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The Treatment of Biliary Atresia in Europe 1969-1995

EDWARD R. HOWARD and MARK DAVENPORT

Department of Paediatric Surgery, King's College Hospital, Denmark Hill, London SE5 9RS, UK

HOWARD, E.R. and DAVENPORT, M. *The Treatment of Biliary Atresia in Europe 1969-1995.* Tohoku J. Exp. Med., 1997, **181** (1), 75-83 —— European studies of biliary atresia have suggested that the aetiology is heterogeneous. Histological studies of the liver and biliary remnants excised at portoenterostomy have failed to identify any prognostic features except for the size of bile ductules in the porta hepatis. Most of the major series have confirmed that there is a relationship between age at portoenterostomy and clearance of jaundice which has been achieved in more than 67% of infants under 10 weeks of age. Cholangitis reduced survival and bleeding from esophageal varices has occurred in more than 19% of long-term survivors. The 5-year jaundice-free survival rate after portoenterstomy is 37% and the 10 year rate is 18%. It is predicted that these survival rates will improve. Orthotopic transplantation now results in long-term survival in 70% of patients who fail the portoenterostomy operation and long-term survival is now achieved in a majority of children born with biliary atresia. ——
portoenterostomy; aetiology; prognosis; survival

Treatment of biliary atresia with the portoenterostomy operation was established in Japan for at least 10 years before its general acceptance in Europe and the USA and there were no reports of significant survival from European centers until several years after the original description by Kasai and Suzuki (1959). Long-term survival after portoenterostomy was confirmed in the extensive survey of Japanese results published by Hays and Kimura (1980) which also included data on the complications of treatment such as cholangitis and portal hypertension. It is now possible to analyze the treatment of biliary atresia in Europe during the last 26 years and to compare it with the experience in Japan.

Early results

The results of portoenterostomy were extremely variable at first and opinion was divided on the efficacy of the procedure. The early results in the UK were

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Address for reprints: Edward R. Howard, M.D., Department of Paediatric Surgery, King's College Hospital, Denmark Hill, London SE5 9RS, UK.

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analyzed by McClement et al. (1985), and the effectiveness of portoenterostomy was shown to be related to the experience of the surgeon. The radical nature of the dissection in the porta hepatis was not widely appreciated at first and surgeons performing only one portoenterostomy per year achieved satisfactory biliary drainage in only 18% of cases. This compared with a jaundice-free survival rate of 45% in centers treating more than 5 cases per year.

Early French results-1983

In the 1983 Sendai Symposium Alagille et al. (1983) presented their results for 1968 to 1982. The 5 year survival rate was 36.6%. A temporary enterostomy was used in this series to try and reduce episodes of cholangitis which occurred in 27% of the cases. The authors noted that portal pressure was always elevated when measured during the initial surgery but did not appear to be worsened by episodes of cholangitis.

Surgical wedge biopsies of the liver were taken from 20 children 5 to 8 years after restoration of bile flow and clearance of jaundice. Disappointingly the biopsies showed micronodular cirrhosis in 13 and macronodular cirrhosis in 7 of the cases. It was also reported that percutaneous cholangiography in late survivors revealed a bizarre arrangement of bile ducts which were plexiform and irregular. These ducts drained towards the hepato-jejunal anastomosis and were commonly associated with hyperplastic lymphatic channels and ductal cystic change was noted in two cases. The authors reported that 44 long term survivors were leading almost normal lives.

Preoperative investigation in Europe

The standard method of investigation of conjugated hyperbilirubinaemia in Europe has included ultrasonography, percutaneous liver biopsy (Manolaki et al. 1983), and hepatobiliary nuclide excretion scans, (Dick and Mowat 1986). Endoscopic retrograde cholangiography has been evaluated in neonatal jaundice by Wilkinson et al. (1991) who reported the demonstration of normal bile ducts in 4/9 jaundiced infants. In 4 cases the investigation suggested atresia but a patent biliary tract was demonstrated at surgery in one of these. One examination was technically unsatisfactory. An accurate examination was therefore achieved in 7/9 cases (78%).

Studies of aetiology

A possible toxic effect of monohydroxy bile acids on the biliary tract of fetal and newborn infants was investigated in rabbits (Jenner and Howard 1975). The injection of the monohydroxy bile acid lithocholic acid into pregnant animals cause obstructive lesions in the biliary tract of two of the offspring.

Desmet and Callea (1991) considered biliary atresia to be a disease in which inflammatory destruction of the bile ducts occurred after the completion of their

TABLE 1. *Endoscopic retrograde cholangiography in the diagnosis of biliary atresia*

Normal bile ducts	4
"Absent" bile ducts	4 (3 confirmed atresia)
Inconclusive	1 (normal ducts at surgery)
Accurate in 7/9 (78%)	

(Wilkinson et al. 1991)

development. They pointed out that epithelial damage and destruction is observed within ducts with a mature tubular shape but that in 20 to 25% of cases a variable number of intrahepatic bile ducts show features reminiscent of "Ductal Plate Malformation". This consists of the partial or complete persistence of the original embryonic form of the intrahepatic ducts.

Silveira et al. (1993), tested the hypothesis that there might be host genetic factors in aetiology by studying the HLA system in 55 children with biliary atresia. They found a significantly higher frequency of HLA-B 12, of haplotypes A9-B5 and A28-B35, and of their disequilibrium values compared with controls. This study suggested that immunogenetic factors may have a role in determining susceptibility to the disease and the results of the study also indicated that HLA frequencies were different in those with and without major extrahepatic anomalies.

Further evidence of an embryological origin for biliary atresia was reported by Tan et al. (1994), who showed from embryological studies that there were similarities between the abnormal ductules within the porta hepatis in biliary atresia and the developing bile ducts in the first trimester. It was concluded that biliary atresia may be the result of a failure of the remodelling process at the hepatic hilum with persistence of fetal bile ducts and that bile leakage from these abnormal ducts may trigger a severe inflammatory reaction.

Davenport et al. (1993), analyzed the case records of 23 infants with polysplenia syndrome and biliary atresia together with 4 other cases of splenic abnormality which included 2 cases of asplenia. They agreed with the conclusion of Silveira et al. (1993) that children with biliary atresia and splenic malformation (BASM syndrome) probably represented a sub-group which may have a different cause from the more common "non-syndromic type of atresia".

Complications of surgery

The main complications of surgery continue to be ascending bacterial cholangitis and portal hypertension.

Cholangitis. The effects of cholangitis are variable. During the 1983 Sendai Symposium Alagille et al. (1983) suggested that the number and severity of episodes of infection do not influence long-term growth. In contrast other

European authors have reported a significant deleterious effect on survival from repeated episodes of cholangitis. The two largest studies are summarised in Table 2. Similar incidences of cholangitis in long-term survivors have been seen in our own series (Table 3).

It is generally agreed that episodes of infection must be treated rapidly and effectively with broad spectrum antibiotics but no effective methods of prophylaxis have been proven. Ecoffey et al. (1987), pointed out that cholangitis is seen most frequently in the children who have good bile flow after portoenterostomy, (70%) and least frequently in those who have no bile flow, (13%). Temporary enterostomies have mostly been abandoned because of bleeding complications from the stoma circumference, the additional problems they may cause during transplantation operations and the failure of the procedures to prevent infection in many cases.

Portal hypertension. Portal hypertension can be identified in a majority of infants at their at their first operation for biliary atresia. Valayer (1983), for example reported elevated portal pressure, measured via the umbilical vein or a branch of a colic vein, in 72.1% of 151 infants. Nine patients had repeat pressure measurements 2–7 years later and significant increases in pressure were recorded in 7. Fortunately the elevation in portal pressure does not always cause variceal bleeding and Table 4 analyses the frequency of this complication in the three largest European studies of survivors.

Significant varices therefore occur in approximately half of the long-term survivors. A previous analysis of the King's College Hospital series showed that there was no correlation with type of atresia, liver histology or age at surgery although the patients who had varices did tend to have worse biochemical liver

TABLE 2. *Relationship between repeated attacks of cholangitis and survival after portoenterostomy*

Study	Survivors	
	Cholangitis	No cholangitis
Houwen et al. (1989) (Netherlands)	54%	91%
Caccia et al. (1991) (Italy)	36%	54%

TABLE 3. *Incidence of cholangitis in survivors after portoenterostomy — King's College Hospital, London*

	Cholangitis	
Survival over 10 years	17 patients	7 (41.2%)
Survival 5 to 10 years	71 patients	26 (36.6%)

TABLE 4. *The incidence of esophageal varices and bleeding in long-term survivors after portoenterostomy*

Study	Survivors	Varices	Bleeding
Laurent et al. (1990) (France)	40	24 (60%)	15 (37%)
Dessanti et al. (1991) (Italy)	30	13 (43%)	?
*Howard and Davenport (1996) (UK)	51	21 (41%)	8 (16%)
Total	121	58 (48%)	23 (19%)

*Unpublished data.

function tests (Davenport et al. 1991).

Prognostic studies after portoenterostomy

Prognostic data on the chances of long-term survival after portoenterostomy have remained elusive apart from the data on cholangitis which suggests that frequent attacks are associated with a poor prognosis and the observation that age at surgery is related to bile flow. Five European studies which have attempted to define prognostic criteria are summarized in Table 5 and the results showing the beneficial effects of early operation are listed in Table 6.

The figures in Table 6 substantiate the results from centers outside of Europe which have also shown the advantage of early operation for biliary atresia.

Long-term survival after portoenterostomy

Results from the three largest series of cases in Europe show that more than one third of the portoenterostomy cases will survive for more than 5 years and that most of these will be free of jaundice (Table 7).

The 10 year figures also show that approximately one third will survive but a significant number of cases will have suffered a deterioration in liver function and the number free of jaundice will be reduced to approximately 18%. These

TABLE 5. *A summary of prognostic studies concerning portoenterostomy*

Lawrence et al. (1981) (UK)	Bile drainage not related to histology of porta hepatis
Lopez Gutierrez et al. (1991) (Spain)	Bile flow not related to histology of liver or porta hepatis
Lopez Gutierrez et al. (1992) (Spain)	Prognosis related to portal and hepatic arterial flow
Kang et al. (1993) (UK)	No relation between hepatic histology at portoenterostomy and development of varices
Trivedi et al. (1993) (UK)	Progresive liver damage associated with increasing levels of serum hyaluronic acid

TABLE 6. *The relationship between the age at which portoenterostomy is performed and the restoration of bile flow*

Caccia et al. (1983) (Italy)	Under 10 weeks 31/48 (60%)	Over 10 weeks 4/10 (25%)
Houwen et al. (1989) (Netherlands)	Under 11 weeks 40/59 (68%)	Over 11 weeks 6/12 (50%)
Mieli-Vergani et al. (1989) (UK)	Under 8 weeks 12/14 (86%)	Over 8 weeks 13/36 (36%)
Gauthier et al. (1991) (France)	Under 8 weeks 31/50 (62%)	Over 8 weeks 52/143 (36%)
Total	114/171 (67.6%)	75/207 (37.2%)

TABLE 7. *Collected 5 years survival figures after portoenterostomy*

	Number	5 year (survival)	No jaundice
Houwen et al. (1989) (Netherlands 1977–87)	71	17 (24%)	11 (15%)
Gauthier et al. (1991) (France 1984–87)	69	31 (45%)	23 (33%)
*Howard and Davenport (1996) (UK 1980–89)	184	71 (39%)	68 (37%)
Total	324	119 (37%)	102 (31%)

*Unpublished data.

figures compare very well with collected series from countries outside of Europe. In a recent survey of the results from 6 countries (Howard 1995) which included the USA, Australia and Taiwan, the long term survival in 774 cases varied from 17 to 57%. The mean overall survival was 32% which is almost identical with the 10 year European figure of 34% shown in Table 8.

TABLE 8. *Collected 10 years survival figures after portoenterostomy*

	Number	10 year (survival)	No jaundice
Laurent et al. (1990) (France 1968)	122	40 (33%)	21 (17%)
Caccia et al. (1991) (Italy 1975–80)	46	13 (28%)	8 (17%)
*Howard and Davenport (1996) (UK 1973–79)	39	17 (43%)	9 (23%)
Total	207	70 (34%)	38 (18%)

*Unpublished data.

TABLE 9. *Results of liver transplantation for biliary atresia in Europe*

	Number	Survivors
Beath et al. (1993) (UK)	39	28 (72%)
Martinez et al. (1993) (Spain)	32	22 (70%)
Total	71	50 (70.4%)

Liver transplantation

It is now clear that a significant number of patients will require hepatic transplantation after portoenterostomy. A small proportion of cases will fail to drain any bile and will require urgent transplantation in the first year of life. Others, in whom satisfactory bile drainage is established, remain at risk from portal hypertension and progressive liver failure and may become candidates for liver replacement after several years of reasonable health. Survival after transplantation in now commonly over 70% and the results of two European series are illustrated in Table 9.

Conclusion

The European experience of the management of biliary atresia has confirmed that the portoenterostomy operation provides long-term biliary drainage in more than 30% of cases. It also confirms the value of transplantation in the management of patients who either fail to drain bile or who progress to liver failure.

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