NON-SYNDROMIC ASSOCIATION OF
CONGENITAL HEPATIC FIBROSIS AND BILATERAL
CYSTIC RENAL DYSPLASIA

Hsuan-Ying Huang, Hsu-Yiu Huang, and Wei-Jen Chen

Abstract: Congenital hepatic fibrosis (CHF) is associated with autosomal recessive polycystic kidney disease (ARPKD). Although cystic renal dysplasia (CRD) is the most common form of newborn cystic renal disease, this disorder of anomalous metanephric differentiation is only rarely found concurrent with CHF. Our literature review found only 13 sporadic and 12 familial non-syndromic cases of combined bilateral CRD and CHF reported outside Taiwan. We report the first domestic case, occurring in a fetus of 18 weeks' gestational age, which was the second pregnancy of a 24-year-old mother with a previous history of spontaneous abortion at 10 weeks' gestational age. Postmortem autopsy confirmed the concurrence of bilateral CRD and CHF without associated anomalies of other visceral organs and external appearance. This particular association must be differentiated from ARPKD and liver disease, in regard to ultrasonographic examination and genetic counseling.

Key words: congenital hepatic fibrosis, cystic renal disease, renal dysplasia

Kissane’s review of cystic renal diseases described sporadic unilateral or bilateral multicystic renal dysplasia as a common finding in prenatal and pediatric renal disorders, especially in connection with obstructive anomalies of the urinary tract [1]. However, he also noted that bilateral diffuse renal dysplasia was uncommon and importantly but not invariably associated with teratogenic syndromes, such as Ivemark’s syndrome, Meckel’s syndrome, and trisomy 13. In Meckel’s syndrome, renal dysplasia is often accompanied by congenital hepatic fibrosis (CHF) [2]. However, in non-syndromic circumstances, CHF has a well-established association with autosomal recessive polycystic kidney disease (ARPKD) rather than bilateral renal dysplasia [1]. Here, we describe the first reported case of CHF with cystic renal dysplasia (CRD) in Taiwan.

Case Report

A female fetus of 18 weeks' gestational age, born to a 24-year-old mother, was delivered by prostaglandin (PG) F2α induction because of polycystic renal disease with oligohydramnios demonstrated by ultrasound examination. The Apgar scores of the fetus were 0 and 0 at 1 minute and 5 minutes, respectively.

The mother’s first pregnancy had been terminated in spontaneous abortion at 10 weeks' gestational age. There was no history of exposure to chemical or toxic agents. The results of serologic investigations for syphilis, hepatitis, toxoplasmosis, rubella, and cytomegalovirus were all negative. A chromosomal study of the fetus revealed a normal karyotype of 46,XX.

At postmortem examination, the fetus weighed 315 g and measured 25.5 cm from crown to heel. The head circumference was 17.0 cm, with both anterior and posterior fontanelles of appropriate size. External examination revealed neither Potter’s face nor other gross abnormalities of the limbs and trunk. Major anomalies of visceral organs were noted in the liver and bilateral kidneys.

The liver weighed 13.5 g and was grossly unremarkable. Microscopically, irregular fibrous enlargement of portal tracts with interconnecting proliferative bile ductules was present, especially at the edges of portal zones. In addition, polypoid projections of fibrous stroma into dilated ductular lumina were found; these had a single layer of cuboidal epithelium. These findings are consistent with CHF (Fig. 1).
Both kidneys were asymmetrical in size and weight but had similar gross and microscopic features. The right kidney weighed 5.81 g and measured 3.20 cm in greatest dimension. Both kidneys retained fibrous capsules and were seemingly lobulated on the external surfaces. On sectioning, they revealed blurred corticomedullary junctions (Fig. 2). Many cysts of various sizes were diffusely present on cut surfaces. Overall, the cysts were small, contrasting with the large cysts of classical multicystic renal dysplasia, and spherical, unlike the vertically elongated cylindrical cysts observed in ARPKD. Obstructive abnormalities of the urinary tract were not found. There was no ureteropelvic occlusion; both ureters and the urinary bladder were normal.

Microscopically, both kidneys were generally dysplastic and composed of cysts lined by a single layer of flattened cuboidal or columnar epithelium in fibromyxoid stroma with peritubular or pericystic condensation of primitive mesenchymal fibroblasts. These dilated tubulocystic structures appeared to be collecting ducts and were most prominent in the medulla. In the outer portion of the kidney, there were poorly developed nephrogenic zones along the capsule where the primitive anlage is induced to differentiate into nephron units by collecting ducts. Nonetheless, there were no islets of metaplastic cartilage in either kidney (Figs. 3A & B). Neither the pancreas nor the lungs were hypoplastic, and all revealed microscopic features appropriate for gestational age.

**Discussion**

The reported incidence of renal lesions in CHF varies in different studies, and recent investigations have demonstrated renal lesions in more than 70% of patients with CHF [3]. Although CHF is most widely associated with ARPKD, it is also associated with autosomal dominant polycystic kidney disease, with nephronophthisis, and even rarely with bilateral renal dysplasia, as seen in our patient [3–5]. On the other hand, bilateral renal dysplasia can also occur in Meckel’s syndrome, and Ivemark’s syndrome, or in combination with situs inversus, cardiac malformation, or Dandy-Walker cysts [1, 2, 5, 6]. Owing to the perplexing multitude of the various associations, some authors have suggested that CHF is not a single clinical entity, but comprises a spectrum of various hepatic and renal lesions [3].

Unique to the present case is the isolated concurrence of bilateral renal dysplasia and CHF in a fetus with neither additional developmental malformations nor other syndromic genetic disorders. However, Neuhaus et al mentioned in their review that 20 of 25 previously reported cases of combined bilateral renal dysplasia and CHF had evidence of additional pancreatic dysplasia based on histologic examination or image findings [6]. Despite the lack of associated pancreatic dysplasia, the present case still fits into the wider spectrum of renal-hepatic-pancreatic dysplasia and probably represents an incomplete form. Renal-hepatic-pancreatic dysplasia presumably carries an autosomal recessive mode of inheritance, an entity proposed by Bernstein et al that is not yet well understood [7].

Patients with the classical combination of CHF and ARPKD usually die of early renal failure, while for those who survive into late childhood or adolescence, CHF often causes portal hypertension or cholangitis if concomitant with Caroli’s disease [3]. The liver function is usually well preserved. However, in renal-hepatic-pancreatic dysplasia, the liver function usually deteriorates in early infancy, accompanied by severe renal failure. The only successful method of treatment is combined liver-kidney transplantation, as reported by Neuhaus et al [6].
Hepatic Fibrosis Associated with Renal Dysplasia

Fig. 3. Photomicrographs of renal dysplasia. (A) Under medium-power magnification, tubulocystic structures, resembling collecting ducts of the medullia, are surrounded by abundant fibromyxoid stroma. Poorly-developed subcapsular nephrogenic zones are seen (at top of figure) with rudimentary nephron units; however, metaplastic cartilaginous islets are absent (hematoxylin & eosin, x 100). (B) These tubules or dilated cysts are lined by either low columnar or flattened cuboidal epithelium with cuffs of undifferentiated spindle cells (hematoxylin & eosin, x 200).

Total diffuse renal dysplasia of bilateral kidneys usually leads to severe oligohydramnios with secondary pulmonary hypoplasia and Potter’s face [1]. Although oligohydramnios was noted in our patient, there were no secondary pulmonary or facial complications; this lack of secondary complications could be explained by early termination at 18 weeks’ gestational age, prior to the development of such consequences.

The pathogenesis linking CHF and cystic renal diseases remains to be established. There appears to be a remarkable parallelism in the type and evolution of both renal and hepatic lesions. The basic insult of CHF is ascribed to ductal plate malformation of interlobular bile ducts with ensuing fibroblastic proliferation [3]. The cystic ectasia seen in various congenital renal diseases appears to result from faulty epithelial-mesenchymal inductive interaction; both renal and bile ductular epithelial tubules are subject to a rapidly or slowly progressive destruction of epithelial involution with increasing amounts of interstitial fibrosis [2]. Little is known about the factors that determine the distinct type of cystic renal diseases associated with CHF, the predominance of hepatic or renal symptoms in surviving patients, and the speed of disease progression. Further elucidation of these factors may resolve the linkages of these diverse entities.

In conclusion, it should be emphasized that, in addition to ARPKD, CHF may also be observed in autosomal dominant polycystic kidney disease, nephronophthisis, or renal dysplasia, as noted in our patient. Therefore, autopsy examination is recommended to facilitate genetic counseling.

References