Prognosis of extrahepatic biliary atresia

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SUMMARY We carried out a retrospective investigation of the 89 patients with extrahepatic biliary atresia born in The Netherlands during a 10 year period. Of these 89 patients 10 had a diagnostic laparotomy only. Eight patients had an anastomosis between the proximal bile duct and the intestine, and the remaining 71 had hepatic portoenterostomies. Bile drainage was re-established in 46 (65%). After successful hepatic portoenterostomy the development of cholangitis was the most important determinant of long term survival; five year survival was 54% in the 19 patients who had cholangitis and 91% in the 27 who did not. In the whole group of 71 patients the five year survival was 47%. Seventeen patients were at least 5 years of age at the time of writing, three of whom had had liver transplantation. Three patients have cirrhosis and hyperbilirubinaemia, and the other 11 have normal bilirubin concentrations and normal or slightly raised transaminase activities. To improve these results early surgical intervention in all children with extrahepatic biliary atresia is necessary, as are better methods of prophylaxis and treatment of cholangitis.

Extrahepatic biliary atresia is an important cause of cholestasis in infancy. If unrecognised it leads to death from cirrhosis of the liver at a median age of 12 months.¹ Nevertheless it is a rare disease, the incidence varying from 1:15 000 to 1:22 000 among white races.^{2–5} It is probably the end result of a destructive inflammatory process that results in fibrosis and obliteration of the biliary tract.⁶ This occlusion can extend over a part of, or the whole length of the extrahepatic bile duct system. In the past, cases were divided into correctable and non-correctable, depending on the length of the atretic segment.⁷ Surgical treatment was confined to the 15% with correctable lesions until Kasai described the surgical technique of the hepatic portoenterostomy.⁸ The results of this operation have gradually improved since its introduction. Bile drainage after hepatic portoenterostomy can now be achieved in more than 80% of patients operated on before the 60th day of life.^{9 10} Restoration of bile flow should be an indication of long term success, and indeed individual survival into the second decade after hepatic portoenterostomy has been described.⁹ There have, however, been only a few

reports dealing with the long term prognosis after operation for groups of patients with extrahepatic biliary atresia.^{9–12} We have therefore investigated the long term results of 10 years of surgical treatment for extrahepatic biliary atresia in The Netherlands.

Methods

Data were obtained from the eight Dutch university medical centres. In addition principal hospitals were contacted to ascertain whether any patient was operated on outside the university centres. The hospital notes of all patients were scrutinised by the principal investigator and relevant data such as results of laboratory investigations at presentation, age at operation, and findings at laparotomy were recorded. The anatomy of the diseased biliary tract was described as type I or II (formerly called correctable), and type IIIA, or IIIB (formerly called non-correctable), according to the classification of the Japanese Society of Pediatric Surgeons.¹⁰

Restoration of bile flow after operation was defined as a reduction in the bilirubin concentration

of more than 50% of the preoperative value. A lesser reduction in the bilirubin concentration denoted failure to obtain bile drainage. Episodes of cholangitis were recorded. An arbitrary definition of cholangitis as a pyrexial illness with at least a 50% rise in bilirubin concentration or doubling of the transaminase activities was used. Other complications and age at death were listed. For patients surviving for at least five years, the results of the most recent biochemical tests of liver function were recorded as were the presence or absence of splenomegaly, and the findings at oesophagoscopy (when done). Height and weight were also recorded.

This report includes data of all children with extrahepatic biliary atresia born in The Netherlands between 1 January 1977 and 1 January 1987.² Follow up continued until 1 July 1987. Survival curves were constructed according to Kaplan and Meier¹³ and were compared by the log rank test.¹⁴

Results

From 1 January 1977 to 1 January 1987 a total of 89 patients (49 girls and 40 boys) with extrahepatic biliary atresia were born in The Netherlands, an incidence of 1:19 800.² Some form of the malrotation situs inversus sequence was present in eight patients (9%), malrotation alone in four, malrotation together with situs inversus in two, malrotation, situs inversus and polysplenia in one and situs inversus and polysplenia in one.

Eight patients had type I or II lesions. All these infants had an anastomosis between residual elements of the bile ducts and the small bowel—that is, hepaticojejunostomy or choledochojejunostomy. Operations were performed between the 44th and 87th day of life. Bile drainage was restored in all, but it was inadequate in one who subsequently died. Another patient died of persistent cholangitis. Six patients were alive and well two to eight years after operation, and four of these had at least one attack of cholangitis.

Of the 81 patients with type III lesions, 10 had only exploratory laparotomies, when the diagnosis was established. Seven of these patients were seen during the first three years of the study period at which time the hepatic portoenterostomy was not yet the operation of choice in all centres in The Netherlands. In two cases the porta hepatis could not be visualised, and in a further patient the parents refused more definitive treatment. In the remaining 71 patients the mean age at operation was 68 days (range 25–221). All 71 patients had an original hepatic portoenterostomy (Kasai I), a hepatic portoduodenostomy, or a hepatic portocholecys-

tostomy. Two of the three patients with hepatic portocholecystostomy had conversions to standard portoenterostomies because of inadequate bile flow.

In the 71 patients bile drainage was established in 46 (65%). Of 12 infants operated on after the 80th day of life bile flow was re-established in only six. In 59 infants who had a hepatic portoenterostomy before the 80th day of life, bile flow was re-established in 40 (68%). A further subdivision of this group with respect to the timing of laparotomy, however, showed no further improvement of the results with earlier operation.

At least one attack of cholangitis occurred in 19 of the 46 patients with postoperative bile flow. A further six patients had raised temperatures, persistently high serum bilirubin concentrations, and organisms cultured from their blood postoperatively; these attacks were treated as cholangitis, but were not within the limits of our present definition. No cholangitis was recorded in the patients in whom hepatic portoenterostomy had been unsuccessful. Cholangitis was associated with substantial morbidity and mortality. Eight out of the 19 patients who had cholangitis died, all of infection or the results of infection such as liver cirrhosis with portal hypertension, bleeding oesophageal varices, or liver failure. In the 27 patients without cholangitis there were two deaths due to secondary obstruction, both in the first year after operation. Most important, the five year survival in the patients who had had cholangitis was 54%, compared with 91% in the patients who did not have cholangitis ($p < 0.02$) (fig 1).

In the 71 patients with hepatic portoenterostomies, the five year survival was 47% (fig 2). Because all 25 patients in whom hepatic portoenterostomy failed, died of liver cirrhosis within one year of operation, there is a steep fall in the survival curve

Fig 1 Five year survival after successful hepatic portoenterostomy in 19 patients with and 27 patients without cholangitis.

Fig 2 Five year survival in 71 patients after hepatic portoenterostomy.

during the first year. In two patients orthotopic liver transplantations were carried out before the age of 5 years; the survival rate was corrected for these two patients.¹²

At the time of writing, 17 patients with extrahepatic biliary atresia and hepatic portoenterostomy were alive aged 5 years or more. Three of them had orthotopic liver transplantation because of severe liver cirrhosis and impending liver failure. These three patients were in good general health, with normal growth and psychosocial development. Growth was also normal in the other 14 patients. One patient whose height was below the third centile was of non-white race, and growth was normal by race specific standards. The other child whose height was below normal was severely retarded and lived in an institution after a massive intracranial bleed at the age of 3 weeks caused by vitamin K deficiency, which in turn was caused by the combined effect of cholestasis and breast feeding.¹⁵ With the exception of this child all the others have had normal psychosocial development.

To categorise the liver condition we have divided the long term survivors into four groups (table).

Five patients had normal liver function and no signs of portal hypertension. A further six patients had moderately disturbed transaminase activities, which were stable (n=2), slowly deteriorating (n=2), or improving (n=2). Three patients had clearly abnormal liver function with portal hypertension, and bleeding oesophageal varices that were treated by sclerotherapy. The three patients with transplants all had normal or slightly raised transaminase activities, with no signs of portal hypertension and normal liver on histological examination.

Discussion

For most of the patients with extrahepatic biliary atresia, no treatment was available until Kasai divided the hepatic portoenterostomy.⁸ This operation provided the first chance for cure in infants with the more common non-correctable type of extrahepatic biliary atresia, and it is now clear that the best results are achieved in patients operated on before the 60th day of life.^{9 10} This effect of age on the restoration of bile flow is more pronounced in series operated on by a single surgeon, but it is also discernible in multicentre surveys such as the present one,^{3 16} so the importance of early operation is emphasised. In addition the experience of the surgeon carrying out the hepatic portoenterostomy also contributes to its success,^{3 9} so centres with wide experience are most likely to have the best results.^{3 17}

After the successful restoration of bile flow, cholangitis is the most important determinant of long term survival. The 19 patients with cholangitis had a five year survival of 54% and this rose to 91% in the 27 patients who had not had cholangitis (fig). In addition the three long term survivors with grossly abnormal liver function had all had severe attacks of cholangitis in the first years of life. A reliable method of prophylaxis against cholangitis is therefore needed. Because cholangitis is presumed to be an infection ascending from the small in-

Table Mean measurements of liver function in 17 patients who survived for at least five years after hepatic portoenterostomy

	No of patients	Aspartate aminotransferase (IU/l)	Alanine aminotransferase (IU/l)	Bilirubin (μ mol/l)	γ Glutamyl transferase (IU/l)
All measurements normal	5	26	25	<10	25
Bilirubin normal, all other measurements abnormal	6	75	88	<10	196
All measurements abnormal	3	210	210	64	270
One to three years after orthotopic liver transplantation	3	26	23	<10	15

testine, several methods of prophylaxis are possible; by prevention of intestinal reflux into the Roux-en-Y loop, by increasing the bile flow, and by giving antibiotics. All these methods have been tried,^{9 18-27} but with limited success. Recent reports indicate that external diversion of the bowel loop that is used in the hepatic portoenterostomy does not decrease the incidence of cholangitis.^{9 18 19} For this reason and because of the detrimental effect of chronic external bile drainage on fat absorption and growth, no operations that entail a biliary stoma have been used in The Netherlands. Another variant of the original Kasai procedure, hepatic portocholecystostomy, almost always prevents cholangitis.^{9 18 19-21} This can be used in about a quarter of patients,²¹ but secondary biliary obstruction and bile leakage into the abdominal cavity are common complications.^{20 21} The overall survival with this procedure is no better than that for the standard hepatic portoenterostomy.²² Probably confining the hepatic portocholecystostomy to the few patients with fairly large distal bile ducts, combined with temporary tube decompression of the biliary conduit, is needed to overcome these problems.^{9 23}

Because of the high incidence of cholangitis after corrective surgery for extrahepatic biliary atresia, which cannot be treated adequately by modification of the operation, medical treatment has been tried. There have been several reports of the choleric effect of glucagon²⁴ and prostaglandin²⁵ and their presumed effects on the occurrence of cholangitis. A double blind trial corroborating these data, however, is still lacking. Antibiotic prophylaxis too has been tried. While co-trimoxazole initially seemed promising it did not produce significant results in a large number of children.^{19 26} We have recently used ciprofloxacin as prophylaxis in some patients with frequent attacks of cholangitis and achieved favourable results,²⁷ so this new quinolone might have a potential in lowering the incidence of cholangitis, but this too must be substantiated first in a larger trial.

Our overall five year survival rate of 47% in an unselected group of patients is comparable with the 30-60% five year survival rates reported from other centres.⁹⁻¹² When a group of patients is singled out—for example, patients with good bile flow,⁹ or who have not had attacks of cholangitis (fig 1), better survival rates are obtained, thereby illustrating the importance of these factors in long term survival.

The long term survivors in our survey usually had normal bilirubin concentrations with normal or slightly raised transaminase activities, in common with other series.⁹⁻¹² In about half the patients however, portal hypertension will still

develop^{11 12 28} and 25-50% of this subgroup will ultimately require some form of treatment for bleeding oesophageal varices.^{11 12} Our long term survivors all had an adequate growth, but slightly below average, as is the case in most series.^{11 12} With exceptions due to unrelated causes, the normal psychosocial development in our survey has been confirmed by others.^{9 29}

These results show that it is possible to achieve long term survival with good quality of life in a substantial proportion of the patients with hepatic portoenterostomies. For the remaining group liver transplantation has become a feasible option within the last few years even for the very young,³⁰⁻³³ but although liver transplantation has great potential in the ultimate treatment of extrahepatic biliary atresia the first procedure for all affected children should be hepatic portoenterostomy,³³ because nearly half the patients will live and thrive with no—or mild—liver damage. The proportion in this group will increase with early referral, if treatment is concentrated in a few experienced centres, and if effective methods are found for prevention and treatment of cholangitis.

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