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The timing of surgery of antenatally diagnosed choledochal malformations: A descriptive analysis of a 26-year nationwide cohort☆

For the Netherlands Study Group for Choledochus Cysts/Malformations (NeSCHoC), Maria H.A. van den Eijnden [a,1], Ruben H. de Kleine [b,1], Ivo de Blaauw [c], Paul M.J.G. Peeters [b], Bart G.P. Koot [d], Matthijs W.N. Oomen [e], Cornelius E.J. Sloots [f], Wim G. van Gemert [g], David C. van der Zee [h], L.W. Ernest van Heurn [e], Henkjan J. Verkade [i], Jim C.H. Wilde [j], Jan B.F. Hulscher [a,*]

[a] Department of Pediatric Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[b] Department of Hepato-Pancreatico-Biliary Surgery and Liver Transplantation, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[c] Department of Pediatric Surgery, Radboudumc-Amalia Children's Hospital, Nijmegen, The Netherlands
[d] Department of Pediatrics, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands
[e] Department of Pediatric Surgery, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands
[f] Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
[g] Department of Pediatric Surgery, University Medical Center Maastricht, Maastricht, The Netherlands
[h] Department of Pediatric Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[i] Department of Pediatrics, University of Groningen, University Medical Center Groningen, University of Groningen, The Netherlands
[j] University Center of Pediatric Surgery of Western Switzerland, Division of Pediatric Surgery, University Hospitals of Geneva, Geneva, Switzerland

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ABSTRACT

Introduction: Choledochal malformations (CMs) are increasingly diagnosed antenatally. There is a dilemma between early surgery to prevent CM-related symptoms and postponing surgery to reduce complications. We aimed to identify the optimal timing of surgery in asymptomatic neonates with antenatally diagnosed CM and to identify predictors for development of symptoms.
Methods: Using the Netherlands Study group on CHoledochal Cyst/malformation (NeSCHoc) we retrospectively collected demographic, biochemical and surgical data from all Dutch patients with an antenatally detected CM.
Results: Between 1989 and 2014, antenatally suspected CM was confirmed in 17 patients at a median age of 10 days (1 day–2 months). Four patients developed symptoms directly after birth (24%). Thirteen patients (76%) remained asymptomatic. Two of these progressed to symptoms before surgical intervention at 0.7 and 2.1 months resp. Postoperatively, four patients developed short-term complications and three developed long-term complications. Patients <5.6 kg (the series median) showed more short-term complications (66%) when compared to patients >5.6 kg (0%, $p = 0.02$).
Conclusion: When not symptomatic within the first days of life, the majority of children with antenatally detected CM remains asymptomatic. Surgery might safely be delayed to the age of 6 months or a weight of 6 kg. Postponing surgery in the clinically and biochemical asymptomatic patient might decrease the complication rate.
Levels of evidence: Level III.

In developed countries up to 15% of all choledochal malformations (CMs) are detected before birth and this rate is expected to rise [1–4]. The availability of improved antenatal screening is the main reason for this increase. Symptomatic CM requires rapid surgical intervention as soon as the infant's clinical condition permits [2,5–7]. However, the majority of infants in whom CM is detected antenatally will be asymptomatic at birth. In the absence of symptoms the timing of surgical intervention remains open to debate [8]. The risk of the patient developing symptoms and possibly even liver damage owing to persistent bile stasis needs to be weighed against the risks of prophylactic surgery at a young age. In the case of asymptomatic neonates, watchful waiting until their weights have increased might be a valid option [1–3]. Fewer long-term complications are expected when operating on infants older than six months, because by this age surgery, especially biliodigestive anastomosis, is technically less demanding [9,10]. Moreover, in young infants anesthesia should be avoided as much as possible. A rapidly growing body of evidence suggests deleterious effects of anesthesia and analgesia on developing infants' brains [11,12]. Our main aim

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* Corresponding author at: Department of Pediatric Surgery, University Medical Center Groningen, Hanzeplein 1, HPC BA20, PO Box 30.001, Groningen, 9700RB, The Netherlands.
E-mail addresses: j.b.f.hulscher@umcg.nl, jbfhulscher@hotmail.com (J.B.F. Hulscher).

[1] Contributed equally to this manuscript.

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was to identify the most appropriate time to initiate surgical intervention in asymptomatic, antenatally diagnosed neonates, with a focus on surgical complications. Our second aim was to identify possible predictors of progression to symptoms in asymptomatic neonates with CMs.

1. Patients and methods

By using the nationwide database of the Netherlands Study Group on Choledochal Cyst/Malformation (NeSCHoC) we identified all patients with antenatally detected CMs who were treated at a Dutch pediatric surgical center. The NeSCHoC database contains data on all patients younger than 18 years who had undergone surgery for CMs in one of the six Dutch pediatric centers between January 1, 1989 and December 31, 2014. The primary investigator, ME, collected data from the database on patient demographics, age at definite diagnosis, type of CM according to Todani [13], clinical course, biochemical results, surgical parameters, and postoperative outcomes. Patients recorded in the NeSCHoC were cross-checked with the Dutch national registry for biliary atresia (NeSBAR) in order to exclude patients diagnosed with cystic biliary atresia. Postoperative complications were subdivided into short-term complications (less than 30 days) and long-term complications (more than 30 days). We graded the severity of short-term complications by using the Clavien–Dindo classification [14]. The definitions of CM-related symptoms and postoperative complications are as follows:

- jaundice, defined as serum bilirubin levels of >100 μmol for infants between one and five days of age, and serum bilirubin levels of >17 μmol for infants older than five days with clinical signs of jaundice;
- cholangitis, defined as fever higher than 38.5 °C with abdominal pain and jaundice;
- pancreatitis, defined as abdominal pain with elevated serum amylase of >140 U/L;
- bile leakage, defined as abdominal pain and high amounts of bilirubin in abdominal drain fluid.

The patients were followed up by using the hospital files. As CMs are only treated in these six pediatric surgical centers, all postoperative complications are registered in the patients' electronic or paper files in the pediatric center where resection was performed. Follow-up analysis was conducted from January 1, 1989 until October 1, 2015. The study was approved by the ethics committee of University Medical Center Groningen (METC2015/115).

1.1. Statistical analysis

Differences between groups were tested with the *t* test, Mann–Whitney test, and Wilcoxon signed rank test as appropriate. To determine statistical differences between ordinal values the chi-squared test or Fishers' exact test was used as appropriate. *P* values <0.05 were considered statistically significant. The SPSS IBM 22 package (Armonk, New York, United States) was used for statistical analysis.

2. Results

2.1. Antenatally detected CM

During the study period we identified 91 patients with CMs, seventeen (19%) of whom were diagnosed antenatally with intraabdominal abnormalities. The diagnoses were confirmed by ultrasonography after birth. Four patients (4/17, 24%) became symptomatic with jaundice and/or discolored stools within two weeks after birth, even before a definite diagnosis could be established. The remaining 13 patients (13/17, 76%) were asymptomatic at the time of diagnosis and their data were used for analysis. There were two boys (15%) and 11 girls (85%) leading to a male to female ratio of 1:5.5. Median age at the time of diagnosis was 6 days, ranging from one day to 2.1 months. Twelve patients were diagnosed with Type I CM (92%) and one with Type IVb (8%). Eleven patients (85%) remained asymptomatic between diagnosis and surgical intervention. Two patients (15%) progressed to CM-related symptoms before surgery. Symptoms consisted of jaundice and/or discolored stools.

2.2. Predicting progression to CM-related symptoms

The two patients who progressed to CM-related symptoms were diagnosed with CM Type I. We were able to retrieve biochemical investigations at the time of diagnosis (thus prior to CM-related symptoms) from 11 patients (85%, Table 1).

No significant differences were found in the individual liver enzymes between patients who remained asymptomatic and those who progressed to CM-related symptoms. We did, however, observe a tendency towards higher values on almost all liver enzyme tests in the two patients who progressed to CM-related symptoms. No records were found of clinically objective progression to CM-related symptoms with discolored stools and/or jaundice in the patients who were said to be asymptomatic at the time of surgical intervention.

Nine patients had elevated serum total bilirubin levels. In three patients there was also an increase in conjugated bilirubin (> 20% of total bilirubin) suggesting a posthepatic obstruction. These three patients were operated within one week after diagnosis to rule out biliary atresia. Two other patients with elevated total bilirubin levels were operated within two months after diagnosis. In two cases the hospital protocols at the time did not indicate surgery because patients remained

Table 1
Biochemical investigations in the asymptomatic, antenatally diagnosed patients at the time of definite diagnosis.

	All[a] (n = 11)	Asymptomatic (n = 9)	Progressed to symptoms (n = 2)	p-value
Median age (days)	16 (1–130)	16 (1–130)	33 (1–64)	1.0
AST (U/L) (normal <89)	49 (26–190)	49 (26–190)	74 (40–108)	0.6
ALT (U/L) (normal <60)	24 (13–80)	24 (13–41)	49 (17–80)	0.6
GGT (U/L) (normal <204)	250 (17–1344)	208 (17–1344)	489 (424–547)	0.5
ALP (U/L) (normal <510)	226 (161–831)	298 (141–495)	529 (226–831)	0.3
Bilirubin (μmol/L) (normal <17/<100)	85 (3–201)	66 (3–168)	151 (102–201)	0.1
Conjugated bilirubin (μmol/L) (normal <20% of total bilirubin)	14 (1–90)	11 (1–52)	52 (13–90)	0.4
Median (minimum-maximum)				

Abbreviations used: AST (Aspartate Aminotransferase), ALT (Alanine Aminotransferase), GGT (Gamma-Glutamyl Transpeptidase), ALP (Alkaline Phosphatase) U/L (units per liter), μmol/L (micromoles per liter)

[a] Laboratory data were available from 11 out of 13 asymptomatic patients only.