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ORIGINAL ARTICLE

Efficacy of the circulatory management of an antenatally diagnosed congenital diaphragmatic hernia: outcomes of the proposed strategy

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Abstract
Object The purpose of this study is to evaluate the outcome of our therapeutic strategy for antenatally diagnosed congenital diaphragmatic hernia (ADCDH).
Methods We treated 61 cases of ADCDH according to our strategy. Prostaglandin E1 was required to be maintained the patency of the ductus arteriosus (PDA) in 39 cases (Group I) while it was not administered in 22 cases (Group II). Left ventricular end-diastolic dimension (LVDD) and Tei index were measured with echocardiography on days 0, 2, and 7 after birth. Radical surgery was performed on all cases by day 2.
Results On day 0, Group I showed smaller LVDD and Tei index than those in Group II. Between day 0 and day 2, these parameters increased significantly in Group I, but not in Group II. On day 7, no significant difference in these parameters was observed between the two groups. Five patients died of cardiac and respiratory failure, resulting in a survival rate of 92 %.
Conclusion Our therapeutic strategy improves the clinical outcome of ADCDH. This can be attributed to two factors: earlier surgery resulting in improved LV function. The latter attenuates pulmonary hypertension and maintains PDA with a consequent decrease in right ventricular afterload to compensate for the low cardiac output resulting from PDA.

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Keywords Congenital diaphragmatic hernia · Left ventricular performance · Doppler echocardiography · Isovolumic relaxation time · Diastolic disorder

Introduction

Despite the implementation of several therapeutic strategies, such as early surgery with inhalation of nitric oxide (NO) [1] or a delayed operation with extracorporeal membrane oxygenation (ECMO) [2], and delayed surgery after cardiopulmonary stabilization with high-frequency oscillatory ventilation [3], the survival rate of infants with an antenatally diagnosed congenital diaphragmatic hernia (ADCDH) still remains approximately 70–80 % [4–6]. The treatment of antenatally diagnosed ADCDH had focused on respiratory failure. However, in severe cases of antenatally diagnosed ADCDH, the left ventricle is markedly underdeveloped, and the hypoplastic lung presents intractable pulmonary hypertension [7]. Therefore, the severe cases of antenatally diagnosed ADCDH frequently develop left ventricular failure secondary to an underdeveloped left ventricle and right heart failure due to pulmonary hypertension after birth [8]. Therefore, we considered that circulatory management would be dispensable for the treatment of severe ADCDH. We thus proposed a new therapeutic strategy for ADCDH with a special emphasis on circulatory management [9]. The purpose of this study was to evaluate the outcome of the proposed strategy.

Methods

Patients and methods

We treated 61 cases of ADCDH between January 1996 and December 2011 at Osaka Medical Center and Research

Institute for Maternal and Child Health and reviewed these cases. Cases with ADCDH associated with complex heart disease or chromosomal aberrations were excluded from this study.

Sixty-one inborn cases of ADCDH that were born at our institute were enrolled in this study. The affected site was the left side in 59 cases and right in two. The severity of the condition was quantified by measuring the lung/thorax transverse area ratio (L/T) and the lung-to-head ratio (LHR) by antenatal ultrasonography, as described previously [10, 11]. The prenatal and postnatal medical records were reviewed for clinical information, including the eventual outcome.

Therapeutic strategy

From 1988 through 1995, delayed surgery after prolonged preoperative stabilization (more than 48 h) was used in ADCDH. Surgical repair of CDH was undertaken when the resolution of persistent pulmonary hypertension was confirmed by echocardiography. The survival rate in this period was 38 % [12]. From 1996, we started a new therapeutic strategy for ADCDH with a special emphasis on circulatory management. The method of delivery was decided according to the L/T; a planned cesarean section was chosen in cases with a L/T less than 0.12, and a vaginal delivery was chosen in cases with a L/T of 0.12 or more. High-frequency oscillatory ventilation was used routinely, and NO was given in cases with a preductal arterial saturation of 90 % or less [12].

We considered a case with liver-up and a L/T less than 0.1 to be the most severe cases, and prostaglandin I_2 (PGI_2) was administered in addition to PGE_1 in these cases. PGI_2 (intravenous PGE) was given when the preductal arterial saturation did not exceed 80 % following the above treatments. The PGI_2 infusion was initiated at 2.0 ng/kg/min, and was subsequently increased to a maximum of 20 ng/kg/min.

When the percutaneous oxygen saturation of the right hand increased above 88 %, radical surgery was performed. Subsequently, most cases underwent definitive surgery within several hours after birth. ECMO was applied in cases in which the preductal oxygen saturation did not increase above 88 %. Recently, we waited until the patient became stable without using ECMO.

The patients were divided into two groups according to the requirement of PGE_1: cases in which PGE_1 was required to keep the patency of the ductus arteriosus to decrease the afterload of the right ventricle, and to attenuate pulmonary hypertension (Group I), and those in which PGE_1 was not required (Group II).

To determine the need to use PGE_1, the blood flow through the ductus arteriosus was measured just after birth by Doppler ultrasonography (Doppler US). We set a speed range of Doppler US at a low speed of 40 cm/s to record the left-to-right shunt in the diastolic phase precisely. When the duration of the right-to-left shunt through the ductus arteriosus was longer than that of left-to-right shunt, PGE_1 was administered (Fig. 1). In PGE_1, lipoPGE_1 was used not PGE_1CD. The lipo-PGE_1 infusion was initiated at 5.0 ng/kg/min, and was subsequently decreased to a minimum of 3 ng/kg/min.

Echocardiographic study

Based on the findings of Doppler US, PGE_1 was given to 39 cases (Group I), and it was not given to the other 22 cases (Group II). Echocardiographic studies with M-mode imaging and Doppler imaging were performed on postnatal day 0, 2 and 7. All images were recorded on videotape for the offline analysis. The left ventricular end-diastolic diameter (LVDD) and the ejection fraction (EF) were calculated with the M-mode images from the short axis view. The LVDD was corrected by the body surface area (LVDD/BSA).

A Doppler index of combined systolic and diastolic ventricular myocardial performance, the Tei or myocardial performance index, has been proposed as a potentially useful predictor of global cardiac function. Left ventricular Tei index has been shown previously to be abnormally high in neonate with ADCDH [9].

Doppler spectra were recorded at the point where there was simultaneous left ventricular inflow and outflow. Doppler spectra were recorded, and the isovolumic relaxation time (IRT) (time from the cessation of ventricular outflow to the onset of ventricular filling), the isovolumic contraction time (ICT) (time from the offset of mitral inflow to the onset of aortic outflow) and the ejection time (ET) (time from the onset of aortic inflow to the offset of aortic outflow) were measured. The left ventricular Tei index was calculated from Doppler measurements (Fig. 1), as the IRT plus ICT divided by the ET (IRT + ICT/ET) [13]. The measured value by Doppler was corrected by RR time (1 heartbeat interval) and was standardized.

Four patients did not survive ECMO, and one patient died within 24 h after birth without ECMO. We measured the LVDD/BSA, LVEF and LV Tei index of the cases on ECMO on days 0, 2 and 7 after birth.

Statistical analysis

The results of the echocardiographic studies were expressed as the means ± standard deviation (SD). All of the statistical analyzes were performed using a professional statistical software program (JMP 9, SAS Institute Inc.). Wilcoxon's test was employed to compare the mean values

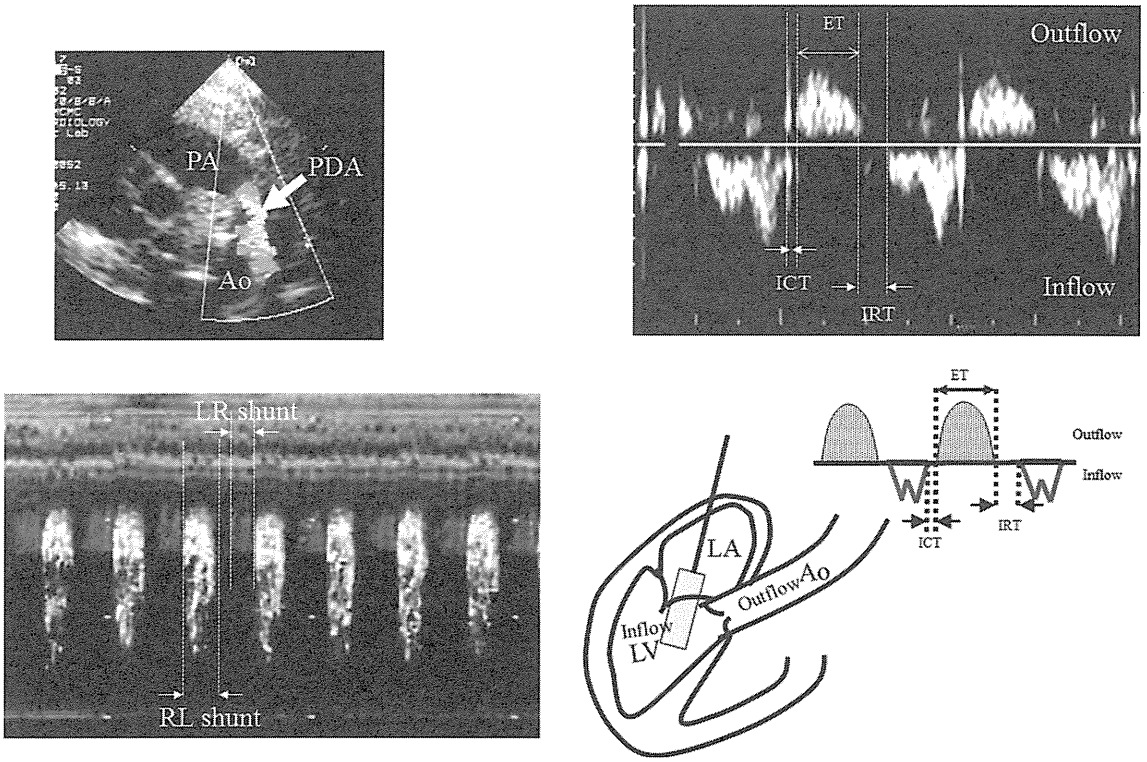

Fig. 1 **a** To determine the need to use PGE_1, the blood flow through the ductus arteriosus was measured just after birth by a color Doppler method. We set the speed range of the color Doppler instrument at a low speed of 40 cm/s to record the left-to-right shunt in the diastolic phase precisely. When the duration of the right-to-left shunt through the ductus arteriosus was longer than that of left-to-right shunt, PGE_1 was given. **b** Measurement of the Tei index. We fixed the sample point on the left ventricle to simultaneously record the inflow and outflow of the left ventricle's blood flow. The Tei index was calculated as: (ICT + IRT)/ET. *ICT* isovolumic contraction time, *IRT* isovolumic relaxation time, *ET* ejection time

of two groups on days 0, 2 and 7. A paired t test was used to compare the mean values between days 0 and 2 and days 2 and 7. Statistical significance was taken at $p < 0.05$.

Results

Clinical characteristics and outcomes (Table 1)

Thirty-nine cases (64 %) required PGE_1 and 22 cases (36 %) did not. The gestational age and body weight of the two groups were comparable. Regarding the indicators of lung development, the L/T and LHR in Group I were significantly lower than those in Group II (L/T 0.10 ± 0.01 vs. 0.16 ± 0.01, $p < 0.0001$, LHR 1.38 ± 0.76 vs. 2.4 ± 1.09, $p < 0.01$). The number of liver-up cases in Groups I and II were 22 and three cases, respectively ($p < 0.001$). The time from birth to radical surgery ranged from 1 to 96 h (median, 2 h) in Group I and from one to 95 h (median, 3.5 h) in Group II, and there was no significant difference between the two groups.

In five cases, the preductal oxygen saturation did not reach above 88 %. Four of these cases required ECMO to avoid death from hypoxia, and the other one was not indicated for ECMO due to severe hypoxia, and died within 24 h of birth. The overall survival rate was 92 %. Five patients in Group I died, while none in Group II died. The

Table 1 Clinical characteristics and outcome

	Group I	Group II	*p*
n	39	22	
GW	36.9 ± 0.3	36.6 ± 0.3	0.36
BW	2624 ± 85	2633 ± 99	0.93
L/T	0.10 ± 0.01	0.16 ± 0.01	<0.0001
LHR	1.38 ± 0.76	2.40 ± 1.09	<0.01
Liver up	22	3	<0.0001
Surgery (h)	1–94 (median 2)	1–95 (median 3.5)	0.19
ECMO	4	0	0.04
Died	5	0	
Survival rate	87 %	100 %	0.02

PGE_1 prostaglandin E_1, *n* number, *GW* gestational weeks, *BW* body weight, *L/T* lung thoracic area ratio, *LHR* lung-to-head ratio, *ECMO* extracorporeal membrane oxygenation

Table 2 Echocardiographic parameters

	Group I	Group II	*p*
IRT/RR			
Prenatal	0.15 ± 0.04	0.12 ± 0.02	<0.01
Day 0	0.20 ± 0.05	0.10 ± 0.03*	<0.001
Day 2	0.13 ± 0.03*	0.09 ± 0.04	0.05
ICT/RR			
Prenatal	0.067 ± 0.03	0.064 ± 0.02	0.861
Day 0	0.108 ± 0.04*	0.063 ± 0.03	<0.01
Day 2	0.061 ± 0.04	0.058 ± 0.05	0.617
LV Tei index			
Prenatal	0.57 ± 0.19	0.47 ± 0.08	0.66
Day 0	0.64 ± 0.06	0.37 ± 0.08	<0.01
Day 2	0.34 ± 0.03*	0.36 ± 0.04	0.182
Day 7	0.32 ± 0.04	0.18 ± 0.11	0.268
LVDD/BSA			
Day 0	70.1 ± 12.2	78.2 ± 12.6	<0.01
Day 2	84.9 ± 13.3**	87.2 ± 13.1	0.366
Day 7	90.4 ± 12.0	83.7 ± 12.5	0.182
LVEF			
Day 0	71.9 ± 0.7	64.1 ± 15.9	0.111
Day 2	67.2 ± 8.7	61.5 ± 6.4	0.549
Day 7	69.2 ± 6.5	70.0 ± 5.7	0.812

* $p < 0.01$, prenatal vs. day 0, ** $p < 0.01$ day 0 vs. day 2, *** $p < 0.01$ day 2 vs. day 7

survival rates of Groups I and II were 87 and 100 %, respectively ($p = 0.02$).

Echocardiographic findings (Table 2)

The prenatal IRT corrected for the RR time (IRT/RR) of Group I was longer than that of Group II, or the left ventricular diastolic function was worse in a severe ADCDH. The IRT/RR on day 2 after radical surgery decreased compared to that on day 0. Therefore, the LV Tei index also improved after surgery. Although there were no significant differences in the prenatal ICT corrected for the RR time (ICT/RR) between Groups I and II, the ICT/RR of Group I was longer than that of Group II on day 0 just after birth. As a result, the LV Tei index on day 0 was worse in Group I than in Group II.

The LVDID/BSA of Group I was smaller than that of Group II on day 0. However, on days 2 and 7, the LVDID/BSA in Group I did not differ from that in Group II.

Figure 2 shows the changes in the left ventricular function. In Group I, the IRT/RR was shortened after surgery, and the LVDD/BSA increased, and the LV Tei index improved. On day 7, there were no significant differences in the left ventricular performance between Groups I and II.

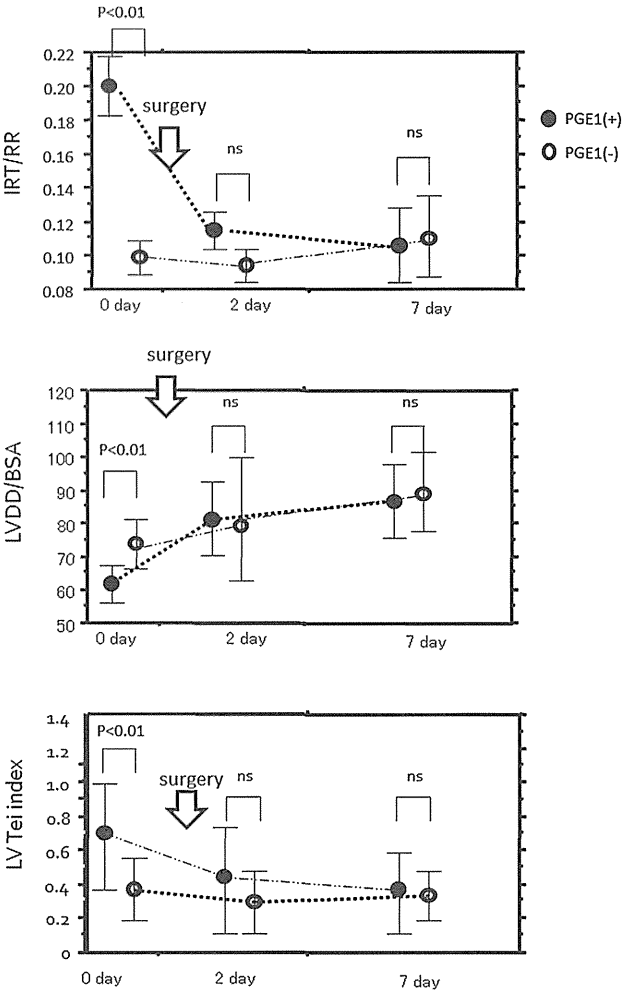

Fig. 2 The changes in the IRT/RR, LVDD/BSA and LV Tei index on day 0, 2 and 7 after birth. A *closed circle* shows the cases that required PGE_1, and the *open circles* show the cases that did not need PGE_1

Left ventricular performance of the ECMO cases (Fig. 3)

Three representative cases of the left ventricular performances in the cases treated with ECMO are shown in Fig. 3. The change was small, but the LVDD/BSA of the ECMO cases rapidly dilated after the induction of ECMO from 72 ± 11 on day 0 to 98 ± 9 on day 2. In contrast, the LVEF of ECMO cases drastically decreased after ECMO from 55.0 ± 0.8 on day 0 to 30.0 ± 7.6 on day 2. After closure of the ductus arteriosus on day 7, the LVEF returned to the original value, however, the LVDD/BSA returned to the original size or smaller. Although the LVDD/BSA increased after ECMO, the LV Tei index did not improve after ECMO, changing from 0.9 ± 0.4 to 0.73 ± 0.2 during this period.

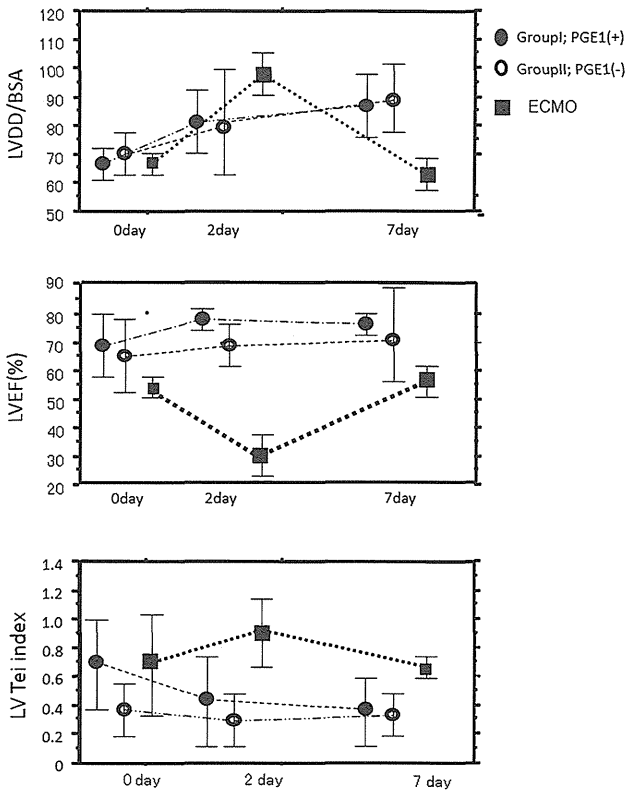

Fig. 3 The changes in the LVDD/BSA, LVEF and LV Tei index of the cases treated with ECMO at 0, 2, and 7 days after birth. A *closed square* shows the cases in which ECMO was used. A *closed circle* shows the cases that required PGE_1 and an *open circle* shows the cases that did not require PGE_1

Discussion

In cases of ADCDH, the herniated visceral organs affected the lung development and lead to hypoplastic lung, which decreased preload to LV, resulting in an underdeveloped LV in fetal period [14]. Therefore, the LV may be hypoplastic at birth, especially in those cases which require PGE_1, and the LVDD just after birth may be as small as one-third of the size of the RV [15]. From our study of ADCDH, we found that severe ADCDH presented as not only a hypoplastic LV, but also impaired LV performance. Before birth, the systemic circulation is supplied from both the LV and RV in parallel, however, just after birth; it starts to be supplied only from the LV [16, 17]. Therefore, the systemic circulation deeply depends on the size of the LV developed by the time of birth.

In 2006, we proposed a new therapeutic strategy focusing on circulatory management, which substantially improves the clinical outcome of ADCDH. This can be attributed to two factors: earlier surgery resulting in improved LV performance; and the use of PGE_1. The latter attenuates pulmonary hypertension and maintains the patent ducts arteriosus with a consequent decrease in RV afterload to compensate for the low cardiac output resulting from ductus arteriosus [18].

In the present study, we clarified the perinatal changes in the circulatory dynamics in cases of ADCDH to evaluate the LV performance in patients treated with the new therapeutic strategy. The fact that the prolonged IRT, small LVDD and high LV Tei-index were significantly improved after early surgery clearly demonstrated that early surgery can eliminate the LV diastolic disorder and improve the LV performance.

Another crucial point of the new therapeutic strategy is to relieve persistent pulmonary hypertension in severe cases of ADCDH. The administration of PGE_1 to cases with a persistent ductus arteriosus prevented the RV systolic pressure from becoming higher than the LV systolic pressure, and decreased the afterload of the RV. Consequently, the systolic blood flow at the ductus arteriosus was shunted in a right-to-left direction, or a right-to-left shunt was formed, which could compensate for the insufficient cardiac output from the undeveloped LV, eventually preventing cardiac failure. Moreover, in the present study, we did not experience any crisis of pulmonary hypertension nor RV failure secondary to persistent pulmonary hypertension.

Early surgery and PGE_1 administration were proven to improve the LV performance and to prevent RV failure in severe cases of ADCDH. However, five neonates (8 %) died of marked hypoxia and heart failure secondary to a lethal hypoplastic lung with an undeveloped LV. These fatal cases did not undergo surgery. ECMO was applied in four of these five patients. The LVDD dilated remarkably with ECMO because of the increase in pulmonary blood flow secondary to the attenuated pulmonary hypertension, however, the LVEF was worsened by ECMO. Decreased pulmonary arterial pressure causes an excessive pre-load to the left ventricle, which dilates the LV, and the LVDD returns to the original size after weaning off ECMO. Thus, ECMO cannot increase the LV development, or prevent LV failure, and thus does not improve the outcome of severe cases of ADCDH. This is a limitation to the postnatal treatment of severe ADCDH, and prenatal treatment, such as the fetoscopic tracheal occlusion, should be considered in similar cases. This excessive pre-load worsened the LVEF. The ductus arteriosus was closed on the seventh day, and the LVDD decreased, and the LVEF was improved. However, the LV performance, as indicated by the Tei index, was poor, and did not change during the observation period. Based on the above-mentioned results, we think that these cases would not be saved by any of our strategies for treatment, including the new protocol. These severe cases should therefore be considered for prenatal treatment.

Limitations of the study

In this study, we demonstrated the changes in the circulatory dynamics and the usefulness of the circulatory management of ADCDH in the perinatal period. Our proposed therapeutic strategy markedly improves the clinical outcomes of ADCDH. However, there were some limitations. First, there were some problems with the method used in the study. The patients were divided into two groups according to the requirement for PGE_1. We classified the two groups based on the postnatal color echocardiography views. This classification needs randomization. In addition, the prenatal disease severity was significantly different between the two groups. These limitations may have influenced our results.

Second, we perfected "early surgery" during the study period. The timing of surgery may influence the results. However, we do not mention the effect of the timing of surgery in this study.

To confirm whether the circulatory management leads to a better clinical outcome, more clinical follow-up studies are necessary.

Conclusion

Antenatally diagnosed congenital diaphragmatic hernia is a circulatory disease that is associated with abnormalities of the fetal circulation and perinatal circulatory changes. The implementation of circulatory management during the fetal period is important to improving the postnatal treatment.

Our early treatment and the use of circulatory management with PGE_1 improved the treatment outcome of the severe ADCDH cases.

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CASE REPORT

A case of congenital diaphragmatic hernia with intradiaphragmatic pulmonary sequestration: case report and literature review

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Abstract Extralobar pulmonary sequestration (EPS) can occasionally be found incidentally in congenital diaphragmatic hernia (CDH). Extralobar pulmonary sequestration usually arises in the chest or the abdomen; rarely in the diaphragm. We report a neonatal case of antenatally diagnosed CDH associated with intradiaphragmatic EPS.

Keywords Congenital diaphragmatic hernia · Pulmonary sequestration · Extralobar · Intradiaphragmatic

Introduction

Pulmonary sequestration (PS) is a congenital malformation defined as immature, nonfunctional pulmonary tissue without bronchial communication. Only some 25 % of PS exist outside the lobes of the lungs as extralobar PS (EPS) with the rest being intralobar [1]. EPS is commonly found in the thoracic cavity, also in the peritoneal cavity, but rarely in the diaphragm [2]. Here we present an extremely rare case of congenital diaphragmatic hernia (CDH) associated with intradiaphragmatic EPS.

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Case report

A female with antenatally diagnosed CDH was delivered vaginally at 39 weeks' gestation weighing 3,009 g. Although fetal ultrasound (US) and magnetic resonance imaging (MRI) at 37 weeks' gestation revealed left-sided CDH, no other abnormalities were detected. Upon transfer to our neonatal intensive care unit she was found to be in no respiratory distress but had signs of moderate pulmonary hypertension. After clinical stabilization, a laparotomy was performed on day 7 of life. A hernia sac containing stomach and small intestine was found and its contents reduced gently into the abdomen. During excision of the hernia sac, a cystic mass containing yellowish mucus was found in the abnormally thickened posterior rim of the diaphragm (Fig. 1). The mass and the sac were resected en block and the defect in the diaphragm was approximated by direct closure. Although major feeding vessels to the mass from the descending aorta did not exist, several vessels were observed to enter the mass from the posterior rim of the diaphragm. Her postoperative recovery was uneventful, being extubated on the 1st postoperative day and discharged home on the 13th postoperative day. On histopathology, the mass comprised immature alveolar tissue and bronchial component containing cartilages compatible with EPS (Fig. 2), and a final diagnosis of CDH with intradiaphragmatic EPS was made. She is now 5 months old with no signs of recurrence.

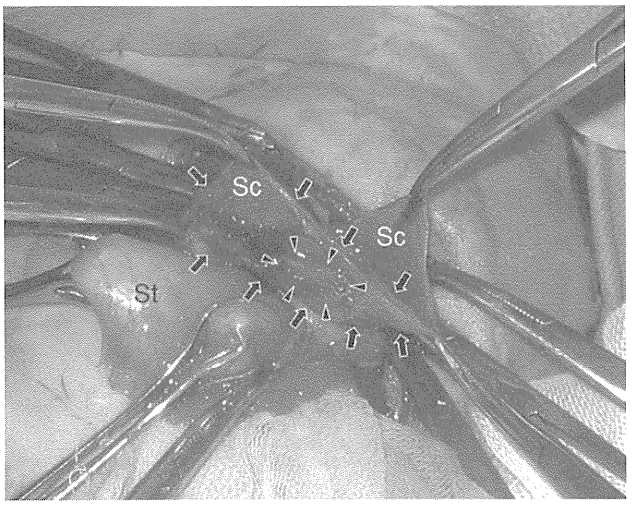

Fig. 1 Operative findings. The cystic lesion is the intradiaphragmatic EPS (*arrowheads*) in the abnormally thickened posterior rim of the diaphragm (*arrows*). Sc; diaphragm (hernia sac), St; stomach

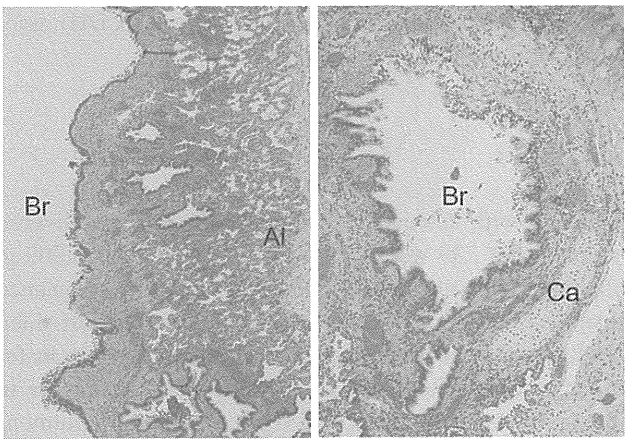

Fig. 2 Histopathology reveals immature alveolar tissue (Al) (*left panel*) and bronchial component (Br) containing cartilages (Ca) (*right panel*) compatible with EPS

Discussion

Pulmonary sequestrations are masses of nonfunctioning lung tissue that are supplied by an anomalous systemic artery and only rarely have a bronchial connection to the native tracheobronchial tree. They account for up to 6 % of congenital pulmonary malformations and are classified into intralobar and extralobar types, depending on whether the lesions are contained within the visceral pleura of the normal lung or not [1, 2]. They are considered to arise as a result of an accessory tracheobronchial bud originating from the foregut. During development at the end of the third week of gestation, a laryngotracheal diverticulum forms from the embryonic foregut. This ventral outpouching separates from the primitive esophagus with the formation of the tracheoesophageal groove. The diverticulum undergoes multiple divisions to form the tracheobronchial tree [3]. An abnormally placed accessory bud forming at any level along the primitive foregut can form a pulmonary sequestration. Meanwhile, development of the diaphragm begins with fusion of the septum transversum, pleuroperitoneal membranes, mesoesophagus, and body wall musculature [4]. The pleuroperitoneal canal closes from the eighth to tenth week of gestation [5] and a wandering accessory bud forming at the level of the diaphragm in association with the fusing diaphragmatic components could be the mechanism of intradiaphragmatic EPS occurring. We could speculate that in addition to these abnormal events, incomplete fusion of the diaphragmatic components could be a cause of CDH with intradiaphragmatic EPS. An association between pulmonary malformations and CDH has been described previously [6, 7]; Fauza et al. [8] examined 166 infants born with CDH and found that 5 % had associated pulmonary anomalies. Intrathoracic or abdominal EPS appear to have a propensity for CDH over other pulmonary malformations.

Pulmonary sequestration can usually be identified using diagnostic imaging modalities such as US, computed tomography (CT), or MRI. However, intradiaphragmatic EPS can be difficult to differentiate from other anomalies such as intraabdominal EPS, renal tumor, adrenal tumor, adrenal bleeding, foregut duplication, accessory spleen, and lymphatic or vascular malformation [3].

EPS can exist rarely outside of the thoracic cavity; i.e., intraabdominal, retroperitoneal, or peridiaphragmatic [9]. Intradiaphragmatic EPS is extremely rare in children and, as far as we know, there have only been five cases reported [3, 10–12] (Table 1). Meier et al. [10] presented the case of a 16-month-old boy with EPS diagnosed on prenatal US and MRI. In their case, the arterial blood supply to the lesion arose from the celiac axis and its venous drainage was the splenic vein. After exploring the diaphragm both laparoscopically and thoracoscopically, a definitive diagnosis of intradiaphragmatic EPS was made. McAteer et al. [3] experienced two cases of intradiaphragmatic EPS (4-week-old male and 7-week-old female) both resected thoracoscopically. They could not identify feeding or draining vessels, but a bulge in the diaphragm was suspicious and led to diagnosis. Escobar and Acierno [12] presented the case of a 7-month-old female diagnosed with intradiaphragmatic EPS both thoracoscopically and laparoscopically. In our case, no mass was observed initially during laparotomy for CDH repair, but when an incision was made into the relatively thickened hernia sac and posterior rim of the diaphragm, a cystic lesion was found. Although there was no evidence of aberrant vascular

Table 1 Reported cases of intradiaphragmatic EPS

Case no.	Age	Sex	Symptom	Imaging studies	Initial diagnosis	Surgical treatment
1 [11]	N.A.	N.A.	N.A	N.A	N.A	N.A
2 [10]	16 months	M	Asymptomatic	Prenatal US, prenatal MRI and CT	Intraabdominal EPS	Laparoscopic/thoracoscopic excision
3 [3]	7 weeks	F	Asymptomatic	Prenatal US and CT	Intraabdominal mass	Laparoscopic exploration and thoracoscopic excision
4 [3]	4 weeks	M	Asymptomatic	Prenatal US and CT	Intrathoracic mass	Thoracoscopic exploation and excision
5 [12]	10 months	F	Asymptomatic	Prenatal US and CT	Intrathoracic EPS	Laparoscopic/thoracoscopic excision
6 [Present case]	7 days	F	Respiratory problem due to CDH	CXR and CT	Incidental	Excision during CDH repair by laparotomy

CT computed tomography, *CXR* chest X-ray, *F* female, *M* man, *MRI* magnetic resonance imaging, *N.A.* not available, *US* ultrasound

supply from the aorta, the mass may have been fed by branches of diaphragmatic arteries arising from the systemic blood supply. These operative findings and histopathology allowed a definitive diagnosis of intradiaphragmatic EPS to be made.

To the best of our knowledge, there are no previous reports of CDH with intradiaphragmatic EPS in the English literature. This is the first report of CDH with incidental intradiaphragmatic EPS in a neonate that was treated successfully.

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Prenatal administration of neuropeptide bombesin promotes lung development in a rat model of nitrofen-induced congenital diaphragmatic hernia

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ABSTRACT

Background/purpose: Fetal medical treatment to improve lung hypoplasia in congenital diaphragmatic hernia (CDH) has yet to be established. The neuropeptide bombesin (BBS) might play an important role in lung development. The present study aims to determine whether prenatally administered BBS could be useful to promote fetal lung development in a rat model of nitrofen-induced CDH.

Methods: Pregnant rats were administered with nitrofen (100 mg) on gestation day 9.5 (E9.5). BBS (50 mg/kg/day) was then daily infused intraperitoneally from E14, and fetal lungs were harvested on E21. The expression of PCNA was assessed by both immunohistochemical staining and RT-PCR to determine the amount of cell proliferation. Lung maturity was assessed as the expression of TTF-1, a marker of alveolar epithelial cell type II.

Results: The lung-body-weight ratio was significantly increased in CDH/BBS(+) compared with CDH/BBS(−) ($p < 0.05$). The number of cells stained positive for PCNA and TTF-1 was significantly decreased in CDH/BBS (+) compared with CDH/BBS(−) ($p < 0.01$). The TTF-1 mRNA expression levels were significantly decreased in CDH/BBS(+) compared with CDH/BBS(−) ($p < 0.05$).

Conclusions: Prenatally administered BBS promotes lung development in a rat model of nitrofen-induced CDH. Neuropeptide BBS could help to rescue lung hypoplasia in fetal CDH.

The treatment of newborn babies with congenital diaphragmatic hernia (CDH) remains challenging for pediatric surgeons [1]. Recently, we have introduced new therapeutic approaches in addition to a gentle ventilation strategy and achieved a survival rate of more than 90% in cases of isolated CDH [2]. However, it continues to be impossible to rescue babies with extreme pulmonary hypoplasia. In order to solve this problem, several surgical fetal therapies, including tracheal occlusion, have been developed to promote fetal lung growth [3]. However, the risk of premature birth remains a serious problem with no improvements.

Neuropeptide bombesin (BBS) is a 14-amino acid peptide originally identified in skin of the frog *Bombina bombina*[4]. Its mammalian homologue, which has been identified as gastrin-releasing peptide (GRP), and BBS are referred to collectively as "bombesin-like peptides" (BLPs). The receptors of BBS are known to be widely distributed in the central nervous system and gut [5]. The authors have previously noticed the concept of the brain–gut axis and reported that BBS maintained intestinal mucosal structures and exhibited an immunomodulatory effect in transplanted intestinal allografts while preserving the graft microcirculation and preventing ischemic reperfusion injury [6–10]. In addition, this multipotent neuropeptide has been reported to promote the growth and maturation of the developing fetal lung in both humans and nonhuman primates [11–13]. It was also reported that the highest level of bombesin-like peptide occurred in mid-gestation human fetal lung [14]. However, there have been no reports that exogenously administered BBS could promote growth and maturity of immature lung in pathological condition like immature lungs in CDH.

To evaluate lung maturity, immunohistochemical staining against proliferating cell nuclear antigen(PCNA) has been widely used and reported that PCNA-positive cells in the fetal lung decrease during the late stage of pregnancy in rats [15]. TTF-1 is known as a marker of alveolar epithelial cells type II (AECs-II) and is considered to play an important role in stem cell production in the alveolar epithelium [16]. The differentiation from AECs-II into alveolar epithelial cells type I (AECs-I) should be one of the key processes in lung development in late gestation and the number of TTF-1-positive cells was reported to increase in immature lungs. TTF-1 should be appropriate to evaluate lung maturity in addition to PCNA.

The aim of this study was to investigate whether BBS promotes lung growth and maturity in a rat model of nitrofen-induced CDH.

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1. Materials and methods

1.1. Animal model

Pregnant Sprague–Dawley rats were purchased from Shimizu laboratory (Kyoto, Japan). The day in which the vaginal plug was confirmed was considered to be day 0 of gestation (E0). In order to produce the fetal CDH rat model, 100 mg of nitrofen (2,4-dichorophenyl-p-nitrophenylether: WAKO Chemical, Osaka, Japan) dissolved in 1 ml of olive oil was administered via an orogastric tube under short anesthesia on E9.5 (term, 22 days). As a control, some rats were given the same dose of olive oil without nitrofen. The animals were divided into three groups on E14: 1) CDH/BBS(+) group, in which the nitrofen-treated rats were administered BBS (50 μg/kg/day: Peptide Institute, Inc., Osaka, Japan) using an osmotic minipump (Alzet 2002: Palo Alto, CA, USA) implanted in the peritoneal cavity under general anesthesia; 2) CDH/BBS(−) group, in which the nitrofen-treated rats were administered normal saline instead of BBS using an osmotic minipump; and 3) control group, in which rats treated without nitrofen were administered normal saline instead of BBS using an osmotic minipump. The fetuses were harvested via cesarean section and weighed on E21. The peritoneal cavity of each fetus was opened and a defect in the diaphragm was confirmed with a visual inspection of the diaphragm. The bilateral lungs were removed and weighed, and the lung-body-weight ratio (both lungs (mg)/body (g) weight: LBWR) was measured. The expression of proliferating cell nuclear antigen (PCNA) was assessed using both immunohistochemical staining and real-time polymerase chain reaction (PCR) in order to determine the amount of cell proliferation. The degree of lung maturity was assessed as the expression of thyroid transcript factor-1 (TTF-1), a marker of alveolar epithelial cell type II.

1.2. Immunohistochemical staining

The left lungs were immersed and fixed in 4% paraformaldehyde for eight hours and embedded in paraffin. The samples were cut into 5-μm-thick sections and deparaffinized. Subsequently, antigen retrieval was performed by boiling the sections in a 10 mmol/L of sodium citrate solution at a pH of 6.0 for two periods of five minutes in a microwave at medium heat. After rinsing the slides in PBS, the endogenous peroxidase activity was blocked by exposing the slides to a 3% hydrogen peroxide in methanol solution for a period of 10 minutes.

To detect positive cells of PCNA or TTF-1 in the lungs, immunohistochemical staining was performed using a primary antibody to rat PCNA (PC10: Nichirei, Tokyo, Japan) or TTF-1 (SPT24: Nichirei, Tokyo, Japan). The sections were incubated with the primary antibodies for one hour at room temperature. The primary antibodies were visualized using the Histofine Simple Stain MAX-PO (M) kit (Nichirei, Tokyo, Japan) according to the instruction manual. The slide was counterstained with hematoxylin. Using a Dynamic Cell Count (BZ-H1C: Keyence, Tokyo, Japan) with high power field (×400), the number of positive cells was counted and averaged for five sites in each group.

1.3. RT-PCR and real-time RT-PCR

The left lungs obtained from the three groups, control (n = 8), CDH/BBS(−) (n = 7) and CDH/BBS(+) (n = 7), were analyzed. Total RNA was extracted according to the guanidinium acid phenol method using ISOGEN II (Nippon gene, Toyama, Japan). In addition, total RNA was reversed transcribed using ReverTra Ace® qPCR RT Master Mix (Toyobo, Tokyo, Japan) according to the manufacturer's instructions.

Real-time reverse transcription-PCR (RT-PCR) was performed using the Real-time PCR Master Mix (Toyobo, Tokyo, Japan) and the 7500 Real-Time PCR Systems (Applied Biosystems, Foster, CA, USA) according to the manufacturer's instructions. The matching primers for PCNA (Rn01514538_g1), TTF-1 (Rn01436110_m1) and β-actin (Rn014244440_s1) were purchased from Applied Biosystems.

1.4. Statistical analysis

The statistical analysis was performed using Student's *t*-test for unequal variances. A *p* value of less than 0.05 was considered to be statistically significant.

2. Results

The incidence of CDH in this study was 50% (13/26 fetuses) among the nitrofen-treated rats not administered BBS and 49% (24/49) in those administered BBS. The defect in the diaphragm was observed on the left side in all CDH fetuses, and no other anomalies were found.

There were no significant differences in body weight between the CDH/BBS(−) group and the CDH/BBS(+) group. The LBWR values were compared between the three groups: control (nitrofen(−), BBS(−)) (n = 23), CDH/BBS(−) (nitrofen(+), BBS(−)) (n = 13), and CDH/BBS(+) (nitrofen(+), BBS(+)) (n = 24). Consequently, the LBWR in the CDH/BBS(−) group was significantly less than that observed in the control group (16.05 ± 2.32 v.s. 23.86 ± 2.78; $p < 0.01$). On the other hand, the LBWR in the CDH/BBS(+) group was significantly greater than that observed in the CDH/BBS(−) group (18.29 ± 3.03 v.s. 16.05 ± 2.32; $p < 0.05$) (Fig. 1).

Regarding the immunohistochemical stainings, both PCNA- and TTF-1-positive cells were localized to the alveolar endothelium in the fetal rats. The number of PCNA-positive cells in the CDH/BBS(−) group was significantly greater than that observed in the control group (877.0 ± 87.8 v.s. 290.4 ± 50.65; $p < 0.01$). Meanwhile, the number of PCNA-positive cells in the CDH/BBS(+) group was less than that observed in the CDH/BBS(−) group (501.8 ± 72.7 v.s. 877.0 ± 87.8; $p < 0.01$) (Fig. 2). In addition, the number of TTF-1-positive cells in the CDH/BBS(−) group was significantly greater than that observed in the control group (664.0 ± 90.5 v.s. 238.4 ± 52.8; $p < 0.01$). Conversely, the number of TTF-1-positive cells in the CDH/BBS(+) group was significantly less than that observed in the CDH/BBS(−) group (267.6 ± 30.0 v.s. 664.0 ± 90.5; $p < 0.01$) (Fig. 3).

On RT-PCR, the mRNA expression levels of PCNA (PCNA/β-actin) were low in the CDH/BBS(+) group. However, there were no significant differences between the CDH/BBS(−) and CDH/BBS(+) groups (2.49 ± 1.11 v.s. 1.69 ± 0.58) (Fig. 4). On the other hand, the mRNA expression levels of TTF-1 (TTF-1/β-actin) in the CDH/BBS(+) group were significantly decreased compared with those observed in the CDH/BBS(−) group (2.55 ± 1.21 v.s. 1.45 ± 0.23; $p < 0.05$) (Fig. 5).

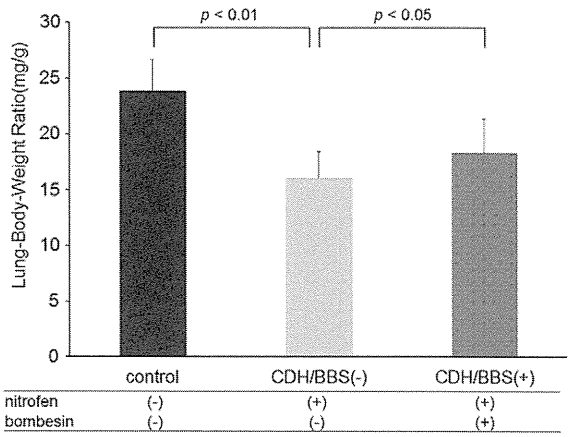

Fig. 1. Lung-body-weight ratio (LBWR) values in the control, CDH/BBS(−) and CDH/BBS(+) groups. The LBWR values in the control group were significantly greater than those observed in the CDH/BBS(−) group ($p < 0.01$). The LBWR values in the CDH/BBS(+) group were also significantly greater than those observed in the CDH/BBS(−) group ($p < 0.05$).

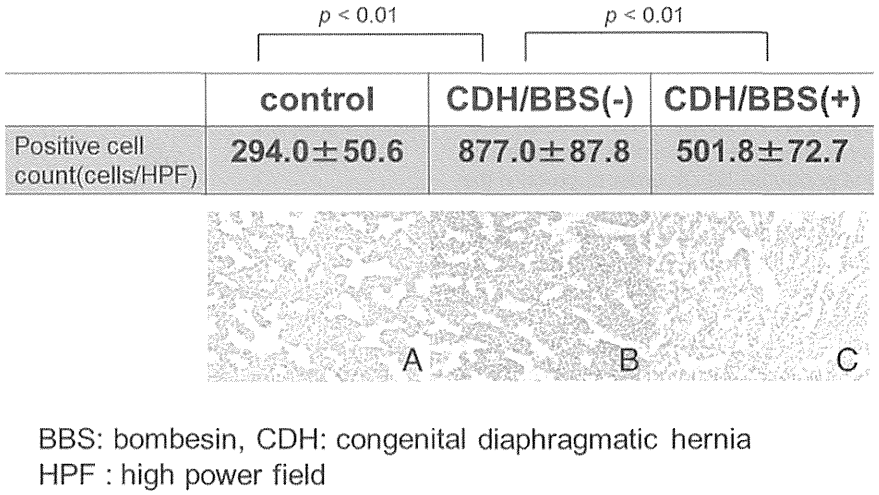

Fig. 2. Immunohistochemical staining for PCNA. Micrographs show the nuclear localization of PCNA and TTF-1 in the lung alveolar epithelium. The number of PCNA-positive cells in the CDH/BBS(−) group was significantly greater than that observed in the control group. Meanwhile, the number of PCNA-positive cells in the CDH/BBS(+) group was less than that observed in the CDH/BBS(−) group. PCNA staining; control group (A), CDH/BBS(−) group (B), CDH/BBS(+) group (C) Original magnification: ×400.

3. Discussion

The present study demonstrated that the prenatal administration of BBS promotes lung growth and maturity in a rat model of nitrofen-induced CDH without inducing other serious anomalies. To our knowledge, there have been no previous reports showing that prenatal medical treatment increases fetal lung weight in a rat nitrofen-induced CDH model.

The use of prenatal medical treatment with corticosteroids in fetuses with CDH has been reported both experimentally and clinically [17]. There are many reports showing that the antenatal administration of corticosteroids may correct lung immaturity; however, no experiments using corticosteroids have succeeded in increasing the fetal lung volume. With respect to clinical studies, late gestational maternal corticosteroid administration has been found to have no effect in improving fetal lung hypoplasia to date [18].

There are various experimental reports indicating that the administration of antenatal retinoic acid affects the expression of various genes related to lung maturity in CDH rat models [19–21], and Montedonico et al. found that prenatal treatment with retinoic acid stimulates alveologenesis in hypoplastic lungs under the setting of CDH [22]. However, Gonzalez-Reyes et al. reported no changes in the lung weight-to-body weight ratio using similar rat models [23]. Furthermore, retinoic acid appears to be unlikely as a candidate of prenatal treatment for CDH, because the prenatal administration of this agent carries the potential risk of inducing many major anomalies, such as intestinal atresia and anorectal malformations [24]. As a pilot study, we investigated the effect of BBS to pregnant rats without nitrofen administration from day 1 to investigate whether BBS might have other effect to the fetus. As a result, it was confirmed that there were no increase of lung volume and no major anomalies found in fetuses. In the present study, no other anomalies were found in the nitrofen-induced rat CDH model and the additional administration of BBS did not induce any further anomalies. Considering the potential for teratogenic risk and safety, BBS may be a candidate for use in prenatal medical therapy. In order to access the actual effect of BBS to lung of CDH rat in this study, the parameters of lung maturation were compared between CDH/BBS(−) group and CDH/BBS(+) group.

In this study, both PCNA and TTF-1 were used as markers of lung maturation. The number of PCNA-positive cells is increased in immature lungs. Similarly, in our CDH model with lung hypoplasia, both the number of PCNA-positive cells and the mRNA expression of it were significantly increased, thus indicating that lungs in our CDH model were immature ones. TTF-1 is a marker of alveolar epithelial cells type II

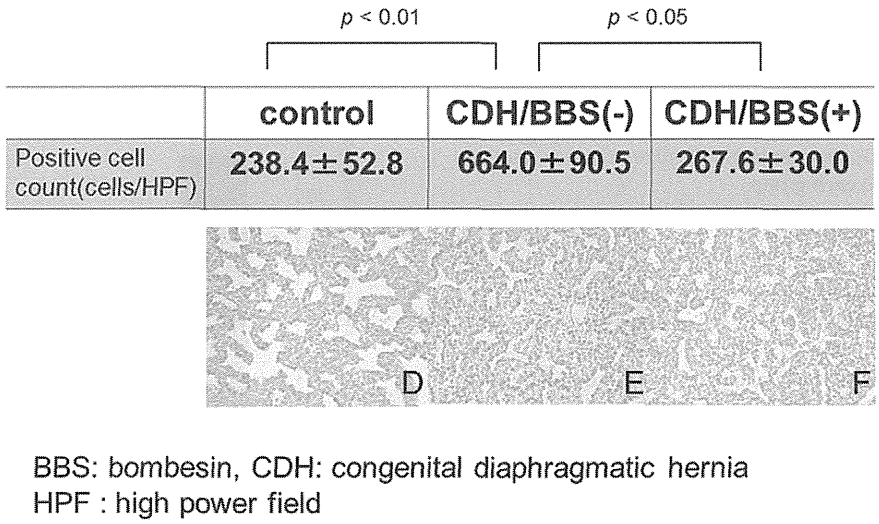

Fig. 3. Immunohistochemical staining for TTF-1. Micrographs show the nuclear localization of TTF-1 in the lung alveolar epithelium. The number of TTF-1 positive cells in the CDH/BBS(−) group was significantly greater than that observed in the control group. The number of TTF-1 positive cells in the CDH/BBS(+) group was less than that observed in the CDH/BBS(−) group. TTF-1 staining; control group (D), CDH/BBS(+) group (E), CDH/BBS(+) group (F).

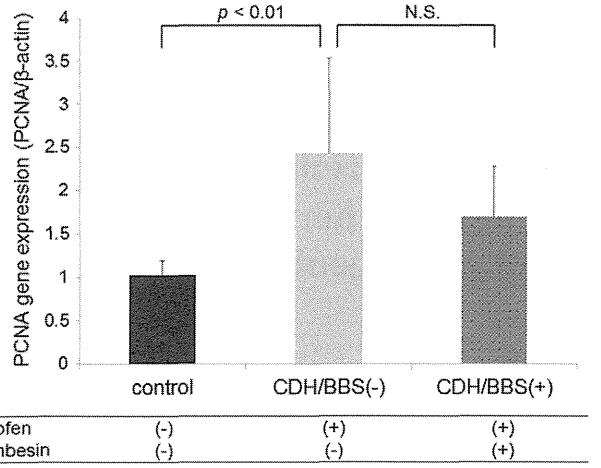

Fig. 4. mRNA expression levels of PCNA on RT-PCR. The expression levels of PCNA were increased in the lungs of the CDH/BBS(−) group compared to that observed in the control group ($p < 0.01$). There were no significant differences between the CDH/BBS(−) and CDH/BBS(+) groups.

(AECs-II). It has been reported that the AEC-II levels are also increased in the hypoplastic lungs of animals with CDH [25]. In the present study, it was also confirmed that both the number of TTF-1-positive cells and the mRNA expression of TTF-1 in the CDH group were also significantly increased, compared with that observed in the control group. Therefore, based on our results in PCNA and TTF-1, the hypoplastic lungs in our rat CDH model indicated to be immature.

As for the effect of BBS administration on fetal lung maturity, the expression levels of PCNA and TTF-1 were significantly decreased in the CDH/BBS(+) group. Our results showed BBS was considered to have promoted fetal lung maturity. As described previously, we investigated the effects of the BBS and elucidated its multipotent ability to maintain and modulate the mucosal structure and immunity of the gastrointestinal system [6–10]. Based on present and previous data, we speculate that BBS plays an important role via the same pathways in the respiratory and intestinal mucosa systems. In this study, it is impossible to deny that BBS affected maternal metabolism and had some secondary effect to the fetus. However, in our previous study of rat intestinal transplantation, it was confirmed that BBS surely had direct effect on the intestinal mucosal system. Therefore, we now speculate that BBS affected directly the lung of the fetuses as well as their intestine.

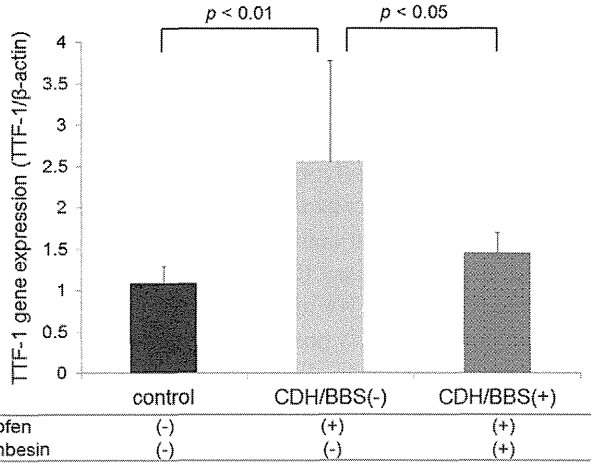

Fig. 5. mRNA expression levels of TTF-1 on RT-PCR. The expression levels of TTF-1 were increased in the lungs of the CDH/BBS(−) group compared to that observed in the control group ($p < 0.01$) and CDH/BBS(+) group ($p < 0.05$).

In conclusion, the prenatal administration of the neuropeptide bombesin increases the fetal lung volume and promotes fetal lung maturity without inducing other anomalies in a rat nitrofen-induced CDH model. The prenatal administration of neuropeptide BBS may be a possible candidate therapy for improving lung hypoplasia in patients with fetal CDH.

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ORIGINAL ARTICLE

Surgical complications, especially gastroesophageal reflux disease, intestinal adhesion obstruction, and diaphragmatic hernia recurrence, are major sequelae in survivors of congenital diaphragmatic hernia

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Abstract
Purpose This study aimed to characterize the surgical complications, especially gastroesophageal reflux disease (GERD), intestinal adhesion obstruction (IAO), and diaphragmatic hernia recurrence, in patients with congenital diaphragmatic hernia (CDH).
Methods Between January 1995 and December 2013, we determined the incidence of surgical complications and their predictors in CDH patients. We also examined whether the CDH repair and patch closure were associated with the incidence of IAO and the severity of adhesion.
Results Seventy-four CDH survivors were evaluated. GERD occurred in 28 patients (37.8 %) and recurred in 8 patients (10.8 %). Stomach herniation was a risk factor for GERD, and occurred in 25 patients. IAO occurred in 13 patients (17.6 %). In 240 neonatal laparotomies in the same period, the incidence of IAO was significantly higher in patients who underwent CDH repair than in patients who underwent other neonatal laparotomy ($p = 0.023$). Surgical time and intraoperative bleeding were significantly greater following CDH repair with an artificial patch compared with CDH repair with direct closure.
Conclusion Surgical complications are major sequelae in survivors of CDH repair. CDH repair and artificial patch closure were significantly associated with the incidence of IAO and the severity of adhesion.

Keywords Congenital diaphragmatic hernia · Complication · Hernia recurrence · Gastroesophageal reflux disease · Intestinal adhesion obstruction

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Introduction

Congenital diaphragmatic hernia (CDH) is a life-threatening congenital anomaly that occurs in between 1 in 2,500 to 1 in 4,000 live births. Advances in neonatal intensive care and ventilatory management have led to an improvement in the overall survival rate of CDH patients of up to 90 % in single-institution studies [1–3]. However, the improved survival of patients with CDH has also resulted in an increase in the incidences of early and late postoperative complications [4, 5]. Consequently, clinicians are now focusing on the long-term outcomes of these patients. Common disorders associated with CDH include pulmonary sequelae, neurodevelopmental deficits, chest wall and spinal deformations, hearing loss, and other abnormalities [6]. To date, however, very few studies have described the surgical complications, especially intestinal adhesion obstruction (IAO), in survivors of CDH.

The aim of this study was to describe the incidence and characteristics of surgical complications, focusing on gastroesophageal reflux disease (GERD), IAO, and diaphragmatic hernia recurrence. We also retrospectively examined the surgical data to identify possible risk factors for specific adverse surgical outcomes. Focusing on IAO after CDH repair, we compared the incidence of IAO after CDH repair with that of IAO after neonatal laparotomy. We also compared operative time and the amount of intraoperative

bleeding during ileus surgery between artificial patch repair and direct closure.

Patients and methods

Between January 1995 and December 2013, 83 patients with early symptoms of CDH were managed in Nagoya University Hospital. Seventy-four patients (89 %) survived and were included in this study. The treatment regimen comprised delayed closure, which was preceded by preoperative stabilization with high-frequency oscillatory ventilation, inhaled nitric oxide (iNO), and administration of drugs (e.g., prostaglandin) until pulmonary hypertension was attenuated. The median duration of preoperative stabilization was 4 days. All 74 patients underwent repair of the diaphragmatic defect via subcostal laparotomy. Direct closure was attempted to the best of our ability. Artificial patches (Goretex; W. L. Gore & Associates, Inc., Tokyo, Japan) were only used when it was impossible to perform a primary repair without significant tension. Twenty-four-hour esophageal pH-metry was performed just before discharge and at about 6 months old.

The following information was recorded from the patients' medical records as possible predictors: prenatal diagnosis of CDH, presence of the liver or the stomach in the thoracic cavity, iNO, use of extracorporeal membrane oxygenation (ECMO), and the method used to close the diaphragmatic defect (i.e., direct closure or use of an artificial patch). The data were analyzed to determine which of these factors were significantly associated with GERD, IAO, or hernia recurrence.

In the same period, 240 patients underwent open laparotomy to treat a variety of diseases other than CDH closure, including necrotizing enterocolitis, intestinal atresia, meconium ileus, and malrotation. We, therefore, compared the incidence and characteristics of IAO between patients who underwent CDH repair or other neonatal laparotomies. We also compared the effects of direct closure or closure with an artificial patch on complications after CDH repair.

Univariate analyses were performed using the χ^2 test or Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. Values of $P < 0.05$ were considered statistically significant.

This retrospective survey was approved by the ethics committee in Nagoya University Hospital.

Results

Seventy-four newborns who were diagnosed with CDH <24 h after birth and who were alive at hospital discharge were included in this study. Their characteristics are shown in Table 1. The median birth weight was 2,760 g (range 982–4,102 g). The median follow-up of the 74 patients was 50 months (range 4–225 months). Four patients had the right side hernia. Of the 74 patients, 47 (63.5 %) were ventilated with iNO. Thirteen (17.6 %) patients were treated with ECMO and 25 (33.8 %) received artificial patch repairs. The most common surgical complications that needed another operation after CDH repair were GERD, IAO, and hernia recurrence. The numbers and timing of the operations after CDH repair are shown in Table 2. The relationships between the clinical variables and the surgical complications are shown in Table 3. Patients with their stomach located in the thoracic cavity were significantly more likely to undergo surgery for CDH recurrence and fundoplication for GERD than patients with the stomach in the correct location. Prenatal diagnosis, liver located in the thoracic cavity, iNO, use of ECMO, and patch repair method were not significantly associated with complications of CDH repair.

Reoperation for IAO was required in 13/74 (17.6 %) patients who underwent CDH repair compared with 16/240 (6.7 %) patients who underwent other neonatal laparotomies. Of these 16 patients with IAO after neonatal laparotomy, 6 had intestinal perforation, 4 had intestinal atresia, 3 underwent Ladd's operation, 1 had

Table 1 Characteristics of the infants

	n	%
Total	74	100
Males	44	59.5
Right side hernia	4	5.4
Prenatal diagnosis	60	81.1
Liver located in the thoracic cavity	29	39.2
Stomach located in the thoracic cavity	50	67.6
Inhaled nitric oxide	47	63.5
Use of ECMO	13	17.6
Patch repair	25	33.8

ECMO extracorporeal membrane oxygenation

Table 2 Surgical complications and timing of operations after CDH repair

	n (%)	Timing of subsequent operation (months)[a]
GERD	28 (37.8 %)	8 (0–83)
IAO	13 (17.6 %)	4 (1–48)
Hernia recurrence	8 (10.8 %)	2.5 (0–10)

CDH congenital diaphragmatic hernia, *GERD* gastroesophageal reflux disease, *IAO* intestinal adhesion obstruction

[a] Median (range)

Table 3 Associations between clinical variables and surgical complications after CDH repair ($n = 74$)

Variables	GERD			IAO			Hernia recurrence		
	Yes ($n = 28$)	No ($n = 56$)	p	Yes ($n = 13$)	No ($n = 61$)	p	Yes ($n = 8$)	No ($n = 66$)	p
Prenatal diagnosis	24 (86 %)	34 (74 %)	0.55	10 (77 %)	50 (82 %)	0.7	8 (100 %)	52 (79 %)	0.34
Liver located in the thoracic cavity	15 (54 %)	14 (30 %)	0.055	7 (54 %)	22 (36 %)	0.35	5 (63 %)	4 (36 %)	0.25
Stomach located in the thoracic cavity	25 (89 %)	25 (54 %)	**0.002**	9 (69 %)	41 (67 %)	>0.99	8 (100 %)	42 (64 %)	**0.048**
Inhaled nitric oxide	20 (80 %)	27 (59 %)	0.33	10 (77 %)	37 (61 %)	0.35	5 (63 %)	42 (64 %)	>0.99
Use of ECMO	4 (12 %)	9 (20 %)	0.76	3 (23 %)	10 (16 %)	0.69	3 (38 %)	10 (15 %)	0.14
Patch repair	12 (43 %)	13 (28 %)	0.22	6 (46 %)	19 (31 %)	0.34	5 (63 %)	20 (30 %)	0.11

CDH congenital diaphragmatic hernia, *GERD* gastroesophageal reflux disease, *IAO* intestinal adhesion obstruction, *ECMO* extracorporeal membrane oxygenation

Bold values are statistically significant at $p < 0.05$

Table 4 Comparative of operative time and blood loss during reoperation for IAO after CDH repair with an artificial patch, CDH repair with direct closure, or neonatal laparotomy other than CDH repair

	Operative time (min)		Blood loss relative to body weight (g/kg)	
CDH repair with direct closure	79.7 ±36.3	§	3.68 ±3.8	§
CDH with an artificial patch	199.4 ± 50.4	§	40.0 ± 48.8	§
Neonatal laparotomy other than CDH repair	125.6 ± 70.0		7.4 ± 10.1	

IAO intestinal adhesion obstruction, *CDH* congenital diaphragmatic hernia

§ $p < 0.05$

retroperitoneal tumor, 1 had torsion of small intestine and 1 had gastroschisis. Median timing of these IAO operations after neonatal laparotomy was 8 months (range 1–190). The incidence of IAO was significantly greater in patients who underwent CDH repair than in patients who underwent other neonatal laparotomies ($p = 0.023$). The mean duration of the reoperation for IAO was 129.6 ± 72.9 min after CDH repair compared with 125.6 ± 70 min after other neonatal laparotomies ($p = 0.98$). The mean intraoperative blood loss during IAO reoperation relative to the patient's body weight was 18.8 ± 36.3 g/kg after CDH repair compared with 7.4 ± 10.1 g/kg after other neonatal laparotomies ($p = 0.26$). The severity of intestinal adhesion in all patients of the CDH repair was not significantly different from that in patients of other neonatal laparotomies.

In terms of CDH repair methods, the operative time and intraoperative blood loss relative to body weight were greater in patients who received an artificial patch compared with patients who underwent direct closure or patients who underwent other neonatal laparotomies (Table 4). These results suggested that ileus operation after CDH repair with an artificial patch is a technically difficult procedure associated with increased blood loss.

Discussion

Surgical complications that require another laparotomy are thought to be common in CDH survivors, but data are limited regarding the long-term incidences of these complications and their risk factors [4, 6–9]. According to prior reports, the most common conditions that require surgical treatment after CDH repair include GERD, IAO, and diaphragmatic hernia recurrence [8–14]. In our study, we examined the relationships between CDH repair and these complications, and evaluated possible risk factors, including prenatal diagnosis, location of the liver or stomach in the thoracic cavity, iNO, use of ECMO, and the use of an artificial patch for hernia repair.

Gastroesophageal reflux disease is a well-known complication of CDH repair, and is thought to occur in 12–81 % of patients with CDH, including 38 % of patients who underwent CDH repair in our study [6]. The mechanisms responsible for GERD have not been fully clarified in CDH survivors. In our study, stomach translocation to the thoracic cavity was the only risk factor for GERD. Liver located in the thoracic cavity or patch repair was not associated with GERD. Three patients with liver herniation and two with patch repair did not have stomach herniation because they had CDH on the right. All of them did not have GERD. So in this study, liver herniation or patch repair was not significantly associated with GERD. Kieffer et al. [15] reported that the presence of an intrathoracic stomach at operation is associated with pathological GERD, and that a shortened abdominal esophagus and obtuse angle of His were implicated in the phenomenon.

Closing a large defect by approximation and direct suture under tension may place excess strain on the crus, increasing the risk of a hiatal hernia [11]. Esophageal and gastric manometry in CDH patients revealed that abnormal peristaltic contractility and propagation could predispose to GERD. Therefore, a combination of these congenital abnormalities may result in GERD after CDH repair.

Hernia recurred in eight CDH survivors (10.8 %). Recurring diaphragmatic hernias have been reported in 8–50 % of patients with CDH [8]. Therefore, a large defect that requires patch repair might increase the risk of recurrence [10]. However, in our study, only the location of the stomach in the thoracic cavity was a significant risk factor for hernia recurrence. In our patients, the hernias recurred soon after CDH repair, but they can recur several months to several years after the CDH repair. Patients may remain asymptomatic and the recurrence is often found incidentally. Therefore, the long-term risk and incidence of recurrence are still unclear.

Intestinal adhesion obstruction was one of the most common reasons for reoperation after CDH repair in our patients. IAO was reported to occur in approximately 10–20 % of CDH patients [11]. Some prior studies have described about GERD or diaphragmatic hernia recurrence, but very few studies have described IAO after CDH repair. So we performed a close examination of the cases of IAO after CDH repair. In our study, IAO was found in 13 patients (17.6 %) after CDH repair; this rate was significantly greater than that in patients who underwent other neonatal laparotomies. Other neonatal laparotomies were performed under many different causes and conditions. In this point of view, our comparative study may include any bias, but it has some informative one. In other reports, the incidence of IAO ranged from 2.2 to 6 % after neonatal laparotomies other than CDH repair [16–18]. Although comparative studies of CDH patients and patients undergoing neonatal laparotomy have not been performed, these earlier data support our findings. Several mechanisms may contribute to the increased susceptibility to IAO in CDH patients. For example, abnormal positioning of the intestine may cause intestinal kinking and increased intra-abdominal pressure may impair peristalsis [13]. Furthermore, prolonged illness and intestinal paralysis could increase the risk of intestinal adhesion and bowel obstruction.

We also showed that the mean operative time and blood loss were significantly greater in CDH patients who received an artificial patch than in CDH patients who underwent direct closure or patients who underwent other neonatal laparotomies. It was reported that patch repair significantly increased the risk of IAO in CDH patients [11]. We did not observe a similar association between IAO and CDH repair, but patch repair did increase the severity of intestinal adhesion and ileal release. Large CDH defects requiring an artificial patch for closure pose a surgical challenge, and may increase the risk of future operations, which will also be technically difficult. It is possible that intraperitoneal placement of a patch may have pathologic effects that promote tissue adhesion. Therefore, operative time and intraoperative blood loss were significantly greater in patients who received an artificial patch compared with patients who underwent direct closure. Adverse surgical outcomes were reported to be more common in patients with a large CDH defect requiring patch repair [7, 10, 19–22], and our results support the validity of this clinical condition.

In conclusion, although advances in the treatment of CDH have remarkably improved its survival rates, CDH survivors frequently develop surgical complications, including GERD, IAO, and hernia recurrence. The location of the stomach in the thoracic cavity at initial surgery was the only predictor of these complications in this study. The incidence of IAO was significantly greater after CDH repair than after other neonatal laparotomies. The operative procedure involved in the release of an IAO after CDH repair with an artificial patch is very difficult and is associated with a high risk of bleeding because of the formation of firm adhesions. Neonates are faced with a long time to experience complications associated with CDH repair. Therefore, it is vital that pediatric surgeons evaluate new strategies to reduce the risk of these surgical complications.

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TECHNICAL INNOVATION

Balloon tracheoplasty as initial treatment for neonates with symptomatic congenital tracheal stenosis

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Abstract Neonates with congenital tracheal stenosis (CTS) sometimes develop respiratory distress and may be difficult to intubate. We used balloon tracheoplasty with a rigid bronchoscope for emergency airway management in neonates with symptomatic CTS. Herein, we describe the balloon tracheoplasty procedure and the early outcomes following its use as the initial treatment of neonatal symptomatic CTS. We performed a retrospective analysis of five neonates with CTS who were initially treated with balloon tracheoplasty at our institution from January 2010 to December 2013. Five patients with a mean birthweight of 2,117 g were treated during the study period. Of these, four developed respiratory distress after birth, and all patients had difficult intubations. In all five patients, definitive diagnosis of CTS was made by rigid bronchoscopy and 3-dimensional reconstruction scan. A total of nine balloon dilatations were performed in five patients. Following balloon tracheoplasty, two patients were extubated, one was extubated after resection and end-to-end anastomosis following initial balloon dilatation, and one remained hospitalized with tracheostomy for tracheomalacia. The remaining patient died from tracheal bleeding associated with congenital heart disease. Although our sample size was small, balloon tracheoplasty is a potentially effective initial treatment for selected cases with neonatal symptomatic CTS.

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Keywords Congenital tracheal stenosis · Balloon tracheoplasty · Neonate

Introduction

Congenital tracheal stenosis (CTS) is a rare, difficult-to-treat condition with a high mortality rate, particularly in neonates. A number of reports have described a variety of management approaches and surgical procedures for patients with CTS [1–5]; however, technical difficulties may occur in neonates. In symptomatic cases, it may be necessary to dilate stenotic tracheas, intubate safely, and secure airways as quickly as possible.

Herein, we describe the balloon tracheoplasty procedure and the efficacy and safety of its combined use with rigid bronchoscopy as the initial management for symptomatic CTS.

Materials and methods

We used a Storz ventilating bronchoscope to perform emergency airway assessment and management in neonates with CTS. We retrospectively analyzed all neonates with CTS treated in our institution from January 2010 to December 2013. Medical charts were reviewed to analyze the patients' demographics, clinical data, diagnostic and treatment procedures, and outcomes.

Definitive diagnosis of CTS was made by means of rigid bronchoscope and computed tomography scan with 3-dimensional reconstruction (3D-CT). In all patients, 3D-CT revealed possible CTS and the location of stenosis (Fig. 1). Under general anesthesia, a Storz ventilating bronchoscope was used to identify complete cartilage rings