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Biliary atresia: we still operate too late

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Abstract

Objective: To analyze the age at surgery for children with biliary atresia and their survival periods without need for liver transplantation. The study was performed at Hospital de Clínicas de Porto Alegre, in Porto Alegre, state of Rio Grande do Sul, Brazil.

Methods: The medical records of patients operated between 1982 and 2007 who were residents of the state of Rio Grande do Sul were reviewed.

Results: Of the 112 cases of children with biliary atresia studied, 38 (33.9%) occurred between 1982 and 1989, 46 (41.1%) between 1990 and 1999 and 28 (25.0%) after 2000. Portoenterostomy was not performed for 12 cases (10.7%). Age at surgery ranged from 25 to 297 days (median: 80.5; IQR25-75: 61.3-109.0 days); for 20.5% of cases, the age was below 60 days. There was no age difference at diagnosis for the three decades in the study. Patients from the countryside (median: 87.0; IQR25-75: 69.0-115.0 days) were referred significantly later ($p = 0.007$) than those living in Porto Alegre and the metropolitan area (median: 68.0; IQR25-75: 55.5-98.0 days). The ratio of patients younger than 60 days was significantly lower ($p = 0.013$) for those from the countryside. Survival periods with native liver for all patients was 46.2% in 2 years, falling continuously until reaching 15.3% in 20 years. Patients operated before reaching 60 days of age had longer survival periods with native livers (log rank < 0.0001).

Conclusions: Late performance of portoenterostomy was a constant in the past 25 years, and this delay led to shorter survival periods with native livers for biliary atresia patients.

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Introduction

Biliary atresia (BA) is a chronic hepatic disorder which predominantly affects children and is the most common cause of neonatal cholestasis. Its etiology remains unknown, but BA probably results from a heterogeneous process in which an initial insult (whether infectious, ischemic or chronic) leads to the progressive inflammatory destruction of bile ducts in genetically susceptible patients.[1] BA is universally distributed. It is estimated that 1 in every 5,000-18,000 live births are affected by the disease.[2] Symptoms are seen in the first weeks of life and, without early treatment, evolve into chronic cholestasis, biliary cirrhosis and death within 2 years.[3] Untreated BA is fatal. The first line of treatment is portoenterostomy (PE), and the only alternative is liver transplantation.[4] The initial success of PE is important for the long-term survival of children suffering from BA.[5] The reestablishment of bile flow after PE can be assessed by the normalization or partial reduction of serum bilirubin levels. Even in patients

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with significant hepatic fibrosis, decreased jaundice is associated to longer survival periods with native livers, thus retarding the need for liver transplantation.

Some individual characteristics of each patient influence the BA prognosis after PE, such as type of atresia and the presence of congenital extrahepatic anomalies. These factors are intrinsic to each patient and may not be modified. On the other hand, factors such as infant age, surgeon experience and the number of portoenterostomies performed per year at the institution are directly related to the organization of healthcare for these children and may be changed.[3,5]

Patient age at the time of surgery has been found to be an important prognostic factor. Patients who undergo surgery at later dates present the worst results in terms of restoration of bile flow and are subject to transplants and premature death. The best results are found when the surgery is performed before 60 days of life.[3,4]

The objective of the present study was to assess the age of primary surgical treatment for BA and how the experience of Hospital de Clínicas de Porto Alegre (HCPA), a tertiary referral care center in the state of Rio Grande do Sul, has evolved in the past 25 years.

Methods

The medical histories of BA patients followed at HCPA from 1982 to 2007 were reviewed. Of the 176 case histories available, 112 were studied. The patients came from the capital city of Porto Alegre and 30 other cities less than 75 km from Porto Alegre (those in its metropolitan area) or from cities further away in the state. Members of the latter group were categorized as countryside patients.

Initial investigations consisted of clinical histories, physical examination, seeking congenital infections and innate metabolic illnesses, abdominal ultrasound scanning and bile duct radionuclide scanning; cholestatic infants with no biliary permeability were submitted to exploratory laparotomy, during which cholangiography was performed. The final diagnosis of BA was established by the absence of biliary permeability, followed by exploratory surgery to the hepatic hilum and enterostomy. All procedures were performed by the same surgical team. Age at surgery was divided into three ranges: up to 59 days, 60 to 89 days and ≥ 90 days. Treatment was categorized as delayed when it was provided after the 59th day of life. Surgery years were grouped into time periods divided by decade: from 1982 to 1989, from 1990 to 1999 and from 2000 onwards.

All patients were followed during admission and at the outpatient pediatric gastroenterology department by the same clinical staff. Assessment of clinical evolution included records of years of survival without need for liver transplantation (survival period with native liver) or age at transplant and/or death.

Category variables were described in frequency distribution tables, while continuous variables were described as medians and interquartile ranges (IQR). Chi-square, Fischer exact, Mann-Whitney, Kruskal-Wallis and Kaplan-Meier tests were used for statistical analysis, with significance level < 0.05. Microsoft Excel version 2003 and SPSS version 11.0 were used for storing and analyzing the data.

The present study was approved by the HCPA research ethics committee and was funded by the Fundo de Incentivo à Pesquisa e Eventos at HCPA.

Results

In the 25 years included in the present study, of the 112 children suffering from BA, 26 (23.2%) came from the city of Porto Alegre, 27 (24.1%) from the metropolitan area and 59 (52.7%) from the countryside. The number of cases per year ranged from 1 to 13, averaging 4.5 patients per year. Thirty-eight patients (33.9%) were operated before 1989, 46 others (41.1%) during the nineties and 28 (25.0%) from 2000 onwards. Fifty-nine (52.7%) patients were girls.

Age at surgery ranged from 25 to 297 days of life (median: 80.5; IQR25-75: 61.3-109.0 days). PE was not performed in 12 children (10.7%). The cause for 9 was their advanced age (median: 169.0 days; IQR25-75: 123.5-248.5 days), associated to their severely compromised general condition, while the parents of the other three did not authorize PE (median: 77.0; IQR25-75: 61.0-156.0 days). Comparisons between age at surgery and origin, performance of PE and decade of procedure are shown in Table 1.

Most children (79.5%) were 60 days-old or older at surgery. Only 23 (20.5%) were operated before reaching 60 days of life. Forty-five surgeries (20.5%) were performed between the 60th and 89th day of life, while the remaining 44 (39.3%) were performed at 90 days or more. Age range frequencies differed significantly depending on the origin and the performance or not of PE (Table 2). There was no difference in the ratio of age ranges between the three decades studied (Table 2 and Figure 1).

Of the 112 patients, 43 (38.4%) are alive, 23 of which (20.5%) with their native livers. Since March 1995, when the HCPA Pediatric Liver Transplantation program began,[6] 26 (23.2%) patients were submitted to transplants, 20 of which (77%) are alive (age: 5.3±4.7 years).

Survival period with native liver (Figure 2 and Table 2) was influenced by performance of PE and age range at time of surgery (log rank < 0.0001). All children not submitted to PE either died or underwent liver transplantation before 2 years of age. Among children submitted to PE, the survival period with native liver was 46.2% at 2 years, 33.1% at 5 years, 24.2% at 10 years and 15.3% at 20 years.

Table 1 - Relation between age at surgery and origin, performance of PE and year of surgery

Age at surgery (days)	n (%)	Median (IQR25-75)	p
Origin			
Countryside	59 (52.7)	87.0 (69.0-115.0)	0.007*
Porto Alegre/Metropolitan area	53 (47.3)	68.0 (55.5-98.0)	
Surgery			
PE	100 (89.3)	76.5 (60.3-98.0)	0.000*
No PE	12 (10.7)	152.5 (110.5-239.0)	
Year of surgery			
1982 to 1989	38 (33.9)	83.0 (61.8-120.3)	0.498†
1990 to 1999	46 (41.1)	82.5 (64.0-102.3)	
2000 to 2007	28 (25.0)	70.5 (60.3-96.3)	

IQR = interquartile ranges; PE = portoenterostomy.
* Mann-Whitney test.
† Kruskal-Wallis test.

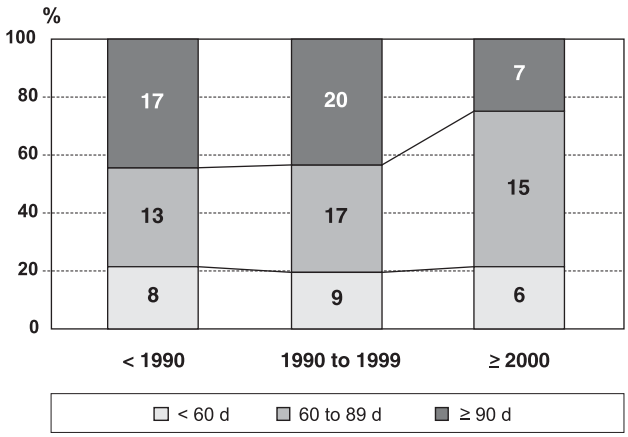
Table 2 - Relation between age range at surgery with origin, performance or not of PE, year of surgery and survival with native liver

Age at surgery (days)	< 60 n (%)	60-89 n (%)	≥ 90 n (%)	p
Origin				
Countryside	6 (10.2)	26 (44.1)	27 (45.8)	0.013*
Porto Alegre/ Metropolitan area	17 (32.1)	19 (35.8)	17 (32.1)	
Surgery				
PE	23 (23.0)	43 (43.0)	34 (34.0)	0.004*
No PE	0 (0.0)	2 (16.7)	10 (83.3)	
Year of surgery				
1982 to 1989	8 (21.1)	13 (34.2)	17 (44.7)	NS*
1990 to 1999	9 (19.6)	17 (37.0)	20 (43.5)	
2000 to 2007	6 (21.4)	15 (53.6)	7 (25.0)	
Survival with native liver				
1 year	21 (91.3)	32 (74.4)	19 (55.9)	0.026†
3 years	12 (52.2)	19 (44.2)	7 (20.6)	0.022†
5 years	12 (52.2)	17 (39.5)	6 (17.7)	0.014†
10 years	12 (52.2)	13 (30.2)	3 (8.8)	0.002†
20 years	10 (43.5)	11 (25.6)	2 (5.9)	0.002†

PE = portoenterostomy.
* Fischer exact test and chi-square test.
† Kaplan-Meier estimator (log rank).

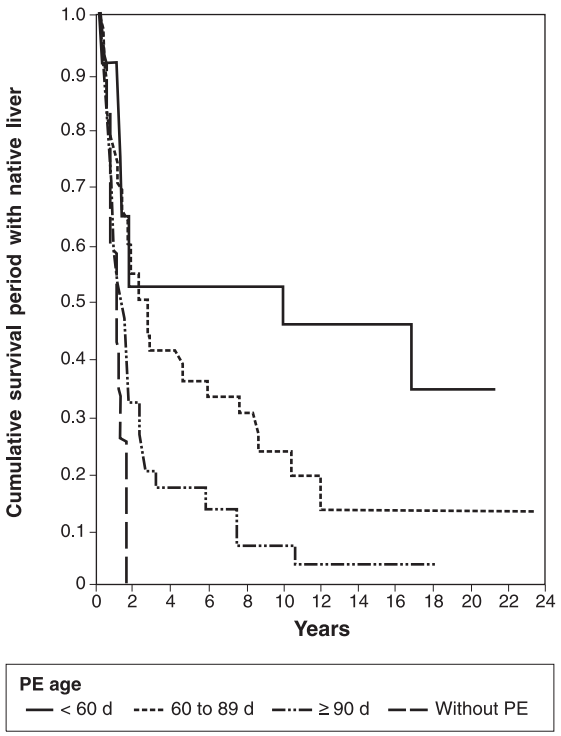
Discussion

There are few reports of experience with BA in Brazil,[7-10] but they all share that most diagnoses (76 to 94.7%) are made after the eighth week of life. In a previous analysis of our group ten years ago, in 1997, most (73.5%) BA diagnoses were made, as in the present study, after the eighth week of life.[11] Only 20% of patients were submitted to PE before 60 days of life, and there were no changes to that scenario in the three decades studied. A similar situation was recently described



d = days of life.

Figure 1 - Ratio of age ranges at time of surgery for each decade (p = 0.45)



d = days of life; PE = portoenterostomy.

Figure 2 - Survival time with native liver for patients with biliary atresia by age at time of portoenterostomy (Kaplan-Meier, log rank p < 0.0001)

for a Thailand center, in which only 22.8% of patients were operated before 60 days of life.[12]

Experience in other countries shows that this scenario can change. In England, the rate of children operated before 60 days of life went from 18% in the seventies to 38% in the eighties and 61% in the nineties.[13] In Japan, circa 34% of patients were operated before 60 days of age in 1989, but that rate jumped to 45% after ten years.[14] In the US, recent reports indicate that 66% of children were operated before completing two months of life.[15]

Median age at surgery in our series was 80.5 days, higher than both older series (61 to 69 days)[16,17] and more recent ones (54 to 68 days).[5,14,18-21] Only the average PE age of the Thailand series (90.3±36.4 days) was similar to that found in the present study (93.7±51.3 days).[12]

In the present study, patients from the countryside were significantly older at the time of surgery. Lack of access to healthcare services, lack of conditions to investigate jaundice and problems referring patients to the HCPA are possible explanations for the greater delay in diagnosis.

The rate of patients not submitted to PE in our series was higher than rates recorded in scientific literature (0.3 a 10.4%).[3,5,14-22] The presence of uncompensated cirrhosis or malformations in other organs which could rule out surgery.[3,22] Nine patients over three months old and with advanced hepatic failure were not submitted to PE. On the other hand, some parents resisted the surgical procedure.[4,23,24] For three other cases without PE, religious conviction influenced the decision of parents and caretakers not to authorize the procedure, despite suitable age and clinical conditions.

Life expectancy for children with BA who did not undergo operations is 2-3 years.[3] Without liver transplantation, patients without PE included in this study survived only to the age of two. Performing PE enables a survival period which can go beyond 20 years for 20% of patients.[20,22] Survival periods range from 30 to 59.7% at 4-5 years, and from 24 to 52.8% at 10 years after surgery, as reported by European[5,17-22], North American[25,26] and Asian[14,20] studies. The best results were seen in Japan.[14] Survival periods for patients in our study who did not require transplantation were lower than those mentioned above, at 24 and 15% after 10 and 20 years, respectively.

As shown in several series, patient age at the time of surgery is one of the main factors for long-term survival.[3,4,14,16,17,20,21] In the present study, patients submitted to PE before completing 60 days of life achieved survival rates of over 50% in 5 and 10 years, similar to what has been described for other countries.[16,20]

Results from some studies have suggested that the earlier the PE, the longer the survival period with native liver in the long run.[16,17,21,26] A recent study from Switzerland showed a survival period with native liver of 75% for five years when PE is performed during the first 45 days of life, decreasing to 33% when it is performed from the 46th to 75th day of life and to 11% if performed after the 75th day.[21]

In the present study, performance of PE after 90 days of life results in loss of native liver in the first three years of life

for 80% of cases, similar to results seen in Canada.[26] The timely diagnosis and treatment of BA reduces the need for early liver transplantation. Due to the lack of organ donors, particularly small-sized donors, the ability to postpone transplantation increases the odds of finding a suitable organ and decreasing the need for alternative techniques, such as reducing or "splitting" grafts and transplantation from a living donor, shortening immunosuppression time and its attending long-term complications, as well as being cost-effective.[4]

The pursuit of longer survival periods with native livers has led to debates over the need to make earlier diagnoses of BA.[2,19] Currently, BA has not been included in any routine neonatal screen program.[2] Theoretically, the analyses of bile acid and bilirubin in samples collected for routine neonatal screening would be useful; however, they still have not shown themselves to be useful in clinical practice.[27]

In some countries, routine BA screening has involved distributing a colored card with a stool color scale to parents.[23,28-30] This method has shown elevated specificity for diagnosing cholestatic diseases, including BA, though with lower sensitivity than the ideal for a screening test.[2,23,29] The need for using this sort of card was recently shown in Taiwan, as it decreased the age of referral for neonatal cholestasis patients.[6,24] The national rate of PE before 60 days rose from 41.1 from 1977 to 2000[20] to 72.5% in 2004 and to 97.1% in 2005.[24] Likewise, the rate of children without jaundice 3 months after PE rose from 37% before 2000 to 59.5% with the screening program.[24]

The present study indicates that there is still a long way to go to improve life expectancy for BA children in Brazil. We argue that an active strategy, such as the use of a chromatic scale comparing the color of infants' stool, should be developed to decrease delays in BA diagnosis and treatment. Since the Child's Health Record[31] (a document distributed by the Brazilian Ministry of Health to all parents of newborns) is colored, it could easily be adapted to include images and instructions of behavior for cases of hypocholic or acholic stool.

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