Bilateral absence of the kidneys and ureters

Three cases reported in one family

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SUMMARY Three infant boys with bilateral absence of the kidneys and hypoplasia of the lungs are described. Two of the infants were brothers and the third was a first cousin. They were born to 2 sisters whose husbands were unrelated to their wives and to each other. None of the parents had renal problems. The occurrence of this syndrome in 2 male sibs is suggestive of an autosomal recessive inheritance pattern which has been previously described. An additional male first cousin born to the mother's sister is suggestive of sex-linked inheritance for this particular family, an inheritance pattern not previously described.

In 1946a, b Potter described the characteristic appearance of infants with bilateral renal agenesis. The extrarenal manifestations include typical facies (frequently referred to as Potter's facies), skin changes, spade-like hands, club feet, and pulmonary hypoplasia.

The aetiology of bilateral renal agenesis is still unknown. The majority of the cases are sporadic (Potter, 1965; Almolsch, 1937; Davidson and Ross, 1954; Bain and Scott, 1960; Pasquier *et al.*, 1971); however, a number of familial cases have been reported (Madisson, 1934; Schmidt *et al.*, 1952; Baron, 1954; Arends, 1957; Rosenfeld, 1959; Rizza and Downing, 1971; Whitehouse and Mountrose, 1973; Buchta *et al.*, 1973; Hack *et al.*, 1974).

The authors recently saw a patient (Fig. 1, II.2) for genetic counselling. She had had 1 normal son followed by 2 male full term infants born with bilateral absence of the kidneys who died shortly after birth. The patient's sister (Fig 1, II.3) who was married to a man unrelated to herself or to her brother-in-law had also had a son with bilateral absence of the kidneys.

The purpose of this report is to discuss counselling such a family and to pose questions about possible aetiology.

Case reports

The parents of the 2 affected brothers are healthy, nonconsanguineous Caucasians. The mother's first pregnancy resulted in the birth of a normal infant.

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CASE 1

The second pregnancy (Fig. 1, III.2) resulted in a male infant. The delivery was vaginal and presentation was breech. His birthweight was 2334 g. His condition deteriorated rapidly and he died at 2 hours of age. The mother gained 8164 g during the pregnancy, and at delivery there was decreased amount of amniotic fluid.

On physical examination the infant was reported as having a dolichocephalic head. The ears were apparently low set with very little cartilage. The bridge and the tip of the nose were flat. The neck was short, and the lower limbs showed bilateral bowing.

Fig. 1 Pedigree of family.

Fig. 2 Full face view of the second affected son born to the counsellee. Pedigree No. III.3. Facies is typical of Potter's facies except the epicanthic folds are not as obvious as described by Potter.

At necropsy the lungs weighed 30 g and showed minimal consolidation of the basal portions and emphysema of the rest. Air was found in the mediastinum, interstitial, and subpleural portions. There was bilateral absence of the kidneys and ureters. The liver and spleen were congested, and the brain showed incomplete separation of the hemispheres.

Fig. 3 Profile view of patient III.3.

CASE 2

The mother presented with her third pregnancy in 1974 (Fig. 1, III.3). Weight gain during that pregnancy was 12 kg and the infant's heart beat was reported to be strong all through the pregnancy. The pregnancy lasted 39 weeks. The presentation was cephalic and delivery was vaginal. The membranes had to be ruptured in the delivery room and amniotic fluid was reported to be of adequate quantity. At birth the infant weighed 2446 g. He had an Apgar score of 3 and died at 1½ hours of age despite an attempt to resuscitate him.

On physical examination the facial appearance (Fig. 2 and 3) was typical of that described by Potter except that the bilateral deep epicanthal folds were not as prominent. Skin of the extremities showed numerous folds. The neck was short and webbed. The hands were spade-like, and the feet were clubbed. At necropsy the lungs were reported to be extremely rubbery and deep red in colour. The combined weight of the lungs was 20 g. There was complete absence of both kidneys and ureters. The urinary bladder was present and was reported to have a lumen.

Chromosomes done on post-mortem spleen and thymus tissues were reported to be 46 in number showing a normal male karyotype.

CASE 3

The third affected male (Fig. 1, III.4) was born to the mother's sister (II.3) after a full-term, uneventful pregnancy. Delivery was vaginal with breech presentation, and at the time very little amniotic fluid was reported to precede the delivery. The infant weighed 1940 g and had an Apgar score of 2. He was very cyanosed and died at 3 hours of age despite

vigorous resuscitation. His nose was described as having a broad bridge and flat tip. His ears were malformed and apparently low set. There was no mention of limb malformations. Necropsy showed complete absence of the kidneys and ureters, a hypoplastic bladder, undescended testes, and small and unexpanded lungs with numerous emphysematous blebs. The lungs were solid in consistency and pinkish red with numerous small haemorrhagic foci. Haemorrhagic foci were also noted in the brain and adrenals.

The youngest sister (II.5) recently delivered a normal female infant.

Discussion

Bilateral renal agenesis is a disorder occurring in 0.3 per 1000 births (Potter, 1946a, b). Usually the condition includes bilateral renal agenesis, typical facies, hypoplasia of the lungs, frequently associated genitourinary and anorectal anomalies, and abnormalities of the extremities (Potter, 1965; Almolsch, 1937; Davidson and Ross, 1954; Bain and Scott, 1960; Madisson, 1934).

The disorder shows a male to female ratio of 2.7/1. The amniotic fluid is either completely absent or greatly reduced in amount (Ratten *et al.*, 1973; Potter, 1972). The infants are usually small for gestational age and are either stillborn (60%) or die within the first 48 hours of life because of pulmonary hypoplasia. Those infants who escape early pulmonary death succumb to renal insufficiency within the first 2 weeks of life (Potter, 1972). The facial features common to all affected infants are alike, including dry skin with a wrinkled prematurely aged appearance, a prominent skin-fold beginning above the eye and passing over the inner canthus and extending down and across the cheek, a flat 'parrot beak' nose, a long filtrum, and a prominent depression between the lower lip and chin. The ears are usually low set and pressed flat against the head. Most infants also have bowed legs, clubbed feet, and spade-like hands. The most common concomitant internal abnormality is severe pulmonary hypoplasia (Bain and Scott, 1960; Ratten *et al.*, 1973; Potter, 1972). The lungs are small and usually weigh less than 50% of normal for an infant of comparable body size.

It has been suggested and recently reported (Fontel and Shepard, 1975), in a fetus with normal kidneys, that the typical facial and limb abnormalities in Potter's syndrome are caused by compression of the fetus by the uterine walls secondary to extreme oligohydramnios (Potter, 1972). Experimentally induced oligohydramnios in rats was shown to result in small pups with microstomia, short extremities, and clubbed feet (DeMyer and Baird, 1969). A recent

report of unilateral and bilateral renal agenesis in monoamniotic twins (Mauer *et al.*, 1974) in whom the typical facial features of Potter's syndrome were absent strongly supports the role of oligohydramnios in the genesis of these defects. Absence of external features of Potter's syndrome is also reported in an infant with anencephaly and normal quantity of amniotic fluid (Bain and Scott, 1960). A normal quantity of liquor has been documented in 1 infant with the external features of Potter's (Sylvester and Hughes, 1954) as well as in our second case. One explanation for this is that amniotic fluid in these cases is accumulated late in gestation after the defects are well established (Mauer *et al.*, 1974).

The aetiology of this disorder is still unknown. A teratogenic substance has not been found. A genetic cause was first suggested by Almolsch (1937). The majority of reported cases of bilateral renal agenesis are sporadic, but a number of familial cases are known (Table 1). The familial cases show the same sex ratio, with male preponderance. Affected infants are of low birthweight and usually small for dates. Whenever tested the chromosomes are normal. A recent report by Mauer *et al.* (1974) of unilateral and bilateral renal agenesis in monoamniotic male twins not only suggests a genetic component, but also, contrary to previous theories (Sylvester and Hughes, 1954), suggests that these abnormalities may be caused by similar mechanisms. Table 2 lists other reports of families showing both unilateral and bilateral renal agenesis.

Autosomal recessive inheritance with a sex limiting factor to explain the predominance in males has been suggested to explain the familial cases. In the absence of parental consanguinity autosomal recessive inheritance is unlikely. Since approximately 1/3 to 1/4 of affected infants are female it is also unlikely that we are dealing with an X-linked recessive trait.

In the family described in this report, the observation of the syndrome in two brothers and a first

Table 1 Known familial cases of bilateral absence of kidneys and ureters

Author	No. of affected/family	Sex of infants
Madisson (1934)	2	M M
Schmidt <i>et al.</i> (1952)	2	F F
Baron (1954)	2	M F
Arends (1957)	2	M M
Rosenfeld (1959)	2	F F
Rizza and Downing (1971)	2	M M
Whitehouse and Mountrose (1973)	2	F M
Buchta <i>et al.</i> (1973)	(A) 2 (B) 2 (C) 4	F M M M M M M M
Hack <i>et al.</i> (1974)	2	M M

F, Female; M, Male.

Table 2 Known familial cases of unilateral and bilateral renal aplasia

Author	No. of affected/family	Sex of infants with	
		Unilat. renal aplasia	Bilat. Renal aplasia
Hilson (1957)	2	F	M
Winter <i>et al.</i> (1968)	3	F	M M
Kohn and Borns (1973)	4	M F	M F
Buchta <i>et al.</i> (1973)	(D) 6	F F F	M M M
Cain <i>et al.</i> (1974)	2	M	M
Mauer <i>et al.</i> (1974)	2	M	M

F, Female; M, Male.

male cousin is of great interest. One could resort to the explanation that one of the parents (in these cases it will have to be the mother) had the (dominant) trait in a minimal form and passed it on to some of the offspring in whom the syndrome was expressed in a much more severe manner. This also means that one of the maternal grandparents would have to have had the trait and passed it on to at least 2 of their daughters. In this family neither of the mothers had renal problems that could be observed by intravenous pyelography. Another explanation would be to assume that the 2 mothers had a balanced chromosomal translocation and that in the affected children an unbalanced form of the translocation resulted in anomalies. In the absence of any detectable changes in the karyotypes of the parents of cases 1 and 2 and of case 2 himself, this interpretation becomes hypothetical. Another assumption would be that the mothers had gonadal mosaicism which could result in repeated births of children with similar congenital malformations not present in the maternal phenotype. This assumption is also speculative and not demonstrable. In addition to genetic explanations one could turn to implication of repetitive environmental factors. Such nongenetic causative factors could be in the external environment or more likely within the mother's organism. It would, however, be unlikely for the same factors to act for both sisters. Because the sisters are married to unrelated fathers it is unlikely though not impossible that the syndrome can be attributed to homozygosity of an autosomal recessive gene. X-linked recessive inheritance is a more likely explanation, at least for this family. This, however, does not explain the occurrence of the syndrome in females in other families and in cases where 2 sibs of different sex have been reported.

The parents of the 2 affected sibs were told that their situation was different from those already reported. In their case, an X-linked recessive mode of inheritance could not be ruled out.

It is very likely that once again we are dealing with another example of genetic heterogeneity, and

determination of the genetic mechanism or mechanisms will require that clinical variability be carefully documented and defined.

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