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ORIGINAL ARTICLE

Widespread kidney anomalies in children with Down syndrome

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Abstract

Background Rare autopsy studies have described smaller kidneys as well as urinary tract anomalies in Down syndrome. This observation has never been investigated in vivo and little is known about the possible consequences upon kidney function. Here we wish to confirm whether children with Down syndrome have smaller kidneys and to evaluate their kidney function in vivo.

Methods This retrospective cohort study enrolled 49 children with Down syndrome, as well as 49 age- and sex-matched controls at the Queen Fabiola Children's University Hospital in Brussels, Belgium. Doppler and kidney ultrasonography, spot urine albumin to creatinine ratio, estimated glomerular filtration rate (eGFR), and anthropometric data were recorded.

Results Kidney size in children with Down syndrome was smaller than age- and sex-matched controls in terms of length ($p < 0.001$) and volume ($p < 0.001$). Kidney function based on eGFR was also decreased in Down syndrome compared to historical normal. Twenty-one of the children with Down syndrome (42%) had eGFR < 90 mL/min/1.73 m^2, with 5 of these (10%) having an eGFR < 75 mL/min/1.73 m^2. In addition, 7 of the children with Down syndrome (14%) had anomalies of the kidney and/or urinary tract that had previously been undiagnosed.

Conclusions Children with Down syndrome have significantly smaller kidneys than age-matched controls as well as evidence of decreased kidney function. These findings, in addition to well-noted increased kidney and urologic anomalies, highlight the need for universal anatomical and functional assessment of all individuals with Down syndrome.

Keywords Down syndrome · Trisomy 21 · Kidney anomalies · Kidney size · CAKUT

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Abbreviations

eGFR	Estimated glomerular filtration rate
CKD	Chronic kidney disease
BSA	Body surface area
IDMS	Isotope-dilution mass spectrometry
PACS	Picture archiving and communication system
SD	Standard deviation

Introduction

Kidney and urinary tract anomalies have been considered to constitute the fourth most common major congenital birth defect in Down syndrome, preceded by heart defects and gastrointestinal and musculoskeletal anomalies, with prevalences at birth varying between 0.03 and 3.2% [1–3]. An increased frequency of kidney and urinary tract pathology developing later in life has also been reported in individuals with Down syndrome [4–7]. Little is known about the cause of these congenital anomalies and their long-term

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effects on kidney function. Though not the most severely handicapping, the vast majority of children with Down syndrome have various ocular anomalies [8–10] with an even higher prevalence of congenital ocular anomalies relatable to hypoplasia [10–13]. With shared features of development, there are a number of known associations between ocular and kidney anomalies. These appear most specifically in the von Hippel-Lindau and papillorenal syndromes, both related to abnormalities of angiogenesis [14–16]. We hypothesized that the degree of kidney involvement in Down syndrome might have been yet underestimated and that, similar to the papillorenal syndrome, in addition to congenital anomalies of the kidney and urinary tract, smaller kidney size and reduced function might also be highly prevalent.

Two prior autopsy studies in individuals with Down syndrome had reported reductions in kidney mass, one revealing a 14.4% decrease [17], and the other 31.1% [18]. However, in vivo kidney size in children with Down syndrome has not yet been systematically assessed. Using kidney ultrasonography, we wished to determine whether smaller kidneys are a developmental feature of children with Down syndrome as compared to healthy controls. Urinary tract anomalies, eGFR, and albuminuria were also evaluated.

Methods

Type of study

This is a single-center, retrospective cohort study comparing the association of children with Down syndrome (Trisomy 21) as an exposure to those without Down syndrome, with kidney size and function.

Subjects and setting

Forty-nine children with Down syndrome, aged between 0 and 18 years, and forty-nine age- and sex-matched healthy volunteers between October 2017 and May 2019, were prospectively included in the study to compare kidney parameters.

The subjects included were children with Down syndrome followed by a multidisciplinary team at the Queen Fabiola Children's University Hospital. All parents were invited to take part; we included in consecutive order those children for whom the parents consented to participate. We included healthy volunteers recruited via announcement as controls. Age- and sex-matched controls were excluded if they had already known kidney and urinary tract anomalies. Any subject who could not cooperate sufficiently for the study-related examinations was also excluded.

All clinical investigations were performed at Queen Fabiola Children's University Hospital in partnership with the Université Libre de Bruxelles in Brussels, Belgium. Serum creatinine and urine albumin and creatinine measures were performed at the University Central Laboratory (LHUB-ULB), Brussels, Belgium.

Written informed consent was obtained for all subjects with both parents providing consent. Approval for this study was obtained from the Institutional Review Boards and Institutional Ethics Committees of both the Queen Fabiola Children's University Hospital (CEH 69/17), and the Erasmus Hospital (P2017/391; B4062017329655). All examinations were performed in accordance with the principles and tenets of the Declaration of Helsinki.

Examinations

Physical examination

Weight, height, and blood pressure data were recorded for all children. Blood pressure was measured using an appropriately sized sphygmomanometer in the sitting position with the subject's arm supported at the level of the heart and recorded to the nearest millimeter of mercury. Systolic and diastolic blood pressures were measured 3 times, at 2-to-3-min intervals. The arithmetic mean of the last 2 blood pressure measurements was then used as the mean blood pressure. Body surface area (BSA) was calculated using the Mosteller formula [19] where BSA = the square root of (weight (kg) × height (m)/3600).

Laboratory analysis

Kidney function was assessed using the estimated glomerular filtration rate (eGFR) using the Bedside Schwartz formula [20] which estimates the glomerular filtration rate in children and adolescents, and incorporates serum creatinine along with height and sex. Creatinine levels were determined according to the spectrophotometric Jaffe method [21] using a Roche Cobas platform, based on the chemical reaction between creatinine and picric acid in alkaline conditions [22] with calibration traceable to IDMS reference measurement procedure.

We determined the level of albuminuria from a spot urine sample collected from the first morning void, and we calculated the urine albumin to creatinine ratio. Urinalysis was performed in all children with Down syndrome, as well as their age- and sex-matched controls.

Kidney and urinary tract Doppler ultrasound

Kidney Doppler ultrasound and two-dimensional kidney and urinary tract ultrasonography were performed for all children. Scans were acquired with the child in prone position.

We used an EPIQ 7 Model ultrasound device (Philips, Amsterdam, the Netherlands) equipped with an 8-MHz transabdominal curved probe. Measurements for each kidney included maximum kidney bipolar length in the sagittal plane along with kidney width and cortical thickness in an axial plane perpendicular to each other at the level of the renal hilum. A visual estimation of the intensity of corticomedullary differentiation was performed by the same radiologist (GB). Doppler ultrasonography was used to determine renal arterial resistivity indices, including the renal arteries and peripheral (arciform) arteries at the 3 poles of each kidney. The arithmetic mean of the Doppler estimates at the 3 poles was used in the statistical analysis.

All kidney measurements were reviewed by a second radiologist (PS) who was blinded to the subjects' demographics and clinical and laboratory findings, 3 months later using the picture archiving and communication system (PACS) in order to check the consistency of the data. Kidney volume was subsequently calculated in cubic centimeters using the equation for an ellipsoid: volume (cm^3) = mean length (L) × mean width (W) × mean depth (D) × 0.523.

Accounting for effect of body size on kidney size

Kidney length has been shown to be associated in varying degree with age, sex, height, and weight, which are all correlated to each other. BSA, which accounts for height and weight, has been noted as a strong correlate for kidney size and is also used as the standard for normalizing GFR values to body size. Accordingly, we considered BSA to be an appropriate measure to normalize differences in body size between Down syndrome and controls. Moreover, as a secondary approach, we applied a previously developed equation which can be used to calculate expected kidney bipolar length in children, based on age, weight, and height [23] to compare with actual bipolar kidney length in our study participants. The formulas used were right kidney length = 5.91 + age (0.04) + height (0.01) + weight (0.03) and left kidney length = 5.58 + age (0.05) + height (0.01) + weight (0.021) [23].

Statistical analysis

Results were expressed as mean and standard deviation (SD) for quantitative variables and as frequency tables (numbers and percent) for categorical variables. The correlation coefficient was used to quantify the association between 2 variables. Matched groups were compared by the unpaired *t*-test or the Wilcoxon signed-rank test for skewed data. The paired *t*-test was also used to compare actual versus expected kidney length in cases and controls, separately. The McNemar test and the test of symmetry were applied to compare paired proportions. All tests were two-sided and the significance level was set at 5% ($p < 0.05$). All calculations were performed with SPSS (IBM SPPS, version 2020, Armonk, NY) or SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Demographics

Kidney function and morphology were evaluated in 49 children with Down syndrome and in their age- and sex-matched controls; thus, 49 pairs of subjects/controls were available for the statistical analysis. The mean age of subjects and controls was 8.0 ± 4.2 years and 8.3 ± 4.0 years, respectively, and there were 30 boys and 19 girls in each group. The 2 groups showed slight but not significant difference in race, with 18% African ancestry in Down syndrome versus 12% in controls ($p = 0.41$).

Clinical measures

Anthropometric data of the 49 pairs of subjects and controls summarized in Table 1 show that children with Down syndrome were shorter and had a higher BMI than their corresponding controls. In the present study, the mean systolic and diastolic blood pressures were the same in children with Down syndrome compared to controls (Table 1).

Laboratory test results

Mean urine albumin to creatinine ratios were comparable at 9.3 mg/g and 9.5 mg/g in Down syndrome and in controls, respectively. Similarly, the number of individuals with microalbuminuria, defined as 20–50 mg/L, was 7 among Down syndrome children versus 6 in controls.

Table 1 Anthropometric data for children with Down syndrome as compared to age- and sex-matched healthy volunteers (controls)*

Variable	Children with Down syndrome N = 49	Controls N = 49	p-value
Age	8.0 ± 4.2	8.3 ± 4.0	0.72
Weight (kg)	29.4 ± 18.5	30.4 ± 16.1	0.77
Height (cm)	115 ± 20	128 ± 24	< 0.003
BMI	20.2 ± 6.3	17.3 ± 3.1	0.005
BSA	0.95 ± 0.36	1.03 ± 0.36	0.27
SBP (mmHg)	108 ± 12	109 ± 12	0.53
DBP (mmHg)	61.0 ± 8.4	61.3 ± 7.7	0.99

Key: Controls (age- and sex-matched healthy volunteers)

BMI, body mass index; *BSA*, body surface area; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *N*, number

*Results are expressed as mean ± standard deviation (SD)

Serum levels of creatinine and the eGFR Schwartz formula were evaluated in children with Down syndrome only, as shown in Table 2. The average eGFR was 94.3 mL/min/1.73 m^2, which is lower than expected based on historical controls. We found 21 of the children to have an eGFR < 90 mL/min/1.73 m^2 (only 1 with age < 2 years) and 5 of them with eGFR < 75 mL/min/1.73 m^2. Given potential limitations in Jaffe-based creatinine measures in younger children, we also performed a sensitivity analysis in our adolescent subpopulation of 8 children aged 12 to 17 and found their eGFR to be even lower at 85.4 mL/min/1.73 m^2, of which 75% had an eGFR < 90 mL/min/1.73 m^2.

Imaging findings

Unadjusted data relating to kidney morphology as estimated by bidimensional ultrasonography are displayed in Table 2 for children with Down syndrome and controls. We noted significant differences for kidney bipolar length (7.56 ± 1.2 vs. 8.27 ± 1.13 cm; $p < 0.0001$) and volume (52.2 ± 25.1 vs. 69.8 ± 29.2 cm^3; $p < 0.001$) as well as other kidney measures (Table 2). Considering differences in body size in the 2 groups, we also adjusted for BSA alone or along with race and age and found differences in kidney length and volume in Down syndrome versus controls to both still be highly statistically significant with consistent p-values < 0.001 in all of our models.

The kidney bipolar length observed in controls was consistent with the estimated kidney length when using an equation developed to estimate expected kidney size based on age, height, and weight [23] with actual versus estimated lengths being 8.27 ± 1.13 cm and 8.18 ± 0.81 cm ($p = 0.28$), respectively. However, in children with Down syndrome, the measured mean kidney length was less than the calculated expected kidney size study at 7.56 ± 1.25 cm versus 8.01 ± 0.83 cm ($p < 0.001$), respectively.

The resistivity index of the central renal artery was evaluated by kidney Doppler ultrasound in 33 pairs of subjects and controls; no significant differences were found between the two groups (0.713 ± 0.074 vs. 0.704 ± 0.082; $p = 0.56$). Similar homogeneity was observed with regard to mean resistivity index in the arciform arteries, which was evaluated for 35 pairs of subjects and controls (0.673 ± 0.065 vs. 0.668 ± 0.060; $p = 0.74$). For all these measurements, the results were comparable if we considered each kidney individually; this was the case regardless of whether we used bidimensional ultrasonography or Doppler ultrasonography.

Data analysis allowed us to identify 5 additional children with Down syndrome with previously unsuspected kidney and urinary tract anomalies. One had bilateral hydronephrosis and another had unilateral hydronephrosis; both of these children had pyelocaliceal dilatation. We also detected 1 child with pyelectasis, and 2 children with reduced corticomedullary differentiation requiring further investigation. No kidney or urinary tract anomalies were detected in the control group.

Given that 27 of the Down syndrome participants had a history of congenital heart disease, we checked to see if it might correlate with kidney function and found no association between congenital heart disease and eGFR, albuminuria, or kidney length.

Discussion

The present prospective study is the first investigation to systematically compare the ultrasonography features of kidneys in children with Down syndrome to a control

Table 2 Kidney morphology and function for children with Down syndrome as compared to age- and sex-matched healthy volunteers (controls)*

Variable**	Children with Down syndrome N = 49	Controls N = 49	p-value
Kidney max bipolar length (cm)	7.57 ± 1.25	8.27 ± 1.13	< 0.001
Cortical thickness (cm)	0.84 ± 0.3	0.80 ± 0.35	0.52
Kidney width at the hilum level (cm)	3.38 ± 0.68	3.69 ± 0.61	0.022
Kidney thickness at the hilum level (cm)	3.60 ± 0.66	4.20 ± 0.78	< 0.001
Kidney volume (cm^3)	52.2 ± 25.1	69.8 ± 29.2	< 0.001
Abnormal cortico-medullary differentiation (number, %)	3 (6.1)	0 (0.0)	0.39
Urine albumin to creatinine ratio (mg/g; number)	9.30 ± 12.2	9.50 ± 9.2	0.94
Serum creatinine (mg/dL; number)	0.5 ± 0.1	NA	NA
eGFR Schwartz formula mL/min/1.73 m^2	94.3 ± 16.6	NA	NA

Key: Controls (age- and sex-matched healthy volunteers)

GFR, glomerular filtration rate; *N*, number

*Results are expressed as mean ± standard deviation (SD), or number (%)

**Evaluation by two-dimensional ultrasound of the kidneys, and ultrasound of the urinary tract

population. Two prior reports based on autopsy results suggested that individuals with Down syndrome had smaller kidneys compared to unaffected individuals [17, 18]. In the present study, ultrasound-based measures in vivo confirm that children with Down syndrome have significantly smaller kidneys developmentally, based on either length or volume, while accounting for body surface area, than matched controls. We also verified that the kidney lengths in our control population matched the expected kidney length, based on an algorithm derived using age, height, and weight in an independent population, whereas the kidneys of children with Down syndrome were significantly smaller than the calculated expected lengths.

We also observed previously unsuspected kidney and urinary tract anomalies in 7 out of the 49 (14%) children with Down syndrome. This result was in keeping with previous studies, evaluating children and adolescents with Down syndrome showing a prevalence of kidney and urinary tract anomalies between 7.2 and 20% [4–6]. Previous population-based registry studies reported that the majority of morbidity-related kidney and urinary tract congenital defects were due to an obstructive syndrome [2, 24], including vesicoureteral reflux [25], obstructive uropathies (focal cystic dysplasia, hydronephrosis, bladder neck stenosis, and hydroureters) [17], and posterior urethral valves [3]. Severe non-neurogenic bladder sphincter dysfunctions have also previously been found in up to 30% of children, and in 8.7% of adults, with Down syndrome [26, 27].

In this study, we also noted, as our secondary endpoint, overt decrease in kidney function in children and adolescents with Down syndrome as compared to historical controls. Most notably, we found 42% of our Down syndrome patients to have eGFR < 90 mL/min/1.73 m^2. Even more strikingly, 10% of these had an eGFR < 75 mL/min/1.73 m^2 meeting suggested criteria for significant CKD [28]. Similarly, Yamakawa and colleagues noted that eGFR and cystatin-C eGFR in Down syndrome were approximately 80% that of healthy children [29]. A reduced glomerular filtration and tubular secretion (the reduced clearance of creatinine and uric acid) was also reported in older individuals with Down syndrome during their third and fourth decades of life [30, 31].

We had expected to find and confirm a mild kidney hypoplasia as a developmental anomaly in Down syndrome, given the proportionally higher documented levels of endostatin, an inhibitor of angiogenesis encoded on chromosome 21 along with several other angiogenesis inhibitor genes such as DSCR1, triply expressed [32–34]. Hence, we expected the susceptibility of certain organs, notably the kidneys and eyes, heavily dependent on angiogenesis for their development [14, 16] to be affected. Such kidney as well as ocular hypoplasia attributed to reduced angiogenesis had been noted in papillorenal syndrome [14, 16]. Growth and guidance factors involved in angiogenesis have been found also to be responsible for the growth of other tubular structures in the body, including axons as well as those formed by the kidney epithelial cells from the ureteric bud [35–38]. Therefore, deficiency in systemic angiogenesis can disturb ureteric branching, morphogenesis, and elongation, and perturb the microvessel density of the distal ureter and the angle of insertion of the ureter into the bladder resulting in vesicoureteral reflux (VUR), as well as produce kidney hypoplasia [16, 37, 38].

Indeed, on histological section of kidneys from 25 fetuses with Down syndrome, Desogus and associates found more immature and morphologically abnormal glomeruli that resulted in an overall increase in glomerular area; collectively, these abnormalities suggested impaired nephrogenesis and glomerular development, which could result in continual loss of kidney function and hypertension later in life [39]. Lo and co-workers reported various abnormalities including immature glomeruli and focal segmental glomerulosclerosis, with glomerular microcysts representing a significantly different feature in a series of 43 Down syndrome autopsies with controls [40].

Currently, there are no official guidelines to screen for kidney defects in patients with Down syndrome [41, 42]. Evidence from some recent reports indicate a potential benefit in performing such screening procedures in newborns [4] as well as in subjects entering their second and third decades of life [43]. The findings of our study support such notions as kidney and urinary tract anomalies could be missed if imaging examination is not systematically performed. Screening for kidney function in individuals with Down syndrome would allow proper assessment for strict blood pressure control as well as the potential use of renin-angiotensin system (RAS) blockade. In addition, follow-up in children with abnormal imaging findings and/or obstruction could be provided in order to better preserve their kidney function going into adulthood [44–46].

Limitations

The study had some limitations. Examinations that required the subject to remain still were difficult to perform and, in some cases, unfeasible due to difficulties obtaining necessary cooperation (e.g., when measuring the renal resistivity index).

Other limitations were in obtaining several measurements such as serum creatinine in our age- and sex-matched controls since phlebotomy in minors, without a compelling medical reason to do so, was deemed excessively invasive by the Institutional Review Board. However, multiple publications consistently demonstrate higher eGFR in populations of healthy children [47–50]. Calculation of kidney volume based on ultrasound measures are not always accurate, however, and we expect any errors to

be present in both Down syndrome and controls equally, as the technique and ultrasound operator were the same for both. As such, the difference in volume between the 2 groups is expected to be reasonably accurate. The formula we used for the calculations of expected kidney length was derived in a general population and has not been validated in children with Down syndrome. However, given that it was based on age, height, and weight combined, we felt it might be the most comprehensive estimation tool available. Blood pressure was found to be similar in Down syndrome compared to controls. But, given the shorter stature of individuals with Down syndrome, it is possible that we underestimated their blood pressure in contrast to the controls. However, trunk size is the main determinant of blood pressure association with height, as opposed to leg length [51, 52], and since trunk size is fairly similar in Down syndrome compared to healthy controls (i.e., shorter leg length is primary cause of shorter stature in Down syndrome), underestimation of blood pressure in our cases is likely minimal [53, 54]. We used the Schwartz formula to estimate GFR in our participants with Down syndrome, which may decrease the accuracy of the eGFR in Down syndrome, as creatinine production may be altered [55]. However, lean muscle mass appears to be lower in Down syndrome [56], meaning that this might potentially bias the eGFR to a higher number than actual, and meaning that the actual GFR in our patients may be even lower than the estimated value. Lastly, our lab utilized a Jaffe creatinine assay, calibrated to IDMS, as opposed to an enzymatic assay, as used in the bedside Schwartz eGFR formula, which could lead to increased error. However, we used the Roche Cobas Jaffe platform which, unlike some other platforms, has shown excellent correlation with enzymatic approaches ($r^2 = 0.99$), along with negligible bias [57].

Conclusion

Using ultrasound measurements obtained in vivo, we found that kidneys of children with Down syndrome are significantly smaller than their age- and sex-matched controls. We also noted kidney function to be lower than those of historical controls and confirmed that a significant percentage of children with Down syndrome have undiagnosed anomalies of kidneys and urinary tract. These findings demonstrate that kidney development is remarkably affected in Down syndrome and strongly suggests that all affected individuals should be screened to assess for both kidney function and anatomical anomalies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-022-05455-y.

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Data Availability All data are available upon request.

Declarations

Ethics approval Approval for this study was obtained from the Institutional Review Boards and Institutional Ethics Committees of both the Queen Fabiola Children's University Hospital (CEH 69/17) and the Erasmus Hospital (P2017/391; B4062017329655). All examinations were performed in accordance with the principles and tenets of the Declaration of Helsinki.

Consent to participate Written informed consent was obtained for all subjects with both parents providing consent.

Consent for publication **NA**

Conflict of interest The authors declare no competing interests.

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