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RENÉE BERNSTEIN, ANTHONY T. MILNE,
AND TREFOR JENKINS

*Department of Human Genetics, School of Pathology,
The South African Institute for Medical Research
and University of the Witwatersrand, Johannesburg*

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Requests for reprints to Dr R. Bernstein, Cytogenetic Unit, Department of Human Genetics, South African Institute for Medical Research, P.O. Box 1038, Johannesburg 2000, South Africa.

Bilateral renal agenesis in 2 male sibs born to consanguineous parents

SUMMARY Two boys with bilateral agenesis of kidneys and ureters were the product of a consanguineous marriage. This family and previous reports of familial bilateral renal agenesis support the supposition that a minor proportion of cases of BRA is caused by the homozygous state of an autosomal recessive gene.

Case reports

The pedigree of the family is shown in the Fig. Both parents (IV.7 and IV.8) were healthy and came from a village near Naples, Southern Italy. The father's mother and the mother's maternal grandfather were sibs. The family history was otherwise unremarkable except for one stillbirth for unknown reasons (V.4).

The gestational histories and perinatal courses of both patients were essentially identical and therefore are reported simultaneously, with any variation in the second sib shown in parentheses. There was no history of drug intake. Oligohydramnios was noticed during the second trimester, and spontaneous delivery from a vertex presentation took place in the 35th (36th) week of gestation. The prematurely born male infants suffered from severe neonatal asphyxia which, despite efforts at respiration, led to death 11 (8) hours after birth. The probands were anuric, and no kidneys were evident either on palpation or on x-ray. Birthweights (2250 g and 2500 g, respectively) were normal for gestational ages of 35 and 36 weeks. Dysmorphic features in the 2 sibs were similar and typical of the oligohydramnios tetrad. They included a wrinkled senile-looking face with receding forehead, widely spaced eyes, inner epicanthal folds extending downwards to the middle of the cheeks, a bird-like nose, an underdeveloped chin, low-set, folded, and misshapen ears, narrow chest, scoliosis of the thoracic spine, and short, broad hands with tapering fingers. The younger sib, in addition, had right cryptorchidism and his placenta contained a single umbilical artery. Neither of them had club feet or other significant limb positioning defects.

Necropsies showed bilateral renal and ureteral agenesis, with hypoplasia of the urinary bladder, pulmonary hypoplasia with hyaline membranes and pneumonic infiltrates, and a (physiologically) open foramen ovale and ductus Botalli.

Fig. Pedigree of the 2 patients

Discussion

The 2 sibs showed the typical clinical features secondary to bilateral renal agenesis (BRA). The primary defect, absence of both kidneys and ureters, causes a lack of amniotic fluid and consequent fetal compression. This gives rise to the extrarenal features of BRA; 'Potter facies', limb positioning defects, and hypoplasia of the lungs. Therefore, these features are also seen after long term continuous leakage of amniotic fluid through ruptured fetal membranes (Fantel and Shepard, 1975), whereas they are absent in a twin with BRA if the monoamniotic cotwin does not have BRA (Mauer *et al.*, 1974).

BRA may occur as part of many recognised malformation syndromes, and these should be identified through careful clinical examination, pedigree examination, detailed necropsy report, and chromosome examination, if warranted. Examples include the recessively inherited cerebro-oculo-facio-skeletal syndrome (Preus *et al.*, 1977); the 4p- syndrome (Mikelsaar *et al.*, 1973); and partial trisomy for an undetermined chromosome segment, possibly a segment of chromosome 22 (Ferrandez and Schmid, 1971). While the recurrence risk in the first of these instances is 25%, it is very low in the two latter instances, unless the chromosome examination in the parents discloses translocation heterozygosity or mosaicism in one of them. The chances that a further affected child would also have BRA are probably very low in all 3 instances. BRA can also be found as a feature of sirenomelus which almost invariably occurs sporadically (Carpenter and Potter, 1959).

In the majority of cases, BRA presents as a single malformation together with its subsequently derived structural changes. Three-quarters of the probands are male. The incidence is about 1 in 3000 newborns, and recurrence lies within the range of 2 to 5% (Pescia *et al.*, 1976). Though the majority of cases occurs

sporadically, there is some evidence from the familial cases that the condition may sometimes be caused by a single mutant gene. Our pedigree with parental consanguinity and 2 affected sibs suggests autosomal recessive inheritance. The pedigree of the family reported by Pashayan *et al.* (1977), with 3 affected males (2 brothers and their cousin born to the sister of the mother), suggests X-linked inheritance in that instance. Though it is less likely, autosomal recessive inheritance has to be considered as an alternative in Pashayan's family, and X-linked inheritance in our family. In the other 12 families, each with 2 affected sibs, in 6 cases the probands were 2 males, in 3 cases 2 females, and in 3 cases sibs of opposite sex (Morillo-Cucci *et al.*, 1971; Pashayan *et al.*, 1977). Though familial occurrence of a malformation in a minority of cases does not, of course, necessarily imply autosomal or X-linked recessive genes causing these instances, the 14 families present some evidence that 2 genes which both cause BRA might exist: one autosomal recessive gene, of which the present family with parental consanguinity, and the families with affected females would be examples; and one X-linked recessive gene, which would have caused BRA in the family of Pashayan *et al.* (1977), and in a proportion of the families with 2 affected male sibs. These 2 possibilities should therefore be taken into consideration in genetic counselling after the birth of a child with BRA, especially if the pedigree is suggestive of either of them.

A. SCHINZEL¹, CHRISTINE HOMBERGER²,
AND T. SIGRIST³

¹*Division of Medical Genetics, Department of
Paediatrics,*

University of Zurich;

²*Paediatric Hospital, St. Gallen; and*

³*Institute of Pathology, Kantonsspital, St. Gallen,
Switzerland*

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Requests for reprints to Dr A. Schinzel, Abteilung für Medizinische Genetik, Universitäts-Kinderklinik Zürich, Steinwiesstrasse 75, CH-8032 Zürich, Switzerland.