign of global renal dysfunction highlighted by the lack of compensatory hypertrophy in the remaining kidney.

It has been hypothesized that compensatory hypertrophy in the long-term may be deleterious in that hyperfiltration and ultimately renal insufficiency will occur. We did not see any evidence of this phenomenon in either our MCDK or cohort during the study period.

Regarding pediatric patients, there are limited studies that evaluate renal length correlation to GFR. One of such studies verifies that there is a correlation between kidney size and GFR but this was performed in children with neuropathic bladder and bilateral kidneys. Adult patients have been evaluated to assess if renal length or volume can correlate to renal function. Kidney volume has been emphasized as a more accurate predictor of kidney health and estimates the mass of functioning nephrons. For adults with chronic kidney disease, small patient studies correlate kidney volume to GFR. Similar studies demonstrate analogous results but utilizing renal length instead of volume to estimate residual renal function in those on hemodialysis. This is encouraging for resource poor medical care that laboratory values may not be always necessary. Renal length by ultrasonography has also been correlated with MRI imaging for predicting chronic kidney disease in patients with autosomal polycystic kidney disease, indicating ultrasonography can be just as effective as advanced imaging technologies. Currently, renal length remains a steadfast measurement commonly reported and easily calculated by radiologic technicians.

Large limitations of these studies include patients with renal disease or those with bilateral functioning kidneys. We sought to identify only children with a solitary functioning, nonhydronephrotic kidney to reduce any confounding variables like dysplasia. Additionally, we were able to identify a useful point of reference that 1 cm of renal length can equate to a 7.8 mg/mL/1.73 m² improvement in GFR. This is only relevant in patients without hydronephrosis or other renal anomalies. Additionally, renal length does not necessarily correlate to renal health in those with WT as they likely systemic chemotherapy, which may have caused microscopic damage to the kidney.

Limitations of the study include use of reported renal measurements from ultrasonography. In the ideal scenario, all imaging studies would have been rereviewed by a single pediatric radiologist to reduce interobserver error. Additionally, not every patient had creatinine and subsequently GFR measurements performed limiting our knowledge of possible renal dysfunction within the population. Those patients with creatinine results in our records may be different than patients without creatinine results. The Bedside Schwartz formula may overestimate GFR in patients where creatinine clearance is above 75 mL/min/1.73 m² depending on the method of serum creatinine calculation. Therefore, the absolute creatinine clearance presented in our analysis may be overestimated; however, we do not anticipate this misclassification to be dependent on renal length measurements. This non-differential misclassification would bias our results toward the null and thus our estimates may underestimate the relationship between renal length and creatinine clearance. Lastly, the ideal matched cohort for MCDK patients would be patients who underwent a nephrectomy secondary to trauma, but this is a small cohort with limited data available. The WT cohort received systemic treatment for oncologic control and therefore poses a potential risk of future renal dysfunction not detectable by ultrasonography. Future areas of study would include the use of renal volume calculated by either ultrasonography or 3D reconstruction utilizing contrast tomography.

Additionally, our hypertrophy cut-offs were based off children from an older study. Our study evaluated children between 1997 and 2016 and there is reasonable time overlap with the Konus patient population. It is possible that children from this study differed in terms of height compared to the patients in our study. To test this limitation, we examined the height range within this study compared to patients in our study. We had height data at diagnosis available in 12 WT patients and 30 MCDK patients. In the WT patients, 11/12 was within the range of the Konus et al population, and 1 patient was below their height range. The range of height in patients less than 3 months of age in the control group was 48-64 cm, whereas the median and IQR of height in our MCDK patients was 52 (49-76) cm. This suggests we may be overestimating hypertrophy in this group; however, we do not expect this misclassification to change the rate of hypertrophy within the cohort. Additionally, height is one of the strongest predictors of renal length, not country of origin. In fact, Spira et al 2009 estimates the correlation between height and renal length to be anywhere from \( r^2 = 0.8-0.86 \). As our WT cohort were in the exact same height range as those in the Konus et al article as provided in the supplemental table, we do not believe that estimating hypertrophy off these values introduces bias.

Lastly, as our correlation analysis used actual renal length and not “hypertrophy” status, we do not anticipate this misclassification to affect the regression study estimate. Further long-term data is necessary to define hypertrophy in childhood that represents favorable renal health outcomes in adults.

CONCLUSION
Compensatory hypertrophy of a solitary kidney is typical, persistent, and correlates well with renal function. Therefore, solitary kidney lengths that fall below expected lengths should prompt further clinical workup to identify causative abnormalities and prevent possible renal insufficiency. Future studies are needed to evaluate the exact mechanism of renal hypertrophy in the setting of a solitary kidney.
References