INVITED REVIEW

What is congenital hepatic fibrosis?

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Introduction

Congenital hepatic fibrosis is a developmental disorder which has been known, under a variety of names, for over a century. The present term was introduced by Kerr et al. in 1961 and is the most commonly used. In the French literature, the condition is also known as 'biliary fibroadenomatosis' and 'hepatic fibroangioadenomatosis', whereas the German literature describes the disorder as 'cholangiodysplastic pseudo-cirrhosis'.

Congenital hepatic fibrosis is a cause of hepatosplenomegaly and portal hypertension, and is encountered principally in children and young adults. Its morphological hallmark is the presence of fibrous enlargement of portal tracts or portal-portal bands of fibrous tissue containing abnormal bile ducts. The latter are lined by normal cuboidal epithelium (Figure 1). The normal lobular architecture of the liver is preserved and hepatocellular function is good. In many cases, perhaps in all, renal tubular ectasia is an associated anomaly.

Congenital hepatic fibrosis: facts and problems

TERMINOLOGY AND NOSOLOGICAL CONFUSION

Perhaps the most controversial aspect of congenital hepatic fibrosis is its nosological status; this controversy has been enhanced by continuous change in concepts and classifications of hepatic and renal cystic disease. Congenital hepatic fibrosis was described to be
associated with renal tubular ectasia, which has been labelled idiopathic medullary sponge kidney or Cacchi and Ricci's disease. It is now agreed, however, that medullary cystic disease, medullary sponge kidney and Cacchi and Ricci's disease are totally different disorders, and that the renal abnormality associated with congenital hepatic fibrosis corresponds to autosomal recessive, polycystic kidney disease. The latter term replaces the previous infantile polycystic disease, since symptoms may not develop until adult life.

Confusion still persists with regard to the nosological status of the hepatic cystic lesion. The hepatic abnormalities in congenital hepatic fibrosis are usually considered part of autosomal recessive polycystic kidney disease which represents a spectrum of lesions. Four types may be identified: perinatal, neonatal, infantile and juvenile, depending on the age of manifestation of the disease and the severity of the renal lesions. There is reasonable consensus that the perinatal, neonatal and infantile forms of autosomal recessive polycystic kidney are variants of the same disorder, but there is still debate as to whether the juvenile form represents a separate entity. Furthermore, some authors use the term congenital hepatic fibrosis for the liver lesion in the neonatal form of autosomal recessive polycystic kidney disease. In this review, the term congenital hepatic fibrosis refers to the liver lesion in the juvenile variant of autosomal recessive polycystic kidney disease. The liver lesion in the perinatal, neonatal and infantile forms is referred to as ductal plate malformation.

The persistent confusion about the nosological status of congenital hepatic fibrosis is in large part due to the fact that the aetiology and pathogenesis of congenital hepatic fibrosis remain unknown, and the precise nature of the liver lesion at the time of birth has not been described.

**VARIABLE HISTOPATHOLOGY**

Some authors distinguish cystic and non-cystic forms of cholangiodysplastic pseudo-cirrhosis (congenital hepatic fibrosis) which is due to the term being used for
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Figure 2. Needle biopsy, showing focal type congenital hepatic fibrosis, without portal-portal fibrous bridging. This small fibrous portal area contains an excess of bile ductules and reveals mild features of inflammation. Same patient as Figure 1. H & E, × 500.

the liver lesion in all variants of autosomal recessive polycystic kidney disease. If it is restricted to the juvenile variant then the liver lesion is largely of the non-cystic type. Even with the working definition of congenital hepatic fibrosis as proposed here, the histopathology of congenital hepatic fibrosis is not uniform. In some patients, congenital hepatic fibrosis is characterized by fibrous enlargement of portal tracts containing variable numbers of abnormally shaped bile ducts—focal form (Figure 2); in others, the liver shows bands of connective tissue of variable thickness linking adjacent portal tracts—diffuse form (Figure 1). Furthermore, cases are on record with only partial involvement of the liver, e.g., one lobe.

VARIABLE CLINICAL EXPRESSION

Four clinical forms of congenital hepatic fibrosis are recognized: a form with portal hypertension, which is the commonest; a form in which cholangitis is the dominant feature and portal hypertension is absent; a mixed portal hypertensive–cholangitic form, and a latent form. The symptoms of cholangitis appearing in the cholangitic and portal hypertensive-cholangitic forms are due to an associated Caroli’s disease—congenital dilatation of the larger intrahepatic bile ducts.

CONGENITAL HEPATIC FIBROSIS IN LATE CHILDHOOD AND ADULTHOOD; LATENT FORMS OF CONGENITAL HEPATIC FIBROSIS

Congenital hepatic fibrosis in its classical appearance causes symptoms of portal hypertension in children and young adults. However, cases are on record in whom symptoms appeared neonatally and others who became symptomatic only in adulthood. Furthermore, there are latent or asymptomatic forms of congenital hepatic fibrosis which are incidentally discovered in the course of an investigation, at surgical exploration, or at necropsy. One wonders what the variables might be which cause these age-related differences in the clinical appearance of
the disease or its non-appearance. If congenital hepatic fibrosis is truly a congenital, autosomal recessive inherited disorder, what is the lesion at birth and what are the progressive changes taking place in the liver from birth until childhood or adult life? The late appearance of symptoms suggests that congenital hepatic fibrosis is a dynamic and progressive lesion. Some studies do, in fact, indicate that there is a progression in the amount of liver fibrosis over the years. This concept of a dynamic disease is supported by the evolution of some cases of congenital hepatic fibrosis into true cirrhosis of the liver, although transition into biliary cirrhosis is usually thought to be the result of an associated Caroli's disease causing repeated bouts of cholangitis.

ASSOCIATED MALFORMATIONS

In most, if not all cases, congenital hepatic fibrosis is associated with renal tubular ectasia, corresponding to autosomal recessive polycystic kidney disease but the hepatic lesion is also observed in a number of syndromes: Meckel-Gruber syndrome (Figure 3), Ivemark syndrome, vaginal atresia and tuberous sclerosis. Congenital hepatic fibrosis may also be accompanied by other hepato-biliary malformations, which include Caroli's disease, von Meyenburg complexes and choledochal cyst. A series of further associations have been described: pulmonary emphysema, arteriovenous pulmonary fistula, mental retardation and facial dysmorphism, the Laurence-Moon-Biedl syndrome, hypoplasia of the musculus depressor anguli oris, and lymphangiectasia.

Although the classical renal lesion in congenital hepatic fibrosis corresponds to autosomal recessive polycystic kidney disease, reports have been published on the association of congenital hepatic fibrosis with adult type polycystic kidney disease (now termed autosomal dominant polycystic kidney disease) with renal dysplasia and with nephronophthisis. As a result of the perplexing multitude of the various associations, several authors have suggested that congenital hepatic fibrosis does not represent a single clinical entity, but comprises a spectrum of various hepatic and renal lesions.

Figure 3. Autopsy specimen from newborn infant with Meckel-Gruber syndrome. Note portal tract with circular profile of bile duct—ductal plate malformation. H & E. × 310.
What is congenital hepatic fibrosis?

CHOLESTATIC FEATURES IN CONGENITAL HEPATIC FIBROSIS

Most reports on the histopathology of congenital hepatic fibrosis emphasize the bland appearance of the fibrosed portal tracts or connective tissue bands, with absence of inflammatory infiltration. In the clinically cholangitic forms of the disease, histological changes of cholangitis and cholangiolitis indicate an associated Caroli's disease. However, features suggesting chronic cholestasis, cholangiolitis and degenerative lesions of the epithelial lining of the bile ducts may occasionally be seen in the absence of Caroli's disease. These observations suggest that congenital hepatic fibrosis, or at least some cases grouped under this heading, might represent a smouldering biliary or cholestatic disease (Figure 4). Some authors mention the occurrence of an episode of neonatal cholestasis in the history of patients with congenital hepatic fibrosis. These observations, together with the resemblance to biliary fibrosis, emphasize the need to search for signs of chronic cholestasis or mild cholangiolitis in liver biopsies from patients with congenital hepatic fibrosis.

CONGENITAL HEPATIC FIBROSIS WITHOUT ASSOCIATED CYSTIC RENAL DISEASE

The reported incidence of renal lesions in congenital hepatic fibrosis varies in different studies. In 1974, Fauvert & Benhamou recorded an incidence of 60%, but emphasized that this was probably an underestimate and more recent studies report renal lesions in the great majority of patients. This variability may be due to improvements in the sensitivity of imaging techniques and the intensity with which the renal abnormalities are searched for. Nevertheless, occasional cases of congenital hepatic fibrosis have been reported in which no renal abnormality could be demonstrated at autopsy.

PORTAL VASCULAR ABNORMALITIES IN CONGENITAL HEPATIC FIBROSIS

Several studies have documented abnormalities in the portal vessels in congenital hepatic fibrosis. The intrahepatic portal vein branches are said to be fewer than normal and many of them appear hypoplastic (Figure 1), whereas the portal branches of the hepatic artery are
often found to be abnormally numerous\(^1\). Other authors failed to observe or even denied the purported hypoplasia of the portal vein branches\(^4\). It remains a matter of debate whether the portal hypertension in congenital hepatic fibrosis results from hypoplasia and paucity of intrahepatic portal vein radicles, or from their compression by fibrosis\(^1\).

**ABNORMAL BILE DUCTS IN CONGENITAL HEPATIC FIBROSIS**

In early studies, the increased number of abnormally shaped bile ducts was often described as ductal and ductular proliferation\(^4\). Jørgensen\(^4\) drew attention to the alternative explanation, that the abnormally shaped ductal structures are remnants of incompletely remodelled ductal plates, which represent the early, immature form of intrahepatic bile ducts during their embryogenesis. Some studies have illustrated concentric rings or double layers of ductal plate remnants in the portal tracts of patients with congenital hepatic fibrosis\(^3\). There is general agreement that the hepatic bile duct lesion in autosomal recessive polycystic kidney disease and in congenital hepatic fibrosis belongs to the communicating category of 'cystic' bile duct lesions: i.e. the abnormally shaped ducts are in continuity with the rest of the biliary system\(^1,18,19\).

**Recent observations, which may help to clarify the pathogenesis of congenital hepatic fibrosis**

**EMBRYOLOGICAL DEVELOPMENT OF THE INTRAHEPATIC BILE DUCTS**

Recent investigations have supported the theory that intrahepatic bile ducts develop from primitive liver precursor cells, sometimes called hepatoblasts\(^48,52\). The following observations are relevant with regard to the lesions observed in congenital hepatic fibrosis.

1. Intrahepatic bile ducts develop by a phenotypic change from liver cell precursors which are in contact with the mesenchyme surrounding the developing portal vein. The most primitive or immature state of the bile duct corresponds to an interrupted cylindrical layer around the future portal tract; this is soon doubled by a second layer of bile duct epithelium over several segments of its circumference. This structure is referred to as the ductal plate\(^53\).

2. The ductal plate is remodelled by incorporation of dilated parts of the double epithelial layer into the portal mesenchyme, while the rest disappears. This process is termed remodelling of the ductal plate\(^41,48\). The precise mechanisms inducing formation and subsequent remodelling of the ductal plate remain unknown, but some evidence suggests an important role for epithelial-mesenchymal inductive interactions\(^48,54\). Arrest of remodelling or faulty remodelling results in the persistence of the excess of primitive epithelial bile duct structures: ductal plate malformation\(^41\) (Figure 3).

3. The development of intrahepatic bile ducts starts during the third month of gestation around the largest (future) portal tracts near the hilum of the liver, and continues throughout fetal life along the successively developing arborization of the portal vein branches. The smallest intrahepatic bile ducts develop in the first 4–6 weeks of post-natal life\(^48\). Thus, the different segments of the intrahepatic biliary tree (larger ducts, segmental and area ducts, interlobular ducts and smallest bile duct ramifications) develop sequentially during successive periods in fetal life.

**'VANISHING BILE DUCT' DISEASES**

**Extrahepatic bile duct atresia**

Extrahepatic bile duct atresia does not represent agenesis of the bile ducts, but results from a progressive destruction of the bile ducts by a necro-inflammatory process of unknown aetiology\(^55\). Despite the terminology, this destructive and sclerosing form of cholangitis affects not only all or part of the extrahepatic bile ducts, but involves the intrahepatic branches of the biliary tree as well; leading to 'paucity' of interlobular ducts.

It is of interest that in some 20–25% of cases of extrahepatic bile duct atresia, the damaged interlobular ducts still appear in their primitive embryonic shape—ductal plate malformation\(^55,57\) (Figure 5). This observation suggests that the causative factor of atresia starts early in fetal life in these cases, and might explain the often advanced degree of fibrosis observed in the liver biopsies of these infants even at a very young age (30 days). For this reason, this subgroup of patients with extrahepatic bile duct atresia and ductal plate malformation of the interlobular ducts has been designated as early severe extrahepatic bile duct atresia\(^55\).

Two further observations in early severe extrahepatic bile duct atresia deserve mention.

1. Several portal areas may show double and even triple concentric layers of bile duct structures in ductal plate configuration, suggesting that succes-
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**Figure 5.** Liver specimen from infant with extrahepatic bile duct atresia. Note circular profile of bile duct and focal degenerative changes of the lining epithelium (large arrow). The centre of the portal tract contains a flattered hypoplastic portal vein (small arrow). H & E. × 300.

Progressive inductions of ductal plates have taken place. This pattern can be interpreted as a fetal type of ductular reaction.

Liver biopsies from infants with early severe extrahepatic bile duct atresia often reveal large, irregular portal tracts, containing clusters of ductal plate remnants, each arranged around a small, hypoplastic portal vein or no vessel at all. This pattern has been interpreted as a plane of section through an area of abnormal branching of the portal vein tributaries, comparable to the arborization pattern of a 'pollard willow'. This abnormality indicates a form of hypoplasia of the portal vein branches, and may explain the portal hypertension observed at the time of hepatic porto-enterostomy.

**Paucity of interlobular bile ducts**

Paucity of interlobular bile ducts is not due to agenesis of the interlobular ducts, but equally represents a 'vanishing bile duct' disorder, in which the interlobular ducts are progressively destroyed by a necro-inflammatory and sclerosing process of unknown aetiology. This holds true for the syndromic form (Alagille syndrome) as well as for the non-syndromic form. The interlobular ducts seem to disappear at a variable rate over different time periods in these disorders, indicating that bile duct destruction may be a slowly progressive process. A neonatal form of sclerosing cholangitis also exists, which bears similarities with both extrahepatic bile duct atresia and paucity of interlobular bile ducts.

**Idiopathic adulthood ductopenia**

A peculiar form of paucity of interlobular bile ducts has been described in adults under the name idiopathic adulthood ductopenia. This disease, of unknown aetiology and pathogenesis, draws attention to the existence of pathological mechanisms which destroy the intrahepatic bile ducts in a way that differs from primary biliary cirrhosis and primary sclerosing cholangitis. Some observations indicate that the speed of bile duct destruction may be extremely slow over several decades, but is nevertheless progressive.
FOLLOW-UP AFTER HEPATIC PORTO-ENTEROSTOMY FOR EXTRAHEPATIC BILE DUCT ATRESIA

Hepatic porto-enterostomy or the Kasai operation has become the treatment of choice for extrahepatic bile duct atresia. However, long-term follow-up of patients reveals that this operative reconstruction of bilio-enteric continuity does not result in a definite cure in the majority of patients. Although post-operative ascending cholangitis may play a role in the development of liver fibrosis and cirrhosis, there is increasing evidence that post-operative liver alterations are caused by the necro-inflammatory bile duct destruction which is intrinsic to extrahepatic bile duct atresia. Hepatic porto-enterostomy relieves the obstruction and thus saves the patient from rapid progression to biliary cirrhosis, but the re-establishment of bilio-enteric continuity does not by itself cure the basic disease process. In some, it is rapidly progressive, in others slow and, in some, it seems to burn out, resulting in real cure.

An observation of interest was made from the study of patients several years after successful hepatic porto-enterostomy. In those who displayed ductal plate configuration of the interlobular bile ducts at the time of porto-enterostomy, the follow-up biopsy after 4 or 5 nearly symptom-free years revealed a histopathological picture closely resembling that of congenital hepatic fibrosis (Figure 6). This lesion was interpreted as representing a fetal type of ductular reaction and fibrosis. Close analysis revealed features of mild, but still ongoing, bile duct destruction, suggesting a persistence of the basic disease process of extrahepatic bile duct atresia. This remarkable observation indicates that a neonatal disease process, characterized by destruction of immature bile ducts (early severe extrahepatic bile duct atresia), may result in a histopathological lesion which is indistinguishable from congenital hepatic fibrosis, provided that the patient is given the chance to survive long enough by hepatic porto-enterostomy. It raises the suspicion that a spontaneously abortive or self healing
form of bile duct ‘atresia’ might lead to similar sequelae, and thus that congenital hepatic fibrosis might be the result of an arrested or mild form of destruction of immature interlobular bile ducts.

The pathogenesis of congenital hepatic fibrosis

MORPHOGENESIS OF LIVER LESIONS

It is proposed that congenital hepatic fibrosis is a fetal type of biliary fibrosis, resulting from a smouldering, destructive cholangiopathy in a liver with arrested or incomplete remodelling of its interlobular ducts—ductal plate malformation. This hypothesis is based on the analogy of congenital hepatic fibrosis with the lesions observed in the follow-up biopsies of children with ‘early severe’ extrahepatic bile duct atresia, several years after successful hepatic porto-enterostomy. The initial events may be ductal plate malformation of interlobular ducts and abnormal branching patterns of the portal vein radicles—‘pollard willow’ pattern of hypoplastic portal vein branches. This corresponds to the liver changes observed in the perinatal and neonatal forms of autosomal recessive polycystic kidney disease (the ‘cystic’ form of cholangiolytic pseudo-sclerosing cholangitis)\(^1\). The progressive, destructive cholangiopathy may vary in speed and duration or arrest after a few years. The destructive cholangiopathy entails:

1. degenerative epithelial changes in the lining of the immature ducts, and gradual disappearance of segments of the ductal plate remnants;
2. fetal type of ductular reaction, resulting in a second and perhaps a third and further waves of ductal plate induction, creating concentric rings of incompletely remodelled ductal plate configurations in the portal tract; and
3. increasing fibrosis as in destructive bile duct diseases in the adult, like primary biliary cirrhosis or primary sclerosing cholangitis.

The hypothesis does not mean that the ‘destructive cholangiopathy’ of congenital hepatic fibrosis is identical to the ‘basic disease process’ in extrahepatic bile duct atresia. On the contrary, evidence suggests that despite morphological and other similarities, the aetiology and pathogenesis of the latter are different since, unlike congenital hepatic fibrosis, extrahepatic bile duct atresia is not associated with renal cystic disease. Thus, congenital hepatic fibrosis may represent the juvenile form of autosomal recessive polycystic kidney disease, as previously suggested by some authors\(^1,2,4\).

Comparison of the lesions in the neonatal and perinatal forms with those in juvenile forms of autosomal recessive polycystic kidney disease strongly suggests that they represent successive phases of the same disease rather than separate nosological entities\(^1,2,3,4\). It should be mentioned, however, that there are also reports to the contrary. Landing et al.\(^4\), reported two patients who showed no change in the degree of hepatic fibrosis during intervals of 4.4–7.4 years between biopsy and autopsy examination. The hypothesis that congenital hepatic fibrosis corresponds to a fetal type of biliary fibrosis as described above, would explain a number of observations which were made in congenital hepatic fibrosis:

1. the variable time period before the appearance of signs of portal hypertension (ranging from neonatal age to advanced adulthood)\(^2\);
2. the existence of latent forms of congenital hepatic fibrosis\(^1\), comparable to symptomless idiopathic adulthood ductopenia;
3. the variable degree of fibrosis in different patients with congenital hepatic fibrosis\(^1\);
4. the variable number and shape of bile duct structures, depending on the degree of fetal ductular reaction, the extent of remodelling of the ductal plates, and the extent of their subsequent destruction, similar to the ‘congenital hepatic fibrosis-like’ picture observed several years after successful porta-enterostomy\(^5,6,5\);
5. the communication of the bile duct ‘cysts’ in congenital hepatic fibrosis with the rest of the intrahepatic biliary tree\(^6\);
6. the possible evolution of congenital hepatic fibrosis into cirrhosis, even in the absence of associated Caroli’s disease\(^7\), on the assumption that the destructive cholangiopathy remains active and progressive;
7. the histological features of bile duct destruction and of chronic cholestasis observed by some authors\(^8,9\);
8. the occurrence of a period of neonatal cholestasis in some patients with congenital hepatic fibrosis\(^10,11\);
9. the association of congenital hepatic fibrosis with Caroli’s disease, since the latter represents a ductal plate malformation of the larger intrahepatic ducts\(^12,13,14\) implying that the factor(s) which caused lack of remodelling of the ductal plate started earlier during fetal life, during the period that the larger bile ducts were developing;
10. the association of congenital hepatic fibrosis with von Meyenburg complexes, since the latter may be explained as ductal plate malformations of the finest branches of the intrahepatic biliary tree\(^15\), implying that the factor(s) which cause the arrest of remodelling of ductal plates remained active also during a later period in fetal life, during which the...
smaller intrahepatic bile ducts were developing; and
the association of congenital hepatic fibrosis with abnormalities in other viscera or systems: these
could be explained by a variable duration of the
factor(s) (and the possible association of additional
factors) causing the embryopathy, and by the
coincidence of simultaneous embryonic develop-
ment of different organs and systems even in
separate anatomical locations (developmental
fields).

MORPHOGENESIS OF RENAL LESIONS

The appearance of the kidneys in autosomal recessive
polycystic kidney disease depends very much on the
extent and duration of the process. When death occurs
in the newborn period (perinatal and neonatal forms of
autosomal recessive polycystic kidney disease), the
kidney is made up almost entirely of cystic tubules which
appear elongated in the cortex and round or oval in the
medulla. Microdissection has revealed that they
mostly correspond to dilated collecting ducts, so-called
Potter type.

When death occurs after the newborn period, the
extent of cystic involvement tends to be less in those who
survive longer (infantile and juvenile forms of autosomal
recessive polycystic kidney disease). The cysts are also
more irregularly distributed, larger and are accompa-
nied by progressive glomerular obsolescence, tubule
atrophy and interstitial fibrosis. It is not clear whether
the kidneys with fewer cysts and greater fibrosis reflect
regression of cysts or the failure of such cysts to develop
in the first place. It has been suggested that perhaps the
disease in older individuals takes the form of tubule
damage without cyst formation.

The aetiology and the pathogenesis of renal cysts in
autosomal recessive polycystic kidney disease are
unknown, but it appears that collecting duct dilation
may occur in the presence or in the absence of significant
glomerular filtration and thus might be independent of
the mechanical forces generated by urine production.

PARALLELISM BETWEEN HEPATIC AND RENAL LESIONS
IN CONGENITAL HEPATIC FIBROSIS

There is a remarkable parallelism in the type and the
evolution of both the renal and the hepatic lesions (Table
1). The renal lesion originally consists of a fusiform
dilatation of the collecting ducts and the hepatic lesion of
ductal plate malformation of the interlobular bile ducts.
Atrophy of tubules and ducts occurs and fibrosis follows
later. It appears that the early lesion, both in the kidneys
and in the liver, can be conceived of as a malformation,
i.e. a disturbance in normal development. Both fusiform
ectasia of the collecting ducts in the kidney and ductal
plate malformation of interlobular bile ducts in the liver
seem to result from a faulty epithelial–mesenchymal
inductive interaction.

Both types of epithelial tubes (collecting ducts in the
kidney and interlobular bile ducts in the liver) seem to be
subject to a slowly progressive, destructive process of
epithelial involution, resulting in the disappearance of
increasing numbers of epithelial tubes (both renal and
hepatic) and associated with increasing amounts of
interstitial fibrosis. The speed of renal duct destruction
does not seem to strictly parallel the speed of hepatic duct
destruction, so that in surviving patients either renal or
hepatic symptoms may predominate.

The occasional association of congenital hepatic
fibrosis and nephronophthisis is of interest. The aetio-
logy and pathogenesis of nephronophthisis remain
unknown, but histopathology can be interpreted as a
tubulo-interstitial nephropathy resulting in a rapid
destruction of renal tubules. It is possible that nephro-
phthisis-congenital hepatic fibrosis is a variant of
autosomal recessive polycystic kidney disease in which
the renal epithelial destructive process is faster. One
could also speculate that early severe extrahepatic bile
duct atresia represents the hepatic mirror image of
nephronophthisis, i.e. a condition in which the basic liver
abnormality of autosomal recessive polycystic kidney
disease—ductal plate malformation of interlobular
ducts—is subject to an accelerated destruction of the
hepatic ductular epithelial components (Table 1).
Furthermore, cases have been reported of an associ-
ation between a hepatic disease ‘resembling congenital
hepatic fibrosis’ and a renal disease ‘resembling nephro-
phthisis’. The hepatic disease was thought not to
be correspond to true congenital hepatic fibrosis, because
some patients had signs of chronic cholestasis (increased
serum levels of bile acids) and the liver biopsy was
thought to show features of regeneration in the form of
liver cell rosettes and thus, to represent a feature of chronic
cholestasis (see Figure 6 in Harris et al.). As discussed
in this paper, features of chronic cholestasis would be
expected to be a normal component of congenital
hepatic fibrosis, representing the subgroup of patients in
whom the destructive cholangiopathy has not yet burnt
out. Hence, the cases reported by Harris et al. would
represent a more cholestatic variant of nephronophthisis-
congenital hepatic fibrosis syndrome.
**Table 1. Autosomal recessive polycystic kidney disease**

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<thead>
<tr>
<th>Hepatic lesions</th>
<th>Renal lesions</th>
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<tbody>
<tr>
<td><strong>Early stage</strong></td>
<td>Fusiform dilation of collecting ducts (neonatal form of ARPKD&lt;sup&gt;12&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Ductal plate malformation of interlobular ducts ('cystic' form of cholangiodysplastic pseudo-cirrhosis&lt;sup&gt;17&lt;/sup&gt;)</td>
<td>(rapid variant: 'early severe EHBDA')</td>
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<tr>
<td>Progression</td>
<td>Destructive tubulopathy</td>
</tr>
<tr>
<td>'Destructive cholangiopathy'</td>
<td>(rapid variant: 'nephronophthisis')</td>
</tr>
<tr>
<td><strong>Later stage</strong></td>
<td>Renal failure</td>
</tr>
<tr>
<td>CHF (non-cystic form of cholangiodysplastic pseudo-cirrhosis&lt;sup&gt;17&lt;/sup&gt;)</td>
<td>Renal cysts, tubular atrophy, interstitial fibrosis (later infantile and juvenile form of ARPKD&lt;sup&gt;12&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Biliary cirrhosis + liver failure</td>
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CHF = congenital hepatic fibrosis; EHBDA = extrahepatic bile duct atresia; ARPKD = autosomal recessive polycystic kidney disease.
Congenital hepatic fibrosis without ductal plate malformation and without renal lesions

The number of bile duct structures in the portal fibrous areas of congenital hepatic fibrosis is extremely variable. According to the hypothesis presented, this may be explained by variations in the degree of fetal ductular reaction and the extent of duct disappearance by the destructive cholangiopathy. In cases with extensive disappearance of epithelial bile duct structures, only small numbers of ductal remnants may remain, and recognition of ductal plate configuration may become difficult if not impossible. Alternatively, some cases in fact may never have had ductal plate malformation, and the endstage lesion—considered to represent congenital hepatic fibrosis—in fact corresponds to an adult type of biliary fibrosis. If that is true, it would not be surprising that in these cases there are no associated renal cystic lesions, since these patients never suffered from autosomal recessive polycystic kidney disease, but only from an obscure cholangiopathy.

References

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