Netherlands
The Journal of Medicine

REVIEW

The long-term outcome of the Kasai operation in patients with biliary atresia: a systematic review

E.J. Bijl[1], K.D. Bharwani[1], R.H.J. Houwen[2], R.A. de Man[1]*

[1]Department of Gastroenterology and Hepatology, Erasmus University, Rotterdam, the Netherlands,
[2]Department of Paediatrics, University Medical Centre Utrecht, Utrecht, the Netherland,
*corresponding author: tel. +31 (0)10-7033793, fax +31 (0)10-4365916, e-mail: r.deman@erasmusmc.nl
The first two authors contributed equally to this article

ABSTRACT

Background: Biliary atresia (BA) is a progressive inflammatory destructive process of the bile ducts occurring in about one of every 20,000 live births. If left untreated, biliary atresia can lead to liver failure. The only effective treatments for BA at the moment are the Kasai operation and liver transplantation. Kasai portoenterostomy increases the survival of children with BA and postpones subsequent liver transplantation. Because long-term survival is rare, there is not much known about the long-term efficacy of the Kasai operation.

Methods: The aim of this review was to study the outcome of patients with BA who survived more than 20 years on their native liver. We performed a systematic search on PubMed using MeSH terms for articles describing the long-term outcomes of patients with biliary atresia. We searched for patients who have lived at least 20 years with their native liver and we registered the number of complications. The endpoints identified in these articles were: death, cholangitis, portal hypertension and gastrointestinal bleeding.

Results: From 53 articles we included 14 articles for analysis. In total 184 patients were above the age of 20 years. Of these 162 patients, 88% (162/184) were still alive with their native liver and 60.5% (98/162) were suffering from liver-related complications.

Conclusions: It is possible for patients with biliary atresia to survive more than 20 years on their native liver after undergoing the Kasai operation during early infancy. However, 60.5% of the long-term survivors alive on their native liver end up suffering from progressive liver-related complications.

KEYWORDS

Biliary atresia/surgery, cholangitis, follow-up, portoenterostomy, survival rate

INTRODUCTION

Biliary atresia (BA) is a progressive inflammatory destructive (obliterative) process of the bile ducts.[1] It is characterised by a perinatal complete obstruction of all or part of the extrahepatic bile ducts and is always associated with abnormalities of the intrahepatic biliary tree.[2] If left untreated, biliary atresia will lead to liver failure. Biliary atresia is a rare condition with a prevalence of about one patient per 20,000 live births; patients are destined for a fatal outcome if they are not treated during the first few months of life. The only effective treatments for BA at present are hepatic portoenterostomy (Kasai operation) and liver transplantation.

The Kasai operation was introduced in 1959,[3] and consists of constructing a new bile drainage system, generally by creating an anastomosis of the jejunum by a Roux-en-Y loop to the porta hepatis region to re-establish a connection between the intrahepatic bile ducts and the intestine. If successful, Kasai portoenterostomy increases the survival of children with BA and consequently postpones subsequent liver transplantation. Studies have reported 20-year survival rates in patients with their native liver of 21%,[4] 25%,[5] 22%,[6] 23%[2] and 44%.[7] However, most long-term survivors develop complications.[8] Until the age of 18, BA patients are generally managed by paediatricians or paediatric surgeons. After the age of 18 these patients are referred to and managed by gastroenterologists. It is

therefore important that gastroenterologists become aware of the fact that in long-term survivors who have undergone the Kasai operation, complications such as recurrent cholangitis and portal hypertension may occur.

The aim of this review is to study liver condition and liver-related complications in patients treated with this operation during early infancy after a follow-up of 20 years while retaining their own liver. This review attempts to give an overview of the most important complications suffered by these patients and the prevalence of these complications.

METHODS

Literature search

The PubMed database was searched on 7 January 2012 using the MeSH term combination:

("Biliary Atresia/surgery"[MeSH Terms] AND ("Follow-Up Studies"[MeSH Terms] OR "Survival Analysis"[MeSH Terms] OR "cholangitis"[MeSH Terms] OR "Portoenterostomy, hepatic"[MeSH Terms])). The limits were set to 'English' and 'Aged 19+ years'.

Selection of studies

Articles were excluded based on title and abstract when research on liver transplantation, non-gastrointestinal complications, diagnostic tools used for follow-up and alternative postoperative treatment were described. Articles that described studies with a population younger than 20 years, articles that did not contain information on BA or the added complications and articles that were not available for Erasmus MC were also excluded.

After reading the articles, some were excluded because the minimum follow-up was shorter than 20 years or the age of the population was unclear. One article contained no information on the complications of biliary atresia. After excluding all these articles, the references of the remaining articles were scanned, which yielded additional relevant articles. Some articles that were retrieved described the same population, thereby creating an overlap. To resolve this issue we included the most recent article that described the whole population.

Outcome

Using the articles retrieved from the systematic review we defined a cohort of patients that survived for 20 years after a hepatoporto-enterostomy with their own liver. Within this cohort the number of patients who died or underwent a liver transplant after they had reached 20 years of age and the number of patients who are still alive with their native liver were described. We also retrieved information on complications in patients aged 20 years or older, who are still alive with their native liver after 20 years of age as the secondary outcome. The complications described in this article are: cholangitis, portal hypertension and gastrointestinal bleeding.

Data analysis

We extracted the study characteristics and the primary and secondary outcome measures from each article. The study characteristics included the authors, year, journal of publication, country of study and population above 20 years of age. For each outcome (death, alive with/without liver transplantation, with/without complications, cholangitis, portal hypertension, gastrointestinal bleeding or hepatocellular carcinoma) separately, we counted the number of patients in each article, summed them up and displayed them in a table or graphic.

RESULTS

The literature search and selection of studies

The results of our systematic literature search and our study selection is shown in a flowchart (*figure 1*). From the literature search we identified 53 studies, from which

Figure 1. *Results of systematic literature search and study selection*

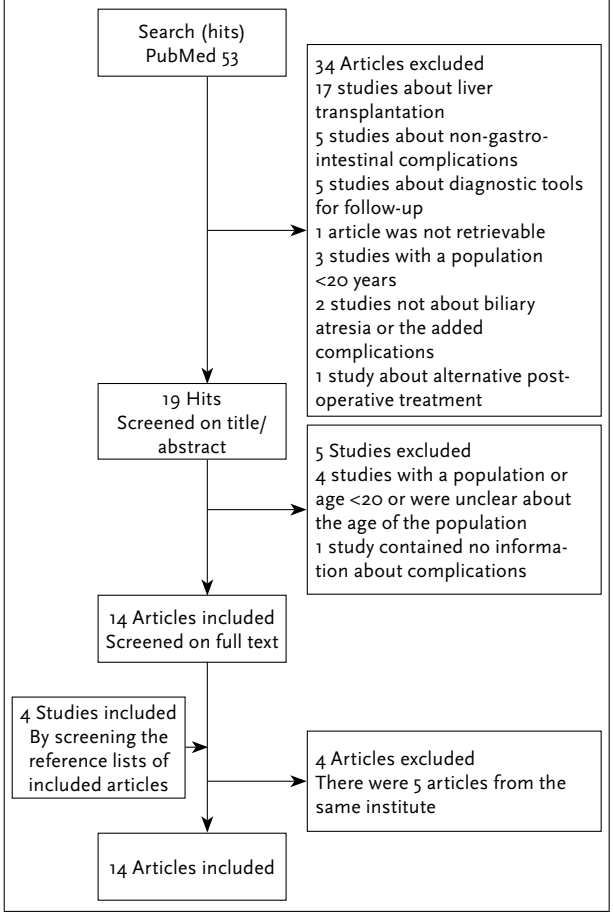

Table 1. *Characteristics of the articles*

Source	Publication date	Journal	Country of study	N alive at 20 years with native liver
Lykavieris et al.[2]	2005	Hepatology	France	63
Shinkai et al.[7]	2009	J Pediatr Gastroenterol Nutr	Japan	35
Nio et al.[6]	1997	Tohoku J Exp Med	Japan	30
De Vries et al.[5]	2011	Clin Gastroenterol Hepatol	Netherlands	28
Toyosaka et al.[14]	1993	J Pediatr Surg	Japan	6
Shimizu et al.[11]	1997	Tohoku J Exp Med	Japan	6
Pintér et al.[1]	2004	J Pediatr Surg	Hungary	4
Watanabe et al.[15]	1997	Tohoku J Exp Med	Japan	3
Hung et al.[3]	2006	J Pediatr Gastroenterol Nutr	Taiwan	2
Takahashi et al.[13]	2009	J Pediatr Surg	Japan	2
Raffensperger[9]	1991	J Pediatr Surg	US	2
Hol et al.[8]	2008	Eur J Gastroenterol Hepatol	Netherlands	1
Kasai et al.[12]	1988	J Pediatr Surg	Japan	1
Yamanaka et al.[16]	2005	J Pediatr Surg	Japan	1

34 studies were excluded based on title and abstract. We read the full text of 19 articles from which five articles were excluded. We screened the reference lists of the 14 remaining articles; this resulted in four additional articles. Finally, we excluded four articles because they contained an overlap in population. Thus, 14 articles were included for further analysis.

Characteristics of the articles

Of the 14 articles included, seven described a follow-up study, three articles described a retrospective cohort study and four articles were case reports. Of the 14 studies, eight studies are from Japan. There are ten studies that described very few or only one patient. Four articles described a larger patient group (*table 1*).

Population

The 14 studies included a total group of 184 patients above 20 years of age. In this group, eight patients died and 14 were alive with liver transplantation after 20 years of age. There were 162 patients living with their native liver (*table 2*). All patients who died or had undergone liver transplantation had end-stage liver disease or suffered from severe liver-related complications.

Complications

Of the 162 patients who are alive with their native liver, 39.5% (64/162) are alive without complications. The remainder of the patients have developed complications (*table 2*).

All the patients who developed complications had experienced episodes of cholangitis. Of the 98 patients with cholangitis, 80% (78/98) developed portal hypertension. Of the patients with portal hypertension, 45% (35/78) experienced gastrointestinal bleeding. In one patient a hepatocellular carcinoma was found (*table 2*).

Table 2. *Analysis of the population*

	Number
Total population >20 years	184
Death	8 (4.3%)
Alive with Ltx	14 (7.6%)
Alive without Ltx	162 (88%)
Without complications	64 (39.5%)
With complications	98 (60.5%)
Cholangitis	98 (100%)
Portal hypertension	78 (80%)
Gastrointestinal bleedings	35 (45%)
Hepatocellular carcinoma	1 (1.3%)

Ltx = liver transplantation.

DISCUSSION

This systematic review shows that there are patients born with biliary atresia who can survive for more than 20 years with their native liver. This review included 184 patients of which 60.5% of the patients eventually developed severe complications such as cholangitis, portal hypertension, gastrointestinal bleeding and hepatocellular carcinoma. One can assume that in the end, most of these patients will need to undergo a liver transplantation.

It was not possible to calculate a survival rate because not all the included articles were follow-up studies, other included articles did not provide information on deceased and transplanted patients before the age of 20. Earlier publications have described 20-year survival rates on a native liver, which varies from 21% to 44%.[2,4-7]

The importance of these findings can be *extrapolated to clinical practice* where until the age of 18 these patients are generally managed by a paediatrician or paediatric

surgeon. After the age of 18 most of these patients are managed by the gastroenterologist. It is especially necessary for the gastroenterologist to realise that in long-term survivors after Kasai operation developing recurrent cholangitis and portal hypertension liver transplantation should be considered early to avoid death to liver-related mortality. This review shows that the majority of these patients have severe liver disease that requires close follow-up.

Almost all the articles we included for this review describe only a small population of BA patients. This is why we also took case reports into account. Some case reports described detailed outcomes that were not available in other articles. When analysing the complications, it became difficult to understand which patients suffered from which complications in the articles. To avoid overlap in patients who had more than one complication we assumed the following: cholangitis led to portal hypertension which led to gastrointestinal bleeding. That means that we assumed that patients who had portal hypertension were the same patients who suffered from cholangitis.

Most of the articles we analysed were publications from Japan. The Kasai operation was introduced in Japan in 1959 and at first was probably only used in Japan to treat biliary atresia. It only became accepted in America[9] and the Netherlands[10] in around 1970. Before that, Japan was practically the only country using the operation to treat BA. This could be the reason why Japan has more long-term survivors.

We would suggest that more research is needed on the further development of the disease after 20 years of survival on a native liver. It could be a great asset to the treatment of biliary atresia if research was done to assess whether patients should be added to the liver transplantation waiting list after clinical manifestation of cholangitis.

Altman *et al.* provided an important insight into survival rates in patients with biliary atresia.[4] However, due to the fact that suffered complications were not described, this article had to be excluded from this review.

Taking everything into account, we can conclude that there is an extensive lifelong follow-up needed in these patients, so complications can be identified and the optimal treatment can be initiated.

REFERENCES

1. Pintér AB, Farkas A, Par A, Kovesi T, Appelshoffer S. A long-term follow-up of five patients with atresia of the common bile duct. J Pediatr Surg. 2004;39:1050-4.
2. Lykavieris P, Chardot C, Sokhn M, Gauthier F, Valayer J, Bernard O. Outcome in adulthood of biliary atresia: a study of 63 patients who survived for over 20 years with their native liver. Hepatology. 2005;41:366-71.
3. Hung PY, Chen CC, Chen WJ, et al. Long-term prognosis of patients with biliary atresia: a 25 year summary. J Pediatr Gastroenterol Nutr. 2006;42:190-5.
4. Altman RP, Lilly JR, Greenfeld J, Weinberg A, van Leeuwen K, Flanigan L. A multivariable risk factor analysis of the portoenterostomy (Kasai) procedure for biliary atresia: twenty-five years of experience from two centers. Ann Surg. 1997;226:348-53; discussion 353-5.
5. de Vries W, Homan-Van der Veen J, Hulscher JB, Hoekstra-Weebers JE, Houwen RH, Verkade HJ; Netherlands Study Group of Biliary Atresia Registry. Twenty-year transplant-free survival rate among patients with biliary atresia. Clin Gastroenterol Hepatol. 2011;9:1086-91.
6. Nio M, Ohi R, Shimaoka S, Iwami D, Sano N. The outcome of surgery for biliary atresia and the current status of long-term survivors. Tohoku J Exp Med. 1997;181:235-44.
7. Shinkai M, Ohhama Y, Take H, et al. Long-term outcome of children with biliary atresia who were not transplanted after the Kasai operation: >20-year experience at a children's hospital. J Pediatr Gastroenterol Nutr. 2009;48:443-50.
8. Hol L, van den Bos IC, Hussain SM, Zondervan PE, de Man RA. Hepatocellular carcinoma complicating biliary atresia after Kasai portoenterostomy. Eur J Gastroenterol Hepatol. 2008;20:227-31.
9. Raffensperger JG. A long-term follow-up of three patients with biliary atresia. J Pediatr Surg. 1991;26:176-7.
10. Houwen RHJ, Molenaar JC, Sinaasappel M. Biliary atresia and Kasai's operation: experiences during the period 1972 through 1981. Ned Tijdschr Geneeskd. 1983;127:1565-8.
11. Shimizu Y, Hashimoto T, Otobe Y, Ueda N, Matsuo Y, Manabe T. Long-term survivors in biliary atresia--findings for a 20-year survival group. Tohoku J Exp Med. 1997;181:225-33.
12. Kasai M, Ohi R, Chiba T, Hayashi Y. A patient with biliary atresia who died 28 years after hepatic portojejunostomy. J Pediatr Surg. 1988;23:430-1.
13. Takahashi Y, Matsuura T, Saeki I, Zaizen Y, Taguchi T. Excellent long-term outcome of hepaticojejunostomy for biliary atresia with a hilar cyst. J Pediatr Surg. 2009;44:2312-5.
14. Toyosaka A, Okamoto E, Okasora T, Nose K, Tomimoto Y. Outcome of 21 patients with biliary atresia living more than 10 years. J Pediatr Surg. 1993;28:1498-501.
15. Watanabe Y, Todani T, Toki A, et al. Changes of hepatic volume after successful Kasai operation. Tohoku J Exp Med. 1997;181:185-91.
16. Yamanaka J, Iimuro Y, Hirano T, Kosaka H, Fujimoto J. Successful liver resection for biliary atresia with intrahepatic biliary cysts after Kasai procedure. J Pediatr Surg. 2005;40:E9-11.