A Tertiary Centre Experience in the Diagnosis of Biliary Atresia

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ABSTRACT

Biliary atresia (BA) is rare but is the most common cause of liver transplant in children. Early diagnosis and Kasai portoenterostomy (KP) improves outcomes. A retrospective chart review of all infants diagnosed with BA between January 1, 2002 and December 31, 2009 was conducted. The median age at referral, KP, and place of residence at presentation were determined. Age at which a conjugated bilirubin was first ordered was compared for various health care providers. Survival at 2 years of age with a native liver was determined.

Seventeen patients were diagnosed with BA and 13 underwent a KP. Biliary atresia splenic malformation (BASM) was present in 23.5% of patients. The median age of referral to a tertiary centre was 56d (IQR: 42; range: 26-102 d), neither of which differed significantly from established Canadian medians. Paediatricians requested conjugated bilirubin level more frequently than family physicians; 58% vs 29%. Neither the rurality of patients’ residence nor the type of health care provider for well-baby care influenced age at referral to subspecialist. Two-year survival with native liver was 15.4%.

There was no evidence of a difference in age at referral or age at KP observed in this study compared with established median for Canada. The place of residence didn’t influence timing of referral. The study noted a lower than expected survival with native liver at 2 years.

Key words: Biliary Atresia; Kasai; Portoenterostomy; Age factors; Time factors; Prognosis


INTRODUCTION

Biliary atresia (BA) is a condition characterized by progressive fibroliteration of the bile ducts shortly after birth that leads to end stage liver disease and death if not diagnosed and treated surgically in early infancy. While relatively rare (occurring in 1 in 10 000-20 000 live births), it is the most common cause of liver transplantation in pediatrics[1,2]. Multiple studies have established that early diagnosis and Kasai portoenterostomy (KP) improves mortality and survival with native liver[3,4]. The optimal age for diagnosis and timing of the KP is not clear. However, numerous publications have noted an improved outcome with earlier KP, with a wide variation in suggested optimal timing (30-100 d of life)[5,6,8,9,10]. A recent study of Canadian centres noted that the mean patient age at time of referral to a tertiary pediatric hospital was 55 d and that the median age at time of KP was 65 d[11]. Survival was significantly higher in children who did undergo the KP, while patients who did not have a KP were significantly older at referral[11].

This study aimed to identify if there is a significant disparity in the age at referral and at KP at our centre in comparison with the Canadian median. The study also attempted to identify reasons for late referral such as type of healthcare provider and rurality of residence in the catchment area. The population density for the Stollery Children’s Hospital (SCH) catchment area ranges from 0.04 to 1.186/km².

METHODS

A retrospective chart review of all infants with confirmed biliary atresia at the SCH between January 1, 2002 and December 31, 2009 was performed. Charts were identified through the Pediatric Gastroenterology list of patients seen for biliary atresia. This list was cross-referenced with Department of Pathology records. Data collected from each patient record included date of birth, sex, ethnicity, birth weight, gestational age, location of mother’ s permanent residence at time of delivery, hospital of birth, date...
of original discharge from birth hospital, whether the patient had a regular physician for postnatal care, date jaundice was first noticed, date that the first conjugated bilirubin level was ordered and what type of health professional ordered the test, date of referral to pediatric gastroenterologist or tertiary pediatric centre, dates and results of HIDA scan, liver biopsy, and intraoperative cholangiogram, presence of biliary atresia splenic malformation syndrome (BASM), date of KP if performed, date of return to normal bilirubin level (if achieved), and date of transplantation or death. A functioning Kasai is defined as clinical resolution of jaundice with pigmented stools or serum total bilirubin <40µmol/L. The Metavir scoring system for fibrosis was used to categorize severity of liver disease on percutaneous and intraoperative liver biopsies (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Severity</th>
<th>Fibrosis Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>F0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>Moderate</td>
<td>F2</td>
<td>Portal fibrosis without septa</td>
</tr>
<tr>
<td>Severe</td>
<td>F4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

If there was a discrepancy in the chart about any date, the earliest date recorded in the chart was used to minimize effect size. Patients were excluded if they were diagnosed and had their KP at another centre in Canada and were referred to Edmonton for liver transplantation alone, or if the diagnosis of biliary atresia by intraoperative cholangiogram or liver biopsy was made outside of the study inclusion dates. Approval to conduct the study was obtained from the Health Research Ethics Board of the University of Alberta.

Statistical analysis was performed using SPSS software. The values were expressed as means with standard deviations or medians with interquartile ranges (IQR). Nonparametric tests (Mann Whitney U and Kruskall-Wallace) were used to compare means or medians of continuous data, while the chi-square or Fisher exact test were used to determine comparative differences of categorical data. Results were considered statistically significant with a p<0.05.

RESULTS

A total of 17 children met study criteria. Sixteen patients were identified through the Pediatric Gastroenterology list and one additional patient was identified through pathology. Thirteen patients (76.5%) underwent a KP. Demographic data is displayed in table 2. Ethnicity was only recorded for 6 patients.

Seven children were referred directly from a tertiary centre (range 6-118 d). Family physicians ordered the test, date of referral to a tertiary care centre, There was no evidence of a statistical difference between those with BASM (76 d) and those without (49 d) (p=0.234).

Seventy five percent of patients with BASM underwent a KP and there was no evidence of a difference in median age at referral between those with BASM (76 d) and those without (49 d) (p=0.234).

The median distance of residence from the SCH was 14.4 km (IQR 240; range 0-1955 km). Neither distance from Edmonton (p=0.973; Edmonton 55.0±51 d, other Alberta 56.0±48d, rest of Canada 60.0 d) or whether the family lived in a rural or urban centre (p=0.671; urban 62.9±31 d, rural 57.8±12 d) affected age at referral.

Eleven patients received a HIDA scan (70.6%) and 11 of these patients (91.7%) had no excretion at 24 h. All 17 patients underwent an attempt at intraoperative cholangiogram. In 8 patients (47.1%) it was documented that the biliary tree was unable to be cannulated because of severe biliary fibrosis or absence of biliary structure. The remaining patients had cholangiograms consistent with biliary atresia.

Eleven patients had a percutaneous liver biopsy (64.7%) and 16 had intraoperative biopsies done at the time of cholangiogram (94.1%). The severity of liver fibrosis at the time of biopsy is shown in table 3. There was no correlation between severity of fibrosis at percutaneous biopsy compared with intraoperative biopsy (r=0.482; mild fibrosis 47.0±46 d, moderate fibrosis 59.5 d) or intraoperative biopsy (r=0.080; mild fibrosis 52.5±35 d, moderate fibrosis 42.5±35 d, severe fibrosis 104.5 d).

Six of thirteen (46%) patients with KP had their bilirubin return to a normal level (<40µmol/L) prior to death or transplant at a median time of 139 days after KP. KP was not significantly delayed in the other seven patients who did not have their bilirubin normalize prior to transplant or death (p=0.109). Severity of liver fibrosis did not predict which patients subsequently required liver transplantation or died (p=0.439; Figure 1). Eleven patients received liver transplants (64.7%) at a mean age of 282 d (range 169-495 d), four patients died (23.5%), and 2 patients were alive with their native livers (11.8%) at most recent follow up (36 and 61m of age). Two of 13 patients survived with their native liver following KP (15.4%). Two of the patients who died had congenital heart disease and only one of them underwent a KP; neither had a liver transplant. One of these patients died from respiratory failure; the other from pulmonary haemorrhage due to liver failure. The other two patients who died within 2 months post-liver transplantation from multi-organ failure after transplant in one case and from profound neurological sequelae after transplant.
leading to a decision for palliative care in the other. There was no evidence of a difference in the median age at KP between patients who died (63 d) and those who survived (54 d) \((p=0.446)\).

Severity of liver fibrosis and survival with native liver in children with biliary atresia.

**Figure 1** Kaplan Meier curve showing survival with native liver in days since birth for patients with mild (solid line) or moderate/severe fibrosis (dashed line), \(p=0.439\).

**DISCUSSION**

This study didn’t show a difference in age at referral (56 d) or age at time of Kasai (55 d) compared with Canadian median times of 55 d and 65 d respectively. Patients who underwent a KP were diagnosed with biliary atresia earlier than those who did not undergo a KP, in keeping with the recognized challenges in performing a KP in children with greater disease severity\(^{[1-3]}\) and the probable reluctance or inability of surgeons to perform a KP in patients referred beyond 3 months of age.

A number of factors were examined to identify any reasons for late referral. Age at referral did not appear to be impacted by type of health professional that provided neonatal care. Neither did place of patient’s residence in the catchment area impacted age at referral. The age when the first conjugated bilirubin was ordered (57 d) is late, particularly given current recommendations for earlier timing of KP. It is unclear why physicians are not ordering conjugated bilirubin levels earlier. Physiologic and breast milk jaundice is very common in neonates and physicians may not be recognizing the importance of investigating prolonged jaundice in neonates greater than 2 weeks of age. Other possible reasons for the delay include laboratories are not automatically performing differentiated bilirubin levels in infants older than 2 weeks and infants in Alberta are not routinely seen by a physician between 2 weeks and 2 months of age.

All but one patient in this study had intraoperative biopsy and 62.5% had mild fibrosis. Severity of fibrosis did not correlate with age at referral or survival with native liver, suggesting that postnatal age may not be the most important factor in individual progression of disease and highlights our lack of understanding of the etiology of this disease.

While this study was not designed to detect postoperative factors, such as recurrent cholangitis, nutritional status, or practice differences between surgeons or paediatricians that may have influenced the outcomes of KP, notable was the rate of survival without native liver at 2 years. While 46% of patients with a KP were considered to have a functioning KP prior to death or transplant as evident by a normalized bilirubin, only 15.4% of patients who had a KP were alive with their native liver at 2 years compared with 55.8% in a multicentre American study\(^{[9]}\) and 57.1% in a French National study\(^{[9]}\). Median age at KP in all of these studies did not differ from the present study. The reasons for differences in survival may be because of the small number of patients included in the study or that 23.5% of patients in this study had BASM, which is a known risk factor for poor prognosis in BA\(^{[10]}\). In comparison, only 11% of patients in the overall cohort in the American study\(^{[9]}\) and 8% in the French study\(^{[9]}\) had BASM. It is also documented that improved outcomes are seen in centres with higher volume of cases\(^{[12,13]}\). In a country as large as Canada it may be challenging to achieve a more centralized policy for KP. A possible solution would be performing KPs only at liver transplant referral centres. This would have the drawbacks of both cost and delays in time to KP associated with transportation and coordination of services in alternative centres. It was interesting to find that rural residence did not seem to make a delay referral, a finding that to our knowledge has not previously been reported.

A clear limitation to distinguishing factors contributing to delays in referral and diagnosis was the small number of patients included in this study. National or international databases such as those in Europe may be better able to cite reasons for delays in diagnosis but will not identify factors specific to the local population. For example, ethnicity may be an important risk factor in our population, as the Aboriginal population in Alberta are less likely to access regular health care and are theoretically at risk of delayed diagnosis of biliary atresia\(^{[14,15]}\).

While we did not observe a delay in diagnosis of biliary atresia, our rates of death and need for liver transplantation raises concerns. As seen in the literature, there is no consensus on timing of KP\(^{[13-16]}\). However, part of the reason for not knowing the ideal timing of KP is the lack of understanding behind the pathophysiology and etiology of biliary atresia. Further studies could clarify these issues permitting better care and outcomes to children affected by this disease.

**REFERENCES**


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