Congenital dilatation of the intrahepatic bile ducts associated with the development of amyloidosis

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SUMMARY Two cases of pure congenital dilatation of the intrahepatic bile ducts are presented. One patient developed amyloidosis secondary to suppuration, and had isolated cysts in the renal medulla. The position of congenital dilatation of the intrahepatic bile ducts compared with cysts in the liver and its association with 'cystic' diseases of the kidneys is discussed.

Pure congenital dilatation of the intrahepatic bile ducts was first described as a separate entity by Caroli, Couinaud, Soupault, Porcher, and Etevé (1958a) and Caroli, Soupault, Kossakowski, Plocker, and Paradowska (1958b) and in the monograph of Caroli and Corcos (1964). Up to date some 20 cases are described in the literature, most of them associated with congenital hepatic fibrosis (or fibro-angioadenomatosis). Only a few pure cases could be found (Caroli *et al.*, 1958a and b; Caroli and Corcos, 1964; Guillemin, Marcy, Naudin, Braillon, Cuilleret, Spay, Gilly, Pinet, and Bernard, 1965; Hélou, Farak, and Nassr, 1965; Hunter, Akdamar, Sparks, Reed, and Brown, 1966; Turnberg, Jones, and Sherlock, 1968; Jones and Schreeve, 1970). This study adds two new cases, one of which developed amyloidosis. This is the first reported case of amyloidosis associated with this condition.

Case Reports

PATIENT C.A. (CASE 1)

This 33-year-old man of Greek origin suffered in 1962 from recurrent attacks of pain, in the right upper abdomen, associated with fever and chills. He was treated for cholecystitis and cholangitis and finally he underwent a cholecystectomy. At that time diabetes was observed. From 1962 to 1965 his symptoms reappeared episodically. Clinical and biochemical examinations did not reveal any abnormality. In February 1965 he was admitted to a local hospital with acute abdominal pain, increasing jaundice of the obstructive type, and slightly elevated serum amylase levels. He was referred

because of a deteriorating general condition. On clinical examination a hard abdomen and pronounced hepatomegaly were noted. Laboratory examination revealed a cholestatic jaundice, normal white blood cell count, and normal amylasaemia. He died the same day in toxic collapse.

The main finding at postmortem examination was a greatly enlarged liver, weighing 4000 g. The surface appeared coarsely nodular but no cysts could be seen under the capsule, which showed numerous fibrous strings and opaque plaques. On section several cyst-like cavities of variable diameter were seen throughout the parenchyma of both lobes. The dilatations were especially large in the central parts and contained greenish black, soft, friable stones with a maximum diameter of 70 mm (70 × 50 × 40). On section these stones were laminated. In the peripheral parts of the liver the dilatation of the bile ducts was not so conspicuous but on close examination numerous small bile stones (1-2 mm) could be detected (Fig. 1).

Microscopical examination of multiple tissue blocks revealed a normal liver architecture. The portal tracts were enlarged and contained dilated bile ducts. Usually the epithelium was destroyed, while the lumen was filled with polymorphonuclear leucocytes, sometimes resulting in abscess formation. In some places the epithelium was still preserved, and was found to be tall columnar and very regular. There was no excessive fibrosis around the bile ducts; only a few areas with fibroblastic proliferation could be found, always associated with an acute inflammatory infiltration. An occasional portal zone contained an increased number of large bile ducts, covered with regular, normal epithelium. No atypical bile duct proliferation nor 'adenomatosis'

Fig. 1 Section of the liver of patient C.A. showing large dilatations in the central part with black soft pigment stones, and smaller ones at the peripheral parts of the liver.

structures were found. The lobular parenchyma showed signs only of acute centrilobular congestion and marked postmortem autolysis.

The kidneys were moderately enlarged (200 g both) due to marked congestion. No cysts nor ectasia of the precaliceal ducts could be detected.

PATIENT L.G. (CASE 2)

This 46-year-old medical man had scarlet fever in 1928, followed by proteinuria for six months. From 1948 till 1953 he complained of recurrent 'cholangitis' although clinical and biochemical examinations and

a cholecystogram were normal. In 1959, a tuberculous infiltrate of the right upper lung was treated with streptomycin, isoniazid, and paraaminosalicylic acid and considered to be cured by the end of 1960. From 1959 to 1964 he had recurrent attacks of cholangitis and slight hepatomegaly was noted. In 1964 radiological examination revealed calcifications below the twelfth rib. During cholangiography some mottling could be seen in the liver region but gall-bladder and bile ducts were not visualized. The patient was operated on with the presumed diagnosis of choledocholithiasis, but no stones were detected. Radiomanometry during the operation showed no passage of contrast medium through the papilla at a pressure of 30 cm water, suggesting some stenotic lesion at the papilla, although mechanical exploration was normal. The extrahepatic bile duct was dilated, but at the same time a large cyst-like dilatation of the intrahepatic bile ducts (Fig. 2) was noted. A cholecystectomy and choledochoduodenostomy were performed and a T-tube was inserted in the common bile duct.

Liver biopsy showed dilatation of some of the interlobular bile ducts with periductal fibrosis and infiltration by mononuclear and some polymorphonuclear leucocytes. In some portal tracts foreign body giant cells were found surrounding clefts previously occupied by crystalline material suggesting antecedent extravasation of bile duct contents into the surrounding connective tissue. A few smaller portal tracts did not contain an interlobular bile duct, suggesting inflammatory destruction of the duct, with only scar tissue replacing it. Examination

Fig. 2 Peroperative radiomanometry through the cystic duct showing dilatations of intra- and extrahepatic ducts with saccular 'cyst-like' structures (patient L.G.).

Fig. 3 Tomograph of the liver revealing air-filled, cyst-like cavities.

Fig. 4 Patient L.G. Necropsy specimen of large portal tract showing some increase in collagenization of its connective tissue. One bile duct (long arrow) with complete erosion of its epithelium is surrounded by mononuclear inflammatory infiltrate. Note increased number of bile duct structures, some of which are moderately dilated. Presence of papillary projection in larger duct (short arrow). HE $\times$ 64.

again of the biopsy taken in 1966 showed that discrete amyloidosis of vessel walls was already present.

One month later, surgical drainage of a large cavity in the liver had to be performed because of attacks of fever. *Proteus mirabilis* was isolated from the cavity. Injection of cholangiographic media through the T-tube visualized the dilated bile ducts. One cavity showed a filling defect caused by an intrahepatic stone. Tomographs showed air-filled cavities in the liver (Fig. 3). In May and July 1965 the patient again complained of cholangitis. At that time a greatly enlarged liver and spleen were noted, and a marked proteinuria (up to 15 g per 24 hr) with hypoalbuminaemia (Table I). This was attributed to the development of amyloidosis, secondary to the longstanding intrahepatic suppuration. The patient was moderately active and free of attacks of cholangitis during 1965. In January 1966, however, he again suffered from a severe attack of cholangitis; acidosis due to renal insufficiency was demonstrated. He died suddenly in renal acidosis in March 1966.

	Date		
	1959	1/1965	1/1966
ESR (mm)	14	110	158
Urine albumin (g/24h)	—	15	30
Serum bilirubin (mg/100 mg)	1.5	1.5	1.75
BSP (% retention 45 min)	17	38	—
Alkaline phosphatase (BU)	4	16.6	21
Albumin (g/100 ml)	4.22	0.70	0.75
α_1 -globulin (g/100 ml)	0.29	0.35	0.45
α_2 -globulin (g/100 ml)	0.90	1.40	1.60
β globulin (g/100 ml)	0.89	1.05	0.70
γ globulin (g/100 ml)	1.70	1.50	1.30
Total serum proteins	7.40	5.00	4.80
Na ⁺ (m-equiv/l)	140	132	138
K ⁺ (m-equiv/l)	3.7	3.6	4.1
Cl ⁻ (m-equiv/l)	100	96	104
HCO ₃ ⁻ (m-equiv/l)	25	27	15
Urea (mg/100 ml)	24	128	174
Cholesterol (mg/100 mg)	280	219	278

Table I Evolution of the chemical data in L.G.

At postmortem examination numerous dilations of the intrahepatic bile ducts, filled with pus and pigment stones, were observed in a markedly enlarged (4300 g) and nodular liver. Some cysts were found in the renal medulla and there was macroscopic evidence of amyloidosis in the liver, spleen, and adrenals. Microscopic examination of the liver (Fig. 4) showed a normal lobular architecture but the portal tracts were enlarged. They contained an increased number of bile ducts; their lining epithelium was a typical bile duct epithelium made up of cylindrical cells with a basal, oval nucleus. The calibre of the ducts varied considerably. Papillary projections of the epithelium on a fibrovascular stalk were found in some of the larger ducts. Most of the dilated ducts were surrounded by concentric

layers of fibrous tissue and an inflammatory infiltrate made up of lymphocytes, plasma cells, histiocytes, and polymorphonuclear leucocytes. The lumen contained purulent material. Except for this concentric fibrosis there was very little fibroblastic proliferation. The main part of the portal connective branches seemed normal. The portal veins were not conspicuous, but it was difficult to assess whether their number was really reduced.

In several places abscesses with destruction of the ductular walls were noted, usually together with enlargement and fibrosis of the portal fields. Occasionally a palisade of epithelioid histocytes was present around an abscess. A severe degree of amyloidosis was noted. Amyloid was demonstrated in the lobular parenchyma as well as in the tunica media of the arteries. However, the lobular amyloid was irregularly deposited in two respects; first, scattered amyloidotic areas alternated with normal parenchymal masses throughout the liver, and secondly, in the amyloid areas the lobular amyloid deposited did not affect the whole lobule of the liver to the same extent. No clear-cut zonal distribution could be distinguished, although a predilection for zone 2 of Rappaport's liver acinus seemed most probable.

Amyloid was also found in the kidneys, pancreas, spleen, adrenals, lymph nodes, and in the small arteries of the myocardium.

One of the lung sections contained a focus of old tuberculosis with some epithelioid rimming of the caseous masses.

Discussion

In the liver several types of cystic disease can be distinguished. These cysts may be an isolated finding or they may have a diffuse distribution.

LIVER CYSTS

The simple liver cyst is lined by a columnar epithelium and surrounded by a small rim of fibrous tissue. In the wall of the greater cysts there may be smaller satellite cysts. In polycystic liver disease there are numerous cysts with a quite variable diameter. They do not differ histologically from the simple cysts. According to some authors they are never connected to the biliary tract but according to others they may communicate with it (Etevé, Trad, and Caroli, 1964; Le Tan Vinh, 1964; Watchi and Nezeloff, 1964; Hunter *et al*, 1966). They are connected with the portal tracts, which otherwise show no special abnormalities. In polycystic liver disease one can also find the so-called Meyenburg complexes.

CONGENITAL DILATATION OF THE INTRA-HEPATIC BILE DUCTS

In this disease, there are no real cysts but only saccular dilatations of the segmental intrahepatic bile ducts. Very often also the extrahepatic bile ducts are dilated. This may be associated with congenital liver fibrosis in which disease microscopical cysts can be detected; they consist of a proliferation of bile ducts, associated with that of connective tissue (fibroadenomatosis). Capillary blood vessels may be numerous (fibroangioadenomatosis). The portal veins may be decreased in number. The degree of fibrosis is quite variable. This form is clinically associated with portal hypertension except in newborn infants (Kerr, Harrison, Sherlock, and Milnes Walker, 1961; McCarthy, Baggenstoss, and Logan, 1965).

Furthermore, it may be difficult or even impossible to distinguish between fibroadenomatosis and the Meyenburg complex. The difference is one of quantity, the Meyenburg complex being an isolated finding, and consisting of a small complex of dilated and communicating ducts which sometimes seem to be situated in the parenchyma without being connected to the portal tracts; this last impression, however, is a bias introduced by the fact that histological slides are only bidimensional. Meyenburg complexes can be found in true polycystic liver disease, in congenital liver fibrosis, and even as an isolated finding in an otherwise normal liver from a normal human subject.

Pure form

In the pure form there is polyectasia of the intrahepatic bile ducts, leading to the formation of cavities with secondary stasis of bile, cholangitis, and lithiasis. In all but two cases reported up to now the dilatations are spread throughout the whole liver. Caroli *et al* (1958a) and Hérou *et al* (1965) described each a case with dilatations as confined to the left lobe and cured by hemihepatectomy.

The liver is enlarged and dark. Sometimes nodular zones corresponding to subcortical cavities can be observed, but usually the cysts themselves are not visible on the surface. Intrahepatic lithiasis is rarely palpable. Section of the liver tissue reveals the large dilated bile ducts which may be filled with pus and may contain soft bile stones. On microscopic examination a normal lobular architecture is found. There is neither cirrhosis nor true septum formation. Scarring seems to be a sequence of superimposed infection. The portal tracts are large and contain numerous bile ducts. The number and the calibre of these bile ducts varies widely, some of them with an extreme degree of dilatation. They are covered with

a typical bile duct epithelium. Sometimes papillary projections can be noted.
The predominant clinical symptoms are those of recurrent attacks of cholangitis in the absence of cholelithiasis.

Combined with congenital hepatic fibrosis
In the form combined with congenital hepatic fibrosis or fibroadenomatosis (Boquien, Léger, and Guyet, 1958; Boquien, Delumeau, Lenne, Perrin, and Veyrac, 1967; for further references see Caroli and Corcos, 1964) the liver is extremely hard. Microscopic examination reveals proliferation of biliary structures embedded in enlarged portal tracts and serpiginous septa of mature fibrous tissue.
Clinically, signs and symptoms of portal hypertension become the prominent features.

Clinical picture
In both forms, liver function tests remain normal in the early course of the disease. After several years intermittent jaundice may develop, with increased serum alkaline phosphatases and BSP retention.
X-ray films should be examined with great care. Sometimes air-filled cavities in the liver can be seen, especially after surgical intervention on the common bile duct, such as sphincterotomy, choledocoduodenostomy, or choledocojejunostomy (Roux anastomosis). During intravenous cholangiography with tomography a contrast mottling may be seen in the dilated intrahepatic ducts.

In most of the reported cases dilatation of the extrahepatic bile duct and of the gallbladder was noted with a relative stenosis of the papilla (Caroli and Corcos, 1964). This could be due to abnormalities in the innervation of the extrahepatic bile ducts and poses the question whether the intrahepatic dilatations are not a secondary phenomenon. The dilatations are best visualized by preoperative radiomanometry or postoperative cholangiography through a T-tube; these procedures establish the diagnosis beyond doubt.

The clinical evolution of congenital dilatation of the intrahepatic bile ducts is extremely poor. Bile stasis causes recurrent cholangitis and pigment stones, which in turn again produce cholangitis. Long-standing suppurative can give rise to a secondary amyloidosis as observed in our second case. Until now this complication has not been mentioned in the literature. Although the patient had been treated for pulmonary tuberculosis in 1959 and 1960, we do not feel that this was sufficient to cause the extent of amyloidosis as found by necropsy. Furthermore, amyloidosis was already present in the liver biopsy taken in 1964, whereas the patient had been complaining of cholangitis attacks since 1948 and

contracted tuberculosis only in 1959. Biliary secretion originating from the dilated ducts, seems to be greatly enhanced (Turnberg *et al*, 1968). A cholangiocarcinoma developing in these abnormal ducts was reported by Jones and Shreeve (1970).

ASSOCIATION WITH 'POLYCYSTIC' KIDNEYS (TABLE II)
Congenital dilatation of the intrahepatic bile ducts may be associated with precaliceal tubular ectasia (medullary sponge kidney or Cacchi and Ricci's disease, 1949). This was the case in patient L.G. In

Type	Kidney	Liver
I	Infantile polycystic kidney (diffuse sponge kidney)	Congenital hepatic fibrosis
II	Dysplastic polycystic kidney	—
III	Familial polycystic kidney	polycystic liver
IV	Dysplastic polycystic kidney with obstruction of the urinary tract	—
	Cacchi and Ricci's disease: precaliceal tubular ectasia	1 Congenital hepatic fibrosis 2 Congenital dilatation of the intrahepatic bile ducts 3 Combined form (of 1 and 2)

Table II Association of 'cystic' abnormalities in liver and kidney

general, the association of liver 'cysts' with 'cysts' of the kidneys is a very confusing chapter. With the rather careless use of the terms 'polycystic' kidney and 'polycystic' liver, the reference is nearly always to the familial polycystic disease. Obviously this is wrong. It only should signify the presence of multiple closed or open cavities. If we accept only closed cavities then polycystic disease of the kidney is almost non-existent (Osathanondh and Potter, 1964). Further confusion is brought about by the fact that many authors make a distinction between several types of polycystic diseases in one organ but not in the other; which specific type of polycystic kidney is associated with which particular type of liver cyst is still a neglected field of research.

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