Original Article

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Factors associated with cholestasis after surgery for congenital duodenal atresia

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KEYWORDS

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ABSTRACT

Background: This study assessed the characteristics of neonates with duodenal atresia (DA) who developed transient postoperative cholestasis which resolved spontaneously, without identifiable congenital anomalies or surgical complications, and identified potential risk factors for cholestasis.

Methods: Neonates with DA who underwent surgery at our institution between January 2009 and July 2022 were retrospectively reviewed. Demographic factors, intraoperative findings, placement of a trans-anastomotic tube (TAT), and postoperative outcomes were compared between patients who developed cholestasis (conjugated hyperbilirubinemia >2.0 mg/dL) after surgery (Group A) and those who did not (Group B). This report is a retrospective cohort study and complies with the STROBE statement.

Results: Among 19 neonates with DA, 6 (31.6%) developed cholestasis after surgery, with the highest direct bilirubin value being 4.3 (2.4-6.5) mg/dL (median, [range]) on postoperative day 14.5 (2-23) that persisted for 67 (47-116) days until spontaneous resolution. Neonates in Group A had a significantly younger gestational age (36.6 vs. 38.0 weeks) (median) (p=0.038), a higher rate of Down syndrome (66.7 vs. 15.4%) (p=0.046), a higher rate of TAT placement (66.7 vs. 15.4%) (p=0.046), and longer administration of total parenteral nutrition (15.5 vs. 7.0 days) (p=0.027) than those in Group B.

Conclusion: Transient cholestasis after surgery for DA seemed to be associated with prematurity, Down syndrome, parenteral nutrition, and TAT placement.

INTRODUCTION

Biliary tract abnormalities, such as biliary atresia, congenital biliary dilatation, and distal common bile duct stenosis, have been reported to be rarely associated with duodenal atresia (DA). [1-3] Therefore, when we encounter cholestasis after surgery for DA, close investigations, including imaging studies and rarely histological investigations, are necessary to rule out not only surgical complications, i.e. accidental suturing of the papilla of Vater but also accompanying anomalies that require further surgical intervention as mentioned above.

Cholestasis is sometimes seen in neonates with small bowel atresia [4], but its mechanisms and risk factors have never been clearly identified. We experienced several cases of DA that developed worrisome cholestasis after surgery but resolved spontaneously without identifiable congenital anomalies or surgical complications. In the present study, our aim was to assess the characteristics of this cohort and explore potential risk factors for the development of cholestasis after surgery.

METHODS

This retrospective cohort study adhered to the STROBE checklist. Medical charts of all neonates with DA treated at Fukushima Medical University Hospital between January 2009 and July 2022 were retrospectively reviewed. This study has been approved by the institutional review board of Fukushima Medical University (No. 2022-032).

Among the identified 29 neonates operated on for DA, those with fatal congenital heart diseases, chromosomal abnormalities except for Down syndrome (21-trisomy), esophageal atresia, anorectal malformations, transient abnormal myelopoiesis (TAM), and cholestasis preoperatively and who developed congenital biliary dilatation within a few years after surgery were excluded, leaving 19 ultimately included in this study.

All operations were open procedures with either right-upper quadrant or umbilical incisions with the administration of prophylactic antibiotics using first-generation cephem during the two days after surgery.

The placement of a trans-anastomotic tube (TAT) at the time of the operation had not been performed until the middle of 2017. Since 2017, when a new professor was assigned to our department, it has been the policy to perform TAT placement whenever possible, unless its insertion is considered difficult for reasons such as small size or twisting of the intestines.

Patients who developed conjugated hyperbilirubinemia (>2.0 mg/dL) after surgery and those who did not, were classified into Groups A and B, respectively. The clinical demographic factors (sex, gestational age, birth weight, and association with Down syndrome, congenital heart disease, or other comorbidities), intraoperative findings (age at surgery, type of atresia using the Gray and Skandalakis classification, association with annular pancreas, type of surgery, e.g. diamond-shaped anastomosis or membrane resection), placement of a trans-anastomotic tube (TAT), and postoperative outcomes (start of feeding, duration of parenteral nutrition, and serum C-reactive protein levels) were compared between patients in Groups A and B.

Statistical analyses were performed using the IBM SPSS Statistics software program (version 26; International Business Machines Corporation, Armonk, NY). The chi-square test or Fisher's exact test was used for the analysis of categorical variables and the Mann-Whitney U test for continuous variables. In univariate analyses, p-values less than 0.05 were considered statistically significant.

RESULTS

Among the 19 neonates with DA, 10 (52.6%) were male, the median gestational age was 37.7 weeks, and the median birth weight was 2712 g. Six (31.8%) had Down syndrome. The median age at surgery was 2 days, and all of the surgical approaches were performed via laparotomy in the upper abdomen. TATs were placed in 6 cases (31.6%).

Six neonates (31.6%) developed cholestasis accompanied by pale-colored stool after surgery and were classified into Group A with a median follow-up period of 219 (range: 80-2105) days, while the remaining 13 neonates without cholestasis were classified into Group B with a median follow-up period of 2183 (range: 111-3444) days. The highest direct bilirubin value of the neonates in Group A was 4.3 (2.4-6.5) mg/dL (median, [range]) on postoperative day 14.5 (2-23) during hyperbilirubinemia, which persisted for 67 (47-116) days until spontaneous resolution.

Four patients in Group A underwent ultrasonography and biliary atresia was ruled out, and two of them also received magnetic resonance cholangiopancreatography for the closer investigation of biliary and pancreatic problems. These imaging studies revealed no anatomical abnormalities other than temporary intrahepatic biliary dilatation with a small amount of debris in the common hepatic duct in one patient, which resolved spontaneously after administering oral ursodeoxycholic acid.

The pre- and postoperative clinical data were compared between the two groups (Table 1). Neonates in Group A had a significantly younger gestational age (36.6 vs. 38.0 weeks) (median) (p=0.038), a higher rate of Down syndrome (66.7 vs. 15.4%) (p=0.046), a higher rate of TAT placement (66.7 vs. 15.4%) (p=0.046), and longer administration of total parenteral nutrition (15.5 vs. 7.0 days) (p=0.027) than Group B. However, other factors, such as sex, birth weight, congenital heart disease, other comorbidities, age at surgery, type of atresia, presence of annular pancreas, type of surgery, starting day of postoperative enteral feeding or oral intake, highest CRP value, and duration of CRP elevation, were not significantly associated with postoperative cholestasis in neonates with DA. A multivariate analysis was not performed because of the small number of cases in this study.

DISCUSSION

Cholestasis after surgical repair of DA is occasionally noted, with a reported incidence of 11-28% [4-6], similar to the incidence noted in the present study (31.6%). Although all reported cases recovered from cholestasis as expected, the pathophysiology of temporary cholestasis and its risk factors have not been well investigated, except for in a recent paper where Toyama et al. revealed that the occurrence of postoperative cholestasis in patients with DA was associated with preterm delivery and the highest CRP value after the operation. We likewise investigated the association of these factors with cholestasis and revealed that cholestasis seemed to be associated with a younger gestational age, Down syndrome, parenteral nutrition, and TAT placement during surgery, although we only conducted a univariate analysis due to the small number of cases.

The highest direct bilirubin value of the neonates in Group A was noted on postoperative day 14.5 (range: 2-23), which was well after enteral feeding was started, so we felt that the postoperative course was uneventful. Although the cholestasis in our Group A and the previously reported cases all resolved spontaneously, the treating physicians need to rule out biliary tract abnormalities, such as biliary atresia, congenital biliary dilatation, and stenosis of the distal common bile. [1-3] Our imaging surveys revealed temporary intrahepatic biliary dilatation with a small amount of

debris in the common hepatic duct in one patient using ultrasonography, which resolved spontaneously. Therefore, ultrasonography should be the first modality used to screen out the problems mentioned above and repeated at intervals if cholestasis does not start resolving within a few weeks.

Table 1. Univariate analyses to determine risk factors for postoperative jaundice in neonates with duodenal atresia.

	Group A (with cholestasis) (n=6)	Group B (without cholestasis) (n=13)	p value
Male	2 (33.3%)	8 (61.5%)	0.259
Median gestational age [weeks] (range)	36.6 (32.0-38.4)	38.0 (35.7-41.1)	0.038*
Median birth weight [g] (range)	2531 (1534-2932)	2964 (1816-3318)	0.050
Down syndrome	4 (66.7%)	2 (15.4%)	0.046*
Congenital heart disease	2 (33.3%)	3 (23.1%)	0.520
Other minor comorbidities	3 (50.0%)	5 (38.5%)	0.506
Median age at surgery [days] (range)	3.0 (1-18)	2.0 (0-9)	0.250
Types of duodenal atresia			0.370
I	2	7	
II	0	0	
III	4	6	
Annular pancreas	1	0	0.316
Types of surgery			0.520
Diamond-shaped anastomosis	4 (66.7%)	10 (76.9%)	
Membrane resection	2 (33.3%)	3 (23.1%)	
Placement of trans anastomotic tube	4 (66.7%)	2 (15.4%)	0.046*
Median starting days of postoperative enteral feeding [days] (range)	5.5 (2-7)	6.5 (2-10)	0.308
Median starting days of postoperative oral intake [days] (range)	13.5 (8-45)	8.0 (5-20)	0.147
Duration of total parenteral nutrition administration [days] (range)	15.5 (9-18)	7.0 (0-21)	0.027*
C-reactive protein			
Highest value [mg/dL] (range)	1.9 (0.41-9.3)	1.0 (0.36-2.9)	0.248
Duration of elevation [days] (range)	5.0 (1-10)	2.0 (1-7)	0.120

*: statistically significant

Neonates with DA who developed cholestasis postoperatively had a significantly younger gestational age (36.6 vs. 38.0 weeks) (median) (p=0.038) than those without DA in our study. This is compatible with the findings of previous studies. [5,7] Younger gestational age itself is a known risk factor for cholestasis. [8] Neonates with DA tend to be born prematurely due to polyhydramnios, which may contribute to the immature development of the hepatobiliary system, leading to a tendency to develop cholestasis postnatally. [5, 9]

Parenteral nutrition has been well known to cause cholestasis in neonates [7], and this is compatible with our finding that cholestatic neonates had a longer administration of total parenteral nutrition (15.5 vs. 7.0 days) (p=0.027) than those without cholestasis. In the previous study conducted by Toyama et al. [5], the duration of total parenteral nutrition was also identified as a risk factor in univariate analysis, although it was not an independent risk factor for cholestasis. Treating physicians should taper parenteral nutrition once enteral feeding has been started for patients with DA postoperatively. Down syndrome was also shown to be a risk factor for developing cholestasis after surgery for DA in our study, but this was not compatible with the findings of Toyama et al. [5] Although this discrepancy may be due to the small number of cases in our study, care should also be taken, as Down syndrome itself may induce the development of neonatal cholestasis, irrespective of surgical interventions. [10]

Notably, Toyama et al. [5] revealed that the highest postoperative CRP value was an independent risk fac-

tor for postoperative cholestasis in DA, but our results were not compatible with these findings. Postoperative CRP values seem to be influenced by many factors, including surgical technique and perioperative management, so more perioperative factors need to be investigated in order to clarify the importance of the CRP value as a risk factor for cholestasis.

TAT has been widely used in the surgical treatment of DA to reduce the need for parenteral nutrition, decrease the time to full enteral feeding, and reduce the cost of feeding [11, 12]. Aspirot et al. [4] found that 5 of 18 patients (28%) with DA developed cholestasis postoperatively, with the use of TAT having no significant effect on the incidence of cholestasis. Our study, conversely, showed that the cholestatic group had a higher rate of TAT placement than the non-cholestatic group (66.7% vs. 15.4%) (p=0.046).

Antibiotics may also cause direct hyperbilirubinemia. [13] None of our patients had infectious complications, such as surgical site infection or sepsis, and all received perioperative prophylactic antibiotic therapy using first-generation cephem until postoperative day 2. The hyperbilirubinemia in patients in Group A persisted for 67 (47-116) (median, [range]) days until spontaneous resolution occurred, which is quite later than the cessation of antibiotics. Therefore, a causative relationship between antibiotic therapy and hyperbilirubinemia would be unlikely in our patients in Group A.

The precise reason for the cholestasis with pale-colored stool in our Group A is unknown, but as stated above, we assume that it was caused by three factors in varying degrees; the first is cholestasis due to immaturity in the biliary system, which might be accompanied by younger gestational age and/or Down syndrome, the second is parenteral nutrition-related liver damage, and the third is temporal dysfunction of the papilla of Vater possibly due to irritation and edema caused by TAT placement, leading to obstructive jaundice.

The present study was associated with some limitations, including its retrospective design, small sample size, and the fact that it was performed at a single institution. Furthermore, there unmeasured confounding factors may have influenced the associations between cholestasis and gestational age, Down syndrome, parenteral nutrition, or TAT placement. Prospective multicenter studies are necessary to evaluate other risk factors for cholestasis after operations for DA.

CONCLUSION

Temporary cholestasis after surgery for DA seemed to be associated with prematurity, Down syndrome, parenteral nutrition, and TAT placement. Although our data need to be interpreted carefully due to the small number of cases involved, TAT may cause irritation around the papilla of Vater and lead to obstructive jaundice.

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