Unilateral renal agenesis– does it matter?

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Overview

- How unilateral renal agenesis develops
- Diagnosis, incidence and associations
- Investigating the contralateral urinary tract
- Who needs long-term follow-up?
- Conclusions
Renal agenesis

- Implies that the embryonic kidney has failed to begin to form
- True renal agenesis caused by failure of ureteral bud to communicate with the metanephric blastema in the first few weeks of gestation
The beginning of the kidney: Ureteric Bud (UB) penetrates Renal Mesenchyme (RM) (courtesy of Adrian Woolf)

Unilateral renal agenesis

- Diagnosis most commonly made on antenatal US
- Less frequently diagnosed in later life
  - Routine imaging
  - Autopsy
- When diagnosed in the fetus or neonate by US alone
  - False negative
    - Adrenal gland mistaken for kidney
  - False positive diagnosis –
    - Kidney may be ectopic (e.g. pelvic or crossed fused ectopia)
    - Very small kidney secondary to dysplasia, renal artery stenosis, renal venous thrombosis
    - A number of cases of apparent renal agenesis will represent multicystic dysplastic kidneys that have undergone spontaneous involution
      - Reported to occur prenatally as well as postnatally
Involution of the MCDK

Neonatal ultrasound...........and two years later

These massive structures usually ‘involute’ over weeks/months, prenatally or postnatally, often becoming undetectable by US
Unilateral renal agenesis

- Reported incidence 1:500 to 1:3200
- Multiple problems associated with accurately ascertaining this
  - US alone associated with false positive and negative results
  - Autopsy studies perhaps gold standard but perhaps select those with complications
    - Kiprov et al reported incidence of 1:1000 based on >9000 autopsies
Renal agenesis

- May occur in association with anomalies of other organ systems e.g. uterus, vas deferens, vertebrae, genitalia, intestines, anus, limbs, heart, trachea, ear and CNS

- May be part of multi-organ syndrome
  - Several of these will have defined genetic basis
Multi-organ syndromes associated with renal agenesis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branchio-oto-renal syndrome</td>
<td>EYA1 (Eyes Absent 1) dominant mutation; hearing loss, pre-auricular pits, branchial clefts [19].</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>deletion of 22q11: congenital heart disease, hypocalcaemia, immunodeficiency, and neurocognitive disorders [20].</td>
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<tr>
<td>Fanconi anaemia</td>
<td>caused by recessive mutation of several genes; pancytopenia [21].</td>
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<tr>
<td>Fraser syndrome</td>
<td>FRAS1 autosomal recessive mutations; cryptophthalmos, cutaneous syndactyly, malformations of the larynx and ambiguous genitalia [22].</td>
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<tr>
<td>Kallmann syndrome</td>
<td>Anosmin-1 X-linked recessive mutation: hypogonadotropic hypogonadism and anosmia [23,24].</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>47,XXY: small, firm testis, gynaecomastia, azoospermia and hypergonadotrophic hypogonadism [25].</td>
</tr>
<tr>
<td>Rokitansky-Kuster-Hauser syndrome</td>
<td>WNT4 (wingless-type MMTV integration site family member 4) dominant mutation; absent/rudimentary upper vagina and uterus [26].</td>
</tr>
<tr>
<td>MURCS association</td>
<td>genetic basis undefined; Müllerian duct aplasia-hypoplasia (MU), renal malformations (R) and cervicothoracic somite dysplasia (CS) [27].</td>
</tr>
<tr>
<td>Poland syndrome</td>
<td>genetic basis undefined; unilateral hypoplasia of pectoralis major muscle and ipsilateral syndactyly [28].</td>
</tr>
<tr>
<td>Renal cysts and diabetes syndrome</td>
<td>HNF1β (hepatocyte nuclear factor β) dominant mutations; diabetes mellitus, hyperuricaemia and uterine malformations [29].</td>
</tr>
<tr>
<td>Townes-Brocks syndrome</td>
<td>SALL1 (sal-like 1/homologue of Drosophila splalt) dominant mutation: imperforate anus, triphalangeal/bifid thumb, rocker bottom feet, sensorineural hearing loss, hypospadias [30].</td>
</tr>
<tr>
<td>Williams–Beuren syndrome</td>
<td>deletion of 7q11.23; developmental delay, cardiovascular anomalies, mental retardation and facial dysmorphism [31].</td>
</tr>
</tbody>
</table>

Woolf AS, Hillman KA BJU Int 2006
Renal agenesis: teratogenesis

- Association with poorly controlled maternal diabetes mellitus

- Use of specific drugs during pregnancy
  - Inhibition of renin-angiotensin system e.g. ACEI, ARB
  - Vitamin A derivatives in experimental animals
Renal agenesis

- May be familial
  - Dominant inheritance with incomplete penetrance reported

- Increased incidence of asymptomatic renal malformation in first degree relatives of those with bilateral renal agenesis, bilateral severe dysplasia or unilateral renal agenesis and dysplasia of the other
  - 9% affected
  - Around one half of these also have unilateral renal agenesis

- US imaging of first degree relatives may therefore be indicated
Investigating the contralateral urinary tract
Is the single kidney normal

- Ultrasound
  - To assess renal size
  - Solitary kidney may show ‘compensatory hypertrophy’ and be >2SD above mean for age and height
  - Process begins in utero
  - Probably more complex than simple hypertrophy (increased cell size)
Is the single kidney normal?

- **Ultrasound**
  - Normal or small kidney may be considered abnormal e.g. dysplasia or postnatal damage
    - Assess plasma creatinine
  - Will also identify:
    - a previously undetected ipsilateral ectopically sited or v small normally sited kidney
    - hydronephrosis or hydroureter suggestive of obstruction or VUR
Renal agenesis

- Up to 50% will have anomalies in the contralateral kidney
  - VUR (28%)
  - PUJ or VUJ obstruction (20%)

- On basis of this, some have recommended that all are comprehensively investigated, including MCUG

- Some cautioned that some series where incidence of other anomalies was reported
Prudent investigation

- DMSA
  - To confirm absence of functioning renal tissue
  - To detect ectopically sited kidneys that have not been seen on ultrasound
- MCUG
  - Consider where there is hydronephrosis or hydroureter to exclude VUR
- MAG3 renography
  - Consider where there is suspicion of either PUJ or VUJ obstruction because of pelvic or ureteric dilatation without a dilated ureter or evidence of VUR
Investigation

- Plasma creatinine
  - If the single kidney does not show compensatory hypertrophy
  - Perhaps a strong case for doing this in all cases
Who needs follow-up?

- If evidence of adequate compensatory hypertrophy and no other abnormality on ultrasound
  - Outcome likely to be very good
  - Can safely be discharged from hospital follow-up
Long term risks for living kidney donors

Mjoen G et al Kidney Int 2014; 86: 162-167

- Previous studies reported good outcomes
  - However used controls which were less healthy and short follow-up
- 1901 living donors (1963-2007 – median f-u 15.1y) compared with 32,621 controls (median f-u 24.9y) who would have been eligible for donation
- All cause mortality ↑ HR 1.3 (1.11-1.52)
- Cardiovascular mortality ↑ HR 1.4 (1.03-1.91)
- ESRD ↑ HR 11.38 (4.37-29.6)
  - Overall incidence 302/million
  - May have been influenced by hereditary disease
Increased incidence of gestational hypertension and preeclampsia in living kidney donors


- Retrospective cohort study
- 85 living donors (131 pregnancies) compared with 510 matched healthy non-donors (788 pregnancies)

- Gestational hypertension or preeclampsia was more common: 15/131 (11%) vs. 38/788 (5%)
  - OR 2.4 (1.2-5.0, p=0.01)
- No increase in prematurity or LBW
- No donor maternal death, stillbirth or neonatal death
Are unilateral renal agenesis and nephrectomy the same thing?

- Nephrectomy results in 50% of glomeruli being removed
- Sheep model of prenatal unilateral nephrectomy showed single kidney to contain 70% of total number of glomeruli expected in two kidneys
- Histological study of healthy unilateral kidney showed twice the expected number of glomeruli and a mass 1.8x that of normal kidney
  - Maluf NS. Br J Urol 1997; 79: 836-841

- Are the compensatory changes which occur detrimental in the long-term – causing hypertension, glomerulosclerosis, proteinuria and impaired function?
Hypertension and microalbuminuria in children with congenital solitary kidneys

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Departments of ¹Pediatric Nephrology and ²Pediatric Endocrinology, VU University Medical Center, Amsterdam, The Netherlands

- 66 with unilateral kidney
  - 39 agenesis
  - 27 MCDK (25 nephrectomised)
- Excluded those with overt abnormalities on imaging
- Assessed at mean of 8.4y and compared with healthy controls
<table>
<thead>
<tr>
<th></th>
<th>Congenital renal mass reduction (n = 66)</th>
<th>two-kidney controls (n = 34)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at follow-up (year)†</td>
<td>8.4 (5.3)</td>
<td>9.3 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td><strong>17%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of anti-hypertensive agents (%)</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney length SDS‡</td>
<td>3.2 (2.2–4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Creatinine (μmol/L)‡</strong></td>
<td><strong>65 (53–79)</strong></td>
<td><strong>57 (52–67)</strong></td>
<td>0.017</td>
</tr>
<tr>
<td>FeNa§ (%)‡</td>
<td>0.8 (0.6–1.1)</td>
<td>0.6 (0.5–0.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>FeNa§ &gt;1% (%)</td>
<td>38%</td>
<td>6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Sodium intake (mmol/kg/24 h)†</td>
<td>2.8 (1.2)</td>
<td>2.8 (1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>TRP¶ (%)‡</td>
<td>85 (81–88)</td>
<td>88 (87–89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR†† (ml/min/1.73 m²)†</td>
<td>93 (20)</td>
<td>114 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria (mg/m²/h)‡</td>
<td>3 (2–5)</td>
<td>4 (3–5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Microalbuminuria (&gt;20 μg/min)</strong></td>
<td><strong>23%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension and/or use of anti-hypertensive agents and/or microalbuminuria &gt;20 μg/min (%)</td>
<td>50%</td>
<td></td>
<td>0.003</td>
</tr>
</tbody>
</table>
Renal outcome of children with one functioning kidney from birth. A study of 99 patients and a review of the literature

Kieu-Hanh Vu • Maria Van Dyck • Hans Daniels • Willem Proesmans

- 99 patients diagnosed in first year of life
  - A: MCDK with normal contralateral kidney (n=36)
  - B: Normal solitary kidney without uropathy (n=20)
  - C: Obstructive uropathy and one non-functioning kidney
- Followed over 10 years
Reduced GFR
2y: 2/36
5y: 4/36
10y: 2/16

Reduced GFR
2y: 3/20
5y: 2/10
10y: 1/16

Reduced GFR
2y: 14/43
5y: 16/43
10y: 9/31
97 patients 2.9-25y with radiologically normal unilateral kidney
  - 44 congenital (including contralateral MCDK)
  - 53 acquired (tumour, complex urology)
- Measured 24h ABP, GFR (inulin) and microalbuminuria
Congenital versus acquired solitary kidney: is the difference relevant?

Pauline Abou Jaoudé¹, Laurence Dubourg¹,², Justine Bacchetta¹, Julien Berthiller³,⁴, Bruno Ranchin¹ and Pierre Cochard¹,²

Table 3. Hypertension, microalbuminuria and renal impairment in children with solitary kidney

<table>
<thead>
<tr>
<th></th>
<th>SK (97)</th>
<th>CSK (44)</th>
<th>ASK (53)</th>
<th>P (CSK vs. ASK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Alb/crea &gt;2 mg/mmol</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>GFR &lt;80 mL/min/1.73 m²</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>0.02</td>
</tr>
<tr>
<td>Total anomalies</td>
<td>21</td>
<td>9</td>
<td>12</td>
<td>NS</td>
</tr>
</tbody>
</table>

- 7 children with reduced GFR had all been nephrectomised in early childhood for renal tumour
- Had constantly low GFR on repeated assessment since surgery with microalbuminuria in 4/7
Assessment of serum cystatin C in children with congenital solitary kidney

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Agenesis group (I)</td>
<td>Control group (C)</td>
</tr>
<tr>
<td>Number of children</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.8 (3.0–21.0)</td>
<td>10.9 (5.0–21.0)</td>
</tr>
<tr>
<td>Gender Male/female</td>
<td>28/8</td>
<td>27/9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>142.0 (70.0–183.5)</td>
<td>143.2 (108.5–185.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>16.8 (8.9–29.9)</td>
<td>15.9 (10.23–24.91)</td>
</tr>
<tr>
<td>Renal length (cm)–L</td>
<td>10.9 (7.3–15.6)</td>
<td>9.3 (8.4–12.3)</td>
</tr>
<tr>
<td>Renal length/height–L/H</td>
<td>0.08 (0.05–0.12)</td>
<td>0.06 (0.04–0.14)</td>
</tr>
<tr>
<td>Overgrowth of renal length (%)–O%</td>
<td>18.2 (2.5–39.53)</td>
<td>–</td>
</tr>
<tr>
<td>Kidney: right/left</td>
<td>24/12</td>
<td>24/12</td>
</tr>
<tr>
<td>Blood pressure, systolic (mmHg)</td>
<td>108.5 (80–130)</td>
<td>103 (88–136)</td>
</tr>
<tr>
<td>Blood pressure, diastolic (mmHg)</td>
<td>70 (40–90)</td>
<td>68 (49–93)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.54 (0.26–0.96)</td>
<td>0.54 (0.30–0.95)</td>
</tr>
<tr>
<td>Cystatin C (mg/l)</td>
<td>0.88 (0.25–1.37)</td>
<td>0.68 (0.47–0.88)</td>
</tr>
<tr>
<td>GFR (Schwartz), ml/min per 1.73 m² body surface area</td>
<td>128.5 (81.2–191.6)</td>
<td>133.2 (71.8–200.0)</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>114±38</td>
<td>106±27</td>
</tr>
</tbody>
</table>
- 18 children (mean 9.6 +/-3.9y) with unilateral renal agenesis
- 10 children (14.0 +/-2.7y) post nephrectomy (mean 8.7y)
- Weight and height matched control group for each cohort
- 24h ABPM study, urinalysis, plasma creatinine, USS

- Increased mean 24, daytime and night-time SBP and DBP significantly higher in URA group than controls
  - No difference between nephrectomy patients and controls
Documented clinical course of 157 patients with uncomplicated unilateral renal agenesis diagnosed between 1960 and 1975

- Mean age at diagnosis 37y
- Mean age at assessment 56y
  - 43 had died (6 from renal failure)
  - Proteinuria in 19%
  - Hypertension in 47%
  - Impaired renal function in 13%

- Overall survival not different from normal US population
Who needs follow-up?

- If evidence of adequate compensatory hypertrophy and no other abnormality on ultrasound
  - Outcome likely to be very good
  - Can safely be discharged
  - Probably sensible to have BP checked and first morning urinalysis performed by GP annually
  - If absence of compensatory hypertrophy +/- abnormality of renal function, need long-term hospital follow-up
Unmet needs in the measurement of blood pressure in primary care

S Zaheer,1,2 L Watson,1,3 N J A Webb1

ABSTRACT

Background Blood pressure (BP) monitoring in UK children at risk of hypertension takes place predominantly in secondary and tertiary care.

Objectives To investigate (i) the availability of paediatric BP equipment in primary care (PC) and (ii) the confidence of PC professionals in measuring and interpreting children’s BP.

Methods 103 PC practices were approached to complete a questionnaire. BP equipment availability and confidence with BP measurement and interpretation were recorded (interval scale 1–10). Cuff size and equipment type were documented.

Results 95 (92%) practices responded; 40/95 possessed paediatric BP cuffs, 35/51 devices were validated for paediatric use. Median (IQR) confidence in BP measurement was 7 (2–8). Confidence in BP interpretation was 3 (2–6), though this improved if normal ranges were provided (8 [6–9], p<0.01).

Conclusions Investment in appropriate equipment and education is required to allow PC to successfully monitor BP in children.

What is already known

► Blood pressure monitoring is an important part of the management in children with certain conditions that increase their risk of hypertension.
► Normal range data exist to guide professionals in the diagnosis and management of hypertension in children of different ages.

What this study adds

► The majority of primary care centres do not have the necessary equipment to measure blood pressure (BP) in children.
► The widespread circulation of normal range data would enhance confidence in the interpretation of BP readings.
Conclusions

- Limited investigation in the postnatal period required
  - US, DMSA in all
  - (Plasma creatinine)
- If uncomplicated and evidence of compensatory growth
  - GP follow-up
- If kidneys normal size or smaller or any other abnormality
  - Hospital follow-up
- Some caution regarding very long-term prognosis
Thank you

Each year around 20,000 patients take part in clinical research studies at our hospitals.

#WhyWeDoResearch

to discover safe and effective new medicines for children

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