Cholestatic jaundice in infancy. The importance of familial and genetic factors in aetiology and prognosis

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SUMMARY One hundred and twenty-four infants admitted to hospitals in Norway between 1955 and 1974 during the first 3 months of life with cholestatic jaundice were studied retrospectively. Sixty-four infants had had extrahepatic atresia of the biliary tree and 60 had had intrahepatic cholestasis. This gives an incidence of about 1:9000 live births for cholestasis. In 4 of the 64 infants with extrahepatic atresia a bile duct-to-bowel anastomosis had been performed but this was successful in only 2. Sixty of these infants had died by their 2nd birthday. Twenty-six of the infants with intrahepatic cholestasis had died by 1978 and the most common causes of death were cholestasis complicated by infection, bleeding, or hepatoma. The survivors aged between 4 and 23 years were followed up in 1978. In about two-thirds of them aetiological factors—such as α -1-antitrypsin deficiency, arteriohepatic dysplasia, cholestasis with lymphoedema—and other familial or genetic factors, or infections were found. Four of the 34 survivors are known to have cirrhosis. Twenty patients had biochemical abnormalities, and 12 had normal liver function tests. Two patients could not be examined. Of the 19 patients with familial or genetic aetiological factors, 4 had cirrhosis, 14 had biochemical abnormalities, and only 5 had normal liver function tests. Of 11 survivors with idiopathic disease or septicaemia, none had cirrhosis and only 4 had abnormal liver function tests.

Cholestasis with jaundice in the first months of life presents the paediatrician with a difficult diagnostic and management problem. Many causes have been suggested but generally the aetiology is unknown. The prognosis for the affected infant is difficult to ascertain and the overall prognosis contentious. Shiraki *et al.*¹ and Psacharopoulos *et al.*² reported a fairly good prognosis, but Thaler and Gellis,³ Alagille,⁴ and Danks *et al.*⁵ indicated a poorer one. Such studies have limited epidemiological significance because of their short duration, their method of case ascertainment, and because of factors influencing the infant's referral. We report a study of all such infants referred to paediatric departments in Norway during 1955-74, and give an assessment of the survivors who were followed up in 1978.

Materials and methods

During the period all the infants except 2 had been referred to one of four central clinics; these central clinics are referral hospitals for all paediatric departments throughout Norway. The population in Norway during the period was $3\frac{1}{2}$ to 4 million and

the birth rate averages about 60 000 a year. All the infants in the study were white. Each of them had obstructive jaundice with hepatomegaly or splenomegaly, or both, with pale stools, and dark-coloured urine; so all of them had fairly severe cholestasis. The number of infants so identified must have been almost complete for Norway at that time. The clinical course was studied from each patient's records, and all the survivors (except 2) were followed up in 1978.

The follow-up. When the patients were followed up a family history was taken and the child was given a clinical examination; haematological values and biochemical liver function tests—such as levels of bilirubin, prothrombin time, aspartate transaminase, alanine transaminase, alkaline phosphatase, ornithine transcarbamylase, cholesterol, triglycerides, and serum proteins—were estimated. In all the patients (except 2), fasting serum bile acids were studied, and in some, serum bile acids after a standardised test meal were estimated, as described by Fausa.⁶ Lipoprotein X was measured by the method given by Seidel.⁷ Alpha-1-antitrypsin level was measured in patients in whom it had not been

measured earlier. Liver biopsy and radiological examinations were performed only on clinical indications. Infectious aetiology—bacterial cultivation, virus isolation, virus serology, and other serological tests—were performed in most patients, as were metabolic studies for diseases such as galactosaemia, fructosaemia, and amino-acid disturbances. Sometimes other family members were examined. In the group 'other familial cholestasis' there was at least one sibling with confirmed cholestasis. Some patients were so classified if there was a family history that strongly suggested cholestasis.

Results

A total of 124 patients with cholestasis, as described above, with onset in the first 3 months of life had been admitted to Norwegian paediatric clinics during the period.

Extrahepatic atresia. The incidence of extrahepatic atresia was about 1:18 000 live births and the female/male ratio 3:2. All the 64 patients had undergone surgical exploration before age 3 months. In 4 a direct anastomosis between the biliary tree and the intestine had been possible (neither porto-jejunostomy nor cholecystoportoostomy was performed in any patient). Two of these 4 died later of complicating cholangitis, but 2 were apparently cured. The remaining patients developed biliary cirrhosis and all of them had died before reaching age 2 years. In 8 (13%) an associated malformation was found: congenital heart disease of various types in 7 (one of whom also had intestinal atresia), and hermaphroditism in 1. None of these patients had affected relatives.

Intrahepatic cholestasis. The incidence was about the same as for extrahepatic cholestasis, but the female/male ratio was roughly the other way round (3:4). Of the total number of 60 patients, 26 (43%) were dead (Table 1). Among the complications leading to

death, acute infections, dehydration, or bleeding were common. Three had died in early childhood from hepatoma which had arisen secondarily to chronic cholestasis.

Thirty-four patients were still alive in 1978. Table 2 shows the likely aetiological factors, and a known or associated factor was present in 35 (58%) of them. We also looked for the same factors during the last 10 years of the period (36 patients) and found a possible aetiology in at least 70%.

The liver status in 1978 in patients alive is shown in Table 3. Of the patients with α -1-antitrypsin deficiency 2 have had cirrhosis since infancy. Despite this they have developed fairly well with only slight progression of the cirrhosis or none. The 3 patients with merely biochemical abnormalities have shown a steady, but slow improvement over many years, and 2 patients (14 and 23 years old) have made complete recoveries. Only 3 patients with arteriohepatic dysplasia fulfilled our criteria for neonatal cholestasis. A 7-year-old girl is severely affected by liver disease, but her condition will probably improve after the neonatal cholestasis has resolved. The pedigrees of the 6 families with 'other familial cholestasis' are shown in the Figure. The clinical course in the patients has varied considerably; in family 1 two siblings died in early childhood from liver failure, but our 19-year-old patient with liver cirrhosis is still alive. In family 2 both children died early in life with severe cholestasis; one of them developed a hepatoma. In family 3 the patient had neonatal hepatitis. He is now 11-years old and apparently healthy, but with increased postprandial bile acids, a positive lipoprotein X, and a moderate hyperlipaemia. His mother had prolonged jaundice and severe feeding problems throughout her first year of life. She now has no sign of cholestasis. The patient from family 4 is now 7-years old, and her liver function is normal; her cholestasis gradually subsided, clearing when she was about 3-years old. Her

Table 1 Neonatal intrahepatic cholestasis in 26 infants who died

	Died	Remarks
Cholestasis + acute complications	16	Most of them aged <6 months before 1965
Cholestasis + hepatoma	3	
Cholestasis + operation	1	α -1-antitrypsin deficiency
Cholestasis + infection	1	Toxoplasmosis
Inspissated bile syndrome + operation	1	Premature
Others	4	Down's syndrome Epiglottitis Accident

Table 2 Neonatal intrahepatic cholestasis, aetiological factors

	Dead (n = 26)	Alive (n = 34)
Alpha-1-antitrypsin deficiency	1	7
Arteriohepatic dysplasia	0	3
Cholestasis with lymphoedema	2	5
Other familial cholestasis	3	4
Inspissated bile syndrome (erythroblastosis)	1	1
Septicaemia	0	3
Septicaemia + parenteral alimentation	1	0
Toxoplasmosis	1	0
Down's syndrome	2	0
Mucopolysaccharidosis	0	1
No aetiological factors found	15	10
Not examined		2

Table 3 Liver status in 1978 in the 34 survivors with intrahepatic cholestasis

	Age (years)	Sex	Bilirubin	ALT	Bile acids	Lipoprotein X	Liver	Spleen	Biopsy
Alpha-1-antitrypsin deficiency (n = 7)									
	23	M	Normal	Normal	Normal	—	Normal	Normal	NT
	14	F	Normal	Normal	Normal	—	Normal	Normal	NT
	10	M	×2	×6	×2	—	+6	+6	Cirrhosis
	10	F	Normal	×1, 5	×2	+	+3	Normal	NT
	8	F	×5	×4	×15	+	+4	+4	Cirrhosis
	6	M	Normal	×2	IPP	+	Normal	Normal	Normal
	4	F	Normal	×3	×2	+	Normal	Normal	NT
Arteriohepatic dysplasia (n = 3)									
	15	M	Normal	×3	×10	+	Normal	Normal	NT
	7	F	×2	×3	×3	+	+3	Normal	Bile duct hypoplasia
	6	F	Normal	×3	×2	+	Normal	Normal	NT
Cholestasis with lymphoedema (n = 5)									
	23	F	Normal	Normal	Normal	—	Normal	Normal	NT
	17	F	Normal	Normal	×4	+	Normal	Normal	Normal
	16	M	Normal	Normal	NT	NT	Normal	Normal	Fibrosis
	12	F	Normal	Normal	×2	+	Normal	Normal	Normal
	10	M	×2, 5	×4	×10	+	+6	+7	NT
Other familial cholestases (n = 4)									
	19	M	×3, 5	×4	×5	+	+5	+5	NT
	11	M	Normal	IPP	+	+	Normal	Normal	NT
	7	F	Normal	Normal	NT	—	Normal	Normal	NT
	5	M	Normal	×2	×2	+	Normal	Normal	NT
Mucopolysaccharidosis (n = 1)									
	6	M	Normal	Normal	Normal	—	Normal	Normal	NT
Septicaemia (n = 3)									
	9	F	Normal	Normal	Normal	—	Normal	Normal	NT
	4	M	Normal	Normal	Normal	—	Normal	Normal	NT
	4	M	Normal	Normal	Normal	—	Normal	Normal	NT
Inspissated bile syndrome (n = 1)									
	7	F	Normal	Normal	Normal	—	Normal	Normal	NT
Idiopathic neonatal cholestasis (n = 8)									
	22	F	Normal	Normal	Normal	—	Normal	Normal	NT
	19	M	Normal	Normal	Normal	—	Normal	Normal	NT
	15	M	Normal	Normal	Normal	—	Normal	Normal	NT
	13	F	Normal	Normal	×2	+	Normal	Normal	NT
	11	F	Normal	Normal	NT	NT	Normal	Normal	NT
	11	M	×1, 5	Normal	×10	+	Normal	Normal	NT
	4	M	Normal	×2	×3	+	Normal	Normal	NT
	4	M	Normal	×3	×2	+	Normal	Normal	NT
No follow-up examination (n = 2)									
	18	M							
	8	F							

ALT = alanine transaminase. NT = not tested, IPP = increased postprandial bile acids. Liver and spleen enlargement are given in cm below the costal margin in the medioclavicular line. Biochemical values are upper normal limits.

Figure Pedigrees of the families with familial cholestasis for which the cause is unknown.

mother too has a history of prolonged jaundice in infancy, and she has slight signs of cholestasis even now. The patient from family 5 is 5-years old, and his cholestasis varies. Both his father and grandfather have had episodes of cholestasis. In family 6 our patient died when aged 4 years, and his brother, now 4-years old, has liver cirrhosis with portal hypertension.

In some of these patients abnormalities in bile acids or a positive lipoprotein X, each a sensitive test of cholestasis,^{8,9} are the only pathological findings years after clinically apparent cholestasis.

Discussion

Extrahepatic atresia. Many speculations have been made about the aetiology of extrahepatic atresia. The concept of obstructive cholangiopathy was

introduced by Landing¹⁰ and implies an aetiology common to intrahepatic and extrahepatic cholestasis (a descendent infection of Landing's hypothesis). Some observations make this concept unlikely. In our patients associated malformations differed in the two groups. Congenital heart disease seemed more common in extrahepatic atresia, but other disorders, anomalies, and associations seemed more common in intrahepatic cholestasis. The sex difference remains unexplained. Genetic or familial factors are evident in intrahepatic cholestasis. Although familial incidence of extrahepatic atresia have been described,¹¹ it is rare. Generally one does not find affected relatives among such patients.¹²

Intrahepatic cholestasis.

Incidence

The incidence of intrahepatic neonatal cholestasis in the series reported by Psacharopoulos *et al.*² in a prospective study was 1 in about 3400 live births. Previous estimates have been much lower¹² and more in accordance with our findings. However, it is clear that an unknown number of patients with less severe cholestasis must have passed unnoticed.

Aetiology and prognosis

During the last 10 years several conditions have been recognised to be connected with neonatal intrahepatic cholestasis. In α -1-antitrypsin deficiency neonatal cholestasis is known to occur in about 10% of patients with Pi-type ZZ.¹³ Sveger found an incidence of 1 in 2500 live births with Pi-type ZZ in Sweden. From the birth rate one would expect about 2 patients each year with neonatal cholestasis and α -1-antitrypsin deficiency, assuming the same frequency of the gene in Norway as in Sweden. During the 10-year period 1965 to 1974 we found only 6 such patients. This discrepancy is probably due to the fact that our infants had severe cholestasis in whom a differential diagnosis of extrahepatic atresia was possible.

Our observations indicate a fairly good prognosis provided the patient does not develop cirrhosis in infancy. The tendency for the patient's condition to become normal may also explain why α -1-antitrypsin deficiency is a rare cause of liver cirrhosis in adults.

Arteriohepatic dysplasia is a well-known syndrome with hereditary intrahepatic cholestasis and peripheral pulmonary stenosis, with a characteristic facies and other anomalies.¹⁴⁻¹⁶ The cause of the cholestasis is not known. Alagille *et al.*¹⁵ suggested a hypoplasia of the intrahepatic bile canals as the cause of cholestasis. Others¹⁷ have proposed that the hypoplasia of bile canals in the portal areas might be

caused by a disturbance in the bile acid metabolism or by transport on a high level causing a disuse atrophy of the intrahepatic bile canals.

Elsewhere¹⁶ we have shown that the prognosis in arteriohepatic dysplasia seems good, and has a tendency to improve slowly as time goes by. However, only one patient has normal liver function (at age about 12). Our oldest patient, a 35-year-old man, still has an anicteric cholestasis.

Cholestasis with lymphoedema, as described by Aagaes *et al.*,¹⁸ is a disease that occurs rarely outside Norway. Seven patients in this study had neonatal cholestasis primarily diagnosed as neonatal hepatitis. It is another interesting example of an entity formerly known as neonatal hepatitis, but now recognised to be a distinct disease. Aagaes suggested that lymph vessel hypoplasia in the liver might be the cause of the disease. The prognosis is difficult to ascertain. Two patients died in childhood in this study, but after childhood the prognosis seems better; women have recurrent cholestatic episodes, but men seem to recover completely.

The three conditions are all genetically determined; α -1-antitrypsin deficiency and cholestasis with lymphoedema have an autosomal recessive mode of transmission, while in arteriohepatic dysplasia an autosomal dominant inheritance with varying penetrance probably operates.^{14 16}

In the 7 patients with 'other familial cholestasis' we cannot prove the mode of transmission, but in families 1, 2, and 6 (Figure) none of the parents is affected, but the children seem to have a bad outcome. In the other families each patient has an affected parent, and the outcome for the children seems better. Perhaps this reflects recessive and dominant forms of inheritance. We have no further diagnostic clue in any of these families, but findings of abnormal bile acid metabolism in familial cholestasis^{19 20} point to genetic and metabolic aetiologies. We should like to stress the importance of taking a careful family history and giving a thorough examination in families with patients suffering from neonatal cholestasis. In our experience there are often positive findings which make extrahepatic atresia unlikely. An association between Down's syndrome and neonatal cholestasis is known to exist.²¹ We estimate from the 2 patients in this study (and we saw a third patient later), that the incidence of neonatal cholestasis in children with Down's syndrome is about 10 to 14 times higher than in the rest of the population.

One patient who recovered from liver disease, later presented with a mucopolysaccharidosis resembling the Morquio type (S O Lie, 1978, personal communication), an association previously not reported.

Septicaemia can cause cholestasis in infancy and the cholestasis may dominate the clinical picture. Little is known about the prognosis, but the cholestasis in our 3 patients subsided gradually, and there were no signs of liver dysfunction one year later despite a severe liver infection initially. One patient had toxoplasmosis, and except for the patients with septicaemia, he was the only patient with a proved infectious aetiology. Considering the increasing evidence of other aetiologies and the lack of positive infectious findings, one should probably be careful when talking about infection in neonatal cholestasis of the severe variety. Unquestionably the term neonatal hepatitis has been misleading and should be reserved strictly for those few cases with a proved infectious aetiology.

Concluding remarks

More than half of our patients with neonatal intrahepatic cholestatic jaundice had recognisable aetiological factors and in the survivors the same factors were found in at least two-thirds of them (Table 2).

The overall mortality in the whole group was 43%. Danks *et al.*⁵ found a smaller percentage (30%) in their patients but their observation period was shorter, and many of their patients had a less severe form of cholestasis and carried a better prognosis. In fact, the patients studied by Danks *et al.*⁵ indicated a higher mortality, about 40%, if one considers that patients with cirrhosis or persistent inflammation have a poor prognosis. It is puzzling that 11 out of 16 patients died in early infancy and that 10 of these deaths took place before 1965. This might partly reflect the better intensive treatment of the very ill infant in the last years. Our 3 patients with metastasising hepatoma remind us that a malignant development in children suffering from chronic cholestasis is a considerable risk and should be suspected if the condition of a patient rapidly deteriorates with liver enlargement or ascites.

Of the 8 surviving patients with idiopathic neonatal cholestasis none has developed cirrhosis, and these patients as a whole seem better off than those with familial or genetic factors. Among patients with familial or genetic factors there are 4 with cirrhosis and only 5 with normal liver function tests out of a total of 19 patients (Table 3). Our results support the statement of Danks *et al.*⁵ that progression to cirrhosis and then to death due to liver failure was seen mainly in familial cases and in those with a proved second disease. The outlook for the patients with manifest cirrhosis is probably poor in the long run, and may lead to a higher mortality than 40%. In our entire intrahepatic

group, 12 (about 20%) patients have recovered from cholestasis in infancy (Table 3), and some of the other patients have only minimal biochemical abnormalities. Moreover, there seems to be a tendency for the condition of the patient to improve slowly with time if cirrhosis has not developed, so the number of complete recoveries may eventually be even higher than 20%.

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British Paediatric Association Junior Staff Group Meeting, Friday 2 October 1981

This meeting will be held at Guy's Hospital, London, and is open to all interested junior staff. The guest lecture will be delivered by Professor J S Cameron, professor of renal medicine.

In the evening, there will be a dinner for

participants and their wives/husbands. The meeting is officially recognised for study leave.

The registration fee is £10 (including refreshments and dinner). Applications and papers, which may include case reports as well as research items, should be submitted to the organiser, Dr Richard Trompeter, Department of Paediatrics, Guy's Hospital, London SE1 9RT, by Monday 7 September 1981.