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Original Article

Analysis of health care delivery in patients with biliary atresia in a tertiary hospital in Northeast Brazil

Avaliação da atenção em saúde em pacientes com atresia de vias biliares em um hospital terciário no Nordeste do Brasil

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ABSTRACT: *Introduction*: Biliary atresia (BA) is a rare pediatric disease, but it is the main cause of liver transplantation in children, if not reversed with the Roux-en-Y portoentorostomy (Kasai surgery) in adequate time. There is a tendency for the surgical procedure to be delayed throughout Brazil and an investigation of its cause is necessary. *Objective*: to determine the epidemiological profile of the patient with BA and to evaluate the health care focused on it at a tertiary hospital. *Methods*: a descriptive, retrospective, cross-sectional study was performed using medical records of patients with a diagnosis of BA followed up at a tertiary hospital between 1996 and 2015. *Results*: the initial sample had 72 patients, and only 52 patients had complete records available at the hospital. Twenty-six patients were included with mean age at admission of 87,9 days (± 57,9), the ultrasound (US) was performed in 24 cases, and it was repeated in ten cases. The Kasai surgery was performed in 50% of the patients, 38.4% of which during the appropriate time. Of the patients who were operated on later, 25% were transplanted and 50% died, while in the four operated on time, only one was transplanted and there were no deaths. *Conclusion*: the diagnostic difficulties, in particular, failure to suspect BA in primary or tertiary care, in addition to a false-negative USG results, delayed the surgical procedure, confirming the worst outcome when the surgery was delayed.

Keywords: Biliary atresia; Hepatic portoenterostomy; Diagnosis; Epidemiology; Prognosis; Child.

RESUMO: *Introdução*: a atresia de vias biliares (AVB) é uma patologia pediátrica rara, mas é a principal causa de transplante hepático em crianças, se não revertida com a realização da portoenterostomia em Y-de-Roux (cirurgia de Kasai) em tempo adequado. Nota-se tendência de atraso do procedimento cirúrgico em todo o Brasil, sendo necessária investigação de sua causa. *Objetivo:* determinar o perfil epidemiológico do paciente com AVB e avaliar a atenção em saúde voltada para este em hospital terciário. *Método:* foi realizado um estudo descritivo, retrospectivo, transversal, a partir de prontuários dos pacientes com diagnóstico de AVB acompanhados em hospital terciário entre 1996 e 2015. *Resultados:* dos 72 pacientes da amostra inicial, somente 52 pacientes tiveram prontuários completamente disponibilizados pelo arquivo do hospital. Dentre os 26 pacientes incluídos, a média de idade à admissão foi de 87,9 dias (± 57,9), com realização de ultrassonografia (USG) em 24 casos e necessidade de repetição do exame em 10. A cirurgia de Kasai foi realizada em 50% dos pacientes, sendo 38,4% antes dos 60 dias de vida. Dos pacientes operados tardiamente, 25% foram transplantados e 50% foram a óbito, enquanto que, entre os 4 operados em tempo hábil, somente um foi transplantado e não houve óbitos. *Conclusão:* as dificuldades diagnósticas, em especial, falha de suspeição de AVB, na atenção básica ou terciária, além de um percentual de 41,6% de USG com resultados falso-negativos retardaram o momento cirúrgico, confirmando o pior desfecho do paciente operado tardiamente.

Palavras-chave: Atresia biliar; Portoenterostomia hepática; Diagnóstico; Epidemiologia; Prognóstico; Criança.

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INTRODUCTION

Biliary atresia (BA) is a pediatric disease characterized by the absence or obliteration, complete of partial, of the extrahepatic bile ducts due to a fibroinflammatory process leading to a cholestatic condition[1–3]. BA is considered the leading cause of liver transplantation (LTx) in children with an average incidence of one in every 20,000 live births and its universal distribution is variable, being more common in Asia and the Pacific region. The disease is diagnosed in approximately 5 to 6 per 100,000 live births in the United Kingdom and the United States, 10.6 per 100,000 live births in Japan and 32 per 100,000 live births in French Polynesia. As for gender, there is a slight predominance of females, in a ratio of 1.4:1[1,4–9].

BA is categorized in two ways according to the time that bile duct obliteration occurs. The first is the embryonic/fetal form, early or syndromic, which corresponds to 10 to 20% of cases and is often associated with other malformations[10]. The most frequent anomaly is polysplenia syndrome, observed in 8 to 12% of patients with BA and characterized by the presence of polysplenia or asplenia associated with midline liver, interruption of the superior vena cava, preduodenal portal vein, *situs inversus* and/or intestinal malrotation. Other malformations may be observed, such as cardiac anomalies, annular pancreas, immovable eyelashes syndrome, duodenal atresia, esophageal atresia, polycystic kidneys, palatine fissure, and jejunal atresia. The second is the perinatal/postnatal form, late or non-syndromic, representing 80 to 90% of cases, usually alone. In BA, obstruction of the lumen of the bile ducts can affect any part of the extrahepatic biliary tree, and the obliteration site is the basis for a classification of the types of atresia. In type 1 (5%), obliteration affects the common bile duct and the proximal ducts are pervious. In type 2 (3%), obliteration affects the common hepatic duct and type 3 (>90%), atresia involves the right and left hepatic ducts and obstruction extends to *the hepatis port*[1,4,11].

The first step to early diagnosis is to recognize the signs and symptoms of cholestasis, which are jaundice after the second week of life, pale stools, dark urine and hepatomegaly. In case of embryonic BA, the presence of other malformations help guide the diagnosis[4].

OBJECTIVES

To determine the epidemiological profile of patients with BA and evaluate the health care focused on the patient in the tertiary service - Instituto de Medicina Integral Professor Fernando Figueira - IMIP, between 1996 and 2015. In addition to identifying the socioeconomic characteristics of these patients, we collected their mean ages at the time of admission and diagnosis; identified which diagnostic methods were used; evaluated the treatment performed - in particular, whether or not Kasai surgery and liver transplantation were performed; and evaluated the success rate of Roux-en-y portoenterostomy relating with age at the time of surgery.

METHODOLOGY

The project was approved by the Institutional Review Board (IRB), with Certificate of Presentation for Ethical Appreciation (CAAE) number 60207516.2.0000.5569.

A descriptive, retrospective, cross-sectional study was conducted in patients diagnosed with BA, born between January 1996 and December 2015 and followed up at the *Instituto de Medicina Integral Professor Fernando Figueira - IMIP.* Data was obtained by reviewing medical records obtained from the Medical and Statistical Archive Service (SAME) of the institution and the sample size, defined by convenience. The inclusion criteria were: patients born between January 1, 1996 and December 30, 2015 with a diagnosis of BA confirmed through pathology analysis, clinical history or surgical findings; exclusion criteria: patients who did not confirm the diagnosis of BA by pathology, clinical history or surgical findings; patients whose medical records contain less than 50% of the information requested in the data collection form. The medical records were collected from the Epidemiology Center (NEPI), in the databases of Death Certificates diagnosed with BA by research by ICD Q44.2; or from the Department of Information Technologies in the databases of Hospital Admission Authorizations diagnosed with BA by research of the ICD Q44.2 or whose main or secondary procedures are biliodigestive anastomosis (Code: 04.07.03.001-8), cholecystectomy (Code: 04.07.03.002-6), wedge/fragment liver biopsy (Code: 02.01.01.020-8), puncture liver biopsy (Code: 02.01.01.021-6) or partial hepatectomy (Code: 04.07.03.013-1).

The data collected were: age at admission, sex, place of birth, city of origin, gross income, *per capita income,* number of people in the family, parent's education, time between the onset of jaundice and hospital admission, diagnosis on admission, home service, Length of Stay (LOS) in the first diagnostic suspicion, clinical picture on the day of the first diagnostic suspicion of BA, LOS at the time of the request for the pediatric surgery consult and after the consult, LOS in the diagnostic suspicion of BA by the pediatric surgery, LOS of the 1st ultrasound (US) and the 2nd US; findings of the 1st and 2nd US, and the findings suggest: sign of the triangular cord, dilation of bile ducts and atretic gallbladder. Laboratory on admission, preoperatively and postoperatively: hemoglobin (Hb), hematocrit (Ht), white blood cells (WBC), lymphocytes, platelets (PLT), international normalized ratio (INR), albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase

(ALT), total bilirubin (BT), direct bilirubin (BD), gamma glutamyl transferase (GGT), alkaline phosphatase (AF). Surgical procedure performed, place of its performance, age of the patient at the time of surgery, need for hospitalization in intensive care unit (ICU) in the postoperative period, postoperative complications, pathology report, drugs used: ursodeoxycholic acid (UDCA), corticosteroids (CE), phenobarbital (FB) and sulfamethoxazole-trimetropim (SMT). Postoperative day (POD) of starting diet, POD of report of colored stools, hospital discharge day, pediatric score *of* terminal liver disease (PELD), age at the indication of liver transplantation (LTx), age when the LTx was done, place where the LTx was performed. Place of the last follow up visit in the IMIP and current state of the patient.

The information from each medical record was collected twice, in separate forms, by different researchers. SPSS 13.0 *(Statistical Package for the Social Sciences)* software for Windows and Excel 2010 were used for data analysis. The results are presented in table form with their respective absolute and relative frequencies and numerical variables, represented by the measures of central trend and dispersion.

RESULTS

Initially, 72 medical records were selected, of which 21 patients did not have their medical records made available by SAME. Of the 51 we had access to, 20 patients were excluded because their medical records did not contain enough data for evaluation and five were excluded because the patients did not have BA. Thus, we evaluated 26 medical records.

Regarding the epidemiological profile, we observed that most patients were female (65.4%) and there was also a predominance of patients from the Metropolitan Area of Recife (51.8%). In addition, in most medical records (53.8%) there were no family income information and, of those containing them, 91.7% had per capita income of one minimum wage or less. As for parents' education, more than 60% had incomplete high school (Table 1).

Table 1 - Epidemiological profile

Variables	N	%
Sex		
Female	18	66,7
Male	9	33,3
Origin		
Metropolitan Area of Recife (MAR)	14	51,9
Other cities in Pernambuco (except MAR)	10	37
Other states	3	11,1
Gross income		
1 minimum wage or less	8	66,7
2 to 5 minimum wages.	4	33,3
Father's education		
1 to 9 years of study	3	37,5
10 to 12 years of study	5	62,5
Mother's education		
1 to 9 years of study	3	23,1
10 to 12 years of study	8	61,5
More than 12 years of study	2	15,4
	Average ± SD	**Median (Q1; Q3)**
Age at admission	87.3 (± 58.1)	79,0 (53,0; 111,0)

The mean age of admission of the patients was 87.9 (57.9) days, and 18 patients (69.2%) arrived after 60 days of life. The mean time of jaundice until hospital admission was 77.2 days (62.1), with a median of 61 days. Regarding the service of origin, we obtained data from 24 patients, of whom 62.5% were referred from other hospitals, 20.8% came from home, 12.5% from the primary service (Emergency Care Unit or Basic Health Unit) and one patient was born and remained in this service.

Regarding the initial care, in 15 (57.7%) medical records there was no record of BA as a diagnostic hypothesis, although 100% of the patients presented with jaundice, 76.9% with hepatomegaly, 73.1% with pale stools, 46.2% with dark urine and 26.9% with splenomegaly. On admission, most patients presented without changes in liver function, but with elevation of canalicular enzymes (AF and GGT) and liver enzymes (AST and ALT), in addition to hyperbilirubinemia at the expense of direct bilirubin (Table 2).

Table 2 - Results of laboratory tests on admission

Variables in Admission	Average ± SD	Median (Q1; Q3)
Hemoglobin	10.3 ± 1.7	10,1 (9,2; 11,0)
Hematocrit	31.0 ± 4.8	31,0 (28,3; 33,2)
Leukocytes	13276.3 ± 4004.4	12975,0 (10150,0; 16100,0)
Lymphocytes	53.8 ± 11.8	56,0 (46,5; 63,0)
Platelets	423.3 ± 182.8	390,0 (272,5; 564,8)
INR	1.5 ± 0.8	1,3 (1,1; 1,6)
Albumin	3.3 ± 1.0	3,6 (2,9; 3,9)
AST	324.1 ± 318.6	246,0 (153,0; 369,0)
ALT	236.4 ± 271.9	148,0 (86,0; 320,0)
Total bilirubin	10.8 ± 3.2	10,5 (9,2; 12,1)
Direct bilirubin	7.9 ± 2.5	7,7 (6,1; 9,2)
GGT	1213.9 ± 945.4	944,0 (239,5; 1745,5)
Alkaline phosphatase	703.9 ± 364.5	549,5 (398,0; 972,3)

INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase.

In the first days of hospitalization, 24 patients were submitted to ultrasound imaging exam. Of these, 17 (70.83%) had no findings suggestive of BA and seven (29.16%) had at least one of the signs suggestive of the disease (they were considered a sign of the triangular cord, dilation of bile ducts and atretic gallbladder), with an average request of 2.4 days (±1.9), and 75% of patients made it until the second day of hospitalization. Of these, 10 (41.6%) also needed a second ultrasound for diagnostic definition, with an average of 6.18 days (±3.14) between the first and second examinations. Of those who required the second US, 80% had a sign of the triangular cord and, in 70% showed an atretic gallbladder (Table 3).

Table 3 - USG findings

Variables	N	%	N	%
	1st US		2nd US	
Quantity performed	24		10	
Sign of triangular cord	3	12,0	8	80,0
Biliary tract dilation	2	8,0	0	0,0
Atretic gallbladder	3	12,0	7	63,6
No findings corresponding to AVB	18	75,0	0	0,0

US: ultrasound; BA: bile duct atresia.

Pediatric surgery (PS) was consulted in 25 cases, through a request for a consult, which was done, on average, with 4.5 days of hospitalization (±4) and with response in less than 24 hours in all cases. Of these, 92% had BA as a diagnostic hypothesis pointed out by pediatric surgeons at the time of care. In addition, 13 patients underwent Kasai surgery, with a mean age of 72.46 days (±35.85), and only five were operated before 60 days, with a maximum age of 136 days. Liver biopsy was performed in seven patients and five did not undergo surgical procedure. Of the five patients that did not undergo surgery. 4 had inconclusive liver biopsy and 1 patient died. All Kasai surgeries were performed at the service.

During the postoperative time, six patients required ICU stay, one due to sepsis. Nine had colored feces until the 6th postoperative day, two had no data on feces color. Table 4 shows the admission and postoperative laboratories of patients submitted to Kasai. Of these, 11 were discharged from the hospital with an average of 13.9 (±13.4) days postoperatively, two patients died from sepsis in the same hospitalization. Regarding the late outcome, four were transplanted, three became anicteric without transplantation, one remained jaundiced without indication for transplantation, there were two deaths and one patient did not have follow up in the medical records.

Table 4 - Results of laboratory tests at admission and postoperatively

Variables	Admission exams		Postoperative examinations	
	Average (± SD)	Median (Q1; Q3)	Average (± SD)	Median (Q1; Q3)
INR	1.4 (± 0.5)	1,1 (1,1; 1,6)	1.2 (± 0.2)	1,2 (1,1; 1,2)
Albumin	3.6 (± 0.5)	3,8 (3,2; 4,1)	2.7 (± 0.7)	3,0 (2,0; 3,2)
AST	209.7 (± 128.7)	223,0 (108,5; 293,0)	143.6 (± 58.1)	152,0 (89,6; 159,3)
ALT	174.1 (± 129.9)	148,0 (86,5; 202,0)	131.0 (± 75.2)	118,4 (90,5; 143,8)
BT	10.5 (± 2.5)	11,1 (8,7; 11,9)	12.1 (± 4.5)	11,6 (8,5; 15,8)
COMICS	7.6 (± 2.6)	7,9 (5,3; 9,1)	9.1 (± 3.1)	8,0 (6,8; 11,9)
GGT	1481.5 (± 1025.1)	1503,0 (647,0; 2007,5)	1518.9 (± 1054.8)	1394,5 (692,8; 1945,5)
FA	698.5 (± 342.1)	561,0 (405,0; 971,0)	355.8 (± 187.8)	278,0 (221,0; 435,8)

INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BT: total bilirubin; BD: direct bilirubin; GGT: gamma glutamyl transferase.; FA: alkaline phosphatase.

Regarding pathology exams, 15 were compatible with BA and four were inconclusive, but included in this study, since they presented clinical history, other complementary tests (lab tests and US) and surgical findings highly suggestive of BA.

Eleven patients had a formal indication for liver transplant, with a mean age of 145 days-old (45.1), the younger being 53 days-old and the oldest 222 days-old. Only three of these patients had the PELD value recorded in the medical records and, in total, seven patients underwent liver transplantation.

During the follow-up, thirteen patients were anicteric, one icteric was not transplanted, two in a transplant queue, seven transplanted, nine died and four had no follow up in their medical records. In our series, a mortality of 34.6% of patients with BA was identified, three deaths in patients where surgery was performed after 60 days of life; one after surgery in a timely manner and the other five in non-operated patients. (Figure 1)

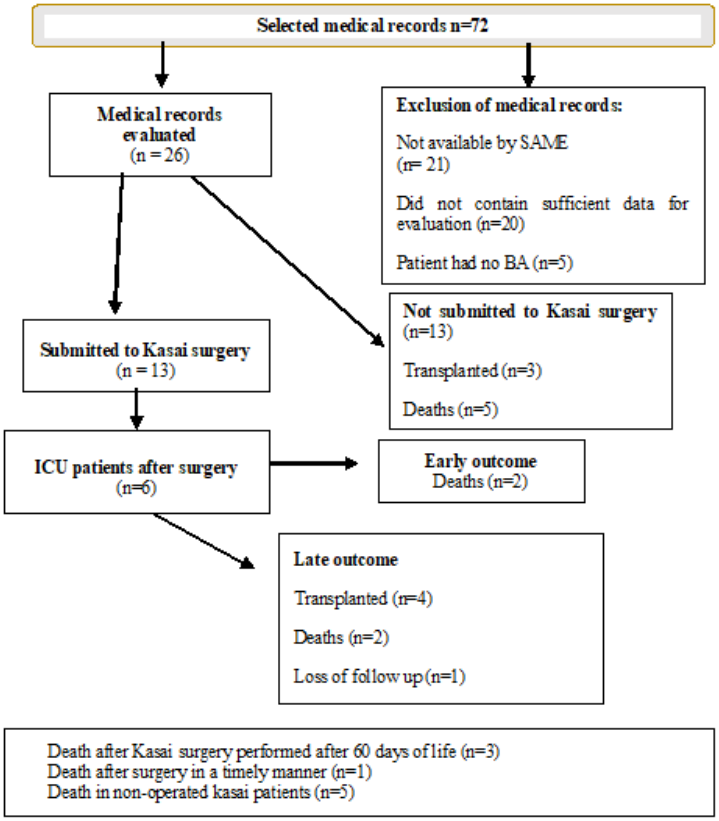

Figure 1. Flowchart of patients selection and follow-up

DISCUSSION

National data show that patients with BA arrive at the referral service late, similar to our patients who were admitted with a mean age of 87.9 (±57.9) days[26,27,28]. In our population, patients arrive at the service with a history of jaundice with a mean age of 77.2 (±62.1) days-old, demonstrating a possible failure of primary care with the screening of the disease or in the education of parents regarding skin, feces and urine changes. In addition, a higher prevalence of families with unfavorable socioeconomic conditions was observed, such as low education and low per capita income, corroborating the hypothesis of failure of orientation.

More than half of the professionals did not support the hypothesis of BA in the first care, demonstrating that the cholestatic picture in the newborn and infant was little associated with BA, which may be justified by the low incidence of the disease but, on the other hand, represents a risk to child health due to the severity of the disease, which can be accentuated by the diagnostic delay. In addition to the clinical history, US is a very useful tool for the diagnosis of BA but is known to have the disadvantage of being operator dependent. In our study, ten of the 24 patients who underwent US presented a false-negative result on initial examination and had to repeat the exam for reasons such as a highly suggestive clinical history of BA. We noticed that the first ultrasounds are usually performed in an emergency context, while secondary exams were performed in the by a specialized pediatric sonographer. This need for a second imaging evaluation caused a delay of, on average, six days in the diagnosis - a relevant value considering that most patients, at admission, were already older than ideal for therapeutic intervention. Another probable reason for the delay in diagnosis was the delay in identifying the need for surgical evaluation. On the other hand, once the consult of pediatric surgery was requested, response readiness was observed, with all consults being performed in less than 24 hours after the request and the majority (92%) citing BA as a diagnostic hypothesis at first contact with the patient (in one case, the hypothesis took two days to be considered and, in another case, it took 11 days, and the case was taken to a clinical meeting for diagnostic discussion). That said, it is concluded that the specialist physician is, as expected, more prepared to identify the BA picture, not excusing the pediatrician from the responsibility of supporting the diagnostic hypothesis and requesting support.

In relation to patients who underwent Kasai surgery, the diagnostic delay or admission caused most of them to be operated after the maximum ideal time of 60 days, from which the prognosis is worse. The surgical procedures mostly took place without serious complications, but due

to the progress of the disease, most of the children had subsequent indication of transplantation or died. Regarding the ideal age for surgery, the five patients who underwent Kasai before 60 days of life had outcomes similar to the literature, with three without indication for transplantation (two currently anicteric), one transplanted and the other died[5,13,23,24].

As limitations of the study, we mainly identified a sample that does not correspond to the proposed period. This deficiency was a consequence of the difficulty to have access to medical records by the SAME (n = 21), especially the oldest ones, and the presence of incomplete medical records (n = 20), causing the sample evaluated to be significantly reduced. Of the 20 years planned for capture, we had access to the last 10 years, being the oldest patient born in 2007.

Thus, we recommend the use of stool staining cards to facilitate the identification of changes early and reduce the time of seeking medical assistance[25]. This proposal can also be explored by primary care services, associated with strict rigor in the follow-up of newborns and infants for symptom detection and immediate referral. In the reference service, we suggest the creation of a protocol for the care of patients with cholestatic syndrome, involving clinical evaluation and request for complementary tests, in addition to the evaluation of early pediatric surgery. In addition, we identified that the US performed in the emergency room, in general, does not confirm the diagnosis and postpones the definitive examination. Therefore, we suggest not requesting emergency US in patients with cholestatic syndrome, except for specific situations, in order to anticipate the examination by a specialist. Thus, we emphasize the importance of disseminating information about BA so we can reduce the incidence of preventable negative outcomes.

Degree of participation: We inform for due purposes that the article was prepared jointly by the group of authors with the following degree of participation: Data collection (*Medeiros C, Holanda E*). Organizational guidance and on the essence, argumentation and relevance of the work: (*Gallindo R, Medeiros C, Netherlands E*). Analysis, research of articles, reading and exclusion of research not relevant to the involvement of the chosen theme: (*Gallindo R, Medeiros C, Holanda E*). Reading and writing the content: (*Gallindo R, Medeiros C, Holanda E, Nogueira R, Lima D*). Revision of the text regarding integrity and veracity as the sources used: (*Gallindo R, Medeiros C, Holanda E, Nogueira R, Lima D, Franco M*). Thus, the group of authors certifies joint participation in the preparation of the article, hoping to contribute to the theme in question.

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