Cholestatic childhood liver diseases

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Cholestatic diseases in childhood assume special interest because (1) they present in most cases in the neonatal period, (2) they are due to a variety of causes ranging from gross malformations to subtle molecular defects of the mechanisms of bile secretion, (3) there have been several recent advances in the understanding of their mechanisms, (4) most of them evolve in a chronic fashion resulting in end stage liver disease within a few months to several years, (5) they constitute 80% of the indications for liver transplantation in children. This review will deal chiefly with the diseases that ultimately may require liver transplantation.

From a pathophysiological viewpoint the various causes of cholestasis in children can be separated in 4 main categories depending on the site of the damage to the bile secretory and excretory pathways (table I) :

Table I. — **Etiology of cholestasis in childhood. (N : disease presenting mostly or exclusively in the neonatal period)**

Disorders of extrahepatic bile ducts :
cholelithiasis
perforation of the bile ducts (N)
congenital dilatation of the bile ducts (choledocal cyst)
congenital stenosis
cancer (botryoid sarcoma, hepatoblastoma, neuroblastoma)
blunt trauma
pancreatitis
retroperitoneal fibrosis
Disorders of extra and intrahepatic bile ducts :
biliary atresia (N)
sclerosing cholangitis
Disorders intrahepatic in origin :
Infections (neonatal hepatitis) :
antenatal (cytomegalovirus, toxoplasmosis, rubella, syphilis) (N)
perinatal (neonatal sepsis) (N)
postnatal (E coli urinary tract infection) (N)
Paucities of interlobular bile ducts :
syndromatic (Alagille syndrome) (N)
nonsyndromatic (N)
Genetic diseases with recessive autosomal inheritance :
alpha-1-antitrypsin deficiency (N)
progressive familial intrahepatic cholestasis (N)
cystic fibrosis (N)
Niemann-Pick disease type C (N)
Gaucher disease (N)
respiratory chain disorders (N)
peroxysomal disorders (N)
benign recurrent intrahepatic cholestasis
Transient neonatal cholestasis (N)
Others :
liver angiomas
adrenal insufficiency (N)
pituitary deficiency (N)
post hemolytic (N)
parenteral nutrition associated (N)
autoimmune cholangitis of the small bile ducts
Kawasaki disease
drug toxicity
prolonged hepatitis A

I. *Disorders of the extrahepatic bile ducts* :

They account for less than 10% of all cases of cholestasis in children and do not require liver transplantation either because there are satisfactory surgical or radiological therapeutic procedures or because their malignant nature is not suitable for transplantation.

II. *Disorders of the extra and intrahepatic bile ducts* :

They account for 45% of cholestatic diseases of childhood.

A-Biliary atresia

It is characterized by a complete occlusion of a variable part of the extrahepatic bile ducts, always associated with lesions of the intrahepatic bile ducts similar to what is seen in sclerosing cholangitis. The incidence, in France, is 1/17500 live births. The cause is unknown. Familial cases are extremely rare. In 8% of cases it is associated with the polysplenia syndrome and in 10% of cases with a biliary cyst along the extrahepatic bile ducts. Untreated it ends in biliary cirrhosis and death at a mean age of 18 months. The various operations described by Kasai improve partially the overall prognosis (1).

Children with biliary atresia present with cholestatic jaundice before the age of one month. Diagnosis is urgent and relies chiefly on clinical data (completely acholic stools and firm enlarged liver), sometimes on liver histology (portal fibrosis with ductular proliferation) or cholangiography (percutaneous, endoscopic retrograde or operative). Kasai operation is to be performed before age 45 days to provide the child with the best possibility of success (2). Restoration of bile flow also depends on the anatomic type of the disease :

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children with atresia restricted to the hepatic duct or who display a biliary cyst fare better in that respect than those with complete atresia.

Nevertheless the overall survival 10 years after Kasai operation is only 30% and cirrhosis is present in virtually all survivors (3). Preliminary results of the study of children followed at Bicêtre hospital for more than 20 years after Kasai operation indicate a 15% survival without liver transplantation (unpublished). Liver transplantation is thus necessary in more than 80% of children with biliary atresia. In fact biliary atresia accounts for 50% of the indications of liver transplantation in children. It may be necessary early on, before 3 years of age, because of early failure of Kasai operation and of persisting jaundice ; serum bilirubin concentration above 300µM, decrease in serum cholesterol concentration and in serum GammaGT activity and/or prolonged prothrombin time and high hepatic artery index on doppler ultrasonography are all indices of impending liver failure and may be used to decide upon liver transplantation. Major œsophageal varices may be present early and are also to be taken into consideration when deciding upon the time of liver transplantation. The latter may be necessary in an emergency when the evolution is complicated by acute ischemic necrosis of the liver which may be life-threatening in a matter of days (4). In all instances careful nutritional management of the child is necessary from the time of diagnosis to the time of transplantation, with enteral caloric intake close to 200 kcal/kg/day provided either through oral supplementation with medium chain triglycerides and maltodextrines or through continuous enteral feeding via a nasogastric tube. When continuous enteral feeding is not well tolerated or in case of refractory ascite, total parenteral nutrition may be required. Liver transplantation may also become necessary at any time in a child in whom Kasai operation has initially been successful in restoring bile flow : relapse of jaundice, refractory pruritus, refractory bacterial cholangitis, intractable portal hypertension, pulmonary arteriovenous shunting (especially frequent in the polysplenia syndrome) (5), pulmonary arterial hypertension (6), hepatocellular carcinoma may all be the occasion of deciding upon liver transplantation during childhood or adulthood. Careful yearly monitoring of all these patients is therefore mandatory.

Survival after liver transplantation in children with biliary atresia is currently 82% (7), regardless of the degree of liver failure at the time of transplantation. This however does not take into account the number of deaths on the waiting lists nor the number of children who do not reach a centre where liver transplantation is available. A recent study, surveying the overall 10 year survival of all French children presenting with biliary atresia during the years 1986-1996 and who were offered Kasai operation and/or liver transplantation indicate an actuarial 10 year survival of 75% in the centre treating more than 20 new children with biliary atresia per year, versus 54% in centres with less experience (8). This extends previous results concerning the outcome of Kasai operation that showed that the experience of the centre was a significant prognostic factor (9). Besides the experience of the centre, the other prognostic factors shown in this study are the early date of Kasai operation which had a positive influence on the overall survival, and the polysplenia syndrome that was a negative factor in terms of survival. This further supports the need for an early detection of biliary atresia in neonates and the referral, from the outset, to a specialized centre where both Kasai operation and liver transplantation are available. Various means of detection of biliary atresia before age 1 month have been proposed but so far none has been satisfactorily implemented. Proper training of parents, nurses and physicians as to the significance of discolored stools in a neonate and of prolonged neonatal jaundice after age 10 days would be crucial in that respect if one is to improve the current results of treatment of biliary atresia.

B-Sclerosing cholangitis

There are currently 5 groups of children with sclerosing cholangitis :

Sclerosing cholangitis with neonatal onset (10) : these children present with neonatal cholestatic jaundice which later subsides but the eventual outcome is that of biliary cirrhosis requiring liver transplantation during the first decade of life. Cholangiography shows anormal intra and extrahepatic bile ducts. The mechanism is unknown ; it may be genetic in origin since the disease was reported to occur in siblings (11).

Sclerosing cholangitis associated with Langerhans' cell histiocytosis (12) : an enlarged and firm liver associated with biochemical signs of cholestasis strongly suggests the possibility of sclerosing cholangitis in a child with Langerhans' cell histiocytosis. Conversely signs of Langerhans' cell histiocytosis should be searched for in any older child presenting with sclerosing cholangitis of unknown origin. The mechanism of the bile duct lesions is not known with certainty but it may be the consequence of periductal fibrosis following infiltration of the portal tracts with histiocytes. The liver condition may be improved with ursodeoxycholic acid treatment ; it is unresponsive to chemotherapy. Liver transplantation is usually required at the end or the first decade or during the second decade of life.

Autoimmune sclerosing cholangitis : as in adults it is frequently associated with inflammatory bowel disease and/or autoimmune hepatitis (12). Serum autoantibodies of the smooth muscle or nuclear types are sometimes present. In most instances it is only partially responsive to immunosuppressive therapy but it may be significantly improved by ursodeoxycholic acid.

Sclerosing cholangitis associated with immune deficiency : several kinds of immune deficiencies, either congenital or acquired, may be complicated by sclerosing cholangitis (13). Infection of the bile and/or

biliary epithelium by cytomegalovirus, Cryptosporidia or Microsporidia have been held responsible for the biliary lesions. Currently the presence of a non corrigible immune deficiency is considered a contra-indication to liver transplantation. New therapeutic methods have to be devised for these children.

Other conditions : in several instances no clearcut associated condition can be found.

Regardless of the etiological classification, the overall long-term prognosis for children with sclerosing cholangitis is ominous. The estimated median survival time is 10 years from diagnosis, lower in children with Langerhans' cell histiocytosis and higher in children with autoimmune sclerosing cholangitis (12). Serum bilirubin concentration persistently above 100μM should lead to consider liver transplantation. Relapse of sclerosing cholangitis on the transplanted liver was not observed.

III. *Disorders of the interlobular bile ducts*

When more than 50% of portal tracts are lacking interlobular bile ducts, a diagnosis of "paucity" of interlobular bile ducts can be made, provided the number of complete portal tracts is above 10 on the biopsy sample (14). The main cause of paucity of interlobular bile ducts is Alagille syndrome (15). In the typical cases children present with at least three of the five main features of the syndrome : neonatal cholestatic jaundice, congenital heart disease consisting mostly of pulmonary artery stenosis, peculiar facies with prominent forehead and small pointed chin, abnormal closure of the vertebral arch of one or of several dorsal vertebræ (butterfly vertebra) and eye abnormalities (chiefly bilateral posterior embryotoxon). Alagille syndrome has recently been shown to be associated with mutations or deletions in the "Jagged1" gene encoding a ligand of the "Notch" receptor which plays an important part in cell fate determination during development (16). Its prevalence is estimated to be 1:100,000 live births. It appears either as sporadic or is transmitted as a dominant trait with variable expressivity.

In a few children with Alagille syndrome jaundice persists relentlessly from the neonatal period and ultimately ends in liver failure during adolescence or adulthood. In these children the quality of life is very poor with the need for continuous enteral feeding with nasogastric tubes or gastrostomy, for parenteral supplementation with vitamins A, D, E and K and for drug therapy to attempt to treat pruritus. Social life and learning at school is severely hampered. For all these reasons liver transplantation may be considered before entering elementary school. In the majority of children, however, neonatal jaundice will subside after a few months but clinical (pruritus often very severe) and biochemical signs of cholestasis will persist throughout life, often exacerbated during episodes of infection. The quality of life in these children, although better than in the previous group, leaves much to be desired ; moreover, during adulthood, impairment of the liver condition may occur, including hepatocellular carcinoma (17). Therefore, liver transplantation may be necessary in some of these patients as well.

The results of liver transplantation in children with Alagille syndrome may be as good or even better than in children with other types of chronic cholestatic conditions (18). Raised pulmonary artery pressure is not a contra-indication to liver transplantation, even when the systolic pressure in the main pulmonary artery or in the right ventricle exceeds 100mmHg (unpublished observations).

IV. *Disorders hepatocytic in origin* : Progressive familial intrahepatic cholestasis (PFIC)

This is an heterogeneous group of cholestatic disorders of childhood, genetically transmitted as autosomal recessive and having several biochemical, histopathological and radiological features in common : normal or low serum cholesterol concentration, presence of interlobular bile ducts on liver histology, (although sometimes small and difficult to see) and normal extra and intrahepatic bile ducts on cholangiograms. Recent advances over the past few years have allowed to identify at least 5 different entities within this group :

A-Progressive familial intrahepatic cholestasis with normal serum gammaGT activity and normal or low serum bile acid concentrations : deficiencies in enzymes of bile acid synthesis. Two such deficiencies have been described :

1-3β-hydroxy-C27-steroid dehydrogenase/isomerase deficiency may present as cholestasis in early infancy as well as later on during childhood (19,20). There is no pruritus. Diagnosis relies on a specific pattern on FAB Gas chromatography-mass spectrometry of urine. Treatment with ursodeoxycholic acid may improve the condition but the best treatment is provided by cholic acid.

2-Delta4-3 oxosteroid 5β-reductase deficiency has been mostly reported in early infancy and may, when untreated, end in liver failure after a few months (21). Diagnosis also relies on FAB GC-MS and treatment with cholic acid allows normalisation of liver function.

B-Progressive familial intrahepatic cholestasis with normal serum gammaGT and high serum bile acid concentration (Byler disease, Byler-like disease)

This is a cholestatic disorder characterised by onset in the first months or years of life with relapsing or ongoing jaundice and severe pruritus. Liver histology displays non specific giant cell transformation in the first months of life then progressive lobular fibrosis with variable portal fibrosis and no or very little ductular proliferation (22). It ends in liver failure and death during childhood or adolescence. Treatment with ursodeoxycholic acid may result in significant improvement in up to 40% of cases (23) ; external biliary

Table II. — **Current understanding of the mechanisms and management of progressive familial intrahepatic cholestasis (* : presumed effective before the distinction between the Byler family disease and the Byler-like was made ; UDCA : ursodeoxycholic acid ; SPGP : Sister P Glycoprotein)**

Molecular defect :	3beta-OH-C27 steroid dehydrogenase	Delta4-3 oxosteroid 5 beta-reductase	SPGP (Byler-like)	P-type ATPase (Byler family)	MDR3
Pruritus :	no	no	yes	yes	yes
Serum gammaGT :	normal	normal or slightly raised	normal	normal	high
Serum primary bile acids :	normal or low	normal or low	high++	high++	high
Treatment :					
Bile acids	effective (cholic acid)	effective (cholic acid)	40% (UDCA)*	40% (UDCA)*	40% (UDCA)
Partial biliary diversion	contra-indicated	contra-indicated	effective*	effective*	unknown
Liver transplantation	not indicated	not indicated	indicated in case of failure of other treatments		

diversion may result in complete restoration of liver function (24) ; liver transplantation is indicated in case of failure of the previous treatment or when the patient is first seen with end stage liver disease (25). In some instances it may be associated with refractory diarrhea. Recent data suggest that this disease may result from a defect in bile acids secretion into bile and may be due to either one of 2 separate genetic lesions :

1-in the original Byler family, the mutated gene is located on chromosome 18 and encodes a P-type ATPase. The same gene carries mutations associated with benign recurrent intrahepatic cholestasis (26).

2-in other patients there is accumulating evidence that the responsible gene is located on chromosome 2 and encodes a Sister P Glycoprotein which plays an important role in the secretion of bile acids in the canaliculus (27).

C-Progressive familial intrahepatic cholestasis with high serum gammaGT activity and high serum bile acids concentration (MDR3 disease)

This is a cholestatic disease characterized by an onset later in life, and variable intensity of pruritus. Liver histology displays patent signs of cirrhosis with slight lobular fibrosis and prominent ductular proliferation. Signs of portal hypertension occur more often than in the other types of PFIC. This disease is due to mutations in the MDR3 gene encoding a phospholipid flippase responsible for the secretion of phospholipids into the canaliculus (28).

V. *Other intrahepatic cholestatic disorders*

Among the other causes listed in Table I some are self limited (hepatitis A, drug-induced cholestasis, intrauterine infections, angiomas..),and others are associated with extrahepatic lesions which precludes the use of liver transplantation in most instances (peroxysomal disorders, respiratory chain disorders, type C Niemann-Pick disease). Alpha 1 antitrypsin deficiency may require liver transplantation and is discussed in another paper of this symposium.

Transient neonatal cholestasis (29) is characterized by jaundice occurring during the very first weeks of life and resolving spontaneously within a few months with no sequelæ. It is probably the consequence of the association of several external factors such as ante or neonatal ischemia, hypoxemia, bacterial infections, prolonged total parenteral nutrition, with the immaturity of bile secretion present in all neonates, even more so in premature infants. Although the outcome is benign, in a few instances the same factors, often associated with intestinal resection, may result in biliary cirrhosis and death (30). Combined gut-liver transplantation may be required in these children.

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