A further family with congenital renal proximal tubular dysgenesis

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Abstract

A new syndrome of oligohydramnios, Potter's syndrome, and anuric renal failure leading to stillbirth or neonatal death from respiratory failure has recently been described. Histologically, there is renal tubular dysgenesis, especially of the proximal tubules, and apparent glomerular crowding. To date, five families have been reported, in four of which there have been affected sibs and in two parental consanguinity. The disorder is, therefore, thought to be inherited in an autosomal recessive manner.

Allanson *et al*¹ reported a family in which two successive girls were stillborn after premature births associated with oligohydramnios and Potter's syndrome. Renal histology in both cases showed absence of normal proximal tubules. The second child was also microcephalic, had a congenital heart defect,

and multiple joint contractures. These two infants differed in some respects from the subsequently reported cases (table), and may possibly represent a different disorder of proximal renal tubules.

Voland *et al*² reported two families, both with parental consanguinity. In the first family a boy was affected and in the second family three boys were affected. As in the family of Allanson *et al*¹ the kidneys were characterised by proximal tubular dysgenesis and the glomeruli appeared crowded together.

The first detailed description of this disorder was given by Schwartz *et al*.³ They reported a case in which a woman had severe oligohydramnios in two successive pregnancies. Both pregnancies ended in the birth of an infant, one male and the other female, who died within 24 hours of birth with an anuric acidosis and pulmonary hypoplasia. Apart from joint contractures and a fractured femur in the first infant there were no other abnormalities. The parents were not consanguineous. The mother gave a history of moderate alcohol intake and cigarette smoking in the first pregnancy, and had had an overdose of cocaine at 25 weeks in the second. In both infants the gross appearance of the kidneys was unremarkable with normal cortical surfaces, corticomedullary differentiation, and pelvicalyceal systems. Histologically, the kidneys of both infants showed tubular immaturity with some increase in interstitial fibrous tissue. The immature tubules had hyperchromatic nuclei, prominent nucleoli, scant cytoplasm, and were all negative to periodic acid-Schiff reagent. Immunoperoxidase staining with epithelial membrane antigen failed to show the normal negative staining of proximal tubules. The tubular immaturity resulted in a relative crowding of normal looking glomeruli.

The authors postulated autosomal recessive inheritance, vascular impairment, possibly owing to cocaine, although maternal cocaine was only documented for the second pregnancy, or a defect in a maternal growth factor as possible aetiologies. They discussed earlier reports of tubular hypoplasia, in one of which there was also an arrest of glomerular maturation,⁵ the other being that of Allanson *et al*¹ mentioned above. They considered that neither of these reports fully corresponded to the findings in their own cases. The mother in their family has since

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given birth to a third normal child (Schwartz, personal communication).

Most recently Swinford *et al*⁴ reported a further family in which they described two affected brothers in detail and gave a history of two earlier affected brothers. As in the family of Schwartz *et al*³ there was oligohydramnios, Potter's syndrome, and anuria, followed by death shortly after birth. The renal abnormality was similarly characterised by absence of normal proximal tubules, confirmed by negative PAS staining of the brush borders, and positive immunoperoxidase staining of primitive proximal tubules. There was also both a relative and an absolute increase in numbers of normal glomeruli. They introduced the term tubular dysgenesis for this new renal disorder.

We present a female infant born to unrelated parents with a picture very similar to that described by Schwartz *et al*³ and by Swinford *et al*.⁴ This is the first report of renal tubular dysgenesis from the United Kingdom or indeed from Europe.

Case report

A 29 year old woman, gravida 2 para 0, with a previous missed abortion in April 1986, delivered a female infant at 39 weeks' gestation in March 1987. The birth weight was 2830 g. The mother had been found to have severe oligohydramnios on ultrasound scanning at 18 and 20 weeks of pregnancy. Subsequently no liquor at all could be detected and the

Figure 1 Renal histology showing tubular dysgenesis and glomerular crowding.

Figure 2 Immunostaining of kidney with epithelial membrane antigen showing positive staining of all tubules and therefore lack of mature proximal tubules.

Comparison of present case and previously reported cases.

	Allanson <i>et al</i> ¹			Voland <i>et al</i> ²			Schwartz <i>et al</i> ³			Swinford <i>et al</i> ⁴			Present case
	1	2	3	4	5	6	7	8	9	10	11	12	13
Clinical features													
Sex	F	F	M	M	M	M	M	F	M	M	F	M	F
Gestation (wk)	34	36	32	36	32	36	36	34	33	33	35	32	39
Age at death	SB	SB	4d	2d	SB	2d	16h	19h	NN	NN	NN	9h	27h
Oligohydramnios	Yes	—	Yes	Yes	Yes	Yes	—	Yes	—	—	Yes	Yes	Yes
Potter's syndrome	Yes	Yes	Yes	Yes	Yes	Yes	—	Yes	—	—	Yes	Yes	Yes
Anuria	—	—	Yes	Yes	Yes	Yes	No	No	—	—	Yes	Yes	Yes
Microcephaly	No	Yes	—	—	—	—	No	No	*	No	Yes	No	No
Congenital heart defect	No	Yes	—	—	—	—	—	No	No	No	No	No	No
Multiple joint contractures	No	Yes	—	—	—	—	Yes	No	No	No	No	No	No
Pathological findings													
Size of kidneys	N	N	E	E	E	E	E	N	E	E	N	N	N
Demarcation of corticomedullary junction	Poor	Poor	N	N	N	N	N	N	—	—	N	N	N
Proximal tubules primitive or absent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	Yes	Yes
Proximal tubular brush border PAS reaction†	—	—	—	—	—	—	Neg	Neg	—	—	Neg	Neg	—
Immunoperoxidase staining with epithelial membrane antigen of proximal tubules‡	—	—	—	—	—	—	—	Pos	—	—	Pos	Pos	Pos
Glomeruli increased in number or crowded	No	No	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	Yes	Yes
Interstitial fibrosis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	Yes	Yes
Medullary rays poorly developed	—	—	—	—	—	—	—	Yes	—	—	Yes	Yes	Yes
Pelvic/ureteral systems and ureters hypoplastic	Yes	Yes	Yes	Yes	Yes	Yes	No	No	—	—	No	No	No
Intraluminal tubular calcification	Yes	Yes	No	No	No	No	No	No	—	—	No	No	No
Parental consanguinity	—	—	—	—	—	—	—	—	—	—	—	—	—

SB=stillbirth, N=not stated, E=enlarged, NN=neonate.

*Gross brain anomaly. †Normal controls are positive. ‡Normal mature proximal tubules are negative.

fetus showed marked deformation. Further ultrasound examination nevertheless showed normal sized fetal kidneys. Fetal chromosomes showed no abnormality.

The mother was well apart from Gilbert's syndrome, from which her brother also suffers. She is unrelated to her 30 year old husband, who is well.

Because of a marginal reduction in fetal growth she was induced at 39 weeks resulting in a normal vaginal delivery. The infant had severe deformation of the head, chest, and hips consistent with Potter's syndrome, and suffered severe respiratory difficulties. She was completely anuric throughout life and died at 27 hours despite appropriate treatment in an intensive care unit.

The parents were seen three months later for genetic counselling and were advised that recurrence risks were probably either 1 in 4 or very low. They were seen again seven months after the birth when one of us had seen the paper by Schwartz *et al*³ and a revised risk of almost 1 in 4 explained. They have subsequently suffered a further miscarriage at 12 weeks, but have a normal son born on 8.11.88.

NECROPSY FINDINGS

Gross findings

There was Potter's facies with petechial haemorrhages over the forehead. The lungs were haemorrhagic and congested but were aerated. There were no gross abnormalities in the cardiovascular, gastrointestinal, endocrine, reticuloendothelial, or central nervous systems. The kidneys showed normal fetal lobulation. The renal cortices were slightly pale, but the kidneys and the rest of the genitourinary system appeared otherwise grossly normal.

Histology of the kidneys

All the proximal tubules were small with reduced thickness of lining epithelial cells and small cross sectional areas. In places there was a slight excess of interstitial connective tissue and the glomeruli appeared relatively crowded together. The cortex was slightly thinned and the medulla also a little attenuated. There was no evidence of maldifferentiation (fig 1). Immunostaining with epithelial membrane antigen was positive in all the tubules confirming an absence of mature proximal tubules (fig 2).

Discussion

Like the previously described infants the infant reported here shows tubular, especially proximal tubular, hypoplasia or dysgenesis with a slight increase in interstitial fibrosis, but no evidence of renal dysplasia. The fact that all the tubules gave a positive immunoperoxidase stain with epithelial membrane antigen, as in the cases of Schwartz *et al*³ and Swinford *et al*,⁴ confirms the absence of normally developed proximal tubules.

The clinical course and histological appearances in this infant are almost identical to those in the earlier reports^{3,4} and she must be assumed to have the same disorder (table).

There was no history of maternal illness, drugs, or irradiation in the present case which, taken together with the sib occurrence and parental consanguinity in the previous reports, strongly favours an autosomal recessive aetiology for this new syndrome. In view of the history of the two spontaneous abortions in this family, and that of Allanson *et al*,¹ it cannot be excluded that these may in some way be related to the genetic defect.

The patient reported by Lorentz and Trillo⁵ with glomerular as well as tubular immaturity probably represents a different disorder, as suggested by Schwartz *et al*.³ The stillborn girls reported by Allanson *et al*¹ had the same basic defect of tubular dysgenesis but also had other features, both renal and extrarenal. However, both microcephaly and joint contractures have been reported individually in later cases. It is not possible to decide retrospectively whether or not their patients had the same disorder.

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