Unilateral renal agenesis and the congenital solitary functioning kidney: developmental, genetic and clinical perspectives

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INTRODUCTION
We review the condition termed ‘unilateral renal agenesis’ (URA), i.e. individuals born with non-ectopic, solitary functioning kidneys (SFKs), with contralateral kidneys which fail to form. We discuss the causes, diagnosis and long-term ‘renal prognosis’ of URA. We do not consider in detail other anomalies resulting in SFK, such as unilateral multicystic dysplastic kidney (MCDK) and fused renal tracts [1,2]. SFK also follows unilateral nephrectomy for disease and living renal transplant donation; the long-term outcomes for these scenarios have been reviewed [3].

DEVELOPMENTAL BIOLOGY
‘RA’ implies that the embryonic kidney has failed to begin to form. The human metanephros is the direct precursor of the mature kidney; it becomes a distinct entity in the fifth gestational week when the ureteric bud epithelium branches from the mesonephric duct [4]. Thereafter, renal mesenchyme condenses to envelop the advancing bud, and forms primitive nephron vesicles; the bud forms the ureter and branches to generate collecting ducts. Thus, RA must be the result of either failure of the ureteric bud to arise, or failure of the bud to engage with renal mesenchyme.

INCIDENCE AND DIAGNOSIS
Kiprov et al. [5], in a histopathology study, reported an incidence of URA of ≈1 : 10,000, based on >9000 (postnatal) autopsies. However, in clinical practice the clinician is generally faced with making a radiological diagnosis of ‘URA’ in a child or adult, or perhaps in a fetus in which just one kidney has been visualized on ultrasonography (US) during mid-gestation. Using US, URA can be ‘missed’ in the fetus or neonate because the adrenal, which then occupies the renal bed, can be mistaken for a kidney [6]. Using US, Roodhooft et al. [7] reported that URA occurred in ≈1 : 500 of the general population, which is more frequent than the autopsy value cited above [5]. There are caveats about using an ‘empty renal bed’ assessed in a fetus or child to diagnose URA. Renal ectopia (e.g. pelvic and cross-fused) kidneys should be considered and sought by US [8] and, if necessary, by functional scanning with IVU and/or isotope renography (e.g. with 99mTc-DMSA, concentrated in functioning tubules). Furthermore, all these radiological techniques might fail to detect a very small (<2 cm across) contralateral kidney affected by renal ‘aplasia’ (a small, dysplastic organ, containing undifferentiated and metaplastic tissues) or atrophy secondary to renal artery stenosis or neonatal renal venous thrombosis [9–11]. Such ‘remnants’, confirmed at laparotomy, have rarely been implicated in causing hypertension [10,12]; MRI might prove a sensitive technique with which to find such rudiments [10].

With the advent of routine fetal US screening, it became apparent that dysplastic kidneys, either of modest size, or even greatly enlarged MCDK, can spontaneously involute prenatally or in the first years after birth [10,13,14]. This process might be driven by apoptosis, a metabolically active form of ‘cell-suicide’, i.e. excess apoptosis [15]. Possibly, URA is rarer than previously considered because some individuals so classified might actually have regressed, malformed kidneys rather than true agenesis.

ASSOCIATED ANOMALIES, AND GENETIC AND TERATOGENIC CAUSATION
Anomalies outside the renal tract can be associated with URA, including absence of a uterine horn [16] or vas deferens [17] ipsilateral to the absent kidney, respectively, emphasizing close relationships between paramesonephric and mesonephric duct development and nephrogenesis itself. Dursun et al. [18] detected non-urological anomalies in 44% of 87 consecutive cases of congenital SFK, with cardiac and gastrointestinal malformations being especially common. Sometimes RA occurs as part of a multi-organ syndrome (Table 1), and several of these have defined genetic bases [19–31]. Not unexpectedly, the normal versions of genes mutated in such individuals are expressed during differentiation of normal kidneys and ureters [4]. Gene mutations in branchio-oto-renal [19], Townes Brockes [30] and the renal cysts and diabetes [29] syndromes encode transcription factor and related proteins that modulate expression of other genes; in Fraser [22] and X-linked Kallmann [23,24] syndromes, the relevant proteins are on surfaces of renal epithelia, and probably mediate cell–cell and cell–matrix interactions; in Rokitansky-Kuster-Hauser syndrome, there is a report of mutation of a locally acting growth factor [26].

Even in the absence of non-renal tract features, RA can be familial, sometimes apparently inherited as a dominant trait with incomplete penetrance [7,32,33]. The risk to close relatives might be greater when the index case has bilateral RA, and Roodhooft et al. [7] recommend ‘ultrasonographic screening for parents and siblings of infants born with agenesis or dysgenesis of both kidneys or with agenesis of one kidney and dysgenesis of the other, since renal malformations may have medical implications even for asymptomatic patients’.
Finally, regarding teratogenic causation, poorly controlled maternal diabetes mellitus and use of specific drugs during pregnancy (e.g. those which inhibit the renin–angiotensin system) have been associated with RA in progeny [34,35]. Other agents, such as high doses of vitamin A derivatives, can cause RA in experimental animals [36].

THE CONTRALATERAL RENAL TRACT

Having diagnosed URA, the next step is to exclude disease of the contralateral renal tract. First, is the SFK ‘normal’? Congenital SFKs are often larger than normal [37,38], and overgrowth initiated prenatally; in one study, the lengths of human fetal SFKs were increased in 44% of cases assessed by US, a phenomenon detectable as early as mid-gestation [37]. The remarkable process has been called ‘hypertrophy’, implying simply an increase in cell size, although other mechanisms are probably operative. In sheep, after experimental unilateral nephrectomy during the period of normal nephrogenesis, final glomerular numbers in the SFK are strikingly greater than in control kidney, bringing the final complement of nephrons in the single kidney to ≈70% of that in two normal kidneys [39]. One histological report which compared a ‘healthy (human) congenitally solitary kidney’ with a normal control, suggested the former contained more nephrons [40]; however, larger scale studies quantifying glomerular numbers by the ‘gold-standard’ technique of stereology [41] are needed to confirm this impression. Only 20–40% of individuals with URA have a significant increase in renal length above the upper normal age-adjusted limits [37,38]; one explanation for this is that kidney length is highly variable even in individuals with two normal kidneys [37,42,43].

A congenital SFK of ‘normal length’ which is echographically bright, or one which is shorter than the normal range, might well be considered abnormal, and might itself either have a degree of dysplasia/hypoplasia, or have been damaged postnatally. The most severe contralateral tract anomaly (apart from RA itself), is severe renal dysplasia. Indeed, URA and MCDK can coexist [44]; many such fetuses will be terminated or, if born, will soon die from renal failure and lung hypoplasia associated with oligohydramnios. Cascio et al. [45] reviewed 46 consecutive children with URA diagnosed in one hospital; all had US and renography, and most had cystography; almost half had an anomaly of the contralateral renal tract, including VUR (often high-grade) and ‘obstruction’, especially at the PUJ. Kaneyama et al. [46] found a similar spectrum and incidence of anomalies, and even suggested that ‘All children with (congenital) solitary kidney should undergo a screening voiding cysto-urethrography . . .’.

While these studies show the range of contralateral anomalies that can occur, index cases in such series might not have been typical of all individuals with URA (e.g. half of the cases analysed by Cascio et al. [45] presented with UTI), and hence suggestions for extra investigations in addition to US are difficult to generalize into clinical imperatives.

LONG-TERM PROGNOSIS

The tendency for ‘normal’ kidneys opposite URA to increase in length can be viewed as a positive, adaptive response. Indeed, in children with uncomplicated URA, SFKs maintain GFRs similar to that of two normal kidneys [38]. However, it has been contended, from rat experiments (reviewed in [3]), that such compensatory growth and functional responses might be detrimental in the long term, with the onset of hypertension, glomerulosclerosis, proteinuria and even progressive renal failure. Is there any evidence that humans, who initially have overtly normal SFKs and lower renal tracts, might acquire a similar spectrum of dysfunction? The answer is ‘yes’, although frustratingly we cannot yet predict the risk for a specific individual with URA.

In a survey of children with URA, Wasilewska et al. [38] found that serum cystatin C, a substance cleared by glomerular filtration, tended to be increased in those over 12 years old, a rise positively correlated with kidney overgrowth. Mei-Zahav et al. [47] used ambulatory blood pressure monitoring and concluded that daytime and night-time systolic blood pressures were significantly higher (4–5 mmHg) in children with URA than in controls; increased blood pressure correlated with increased renal length. By contrast, children with unilateral nephrectomy for renal disease had pressures similar to healthy controls. Perhaps these
studies give indications of 'trouble ahead' for children with URA, who are born with
presumed nephron deficits. Keller et al. [41]
quantified glomerular numbers in kidneys of
adults (with two kidneys), aged 35–59 years,
who died in road traffic accidents, and found
that individuals with histories of 'essential
hypertension' had on average only half the
number of glomeruli/kidney than had age-
matched normotensive controls. Although
not a study of URA, perhaps there is a
message here for the long-term prognosis of
individuals with congenital SFKs.

Heinonen [16] studied pregnant women with
URA and associated uterine anomalies;
outcomes were compared with a control
group of age-matched pregnancies in women
with similar uterine malformations who had
two normal kidneys. The relative risk of
gestational hypertension, pre-eclampsia or
gestational proteinuria was 2.3, significantly
higher. Argeu et al. [48] studied 157 adults
with 'URA and a normal contralateral kidney'
diagnosed at a mean age of 37 years;
proteinuria (>50 mg/day) was found in 19%
of 37 patients tested, hypertension in 47% of
47 patients, renal function was impaired in
13% of 32 patients and, on follow-up, there
were six deaths from chronic renal failure.
Duke et al. [23] reported that URA, in young
adults with Kallmann's syndrome, could be
associated with hypertension, proteinuria and
progressive renal failure. Gonzalez et al. [49],
in a retrospective study of 33 adults with
URA, found that those with hypertension,
proteinuria and renal insufficiency at
diagnosis had a higher body mass index than
had those lacking these signs at diagnosis;
in the former group, progressive renal
impairment was less common in those treated
with drugs which block angiotensin II, while in
the latter group, onset of proteinuria and
renal impairment was more frequent in those
patients with an increased body mass index.

With hindsight, it is difficult to be sure that
some individuals in these reports did not have
regressed unilateral MCDKs; this might be
important because hypertension has (rarely)
be attributed to such remnants themselves
[12]. However, such studies raise concerns
about the long-term renal prognosis of
individuals with URA. The pathology of SFKs in
URA patients with a history of proteinuria
regressed unilateral MCDKs; this might be
some individuals in these reports did not have

• Finding hypertension, proteinuria or
renal impairment or VUR).
• Give consideration to alternative diagnoses
of ectopic kidney or a regressed dysplastic
kidney; in the latter, remnants have been
reported to cause hypertension.
• Did the individual's mother have diabetes
mellitus or was she treated for hypertension
during the index cases' gestation?;
• Anomalies of other organ systems can
occur, and sometimes the picture will fit a
specific syndrome (Table 1); in addition, RA
can be familial, even with disease confined to
the renal tract. Such kindreds might benefit
from genetic counselling and screening of
asymptomatic relatives.
• Ascertain the structure of the contralateral
renal tract, at least by US; in particular, check
whether the solitary kidney shows normal
'compensatory hypertrophy' (i.e. is longer
than normal) and exclude hydronephrosis (in
which case further ascertainment might be
needed to define/exclude urine flow
impairment or VUR).
• For 'uncomplicated cases', secure life-long
follow-up of blood pressure and urinary
protein checks every year or two. Consider
dietary advice to normalize an increased body
mass index.
• The finding of structural anomalies of the
solitary kidney and/or lower renal tract might
demand appropriate specialized urological
observation or surgery.
• Finding hypertension, proteinuria or
impaired renal function will demand
appropriate specialized nephrological follow-
up; such patients might benefit from specific
interventions such as treatment with
angiotensin-converting enzyme inhibitors
and dietary advice to normalize an increased
body mass index.

Suggestions for long-term follow-up and
treatments are given with the caveat that we
currently lack good evidence with which to
accurately predict the risk of life-long
complications for any individual with URA.

CONCLUSIONS
URA occurs in ≈ 1 : 500–1000 individuals;
from the practical clinical perspective, we
suggest that the diagnosis of 'URA' should
prompt the clinician to consider several
points:

• Finding hypertension, proteinuria or
renal insufficiency or VUR.
• Give consideration to alternative diagnoses

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Abbreviations: MCDK, multicystic dysplastic kidney; RA, renal agenesis; SFK, solitary functioning kidney; URA, unilateral renal agenesis; US, ultrasonography.