Journal of Pediatric Surgery (2011) **46**, 1689–1694

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Journal of Pediatric Surgery

www.elsevier.com/locate/jpedsurg

Original articles

Biliary atresia in England and Wales: results of centralization and new benchmark☆,☆☆,★

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Received 27 January 2011; revised 14 April 2011; accepted 16 April 2011

Key words:
Biliary atresia: outcome;
Kasai portoenterostomy;
Biliary atresia splenic malformation;
Cystic biliary atresia

Abstract

Introduction: Biliary atresia (BA) is a rare, potentially life-threatening condition of the newborn presenting with conjugated jaundice. Typically, it is treated by an initial attempt to restore bile flow (the Kasai portoenterostomy [KP]) as soon as possible after diagnosis and, if this fails, liver transplantation. Since 1999, the treatment of BA has been centralized to 3 centers in England and Wales able to offer both treatment options. The aim of this study was to review the outcome of this policy change and provide a national benchmark.

Methods: The management of all infants born within England and Wales during the period January 1999 to December 2009 was assessed using 3 key performance indicators such as median time to KP, percentage clearance of jaundice (≤20 mol/L) post-KP, and 5- and 10-year native liver and true survival estimates. Data are quoted as median (range), and $P < .05$ was considered significant.

Results: A total of 443 infants had confirmed BA; and of these, most were isolated BA (n = 359), with 84 having other significant anomalies (but predominantly BA splenic malformation syndrome). Four infants died before any biliary intervention. Kasai portoenterostomy was performed in 424 infants (median age, 54 [range 7-209] days), and a primary liver transplant was performed in 15. Clearance of jaundice post-KP was achieved in 232 (55%). There were 41 deaths, including 4 (10%) without any intervention, 24 (58%) post-KP usually because of end-stage liver disease and mostly on a transplant waiting list, and 13 (32%) post-LT usually because of multiorgan failure. Overall, the 5- and 10-year native liver survival estimates were 46% (95% confidence interval [CI], 41-51) and 40% (95% CI, 34-46), respectively. The 5- and 10-year true patient survival estimates were 90% (95% CI, 88-93) and 89% (95% CI, 86-93), respectively. Outcome was worse for those with other anomalies (lower clearance of jaundice post-KP [43% vs 57%; odds ratio, 1.7; 95% CI, 1.04-2.8]; $P = .02$) and an increased mortality overall (eg, at 5 years, 72 [95% CI, 64-83] vs 94 [95% CI, 91-96]; $\chi^2 = 33$; $P < .0001$).

☆ Contributors: MD, PM, and DK originated the study. Data collection was provided by all 3 centers, and statistical analysis was by MD and EO. The manuscript was written by MD, with all authors contributing to the final version. MD, PM, and DK act as guarantors.

☆☆ Funding: There was no explicit funding for this study.

★ Ethical approval: We feel that is primarily an audit of performance and outcome and therefore does not need formal ethical approval.

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doi:10.1016/j.jpedsurg.2011.04.013

Conclusions: National outcome measures in BA appear better than those from previously published series from comparable countries and may be attributed to centralization of surgical and medical resources.

Biliary atresia (BA) is a progressive cholangiopathy of essentially unknown etiology presenting with conjugated jaundice and pale stools in the first few weeks of life [1]. Left untreated, infants develop cirrhosis and end-stage liver disease with death within 2 years. Currently, the management of such infants remains an initial attempt to restore bile flow, alleviate jaundice, and salvage the native liver by Kasai portoenterostomy (KP). Liver transplantation (LT) is then usually reserved for those that fail this initial surgical manoeuvre or in cases where KP is considered futile because of decompensated cirrhosis at presentation.

Biliary atresia is a rare disease, with the latest estimate of incidence for England and Wales being 1 in 17,000 live births, which therefore translates to about 50 infants annually [2].

Based on data from a prospective study carried out by the British Paediatric Surveillance Unit on the incidence and outcome of BA [5], the Department of Health (for England and Wales) dictated that infants with suspected BA were to be managed only in those centers who could offer both KP and LT as options. Early results were reported in 2003 [3] and suggested significant improvement in national surgical results when compared with the decentralized approach of the 1980s [4] and early 1990s [5,6].

The aim of this study was to report the surgical outcome over a longer period to provide current data, compare it to published national studies, and suggest recommendations whereby improvements may be sought.

1. Materials and methods

Since January 1999, all infants with BA born in England and Wales have been managed in 1 of 3 supraregional centers (King's College Hospital, London [KCH]; Birmingham Children's Hospital [BCH]; and Leeds Teaching Hospitals [LTH]). A national data registry was collated prospectively and used to identify all infants with BA who were treated between January 1999 and December 2009. The diagnosis of BA was confirmed within each supraregional center by a combination of operative and histological findings. A standard registration pro forma was compiled with data on associated anomalies and presence of cystic change provided by the 3 centers. This was not subject to central review. Therefore, infants with the most common syndromic association, the biliary atresia splenic malformation (BASM) syndrome, and cystic biliary atresia (CBA) were able to be identified [7,8]. No data were collected on perioperative management (eg, use of steroids) or incidence of complications common to BA (eg, cholangitis).

Outcome was followed and assessed with 3 defined outcomes (alive with native liver, alive with transplanted liver, and death) at the census point of January 2010. *Clearance of jaundice* was defined as achieving a level of 20 μmol/L total bilirubin within 6 months of KP. Biliary atresia was classified using the abbreviated Japanese Association of Pediatric Surgeons (JAPS) classification that assesses the most proximal level of extrahepatic biliary obstruction (viz,, type 1, level of common bile duct; type 2, level of common hepatic duct; and type 3, level of porta hepatis).

The effect of age at KP was investigated by excluding infants with anomalies and CBA, as one of our previous studies had shown these subgroups to have a definite detrimental effect with increasing age [9]. Those who underwent primary LT were also excluded, therefore leaving only infants with isolated BA treated in the first instance by KP. To maximize the chances of detecting a statistical difference in outcome, infants were divided into 4 equally sized groups by age. Their median age was 56 days; and therefore, the groups were defined as younger than or equal to 43, 44 to 55, 56 to 69, and 70 days or more.

1.1. Statistics

Data are quoted as median (interquartile range) unless otherwise indicated. Comparisons were parametric (t test, analysis of variance) or nonparametric (Mann-Whitney, Kruskal-Wallis analysis of variance) depending on normality of data. Categorical data was analyzed using Fisher's Exact test. Actuarial survival curves (native liver and true) were compared using a log-rank (Mantel-Cox) test. Data were analyzed using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, CA). A P value of $\leq .05$ was regarded as significant.

2. Results

A total of 443 infants were born within England and Wales and managed during the period January 1999 to December 2009 in 1 of the 3 supraregional centers (KCH, n = 224; BCH, n = 135; LTH, n = 84). Of these, most were isolated BA (n = 359), with 63 defined as BASM and 21 as associated with significant other anomalies (eg, esophageal atresia, various significant cardiac malformations, cleft palate).

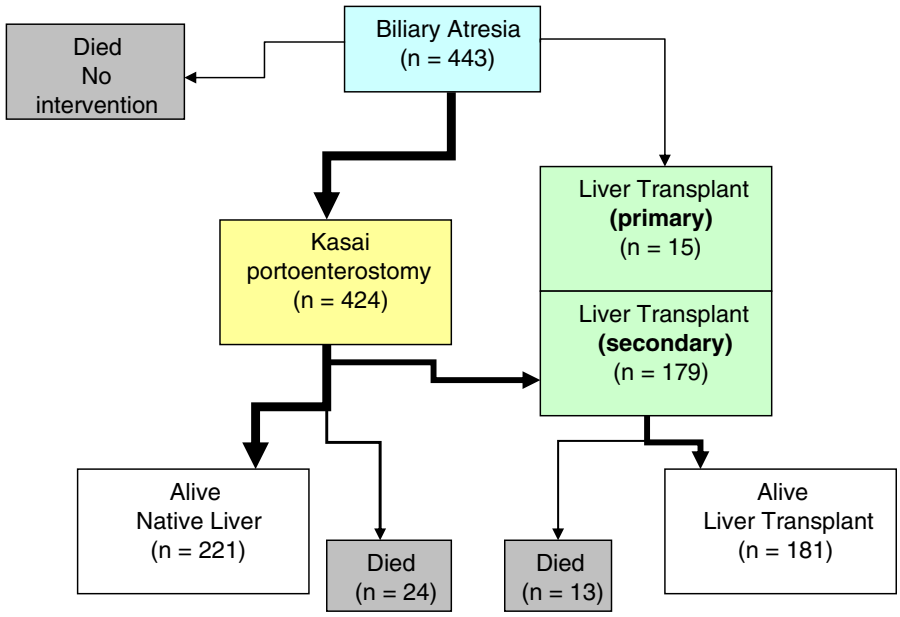

Fig. 1 Summary of outcome of BA in England and Wales (n = 443) treated between January 1999 and December 2009.

Kasai portoenterostomy was performed in 424 infants, with the macroscopic appearance defined as type 1 (n = 12), type 2 (n = 6), or type 3 (n = 406, 96%). Cystic change within an otherwise obliterated biliary tree (CBA) was seen in 40 (9%). Primary LT (n = 15) was performed at 0.64 (0.49-0.77) years (Fig. 1).

2.1. Age at KP

The median age at KP overall was 54 (IQ, 43-69; range, 7-209) days; and within this, 44 (10%) infants were at least 90 days old. There was a significant difference between centers, with KCH having the highest age at surgery at 59 (IQ, 45-72) days and both BCH and LTH the lowest at 50 (IQ, 41-63) and 51 (IQ, 34-58) days, respectively (Kruskal-Wallis, $P < .0001$).

3. Outcome

In January 2010, their status was as follows: alive with native liver (n = 221, 50%), alive with LT (n = 181, 41%), and died (n = 41 [9%], of whom 13 [3%] were post-LT). Four infants had other anomalies, whose severity (principally because of cardiac malformations) precluded an attempt at reconstruction. Three died shortly following assessment, but one who was eventually listed for LT died at 1.1 years (Fig. 1).

There were 41 deaths during the period (Table 1). Of these, 4 (10%) occurred without any intervention (see above); 24 (58%) occurred post-KP usually because of failure and end-stage liver disease; and 13 (32%) occurred post-LT usually because of multiorgan failure and often following retransplantation.

Of those undergoing KP (n = 424), 232 (55%) cleared their jaundice to less than 20 μmol/L within 6 months. Overall, the 5- and 10-year native liver survival estimates were 46% (95% confidence interval [CI], 41-51) and 40% (95% CI, 34-46), respectively (Fig. 2). The 5- and 10-year true patient survival estimates were 90% (95% CI, 88-93) and 89% (95% CI, 86-93), respectively. There was no difference between the 3 centers for both native liver (overall $\chi^2 = 0.37$, $P = .83$; or for trend based on case numbers, $\chi^2 =$

Table 1 Mortality in BA (1999-2009) (n = 41)

No intervention	Post-KP	Post-LT	Age at death median (IQ) y
4 (4[a])	–	–	0.37, 0.74, 0.02, 1.1
–	24 (16[a])	–	0.69 (0.45-1.08)
–	–	13 (0[a]) Multiple LT (n = 4)	1.98 (0.8-3.3)

[a] Number with BASM or defined anomaly syndrome.

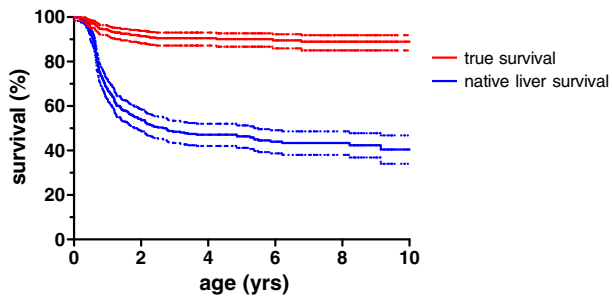

Fig. 2 Actuarial true and native liver survival curves (median [±95% CI]) for BA (n = 443) in England and Wales (1999-2009).

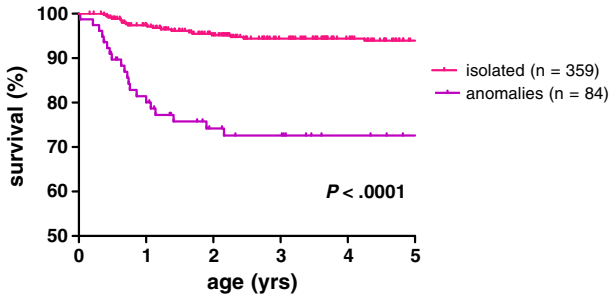

Fig. 3 Effect of anomalies in BA. True survival in BA and other anomalies (n = 84) vs isolated BA (n = 359). Curves are significantly different ($\chi^2 = 33$; $P = .0001$).

0.04; $P = .82$) and true survival (overall $\chi^2 = 1.3$, $P = .5$; or for trend $\chi^2 = 0.17$, $P = .67$).

3.1. Effect of anomalies

Infants were divided by presence of anomalies (n = 84) and compared with those with isolated BA (n = 359). They had a lower median age at KP (where performed) (49 [39-65] vs 54 [43-69] days; $P = .02$) but lower clearance of jaundice post-KP (43% vs 57%; odds ratio, 1.7 [95% CI, 1.04]; $P = .02$). There was a decreased survival overall (eg, at 5 years, 72% [95% CI, 64-83] vs 94% [95% CI, 91-96]; $\chi^2 = 33$; $P < .0001$) (Fig. 3). Survival rates were actually lower in the second half of the period, but did not reach statistical difference (81% [95% CI, 63-90] vs 65% [95% CI, 47-77]; $P = .11$).

3.2. Effect of cystic change

Infants with cystic BA (n = 40) were compared with those without such change (n = 384). They had a lower median age at KP (44 [35-55] vs 55 [43-69] days; $P < .001$) and had an increased native liver survival when compared with those without such change (eg, 5-year survival = 80 % [95% CI, 70-97] vs 44 % [95% CI. 39-49]; $\chi^2 = 12.3$; $P = .0004$) (Fig. 4).

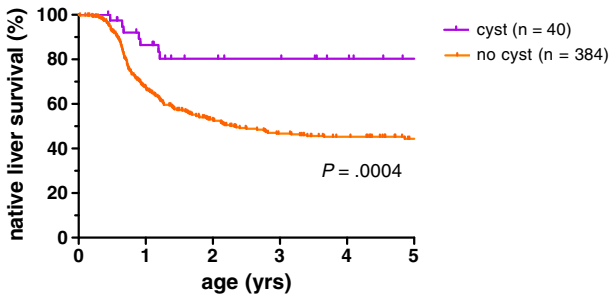

Fig. 4 Effect of cystic change in BA. Native liver survival of cystic change (n = 40) vs obliterated BA (n = 384). Curves are significantly different ($\chi^2 = 12.35$; $P = .0004$).

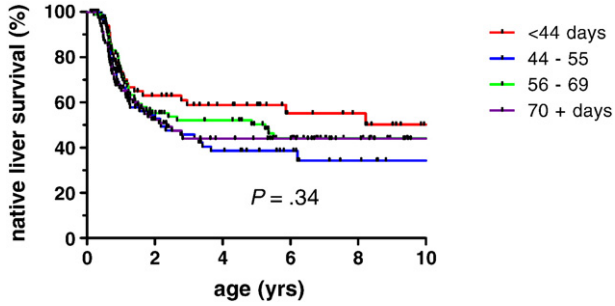

Fig. 5 Effect of age at KP. Infants with isolated BA (n = 318) were divided by age at surgery. No difference overall ($\chi = 3.3$; $P = .34$) or for trend ($\chi^2 = 0.87$; $P = .35$). Specifically, no difference between 2 outermost curves ($\chi^2 = 2.1$; $P = .15$).

3.3. Effect of age at KP

The median age at KP of infants defined as isolated BA (n = 318) was 56 (range, 14-209) days. Fig. 5 illustrates native liver survival divided into 4 age cohorts. Although the youngest group (≤43 days) had the best native liver survival, there was no overall difference between curves ($\chi = 3.3$; $P = .34$) and no evidence of a trend ($\chi^2 = 0.87$; $P = .35$). Even if the 2 curves most clearly "different" were chosen (ie, ≤43 vs 44-55 days), statistical significance was still not reached ($\chi^2 = 2.1$; $P = .15$).

4. Discussion

Biliary atresia is rare and potentially lethal, but its outcome can be changed by effective and timely surgery. This series illustrates how a country can deal with this health issue by centralization of surgical and medical resources to obtain arguably the best possible outcome so far reported (Table 2) [5,6,10-16]. There are several key stages that can affect ultimate outcome: correct diagnosis and time to initial surgery, realization of the potential of the native liver, and timely access to effective (and safe) LT.

Infants with BA arise from a huge population of jaundiced infants. Most will have self-limiting, benign causes such as breast milk jaundice and mild neonatal hepatitis. A yellow needle in a uniformly yellow haystack, as it were. The red flags that should alert physicians and health visitors in primary care are the consequences of an obstructed biliary tract and lack of bile in the gastrointestinal tract, such as pale stools and dark urine. This should prompt measurement of a "split" bilirubin (ie, total and conjugated bilirubin), and then those with a raised conjugated bilirubin should be investigated immediately for liver disease. The index of success in this phase is the time to KP, and our international survey of published series showed that England and Wales achieved the fastest time to KP for any country. There is no national screening

Table 2 National outcome statistics in BA (1986-2010)

Series	Country	n	Median/ mean time to KP	Period	Clearance of jaundice [a]	Native liver survival (%)		Overall survival (%)	
						4/5 y	10 y	4/5 y	10 y
McKiernan et al [5,6]	UK & Ireland	93	54	1993-1994	55%	30 (5)	44 (6)	85 (5)	84 (6)
Nio et al, 2003 [10]	Japan	108	65+	1989	n/a	62	53	69	66
		129	65+	1994	n/a	53	–	78	–
Serinet et al, 2006 [11]	France	472	61	1986-1996	34%	35	26	72	70
		271	57	1997-2002	40%	35	–	87	–
Schneider et al, 2006 [12]	United States [c]	104	61	1997-2000	~40%	56 (@ 2 y)	–	86 (@ 2 y)	–
Schreiber et al, 2007 [13]	Canada	349	55	1985-1995	n/a	35	–	74	–
				1996-2002	n/a	39	–	82	–
Wildhaber et al, 2008 [14]	Switzerland	48	68	1994-2004	n/a	37	–	92	–
Hsiao et al, 2008 [15]	Taiwan	75	55	2004-2005	59% [b]	–	–	–	–
Leonhardt et al, 2010 [16]	Germany	137	57	2001-2005	n/a	20	–	83	–
Davenport et al, 2011	England & Wales	443	54	1999-2009	55%	46	40	90	89

[a] Defined as achieving a level of less than 20 μmol/L (or 1.5 mg/dL).
[b] Defined as achieving a level of less than 2 mg/dL.
[c] Biliary Atresia Research Consortium, 9 centers. Not a national study.

program for BA in the United Kingdom. Indeed, the only coordinated national screening program occurs in Taiwan where they rely on a universal stool color chart distributed at birth and assessed at a health check at 1 month. There is an increased incidence of BA in Taiwan (about 1 in 6000); and although entirely commendable, their mean time to KP is similar to our own nonscreened population at 55 days [15]. It is however noteworthy that there were no infants in Taiwan who underwent surgery at more than 90 days, whereas this occurred in 10% of our series, implying that we still have the potential to improve further.

So does it matter when the KP is done? The intuitive answer is obviously yes; liver fibrosis is time dependent starting from the beginning of the cholangiopathy, and even those with a clear developmental etiology have a virtually normal liver at the time of birth [17]. But *within reasonable limits*, response to KP may be more to do with optimal exposure of biliary ductules in the porta hepatis rather than degree of liver fibrosis at the time of KP. We have previously reported a study from one of our centers showing that the effect of age is complex, being obvious for those with CBA and BASM but not so easy to detect for those with isolated BA [9]. The current study supports this observation. There was no statistical difference between our 4 age-defined cohorts in terms of native liver survival; neither was there a detectable trend. The largest comparable (albeit undivided by subtype) national study (n = 743) is that of Serinet et al from France [18]. Although they quoted an overall significant difference in time of surgery, most of the curves seemed to overlap by 5 and 10 years.

How then to maximize the potential of the native liver? There will be infants who despite appropriately timed surgery (to ensure a "retrievable" liver) by experienced biliary surgeons (to expose the maximal amount of residual bile ductules in the porta hepatis) will not have any restoration of bile flow. These infants will require a transplant to survive. The key measure of outcome to assess this aspect is the percentage that clear their jaundice—arbitrarily to normal values. Our table shows that we achieve this in 55% of infants undergoing KP, without undue selection (only 3% of infants had primary LT). This is appreciably more than in France [11], Switzerland [14], or the United States [12] but perhaps comparable to recent results from Taiwan who quote a less stringent measure [15]. If effective clearance is not achieved, then transplantation should be offered. Our series shows clearly that most BA children who die do so on a transplant waiting list. Donor organ shortage is still a grave issue in the United Kingdom and furthermore does not appear to have improved over the decade. If there are going to be further gains in overall outcome for this disease, then this is the area where change should happen.

Unlike KP, LT is a much more challenging undertaking and has a definite postoperative risk attached to it, with most deaths being related to increasingly desperate measures such as retransplantation for intractable complications such as chronic rejection. Nonetheless, having passed through the first postoperative year, then the vast majority of children become stable on an effective immunosuppression regimen and do not seem to develop problems, at least life-threatening problems, thereafter.

Infants with the syndromic form of BA and those with other "nonsyndromic" anomalies are subgroups where there is still a considerable risk of death. They have a worse outcome, both in relation to the reduced clearance of jaundice after KP (~43%) that seems less effective and in the increased risk of sudden death [19]. Some of this is obviously related to cardiac anomalies and an increased risk

of the development of the hepatopulmonary syndrome as highlighted in our earlier report [3]. This risk even seems to have increased when we compared two 5-year periods, although the reason is not clear.

This survey has not directly addressed the problems associated with centralization; but anecdotally, these appeared to be mostly social, associated with distance from the center together with costs and time devoted to traveling, particularly in the key first year of life. There is undeniably practical deskilling within regional units with respect to non-BA hepatobiliary surgery, emergency management of bleeding oesophageal varices, etc. The concept of medical "shared care" involving a more local pediatric unit however seemed to work with respect to monitoring of growth and development, nutritional intervention, treatment of complications such as cholangitis, and monitoring of the immunosuppression regimen in those posttransplant.

This change in national surgical practice at the end of the 1990s may not have been prompted so much by scientific evidence, as this was already there in the 1980s [4], but by a desire to forestall increased media scrutiny and attention engendered by contemporaneous events surrounding the provision of pediatric cardiac surgery services in the United Kingdom. Nonetheless, consideration of most of the relevant indices would suggest that the national outcome in this particular disease has improved. Whether this would translate to countries with other forms of health provision (eg, United States, Germany) or with extreme geographical constraints (eg, United States and Canada, [20]) remains unclear, but it is a benchmark perhaps for European countries more akin to the United Kingdom.

Acknowledgments

We gratefully acknowledge the vital contributions of the pediatric hepatologists in all 3 centers to the care of these infants. Over the period, a number of other surgeons were also closely involved in the treatment of these infants; and this work reflects their skill and expertise. These include Nigel Heaton and Mohammed Rela (transplantation in London); Mark D Stringer (KP and transplantation in Leeds); and Jean De Ville De Goyet, Alastair Millar, and Christophe Chardot (KP and transplantation in Birmingham). We would also acknowledge the role of data collation in BCH throughout the period made by Carla Lloyd.

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