SHORT REPORT

Renovascular hypertension commencing during fetal life

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We report three infants with severe, early hypertension due to unilateral renovascular disease, whose cardiovascular changes, or polycythaemia, or both, indicated they had been affected as fetuses. All underwent unilateral nephrectomy, and had a similar histology, with patchy areas having relatively normal glomeruli but immature proximal tubules. This pattern may be a marker for renovascular disease in fetal life.

CASE 1

A 37 weeks gestation, 3.3 kg girl, born to a mother with insulin-dependant gestational diabetes, required intravenous glucose and glucagon for symptomatic hypoglycaemia at four hours. Polycythaemia (haemoglobin 210 g/l, haematocrit 0.62 l/l) was present at 24 h, and persisted. On day 3, her systolic blood pressure, measured by Doppler vascular flow detector, was elevated at 80 mm Hg, and she had developed heart failure, with poorly contacting ventricles and asymmetric septal hypertrophy on echocardiography. She had normal femoral pulses, and had not had an umbilical artery catheter. Despite treatment with propranolol 3 mg/kg/d, captopril 0.5 mg/kg/d, and furosemide 1 mg/kg/d, later replaced with spironolactone 1 mg/kg/d and chlorothiazide 15 mg/kg/d, her systolic blood pressure rose to 135 mm Hg by day 7, and 155 by day 14. Her heart failure worsened, and she was transferred to our care.

Her hypertension was renin-driven (plasma renin activity 222 pmol/ml/h; normal <7), and imaging revealed a small (34 mm) left kidney with no perfusion on Doppler ultrasound, and virtually no function on mercaptoacetyl triglycine renography. The 49 mm right kidney was normal on scanning, and produced a normal plasma creatinine for her age and gestation at 68 µmol/l. Her urine contained no blood, protein, or glucose. Her blood pressures remained slightly elevated even when treated with the angiotensin-converting-enzyme inhibitor, captopril, at 5 mg/kg/d. Renal vein blood sampling to measure differential plasma renin activity was not considered justified in view of the invasive nature of this test, combined with the obviously unilateral disease on imaging studies. We therefore removed her left kidney. This showed a patchy histology. Some areas had normal glomeruli, immature poorly differentiated tubules, and marked intimal thickening of the medium sized arteries, while other segments showed old cortical and medullary infarction (fig 1A). Normal mature proximal convoluted tubules do not express epithelial membrane antigen (EMA), so immunostaining for this marker can indicate incompletely differentiated areas, as is seen in the abnormal areas of her cortex (fig 1B).

She was discharged one week post-nephrectomy with a normal blood pressure, off all drugs. At four months, she was thriving, normotensive, had a plasma creatinine of 46 µmol/l, good biventricular function, and normal fundoscopy.

CASE 2

A woman with myotonic dystrophy and polyhydramnios delivered a 2.5 kg girl at 36 weeks gestation who was also myotonic, requiring nasogastric feeding. She had continuous

positive airway pressure for mild respiratory distress for one day, but did not require umbilical artery catheterisation. She was polycythaemic (haemoglobin 232 g/l, haematocrit 0.74 l/l). She began vomiting on day 9, and two days later was severely hyponatraemic (sodium 118 mmol/l) and hypokalaemic (potassium 2.5 mmol/l), but not clinically dehydrated (plasma creatinine 63 µmol/l, urea 6.8 mmol/l). Her fractional excretion of sodium (FENa) was high at 4.2%, indicating that her hyponatraemia was sustained by renal salt wasting, and did not respond to moderate sodium chloride supplements of 4 mmol/kg/d. She was transferred to our care on day sixteen when her Doppler systolic blood pressure was found to be high at 105 mm Hg.

Her hypertension was driven by unilateral renal artery stenosis. The 37 mm right kidney was minimally perfused on Doppler ultrasound, non-functioning on dimercaptosuccinic acid (DMSA) scanning, and had a tapering renal artery stump on computerised tomography with contrast (fig 2). The 51 mm left kidney had normal perfusion, DMSA uptake, and renal artery appearance. It was not possible to measure arginine-vasopressin, erythropoietin levels, or renin activity because her high haematocrit meant her blood samples yielded insufficient plasma. Her femoral pulses and cardiac echocardiogram were normal.

Her hyponatraemia was corrected by infusing intravenous fluid volumes equal to the measured urine output (enabled by catheterising the bladder), and adjusting the sodium concentration of the fluid to be a little higher than that of the urine. Her hypokalaemia was corrected using the same principle. Huge quantities of these cations were required to correct and maintain normal plasma values, with the FENa predictably increasing further as the plasma sodium rose. Daily salt supplements of 16 mmol/kg were required to keep her plasma sodium at 132 mmol/l, at which point her FENa reached 7%. We felt these quantities were unsustainable. Because of this, plus the prospect of relatively longterm hypotensive treatment, we undertook a right nephrectomy, again without measuring renal vein renin concentrations. The renal cortex showed haphazardly arranged glomeruli, loss of proximal tubular differentiation, and prominent medial hypertrophy of the small arteries, and the medulla had extensive recent haemorrhagic necrosis (fig 3A,B). EMA immunostaining confirmed loss of normal fully differentiated proximal tubules (fig 3C). Post-operatively, her blood pressure fell quickly to 80 mm Hg, and she developed an immediate physiological response to this relative hypotension, producing highly concentrated, low volume urine (<0.2 ml/kg/h), and avidly conserving sodium (FENa 0.54%). This state reversed after intravenous furosemide 3 mg/kg, and she has thrived with a normal blood pressure and salt and water balance since.

CASE 3

This previously reported,¹ 3980 g boy was born at term to an insulin-dependent diabetic mother. On day 3, he developed

Abbreviations: DMSA, dimercaptosuccinic acid; EMA, epithelial membrane antigen; FENa, fractional excretion of sodium

Figure 1 Nephrectomy from case 1, showing adjacent sections from the same area. (A) Stained with haematoxylin & eosin, showing normal cortex in the lower area, with prominent proximal convoluted tubules, and abnormal cortex above, with glomerular crowding and loss of proximal tubules. (B) With immunochemical staining for epithelial membrane antigen (EMA) which is normally expressed in distal, but not the proximal tubules, as seen in the area of normal cortex below. Note that virtually all the tubules in the abnormal cortex above (*) are expressing EMA.

severe respiratory distress, had a systolic blood pressure of 80 mm Hg, and had poorly contractile, hypertrophied ventricles, and a dilated aortic arch with tortuous, dilated carotid and subclavian arteries. His left kidney functioned poorly on DMSA scan, and had a patchy nephrogram and abnormal intrarenal arteries on arteriography. His plasma renin activity was high, and he had a nephrectomy at 3 months. He remains normal at follow up, 16 years later.² Histology of the resected kidney revealed similar findings to the other two cases, with segments of the cortex showing patchy old necrosis and loss of proximal tubular differentiation.

COMMENT

Neonatal hypertension is rare, and most often due to postnatal causes, such as a renal artery thromboembolus from an umbilical artery catheter,³ but we believe the three children

we present had been affected by renovascular disease during fetal life. They all had hypertension noted the first time the blood pressure was recorded, and already had haematological and cardiac findings which would be expected to take longer than that to appear. Cases 1 and 2 had very marked polycythaemia from the start; this strongly suggests excessive erythropoietin production, which frequently occurs in parallel to excess renin from renal hypotension or ischaemia, and has been described in early childhood.⁴ We did not measure these babies' erythropoietin levels because their extreme polycythaemia would have necessitated unreasonably large sample volumes. Cases 1 and 3 had cardiac septal hypertrophy noted at day 3, and additionally case 3 had a dilated aorta, and dilated tortuous subclavian and carotid arteries demonstrated soon after this. Though maternal diabetes may have contributed to the myocardial hypertrophy, this could not account for the arterial abnormalities. All three babies had normal apgar scores and none of their parents had any history of renal disease, nor did their mothers take any significant drugs during pregnancy. Only the mothers of case 1 and 3 were diabetic. We are only aware of one previous case of hypertension reported to have begun during fetal life.⁵ However, we believe that three babies previously reported to have presented with early hypertensive heart failure and unilateral renal disease could have been affected as fetuses, rather than perinatally, as postulated by the authors.⁶

All the nephrectomy specimens showed some areas lacking normal proximal convoluted tubules, demonstrated both by routine histology and by immunochemical staining using a marker not expressed by fully differentiated proximal tubules. These changes which are attributed to in-utero renal ischemia,⁷ closely resemble those of renal tubular dysgenesis, which was originally described as a fatal, recessively inherited disorder.⁸ This condition which is characterised by EMA positive immature proximal tubules, has recently been associated with homozygous or compound heterozygous genetic mutations in the renin-angiotensin system (those encoding renin, angiotensinogen, angiotensin converting enzyme, and angiotensin II receptor type 1).⁹ We know from animal studies that the renin-angiotensin system and growth factors (like Transforming

Figure 2 Computerised tomography with contrast of abdomen, from case 2, showing the left renal artery, but just a short stump at the origin of the right renal artery.

Figure 3 Nephrectomy from case 2: (A) Low power view showing medullary infarction. (B) High power view showing loss of proximal tubular differentiation. (C) Adjacent section, showing strong immunochemical staining for EMA in all tubules.

growth factor β and Vascular endothelial growth factor) acting independently or together play a significant role in nephrogenesis including renal vascular and tubular development.^{10–14} It has been postulated that mutation-induced renin-angiotensin system inactivity leads to chronic low renal perfusion in-utero, and that this results in the characteristic renal lesions.⁹

Similar lesions have also been observed in several conditions that cause ischemic insults and lead to hypoperfusion of the fetal kidneys, like twin-to-twin transfusion syndrome,¹⁵ exposure to angiotensin converting enzyme inhibitors¹⁶ or angiotensin II receptor blockers,¹⁰ major cardiac malformations,¹⁷ and severe liver disease.¹⁸ Renal tubular dysgenesis phenotype has also been described as a unilateral lesion beyond the site of renal arterial constriction in adults¹⁹ and young infants⁷ with renovascular hypertension. We believe that our cases may have been caused by the same mechanism, that is in-utero renal ischemia, in their cases due to the renovascular pathology. Hypertrophy of the endothelial and medial cells probably results from mechanical action of the vessels in response to intra-renal hypotension, as also been suggested by Daïkha-Dahmane *et al.*¹⁰ In parts of the kidneys subjected to more profound ischaemia there is progression to medullary infarction, a pattern of necrosis typically associated with the perinatal kidney.²⁰ This pattern may provide a useful marker to suggest fetal renovascular disease. In 1981, Evans *et al* described a boy who had renin-driven hypertension and was cured by unilateral nephrectomy of his small left kidney.⁵ They ascribed his renal lesion to renal vein thrombosis because they noted organised, calcified thrombus within the renal vein and many of its tributaries. However, we speculate that he also had primary renal arterial disease because they describe remarkably similar histology to our cases, including narrowed arteries with fibrointimal thickening. Severe arterial ischaemia could have led to secondary thrombosis of the renal veins.

Two of the pregnancies were associated with diabetes. Recent literature suggests an association between mutations of the transcription factor hepatocyte nuclear factor-1 β (located on chromosome 17q21.3) with both diabetes and some renal conditions (including renal cysts, familial hypoplastic glomerulocystic kidney disease, renal malformations and atypical familial hyperuricaemic nephropathy).^{21–23} However, the patchy and unilateral nature of the pathology in our patients makes it unlikely to be due to a mutation.

Severe hyponatraemia secondary to renal salt wasting, as we saw in case 2, is a well described, but poorly understood, association with neonatal hypertension.²⁴ The dramatic change that we saw in her renal physiology from massive natriuresis to intense salt retention (a 13-fold fall in FENa) happened immediately after the affected kidney was removed, and as her blood pressure fell. It was not possible to know whether one or both kidneys had been responsible for the severe salt leak, or its pathophysiological mechanism.

In summary, fetal renovascular disease may cause hypertension and polycythaemia in newborns. If it causes severe symptoms such as heart failure or major salt wasting, and is due to unilateral disease, unilateral nephrectomy may provide a good longterm therapeutic option. The renal histology with patches of undifferentiated proximal tubules appears to have a characteristic pattern.

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IMAGES IN NEONATAL MEDICINE.....

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Neonatal subcutaneous fat necrosis with characteristic rash and hypercalcaemia

A 3.305 kg baby girl was born at term following an emergency caesarean section for reduced fetal movements and meconium staining of liquor. Cord blood gases showed pH of 7 and base deficit of 13.9. She fed poorly and developed symptoms of hypoglycaemia. Her lowest recorded temperature was 35.5°C. On day 4, she developed an extensive rash over her back, upper thighs and groin area. The rash was erythematous, indurated and tender on palpation, consistent with extensive subcutaneous fat necrosis (SCFN) (fig 1A). Investigations for sepsis revealed negative cultures.

When reviewed at 4 weeks of age the baby was failing to thrive and was hypercalcaemic with adjusted calcium level of 3.99 mmol/l. She received intravenous fluids, oral furosemide and spironolactone. She was given low calcium formula but her adjusted calcium level remained high at 4.0 mmol/l. A renal ultrasound showed medullary echogenicity consistent with nephrocalcinosis. She was given prednisolone (1 mg/kg/day) and diuretics were discontinued. The calcium level normalised and prednisolone was weaned over five weeks. At 9 months of age her weight remains below the 0.4th percentile. Serum calcium and creatinine are normal and the skin changes are less extensive, but areas of induration remain (fig 1B) and ultrasonographically nephrocalcinosis persists.

Subcutaneous fat necrosis is rare, but it requires careful investigation and follow up for potentially serious sequelae.^{1,2} Treatment of hypercalcaemia is controversial.³

Figure 1 Baby girl with subcutaneous fat necrosis at age (A) 5 days and (B) 9 months. Parental/guardian informed consent was obtained for publication of this figure.

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