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Outcomes of biliary atresia in the Nordic countries – a multicenter study of 158 patients during 2005–2016☆,☆☆

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ABSTRACT

Background/purpose: Biliary atresia is the most common reason for newborn cholestasis and pediatric liver transplantation. Even after normalization of serum bilirubin after portoenterostomy, most patients require liver transplantation by adulthood due to expanding fibrosis. We addressed contemporary outcomes of biliary atresia in the Nordic countries.

Methods: Data on center and patients characteristics, diagnostic practices, surgical treatment, adjuvant medical therapy after portoenterostomy, follow-up and outcomes were collected from all the Nordic centers involved with biliary atresia care during 2005–2016.

Results: Of the 154 patients, 148 underwent portoenterostomy mostly by assigned surgical teams at median age of 64 (interquartile range 37–79) days, and 95 patients (64%) normalized their serum bilirubin concentration while living with native liver. Postoperative adjuvant medical therapy, including steroids, ursodeoxycholic acid and antibiotics was given to 137 (93%) patients. Clearance of jaundice associated with young age at surgery and favorable anatomic type of biliary atresia, whereas annual center caseload >3 patients and diagnostic protocol without routine liver biopsy predicted early performance of portoenterostomy. The cumulative 5-year native liver and overall survival estimate was 53% (95% CI 45–62) and 88% (95% CI 83–94), respectively. Portoenterostomy age <65 days and annual center caseload >3 patients were predictive for long-term native liver survival, while normalization of serum bilirubin after portoenterostomy was the major predictor of both native liver and overall 5-year survival.

Conclusions: The outcomes of biliary atresia in the Nordic countries compared well with previous European studies. Further improvement should be pursued by active measures to reduce patient age at portoenterostomy.

Retrospective prognosis study: Level II.

Biliary atresia (BA) is a severe cholangiopathy of infancy and the most common reason for neonatal cholestasis and pediatric liver transplantation (LT) [1,2]. Pathophysiology of BA remains unclear, but rapidly progressing biliary fibrosis leads to liver failure and death within 2 years if untreated [1,2]. The first line surgical treatment is portoenterostomy (PE), which typically resolves cholestasis in around half of the patients [3–6]. Even after normalization of serum bilirubin levels, approximately 70–80% of patients require LT by adulthood due to portally expanding ductal reaction and fibrosis associated with complications of ensuing portal hypertension [1,2,7,8]. Outcome of PE carries vital prognostic

Abbreviations: BA, biliary atresia; LT, liver transplantation; PE, portoenterostomy; ERC, endoscopic retrograde cholangiography; PTC, percutaneous transhepatic cholangiography; CI, confidence interval; OR, odd ratio; HR, hazard ratio.

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significance in BA, because successful PE circumvents the high waiting list mortality during infancy and increases survival after LT compared to primary LT [9–11].

Several patient-dependent factors at the time of PE such as young age, favorable anatomy of the biliary tract remnant, absence of associated congenital malformations and lower stage of liver fibrosis associate with increased PE success rates and improved native liver survival [1,3,4,6,12]. Different postoperative adjuvant medications have been applied to improve PE outcomes. Although randomized trials have failed to show improvement in native liver survival by steroid treatment after PE [13,14], steroids do seem to increase the proportion of patients who clear their jaundice [15,16], while both steroids and ursodeoxycholic acid have a beneficial effect on liver biochemistry [15–17]. Antibiotic prophylaxis aims to prevent recurrent cholangitis episodes, which may jeopardize survival with native liver [3,18]. Adjuvant therapy regimens combining all three above mentioned medications have improved outcomes in small retrospective studies [19,20]. Concentration of clinical experience with BA management has also been shown to improve outcomes, which has led to centralization of BA in several countries such as UK and Finland [21,22].

In recent large European studies the clearance of jaundice rate and the 5-year native liver survival have ranged between 36–55% and 39–46%, respectively [3–5], whereas no data on collective outcomes in the Nordic countries are available. The Nordic countries has a combined population of 27 million people, share similar healthcare systems, socioeconomic status and educational level, and perform LT within a joint organ exchange organization [11]. The principal aims of this study were to characterize current management practices, analyze recent outcomes of BA and assess factors affecting timing and success rate of PE and native liver survival in the Nordic countries.

1. Patients and methods

1.1. Study design and data collection

This was an international multicenter retrospective observational survey. All children with confirmed BA born in the Nordic countries during 1.1.2005–30.6.2016 and followed-up at least for 4 months were included. Data were collected locally by pediatric surgeons, pediatric hepatologists and pediatricians in all Nordic centers involved with the treatment of BA according to a collectively approved questionnaire and data extraction sheet. The participating centers included one from Denmark (Copenhagen), Finland (Helsinki) and Norway (Oslo), and three from Sweden (Stockholm, Gothenburg, Lund), while no BA patients were reported from Iceland during this time period. All participating centers, excluding Lund, also perform pediatric LT within the Scandiatransplant organ exchange organization [11]. The diagnosis of BA was confirmed based on clinical history, laboratory results, surgical findings, imaging such as perioperative cholangiography, endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), liver biopsy and histopathological assessment of the biliary remnant according to local preferences. Patients, who had undergone PE but proved to have Alagille syndrome ($n = 3$) were excluded.

Clinical practices concerning diagnostic modalities, surgical approach to PE and medical therapy and esophageal variceal surveillance after PE were enquired from each center. Data registered for each patient included gender, ethnicity, timing and type of initial operative management (PE, LT or no operation), anatomic type of BA: extrahepatic bile duct obstruction at the level of the common bile duct (type 1), the hepatic duct (type 2) or the porta hepatis (type 3) according to the Japanese Society of Pediatric Surgeons classification [23], observed associated congenital anomalies, presence of asplenia or polysplenia, use of adjuvant medical therapy after PE including steroids, ursodeoxycholic acid or antibiotic cholangitis prophylaxis, clearance of jaundice, endoscopically detected esophageal varices and listing, performance and timing of LT, and data on death. Withdrawal of active treatment and reason for that was also registered. Latest available serum bilirubin concentrations and blood platelet levels while living with native liver were recorded as surrogates of bile flow and portal hypertension among native liver survivors [24]. Clearance of jaundice was defined as decrease in total serum bilirubin below 20 μmol/l at any time point after PE. Physiological foramen ovale, common anatomic variations of cardiac valves or vesicoureteral reflux were not considered congenital malformations.

1.2. Ethics

The ethical review boards at participating hospitals approved the study.

1.3. Statistical analysis

Continuous data are expressed as medians with interquartile ranges (IQR) and categorical data as frequencies unless otherwise stated. Mann–Whitney *U* test was used to compare continuous variables, and χ^2 test to compare frequencies between groups. Cumulative native liver survival (from birth to end of follow-up, LT or death), survival after LT (from LT to end of follow-up or death) and overall survival (from birth to end of follow-up or death) rates were analyzed using Kaplan Meier curves with 95% confidence intervals (CI) and log-rank test. In multivariate analyses, odd ratios (OR) with their 95% CIs were generated with logistic regression models for predictors of age at PE and clearance of jaundice, and hazard ratios (HR) with their 95% CIs with Cox proportional hazards regression models for predictors of 5-year native liver survival. The proportional hazard hypotheses were confirmed graphically and all variables in univariate analyses were entered to multivariate analyses. The variables for multivariate analyses were chosen based on earlier literature [3–6]. The level of significance was set at $p < 0.05$. Statistics were calculated with StatView® 512 software (Brain Power, Calabasas CA, USA).

2. Results

2.1. Center characteristics

The median number of patients treated in the participating six centers annually ranged from 0.7 to 3.7, while only two centers managed over three patients annually (Supplementary Table 1). Cholescintigraphy, operative cholangiography and ultrasound were uniformly used diagnostic investigations, whereas preoperative diagnostic liver biopsy, MRI, PTC and ERC were less commonly employed. In five centers one surgeon or surgical team operated all BA patients and none used laparoscopic surgical approach for PE. Five centers reported routine steroid use after PE, while ursodeoxycholic acid, antibiotic prophylaxis and supplemental fat-soluble vitamins were regularly prescribed after the surgery in all centers. Two centers followed an endoscopic surveillance protocol for esophageal varices.

2.2. Patient characteristics

In total, 158 patients were identified (Fig. 1). Treatment was withdrawn in four cases (2.5%) due to untreatable severe associated malformations affecting the heart or the central nervous system, and they were excluded from further analyses. Of the remaining 154 patients, 148 underwent PE and six (3.9%) had a primary LT. During the study period, 58 patients had undergone a secondary LT after PE, and 137 (89%) of the actively treated patients were alive. Median follow-up time among all patients was 4.9 (1.8–7.9) years.

The majority of patients were of European origin with a slight female predominance (Table 1). The most unfavorable anatomic type of BA (type 3) was observed in 82% of patients and 27% of patients had any associated congenital malformations, which affected the spleen in 12% and the heart in 6.5%. The vast majority of patients had received