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Biliary Atresia – Clinical Series

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Keywords
Biliary atresia · Kasai portoenterostomy · Liver transplantion

Abstract
Introduction: Biliary atresia is the main cause of death by hepatic failure and the main indication for liver transplant in children. This study aims to analyze the population with this diagnosis, treated between 2000 and 2015 at Hospital de São João. ***Material and Methods:*** Descriptive, observational, and retrospective study, including the patients with biliary atresia, diagnosed and treated between January 1, 2000 and December 31, 2015. We analyzed epidemiologic, clinical, biochemical, and image data, as well as registered complications and present status. ***Results:*** Eighteen patients were evaluated. The median age at time of Kasai portoenterostomy was 63 days of life, with better prognosis for those patients who had surgery before 72 days. The procedure was successful in 2/3 of cases. There was a significant association between recurrent cholangitis and survival. Five cases of transplant and 2 deaths, one of them after transplant, were registered. Survival with native liver was 77.8%, 72.2%, and 64.2% at 1, 5, and 10 years of follow-up, respectively. ***Discussion:*** The presentation and evolution of patients was similar to other studies. However, there was a higher surgical success and survival rates at 5 and 10 years of follow-up than most series. Age at surgery and recurrence of cholangitis were the only factors significantly related to prognosis. ***Conclusion:*** In spite of the low number of patients (1,125/year), our results were similar to those of other reference centers.

Atresia das Vias Biliares – Revisão Casuística

Palavras Chave
Atresia das vias biliares · Portoenterostomia de Kasai · Transplante hepático

Resumo
Introdução: A atresia das vias biliares representa a principal causa de morte por insuficiência hepática e a principal indicação para transplante hepático em idade pediátrica. O objetivo deste estudo é analisar a população com este diagnóstico, tratada entre 2000 e 2015 no Hospital de São João. ***Material e Métodos:*** Estudo descritivo, observacional e retrospetivo, incluindo-se doentes com atresia das

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vias biliares diagnosticados e tratados entre 1 de Janeiro de 2000 e 31 de Dezembro de 2015. Foram analisados dados epidemiológicos, clínicos, bioquímicos, imagiológicos, idade à data da cirurgia, complicações ocorridas e o estado atual. ***Resultados:*** Foram avaliados 18 doentes. A idade mediana à data da portoenterostomia de Kasai foi de 63 dias de vida, verificando-se um melhor prognóstico nos pacientes operados antes dos 72 dias. Foi constatada drenagem biliar adequada em 2/3 dos casos aos 6 meses. Verificou-se uma associação significativa entre a ocorrência de episódios recorrentes de colangite e a sobrevida. Registaram-se 5 transplantes e 2 óbitos, um dos quais pós-transplante. A sobrevida com fígado nativo foi de 77.8%, 72.2% e 64.2% ao 1º, 5º e 10º anos de seguimento, respetivamente. ***Discussão:*** A apresentação e evolução dos pacientes coincidiu, de um modo geral, com o descrito na literatura. No entanto, constatou-se uma taxa de sucesso operatório e de sobrevida com fígado nativo aos 5 e 10 anos superiores à maioria das séries. A idade à data de cirurgia e a recorrência dos episódios de colangite foram os únicos fatores que se mostraram significativamente relacionados com o prognóstico. ***Conclusão:*** Apesar do número reduzido de doentes (1,125/ano), foram registados resultados comparáveis a outros centros de referência.

Introduction

Biliary atresia is a rare disease that occurs in 1 per 10,000–16,700 births, with a slight predominance in females [1], in which there is total or partial obliteration of the extrahepatic biliary tract and subsequent proliferation of intrahepatic ducts. It represents the main cause of death by hepatic failure and the main indication for hepatic transplant in children [2–4].

Its etiology is yet to be explained, but it is believed that it can be the result of the interaction of genetic (associated with other malformations in 10–20% of cases), environmental, immune, and infectious factors, individually or in combination [1].

Diagnosis is mostly made at 2–6 weeks of age, presenting with cholestasis – jaundice, acholia [5] and possibly choluria and hepatomegaly [1]. Laboratory results usually show conjugated hyperbilirubinemia associated with an increase in γ-glutamyltransferase (GGT) [6] and soft to moderate cytolysis. Preoperative evaluation may include: abdominal ultrasound, hepatobiliary scintigraphy, endoscopic retrograde cholangiopancreatography, and magnetic resonance cholangiopancreatography (MRCP). However, the definitive diagnosis is confirmed only by exploratory surgery [1] (Fig. 1).

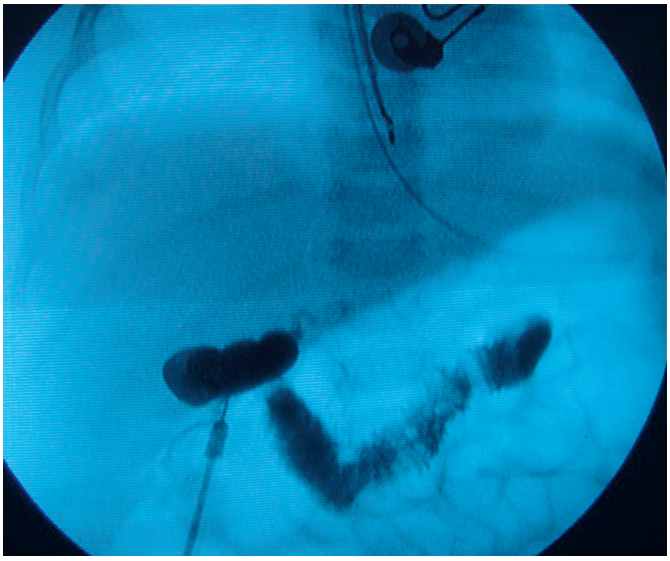

Fig. 1. Perioperative cholangiography that confirms the diagnosis of biliary atresia.

Kasai portoenterostomy (PE) is the gold standard treatment, consisting in total extraction of the hilar fibrosis and subsequent biliary-enteric anastomosis, with favorable results in about 2/3 of cases, in which there is total restitution of the biliary drainage and normalization of total bilirubin levels [7]. Main prognostic factors to short- and long-term survival after this procedure include age at surgery, type of biliary atresia, and surgeon's experience [8, 9]. Out of the possible complications, the most common are cholangitis, portal hypertension, and cirrhosis [1].

This study aims to analyze all the biliary atresia cases diagnosed at Hospital de São João, Porto, Portugal, between the years 2000 and 2015, focusing on these patients' treatment and prognosis.

Material and Methods

This is a descriptive, observational study, approved by the ethics committee of Hospital de São João, in which the clinical files of all the patients who were diagnosed with biliary atresia and treated at Hospital de São João's Pediatric Surgery Department between January 1, 2000 and December 31, 2015, were retrospectively analyzed. Two cases were excluded due to loss of follow-up and misdiagnosis. The patients were evaluated at 6 weeks, 6 months, and

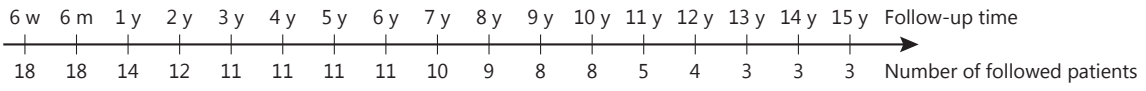

Fig. 2. Evolution of case numbers with follow-up time. w, weeks; m, months; y, years.

each year, between the date of surgery and the date of death, hepatic transplant, or the end of this study's period (Fig. 2).

The study population was characterized according to the following parameters: gender, age at surgery, and presence of other congenital malformations. Referring to preoperative evaluation, it was analyzed: diagnostic tests and preoperative levels of total bilirubin, GGT, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Short- and long-term therapeutics were studied, in particular surgical antibiotic prophylaxis, corticotherapy, and ursodeoxycholic acid (UDCA) administration in the immediate postoperative period, as well as long-term antibiotherapy in order to prevent cholangitis episodes. At 6 weeks, 6 months, and annually after surgery, it was analyzed: total bilirubin levels, occurrence and number of cholangitis episodes, development of portal hypertension, hepatic transplant and its indication, and survival.

Criteria to classify Kasai PE as successful (functioning) were defined as normalization of total bilirubin levels during the first 6 months following the procedure [6, 7]. Increased levels of bilirubin were defined as those higher than 12 mg/L, according to the classification of this Hospital's laboratory. Portal hypertension diagnosis was considered when at least two of the following features were present: esophageal varices, ascites, splenomegaly, and thrombocytopenia.

All the data were entered into a database, created with IBM SPSS Statistics 23®, which was also used to perform the statistical analysis. A descriptive statistical analysis was made, with measures of both central and dispersion tendency. The quantitative variables are presented as either median (minimum–maximum) or clustered and evaluated as categorical variables – these results are presented as percentages and analyzed using the χ^2 test. Statistical significance was considered for $p < 0.05$. In order to calculate the postoperative native liver survival rates, Kaplan-Meier method was used, assuming it started at the time of Kasai PE and ended at the time of death or hepatic transplant.

Results

Eighteen patients with biliary atresia were treated (9 females and 9 males) at Centro Hospitalar São João's Pediatric Surgery Department, from 2000 to 2015, with 9.7 years (1.2–15.6) average follow-up time. Among these patients, 5 (27.8%) also presented with other malformations: 3 (60%) with splenic malformations (2 polysplenias and 1 asplenia) and 2 (60%) with cardiac malformations (1 patient with a polymalformative syndrome including left superior vena cava associated with coronary sinus dilation and patent foramen ovale and 1 patient with multiple cardiac malformations, including intraventricular communication, patent foramen ovale, and patent arterial duct).

All these patients were submitted to cardiac ultrasound, ophthalmic evaluation, cervical radiography, and α1-antitrypsin levels and viral markers measurement. Every patient was assessed with abdominal ultrasound, 10 (55.6%) with liver biopsy, 8 (44.4%) with hepatobiliary scintigraphy, and 7 (38.9%) with MRCP. It was noticed that, during the period of this study, while hepatobiliary scintigraphy lost relevance, MRCP gained some importance as a diagnostic method. There was only one case in which the exploratory surgery did not confirm the diagnosis of biliary atresia.

During preoperative care, patients presented with median levels of total bilirubin 114.8 mg/dL (7.8–810). Median levels of AST and ALT were registered as 163.5 U/L (38–496) and 117 U/L (42–456), respectively. At last, GGT median levels were 656 U/L (76–2,214). There was no statistically significant association relating these levels to native liver survival.

Patients were submitted to Kasai PE at a median age of 63 days (34–150). It was noticed that those in whom surgery was performed before 72 days of age (61.1%; 11) had better evolution (none needed liver transplant) than the others (5 transplant cases out of 7; 71.4%). There was a strong association between these two variables, measured with χ^2 test ($p = 0.001$).

During postoperative care, every patient had antibiotic prophylaxis using cefoxitin (25 mg/kg/dose). Medium-term therapy included administration of UDCA (15–20 mg/kg/day) to every patient until they had reached normal bilirubin levels. Thirteen (72.2%) cases were treated with corticosteroids (methylprednisolone) using the following scheme: 20 mg/day i.v. during the first day, decreasing by 2.5 mg/day until 5 mg. Weaning was done by giving prednisolone p.o. 5 mg/day during 1 week. Two

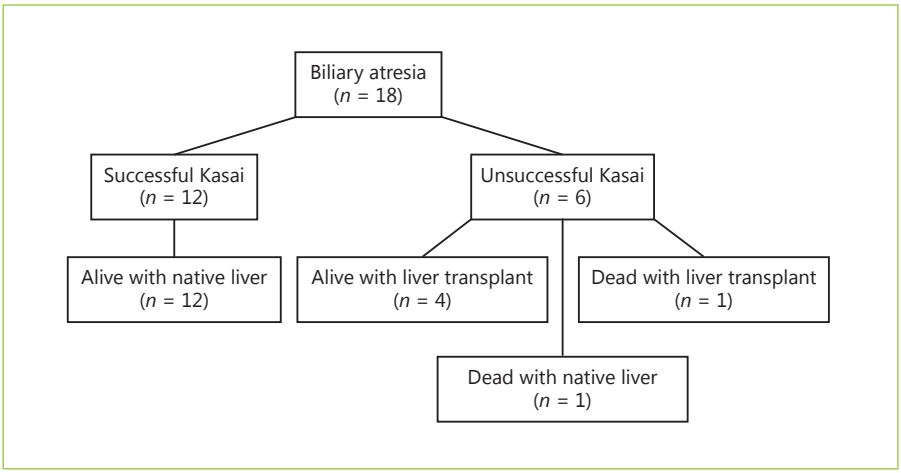

Fig. 3. Evolution of studied cases.

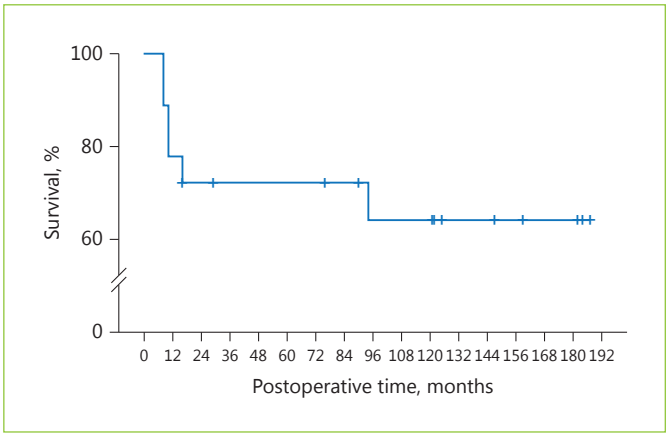

Fig. 4. Kaplan-Meier curves, representing native liver survival during postoperative time.

Table 1. Native liver survival rates at 1, 5, and 10 years of follow-up, obtained with Kaplan-Meier method

Follow-up time	Native liver survival
1 year	77.8%
5 years	72.2%
10 years	64.2%

(11.1%) patients also did long-term prophylactic antibiotherapy using amoxicillin and clavulanic acid.

Two-thirds (12) of the patients met the criteria for functioning Kasai PE. Out of these, 6 had normal levels of total bilirubin at 6 weeks after surgery; the remaining 6 reached normal levels by the 6th month (Fig. 3).

During follow-up, 11 patients (61.1%) had at least one episode of cholangitis, and 3 of them (27.2%) had multiple episodes. Out of the latter group, 1 patient has kept his native liver and the remaining 2 patients are the only ones who did not survive – 1 after liver transplant and 1 while in the waiting list for transplant. Among those who only had one episode of cholangitis (8), 3 (37.5%) needed liver transplant. Among the patients without any episode of cholangitis, only one (14.3%) was transplanted. However, this difference was not statistically significant. On the other hand, after using the χ^2 test, a statistically significant difference ($p = 0.011$) was noted when comparing survival rates in patients who only had one cholangitis event to those who had recurring episodes of this complication. The global rate to develop portal hypertension is 44.4% (11).

Among those patients who had other associated malformations (5), only one needed liver transplant. There was no statistically significant difference between the presence of other congenital malformations and native liver survival, using χ^2 analysis.

Four (80%) patients who were submitted to liver transplant were indicated because of hepatic failure and 1 (20%) because of portal hypertension exacerbation, at 8 years of follow-up. It is relevant to note that this latter patient presented with increased total bilirubin levels close to normal until the 5th follow-up year, having stabilized at that time.

The median time between Kasai procedure and transplant was 9 months (8–94); the average time was 29.75 months. By the end of the first follow-up year, 77.8% of patients had their native liver (Table 1; Fig. 4).

Global survival rate is 88.9% (16 out of 18). Two deaths were documented, both in female patients – one due to post-transplant complications and the other one as consequence of primary peritonitis, while the patient was waiting for liver transplant.

Discussion

The results presented in this study report a follow-up period of 16 years (2000–2015) during which 18 cases were analyzed. The sample size is an important limitation to the statistical analysis of the collected data. However, during this period of time, all the patients were approached by the same surgical team and the follow-up was made by the same gastroenterology team, which represents an advantage, as the recommended treatment strategy has remained the same during the last years.

Biliary atresia patients typically present with total bilirubin levels higher than 58.5 mg/L, GGT levels higher than 100 UI/L, and AST and ALT levels between 80 and 200 UI/L [7]. The patients studied in this clinical series presented, both clinically and analytically, as expected. However, a statistically significant difference was not documented when comparing preoperative levels to the prognosis of this disease.

The biliary atresia variant that associates with other congenital malformations is described in multiple studies, its percentage oscillating between 10 and 25% [5–7, 10–15]. However, it is not consensual that it is related to worse prognosis [8, 16]. In this clinical series, in 27.8% of patients, an association with other congenital malformations was documented. This rate is slightly higher than what is described in other studies; however, a statistically significant association to native liver survival was not registered.

An evolution was noted when it comes to diagnostic tests, seeing that there was a progressive replacement of hepatobiliary scintigraphy by MRCP. The fact that only once was there a need for exploratory surgery shows the adequacy of the diagnostic methods used on these patients' evaluation. In this series, there was a single prenatal suspicion of biliary malformation, in which the diagnostic suspicion of choledochal cyst turned out to be a biliary atresia in the postnatal period.

All the patients were given UDCA in the postoperative period, even though its beneficial effects, related to the increase in biliary acid drainage, hence preventing fibrosis and consequent progression of hepatic injury and a possible immunomodulator effect [4, 15], are still unclear [9, 12]. On the other hand, corticoids were not systematically prescribed, having only been given to those patients in whom early biliary drainage was not satisfactory. Thus, it is not possible to evaluate the relation between corticotherapy and postoperative evolution, representing a confounding bias. Accordingly, long-term prophylactic antibiotherapy was only prescribed to patients who had multiple cholangitis episodes after surgery.

One of the main prognostic factors after Kasai procedure is the patient's age at time of surgery. Higher success is documented, in multiple studies, when patients are 60–90 days old [1, 8, 10, 12, 15] and surgery after 100 days of age is controversial [7]. In this study, patients had surgery at a median age of 63 days. There was a positive relation, with statistical significance, to native liver survival in patients who were submitted to surgery before 72 days of life, which supports the data referred to in other studies.

In the literature, it is assumed that 40–60% of patients who go through Kasai PE have appropriate biliary drainage [17]. Even though some studies defend that treatment in specialized centers is an important prognostic factor [18–20], in this series, a success rate of 67.7% was documented. This number is favorably compared to most of other published series, including a study conducted in the United Kingdom, after these patients' treatment was focused in only 3 reference centers [20].

Multiple studies describe a cholangitis rate between 30 and 60% [10, 12, 13, 15]. In this series, a similar rate for this complication was documented (61.1%). The fact that there was no statistically significant relation between prognosis and the occurrence of cholangitis is most likely due to the small size of this study's sample. Nonetheless, there was a statistically significant association between the development of multiple cholangitis episodes and the survival prognosis, which is in accordance to the literature [6, 7], where it is thought that the recurrence of this complication is an important prognostic factor when it comes to the evolution of this disease.

Moreover, a portal hypertension development rate (44.4%) inferior to that registered in other studies [13, 16, 21] was documented in this series. These studies describe that over 2/3 of biliary atresia patients will present with this complication. This difference is probably related to the short follow-up time of some of the studied patients, in whom portal hypertension may be documented in the future. However, since this diagnosis is often clinical and based on diagnostic tests – in the same way as it was defined in this series – portal hypertension prevalence in biliary atresia may be underestimated [21].

Multiple studies document a native liver survival rate of approximately 30% after 20 years of follow-up [4, 10, 15]. Two studies conducted in France and the United Kingdom registered a survival rate without liver transplant of 43 and 51%, respectively, at 4 years of follow-up [16]. In this study, a rate of 72.2% at 5 years and 64.2% at 10 years of follow-up was recorded. Global survival rate was 88.9%, in line with other numbers documented in the literature [4, 10, 12, 15, 16], even though one of the registered deaths was due to post-transplant complications and is not directly related to the primary disease.

Conclusion

These results allow the conclusion that an appropriate and timely approach was ensured to this department's biliary atresia cases. Despite the average number of 1.25 cases per year, this study presents results that are comparable to those of other international reference centers with higher case numbers.

Nevertheless, more comprehensive studies with larger and more representative samples are needed in order to understand the exact etiology of biliary atresia, as well as other prognostic criteria for both the disease and its standard surgical treatment, and to integrate these findings in a national level, so that measures can be taken to provide for the best possible care of Portuguese patients.

Statement of Ethics

This study was approved by the ethics committee of Centro Hospitalar de São João.

Disclosure Statement

The authors have no conflicts of interest to declare.

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