Chapter 3

Preterm infants with biliary atresia: a nationwide cohort analysis from the Netherlands

Daan BE van Wessel, Thomas Boere, Christian V Hulzebos, Ruben HJ de Kleine, Henkjan J Verkade, Jan BF Hulscher

On behalf of the Netherlands Study group on Biliary Atresia Registry (NeSBAR)

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ABSTRACT

OBJECTIVES

Biliary atresia (BA) occurs in 0.54/10.000 of overall live births in The Netherlands. BA has an unfavourable prognosis: less than 40% of patients are cleared of jaundice after Kasai portoenterostomy (KPE), 4-year transplant-free survival rate is 46% and the 4-year survival rate is ~75%. Little is known on difficulties in diagnosis and the outcome of BA in preterm infants. We aimed to analyse the incidence and outcome of BA in preterm infants in The Netherlands.

METHODS

Retrospective study including Dutch preterm infants treated for BA. Parameters included gestational age (GA), congenital anomalies, age at KPE, days between first symptoms and KPE and referral interval (first hospital to KPE). Outcome parameters were clearance of jaundice (COJ) and (transplant-free) survival. Data are presented as medians [ranges].

RESULTS

We included 28 preterm infants (13 males/15 females) between March 1988 and December 2015. The incidence of BA was 1.06/10.000 preterm live births. GA was 34.8 [27.3–36.9] weeks. Congenital anomalies were present in 11/28 (39%) infants. Time between first symptoms and KPE was 57 [9-138] days. Referral interval was 28 [8-86] days. Age at KPE was 70 [35-145] days. COJ was achieved in 23% of cases. 4-year transplant-free survival rate was 21%. Four-year overall survival was 61%.

CONCLUSIONS

BA has a higher incidence in the preterm population compared to the overall BA population. The outcome of BA in preterm infants is poor, regarding COJ and (transplant-free) survival. We speculate that timely recognition of BA-related signs and symptoms in preterm infants will improve prognosis.

INTRODUCTION

Biliary atresia (BA) is a rare, but life-threatening liver disease of infancy with an unknown aetiology, occurring between 0.54-1.51 in 10.000 in the overall population (1-4). Progressive scarring of the bile ducts due to an as yet unknown event, results in cholestasis and pale stools in the first weeks of life. Surgical treatment consists of the Kasai hepatoportoenterostomy (KPE) (5). Adequate drainage of bile is achieved in 38-75% of cases (2,3,6,7).

Studies with almost exclusively term BA patients showed that early KPE is associated with better transplant-free survival; a KPE after 60 days of age has a negative effect on transplant-free survival (2,8-10). In total, 70-80% of BA infants will need a liver transplantation (LTx) due to an ongoing process of liver fibrosis (11). In fact, BA is the main indication for paediatric LTx (12,13).

Prematurity has been reported as a risk factor for BA, though the exact mechanism remains unclear (4,14,15). Also data on the clinical condition and outcome of preterm infants suffering from BA are scarce (16,17). The diagnosis of BA in preterm infants is difficult due to the multifactorial origin of cholestasis in these patients (e.g. prematurity of the enterohepatic circulation, sepsis, prolonged total parenteral nutrition) (18,19). These diagnostic difficulties might result in delayed referral, later treatment and subsequently, worse outcome.

The aim of this study was to analyse the incidence and outcome of disease in preterm infants treated for BA using a nationwide BA registry in The Netherlands and to identify possible areas for improvement.

PATIENTS AND METHODS

This retrospective study was performed in accordance with the guidelines of the Medical Ethical Committee of our centre (UMCG Trial Registry, No. 201600837). To identify patients we used the Netherlands Study Group on Biliary Atresia Registry (NeSBAR) database.

For this study, we included all preterm BA infants treated between March 1988 and December 2015. For the comparison with term born infants, we used term infants from De Vries et al [2]. Prematurity was defined as gestational age (GA) <37 weeks. GA was calculated from the date of last menstruation of the preterm's mother and/or by ultrasound. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile for GA [20]. Patients were categorized in

'extremely to very preterm (27 to < 32 weeks of GA) and 'moderate to late' (32 – < 37 weeks of GA) preterms, based on the WHO classification of preterm birth. The Dutch perinatal registry uses slightly different categories, enabling us to calculate the incidences for 28 - <32 instead of 27 - <32 weeks. The diagnosis of BA was established by an intraoperative cholangiogram and/or histopathology of the liver and biliary remnant. Clearance of jaundice was defined as total serum bilirubin (TSB) <20 µmol/L (<1.17 mg/dL) within six months after KPE. In case an infant succumbed before 6 months of age, we used the last known TSB. We recorded the following parameters during KPE and follow-up: Presence of congenital anomalies, age at onset of first symptoms of conjugated jaundice, age at presentation in first hospital, corrected age at presentation in first hospital, days between first symptoms and KPE, referral interval (days between presentation at first hospital and KPE), chronological age at KPE, clearance of jaundice, LTx status, transplant-free survival (defined as the time between birth and LTx, death, or last follow-up) and mortality. Transplant-free survival was correlated to age at KPE and age at first presentation. The influence of congenital anomalies was also determined. Corrected ages were calculated by subtracting the number of weeks of prematurity from the chronological age.

Follow-up was standardized with visits to the tertiary KPE centre at one month and six months post-KPE and visits to the local paediatric gastroenterologist in between. Visits were intensified when necessary on clinical grounds. Follow-up ended when the infant died or at the end of the study period on 1st of July 2016. Patient were followed up into adulthood, if applicable.

Statistics

The incidence of BA in term and preterm infants was calculated by dividing the total number of term / preterm infants with BA by the total number of term / preterm live births in The Netherlands in the same period. Data term / preterm birth rates in the Netherlands were provided by Perined, Perinatal Registry, The Netherlands [20]. Since 2001, data on birth rates from general practitioners, obstetricians and gynaecologists are combined into one registry. Before 2001, only estimated birth rates were retrievable. We therefore refrained from drawing conclusions on these data. Live birth rates from 2001 to 2015 were retrievable as birth rates of 2016 were not yet available at time of submission. Data are expressed as median (range) unless specified otherwise. Continuous variables were compared with the Mann-Whitney U test, categorical data by using the Chi2 test or the Fisher's exact test. For (transplant-free) survival analyses, we used the Kaplan-Meier method. Survival curves were compared with the log rank test. We used partial correlations for assessing the

degree of association between transplant-free survival and (corrected) age at first presentation/ KPE, whilst correcting for GA. A P-value < 0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY).

RESULTS

Incidence

From 2001 to 2015, 2.445.624 term infants were born in The Netherlands. A number of 127 patients were diagnosed with BA in the same time span. Therefore, the incidence of BA in in term infants was 0.52 per 10.000 term live births (95% CI 0.43 – 0.62). In the same time period, 179.721 preterm infants were born. Nineteen of these preterm infants were diagnosed with BA. The incidence of BA in preterm infants born between 2001 and 2015 in The Netherlands was therefore 1.06 per 10.000 living births (95% CI 0.66 – 1.62), twice as high as in term infants. Within the same time span, the incidence of BA in preterm infants with GAs of 28 - <32 weeks was 2.54 per 10.000 preterm live births (95% CI 0.93 – 5.63). The incidence of BA in preterm infants with a GA of 32 - <37 weeks was 0.84 per 10.000 preterm live births (95% CI 0.48 – 1.38). From 2001 to 2015, one patient was diagnosed with BA who did not undergo KPE but primary LTx. This patient was included when calculating the incidence of BA in preterm infants, but was excluded from further analyses in this study. Apart from the 18 preterm infants with BA between 2001 and 2015 we identified 10 preterm infants with BA who had been born between 1988 and 2001.

Characteristics and follow-up

Table 1 depicts the patient characteristics of the 28 preterm infants (13 males and 15 females) with BA. GA was 34.8 [27.3-36.9] weeks. Six out of 28 (21%) infants were extremely to very preterm and 22 (79%) patients were moderate to late preterms. Birth weight was 2387 [960-4065] grams. Three patients (11%) were SGA.

First symptoms of conjugated jaundice consisted of jaundice (n = 9), jaundice combined with pale stools (n = 16) or were unknown (n = 3). Symptoms occurred directly from birth or in the first week after birth in 18 patients. However, there was a considerable range up to 11 weeks regarding first symptoms. Major congenital anomalies were present in 11/28 (39%) infants. These anomalies comprehended intestinal malrotation (n = 3), intestinal atresia (n = 2), or both (n = 2), cardiac anomalies (n = 2), situs inversus (n = 1) and Cri-du-chat syndrome (n = 1). There were no cases with syndromic BA. In the term born population, congenital anomalies were seen in 17%. This difference was statistically significant (P = .02).

The time between first symptoms and KPE was 57 [9-138] days in preterm infants and 50 [15-106] days in term infants (P = .07). The time between first symptoms and KPE did not differ significantly between extremely to very preterm and moderate to late preterm infants (48 [9-85] vs. 59 [18-138] days respectively; P = .36). The referral interval (time between first presentation in hospital and KPE) was 28 [8-86] days in preterm infants and 18 [7-66] days in term infants (P = .008). The referral interval did not differ significantly between extremely to very preterm and moderate to late preterm infants (34 [28-86] vs. 23 [8-71] days respectively; P = .18). KPE was performed at a chronological age of 70 [35-145] days, corresponding to a corrected age of 53 [-28-132] days, where zero is the term equivalent age. Overall, term infants were treated eleven days earlier than preterm infants, i.e. at 59 [22-132] days of age (P = .04).

Patient characteristics	n = 28
GA, weeks	34.8 [27.3–36.9]
GA 27 – <32 weeks, n (%) GA 32 – <37 weeks, n (%)	6 (21) 22 (79)
Birth weight, grams	2387 [960-4065]
Major congenital anomalies, n (%)	11 (39)
Onset jaundice, weeks	1 [0–7]
Onset pale stools, weeks	1 [0–11]
First symptoms to KPE, days	57 [9-138]
Age at first presentation, days	40 [0–136]
Corrected age at first presentation, days	4 [-62–123]*
Referral interval, days	28 [8–86]
Age at KPE, days	70 [35-145]
Corrected age at KPE, days	53 [-28–132]*
KPE <60 days, n (%)	12 (43)
KPE <60 days corrected age, n (%)	18 (64)
Post-operative antibiotics, n (%)	19 (68)
Post-operative steroids, n (%)	3 (11)
Post-operative UDCA, n (%)	12 (43)
Clearance of jaundice, n (%)	6 (23)**
LTx, n (%)	15 (54)
Age at liver transplantation, months	9 [6-68]
Transplant-free survival, months	10 [1-342]
Mortality, n (%)	11 (39)
Age at death, months	8 [1-44]

Table 1. Patient characteristics of preterm infants treated for BA. *: 0 represents term equivalent age; **Unknown in two patients.

Two out of 28 preterm infants succumbed within a week after KPE due to an abdominal compartment syndrome and liver lobe necrosis, respectively. Both were early preterm babies (30+2 and 30+6 GA) and one was SGA. Both patients were

bottle fed. Ages at KPE were 39 and 74 days, respectively. Both patients' heights and weights at time of KPE were below the -2,5SD mark of the weight / height for chronological age curves (1485 and 2175 grams, resp., and 40 and 45 cm resp.).

In the remaining 26 infants, 6 (23%) patients cleared their jaundice after KPE, which was not significantly different from terms. Clearance of jaundice did not occur when KPE was performed before 35 days or after 85 days of age (corresponding to a corrected age of -28 and 73 days respectively). The age at KPE of patients who cleared their jaundice was 68 [35 – 85] days, corresponding with 63 [-78 – 73] days when corrected. The GA of patients who did clear their jaundice did not differ from those who did not clear their jaundice, 35.6 [28.0-36.9] weeks vs. 34.8 [27.3-36.6] weeks, respectively (P = .56) (Figure 1).

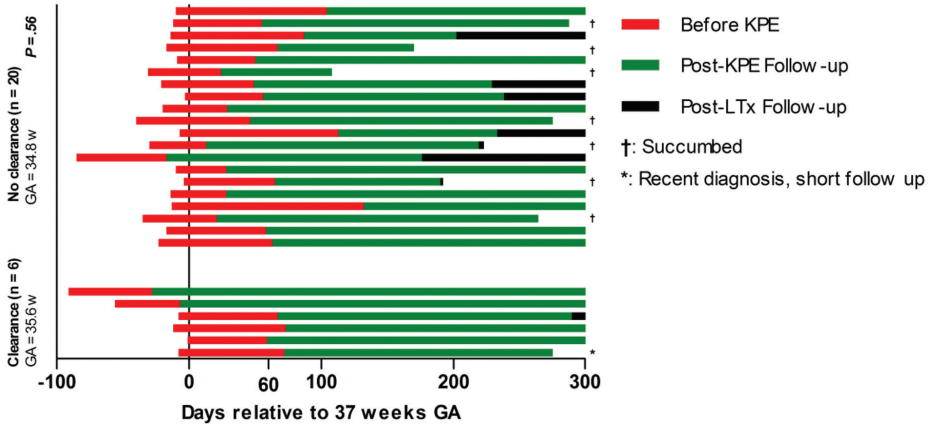

Figure 1. Course of disease in preterm infants who did and did not clear their jaundice.

In total, 15/28 (54%) patients received an LTx during follow up. Age at LTx was 9 [6-68] months. Median follow-up was 46 [0-341] months. The 4-year transplant-free survival rate was 21% in preterm infants and 43% in term infants (P = .03; Fig. 2A). In preterm infants, 50% of patients underwent LTx < 4 years of age, compared to 43% in term infants (P = .32). A partial correlation was run to determine the relationship between transplant-free survival and (corrected) age at KPE and (corrected) age at first presentation whilst controlling for GA. Zero order correlations were negatively weak (-.203 up to -.289), and not statistically significant. After controlling for GA, correlations were again negatively weak (-.185 up to -.246) and not statistically significant. Congenital anomalies had a significant negative effect on transplant-free survival. (Log rank, P = .001). The median transplant-free survival times of

patients with and without congenital anomalies were 8 [1-20] vs. 22 [2-342] months respectively.

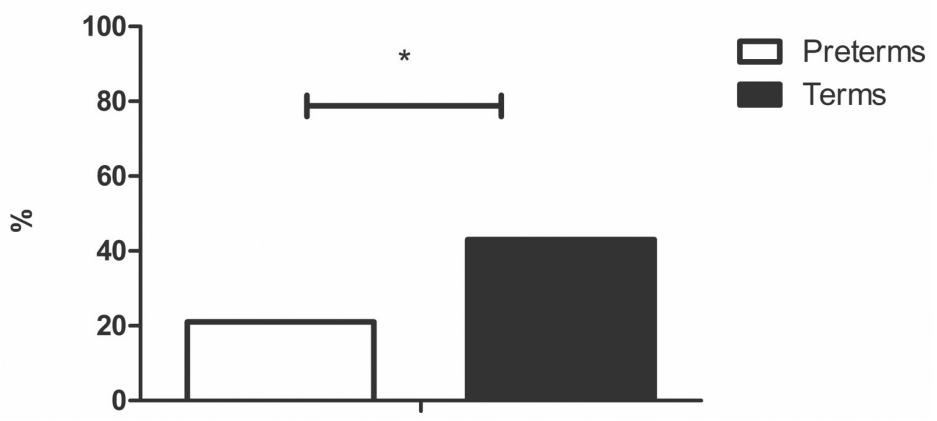

Figure 2A. 4-year transplant-free survival in preterms and terms with BA.

Eleven out of 28 (39%) preterm infants died before four years of age, at an age of 8 [1-44] months, of which five while listed for LTx. Four–year overall survival was therefore 61%. Four-year overall survival was higher in term born infants (79%, P = .04; Fig 2B). Causes of death were liver failure (n = 3), sepsis (n = 2), hepatorenal syndrome (n = 2), multi-organ failure after LTx (n = 1) and unknown cause of death (n = 1).

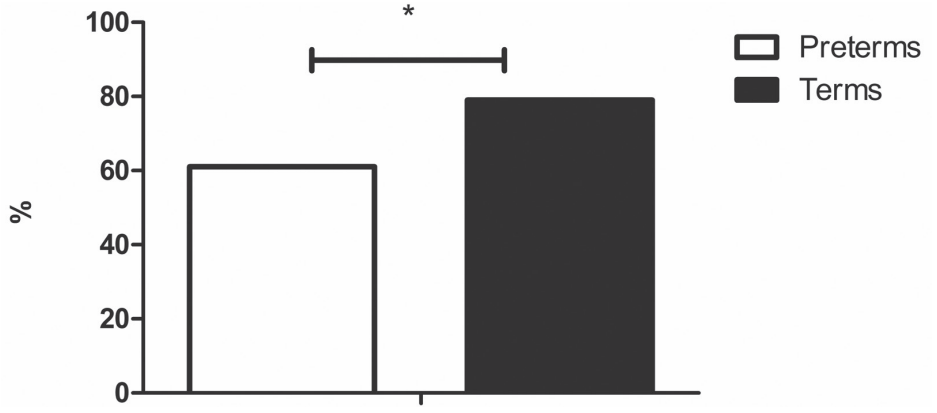

Figure 2B. 4-year overall survival in preterms and terms with BA.

DISCUSSION

This study set out to analyse the incidence and outcome of disease in preterm BA infants in The Netherlands. Our study found that the incidence of BA is higher in preterm infants when compared to term born BA infants. With regard to the chronological age (but not to the corrected age), preterm BA infants are treated relatively late in life. When comparing the outcome of disease to term infants [2], preterm infants have poor post-operative outcomes, regarding clearance of jaundice, need for LTx, and (transplant-free) survival.

Incidence

The incidence of BA is over twice as high in preterm infants (1.06/10.000) when compared to term infants (0.52/10.000) [2]. This suggests that clinicians should, among others, consider BA in the differential diagnosis of cholestasis/be aware of a two-fold increase of chance of BA when jaundice and pale stools appear in the first weeks of life in (especially extremely to very) preterm infants.

Referral

Preterm infants are treated after eight weeks, counting from the onset of their first symptoms. There was a significant difference in referral interval when comparing preterm (28 days) and term infants (18 days), suggesting that delay in preterm infants occurs more frequently and is present after first presentation in the hospital. Subsequently, preterm infants are treated eleven days later in life than term infants. Delay might have been caused by diagnostic difficulties in (extremely) preterm infants, resulting from the fact that cholestasis in preterm infants is often considered to be multifactorial [18,19]. Moreover, preterms with multifactorial cholestasis may have grey stools, and biopsy results with bile duct proliferation might also resemble BA [21,22]. Despite the foregoing, prematurity itself seems not to affect the timing of BA detection [23], but merely delays the timing of the KPE [4]. Our results emphasize that one of the main challenges in BA, i.e. early detection of the disease, is also present in preterm infants. The stool colour card, an effective tool for recognizing discoloured stool, might aid in this matter and should possibly be provided to parents with preterm infants [4,24]. Moreover, clinicians should perform measurement of total and conjugated (direct) serum bilirubin if (preterm) infants are jaundiced after two weeks of age, according to the ESPGHAN/NASPGHAN guidelines [25]. Increased awareness for BA in preterm infants is warranted to prevent delay and subsequently, to increase clearance of jaundice-rates after KPE.

Outcome

1. KPE

Clearance of jaundice did not significantly differ between preterms and terms. In Taiwan, clearance of jaundice (<3 months) is achieved in 37% of preterm infants, and in 62% of term infants. The lower KPE success rate might be caused by increased sensitivity of the immature liver to cholestasis and associated inflammation [14]. Clearance of jaundice was not achieved when the KPE was performed before the chronological age of 35 days or after 85 days. Further studies are needed to establish the best time to operate preterm infants with BA (possibly between 35 and 85 days of chronological age) and to elucidate the best therapeutic option (i.e. KPE vs. LTx) in preterm infants in whom BA is detected at a relatively older age.

2. LTx

The four-year transplant-free survival rate is significantly lower in preterm infants when compared to term born infants, indicating worse outcome of BA in preterm infants. To our surprise, neither chronological age nor corrected age at KPE impacted transplant-free survival significantly. Chiu et al. could not describe a significant effect of a late KPE on the clearance of jaundice-rate in preterm BA infants [4]. This might be explained by the fact that in preterm infants, irreversible hepatic damage might occur earlier than in term-born BA infants due to increased hepatic sensitivity to cholestasis and/or total parental nutrition (TPN), the lack of enteral feeding and sepsis. This, in turn, might lead to lower success rates of the KPE, subsequently resulting in decreased native liver survival. Thus, one might argue that age at KPE in preterm infants is not that important. On the other hand, one might also suggest that it is even more important in these infants, due to increased liver vulnerability. Congenital anomalies had a significant negative impact on transplant-free survival. Also, congenital anomalies were seen more often in preterm infants when compared to term born infants. This is in line with the study of Chiu et al. [4]. As congenital anomalies are associated with worse outcome [26-28], these anomalies might also have contributed to poor BA outcome in preterm infants.

3. Survival

Our data suggest that preterm BA infants are at a high risk for death within the first years of life. Moreover, the four-year overall survival rate of preterm infants is significantly worse when compared to term born infants. Two patients succumbed within a week after KPE due to causes that seemed related to the operation. The patients' weights and heights at time of KPE were below the -2,5SD for chronological age, suggesting that clinicians should strive for proper growth status to optimize

postoperative recovery. Postponing the operation until proper growth is achieved will however decrease the success rate of the KPE. Primary LTx might be considered in these children, after obtaining proper growth status. This should however be studied in larger cohorts. Five patients were already on the list for LTx at time of death. Preterm infants might need closer monitoring than term-born children, especially in the first year of life. It might be necessary to intensify outpatient clinic visits or even consider hospitalization when on the waiting list for LTx. End-stage BA (preterm) infants are more susceptible to infections and sepsis [29], and clinicians should therefore be aware of the increased vulnerability of preterm BA infants on the waiting list for LTx.

We acknowledge several limitations to our study. Firstly, inherent to a retrospective cohort study, we could not retrieve specific information about the cause of delay in referral as well as data on confounding factors for prematurity and poor outcome (e.g. TPN, poor oral intake and need for surgical intervention). Secondly, we could only include 28 patients in almost 30 years, during which care for these patients has undergone significant changes. Outcomes of this study need to be confirmed in larger cohorts with longer follow-up, as our follow-up is relatively short (46 months). Lastly, we could only retrieve birth rates from 2001 – 2015, i.e. not of the total study period. This might have influenced our results and conclusions regarding incidence.

In conclusion, the incidence of BA seems higher in preterm infants when compared to term born infants. Medical professionals should be aware of a two-fold increase of chance of BA when jaundice and pale stools appear in the first weeks of life in preterm infants. Also, preterm infants with BA are treated relatively late in life and have poor post-operative outcome, regarding clearance of jaundice, need for LTx, and (transplant-free) survival. Also, preterm infants might need intense follow up whilst on the LTx waiting list. Timely referral and earlier diagnosis are key to improve prognosis.

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