Neonatal cholestasis as the presenting feature in cystic fibrosis

P Lykavieris, O Bernard, M Hadchouel

Abstract

Between 1960 and 1994 cystic fibrosis was found in nine out of 1474 infants investigated for neonatal cholestasis. Four had delay in passing meconium. In all patients cholestatic jaundice was present during the first 48 hours and in three patients cholestasis was complete, mimicking biliary atresia. Serum cholesterol concentrations were normal in all but two children. Sweat chloride was repeatedly above 95 mmol/l in all instances. Three children had another condition enhancing the risk of cholestasis (α_1-antitrypsin deficiency, hypopituitarism, perinatal asphyxia, and total parenteral nutrition). Liver histology displayed portal fibrosis and inflammation with bile duct proliferation; mucous plugs in bile ducts were observed in only one patient. Only one child died from cirrhosis. These results indicate that cystic fibrosis is not a major cause of neonatal cholestasis. However early signs of intestinal obstruction and low concentrations of serum cholesterol may indicate cystic fibrosis, regardless of liver histology. Neonatal cholestasis has no prognostic value concerning evolution to cirrhosis.

(*Arch Dis Child* 1996;75:67–70)

Keywords: neonatal cholestasis, cystic fibrosis.

The liver is frequently involved in cystic fibrosis. The clinical and histopathological features include cirrhosis, steatosis, biliary stones, portal hypertension, and neonatal cholestasis.[1–3] The prevalence of liver involvement in cystic fibrosis has been extensively studied. Yet, the incidence of cystic fibrosis as a cause of neonatal cholestasis has not been determined. There have been a limited number of reports on children in whom cystic fibrosis presents as neonatal cholestasis and on the prognosis of the liver condition. Here we report on nine infants who were investigated in Bicêtre Hospital for neonatal cholestasis and cystic fibrosis over a 34 year period.

Department of Paediatrics, Hepatology Service, CHU Bicêtre 78 Rue de Général Leclerc, 94275 Le Kremlin Bicêtre, Cedex, France
P Lykavieris
O Bernard
M Hadchouel

Correspondence to:
Dr Lykavieris.

Accepted 22 March 1996

Patients and results

From 1960 to 1994, 1474 infants presenting with cholestatic jaundice were investigated in our unit. Nine (four boys, five girls) were suffering from cystic fibrosis. Proof of cystic fibrosis was provided by at least two iontophoretic sweat tests in each child carried out at a mean age of 2 months in seven children and at an age of 3.5 and 12 years respectively in two other children. Sweat chloride concentrations were above 95 mmol/l. In the four children studied more recently, immunoreactive serum trypsin concentrations were above normal for the age (range 765–1370 µg/l). Only one child was screened for mutations and was found to be homozygous for the haplotypes A-A. An associated condition particularly enhancing the risk of cholestasis was present in three children: homozygous PiZ α_1-antitrypsin deficiency; hypopituitarism due to transection of pituitary stalk; and perinatal asphyxia requiring intubation for a few hours and total parenteral nutrition for one month. Known causes of neonatal cholestasis were excluded in the other children. Pregnancies were uneventful. Children were delivered at term except for one born by caesarean section because of fetal distress at 35 weeks of gestation. Birth weights ranged from 1730 to 3240 g (mean 2605 g). The patient with associated hypopituitarism presented twice with hypoglycaemic seizures. Five children had early gastrointestinal symptoms (table 1): four had delay in passing meconium associated in two children with functional distal intestinal obstruction and one had vomiting. Peritoneal calcifications were observed on standard abdominal radiographs in one patient.

PRESENTING SYMPTOMS AND SIGNS

Jaundice was present during the first 48 hours after birth in all instances. On admission to Bicêtre Hospital (age 15 days to 3 months, mean 1 month and 20 days) stools remained persistently acholic, mimicking biliary atresia in three cases. The liver was enlarged and firm in all children and the spleen palpable in three. All children presented height and weight retardation (range from -1 to -3.5 SD for height and from - 0.5 to -3 SD for weight). Total serum bilirubin concentrations ranged from 70 to 312 µmol/l (mean 155 µmol/l), serum transaminase activity from 1.5 to 4 × N (N=upper normal limit), serum alkaline phosphatase activity from normal to 3.5 × N and serum γ-glutamyltranspeptidase activity from 1.5 to 21 × N in the five children studied. Prothrombin time was normal after parenteral administration of vitamin K in all patients. In seven children serum cholesterol concentration was within normal limits for the age (1.8 to 4.5 mmol/l), and was raised (8 mmol/l) only in one

Table 1 Clinical data of children with neonatal cholestasis and cystic fibrosis

Patient No (year of birth)	Age on admission (months)	Cholestasis	Total serum cholesterol (mmol/l)†	Early gastrointestinal symptoms	Associated conditions	Sweat chloride (mmol/l)	Immunoreactive trypsin (μg/l)	Duration of jaundice (months)	Follow up
1 (1960)	0.5	Incomplete	2.4	Delay in meconium passage		119		2	Death at 19 years from respiratory failure, normal liver function
2 (1968)	1.5	Incomplete	4.9	Vomiting		110		2.5	Death at 3.5 years from cardiopulmonary failure, hepatomegaly
3 (1979)	1	Incomplete	2.7	—		100		1.5	Death at 4 years from respiratory failure, hepatomegaly, normal liver function
4 (1981)	3	Complete*	3.4	Delay in meconium passage, distal intestinal obstruction	TPN‡	120		6	Death at 6 months from meningitis, cirrhosis
5 (1982)	2.5	Complete*	3.7	Prolonged meconium passage, distal intestinal obstruction		100		5	Death at 5 months from liver failure
6 (1985)	2	Complete*	8.0	Delay in meconium passage	α_1-Antitrypsin deficiency	120	765	5	10 years old, pulmonary infections cirrhosis, portal hypertension
7 (1985)	2	Incomplete	3.6	—		95	1215	3.5	6 years old, pulmonary infections, normal liver function
8 (1985)	1	Incomplete	3.6	—		150	835	1	10 years old, pulmonary infections, normal liver function
9 (1989)	1.5	Incomplete	3.7	—	Transection of the pituitary stalk	130	1370	2.5	6.5 years old, normal liver function, treated for hypopituitarism

*Complete cholestasis is defined as permanent acholic stools.
†Normal values for the age: 1.8 to 4.5 mmol/l.
‡TPN: total parenteral nutrition.

Table 2 Histological findings of the liver in children with neonatal cholestasis and cystic fibrosis

Patient No	Age (month)	Portal area: Fibrosis	Portal area: Ductular proliferation	Portal area: Inflammatory infiltration	Mucous plug	Lobular lesions
1	2	+	+	+ + Polymorphonuclear	–	—
3	2	+	+	+ + Polymorphonuclear	–	—
4	5	+ + +	+ + +	+ + + Polymorphonuclear	+ + +	Mild fibrosis
5	4	+ + +	+ + +	+ + Mixed	+	Tubular arrangement of hepatocytes and fibrosis
6	3	+	+ / –	+ Polymorphonuclear	–	Hepatocytes, ballooning, and steatosis
7	3	+ +	+ + +	+ + + Polymorphonuclear	–	Giant cells and haematopoiesis
8	2	+ + + Bridging	+ +	+ + Polymorphonuclear	–	—
9	1.5	+	+ +	+ + Mixed	–	Giant cells and haematopoiesis

patient with associated α_1-antitrypsin deficiency. Standard chest radiographs were normal on admission. Ultrasonographic studies of the abdomen showed a small gall bladder in five children; in three others the gall bladder was not visible. Needle biopsies were carried out at ages from 1.5 to 4 months (table 2): main features included moderate to severe focal fibrosis, variable portal inflammation, and some degree of ductular proliferation. Interlobular bile ducts were present. Mucous plugs in the interlobular bile ducts were seen in only one case. Lobular abnormalities were most often moderate consisting of steatosis in one patient, giant cell transformation in two, and more severe abnormalities in one patient with fibrosis and acinar transformation.

OUTCOME

Neonatal jaundice persisted until death in two children. Patient 4 died at 6 months of age with pneumococcal meningitis, permanently acholic stools, progressive malnutrition, and liver cirrhosis on early postmortem needle liver biopsy. Patient 5 died of liver failure at age 5 months; necropsy disclosed pancreatic lesions typical of cystic fibrosis, patent extrahepatic bile ducts, mucus in the gall bladder, and bile duct and liver lesions consisting of extensive lobular and portal fibrosis and ductular proliferation with mucous plugs.

In seven children jaundice resolved by age 1.5 to 6 months (mean 3.5 months) with normal total serum bilirubin concentrations. Three of the seven children died of respiratory failure and malnutrition at ages 3.5, 4, and 19 years respectively. In two of them, hepatomegaly was still present and liver function tests were normal in the two patients tested (table 1).The other four are alive age 6 to 10 years old. At the latest follow up, hepatosplenomegaly with portal hypertension was present only in the patient with α_1-antitrypsin deficiency; the liver and the spleen were not palpable in the three others, and abdomen ultrasonography was normal in one. Two patients have been treated with ursodeoxycholic acid for two and five years respectively with biologi-

cal improvement in only one of them. All but one of these seven children presented with relapsing episodes of bronchopulmonary infections with chest radiography compatible with cystic fibrosis lesions; two had episodes of hyponatraemic dehydration including one during an episode of heat stroke. Hydrocortisone has been administered daily to the patient with hypopituitarism and at the age of 10 months transection of the pituitary stalk was evidenced by magnetic resonance imaging; growth hormone and partial thyroid stimulating hormone deficiency were demonstrated. Treatment by growth hormone and L-thyroxine was added, and resulted in a progressive ability to thrive. This patient is doing well with satisfactory lung and liver status and with no mental retardation.

Discussion

Although several reports have already described neonatal cholestasis in patients suffering from cystic fibrosis, the patients reported here enabled us to stress various points regarding this association.

Neonatal cholestasis associated with cystic fibrosis is a rare condition. We found 31 children described in English language publications,[1 4-19] and seven more in French journals.[20-25] In our series the incidence of cystic fibrosis among causes of neonatal cholestasis was 6/1000. The true incidence may be lower as at least two patients in this series also had another condition known to be associated with neonatal cholestasis.[26] However the presence of mucous material in the lumen of the extrahepatic as well as in intrahepatic bile ducts seen in one patient and already reported is compatible with a bile excretion defect at the origin of cholestasis in these children.[27]

Many of the features of cystic fibrosis associated neonatal cholestasis are non-specific or even misleading. In two patients reported here, the permanently acholic stools and firm hepatomegaly were consistent with a clinical diagnosis of biliary atresia. In one of them however, necropsy showed patency of the extrahepatic biliary duct. Two other reports dealing with the same problem conclude differently. Perkins *et al* consider that a positive sweat chloride test should postpone surgery[15] but Festen *et al* suggest that intervention is essential because they had histological evidence for biliary atresia in one patient with cystic fibrosis.[17] The liver histology is of little help in most cases because, in our series, only one child displayed the typical mucous plug in the interlobular bile ducts. In most cases liver histology shows features compatible with bile duct obstruction. Finally there were no respiratory symptoms during the early months, although all surviving children presented with respiratory symptoms subsequently.[28]

We confirm, as has already been shown,[2 9 12] that delay in meconium passage, present in four of these children, is a valuable marker for the diagnosis of cystic fibrosis in children with neonatal cholestasis. Another valuable finding is the presence of normal serum cholesterol concentration, present in seven of the nine children, despite severe cholestatic jaundice. The only child with a high serum cholesterol concentration also had α_1-antitrypsin deficiency, which may have increased the cholesterol levels. Serum cholesterol concentrations are reported for nine patients described in the literature[6 9 20 22 24] and were normal in seven, in addition to another with raised total serum cholesterol and associated cytomegalovirus hepatitis.

Prognosis of the liver condition in neonates with cystic fibrosis and cholestatic jaundice is varied; it may lead to liver failure after a few months as in patient 4 of our series,[22] or it may progress to early cirrhosis as in patient 6, in whom associated α_1-antitrypsin deficiency may have increased the risk of cirrhosis. In six children of our series, however, there were no evident signs of cirrhosis with a follow up of 3.5 to 19 years. Thus neonatal cholestasis is not necessarily predictive of an early occurrence of cirrhosis.[15] In the 38 cases of neonatal cholestasis associated with cystic fibrosis described in the literature, cirrhosis during infancy has been reported in six cases at ages of 1 month to 1 year, and cirrhosis was seen at necropsy. However, there is no significant follow up for the other children reported, such that it is not possible to estimate the true overall incidence of cirrhosis in children with cystic fibrosis who present with neonatal cholestasis.

As many factors have been proposed as causing neonatal cholestasis in cystic fibrosis, different kinds of treatment, both conservative and aggressive, have been reported in the literature.[6 8 12 17 19] Ursodeoxycholic acid treatment, recommended for patients with meconium ileus, may also benefit patients with neonatal cholestasis due to the same disease.[29 30]

The authors wish to acknowledge Professor C Fessard, Professor C Maurage, and Dr M Barré for follow up information on patients 1, 6, and 9.

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