Renal-hepatic-pancreatic dysplasia: an autosomal recessive malformation

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Abstract

We report two brothers with a cystic malformation of the kidneys, liver, and pancreas. In both cases the malformation was fatal and the children died shortly after birth. The pathological findings, consisting of multicystic dysplastic kidneys, dilated and dysgenetic bile ducts, dilated pancreatic ducts, and polysplenia, correspond to those reported by Ivemark as renal-hepatic-pancreatic dysplasia. Many polymalformation syndromes include cystic affection of these three organs, so this syndrome could be an isolated entity or a final common pathway of response of these organs to a variety of developmental disturbances, which could also include splenic abnormalities. We propose an autosomal recessive pattern of inheritance for renal-hepatic-pancreatic dysplasia.

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Key words: renal-hepatic-pancreatic-dysplasia; autosomal recessive disorder; dysplastic kidneys.

Potter's facies and mild scrotal oedema. Examination of the internal organs showed that both kidneys were enlarged and cystic and the weight of both was 68 g (normal weight 32 g). Neither pelvis nor calyces could be identified. There was agenesis of both ureters and the bladder. The liver was slightly enlarged, weighing 198 g (normal weight 127 g) and showed scarce, small cysts of 0.5 cm in diameter. Both lungs were hypoplastic and weighed 22 g (normal weight 48 g). The spleen weighed 7 g and in the splenic hilum there were four accessory spleens of 0.5 cm in diameter. The brain, spinal cord, and the pancreas appeared normal.

Histological study of the kidneys showed severe distortion of the normal architecture by the presence of numerous dilated ducts lined by cuboidal or flattened epithelium (fig 1). There were primitive duct structures surrounded by collars of mesenchymal connective tissue. Scattered fetal glomeruli were seen. The liver showed microscopically irregular, expanded portal tracts in a varying amount of mature connective tissue and the presence of dysgenetic bile ducts, some of them dilated (fig 2).

CASE 2

A third pregnancy, one year later, was complicated by oligohydramnios which was detected at week 23. On sonography performed at that time, enlarged and cystic kidneys were detected, as well as a hepatic cyst. The rest of the fetal structures were of normal appearance. The infant was born at 34 weeks of gestation

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In 1959 Ivemark *et al*¹ described a syndrome of renal-hepatic-pancreatic dysplasia in two sibs. No other cases were reported during the next 19 years. In 1978, Crawford² described a similar syndrome in two sibs, one of whom had splenic agenesis and cardiac transposition. Shortly thereafter, Strayer *et al*³ published a sporadic case and Bernstein *et al*⁴ reviewed this syndrome in 1987 and reported five unrelated cases of renal-hepatic-pancreatic dysplasia.^{3,4} Lastly, Carles *et al*⁵ in 1988 reported another sporadic case, with clinical features almost identical to the other described cases. We have studied two brothers affected by this syndrome and we suggest an autosomal recessive pattern of inheritance.

Case report

CASE 1

A male infant was born at 37 weeks of gestation and died 4½ hours after birth. The mother was a 29 year old woman with a previous history of spontaneous abortion at 3 months, two years earlier. The pregnancy was complicated by oligohydramnios. The newborn weighed 2800 g and length was 32 cm. Externally he showed

Figure 1 Case 1, microphotography of the kidney showing cysts lined by cuboidal and flattened epithelium and presence of scarce fetal glomeruli (on the right) (HE).

Figure 2 Case 1, microphotography of the liver showing enlarged portal tracts with fibrotic changes and dysgenetic bile ducts, some of them dilated (on the left) (HE).

and died two hours after birth. This second newborn weighed 2600 g and his length was 27 cm. He also had Potter's facies. The dissection of the organs showed both kidneys to be normal in weight (25 g together), but both were cystic. Renal pelvis and ureters were not seen, but the urinary bladder was present. The pancreas was enlarged, weighing 10 g (normal weight 3 g), and was macroscopically cystic: multiple cysts of 0.8 cm in diameter were seen. Both lungs were slightly reduced in weight, the weight of both being 30 g.

Both kidneys showed similar histological characteristics to those observed in his brother, with multiple cysts lined by cuboidal or flattened epithelium. Also primitive duct structures and scarce glomeruli were found. The pancreas showed dilated ducts with periductal fibrosis. There was extensive loss of exocrine and endocrine tissue (fig 3).

The parents were screened by ultrasound for abnormalities in the kidneys, liver, or pancreas, but both examinations were normal. They were also asked for any family history of renal, hepatic, or pancreatic disturbances or any hereditary disease with a negative result. No clear history of consanguinity was known in the family, but the fathers of both parents were born in the same small and isolated village in Andalusia (southern Spain). The karyotypes of both parents and the two affected children were normal.

Figure 3 Case 2. Alteration of the pancreatic parenchyma, with ductal dilatation, pericystic fibrosis, and loss of exocrine and endocrine tissues (HE).

Discussion

Polycystic kidneys are found in a variety of congenital and sporadic syndromes. Potter⁶ discussed polycystic renal disease in a series of classical articles on polycystic kidneys and on the development of human kidneys. According to his classification polycystic kidneys can be of four types. Type I corresponds to what we call nowadays autosomal recessive polycystic kidney disease and is characterised by ectatic collecting tubules. Type II, also termed dysplastic kidney, is characterised by cystic and primitive ducts surrounded by collars of immature fibrous tissue, occasionally containing cartilage. This type may be unilateral as well as bilateral. Although some autosomal recessive cases have been reported, this type of polycystic kidney usually occurs sporadically in the population. Type III corresponds to autosomal dominant polycystic kidney disease and is histologically characterised by the presence of cysts at any point in the nephron. This type of polycystic kidney disease, as well as the recessive type, is bilateral. Type IV is associated with obstruction in the lower urinary tract, but is otherwise indistinguishable from dysplastic kidney type II.

Types I and III constitute the principal monogenic disorders with polycystic kidneys as opposed to types II and IV which are usually sporadic dysplastic kidneys. Autosomal recessive polycystic kidney disease is a genetically homogeneous disorder caused by mutations in a gene localised on chromosome 6p21.1-p12.⁷ Although there is a broad range of phenotypes for this entity among different families, the studies performed in children with mild renal disease⁷ and in children with the severe perinatal phenotype⁸ both showed linkage to 6p21.1-p12. This evidence provides essential data for both cloning the gene and for DNA based prenatal analyses in at risk pregnancies. On the other hand autosomal dominant polycystic kidney disease is genetically heterogeneous and is caused by at least three different genes located on chromosomes 16p13.3 (PKD1),⁹ 4q13-q23 (PKD2),^{10,11} and a third locus which has not yet been identified.¹² PKD1 account for 85 to 90% of the cases of autosomal dominant polycystic kidney disease and is phenotypically more severe than PKD2.^{13,14} The PKD1 gene has been identified and partially characterised by the European Polycystic Kidney Disease Consortium.¹⁵ The PKD1 transcript consists of 14 148 bp, distributed among 46 exons, spanning 52 kb, and is adjacent to the tuberous sclerosis 2 (TSC2) locus.^{16,17} An interesting feature of this gene is that all but 3.5 kb at the 3' end of the transcript is encoded by a region repeated several times proximally in the same chromosome. A few mutations have already been found in the non-repeated sequence^{18,19} and large deletions have been described in TSC2 patients with severe renal cystic disease.²⁰ The predicted protein encoded by the PKD1 gene is called polycystin, consists of 4304 amino acids, and is probably located in the cell membrane,^{16,17,21} but its function remains to be elucidated.

Malformations of the liver, pancreas, and other organs may variously accompany the different kinds of polycystic renal disease. For example, autosomal dominant polycystic kidney disease is associated with cysts in the liver and pancreas, cranial aneurysms, diverticuli in the colon, valvular abnormalities, etc, and autosomal recessive polycystic kidney disease is always associated with hepatic lesions resembling congenital hepatic fibrosis.

The clinical and histological features reported in this case resemble most closely the bilateral renal dysplasia reported by Ivemark *et al.*¹ as well as the subsequent reports by Crawford,² Strayer and Kissane,³ Bernstein *et al.*,⁴ and Carles *et al.*⁵ In none of these cases was there any associated malformation suggestive of a polymalformation syndrome other than the renal-hepatic-pancreatic dysplasia. Only in the reports of Ivemark *et al.*¹ and Crawford *et al.*² were there more than one sib affected. In our patients, as well as in those reported by Ivemark *et al.*,¹ the degree of involvement of the same organs varied between sibs. Although this syndrome is rare, it is of primary relevance to know the pattern of inheritance in order to be able to offer genetic counselling as precisely as possible. Since we report the third case of sibs affected by this disorder, we think that an autosomal recessive pattern of inheritance should definitely be considered, and therefore a risk of 25% recurrence of the syndrome should be given for future pregnancies to parents of an affected child.

A number of syndromes involve varying degrees of renal dysplasia. Probably the best known is Meckel syndrome.²² The diagnostic criteria for this syndrome require at least two of the triad of cystic kidneys, occipital meningoencephalocele, and polydactyly, with certain other major features such as cleft palate and microcephaly. In our case the absence of other organs affected, apart from kidneys, liver, pancreas, and spleen, rules out this diagnosis. Other syndromes that present with renal-hepatic-pancreatic dysplasia, together with other deformities, are Goldston syndrome,²³⁻²⁵ Zellweger syndrome,²⁶ several chondrodysplasias,^{27,28} some chromosome aberrations, such as trisomy 9 and 13, and glutaric aciduria type II.²⁹ In most of these syndromes varying degrees of involvement of the central nervous system, eyes, skeleton, genitals, or heart can be detected. Although the necropsy data and the normal karyotype exclude most of these entities we could not rule out the remote possibility of a phenotypic variant and the possibility that these apparently single cases of renal-hepatic-pancreatic dysplasia form part of a genetically heterogeneous group. In which case it would appear that the renal-hepatic-pancreatic dysplasia could be a non-specific final common pathway of response of the affected organs to a variety of developmental disturbances caused by mutations in different genes.^{4,30,31} The cases we report here seem to be monogenic and belong therefore to the same category as those initially reported by Ivemark *et al.*¹ Although in our cases there were abnormalities of the lower urinary tract, which

were not present in those reported by Ivemark *et al.*, it is expected that the abnormal morphogenesis of the kidneys also includes the lower urinary tract, as has been found in other syndromes that include renal-hepatic-pancreatic dysplasia. The presence of multiple spleens recorded in one of our cases has also been reported in this syndrome by Bernstein *et al.*⁴ Crawford described one case of splenic abnormality in this syndrome consistent with splenic agenesis.² This suggests that splenic abnormalities are also part of this syndrome.

To conclude, we would like to highlight the fact that when genetic counselling is requested by a family with a history of a previous child affected with a renal-hepatic-pancreatic dysplasia, autosomal recessive inheritance should be considered. Finally, prenatal ultrasound examination of pregnancies seems appropriate for fetal detection of this syndrome in couples with a previously affected child until the gene responsible for the disorder has been identified.

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