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Sibs Diagnosed Prenatally With Situs Inversus Totalis, Renal and Pancreatic Dysplasia, and Cysts: A New Syndrome?

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We describe two sib fetuses with situs inversus, cystic dysplastic kidney and pancreas, bowing of the lower limbs and clavicles, severe intrauterine growth retardation (IUGR), and oligohydramnios. Early prenatal diagnosis of pancreatic and dysplastic renal cysts and situs inversus totalis were made in the 18-week-old fetus. This syndrome differs from that of Ivemark and related syndromes because of the presence of situs inversus totalis and absence of hepatic fibrosis and cysts. The parents were first cousins, and did not have any cysts of kidney, liver, or pancreas detected by ultrasonography. Am. J. Med. Genet. 82:166–169, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS: cystic dysplastic kidney and pancreas; pancreatic cyst; limb bowing; situs inversus totalis; prenatal diagnosis

INTRODUCTION

The renal hepatic pancreatic disease (RHPD) spectrum, or Ivemark syndrome, is characterized by various degrees of kidney, liver, and pancreatic involvement. Renal-hepatic or pancreatic dysplasia occur in many well-known syndromes. However we present a unique case of RHPD spectrum without liver involvement in two sibs. Is this a new syndrome or expanded form of RHPD spectrum?

CLINICAL REPORTS

We describe a new autosomal recessive type of renal hepatic pancreatic dysplasia (RHPD) spectrum without liver involvement. Both sibs were diagnosed prenatally. Abnormalities in the first fetus were noticed at 31 weeks of gestation but the pregnancy ended in stillbirth of a female at 38 weeks of gestation. One year later, in the second pregnancy, situs inversus totalis, cystic kidneys and pancreas, and bowing of lower limbs were diagnosed at 15 weeks of gestational age (Fig. 1). Autopsy after termination confirmed the sonographic findings (Figs. 2 and 3). In contrast to findings in the Ivemark syndrome, the liver was normal in both sibs. The clinical, physical, and autopsy findings in both sibs are summarized in Table I.

DISCUSSION

We describe an apparently new entity characterized by situs inversus totalis, bilateral cystic dysplastic kidneys and pancreas, and bowing of the lower limbs and clavicles. The liver of both sibs was normal, but both were severely growth retarded. Bowing of the lower limbs possibly represents the effect of severe oligohydramnios since the skeletal system was histologically normal. Parents were normal. These cases were different from renal hepatic pancreatic disease (RHPD) spectrum with their lack of liver involvement. RHPD is also known as Ivemark syndrome because of the first description of this entity by Ivemark et al. [1959]. Renal-hepatic or pancreatic dysplasia occur in many well-known syndromes (Table II). Common to these syndromes is various degrees of kidney, liver, and pancreatic involvement. However, in 1978, Crawfurd et al. reported on two sibs who died neonatally with a short and possibly webbed neck, a flat nose, and hypotonia. At autopsy, collapsed lungs, large flat adrenals, and absent or small spleen were found in addition to cystic lesions of the pancreas and kidneys. However, their livers were found to be normal. One sib had hypoplasia of left ventricle and transposition of great vessels and the other had a patent foramen ovale and patent ductus arteriosus. Yoshikawa et al. [1981] reported on a similar case with severe pancreatic fibrosis and meconium ileus, situs inversus totalis, bilateral renal dysplasia, and cardiovascular anomalies different from

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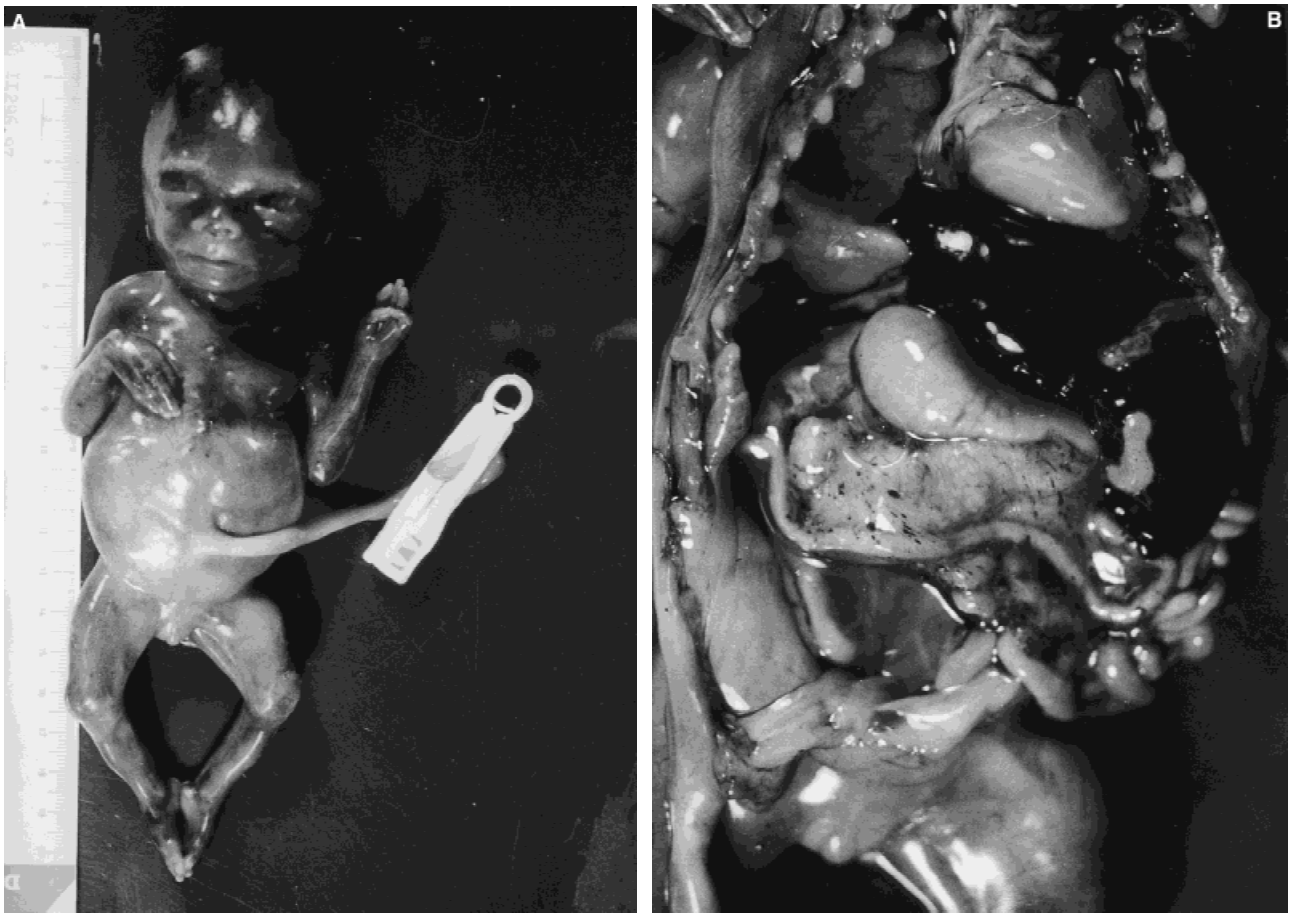

Fig. 1. **A:** Bowing of femora and protuberant abdomen were noted in Case 2. **B:** Situs inversus totalis, left sided liver, enlarged pancreas in Case 2.

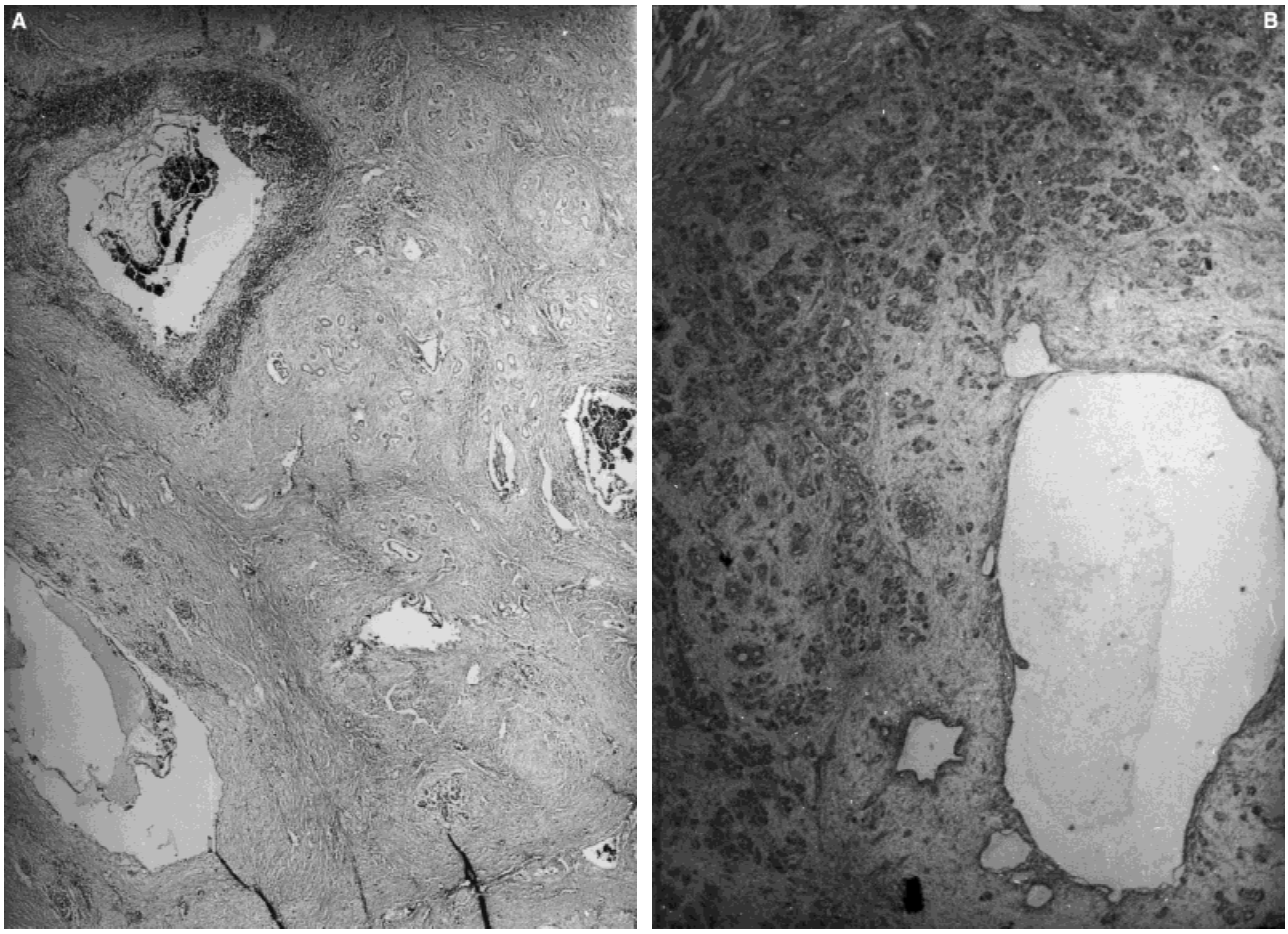

Fig. 2. **A:** Pancreatic cystic dysplasia with ductal cysts and dilatation within the primitive mesenchyme in Case 1. **B:** Pancreatic cystic dysplasia with large ductal cysts within the primitive mesenchyme in Case 2.

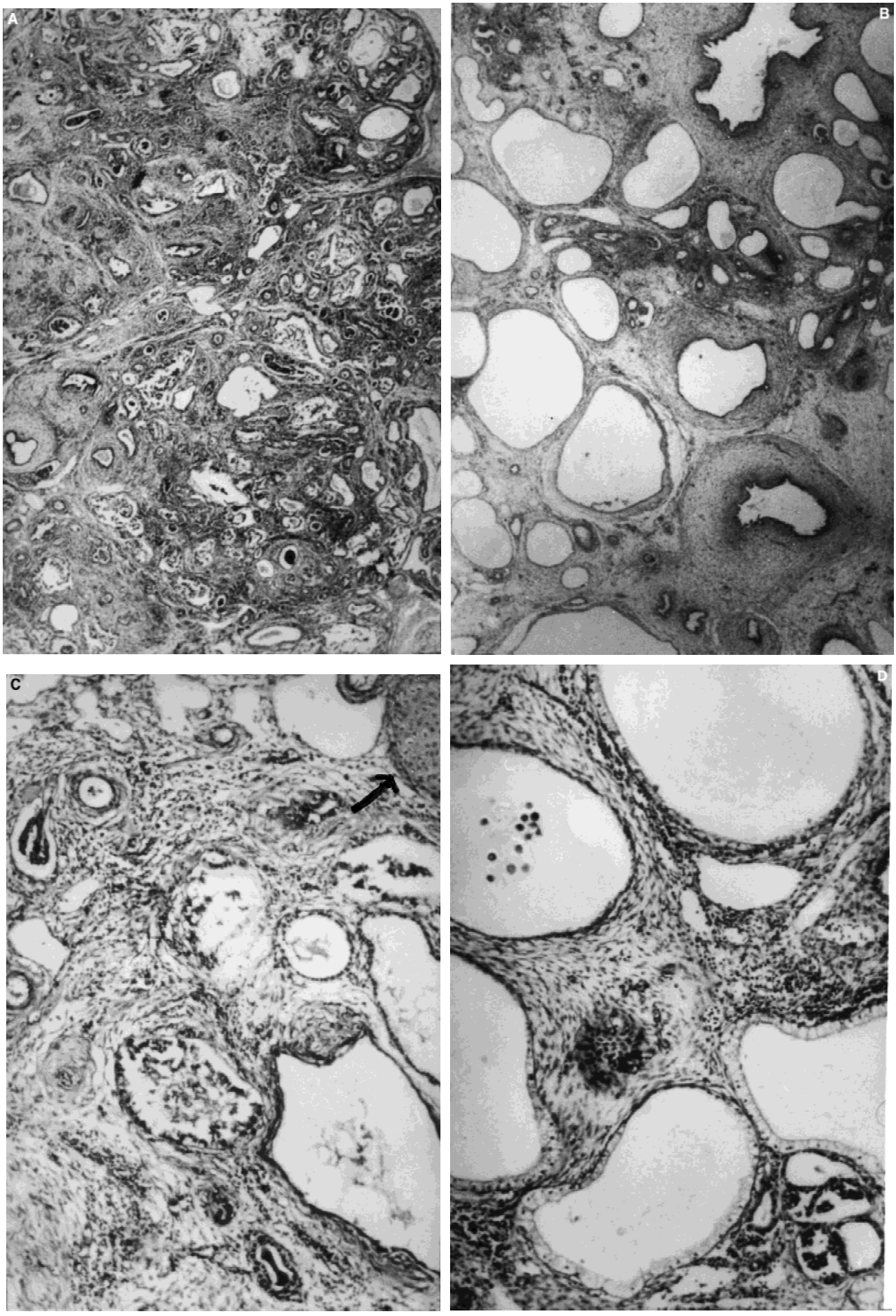

Fig. 3. **A:** Cystic dysplastic kidneys in Case 1: multiple cysts, primitive mesenchyme, and scanty glomeruli (HE ×28). **B:** Cystic dysplastic kidneys in Case 2: multiple cysts, primitive mesenchyme, and scanty glomeruli (HE ×28). **C:** Arrow shows cartilage formation in dysplastic kidney in Case 1 (HE ×115). **D:** Multiple dilated tubules and cysts in dysplastic kidney in Case 2 (HE ×115).

TABLE I. Clinical and Autopsy Findings in Both Fetuses

	Case 1	Case 2
Sex	Female	Male
Gestational age (weeks)	38	18
	First diagnosis was made at 31-week-old gestational age	
Oligohydramnios	+	+
Bowing of lower limbs	+	+
Chromosomes	+	+
Prenatal sonography		
IUGR	+	+
Cystic dysplastic kidneys	+	+
Pancreatic cysts	Unknown	+
Lemon sign	Unknown	+
Situs inversus totalis	+	+
Ventriculomegaly	+	+
Weight (g)	1,550	200
Length (cm)	41	20
Potter face	+	+
Low-set ears	+	+
Pes equinovarus	+	+
Flexion contractures of hands	+	+
Situs inversus totalis	+	+
Dysplastic kidneys with hypoplastic bladder	+	+
Pancreatic dysplasia with ductal dilatation, fibrosis and cysts, and islet cell agenesis/dysgenesis	+	+
Ventriculomegaly of brain	+	+
Hypoplastic thymus	+	+
Local dilatation in both small intestine and colon	+	+
Placenta	Calcification	Ischemia

TABLE II. Differential Diagnosis of Renal-Pancreatic Dysplasia

Ivemark syndrome (renal hepatic pancreatic dysplasia)
Autosomal recessive polycystic kidneys, hepatic fibrosis, included Caroli disease
Polycystic kidney and pancreas + narrow chest + short limbs
Saldino Noonan and Jeune syndrome, Verma-Naumoff and other skeletal dysplasia
Meckel syndrome
Occipital encephalocele, CNS malformation, renal cystic dysplasia, postaxial polydactyly, hepatic fibrosis
Renal dysplasia, situs inversus totalis, and multisystem fibrosis
Trisomy 9
Type II glutaric acidemia
Many irregular cysts within deep cortex and medulla, a strong "sweaty feet" odor

Ivemark syndrome due to lack of hepatic lesions. Bruteon et al. [1990] discussed associations with situs inversus and pointed out the overlap with Jeune and Ellis van Creveld syndromes. These cases also had renal-hepatic-pancreatic dysplasia. Pancreatic cystic dysplasia may also be seen in other well-known entities such as Wiedemann-Beckwith syndrome. Fremond et al. [1997] reported on a case of congenital pancreatic cyst detected prenatally in a fetus with evidence for a diagnosis of Wiedemann-Beckwith syndrome. This was the second reported case of Wiedemann-Beckwith syndrome with this association and the first time that it had been detected prenatally. However, there was no hepatic and renal dysplasia in that case. Pinar and Rogers [1992] reported on a new syndrome of situs inversus totalis, renal dysplasia, and multisystem fibrosis. Although a similar pattern of anomalies, including bilateral renal dysplasia, situs inversus totalis, and pancreatic and hepatic fibrosis was described in three separate reports, the authors suggested that this combination constituted a new syndrome.

In conclusion, these combinations are possibly a reflection of the genotype resulting in a malformation pattern such as Yokoyama et al. [1993] made in transgenic mice, disrupting a gene determining laterality and causing situs inversus. These mice had dilated renal tubules and abnormal glomeruli. The gene mapped to mouse chromosome 4 in a region homologous either to human 6q or 9q [Yokoyama et al., 1993]. Are these combinations a new entity or not? Further molecular studies will solve the problem.

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