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ABSTRACT

**Objectives:** To determine the epidemiology of biliary atresia (BA) in Switzerland, the outcome of the children from diagnosis, and the prognostic factors.

**Patients and Methods:** The records of all patients with BA born in Switzerland between January 1994 and December 2004 were analyzed. Survival rates were calculated with the Kaplan-Meier method, and prognostic factors evaluated with the log rank test. Median follow up was 58 months (range, 5–124).

**Results:** BA was diagnosed in 48 children. Incidence was 1 in 17,800 live births (95% confidence interval 1/13,900–1/24,800), without significant regional, annual, or seasonal variation. Forty-three children underwent a Kasai portoenterostomy (PE) in 5 different Swiss pediatric surgery units. Median age at Kasai PE was 68 days (range, 30–126). Four-year survival with native liver was 37.4%. Liver transplantation (LT) was needed in 31 in 48 children with BA, including 5 patients without previous Kasai PE. Four patients (8%, all born before 2001) died while waiting for LT, and 29 LT were performed in 27 patients (28 in Geneva and 1 in Paris). All of the transplanted patients are alive. Four-year overall BA patient survival was 91.7%. Four-year survival with native liver was 75% in patients who underwent Kasai PE before 46 days, 33% in patients operated on between 46 and 75 days, and 11% in patients operated on after 75 days ($P=0.02$).

**Conclusions:** Overall survival of patients with BA in Switzerland compares favorably with current international standards, whereas results of the Kasai operation could be improved to reduce the need for LTs in infancy and early childhood.

**Key Words:** Biliary atresia—Epidemiology—Prognosis—Pediatric surgery—Liver transplantation. © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Biliary atresia (BA) is a rare neonatal disease of unknown etiology and is characterized by obstruction of the biliary tree, causing severe cholestasis and biliary cirrhosis, that leads finally to death in the first years of life. The recommended treatment of BA is sequential: In the first weeks of life, the Kasai portoenterostomy (PE), or its technical variants, aim to restore the biliary flow to the intestine; in the case of failure of the operation and/or life-threatening complications of the biliary cirrhosis, liver transplantation (LT) may eventually be needed. The reported incidence of BA in several European countries varies between 1 in 14,000 and 1 in 20,000 live births (1–5); however, the epidemiology of BA in Switzerland is unknown.

The outcome of patients with BA has dramatically improved over the last several decades. After the worldwide diffusion of the Kasai operation in the late 1960s (6) and the development of pediatric LT in the 1980s, the reported survival rates of patients with BA in industrialized countries today reach 90% (7). In survivors, the ratio of transplanted patients varies, depending on the results of the Kasai operation and the duration of follow-up. Until now, the outcome of BA in Switzerland has never been studied. Hence, from the analysis of all of the children with BA born in Switzerland between 1994 and 2004, the aim of this study was to describe the epidemiology of BA in Switzerland, to study the outcome of these children from diagnosis, and to analyze the prognostic factors influencing this outcome.

**PATIENTS AND METHODS**

The records of all patients born in Switzerland between January 1994 and December 2004 and diagnosed with BA were reviewed. All 7 pediatric surgery centers (Basel, Berne, Geneva, Lausanne, Lucerne, St Gallen, and Zurich) involved in the management of patients with BA contributed to the study.
Centers were visited and charts were analyzed by a single investigator (B.E.W.) to reassess the diagnosis of BA and to achieve homogenous data collection.

**Inclusion Criteria**

The criteria for inclusion of patients were as follows:

1. Patients with BA diagnosed by means of clinical, biochemical, radiological, histological, and surgical findings, all consistent with BA (8). Histology of the biliary remnant was available for all of the patients, including those without previous Kasai PE.

2. Patients born, living, and treated primarily in Switzerland between January 1994 and December 2004. The Kasai PE or its modifications, as well as LT, were available for every child during this period, the medical costs being covered by the national medicosocial insurance system.

**Analysis of Records**

Recorded data included birth date; clinical and biochemical data of the period pre-, peri-, and post-Kasai PE; surgical and histological findings; whether or not LT was performed; clinical and biochemical data of the period pre-, peri- and post-LT; final outcome; date of last follow-up; cause of death; and possible reasons why a Kasai PE or LT were not performed. Macroscopic classification of BA was based on the anatomical pattern of the extrahepatic biliary remnant according to the French classification (8): type 1 (BA limited to the common bile duct), type 2 (biliary cyst in the liver hilum, communicating with dystrophic intrahepatic bile ducts), type 3 (gallbladder, cystic duct and common bile duct patent), and type 4 (complete extrahepatic BA). Success of the Kasai PE was defined as complete clearance of jaundice and a total bilirubin level of $\leq 20 \mu mol/L$. An intermediate result of the Kasai PE was defined as a minimal bilirubin level after the Kasai bet- level of $20$ and $50 \mu mol/L$. A failed Kasai PE was defined when bilirubin level did not decrease below $50 \mu mol/L$. Median follow-up was 58 months, with a range of 5 to 124 months. Swiss demographic data were obtained from the Swiss Federal Statistic Office.

**Ethical Approval**

The present study was approved by the ethical committee of the University of Geneva, Switzerland. Each family was contacted and informed of this study and gave its written consent.

**Statistical Analysis**

**Epidemiology**

Incidence were expressed as observed value and calculated confidence interval of 95% (95% CI), egional variations in incidence were compared by the $\chi^2$ test, with Yates correction if indicated. Annual and seasonal variations in incidences were analyzed by comparing cumulated observed frequencies by months and years, and expected frequencies according to variations of births, assuming a constant incidence of BA (expected frequency of BA = constant incidence × observed live births during the considered period of time). The comparison used the $\chi^2$ test, with Yates correction if indicated.

**Outcome**

Survival rates were calculated using the Kaplan-Meier method: survival with native liver (SNL) (starting at birth, endpoint being LT or death), survival after LT (starting at birth, endpoint being death), and overall patient survival (OS) (starting at birth, endpoint being death). Survival was expressed in percentage ± standard error. Potential prognostic factors were analyzed by the log rank test. Categorical data used the $\chi^2$ test, with Yates correction if indicated. Statistical significance was defined as $P < 0.05$.

**RESULTS**

**Epidemiology**

BA was diagnosed in 48 children (33 girls, 15 boys) born in Switzerland between 1994 and 2004. Incidence was 1 in 17,800 live births (95% CI 1/13,900–1/24,800). No significant regional variation in incidence was found (Fig. 1). No significant annual and monthly variation in incidence was observed.

**Patients and Analysis of Medical History**

Median birth weight was 3315 g, range 1410 to 4000 g, median gestational age was 39 weeks, range 32 to 42 weeks. Observation of first clinical signs was made in 63% of subjects by the pediatrician, and in 31% of subjects by the mother. Four in 48 children (8%) presented with polysplenia syndrome (syndromatic BA); 6 in 48 children (13%) had other associated anomalies or diseases, including uropathies (ureteropelvic junction obstruction, vesicoureteral reflux, megaloureter), Kartagener syndrome, and glycogenosis type IX.

**Kasai PE**

Forty-three children underwent a Kasai PE. The Kasai PE was performed in 5 different pediatric surgery units: Berne (6 cases), Geneva (21 cases), Lausanne (1 case), Lucerne (1 case), and Zurich (14 cases). The median age at Kasai operation was 68 days (range, 30–126 days). All but 3 patients underwent a classic Kasai PE; without stoma or antireflux valve; 5 patients had an extended Kasai PE according to the technique described by Schweizer et al (9). The biliary remnant was type 4 in 41 of 48 (85%) patients, type 3 in 4 patients, type 2 in 2 patients, and type 1 in 1 patient. No standardized postoperative medical regimen (steroids, ursodeoxycholic acid, antibiotics) was used.
Clearance of Jaundice Post-Kasai

After the Kasai operation, bilirubin levels normalized ($\leq 20 \mu mol/L$) in 17 of 43 (39.5%) patients, decreased between 20 and 50 $\mumol/L$ in 5 of 43 (11.6%) patients, and remained above 50 $\mumol/L$ in 21 of 43 (48.8%) patients. Fourteen of 17 patients whose bilirubin levels returned to normal values did not need LT. Two of 5 patients whose bilirubin levels decreased between 20 and 50 $\mumol/L$ underwent LT. All 21 patients whose bilirubin levels remained above 50 $\mumol/L$ received transplants or died while waiting for an LT.

The postoperative evolution after Kasai PE is represented in Figure 2. Results of the general outcome of patients with BA are summarized in Figure 3.

Survival With Native Liver

Survival with native liver (SNL) (Fig. 4) of all patients with BA from diagnosis was 40.5% ± 7.4% at 2 years and 32.7% ± 7.2% at 4 and 5 years. Survival with native liver in patients who underwent Kasai PE was 43.4% ± 7.9% at 2 years and 37.4% ± 7.9% at 4 and 5 years. Survival with native liver after the Kasai operation was strongly linked to the clearance of jaundice after the Kasai operation: 2- and 5-year SNL was 92.3% ± 7.4% and 83.9% ± 10.4% in patients with successful Kasai operation, 60% ± 21.9% and 60% ± 21.9% in patients with intermediate results of the Kasai operation, and 4.8% ± 4.6% and 0% in patients with failed Kasai operation, the longest SNL being 28 months in this group of patients ($P < 0.0001$).

LT and Survival After LT

Liver transplantation was needed in 31 of 48 children with BA, including 5 patients without previous Kasai PE (4 of those 5 patients were born before 1997, so no Kasai PE was performed because these patients were considered to be too old for the operation). Four patients died while waiting for LT, all before 2001, all of them after failed Kasai PE. Thus, 26 in 43 patients (60.4%) needed LT after the Kasai procedure. In total, 29 LTs were performed in 27 patients, including 2 re-LTs. The types of liver grafts are shown in Table 1. All of the patients received transplant operations in Geneva, except 1 in Paris (Kremlin-Bicêtre, France). Liver transplantation was performed at a median age of 11.7 months (range, 5.3–66.7 months). With a median follow up of 60 months.
Overall Patient Survival

Overall 2-, 4- and 5-year BA patients survival (Fig. 4) was 91.5% ± 4.1%. Two- and 5-year OS of patients after successful Kasai or intermediate result of the Kasai operation was 100%. In patients with failed Kasai operation, 2- and 5-year OS was 81% ± 8.6%. All 5 patients who did not undergo the Kasai PE received transplants and survived.

Deaths of Patients With BA

Four patients (8%, all with previous Kasai PE) died while waiting for LT. All of these deaths occurred before 2001; all of the patients had end-stage liver disease, including 1 who died from intracranial hemorrhage after minor head trauma, and 1 who died following a small bowel volvulus 5 months after undergoing the Kasai operation.

Prognostic Factors

Influence of Age at Kasai Operation

According to the age at Kasai operation, 4-year SNL was 75.0% ± 15.3% in patients who were operated on before 46 days (n = 9), 33.3% ± 10.3% for patients operated on between 46 and 75 days (n = 24), and 11.3% ± 10.6% if operated on after 75 days (n = 10) (P = 0.02) (Fig. 5).

No significant impact on SNL was demonstrated for the anatomical pattern of the extrahepatic biliary remnant (types 1–4), the polysplenia syndrome, and the caseload of the center performing the Kasai operation.

In a sample of 43 patients, 19 (44%) had ≥1 episodes of cholangitis, either suspected (fever, signs of sepsis, increasing cholestasis) or proven (positive blood cultures) after the Kasai operation: 8 of 17 patients with successful Kasai operation, 3 of 5 patients with intermediate result of the Kasai operation, and 8 of 21 patients with failed Kasai operation (P = NS).

DISCUSSION

In Western countries short-term clearance of jaundice can be achieved with the Kasai PE (10) in approximately 50% to 60% of children (11–13), one third of patients can survive with their native liver up to age 10 years (14–16),
and one fourth up to 20 years (16,17). Thus, LT is needed when the Kasai operation fails, and the overall survival of these patients has reached up to 90% in industrialized countries (7). Despite these important gains, detailed national data on the outcome of patients with BA are available only in a few countries.

In this study, the epidemiological characteristics of BA in Switzerland were found to be similar to reported data in other European countries. The incidence of BA in Switzerland was found to be 1 in 17,800 live births (95% CI 1/13,900–1/24,800), whereas it varies between 1 in 14,000 and 1 in 20,000 in other European studies. According to these studies and our results, the incidence of BA in Europe is approximately 1 in 18,000 live births; 1 in 18,000 belongs to the confidence interval of every European study, and compilation of reported European data from six countries (France [2]; Norway [3]; the Netherlands [5]; United Kingdom [6]; Sweden [4]; and Switzerland) leads to a calculated incidence of 1 in 18,400 live births (95% CI 17,200–19,800). Table 2 summarizes the reported worldwide incidences of BA and outlines the high incidence of BA in the Pacific Ocean region (18). In Switzerland we did not find any regional variation in incidence, as well as no significant

<table>
<thead>
<tr>
<th>Type of liver graft</th>
<th>Before 2001 (18)</th>
<th>After 2001 (11)</th>
<th>Total (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole liver</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Reduced liver</td>
<td>12</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Split liver</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Living donor</td>
<td>1 (Paris)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Deaths on LT waiting list</td>
<td>4 (22%)</td>
<td>0 (0%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Median age at LT (range)</td>
<td>15.5 mo (7.6–66.7)</td>
<td>11.1 mo (5.3–35.2)</td>
<td>11.7 mo (5.3–66.7)</td>
</tr>
</tbody>
</table>

Since 2001, the use of split liver grafts and living related liver donation increased, and no death occurred while waiting for LT.

#### TABLE 1. Type of liver graft
FIG. 5. Influence of age at the Kasai PE on SNL.

<table>
<thead>
<tr>
<th>Continent/country</th>
<th>Period</th>
<th>BA cases</th>
<th>Live births</th>
<th>Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France (metropolitan) (2)</td>
<td>1986–1996</td>
<td>421</td>
<td>8,221,167</td>
<td>1/19,500</td>
<td>1/17,800–1/21,600</td>
</tr>
<tr>
<td>Netherlands (5)</td>
<td>1969–1986</td>
<td>89</td>
<td>1,763,577</td>
<td>1/19,800</td>
<td>1/14,400–1/25,000</td>
</tr>
<tr>
<td>Norway (3)</td>
<td>1955–1974</td>
<td>64</td>
<td>1,113,600</td>
<td>1/17,400</td>
<td>1/14,000–1/23,100</td>
</tr>
<tr>
<td>UK (6)</td>
<td>1993–1995</td>
<td>93</td>
<td>1,553,100</td>
<td>1/16,700</td>
<td>1/13,900–1/21,000</td>
</tr>
<tr>
<td>Sweden (4)</td>
<td>1987–1997</td>
<td>85</td>
<td>1,204,791</td>
<td>1/14,200</td>
<td>1/11,700–1/18,000</td>
</tr>
<tr>
<td>Switzerland (present study)</td>
<td>1994–2004</td>
<td>48</td>
<td>854,186</td>
<td>1/17,800</td>
<td>1/13,900–1/24,800</td>
</tr>
<tr>
<td>Europe (compilation)</td>
<td>1955–2004</td>
<td>800</td>
<td>14,710,421</td>
<td>1/18,400</td>
<td>1/17,200–1/19,800</td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Atlanta (51)</td>
<td>1968–1993</td>
<td>57</td>
<td>773,360</td>
<td>1/13,500</td>
<td>1/10,800–1/18,300</td>
</tr>
<tr>
<td>Texas (30)</td>
<td>1972–1980</td>
<td>30</td>
<td>461,910</td>
<td>1/15,400</td>
<td>1/11,300–1/24,000</td>
</tr>
<tr>
<td>Pacific Ocean region</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Polynesia (2)</td>
<td>1986–1996</td>
<td>40</td>
<td>449,528</td>
<td>1/11,200</td>
<td>1/8500–1/16,300</td>
</tr>
<tr>
<td>Hawaii (54)</td>
<td>1947–1971</td>
<td>20</td>
<td>188,564</td>
<td>1/9500</td>
<td>1/6500–1/16,800</td>
</tr>
<tr>
<td>Japan (27)</td>
<td>1989–1999</td>
<td>1381</td>
<td>13,313,000</td>
<td>1/9600</td>
<td>1/9100–1/10,100</td>
</tr>
<tr>
<td>Taiwan (40)</td>
<td>2002–2003</td>
<td>30</td>
<td>119,973</td>
<td>1/2700</td>
<td>1/2400–1/5100</td>
</tr>
<tr>
<td>Victoria, Australia (20)</td>
<td>1963–1974</td>
<td>55</td>
<td>790,305</td>
<td>1/14,400</td>
<td>1/11,400–1/19,500</td>
</tr>
</tbody>
</table>

* Calculated number.
Four-year SNL in patients who underwent the Kasai operation was 37.4% in our series, which is lower than the results obtained in European specialized centers (48% in Paris Bicêtre (20), 51% in the 3 supraregional British centers (Birmingham, Leeds, London) (11), 49% 5-year SNL in Madrid) (21). Caseload of the centers were correlated with the results: in the United Kingdom, 2 studies (5,12) showed a wide variation in SNL according to the experience of the centers in the management of patients with BA. These findings led to the centralization of all British patients with BA in 3 pediatric liver units (for a British population of about 60 million people), which are able to manage the child from diagnosis to LT. This policy proved to be efficient, high level results now being obtained for all children nationwide (11). In France (same population of 60 million people), a similar discrepancy in results was observed according to the center’s caseloads (22). This led to the creation of the French Observatory of Biliary Atresia, and the promotion of an increased collaboration between centers to standardize procedures and optimize results at the highest possible level. This policy has been less effective: SNL remained unchanged in the center performing >20 Kasai operations per year (48% 4-year SNL), improved from 31% to 45% in the centers performing 3 to 5 Kasai operations per year, and remained suboptimal in the centers performing ≤2 Kasai operations per year (20). In the present study, no significant difference in results between Swiss centers could be demonstrated. Nevertheless, the limited caseload in the whole country (population of 7.5 million people, 4–5 new BA cases per year) and the suboptimal results of the Kasai operation nationwide (4-year SNL of 37%) raise the question of a nationwide management of patients with BA, either along the British centralized or French collaborative types, to avoid unnecessary LTs in infancy and early childhood. Comparisons of SNL and overall patient survival show that among the patients alive at 4 years old, 60% have received transplants in Switzerland, 51% in France (20), and 43% in the United Kingdom (11).

Liver transplantation was needed in 31 of 48 children with BA, including 5 patients without previous Kasai operation. In our study 4 patients died while waiting for LT, all of them before 2001. Of note, before 2001 split liver grafts were not commonly used, and neither were LTs performed with parental living donors (Table 1). The advent of these techniques has notably reduced the shortage of organs for pediatric recipients and diminished the loss of patients on the waiting list; the rate of patients dying while waiting for a LT dropped from 22% before 2001 to 0% thereafter. This evolution has also been observed in the United Kingdom, where the mortality without LT diminished from 10.8% in the 1993–1995 national study (5) to 4.7% in the 1999–2002 study (11), and in France from 15.6% in the 1986–1996 study (22) to 7.0% in the 1997–2002 study (20). Survival after LT was excellent in the Swiss series: all of the patients who received transplants are alive.

Four-year OS of all patients with BA was 91.5% in Switzerland, fitting the international western standards. In Europe, 4-year OS was 87.3% in France (271 patients, 1997–2002) (20), and 89% in the United Kingdom (148 patients, 1999–2002) (11). In the Biliary Atresia Research Consortium series (104 patients from 9 US centers, 1997–2000), actual 2-year OS of patients with BA after Kasai operation was 91.3% (23). Five-year overall survival of all patients with BA was 77.3% in Canada (349 patients, 1985–2002) (24), 75.5% in Japan (1381 patients, 1983–1999) (25), and 41.9% in Taiwan (30 patients, 2002–2003), where LT is not as readily available as in Western countries (26).

The age at Kasai PE has been repeatedly shown to influence SNL in large series (22,27–30). There are also contradictory reports that fail to show the influence of the age at Kasai on success of the PE (5,31–33). As outlined by McKiernan et al, these results may be due to insufficient numbers of patients in the subgroups to be compared (5). Nevertheless, in our small series, the effect of age at Kasai operation appeared clearly. These results emphasize the need to diagnose BA early and promptly operate on these patients. In this Swiss series, the median age at Kasai operation was 68 days (range, 30–126), which is higher than in other recent series: 57 days (12–151) in France (20), 54 days (7–175) in the United Kingdom (11), and 61 days (11–153) in the US-BARC series (23). Therefore, efforts are needed to sensitize parents and health personnel to look at stool color, which is a simple method to detect neonatal cholestasis. At the national level, these efforts may lead to the use of a personal stool color card for each neonate, as in Japan (34), Taiwan (35), or Argentina (36). Moreover, every case of neonatal jaundice lasting >14 days should be explored to rule out cholestasis and biliary atresia (37). Even after the age of 3 months, however, appreciable chances of success of the Kasai operation do persist. In the French national series 1986–1996, 25% of the patients operated on after 3 months were alive with their native liver at 5 years (38). At the King’s College Hospital, London, 5-year SNL was 45% in a series of patients with BA who were operated on after 100 days of age (39).

Our results as well as those of other studies show that postoperative clearance of jaundice is a strong indicator for the success of the Kasai PE and thus the need for LT (26,28,40). We failed to demonstrate any correlation between the degree of clearance of jaundice (complete, intermediate, none) and the incidence of episodes of cholangitis. However, cholangitis is known to impair the outcome after the Kasai PE (26,31,41–43), and every
episode needs early and vigorous therapy. In contrast to other studies (22,44), the anatomical pattern of the extrahepatic biliary remnant (type 1 to 4), or the existence of a polysplenia syndrome were not found to have a significant impact on SNL after the Kasai operation. These negative results may be due to the small number of patients in the present study.

In conclusion, our study shows that overall survival of children with BA in Switzerland compares favorably with international standards, whereas results of the Kasai operation for biliary atresia could be improved to reduce the need for LT in infancy and early childhood.

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