Renal Tubular Dysgenesis: Evidence of Abnormality in the Renin-Angiotensin System

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ABSTRACT
Renal tubular dysgenesis is an autosomal recessive condition characterized by short, abnormally developed cortical tubules that lack proximal differentiation. Despite the lack of normal proximal tubules, the major site of water resorption in the kidney, the principal clinical manifestations are caused by fetal and neonatal oliguria. The kidneys in three cases of neonatal renal tubular dysgenesis were found to contain large amounts of immunohistochemically reactive renin in preglomerular arterioles, glomerular hilums, and glomerular mesangial areas, far exceeding the intensity of staining and the numbers of sites stained in control kidneys. The increased accumulation of renin may reflect strong local vasoconstriction, which is responsible for reduced glomerular perfusion. This accumulation suggests faulty feedback control of renin secretion, the basis of which is still to be identified.

Key Words: Tubular dysgenesis, renin, angiotensin II, metanephric differentiation

Renal tubular dysgenesis, originally described by Allanson et al. (1), has been recognized as a cause of fetal and neonatal oliguria, associated with oligohydramnios and the Potter phenotype (2-4). The condition, an autosomal recessive, appears to be relatively uncommon and of undetermined frequency. It is characterized histopathologically by incompletely developed cortical convoluted tubules that are lined with poorly differentiated cells in which lectin-binding studies fail to demonstrate proximal characteristics (3,4). The tubules have been shown by microdissection to be short and relatively straight (2).

The virtual absence of proximal tubular differentiation and elongation has seemed at odds with the clinical manifestation of reduced urine volume. Deficiency of proximal tubules, where the bulk of fluid resorption normally occurs, may ordinarily be expected to result in high urinary volumes. The immunohistochemical demonstration in this study of larger than normal amounts of renin in preglomerular arterioles and glomerular mesangium suggests the mechanism to be reduced glomerular perfusion.

MATERIALS AND METHODS
Autopsy specimens of kidney were available from three cases, two of which have been reported in a clinicopathologic article describing the late onset of oligohydramnios (4). The first of these was a girl delivered spontaneously at 35 wk after a pregnancy complicated by oligohydramnios from at least the 26th week of gestation. The second, a male sibling of the first, was delivered by cesarean section at 32 wk after oligohydramnios had been demonstrated at 23 wk. Both siblings had Potter phenotype with hypoplastic lungs, and both died of respiratory failure shortly after birth. Two older male siblings had also died of respiratory failure shortly after birth and had the same renal abnormality, but tissue was not available for this study. A third case, unrelated to the first two, was that of a girl delivered by cesarean section at 33 wk of a gestation complicated by oligohydramnios. The baby had postnatal respiratory distress and died shortly after birth; the lungs were hypoplastic.

Postmortem examination in all three cases showed kidneys of normal weight, with normal lobar structure and good corticomедial differentiation. The corticomедial rays were close together and ill defined, however, and the glomeruli also appeared to be crowded because of deficient tubular development in the cortical labyrinth. The tubules were lined with crowded, undifferentiated cuboidal and columnar cells. Rudimentary brush border could be demon-
strated by electron microscopy in only occasional tubules. Immunohistochemical staining of the tu-
bular epithelial cells was positive for human epithelial membrane antigen, a marker of normal distal tubules and collecting ducts (5). Peanut (Arachis hypogaea) lectin, a marker of normal collecting ducts (6), bound to almost all tubular segments, whereas winged pea (Tetragonolobus lotus) lectin, a selective marker of proximal tubules (6) was negative, not demonstrating any proximal tubular segments. The third case was not studied by lectin histochemistry.

Postmortem control specimens were obtained from five newborns of comparable gestational age (30, 30, 31, 34, and 36 wk). Two had been delivered vaginally, and three were delivered by cesarean sections. The clinical histories were negative for evidence of renal disease, and the kidneys were histopathologically normal.

Immunohistochemical staining for renin was car-
rried out on sections deparaffinized with xylene and rehydrated through a graded series of alcohol solutions. The sections were rinsed (5 min) in phosphate-
buffered saline (PBS) containing 0.3% Triton X-100 (Fisher Scientific Co., Pittsburgh, PA) and were in-
cubated overnight in a 1:10,000 dilution of polyclonal rabbit antiserum directed against a pure human renin preparation (7).

They were incubated for 1 h with biotinylated goat anti-rabbit immunoglobulin G (Vector Laboratories, Burlingame, CA) at room temperature. After treat-
ment with 2.5% hydrogen peroxidase (H2O2) in meth-
anol to inactivate endogenous peroxidase, the sec-
tions were incubated in a avidin-DH and biotinylated horseradish peroxidase mixture (Vector Laboratories) for 1 h, followed by incubation for 10 min in a solution of 0.05% diaminobenzidine and 0.003% hy-
drogen peroxide in 0.1 M Tris buffer (pH 7.6). Be-
tween steps, the sections were washed several times for a minimum of 30 min. The sections were post-
stained in hematoxylin and mounted with Pro-Texx (Baxter-Scientific Products, McGaw Park, IL). No staining was observed when sections were incubated with nonimmune rabbit serum.

Stained sections of the three abnormal cases and five normal controls were examined microscopically for intensity and distribution of staining. The slides were initially shuffled together and examined in ran-
don order at several sittings, with the examiner blinded as to the source of the specimens.

RESULTS

Strong staining for renin was present in relatively long segments of the preglomerular arteriole, extend-
ing into the juxtaglomerular apparatuses at the glo-
merular hilum (Figure 1A). Focal collections were present in the mesangial regions of many glomeruli. The arteriolar staining was present in the vascular

Figure 1. Immunoperoxidase staining of kidney with antihu-
man renin. (A) Heavy accumulation of renin in the long
segment of the preglomerular arteriole, glomerular hilum,
and glomerular mesangium. (B) Less renin in normal kidney,
limited to the short segment of the preglomerular arteriole
and glomerular hilum. Original magnification of both
panels, ×375.

media. Staining was strongest in the first case, that of
the child delivered vaginally. Both vascular local-
ization and glomerular localization were more pro-
nounced in the inner than in the outer cortex, al-
though localization in the outer cortex exceeded that
present anywhere in the control tissues. Interlobar
and arcuate arteries, tubules, and interstitial cells
did not show localization of renin.

In the control cases, short preglomerular segments
of arteriole and glomerular hilums were positive, with
much less intense staining than that observed in the
three cases described above (Figure 1B). For rough
comparison, the controls could be graded as 1+ and
the abnormal cases could be graded as 3+. Renin localization in the controls rarely extended into the glomerular mesangium beyond the hilums. Vascular staining was present in both the inner and outer cortex, but with an obvious predominance in the inner cortex.

**DISCUSSION**

The renin-angiotensin system is believed to be a factor in local vasoconstriction and in maintaining glomerular perfusion at low levels during normal development (8,9). Plasma renin activity is normally high both in third trimester fetuses and in newborns, and plasma renin activity may be increased even further by vaginal delivery (10). Renin-containing cells have also been demonstrated immunohistochemically in developing kidneys (11,12), and staining for renin granules may be more intense in fetal than in mature neonatal kidneys (13).

Renal tubular dysgenesis is characterized clinically by signs of diminished fetal and neonatal urine production. A similar clinical picture, comprising oligohydramnios, fetal pulmonary hypoplasia, neonatal anuria, and deficient renal tubular development, results from the administration of angiotensin-converting enzyme inhibitor to treat hypertension in pregnant women (14,15). The mechanism of the oliguria is believed to be drug-induced fetal hypotension, with decreased RBF; the mechanism of abnormal tubular development may be the lack of angiotensin II growth stimulation (16). The hereditary and the drug-induced conditions are both associated with deficient calvarial bone growth leading to wide sutures and large fontanelles (15,17), suggesting that calvarial bone growth is also stimulated by angiotensin II.

Immunohistochemical staining for renin in this study was clearly greater, both more intense and more widely distributed, in the newborns with renal tubular dysgenesis than in the five newborn controls of comparable gestational age. The very large amount of immunoreactive renin demonstrated in the kidneys of infants with renal tubular dysgenesis suggests that a large amount of renin is functionally available and that the accelerated conversion of angiotensinogen causes increased local vasoconstriction, resulting in a further reduction of glomerular perfusion and ultrafiltration and leading to oligohydramnios and postnatal oliguria.

The intracellular accumulation of renin in the arterioles and glomerular mesangium may result from impaired secretion, but more likely results from overproduction secondary to a failed feedback mechanism. A recently published abstract (18) describes dramatically increased amounts of renin RNA in the juxtaglomerular cells and vascular smooth muscle in cases of renal tubular dysgenesis. We believe it unlikely that the flawed feedback mechanism is in the impaired conversion of angiotensinogen to angiotensin II, because of the clinical evidence of greatly diminished urine output, implicating a high degree of local vasoconstriction. Whether the abnormality in feedback involves angiotensin II receptors cannot be determined from our data. An abnormality in the receptors may, if one is present, provide a link to the deficiency of tubular development that characterizes renal tubular dysgenesis, because angiotensin II is a renal tubular growth factor (18). However, no angiotensin II receptor abnormality has been demonstrated in renal tubular dysgenesis, the cause of which remains unknown.

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**REFERENCES**


