ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

Twenty-Year Transplant-Free Survival Rate Among Patients With Biliary Atresia

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BACKGROUND & AIMS: Surgical treatment with Kasai portoenterostomy has improved the prognosis for patients with biliary atresia, although most patients 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 the rate of transplant-free survival increases with time. **METHODS:** By using the Dutch national database for biliary atresia, we identified 104 patients, born between 1977 and 1988. We collected data on clinical characteristics, liver biochemistry, and ultrasonography from all transplant-free patients who were alive at age 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 of 49) in the 1977 to 1982 cohort to 32% (18 of 55) in the 1983 to 1988 cohort ($P = .03$). Twenty-one percent of the long-term survivors (6 of 28) had normal liver biochemistry test results and no clinical or ultrasonographic signs of cirrhosis. The 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. Women 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.**

Keywords: The Netherlands Study group on Biliary Atresia Registry (NeSBAR); Cholestasis; Quality of Life; Survival Time; Therapy; Surgery.

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% to 80% of patients within 1 year.[1]

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 approximately 10% of BA patients. In type III, the most prevalent type (~90%), the obstruction of the extrahepatic biliary tract extends into the porta hepatis.[2] In approximately 20% of the BA patients anatomic variants are found, including splenic malformation in Biliary Atresia Splenic Malformation syndrome (BASM). Venous and cardiac malformations, heterotaxy, and intestinal malrotation also are found in BASM.[2,3]

Initial treatment of BA is mainly surgical, consisting of hepaticojejunostomy or choledochojejunostomy in types I and II BA, and Kasai portoenterostomy in type III BA.[4] When bile flow cannot 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 approximately 50% of the indications for pediatric OLT throughout the Western world.[5]

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.[6–8] 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 the latest follow-up evaluation.

Abbreviations used in this paper: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BA, biliary atresia; BASM, biliary atresia splenic malformation syndrome; γGT, γ-glutamyl transferase; GH, general health perception; OLT, orthotopic liver transplantation.

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Table 1. Outcome of BA Patients at 20 Years After Surgical Correction in 2 Cohorts

Overall number of patients	1977–1982 (n = 49)	1983–1988 (n = 55)	*P* value
Median age at surgery, *d*	60 (25–222)	58 (35–126)	.48
Type I/II, %	3 (6%)	9 (16%)	.13
BASM, %	4 (8%)	3 (5%)	.70
Alive with native liver at 20 y	10 (20%)	18 (33%)	.03
OLT at <20 y	8 (16%)	16 (29%)	.16
Death	31 (63%)	21 (38%)	.04

Patients and Methods

Between January 1, 1977, and December 31, 1988, there were 106 patients who 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 1 of the 6 Dutch university medical centers that specializes in pediatric surgery. The short-term results of the majority of this cohort were described in 1989.[9] The Dutch OLT program started in 1979 in adults and in 1982 in children.

Thirteen patients had a type I or II BA; 9 patients underwent a hepaticojejunostomy or a choledochojejunostomy. In 4 patients, a portoenterostomy was performed. Eighty-three patients were classified as type III BA and underwent the classic Kasai portoenterostomy.

Follow-up Evaluation

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

Biochemical parameters were considered normal within the following ranges: total bilirubin level less than 17 μmol/L, ASAT level less than 40 U/L, ALAT level less than 45 U/L, γGT level less than 55 U/L in males and less than 45 U/L in females, albumin level greater than 3.5 g/dL, and an international normalized ratio less than 1.1. During the most recent follow-up evaluation, patients were asked to provide information on current employment or education. In addition, they completed the 5 items concerning GH of the RAND-36 questionnaire, which has been validated in the Dutch population.[10] 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.[11] To assess a possible relationship with their clinical condition, GH was correlated to serum total bilirubin and ASAT values and the 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 the Mann–Whitney *U* test. Comparison of GH scores of patients with 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.[12] Effect sizes between 0.20 and 0.49 were considered small, between 0.50 and 0.79 were considered medium, and 0.80 or greater were considered large. The Pearson correlation analyses were performed to examine relationships between variables. All tests were 2-tailed. Differences and relationships were considered significant at a *P* value of less than .05. Analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, IL).

Results

Twenty-Year Survival After Surgical Correction

Of the 106 children (62 girls), 2 were lost to follow-up evaluation at the ages of 4 (address not found) and 6 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%). The overall 20-year survival with and without OLT was 43% (45 of 104). OLT was performed in 23% (24 of 104) of patients before the age of 20. The survival rate after OLT was 71% (17 of 24). Fifty percent (52 of 104) of the patients died without OLT, mainly because the technique was not yet available in small children at that time.

The transplant-free 20-year survival increased markedly over time. In the 1977 to 1982 cohort, 20% (10 of 49) survived for 20 years without OLT, and 33% (18 of 55) survived for 20 years without OLT in the 1983 to 1988 cohort ($P = .03$; Table 1). In Table 2, the 20-year survival data are compared with available international data.

Twelve percent (12 of 104) of the patients had type I or II BA (Table 3). Survival of type I/II and type III was not statistically different ($P = .15$). Seven percent (7 of 104) of all patients had characteristics of BASM (1 type I/II BA, 6 with type III), of whom 29% (2 of 7, both type III) survived beyond the age of 20 without OLT being necessary.

In Figure 1, the 20-year transplant-free survival rates are shown for the different age groups at Kasai portoenterostomy. Survival was significantly lower when patients underwent surgery after age 75 days when compared with age 60 to 75 days (11% ± 6% vs 42% ± 10%, respectively, $P = .03$). Two of the long-term survivors (7%) underwent surgery after the age of 90 days (96 and 113 d). The perioperative liver biopsy reports of some of the long-term survivors indicated severe cholestasis and fibrosis.

Liver Condition at 20-Year Follow-up Evaluation

At the age of 20 years, 36% (10 of 28) of the patients with 20-year transplant-free survival had normal total serum