Results of surgery in 88 consecutive cases of extrahepatic biliary atresia[1]

Edward R Howard MS FRCS **Marie Driver** MRCPath
Janet McClement BSC **Alex P Mowat** FRCP
Departments of Surgery, Pathology and Child Health
King's College Hospital, London SE5 9RS

Summary: Of 88 cases of extrahepatic biliary atresia, satisfactory bile flow has been established in 46% of the patients who have undergone portoenterostomies and in 25% of patients with hepaticojejunostomies. Histological analysis of the extrahepatic biliary tissue has not shown a consistent correlation with outcome of operation, except that the patients with one or two large residual ducts lined with columnar epithelium have a better chance of developing bile flow. Cholangitis developed in 43% of the cases, and co-trimoxazole was not shown to have any beneficial effect in a small prospective trial in 18 patients. Severe haemorrhage from oesophageal varices has occurred in 4 jaundice-free survivors. Seventeen patients are now over 3 years of age and thriving but many show persistent elevation of liver enzymes.

Introduction

Atresia of the bile ducts in the newborn results from a destructive inflammatory process which affects part or all of the biliary tract. The aetiology is not known and the condition is probably best described as a form of sclerosing cholangitis (Hays & Kimura 1981). Although the process may occasionally involve the entire extrahepatic and intrahepatic biliary duct system, it usually starts as an extrahepatic lesion which is variable in its distribution. Morio Kasai, working in Sendai, Japan, was the first to show that radical excision of all remnants of the extrahepatic ducts could, in a number of cases, result in bile drainage from small residual channels which communicate with intrahepatic ducts in the porta hepatis (Kasai & Suzuki 1959). These channels may measure up to 300 μm or more in diameter and are detectable on histological examination of tissue resected at operation. Cases in which the atretic process extends to the porta hepatis were called 'non-correctable' before the publication of Kasai's work and his description of the operation of portoenterostomy, in which a Roux-en-Y loop of jejunum is anastomosed to the cut surface of residual extrahepatic bile-duct tissue which has been excised to the level of the liver surface at the porta hepatis (Howard 1979). Segments of bile-containing proximal duct are found in a few patients, and conventional biliary-intestinal anastomoses may be possible in this group. These were known previously as cases of 'correctable' atresia. However, with the advent of the portoenterostomy procedure the terms 'correctable' and 'non-correctable' lost their relevance, and the classification of the Japanese Society of Pediatric Surgery is now used to describe the extent of bile duct occlusion (Hays & Kimura 1981). The classification is complex but is based on three principal lesions: atresia restricted to the common bile duct (Type I); atresia of the common hepatic duct (Type II); and atresia of the right and left hepatic ducts at the porta hepatis (Type III).

This paper concerns the surgical results in 88 children with biliary atresia of all three types who underwent treatment in the 8 years between July 1973 and July 1981.

[1] Paper read to Section of Paediatrics, 22 January 1982. Accepted 9 March 1982

0141-0768/82/060408-06/$01.00/0

Methods

Preoperative investigations included liver biopsy, ^{131}I-rose bengal faecal excretion, radionuclide scanning, and ultrasound examination for choledochal cyst. Common genetic causes of complete cholestasis, particularly antitrypsin deficiency, were excluded by appropriate investigations. Percutaneous cholangiography was performed in a small number of children to assess its value in management and prognosis (Howard & Nunnerley 1979).

The male : female ratio was 42 : 46 and associated gastrointestinal anomalies included 2 cases of malrotation and 2 cases of situs inversus with polysplenia. Nine patients had undergone previous laparotomies at other institutions.

Remnants of the common hepatic duct were identified in 20 cases which were considered to be Type I atresia. Hepaticojejunostomy was used in this group with a 30 cm Roux-en-Y loop of upper jejunum. Fifty-six cases of Type II and Type III atresia underwent hepatic portoenterostomy without a jejunostomy (Kasai I procedure, Howard 1979). Lymphatico-jejunostomy (Fonkalsrud *et al.* 1966) was used in 6 cases and 6 patients were considered inoperable because of a lack of residual tissue in the porta hepatis. (All of the surgical procedures were performed by one surgeon, E R Howard.)

Preoperative preparation in all cases included the administration of neomycin (50 mg/kg/day) and metronidazole (22.5 mg/kg/day) for 24 hours. Gentamicin (2 mg/kg/day) and a cephalosporin (12.5 mg/kg/day) were administered intravenously on the day of operation and continued for 5 days. An oral cephalosporin was continued for one month after surgery.

Long-term postoperative management (Psacharopoulos *et al.* 1980) included supplementing milk feeds with medium-chain triglycerides, and a multivitamin preparation (Ketovite) was given to all cases together with cholestyramine (4 g per day in divided doses) and phenobarbitone (15–45 mg each evening). Intramuscular vitamin K (5mg weekly) and vitamin D (10 000 iu monthly) were also given for 3 months after surgery.

Results

Type I: Bilirubin levels have fallen to normal in 5 of the 20 Type I cases of atresia. Operations were performed before 12 weeks of age in 2 children, but after 12 weeks in 3. Of the cases that failed to benefit from operation, 4 had surgery before and 11 after 12 weeks of age (Table 1). The mean follow-up period for the 5 survivors is 22.1 months (s.d. $\pm$ 18.4) and the liver function tests at most recent follow up, from 1.7 to 44 months after surgery, are given in Table 2.

Types II and III: Of the 56 who underwent portoenterostomy, 52 have been adequately followed up. Twenty-four (46%) have normal bilirubin levels (Table 3). Of this 'successful' group 19 (55%) had surgery before and 5 (27%) after 12 weeks of age (Table 4). The mean follow up for the successful cases is 25.6 months (s.d. $\pm$ 20.8) and the liver function tests at most recent follow up, from 2.8 to 80.1 months after surgery, are given in Table 5.

Table 1. Bile excretion after hepaticojejunostomy in 20 cases of Type I biliary atresia

Age at operation (weeks)	Bile flow	
	Good	Absent
4–7	–	1
8–11	2	3
12+	3	11
	5	15

Table 2. Liver enzyme values in 5 jaundice-free survivors after hepaticojejunostomy (mean follow up 22.1 months, s.d. $\pm$ 18.4)

Enzyme	Range	Mean s.d.
ALP (normal range 60–250 iu/l)	209–1052	540.6 $\pm$326.8
AST (normal range 10–45 iu/l)	33–135	85.2 $\pm$ 42.2
GGT (normal range 0–45 iu/l)	42–831	378.2 $\pm$324.9
Albumen (normal range 35–50 g/l)	34–44	39.4 $\pm$ 4.3

ALP, alkaline phosphatase; AST, asparate transaminase; GGT, gamma glutamyl transpeptidase

Table 3. Results after portoenterostomy in 56 cases of Types II and III biliary atresia

	No. of patients
Successful bile flow	24
Partial success	5
Failure	23
Too early for assessment	3
Lost to follow up	1
Total	56

Table 4. Bile excretion after portoenterostomy in 52 cases related to age at operation

Age at operation (weeks)	Bile flow		
	Good	Poor	Absent
4–7	3	–	2
8–11	16 (55%)	2	11
12+	5 (27%)	3	10
	24 (46%)	5	23

Five patients had a partial response after operation, and the bilirubin levels fell to approximately half of the preoperative values. Two of this group died of hepatic failure at $2\frac{1}{2}$ years and 3 years after surgery, but the surviving 3 are now $2\frac{1}{2}$, $3\frac{1}{4}$ and 6 years of age.

Lymphaticojejunostomy performed in 6 cases early in the series produced no clinical or biochemical improvement and is no longer used.

Pathology

Histology of the tissue excised from the porta hepatis in 58 cases of atresia was assessed for maximum size and numbers of residual ducts, degree of inflammation and cholestasis, and maturity of fibrous tissue. These specimens included surgical Types I, II and III.

The residual ducts were easily divided into two groups. In 15 cases there were 1 or 2 large ducts lined by columnar epithelium (Type A). The majority of specimens (35) showed numerous small ducts lined with cuboidal epithelium (Type B) whilst 8 (Type C) contained no obvious ducts. The surgical results (Table 6) showed that 12 of 15 cases with Type A ducts passed bile successfully (80%) and that 19 out of 35 (54%) of Type B were also successful. Remarkably, 2 of the 8 cases without bile ducts in the excised tissue have passed bile, suggesting perhaps a sampling problem in the tissue available for histology. These results indicate that the presence of large ducts lined with columnar epithelium is of good prognostic significance. An absence of ducts however does not necessarily imply an operative failure.

The number of ducts, the degree of inflammation and cholestasis and the maturity of fibrous tissue did not relate to outcome of operation (Lawrence *et al.* 1981).

Postoperative progress

Cholangitis: Bacterial infection of the liver is a frequent complication of operations for biliary atresia. Diagnosis requires typical histological features of increased polymorphs in portal tracts and within bile ducts, and culture of the organism from a liver biopsy. Since many of our children live far from London, febrile illnesses were often treated initially by family doctors or local paediatricians and, although blood cultures were performed in the majority before antibiotics were administered, few had liver biopsy.

Table 5. Liver enzyme values in 21 jaundice-free survivors after portoenterostomy (mean follow up 25.6 months, s.d. ± 20.8)

Enzyme	Range	Mean	s.d.
ALP	125–1469	592.6	±351.2
AST	42–288	132.1	± 71.5
GGT	15–3000	634.5	±707.0

Table 6. Histological classification of ducts at porta hepatis related to outcome of operation in 58 cases

Result of operation	Histological type of duct			
	A	B	C	Total
Successful	12	19	2	33
Unsuccessful	3	16	6	25
	15	35	8	58

Pyrexial illnesses after operations for biliary atresia may be divided into 3 types: (1) a rise in bilirubin with positive blood cultures; (2) a rise in bilirubin with negative blood cultures; and (3) no rise in bilirubin and a negative blood culture. Types 1 and 2 may be associated with bacterial infection in the liver and should certainly be treated as such, but it remains conjectural whether cholangitis was present in those children who developed pyrexia which settled following antibiotic therapy without deterioration of liver function or impaired bilirubin clearance. For logistical reasons we cannot insist on pre-antibiotic liver biopsy in our cases with suspected cholangitis, and advise intravenous gentamicin and a cephalosporin as soon as blood culture has been performed – hopefully before cholangitis causes irreversible liver damage or becomes chronically established.

In a previous analysis of 47 of the cases in this series cholangitis occurred in 43% (Psacharopoulos *et al.* 1980). The prophylactic effect of co-trimoxazole (Septrin) is now being assessed in a prospective randomized trial. Of 18 patients followed for at least 6 months after surgery 10 developed a pyrexial illness. Only 7 of the 10, however, showed a rise in serum bilirubin levels of 25 μmol/l or more; 3 of these were receiving Septrin whilst 4 were in the untreated group. Prophylactic Septrin therefore has not given any benefit in this small series.

Portal hypertension: Of the 40 survivors in this series 4 jaundice-free children have suffered major haemorrhage from oesophageal varices at the ages of $1\frac{1}{2}$, $2\frac{1}{2}$, $4\frac{1}{2}$ and 5 years. The youngest child was treated by oesophageal transection whilst injection sclerotherapy was successful in the others.

Survival figures: Forty patients are alive at the time of this analysis. Twenty-nine are free from jaundice, 11 between 3 and 5 years of age and 5 between 5 and 9 years. Forty-eight children have died, 46 with cirrhosis and 2 from infection and obstruction in the postoperative period.

Nine of the 88 cases had undergone laparotomy at other institutions before definitive surgery. Three with hepaticojejunostomy and 2 with portoenterostomy have had satisfactory results, whilst 4 have died from liver failure.

Discussion

Holmes (1916) was the first to classify biliary atresia into surgically 'correctable' and 'non-correctable' types. He stated that biliary atresia was not as rare as was supposed and he described the great variation which is found in the obliterative process. He also estimated that at least 16% of recorded cases of biliary atresia were correctable by operation and anastomosis of the biliary tract to the bowel, and was the first to suggest surgical correction as a definitive treatment. Prolonged survival following surgical treatment remained a rare event, however, so that Bill (1978) found only 52 reported successes in Western literature before 1970, and most of these included only a short period of follow up.

Detailed histological studies and the development of new operative procedures for biliary atresia were first reported in the Japanese literature (Kasai & Suzuki 1959) and later in English (Kasai *et al.* 1968). These reports included 3 cases treated successfully before 1957 with the radical operation of portoenterostomy, which included resection of the entire extrahepatic biliary tract and a Roux-en-Y anastomosis of jejunum to the porta hepatis. The operation was based on the observation that small residual bile ducts were frequently found in the fibrous tissue at the very top of the extrahepatic biliary tissue, adjacent to the liver. The oldest survivor from this operation is now over 23 years of age (Hays & Kimura 1980) whereas the average life span for untreated cases is 19 months (Hays & Snyder 1963).

The operation of portoenterostomy provided the first chance for cure of infants with the more common type of 'non-correctable' atresia and it soon became clear that the best results were achieved in infants operated on under 12 weeks of age, before the development of irreversible liver damage.

The operation also provided specimens of the whole of the extrahepatic biliary tract for detailed histological examination. A review of the histological features of 17 such specimens together with wedge liver biopsies has confirmed the severe pathological changes that occur in

biliary atresia (Haas 1978). The portal triads showed fibrosis and variable inflammatory change. Excessive numbers of biliary channels replaced the normal intrahepatic ducts and bile was prominent in both hepatocyte and dilated canaliculi. Five cases possessed residual ducts greater than 200 μm in diameter within the fibrous tissue of the porta hepatis as well as fibrotic profiles of obliterated ducts, and inflammatory changes in residual ductules and glands similar to those described in the intrahepatic ducts. Fibrous tissue was prominent in all areas of the porta hepatis and the remainder of the extrahepatic tissue showed a mixture of complete and incomplete obliteration of bile duct lumen. Liver biopsies performed after operation and successful bile drainage showed a persistence or a progression of intrahepatic pathology in 5 patients.

All patients with biliary atresia have parenchymal liver disease, but successful operations have been followed by improvement in the histological appearances with a reduction in bile duct proliferation, disappearance of bile plugs and improvement in hepatic fibrosis (Kasai *et al.* 1975). Unsuccessful bile drainage, on the other hand, results in progressive fibrosis which is worsened by any attack of infection in the biliary tract from ascending bacterial cholangitis.

In the present series the only prognostic factor found in the histological analysis of resected tissue from the porta hepatis was the presence of large residual ducts lined by columnar epithelium. A majority of patients with these ducts excreted bile. Age at operation was also significant and 55% of infants between 8 and 11 weeks of age drained bile after portoenterostomy, compared with 27% of the group over 12 weeks of age.

A review of published series showed that jaundice has cleared in 35 to 45% of children after portoenterostomy (Kasai *et al.* 1978), whilst in a further 10% bile excretion occurs but remains incomplete. In the latter group the children commonly die before 5 years of age (Hays & Kimura 1980).

Apart from age at operation and histology of the porta hepatis, patient survival depends on freedom from ascending cholangitis. Bacterial infection in the biliary tract is a major problem after operations for biliary atresia (Howard & Mowat 1977) and is diagnosed from the triad of pyrexia, rising serum bilirubin and acholic stools. Many organisms have been cultured from blood or liver biopsy and have included *E. coli*, klebsiella and proteus. The complication is serious, as a deterioration of liver function follows each attack and prompt treatment with broad-spectrum antibiotics is imperative. Cutaneous diversion of bile has been used extensively as a prophylactic measure against cholangitis, but the results are disappointing. Sawaguchi *et al.* (1980), for example, reported a 62% incidence of cholangitis in patients without cutaneous diversion, and a 45% incidence with diversion. Attacks of infection are most frequent within the first 6 to 9 months after operation, and when they occur at a later age a mechanical obstruction in the biliary conduit should be suspected (Lilly & Hitch 1978).

Portal hypertension has caused major haemorrhage in 4 of our 88 cases. Elevated portal pressure is probably found in a majority of biliary atresia cases and measurements taken at the initial operations showed values varying from 170 to 400 mm of water in 19 patients (Kasai *et al.* 1978). Follow-up measurements in 16 jaundice-free survivors showed that in 5 out of 6 patients who remained free of infection the pressure dropped to between 44 and 135 mm of water, whereas in 8 out of 10 with a history of cholangitis the pressure remained greater than 200 mm of water (Kasai *et al.* 1981). In another study 12 out of 28 jaundice-free survivors were found to have oesophageal varices on endoscopy and 6 of these children suffered serious haemorrhage (Hays & Kimura 1981). However, a review of 749 survivors from operation in Japan suggested that only 26 had required treatment for portal hypertension, and the conclusion was drawn that the risk of bleeding was low (Hays & Kimura 1980).

Portoenterostomy has provided a new method for the management of biliary atresia, and Hays & Kimura (1980) have summarized the important factors which continue to influence the prognosis of these children. These factors include the age at which the operation is performed; the extent of hepatic parenchymal damage at initial operation; the size of residual ducts in the porta hepatis; the postoperative complications of ascending cholangitis and portal hypertension; and the experience of the surgeon.

References

Bill A H (1978) *World Journal of Surgery* **2,** 557–559
Fonkalsrud E W, Kitagawa S & Longmire W P jr (1966) *American Journal of Surgery* **112,** 188–193
Haas J E (1978) *World Journal of Surgery* **2,** 561–569
Hays D M & Kimura K (1980) Biliary atresia: the Japanese experience. Harvard University Press, Cambridge, Mass.
Hays D M & Kimura K (1981) *Current Problems in Surgery* **18,** 546–608
Hays D M & Snyder W H jr (1963) *Surgery* **54,** 373–375
Holmes J B (1916) *American Journal of Diseases of Children* **11,** 405–431
Howard E R (1979) In: Abdominal operations. 9th edn. Ed. R Maingot. Appleton-Century-Crofts, New York; pp 2729–2748
Howard E R & Mowat A P (1977) *Archives of Disease in Childhood* **52,** 825–827
Howard E R & Nunnerley H B (1979) *Journal of the Royal Society of Medicine* **72,** 495–502
Kasai M, Kimura S, Asakura Y, Susuki H, Taira Y & Ohashi E (1968) *Journal of Pediatric Surgery* **3,** 665–675
Kasai M, Okamoto A, Ohi R, Yabe K & Matsumura Y (1981) *Journal of Pediatric Surgery* **16,** 152–159
Kasai M & Suzuki S (1959) *Shujutsu* **13,** 733–739
Kasai M, Suzuki H, Ohashi E, Ohi R, Chiba T & Okamoto A (1978) *World Journal of Surgery* **2,** 571–580
Kasai M, Watanabe I & Ohi R (1975) *Journal of Pediatric Surgery* **10,** 173–182
Lawrence D, Howard E R, Tzannatos C & Mowat A P (1981) *Archives of Disease in Childhood* **56,** 460–463
Lilly J R & Hitch D C (1978) *World Journal of Surgery* **2,** 581–587
Psacharopoulos H T, Howard E R, Portmann B & Mowat A P (1980) *Archives of Disease in Childhood* **55,** 851–856
Sawaguchi S, Akiyama H & Nakajo T (1980) In: Cholestasis in Infancy. Ed. M Kasai & K Shiraki. University of Tokyo Press, Tokyo; pp 371–379