Strategies to improve the outcome of biliary atresia

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Twenty-year transplant-free survival among patients with biliary atresia

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Chapter 5

ABSTRACT

Background & Aims

Surgical treatment with Kasai portoenterostomy has improved the prognosis for patients with biliary atresia, although most ultimately require liver transplantation. Well-described patients with long-term, transplant-free survival are scarce; we assessed liver status and health perception among Dutch patients who survived 20 years after therapy and investigated whether rate of transplant-free survival increases with time.

Methods

Using the Dutch national database for biliary atresia, we identified 104 patients, born from 1977 to 1988. We collected data on clinical characteristics, liver biochemistry, and ultrasonography from all transplant-free patients who were alive at an age of 20 years (n=28, 27% of the patients). General health perception data (RAND-36) were collected at the last examination.

Results

The 20-year transplant-free survival rate increased from 20% (10/49) in the 1977–1982 cohort to 32% (18/55) in 1983–1988 cohort (P=.03). Twenty-one percent of the long-term survivors (6/28) had normal liver biochemistry test results and no clinical or ultrasonographic signs of cirrhosis. General health perception of female, but not male patients, was lower, compared with controls (RAND-36 score, 54±14 vs 74±18; P=.005).

Conclusions

More than 25% of patients with biliary atresia survive at least 20 years without liver transplantation in The Netherlands. Female patients with biliary atresia have a reduced perception of their health, compared with control patients. Twenty percent of long-term survivors are symptom-free, without clinical or ultrasonographic signs of cirrhosis or portal hypertension.

INTRODUCTION

Biliary atresia (BA) is an important cause of cholestasis in infancy, caused by a destructive inflammatory process resulting in fibrosis and obliteration of the biliary tract. Before the development of surgical treatment, death from cirrhosis occurred in 50-80% of the patients within one year.[163]

Three subtypes of BA are distinguished, classified according to the level of most proximal biliary obstruction. In type I, bile ducts are patent from the porta hepatis to the common bile duct and cystic duct, and in type II to the common hepatic duct. These types account for ~10% of BA patients. In type III, the most prevalent type (~90%), the obstruction of the extrahepatic biliary tract extends into the porta hepatis.[60] In ~20% of the BA patients anatomical variants are found, including splenic malformation in the Biliary Atresia Splenic Malformation syndrome (BASM). Venous and cardiac malformations, heterotaxy, and intestinal malrotation are also found in BASM.[31,60]

Initial treatment of BA is mainly surgical, consisting of hepaticojejunostomy or choledochojejunostomy in type I and II, and Kasai portoenterostomy in type III.[82] When bile flow can not be restored or when, despite a successful restoration of bile flow, liver fibrosis progresses and complications of cirrhosis occur, orthotopic liver transplantation (OLT) is necessary. OLT is a technically challenging procedure in small children. Nowadays, BA accounts for ~50% of the indications for pediatric OLT throughout the Western world.[108]

With surgical treatment of BA, transplant-free survival is possible. Many reports describe the results between 1 and 5 years after surgery. However, data on the long-term survival rates (≥20 years after surgical correction) and especially the clinical condition of those who survived beyond 20 years without OLT are scarce.[57,103,154] Furthermore, only limited information is available on health or health-related problems in this patient group. We, therefore, evaluated the clinical condition of a cohort of Dutch BA patients, who were transplant-free at the age of 20 years, and we assessed the general health perception (GH) of these patients at latest follow-up.

PATIENTS AND METHODS

Between January 1st 1977 and December 31st 1988, 106 patients were diagnosed with BA in the Netherlands. The diagnosis of BA was confirmed in all patients by intraoperative cholangiography and pathology of the liver and biliary remnants. Surgery was performed in one of the six Dutch university medical centers specialized in pediatric surgery. The short-term results of the majority of this cohort were described in 1989.[68] The Dutch OLT programme started in 1979 in adults and in 1982 in children.

Thirteen patients had a type I or II BA; nine underwent a hepaticojejunostomy or a choledochojejunostomy. In four cases, a portoenterostomy was performed. Eighty-three patients were classified as type III BA and underwent the classic Kasai portoenterostomy.

Follow-up

We examined transplant-free survival 20 years after surgical correction, and at last follow-up. Data were collected from patients' hospital records, including biochemical evaluation of liver function (total bilirubin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), γ-glutamyl transferase (γGT), albumin, prothrombin time (PT)) and abdominal ultrasound to assess cirrhosis and portal hypertension, as well as oesophagoscopy to assess oesophageal varices and portal hypertension. Portal hypertension was considered present when at least one of the following characteristics was present, apart from a liver with cirrhotic aspect: decreased velocity or reversal

of the direction of blood flow in the portal vein, presence of collateral veins and enlargement of the spleen at ultrasound, presence of oesophageal varices at oesophagoscopy.

Biochemical parameters were considered normal within the following ranges: total bilirubin <17 µmol/L; ASAT <40 U/L; ALAT <45 U/L; γGT <55 U/L in males and <45 U/L in females; albumin >3.5 g/dL; INR below 1.1. During the most recent follow-up, patients were asked to provide information on current employment or education. Additionally, they completed the five items concerning GH of the RAND-36 questionnaire, which has been validated in the Dutch population.[190] The study was performed according to the guidelines of the Medical Ethical Committee of the University Medical Center Groningen.

The GH of BA patients was compared with that from an age-matched comparison group and gender differences were evaluated.[154] To assess a possible relationship with clinical condition, GH was correlated to serum total bilirubin and ASAT values and presence of portal hypertension and cirrhosis as measures of cholestatic disease severity.

Statistics

Survival rates were analyzed with the Kaplan-Meier method and compared using the log-rank test. Continuous data were compared using Mann-Whitney U test. Comparison of GH scores of patients to the comparison group was performed by unpaired t-tests. To assess the clinical relevance of differences in health perception, effect sizes were calculated by dividing the difference between means by the pooled standard deviation.[24] Effect sizes between 0.20-0.49 were considered small, 0.50-0.79 medium and ≥0.80 large. Pearson's correlation analyses were performed to examine relationships between variables. All tests were two-tailed. Differences and relationships were considered significant at a p-value <0.05. Analyses were performed using SPSS 16.0

RESULTS

Twenty-year survival after surgical correction

Of the 106 children (62 girls), two were lost to follow-up at the ages of four (address not found) and six years (moved abroad). Twenty-eight of the 104 patients (27%) survived for 20 years without OLT (Table 1). Sixteen of these patients were female (57%). Overall 20-year survival with and without OLT was 43% (45/104). OLT was performed in 23% (24/104) of the patients before the age of 20. The survival after OLT was 71% (17/24). Fifty percent (52/104) of the patients died without OLT, mainly because the technique was not yet available in small children at that time.

Transplant-free 20-year survival increased markedly over time. In the 1977-1982 cohort, 20% (10/49) survived for 20 years without OLT, and 33% (18/55) in the years 1983-1988 (p=0.03, table 1). In table 2, the 20-year survival data are compared to available international data.

Twelve percent (12/104) of the patients had type I or II BA (Table 3). Survival of type I/II and type III was not statistically different (p=0.15). Seven percent (7/104) of all patients had characteristics of BASM (1 type I/II BA, 6 with type III), of whom 29% (2/7, both type III) survived beyond the age of 20 without OLT being necessary.

In Figure 1, the twenty-year transplant-free survival rates are shown for the different age groups at Kasai portoenterostomy. Survival was significantly lower when patients were operated on after 75 days of age when compared to 60-75 days of age (11±6% vs. 42±10% respectively, p=0.03). Two of the long-term survivors (7%) underwent surgery after the age of 90 days (96 and 113 days). The peroperative liver biopsy reports of some of the long-term survivors indicated severe cholestasis and fibrosis.

Table 1: Outcome of BA patients at 20 years after surgical correction in two cohorts

Overall number of patients	1977-1982 n=49	1983-1988 n=55	p-value
Median age at surgery (day)	60 (25-222)	58 (35-126)	0.48
Type I/II (%)	3 (6%)	9 (16%)	0.13
BASM (%)	4 (8%)	3 (5%)	0.70
Alive with native liver at 20 years	10 (20%)	18 (33%)	0.03
OLT < 20 years	8 (16%)	16 (29%)	0.16
Death	31 (63%)	21 (38%)	0.04

Table 2: International data on long-term transplant-free survival of BA patients

	Period	Number of patients with surgical correction	Transplant-free survival (20 years)	OLT before the age of 20 years	Overall survival (20 years)
France [103]	1968-1983	271	23%	32 (12%)	-
Japan [128]	1970-1986	80	44%	5 (6%)	49%
Sendai, Japan [129]	1953-1993	289	22 (8%)	-	-
The Netherlands (present study)	1977-1982	49	10 (20%)	8 (16%)	17 (35%)
	1983-1988	55	18 (32%)	16 (29%)	28 (51%)
	1977-1988	104	28 (27%)	24 (23%)	45 (43%)

Table 3: Outcome the different BA subtypes at 20 years after surgical correction

Overall number of patients	Type I/II 12 (12%)	Type III 92 (88%)	p-value
Alive with native liver at 20 years	5 (42%)	23 (25%)	0.15
Alive with native liver and normal serum bilirubin (< 17 µmol/L)	3 (25%)	13 (14%)	0.18
OLT < 20 years	1 (8%)	23 (25%)	0.28
Death	6 (50%)	46 (50%)	1.00
Median age at surgery (day) of patients alive with native liver at 20 years	60 (48-68)	57 (35-113)	0.95

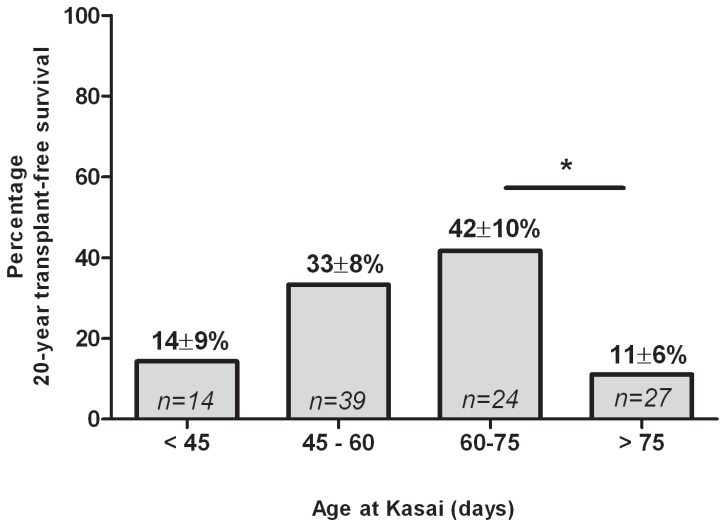

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Figure 1: Twenty-year transplant-free survival of BA patients according to age at Kasai portoenterostomy. Log-rank test, <45 vs. 45-60 days, p=0.24; 45-60 vs. 60-75 days, p=0.62; 60-75 vs. >75 days, p=0.03, <45 days vs. 60-75 days, p=0.18.

Six of the 28 patients (21%) did not have any clinical or ultrasonographic signs of liver cirrhosis (median age at surgery 56 days, range 35-68, two were on UDCA). Four of these six patients had normal liver biochemistry, one patient had a transient slight elevation of transaminases and one patient had isolated elevated γGT levels (~65 U/L). Two patients had an intrahepatic lesion, probably an adenoma, which had been stable in size for many years and was not associated with portosystemic shunting. The levels of alpha-fetoprotein were not elevated. Thirteen patients (46%) experienced one or more episodes of cholangitis during their lives. Seven of these patients (54%) had disturbed liver biochemistry. Of the patients without documented cholangitis, 73% (11/15) had disturbed liver biochemistry.

Liver condition at 20-year follow-up.

At the age of 20 years, 36% (10/28) of the patients with 20 years transplant-free survival had normal total serum bilirubin, transaminase and γGT levels (Table 4). In 21% (6/28) of the patients total serum bilirubin levels were within normal limits with slightly elevated transaminase and/or γGT levels. In the other 12 patients, total serum bilirubin levels were elevated (range: 19-107 μmol/L) combined with elevated serum transaminase and γGT levels in 11 patients (range: ASAT 46-160 U/L; ALAT 47-177 U/L; γGT 68-392 U/L. Prothrombin time was slightly increased in 6 patients, together with hyperbilirubinemia in 4 patients. However, the International Normalized Ratio did not exceed 1.2 in any of the patients. The serum albumin level was below 3.5 g/dL in one patient, in combination with increased total bilirubin levels (97 μmol/L). Six of the 28 patients were using ursodeoxycholic acid at the age of 20 (21%), of whom four had normal liver biochemistry parameters.

Table 4: Clinical characteristics at the age of 20 of the 28 transplant-free BA patients

Condition	Number of patients	Percentage
Normal bilirubin (< 17 umol/l)	16	57%
Normal bilirubin, ASAT, ALAT, γGT	10	36%
Absent signs cirrhosis	6	21%
Cholangitis	13	46%
Portal hypertension	13	46%
Spleen enlargement	15	54%
Oesophageal varices; bleeding	10; 2	36%; 7%
Completed regular education	25	90%

Portal hypertension

Signs of portal hypertension were present in 46% (13/28) of the patients (Table 4). Eleven of them had elevated serum transaminase and γGT levels. Oesophagoscopy was performed in all patients with signs of portal hypertension on ultrasonography. Varices were detected in 77% of the patients (10/13); two of them experienced one episode of variceal bleeding. Unfortunately, the age of onset of portal hypertension was not documented in most cases.

Outcome at last follow up

At the most recent follow-up, 26 of the 28 BA patients described in this report were still alive with their native liver. The median age at latest follow-up was 23.8 years (range: 20.2-31.4). Two of the patients (7%) underwent OLT at the ages of 20 and 24 years. OLT had become necessary because of end-stage liver disease and frequent cholangitis, and because of hepatopulmonary syndrome, respectively. Presently, one patient is listed for OLT. Another patient with BASM (situs inversus, polysplenia and malrotation) was diagnosed with non-compaction cardiomyopathy at the age of 25, a condition which can be associated with heterotaxy.[200] The other patients did not show clear progression of liver damage or cirrhosis at last follow-up as compared with the evaluation at 20 years of age.

Functioning

Information on status of employment or education was available for 25 patients. Twenty-two (88%) are employed or attending college. Two patients (8%) are physically and mentally compromised and need specialised care, one because of infantile encephalopathy with unknown cause, the other secondary to a vitamin K deficiency intracranial hemorrhage at the age of six weeks. Another patient (4%) is attending specialised education. One patient has a relapsing addiction to various substances but is currently employed. Three patients are known with complaints of joint pain and fatigue for which, after extensive investigations, no explanation was found. At the time of writing, one female patient had given birth to a healthy baby and two were pregnant. So far, no deterioration of the clinical condition has been detected during pregnancy.

At last follow-up, twenty-four of the 26 transplant-free patients were invited to complete

the GH items of the RAND-36. Two patients were mentally compromised and not invited. Nineteen patients (79%) responded. The mean score of patients was 64±18 compared to 75±17 in the comparison group (p=0.01; effect size 0.63; Table 5). Women, but not men, scored significantly lower than their counterparts in the comparison group with a large effect size (p=0.005; effect size 1.15). GH did not correlate with total serum bilirubin or ASAT values, presence of cirrhosis or portal hypertension (r=-0.007, p=0.98; r=0.093, p=0.72; r=0.119, p=0.672 and r=-0.05, p=0.853, respectively).

Table 5: Scores (mean±SD) of BA patients on general health perception items of the RAND-36

	BA patients	n	Comparison group[154]	n	p-value	Effect size
Age (years)	24.8±2.7		24.2±3.8			
all	64±18	19	75±17	500	0.01	0.63
female	54±14	11	74±18	238	0.0005	1.13
male	78±13	8	76±16	262	0.68	0.12

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DISCUSSION

Since 1977, the transplant-free 20-year survival of BA patients treated with surgical correction has increased from 20% to 33% in The Netherlands. The 20-year survival rate was not significantly associated with the age at surgical correction. Interestingly, one fifth of the 20-year transplant-free survivors had no signs of liver cirrhosis and a normal liver biochemistry. Female, but not male, transplant-free BA patients had a lowered GH when compared to a reference group.

The 20-year transplant-free survival rates in the cohort 1977-1982 presented in this report were similar to those reported from France in the same period, 20% vs. 23%, respectively. In the cohort 1983-1988 transplant-free survival had increased to 32%. However, survival remained lower than that reported from Japan (58%).[103,154]

Increased surgical experience and improved perioperative management might in part explain the improved transplant-free survival. The first Kasai portoenterostomy in The Netherlands was performed in the early seventies and therefore a rather novel technique at the beginning of the study period. The use of prophylactic antibiotic treatment to prevent ascending cholangitis and subsequent deterioration of liver function has been suggested.[69] However, as its effectiveness was unclear and as it was shown to cause microbial resistance[43], prophylaxis was not generally used in the present cohort. By the end of the study period, some novel treatment strategies were described which might account in part for the increased transplant-free survival rate of patients born in that period: ciprofloxacin and ursodeoxycholic acid.[69,183] Unfortunately, due to lack of detailed data on medication use in the present patients, analysis of effectiveness was not possible. Postoperative corticosteroids were not used in the current study population.

Another factor that likely contributed to the increased survival is the improved management of portal hypertension. Rubber band ligation has become available in the 90s as an alternative to sclerotherapy with fewer complications. Since 1980 it has become clear that propanolol can prevent variceal bleeding but the effects in children are still not objectivated.[114] Unfortunately, we do not have data on the longitudinal management of portal hypertension. Most patients with portal

hypertension are managed by surveillance endoscopy and propranolol is used in selected cases. Early surgical correction is associated with a better outcome in terms of clearance of jaundice and survival with native liver.[26,60,128] In our study, late surgery (>75 days) indeed had a worse outcome. In our study we identified patients operated on at the ages of 96 and 113 days respectively, who were transplant-free at the age of 20. This observation confirms previous reports that portoenterostomy can be a successful initial step in treatment, even in late presenting patients.[20,27] We could not demonstrate a beneficial effect of surgery <45 days, but this may be attributable to the low statistical power as the group consisted of 14 patients. Other factors that might be of importance are an increased technical difficulty in very small infants in combination with a rather novel technique, or rapidly progressive disease in early presenting infants.

We analyzed transplant-free survival in the various subtypes of BA. Survival rates tend to be higher in patients with type I or II BA (42% in type I-II; 25% in type III). These figures are comparable to those form a large French cohort, but inferior to numbers from Japan, who reported a 100% 20-year transplant-free survival 7 patients.[103,154]

Controversy exists in the literature regarding the survival of patients with BASM. Some papers report a survival similar to the non-syndromic form of BA,[4,147] others report a worse prognosis.30 Of note, in our study group, two of the nine BASM patients were transplant-free at the age of twenty, with normal serum bilirubin levels. One of those patients has polysplenia, situs inversus, intestinal malrotation, and developed non-compaction cardiomyopthay at the age of 25. The other patient had polysplenia, intestinal malrotation and a preduodenal portal vene. Thus, the presence of BASM does not exclude a favourable outcome. Furthermore, signs of severe cholestasis and fibrosis in the peroperative liver biopsy specimen are not necessarily indicative of a poor prognosis; as such features were encountered in some of the current long-term survivors.

Interestingly, a rather substantial number of the patients (6/28; 21%) did not have abnormal liver biochemistry or signs of liver cirrhosis at the age of 20. All these patients still had normal biochemistry and a normal liver on ultrasound at latest follow-up, the oldest of these patients now being 28 years old. Only prolonged follow-up will reveal whether Kasai portoenterostomy is a definitive cure in this subset of patients (~5% of all BA patients). OLT may become necessary in the longer term in patients who currently have mild to moderate liver biochemistry disturbances.

The risk and prevalence of cirrhosis-related tumours in BA patients is still unknown.[60,176] Only follow-up of long-term transplant-free survivors and systematic investigation of explanted livers might elucidate the incidence of hepatic malignancies. The development of potentially life-threatening complications of cirrhosis, such as oesophageal varices and hepatopulmonary syndrome, need to be monitored also.[60,176] We argue that all long-term transplant-free BA survivors require regular (probably at 6 or 12 months intervals) review with abdominal ultrasound scans, as is recommended in the AASLD practice guideline on hepatocellular carcinoma, until the true prevalence of tumours after BA is known and the effect of surveillance can be assessed.[16] Gallstones (intrahepatic hepatolithiasis, or stones in the gallbladder remnant) have been described as a frequent finding in BA patients but did not occur in our study population, neither did other comorbidities.[103,129,174]

Quality of life remains a general concern in patients with chronic liver disease. In our study, the majority of the patients either had paid employment or was attending college. Nevertheless, measurement of GH showed that women report having a lowered GH than a comparison group, whereas the GH in men was not deviant. We speculate that the lowered GH in females of this specific age group may be caused by concerns regarding fertility and pregnancy. In a previous study, the

GH of Japanese BA patients was lowered compared to normative data. Gender differences were not evaluated in that study.[70] Due to the small number of patients participating in our study, the data need to be interpreted with caution. Further investigation of the psychological outcome is needed to adjust patient care to the needs of this specific patient group.

In conclusion, we showed that more than 25% of BA patients survive at least 20 years with native liver in The Netherlands. One fifth of the long-term survivors was symptom-free and did not have clinical or radiological signs of cirrhosis or portal hypertension. It is tempting to speculate that a small percentage of BA patients is cured after portoenterostomy, but prolonged follow-up is needed to verify this speculation.

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