Determinants of Life Span after Kasai Operation at the Era of Liver Transplantation

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GAUTHIER, F., LUCIANI, J.-L., CHARDOT, C., BRANCHEREAU, S., DE DREUZY, O., LABABIDI, A., MONTUPET, P., DUBOUSSET, A.-M., HUAULT, G., BERNARD, O. and VALAYER, J. Determinants of Life Span after Kasai Operation at the Era of Liver Transplantation. Tohoku J. Exp. Med., 1997, 181 (1), 97–107 —— The aim of this work is to determine the influence of age, extrahepatic biliary lesions pattern (EHBP) and association to polysplenia syndrome (PS) on 10 years outcome of 164 patients with biliary atresia (BA) treated from 1984 to 1992 by initial Kasai operation (KO) and secondary liver transplantation (LT) when necessary. Actuarial crude survival without or after LT(CS), actuarial survival with native liver (NLS) and jaundice-free actuarial survival with native liver (JFS) were calculated from 1 to 10 years versus age (under/over 45 days), EHBP (favorable/unfavorable) and PS (no/yes). Overall 10-year CS is 70%, overall 10-year NLS and JFS are 14%. In univariate analysis, age at KO under 46 days, favorable EHBP (BA with patent gallbladder, and/or cystic dilatation of extrahepatic bile duct, or BA restricted to choledocus), and absence of PS are significant determinants of a better outcome regarding CS, NLS and JFS. EHBP is more discriminant than age. Influence of PS in this series is redundant with that of EHBP since 11/11 patients with PS had unfavorable EHBP. —— biliary atresia; surgery; liver transplantation

Natural history of biliary atresia (BA) is progressive biliary cirrhosis, leading the patients to death within approximately one year.

The first treatment of BA which proved efficient was the operation described

Received June 30, 1996; revision accepted for publication November 15, 1996.
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This paper was presented at 6th International Sendai Symposium on Biliary Atresia, May 20 and 21, 1996, Sendai.
by M. Kasai in the late fifties (Kasai 1974). The goal of Kasai operation (KO) is restoration of bile flow, and complete clearance of jaundice is the necessary condition for long term survival in BA patients treated with KO. From the past 30 years worldwide experience with Kasai operation it appeared: 1) that a ten-years survival could be expected in about one third of patients submitted to KO, and 2) that these results could be improved by early diagnosis and surgery (Kasai et al. 1989; Mieli-Vergani et al. 1989; Laurent et al. 1990; Gauthier et al. 1992b). Influence of extrahepatic biliary pattern of disease on outcome of KO has been rarely studied, except for the so-called “correctible” types of BA (Lilly et al. 1987). According to a previous report from our team, and also to the report of the Biliary Atresia Registry of the American Academy of Pediatrics, a more favorable prognosis could also be ascribed to BA cases with patent gallbladder (Karrer et al. 1990; Gauthier et al. 1992a).

The second therapeutic possibility for BA patients is liver transplantation (LT), whose clinical development started in the mid eighties after introduction of cyclosporine A as main immunosuppressive drug (National Institute of Health Consensus Development Conference Statement 1984).

LT is a complex and irreversible procedure, its feasibility depends on availability of a graft from either a cadaveric or a living donor, it requires a potentially toxic immunosuppressive therapy, and its long term results are still unknown. On the other hand, KO is a relatively simple surgical procedure for a skilled surgeon, it can be done without any delay in young babies, it does not require any adjuvant therapy, and it does not jeopardize a further LT (Cuervas-Mons et al. 1986). According to these considerations, most of pediatric teams recommend a sequential treatment of BA based on initial KO and secondary LT, proposed as a “second chance” in case of failure of KO (Tagge et al. 1991; Martinez-Ibanez et al. 1992; Suruga et al. 1992; Miyano et al. 1993; Ryckman et al. 1993; Grosfeld 1994; Otte et al. 1994; Ohi et al. 1995).

The aim of this paper is to assess, from the experience of Bicêtre’s team, some determinants of life span, which could be known before KO, in children planned for such a sequential treatment. This information could be used as a background for comparative studies in the fields of diagnostic procedures and surgical technique, and it could also provide guidelines to discuss in some selected cases the principle itself of a Kasai operation as initial treatment of BA.

**Patients and Methods**

From August 1988 to December 1992, 179 BA patients have been submitted to KO in Bicêtre Hospital. One hundred and sixty four patients (male: 82, female: 82) with a follow-up of at least one year have been included in this study.

Extrahepatic biliary pattern (EHBP) of lesions has been defined according to a simplified classification in six types: complete BA involving both main extrahepatic duct and gallbladder, BA with patent gallbladder (suitable for portochole-
cystostomy), BA with cyst at porta hepatitis ("correctable type"), BA with cyst under the level of porta hepatitis, BA with cyst and patent gallbladder and BA involving only choledocus (identical to type I of the JSPS classification).

Initial surgery consisted either in portoenterostomy (123 cases), portocholecystostomy (34 cases), cysto-jejunostomy (4 cases), cystocholecystostomy (1 case) or cholecystojejunostomy (2 cases) depending on intraoperative anatomical findings and/or x-ray investigation. Five portocholecystostomies had to be converted into portoenterostomies because of post-operative bile leakage, and 2 cystojejunostomies into portoenterostomies because of primary failure to restore bile flow.

Seventy two of the 164 patients (44%) required secondary LT. These LTs have been performed by one of following transplant teams: Bicêtre Hospital (pediatric team), Cochin Hospital (Paris), Cliniques Universitaires Saint Luc (Brussels), or Paul Brousse Hospital (Paris) in 55, 9, 7 and 1 patients, respectively.

Following data have been collected prior to (KO) for each patient: age at KO, EHBPs, and association or not with polysplenia syndrome (PS). As far as we have chosen to focus this work on benefits of early diagnosis followed by early KO, we have divided patients into 2 age groups: up to 45 days and over 45 days. According to our previous work assigning a favorable prognosis to BAs with patent gallbladder (Gauthier et al. 1992a), we have divided patients into 2 EHBPs groups: an unfavorable group consisting only in cases with complete atresia, and a favorable group including all other EHBPs; it is noteworthy that each characteristic feature of the favorable group patients (patent gallbladder and/or cyst) can be easily detected prior to surgery by the means of ultrasonography. PS, defined by presence of at least one of its usual components, is also detectable before surgery during ultrasonographic workup.

At follow-up points 1, 3, 6 months, and then yearly from 1 to 10 years of age, one of the 7 following states has been assigned to each patient: alive and jaundice-free with native liver, alive and jaundiced with native liver but not yet registered on LT waiting list, waiting for LT, alive after LT, dead without being registered on LT waiting list, dead during waiting period, dead after LT. Date and cause of death have been reviewed in these three latter groups of children.

Three survival curves have been calculated separately by the actuarial method in both age groups, in both EHBPs groups and in groups with or without polysplenia. Crude survival (CS), means survival after KO with native liver or after LT, survival with native liver (NLS) means survival after KO with or without jaundice at last date of point, and jaundice-free survival (JFS) has been estimated using the formula: \( \text{JFS} = \text{NLS} \times \text{percentage of jaundice-free survivors at follow-up point} \). The logrank method has been used for univariate analysis of survival figures.

A further approach to the evaluation of influence of age and EHBPs on outcome of KO consisted in comparing expected 1-year jaundice-free survival to
age at KO in favorable and unfavorable EHBP groups respectively by the means of linear regression.

Presence or absence of relationships between age and EHBP, age and association with PS, and presence of PS and EHBP have been assessed using Student’s t-test or $\chi^2$ test as required.

RESULTS

Overall results

Median age at KO was 67 days, ranging from 21 to 154 days. Fifty seven patients (34.8%) had a favorable EHBP (patent gallbladder: 34, presence of a cyst: 17, patent gallbladder+cyst: 3, atresia restricted to choledocus: 3) and 107 patients (65.2%) had an unfavorable EHBP. Eleven patients (6.7%) had and 153 (93.3%) had not an associated PS. Mean age of patients with favorable EHBP was 71.4 $\pm$ 30.9 days vs. 69.2 $\pm$ 23.3 days for patients with unfavorable EHBP (t-test: ns). Patients with PS were younger at KO than patients without PS (53.2 $\pm$ 20.4 days vs. 71.2 $\pm$ 26.1 days; t-test: $p=0.026$). All 11 patients with PS had unfavorable EHBP ($\chi^2$ test: $p=0.03$).

At last updating (April 1996), 56 patients (34.1%) were alive and jaundice-free with native liver, 8 patients (4.9%) were alive with jaundice, 2 patients (1.2%) were waiting for LT, 58 patients (35.4%) were alive after LT, 20 patients (12.2%) were dead without registration on the LT waiting list, 5 patients (3.0%) were dead during the waiting period and 15 patients (9.1%) were dead in the course of LT.

Overall survival curves are displayed on Fig. 1.

![Fig. 1. Overall results.](image)

164 patients submitted to initial BA and, if necessary, to secondary LT
$\circ$ $\circ$ crude survival; $\triangle$ $\triangle$ survival with native liver; $\bullet$ $\bullet$ jaundice-free survival.
LTs have been performed within a mean time of 2.60 years (range: 0.41-8.42 years) after KO.

Deaths occurred at a mean age of 1.92 years (range: 0.19-7.59 years; median age: 1.20 years). Among the 20 children who died without being registered on waiting list for LT, 7 died from miscellaneous septic conditions, 6 from ongoing chronic liver failure, 2 from acute liver necrosis, 1 from severe hypoxemia due to pulmonary shunts, 2 from associated congenital cardiopathy, and 3 from other causes. Only 4 of these 20 deaths are exclusively related to the previous KO, namely 3 septic shocks complicating early postoperative cholangitis episodes and one postoperative peritonitis; own mortality rate of KO in this series was then 2.4% and accounted for 8% (4/50) of all causes of death. LT was contraindicated in 2 of these 20 children because of brain damage.

Five children died during waiting time for LT, 4 of them from ongoing chronic liver failure and the last from acute liver necrosis. Mortality rate during LT waiting time is 6.5% (5/77 children registered on waiting list) and accounted for 12.5% of deaths in the series.

Fifteen children died in the course of a first LT or of a retransplantation, namely 4 from massive hemorrhage, 4 from vascular complications, 4 from sepsis, 2 from multiple organ failure and 1 from primary nonfunction of graft. Mortality rate related to LT is 20.8% and accounts for 50% of deaths in the series.

**Influence of age at KO**

In children submitted to KO before 46 days of age, 10-year CS, 10-year NLS and 10-year JFS were 87%, 65% and 47%, respectively (Fig. 2). In children operated on after 45 days of age they were 70%, 16% and 16%, respectively (Fig. 3). Differences between both age groups are significant regarding CS (univariate analysis $p < 0.01$) and NLS ($p < 0.01$).

**Influence of EHBP**

In children with favorable EHBP, 10-year CS, 10-year NLS and 10-year JFS were 83%, 50% and 50%, respectively (Fig. 4). In children with unfavorable EHBP they were 67%, 4% and 4%, respectively (Fig. 5). Differences between both EHBP groups are significant regarding CS (univariate analysis $p < 0.01$) and NLS ($p < 0.001$).

**Influence of associated PS**

In children without associated PS, 10-year CS, 10-year NLS and 10-year JFS were 76%, 22% and 22%, respectively (Fig. 6). In children with associated PS, they were 39%, 14% and 0%, respectively (Fig. 7). Differences between both groups are significant regarding CS (univariate analysis $p < 0.001$) and NLS ($p < 0.001$).
Combined influence of age and EHBP on jaundice-free survival

Combined influence of both age and EHBP on 1-year jaundice-free survival after KO is illustrated on Fig. 8. Two conclusions arise from analysis of these linear regression curves. The first one is that, for any BA patient, whatever his EHBP could be, the probability to become jaundice-free at 1 year of age decreases when age at KO increases. The second one is that, at the same age at KO, this probability is much higher for a patient with favorable EHBP (upper line) than for a patient with unfavorable EHBP (lower line).
Fig. 4. Survival of 57 patients with favorable extrahepatic biliary pattern. See the legend of Fig. 1 for the symbols.

Fig. 5. Survival of 107 patients with unfavorable extrahepatic biliary pattern. See the legend of Fig. 1 for the symbols.

**Relationships between determinants of prognosis**

In the whole series mean age at KO in favorable and unfavorable EHBP groups were 69+/−23 days and 71+/−31 days respectively (Student's test: ns), but there was a more favorable distribution of EHBP (50% of cases with favorable pattern) in children under 46 days and in children over 90 days of age than in the group of children aged 46 to 90 days. Patients with associated PS were younger at KO than patients without PS (53+/−20 days versus 71+/−26 days;
Fig. 6. Survival of 153 patients without polysplenia syndrome.
See the legend of Fig. 1 for the symbols.

Fig. 7. Survival of 11 patients with polysplenia syndrome.
See the legend of Fig. 1 for the symbols.

$p = 0.026$). All patients with polysplenia syndrome had unfavorable EHBP ($p = 0.03$).

**Discussion**

In this cohort of children born during the period of clinical development of LT, sequential treatment of BA with initial KO and secondary rescue LT offered an actuarial 10-year survival of 70%, instead of 32% in a previous cohort treated in our institution with KO only between 1968 and 1977 (Laurent et al. 1990).
Fig. 8. Influence of age at Kasai operation and extrahepatic biliary pattern on probability of achieving 1-year jaundice-free survival (164 patients). Linear regression.
- unfavorable EHBP; △ favorable EHBP; Upper regression line, jaundice-free patients aged 1 year; Lower regression line, patients aged 1 year with jaundice or dead. Curves indicated 95% confidence intervals of each regression line.

Even if an increasing number of patients could be brought to LT after failed KO during the study period, and if progress of LT for BA resulted in a decreasing mortality linked to LT during the same time, surprisingly overall results did not improve during this 8 years period: 5-year CS of children submitted to KO from 1984 to 1988 (83 patients) and from 1989 to 1992 (81 patients) were 75% and 72% respectively (ns). The main reason for this lack of progress is that both groups are not comparable, with a best EHBP distribution in the ancient one than in the recent one (42% and 27% of favorable EHBP, respectively; \( p = 0.05 \)).

In this series, age at KO, EHBP and association or not to PS are strongly significant determinants of life-span, and especially of NLS and JFS, in univariate analysis.

All authors reporting recently on BA have emphasized the need for early KO in BA patients, and as a consequence the need for early diagnosis of the disease (Kasai et al. 1989; Mieli-Vergani et al. 1989; Gauthier et al. 1992b; Emblem et al. 1993). Tagge et al. (1991) however, studying a short series of 34 children, concludes that age has no influence on outcome of KO.

Apart from “correctable” types of BA, influence of EHBP on prognosis of KO has not been studied extensively, and most studies have been rather focused on the influence of microscopical appearance of biliary remnant and of liver histological features. The present work supports and confirms the better prognosis of BA with patent gallbladder already suggested in the eighties (Karrer et al. 1990;
Gauthier et al. 1992a). From our experience, EHBp appears as the main determinant of NLS and JFS in children submitted to KO. However there is some controversy about this point; for instance the work of Tan et al. (1994), based on the pathologic study of 205 patients, concludes that EHBp of obliteration is not indicative of prognosis of KO.

The influence of an associated polysplenia syndrome is a second point of controversy. Davenport et al. (1993) assign a worse prognosis to this subgroup, because of frequent cardiovascular anomalies. Karrer et al. (1991) do not find significant differences in actuarial survival in patients with or without PS. Vazquez et al. (1995) reported a best bile flow restoration rate in PS patients than in other patients. It is striking that publications on BA cases with associated PS usually include a number of patients under 20. Such small samples do not allow to study the influence of PS on prognosis of KO in correlation with other determinants. In our series, PS was associated to unfavorable EHBp in all cases. Studies of large cohorts are necessary to precise relations between PS and EHBp, and also influence of associated cardiovascular anomalies on overall survival in these patients. Outcome of liver transplantation may also be impaired in these patients with multiple vascular anomalies (Falchetti et al. 1991).

The last question to answer is the selection of patients for whom a poor prognosis could be expected after KO, and who could be considered preferentially for initial LT. Our work suggests that, in the usual age range at diagnosis of BA (within the 4 first months of life), it is impossible to assess a 100% risk of failure of KO to a patient. Only a statistical estimation based on EHBp, age and association or not to PS can be done. In cases with an expected poor outcome after KO, this evaluation could be compared to the risks and benefits offered by LT.

References

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