Table 1 The risk of growth retardation in patients with congenital diaphragmatic hernia assessed by univariate analysis

	GR ($n = 35$)	Non-GR ($n = 119$)	p Value
Male sex, n (%)	22/35 (62.9)	63/119 (52.9)	0.338
Gestational age (wk)	37.6 (IQR, 37.1–38.2)[a]	38.0 (IQR, 37.3–38.9)[a]	0.066
Birth weight (g)	2,550 (IQR, 2,331–2,731)[a]	2,794 (IQR, 2,580–2,991)[a]	< 0.001
Birth height (cm)	47.0 (IQR, 45.1–49.1)[a]	48.5 (IQR, 47.0–50.0)[a]	0.034
SGA, n (%)	7/35 (20.0)	9/119 (7.6)	0.054
Apgar score at 1 min < 6, n (%)	23/35 (65.7)	64/119 (53.8)	0.247
Apgar score at 5 min < 6, n (%)	18/35 (51.4)	48/118 (40.7)	0.332
Prenatal diagnosis, n (%)	32/35 (91.4)	101/119 (84.9)	0.140
Outborn, n (%)	3/35 (8.6)	18/119 (15.1)	0.410
Cesarean section at delivery, n (%)	21/35 (60.0)	72/119 (60.5)	1.000
Right side of hernia, n (%)	6/35 (17.1)	7/119 (5.9)	0.076
Non-isolated CDH, n (%)	4/35 (11.4)	4/119 (3.4)	0.079
Surgical finding of liver-up, n (%)	18/35 (51.4)	37/119 (31.1)	0.045
Defect size of the diaphragm ≥ 75%, n (%)	18/34 (52.9)	23/118 (19.5)	< 0.001
Use of iNO, n (%)	31/35 (88.6)	75/119 (63.0)	0.004
Use of ECMO, n (%)	4/35 (11.4)	5/119 (4.2)	0.119
Patch repair at the primary operation, n (%)	21/33 (63.6)	36/119 (30.3%)	< 0.001
Length of hospital stay (d)	75 (IQR, 53–171)[a]	48 (IQR, 34–73)[a]	< 0.001
Weight at discharge (g)	3,612 (IQR, 3,070–4,295)[a]	3,490 (IQR, 3,124–3,975)[a]	0.640
Home oxygen treatment, n (%)	12/35 (34.3)	8/118 (6.8)	< 0.001
Vasodilator administration at discharge, n (%)	7/35 (20.0)	7/119 (5.9)	0.018
Surgery for ileus, n (%)	2/34 (5.9)	13/117 (11.1)	0.523
Surgery for gastroesophageal reflux disease, n (%)	7/35 (20.0)	9/119 (7.6)	0.054
Recurrence of herniation, n (%)	4/35 (11.4)	13/119 (10.9)	1.000
Duration of follow-up (y)	4.2 (IQR, 3.4–6.7)	4.3 (IQR, 3.5–5.9)	0.796

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; GR, growth retardation; iNO, inhaled nitric oxide; IQR, interquartile range; SGA, small for gestational age.
[a]IQR 25th–75th percentiles.

Table 2 The risk of growth retardation in patients with congenital diaphragmatic hernia assessed using multivariate analysis

	Univariate analysis	Multivariate analysis	
	p Value	OR (95% CI)	p Value
Birth weight < 2,698 g	< 0.001	5.5 (2.1–16.8)	< 0.001
Use of iNO	0.004	3.7 (0.9–19.6)	0.067
Patch repair at the primary operation	< 0.001	1.3 (0.5–3.5)	0.617
Length of hospital stay > 57 d	< 0.001	1.5 (0.5–4.5)	0.425
Home oxygen treatment	< 0.001	5.8 (1.6–23.8)	0.007

Abbreviations: CI, confidence interval; iNO, inhaled nitric oxide; OR, odds ratio.

extremely severe CDH cases who met the criteria for fetal tracheal occlusion.[6] Bairdain et al reported a lower GR rate of 8.2% at 1 year of age at a single institution.[5] This outstanding rate was probably a consequence of the institution's specific nutritional management program, which suggests that aggressive nutritional management can reduce the GR rate. According to the Waterlow classification, the wasting type of GR declined and the stunting type of GR increased, as the patients aged. These changes probably reflect the fact that patients will transition to chronic malnutrition if they are unable to overcome acute malnutrition. Hence, we can reaffirm the importance of aggressive and continuous treatment

Table 3 Previously published rates of growth retardation in congenital diaphragmatic hernia

Author	Country	Study duration	Definition of GR	*n*	Age at estimation	GR rate (%)
Chiu et al[18]	Canada	1985–1989	< 25th percentile	24	3	54.2
Kamata et al[8]	Japan	1986–2000	< 25th percentile	33	1	21.2
Muratore et al[10]	USA	1990–2000	< 25th percentile	121	1	56.2
Chiu et al[18]	Canada	1990–2000	< 25th percentile	38	3	57.9
UK Collaborative ECMO Group[17]	UK	1993–1995	< 25th percentile	37	1	11.3
Koziarkiewicz et al[11]	Poland	Not stated	< 25th percentile	48	Various	20.8
Jaillard et al[7]	France	1991–1998	< 5th percentile	51	2	17.6
Crankson et al[19]	Saudi Arabia	1993–2002	< 5th percentile	13	Various	22.6
Pierog et al[20]	USA	2007–2012	< 5th percentile	68	1	35.3
Cortes et al[6]	USA	1999–2001	Z-score < − 2.0	16	1	68.8
				14	2	28.6
Leeuwen et al[4]	Australia	2005–2011	Z-score < − 2.0	24	1	20.8
Bairdain et al[5]	USA	2000–2010	Z-score < − 2.0	110	1	8.2

Abbreviations: ECMO, extracorporeal membrane oxygenation; GR, growth retardation.

for patients with acute malnutrition before they transition to chronic malnutrition.

The multivariate analysis showed that the risk factors for GR were a low birth weight and the need for HOT. The specific reasons underlying the low birth weights were unclear, because neither gestational age nor SGA was associated with GR in the univariate analysis. Therefore, the "low birth weight" factor itself was thought to be a GR risk that was independent of the severity of CDH. Bairdain et al also reported that a birth weight of < 2,500 g was one of the risk factors for GR at 1 year of age.[5] Indeed, it is well known that the anthropometric data at birth have a considerable effect on physical size in later life.[21] During the follow-up of CDH patients, special attention should be given to their nutritional statuses, even if their birth weights were only moderately lower than normal.

In the present study, the HOT requirement rate among the CDH survivors was 13.1%, which is comparable with a previously reported rate of 18.2%.[10] Among patients with more severe CDH who met the criteria for fetal tracheal occlusion, the incidence of HOT was higher at 43.8%.[6] The reasons for HOT in CDH are multifactorial, and include BPD, tracheomalacia, and persistent pulmonary hypertension. Calorie consumption is thought to increase in these patients because of overwork caused by the respiratory effort.[22] Therefore, our finding that HOT is a risk factor for GR in CDH patients is logical and compatible with previous reports.[10] Appropriate nutritional management for infants with pulmonary insufficiency remains controversial. The need for patients with BPD to increase their energy intakes has become the consensus.[22] However, sufficient evidence that supports the benefits of raising the calorie intake by enteral nutrition is not yet available.[23] Another approach may comprise aggressive nutritional regimens that involve early intravenous administrations of high doses of amino acids and lipids. Bairdain et al reported that protein intakes of < 2.3 g/kg/d during stays in intensive care units were a risk factor for GR in CDH patients.[5] Although there is no evidence available that supports the benefits of the early administration of amino acids to preterm infants,[24] the administration of protein above a threshold level may have merit in preventing GR in CDH.

A limitation of the current study is that not all of the survivors visited the clinics at the specified time points. Therefore, our data did not account for those patients who had visited the clinics at different time points or those who were not followed up. Another major limitation of this study relates to the nutritional management strategies and follow-up programs that were not uniform, which means that the results may have been influenced by each doctor's opinion and/or the individual institute's policies. The present study will need to be supported by further studies that collect the data prospectively.

Conclusions

GR was present in 22.7% of the CDH survivors. Body weight, improved between the ages of 1.5 and 3 years in the GR cases, but some cases developed chronic malnutrition via acute malnutrition. The GR risk factors are a low birth weight and the need for HOT. Aggressive management of acute malnutrition may improve growth in CDH patients.

Conflict of Interest
None.

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Risk Factors for the Recurrence of the Congenital Diaphragmatic Hernia—Report from the Long-Term Follow-Up Study of Japanese CDH Study Group

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Eur J Pediatr Surg 2015;25:9–14.

Abstract

Aim of the Study Few follow-up studies focused on the recurrence regarding the postoperative course of congenital diaphragmatic hernia (CDH) survivors. The aim of this study was to report on risk factor for CDH patients who had the recurrence during the follow-up.

Materials and Methods A multicenter retrospective survey was conducted on neonates diagnosed to have CDH between January 2006 and December 2010. Follow-up survey was conducted between September 2013 and October 2013 (ethical approval: No. 25–222). Nine institutions agreed to participate in this survey. Out of 228, 182 (79.8%) patients were alive and 180 patients were included in this study. Two patients were excluded because the defect had not repaired at the primary operation. The patients were divided into the recurrence group ($n = 21$) and the nonrecurrence group ($n = 159$). Postnatal and postoperative variables were compared between these two groups. Baseline variables which showed significance in univariate analysis were entered into multiple logistic regression analysis for analyzing the recurrence. A value of

Keywords
- congenital diaphragmatic hernia
- long-term complication
- recurrence

received
May 22, 2014
accepted after revision
August 21, 2014
published online
December 19, 2014

DOI http://dx.doi.org/10.1055/s-0034-1395486.
ISSN 0939-7248.

$p < 0.05$ was considered to be statistically significant by using the JMP software program (version 9; SAS Institute, Inc, Cary, North Carolina, United States).

Main Results Out of 180, 21 (11.7%) CDH neonates had the recurrence during the course of the follow-up. Five (2.8%) patients had the recurrence before primary discharge and 16 (8.9%) patients had the recurrence after discharge. Univariate analysis showed that liver herniation (crude odds ratio [OR], 7.4; 95% confidence interval [CI], 2.73–23.68), defect size C and D, proposed by the CDH Study Group (crude OR, 7.09; 95% CI, 2.73–19.99) and patch repair (crude OR, 5.00; 95% CI, 1.91–14.70) were risk factors. Multivariate logistic regression analysis showed liver herniation (adjusted OR, 3.96; 95% CI, 1.01–16.92) was the risk factor for the recurrence.

Conclusion A wide spectrum of the disease severity and the rarity of the disease mask the risk of the recurrence for CDH patients. This study showed the only factor to predict the recurrence was the liver herniation. These data will be helpful for providing information for the long-term follow-up of the CDH patients.

Introduction

Recent advances in the prenatal and postnatal congenital diaphragmatic hernia (CDH) treatment strategy, there have been increased improvement in outcome.[1,2] Therefore, much of the clinical interests have shifted to the long-term outcomes of CDH survivors, since as the survivors can suffer from the long-term morbidities, including recurrence, pulmonary disease, gastrointestinal tract disease, hearing loss, impairment in growth and development, and orthopedic deformities.[3]

The reported incidence of recurrent diaphragmatic hernia varies from 5 to 65%.[3–5] The recurrence of the diaphragmatic hernia sometimes causes gastrointestinal tract disorders and respiratory disorders, which will severely affect the quality of life in survivors. Recent articles recommend the chronological follow-up protocol to monitor the recurrence and other complications to be early diagnosed and cured when occurred.[6]

The rarity of CDH makes conducting well-designed clinical studies extremely difficult because no single institution can accrue sufficient patients to reach meaningful conclusions. Therefore, the long-term follow-up study for CDH has based on retrospective studies in a single center experience or from multiple centers using different treatment strategies.[7]

In Japan, the cohort study had started from the multicenter retrospective cohort study for an antenatally diagnosed CDH, and then, performed a nationwide survey to understand the current treatment and the actual outcome during the period from 2006 to 2010.[8] Thereafter in 2013, a long-term follow-up study had performed among the dedicated institutions to better understand the associated long-term complications of CDH survivors. The purpose of this study was to analyze the risk factors for the recurrence among CDH neonates as part of the long-term follow-up study.

Materials and Methods

Patient Selection

This retrospective survey was approved by the ethics committees of the nine representative institutions, including the Graduate School of Medical Sciences, Kyushu University; National Center for Child Health and Development; Nagoya University Hospital; Osaka Medical Center and Research Institute for Maternal and Child Health; Kobe Children's Hospital; Faculty of Medicine, University of Tsukuba; Graduate School of Medical Sciences, Chiba University; Hyogo College of Medicine; and Graduate School of Medicine, Osaka University (representative institutional review board approval no. 25–222, Graduate School of Medical Sciences, Kyushu University).

A nationwide retrospective cohort study was conducted on CDH neonates diagnosed to have CDH between January 2006 and December 2010, and a total of 674 CDH neonates diagnosed during the 5-year period. Subsequent long-term follow-up study was conducted among the Japanese CDH Study Group and finally nine institutions which had 228 CDH neonates in the previous study consented to participate. According to this recurrence survey, 180 patients who had repaired the defect at the primary operation and the survived at least 3 years were included. Two right CDH patients who had not repaired the defect at the primary operation were excluded in this survey. One had to stop the operation because of the decrease in blood pressure during the course of correcting the liver position, while the other had been despaired the operation because of the ipsilateral lung defect.

Data Collection

The postnatal variables, including the presence of a prenatal diagnosis, birth location, sex, the presence of the associated anomalies, the side of the defect, the use of inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO), gestational age at delivery and birth weight, Apgar score at 1 minute, and the lowest oxygenation index (OI)

Table 1 Postnatal characteristics, comparing the Rec and non-Rec

Variables	Rec (n = 21)	Non-Rec (n = 159)	p value
Prenatal diagnosis (%)	21 (100)	134 (84.3)	0.048
Inborn (%)	21 (100)	134 (86.5)	0.048
Male gender (%)	7 (33.3)	91 (57.2)	0.06
Non–isolated CDH (%)	3 (14.3)	9 (5.7)	0.151
Right side of hernia (%)	2 (9.5)	11 (6.9)	0.651
iNO (%)	20 (95.2)	102 (64.2)	0.001
ECMO (%)	1 (4.8)	9 (5.7)	0.863
Continuous variables			
Gestational age (d), mean ± SD	261.8 ± 18.4	264.8 ± 11.0	0.279
Birth weight (d), mean ± SD	2,533.7 ± 601.5	2,703.3 ± 453.7	0.124
Apgar score at 1 minute, median (interquartile range)	5 (2–7)	5 (3–7)	0.358
Lowest OI, median (interquartile range)	4.8 (3.3–6.4)	3.8 (2.8–5.9)	0.906

Abbreviations: ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; non-Rec, nonrecurrence group; OI, oxygenation index; Rec, recurrence group; SD, standard deviation.

within 24 hours after birth were reviewed. An isolated CDH was defined as the CDH without any associated life-threatening or chromosomal anomalies.[8]

The perioperative variables were also examined. The presence of liver herniation, the type of diaphragmatic closure, and the defect size were also reviewed. Liver herniation was defined as CDH patients whose liver had herniated into the thoracic cavity during the operation. The defect size was determined according to the CDH Study Group's criteria, as previously reported in the literature.[8–10]

Statistical Analysis

The patients were divided into the recurrence group (Rec) (n = 21) and nonrecurrence group (Non-Rec) (n = 159). Postnatal and intra- or postoperative variables were compared between these two groups. The frequencies and percentages were used to describe the categorical data. The χ^2 test and Fisher exact test were used for the analysis of the categorical data. The mean and standard deviation or median and interquartile range were used to describe continuous variables. Student t-test and an analysis of variance were used to compare continuous variables. Baseline variables which showed significance in univariate analysis were entered into multiple logistic regression analysis for analyzing the recurrence. Kaplan–Meier analysis and Cox proportional hazards regression were also used for the recurrence analyses. The statistical analyses were performed with the JMP software program (version 9; SAS Institute, Inc, Cary, North Carolina, United States). A value of $p < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient Characteristics and the Comparison between Recurrence Group and Nonrecurrence Group

Out of 228, 182 (79.8%) patients were alive and 180 patients were included in this study. A total of 11.6% (n = 21/180) CDH patients had a recurrence during the course of the follow-up. Out of 21, 20 CDH patients had reoperations and 1 patient have not operated during the follow-up period. Five patients had a primary recurrence before the primary discharge. Three patients had a second recurrence and all of them had repaired by using an abdominal muscle flap procedure.

The postnatal characteristics of the CDH neonates are shown in ▸Table 1, with comparison between the Rec and Non-Rec. There were significant differences in the prenatal diagnosis rate and the inborn rate (Rec vs. Non-Rec = 100 vs. 84.3%, p = 0.048 and 100 vs. 86.5%, p = 0.048, respectively). There were no significant differences between two groups, according to the rate of the male gender, nonisolated CDH, right side hernia, and the use of ECMO. The use of ECMO was only 4.8% (n = 1/21) in Rec and 5.7% (n = 9/159) in Non-Rec. There were no differences in the gestational age, birth weight, Apgar score at 1 minute, and the lowest OI. Other variable which revealed significance was the iNO. These advanced therapies are recognized as the useful instruments for the persistent pulmonary hypertension, although their indications were not standardized in participants.

The perioperative characteristics of the CDH neonates are shown in ▸Table 2. A total of 76.2% (n = 16/21) had liver herniation in Rec and 30.2% (n = 48/159) in Non-Rec. Patch repair was also significantly correlated to the recurrence with 22.1% (n = 15/21) in patch repair group, although 5.4% (n = 6/112) in direct repair group. Defect size was also correlated to the recurrence with 28.6% (n = 14/49) had larger defect (C and D) and 5.3% (n = 7/131) had smaller defect (A and B). Liver herniation, patch repair, and the defect size were valuables which were significantly associated with the recurrence. As would be expected, the patients who had a large defect are likely to involve the liver in thoracic cavity and require the patch during the operation. Another significant variable was the age at operation. The severity of disease might affect the timing of operation; however, there also was

Table 2 Preoperative characteristics, comparing the Rec and Non-Rec

Variables	Rec ($n = 21$)	Non-Rec ($n = 159$)	p value
Liver herniation (%)	16 (76.2)	48 (30.2)	0.0001
Patch repair at the primary operation			
Direct repair, $n = 112$ (%)	6 (5.4)	106 (94.6)	0.001
Patch repair, $n = 68$ (%)	15 (22.1)	53 (77.9)	
Defect size			
A and B, $n = 131$ (%)	7 (5.3)	124 (94.7)	< 0.001
C and D, $n = 49$ (%)	14 (28.6)	35 (71.4)	
Continuous variables			
Age at repair (h), median (interquartile range)	101 (54.5–145.5)	50 (24–77)	0.025
Length of stay (d), mean ± SD	86.2 ± 53.7	84.1 ± 123.8	0.939
Follow-up period (d), mean ± SD	1,645.8 ± 538.4	1,682.4 ± 594.5	0.787

Abbreviations: Non-Rec, nonrecurrence group; Rec, recurrence group; SD, standard deviation.

no definite standardization among participants. Also, the technical and material aspects were also excluded because of the absence of the standardized protocol. Actually, nine out of seven institutions, including 139 patients used the PTFE patch (GORE-TEX Soft Tissue Patch; W. L. Gore & Associates, Inc., Arizona, United States), whereas one institution, including 27 patients used polyester patch (Sauvage Filamentous Fabric; C.R. Bard, Inc., New Jersey, United States) and the other institution, including 14 patients used polypropylene and PTFE composix mesh (COMPOSIX EX Mesh; C.R. Bard, Inc.). There were neither significant differences in the length of hospital stay nor the follow-up period between these groups.

Analysis of Risk Factors and Prediction for Recurrence

A multivariate analysis was performed for all baseline variables which were significant in the univariate analysis for recurrence. Baseline variables were considered as the presence of the prenatal diagnosis, inborn, male gender, nonisolated CDH, right side hernia, gestational age, birth weight, Apgar score at 1 minute, the lowest OI, liver herniation, patch repair, defect size, and the length of stay. Other variables were not included in the multivariate analysis because the postnatal treatment strategy was not standardized among the cooperative institutions.

Univariate analysis in ►Table 3 showed that liver herniation (crude odds ratio [OR], 7.4; 95% confidence interval [CI], 2.73–23.68), defect size C and D (crude OR, 7.09; 95% CI, 2.73–19.99), and patch repair (crude OR, 5.00; 95% CI, 1.91–14.70) were significant risk factors. Multivariate logistic regression analysis in ►Table 4 showed liver herniation (adjusted OR, 3.96; 95% CI, 1.01–16.92) was the only significant risk factor for the recurrence. Defect size C and D (adjusted OR, 3.79; 95% CI, 0.86–23.12) and patch repair (adjusted OR, 1.30; 95% CI, 0.24–8.83) had not showed significance. The Kaplan–Meier analysis associated with the recurrence in ►Fig. 1 showed the recurrence rate after 6 months, 1 , and 2 years of the primary operation. The each recurrence rate was higher in liver herniation group, compared with the nonliver herniation group (liver herniation vs. nonliver herniation = 6 months: 15.7 vs. 1.7%, 1 year: 18.9 vs. 4.4%, and 2 years: 25.4 vs. 4.4%). Cox proportional hazards regression analyses showed significance in liver herniation (hazard ratio, 3.66; 95% CI, 1.03–14.42; $p = 0.045$).

Discussion

As the survival rate for patients with CDH have increased during the past decades with the advent of "gentle ventilation" and specific strategy and care, clinicians has led to focus on the frequency and importance of postoperative morbidities.[1,3,6] Significant morbidities such as the recurrence, respiratory diseases, neurocognitive delay, gastrointestinal disorders, hearing loss, poor growth, chest deformity, and the complications associated with congenital anomalies continue

Table 3 Univariate analysis for the recurrence

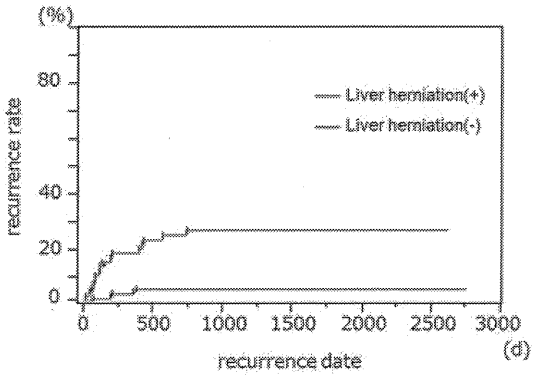
Variables	Crude odds ratio	95% CI	p value
Liver herniation	7.4	2.73–23.68	0.0002
Defect size C and D	7.09	2.73–19.99	< 0.001
Patch repair	5.00	1.91–14.70	0.0017

Abbreviation: CI, confidence interval.

Table 4 Multiple logistic regression analysis for the recurrence

Variables	Adjusted odds ratio	95% CI	p value
Liver herniation	3.96	1.01–16.92	0.0483
Defect size C and D	3.79	0.86–23.12	0.0796
Patch repair	1.30	0.24–8.83	0.7666

Abbreviation: CI, confidence interval.



Recurrence rates	Liver herniation (+) (n=64)	Liver herniation (-) (n=116)
6 months after the operation	15.7%	1.7%
1 year after the operation	18.9%	4.4%
2 years after the operation	25.4%	4.4%

Fig. 1 The Kaplan–Meier analysis for the recurrence ($n = 21$). Cox proportional hazards regression analyses showed significance in liver herniation (hazard ratio, 3.66; 95% confidence interval, 1.03–14.42; $p = 0.045$).

to affect the quality of life of many infants with CDH beyond the neonatal period.[1,3] Recurrence is one of the most insidious complication during the follow-up. Reoperation will be considered when the patients revealed herniation of the stomach or intestinal loops, or progressing elevation of the diaphragm over time. However, few systemic reviews of the CDH patients with recurrence exist, and therefore, risk factors for predicting the recurrence remains controversial.[4–6,11,12] Most of the literatures associated with the recurrence were small case series or the insufficient follow-up period with lack of important data.[4–6,11,12] In this survey, 180 CDH survivors with more than 3-year follow-up period were collected, these numbers and periods might be favorable.

The previously reported risk factors for the recurrence were larger defect, prosthetic patch, surgeon's skills or experiences, ECMO, and minimally invasive surgery (MIS).[4–6,11–13] The risk factors for the recurrence might be composed of two kinds of aspects: one is the severity of the disease, and the other is the technical issue. Likewise, in this study, baseline variables and univariate analysis showed the significant differences in liver herniation, larger defect, and patch repair. These three factors were confounding factors, which will certainly represent the severity of the disease among CDH patients. Finally, multiple logistic regression analysis showed the significance in liver herniation. This result showed the correlation between diaphragmatic defects; otherwise, the disease severity might be strongly associated with the recurrence. In addition, the chronological recurrence rates between liver herniation group and nonliver herniation group were primarily sated as follows: the liver herniation group became plateau to 25.4% at 2 years after the primary operation, and nonliver herniation group become plateau to 4.4% at 1 year after the primary operation. This statistical analysis would be practical and helpful for the parental counseling and the prognostic prediction.

In this study, no one was treated by MIS, 4 were treated via a transthoracic approach, and 176 were treated via a transabdominal approach. The surgical approach for CDH varies regionally and the technical problems might exist, especially, in the field of MIS. Although, a meta-analysis showed a statistically higher recurrence rate in the thoracoscopic group,[13] the actual risk and benefit of MIS might need more time to conclude because the MIS for CDH repair was still not yet to be established at present.

The limitation of this study was the restriction in retrospective multicenter cohort study design. In this study, nine cooperative institutions do not have the standardized protocol, and hence, the indications for treatment were lack of consensus. Therefore, the indication for iNO and the timing of operation were different, in which these factors had to be excluded from the univariate analysis in consideration for bias. Technical and material aspects, such as the cone-shaped Dualmesh (W. L. Gore & Associates, Inc., Arizona, United States) patch, or the PTFE/Marlex composite graft were not also examined; nevertheless, recent literature showed significances in recurrence rate.[4,6] These technical and material factors should be standardized when we plan to perform the prospective study in future.

Two-thirds of CDH patients with recurrence were reported to be asymptomatic at the time of diagnosis.[6] Late diagnosis of recurrence sometimes leads patients to the risk of bowel obstruction, respiratory failure, and the other serious sequelae. Recent CDH follow-up protocol recommends the periodic plain chest X-ray and the other additional complete examinations when the recurrence are to be suspected.[5,6] Ideally, establishing an international, multicenter long-term follow-up registry will be favorable to better understand the incidence patterns of morbidity in CDH patients.

A wide spectrum of the disease severity and the rarity of the disease mask the risk of the recurrence for CDH patients. This study showed the only factor to predict the recurrence was the liver herniation. These data will be helpful for providing information for the long-term follow-up of the CDH patients.

Conflict of Interest
None.

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PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2015) **57**, 682–686 doi: 10.1111/ped.12554

Original Article

Extracorporeal membrane oxygenation for congenital diaphragmatic hernia in Japan

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Abstract ***Background***: The aim of this study was to clarify how extracorporeal membrane oxygenation (ECMO) is used to treat congenital diaphragmatic hernia (CDH) in Japan.

Methods: We completed a nationwide survey of CDH involving 614 infants. The subjects included 43 patients who underwent ECMO. We compared the clinical data of the patients who did and did not survive ≥90 days, and analyzed the 24 h blood gas data in isolated CDH cases in both groups.

Results: Of the 43 CDH patients, non-isolated CDH associated with other life-threatening or chromosomal anomalies was diagnosed in six patients. Only one of these six patients was able to discontinue ECMO and survived, and the other five died shortly after birth. The other 37 patients all had isolated CDH. The reason for initiating ECMO in 31 of these patients was persistent pulmonary hypertension of the newborn (PPHN). In the 37 patients with isolated CDH, ECMO was initiated within 24 h after birth. Sixteen patients (37%) survived ≥90 days, and intact discharge was possible in eight cases. Among the isolated CDH patients, on ROC analysis of the lowest oxygenation index (OI) to predict 90 day survival, the cut-off was 15.

Conclusions: ECMO is used to treat PPHN starting from an early period after birth, but the mortality and morbidity are not favorable. For lowest OI, the index used to predict survival following ECMO, the cut-off was 15.

Key words congenital diaphragmatic hernia, extracorporeal membrane oxygenation, mortality, oxygenation index.

Congenital diaphragmatic hernia (CDH) causes serious respiratory distress shortly after birth due to pulmonary hypoplasia.[1] Several therapeutic strategies, such as high-frequency oscillatory ventilation, gentle ventilation, prostaglandin (PG) E_1 treatment, inhalation of nitric oxide (NO) and extracorporeal membrane oxygenation (ECMO), have improved mortality and morbidity in CDH patients.[2–5]

We previously reported the first Japanese nationwide study to collect and analyze a large number of CDH neonates born between 2006 and 2010.[6] Among the 614 analyzed CDH neonates, the demographic data and correlations between survival rate and pre- or postnatal variables were retrospectively reviewed.

The present study examined the current status of CDH treatment in Japan. The overall survival rate of CDH neonates was similar to that reported in recent studies from other countries (75.4%).[7] In contrast, the frequency of ECMO use was 7%, which was significantly lower than that observed in other countries.[11] Therefore, we analyzed the present situation regarding ECMO use for CDH in Japan. Furthermore, we investigated the indices that can be used to predict survival following ECMO.

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Received 23 June 2014; revised 1 October 2014; accepted 26 November 2014.

Methods

This study was performed as part of a nationwide survey of neonatal CDH conducted in 2010. This nationwide cohort study was designed to use the retrospectively collected data of CDH neonates who were born between January 2006 and December 2010. The present subjects included 43 patients who underwent ECMO among a total of 614 CDH neonates at 72 institutions collected during a 5 year nationwide survey in Japan. ECMO was used in 17 of the 72 institutions.

Among the 43 patients who underwent ECMO, we specifically examined the timing of ECMO (h after birth) and the reason for initiating treatment. The indications for ECMO included persistent pulmonary hypertension of the newborn (PPHN), pneumothorax, pulmonary hemorrhage, and others. The survey

allowed for multiple answers. Six patients with CDH who were treated with ECMO had associated anomalies (non-isolated CDH). Isolated CDH was defined as CDH without associated life-threatening or chromosomal anomalies.[8]

In addition, we investigated 37 isolated CDH patients, excluding the non-isolated cases, in order to identify indices that can be used to predict survival following ECMO. We classified the subjects into two groups based on the outcome of ECMO: survival more or less than 90 days. The primary outcomes were 90 day survival and intact hospital discharge (defined as discharge from hospital without the need for respiratory support, including oxygen supplementation, tube feeding, parenteral nutritional support, or vasodilators to control pulmonary hypertension).

We also compared the timing of ECMO initiation, gestational age (in weeks) at birth, birthweight, Apgar score at 1 min after birth, PPHN as the indication for ECMO treatment, direction of the blood flow in the ductus arteriosus and the 24 h blood gas data. The direction of blood flow in the ductus arteriosus was judged based on echocardiography performed within 24 h after birth. The presence of a predominant or equal right-to-left shunt in the ductus arteriosus was assessed. According to the prenatal disease severity evaluation of CDH in the patients treated with ECMO, we compared the lung-to-head ratio (LHR), observed/expected LHR (o/e LHR), and classification of the size of the defect, according to methods described previously.[10] The 24 h blood gas data used the pre-ductal arterial blood values. In the prenatally diagnosed patients, the most favorable 24 h data obtained after birth were used. In the patients diagnosed after birth, the most favorable 24 h data obtained after hospitalization were used. The 24 h blood gas data adopted not only the pre-ductal, but also the post-ductal, atrial blood values.

The severity of illness was evaluated according to the highest PaO_2 and lowest oxygenation index (OI) within 24 h after birth. The lowest OI was calculated using the following equation: lowest OI = MAP × FiO_2/highest PaO_2 × 100. Next, we determined the 90 day survival cut-off based on receiver operating characteristic (ROC) curves.

Statistical analysis

The results are shown as median and range. Standard deviations were also calculated for certain means. Chi-squared test or Fisher's exact test was used to compare categorical data. The prognostic value of the 24 h blood gas data was also assessed using ROC curves. The data were analyzed using JMP version 8.0 (SAS Institute, Cary, NC, USA). Significance was defined as $P < 0.05$.

Results

Initiation of ECMO

Extracorporeal membrane oxygenation was initiated in 27 of the 43 patients within 24 h after birth. Furthermore, 20 of these 27 patients received ECMO within 12 h after birth (Fig. 1). The indication for ECMO was PPHN in 31 cases, pneumothorax and pulmonary hemorrhage complicated by PPHN in eight cases, and a cause other than PPHN in four cases.

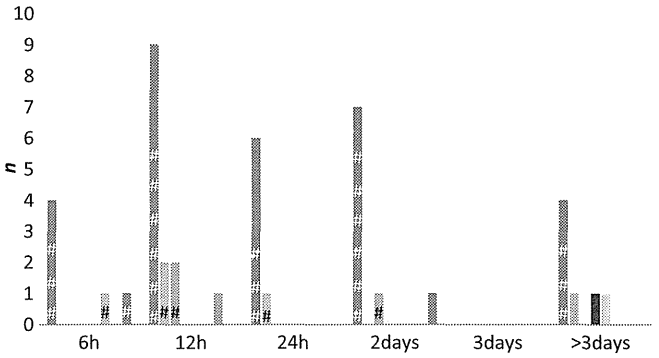

Fig. 1 Timing of and indications for extracorporeal membrane oxygenation initiation. ▩, persistent pulmonary hypertension of the newborn (PPHN; $n = 30$); ■, pneumonia + PPHN ($n = 1$); ▩, cardiac anomaly ($n = 1$); ▩, pneumothorax + PPHN ($n = 4$); ▩, atelectasis + PPHN ($n = 1$); ■, other ($n = 2$); ▩, pulmonary hemorrhage + PPHN ($n = 3$); ▩, hypoplastic lung ($n = 1$). #Deceased. 6 h, 5 dead (83.3%); 12 h, 8 dead (57.1%); 24 h, 4 dead (57.1%); 2 days, 7 dead (77.8%); >3 days, 3 dead (42.9%).

Severity of isolated CDH in ECMO patients

Among the 43 CDH patients, isolated CDH was noted in 37 patients and non-isolated CDH was present in six patients (Table 1). Among the non-isolated CDH patients, three had severe cardiac anomalies and three had non-cardiac anomalies. The three non-cardiac anomalies were hydrops fetalis, huge omphalocele, and Cornelia de Lange syndrome. Only one non-isolated CDH patient with transposition of the great artery discontinued ECMO and survived. None of the other five patients were able to discontinue ECMO, and all died shortly after birth.

Among the isolated CDH patients, cesarean section was performed in 25 cases. The reason for choosing cesarean section was due to the presence of CDH in 22 cases, physiological reasons associated with the mother's body type in six cases, fetal distress in one case, and other reasons in two cases. Apgar score at 1 min, disease site, presence of right-to-left shunt in the ductus arteriosus and presence of PPHN, indicators of the severity of CDH, were not significantly different between the patients who did and did not survive for 90 days.

According to the prenatal disease severity evaluation of isolated CDH in the ECMO patients, median LHR was 1.22 (range, 0.34–1.84) and the o/e LHR was 27.2 (range, 15.7–38.3). The prenatal evaluation of CDH was severe. Prenatal disease severity, however, was not significantly different between the patients who did and did not survive for 90 days. Nevertheless, according to the postnatal evaluation of the severity by the size of the defect, C and D defects were each present in eight patients who survived beyond 90 days (53.3%), and in 12 of 14 patients who did not survive 90 days (90.5%; $P < 0.01$).[9]

The median of the highest PaO_2 observed within 24 h after birth in the patients who survived ≥90 days was 103 mmHg (range, 21–483 mmHg), while that in the patients who died was 47 mmHg (range, 21–122 mmHg; $P < 0.05$). In contrast, the lowest PCO_2 observed within 24 h after birth was not significantly different between the groups. The median of the lowest OI observed within

Table 1 Profile of isolated CDH using ECMO

(*n* survived ≥90 days/*n* survived <90 days)	Survived ≥90 days *n* = 15 *n* (%) or median (IQR)	Survived <90 days *n* = 22 *n* (%) or median (IQR)	*P*-value
Gestational age (weeks)	37 (36–39)	37 (34–40)	.89
Prenatal diagnosis, *n* = 15/22	10 (66.7)	19 (86.4)	0.15
Cesarean, *n* = 37	10 (66.7)	15 (68.2)	0.92
Birthweight (g), *n* = 15/22	2888 (2222–3550)	2776 (2126–3444)	.33
Sex (M/F), *n* = 24/13	9/6	15/7	0.61
Apgar score 1 min (0–5) (*n* = 14/17)	11 (78.6)	16 (94.1)	.22
Disease site (L), *n* = 15/22	12 (80.0)	17 (77.2)	.70
PDA (RL shunt) (*n* = 14/20)	11 (78.6)	16 (80.0)	.92
Liver up (%) (*n* = 10/18)	5 (50)	9 (50)	1.0
LHR (*n* = 8/5)	1.46 (0.74–1.59)	1.26 (0.33–1.84)	.61
o/e LHR (*n* = 8/5)	26.0 (15.7–33.9)	28.6 (19.3–38.3)	.67
Size of defect (*n* = 29)			
A (small)	1	0	
B (medium)	6	2	<0.001
C (large)	5	10	<0.001
D (agenesis)	3	2	
Patch closure (*n* = 15/14)	9 (60.0)	10 (71.4)	0.41
Highest PaO_2 (mmHg) (*n* = 35)	103 (21–483)	47(21–122)	<0.005
Lowest PCO_2 (mmHg) (*n* = 33)	31 (26–142)	42 (19–82)	.19
Lowest OI (mmHg) (*n* = 31)	13.1 (2.7–71.4)	32.4(9.0–143.5)	<0.005

A, artery; CDH, congenital diaphragmatic hernia; L, left.; LHR, lung-to-head ratio; o/e, observed/expected; OI, oxygenation index; PDA, patent ductus arteriosus; R, right; V, venous.

24 h after birth in the patients who survived ≥90 days was 13.1 mmHg (range, 2.7–71.4 mmHg), while that in the patients who died was 32.4 mmHg (range, 9.0–149.5 mmHg; $P < 0.05$).

ECMO patient prognosis

Twenty of the 37 patients undergoing ECMO died (Table 2). The clear cause of death was pneumothorax in eight cases, intraventricular hemorrhage in three cases, sepsis in one case, and other causes in five cases.

With regard to the type of ECMO utilized, veno-venous (VV) ECMO was used in the majority of the patients who survived ≥90 days (60%), while it was used in only 9.1% of the patients who did not survive ≥90 days. In contrast, veno-arterial (VA) ECMO was used in 40.0% of the patients who survived ≥90 days, while it was used in 90.9% of the patients who did not survive ≥90 days ($P < 0.01$).

The number of cases in which ECMO was initiated within 24 h was not significantly different between the two groups. The median duration of ECMO in isolated CDH patients who survived ≥90 days was 5 days (range, 1–13 days), while that in the patients who died was 8.5 days (range, 1–47 days; $P < 0.05$), with the patients who survived ≥90 days being more likely to be weaned from ECMO within 6 days ($P < 0.01$).

Surgery was performed significantly more frequently for CDH in the survivors. Conversely, surgical repair in ECMO patients was performed significantly more frequently for CDH in the non-survivors ($P < 0.01$). A total of 21 of the 37 isolated CDH patients who received ECMO were able to be weaned from it. Of these 21 patients, 15 survived. Intact discharge was possible, however, in only eight of these 15 patients. In the other seven patients, intact discharge was not possible. Five patients needed home oxygen therapy and two needed tube feeding.

Table 2 Prognosis of isolated CDH treated with ECMO

(*n* = survived ≥90 days/Survived <90 days)	Survived ≥90 days *n* = 15 (%)	Survived <90 days *n* = 22 (%)	*P*-value
Type of ECMO (VV)	9 (60%)	2 (18.2)	<0.001
(VA)	6 (40.0)	20 (90.9)	
ECMO started <24 h	10 (45.4)	17 (77.2)	0.61
Duration of ECMO > 6 days (*n* = 15/22)	3 (20.0)	14 (63.6)	<0.01
Surgical repair for CDH (*n* = 15/22)	15 (100)	14 (63.6)	<0.001
Surgical repair on ECMO (*n* = 15/14)	1 (6.7)	12 (85.7)	<0.001
Termination of ECMO (*n* = 15/22)	15 (100)	6 (27.3)	<0.001
Intact discharge (*n* = 15/22)	8 (53.3)	0 (0.0)	<0.001

A, artery; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; L, left; LHR, lung-to-head ratio; o/e, observed/expected; OI, oxygenation index; PDA, patent ductus arteriosus; R, right; V, venous.

Table 3 Central nerve complications related to ECMO use (all patients)

Central nerve complication	$n = 43$ n (%)	Survived ≥90 days $n = 4$
IVH	7 (16.2)	1
PVL	0 (0)	
Hypoxic encephalopathy	1 (2.3)	0
Hydrocephalus	0 (0)	
Convulsion	0 (0)	
Other (cerebral infarction, extradural hematoma, subdural hematoma)	4 (9.3)	3

ECMO, extracorporeal membrane oxygenation; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

The central nervous system complications related to ECMO use are summarized in Table 3. Twelve of the 43 patients (27.9%) had complications. Intraventricular hemorrhage was the most common, occurring in seven cases, followed by cerebral ischemia, which developed in one case.

Prognostic accuracy of the 24 h blood gas data

We investigated 37 cases of isolated CDH to clarify the prognostic accuracy of the 24 h blood gas data. ROC curves were generated for the lowest OI to determine the accuracy of prediction of survival ≥90 days. On ROC curve analysis of the lowest OI in patients surviving 90 days, the area under the curve was 0.76, and sensitivity and specificity were 57% and 96%, respectively (Fig. 2). The lowest OI that had the highest accuracy, was 15. The 90 day survival rate of the patients with OI > 15 was 28%, and the intact discharge rate was 4.5%.

Discussion

In Japan, the overall 90 day survival rate of CDH patients is 75%, while that of patients with isolated CDH is 84%.[6] These results are favorable in comparison with those from other countries.[2–5] In the present study, however, the frequency of ECMO use in Japan was 7% (43/614 CDH cases). It has been reported that the use of

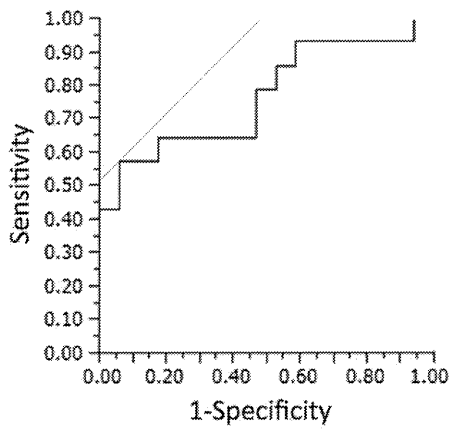

Fig. 2 Receiver operating characteristic curve analysis for survival >90 days: area under the curve, 0.76; sensitivity, 57%; specificity, 96%.

ECMO has recently decreased, and that the frequency of ECMO use in Japan is lower than in previous reports.[10,11] The low frequency of ECMO in Japan is due to the low priority of ECMO in therapeutic strategies for CDH. According to our previous study, the proportion of high-volume hospitals (i.e. no. CDH patients treated in 5 years >21) offering ECMO was 85.7%. In contrast, in low-volume hospitals (no. CDH patients treated in 5 years <10), it was available in only 46.8% of the institutions.[12] In other words, high-volume hospitals tend to attract move severe cases of CDH requiring ECMO. The criteria for initiating ECMO, however, are different in high-volume hospitals. For example, among CDH patients who receive a prenatal diagnosis, some hospitals do not provide ECMO for CDH within 24 h after birth. In contrast, treatment of CDH involving gentle ventilation and the use of nitric oxide and PGE_1 is common, and this therapeutic strategy achieves a favorable outcome without the use of ECMO. Therefore, ECMO is used only in severe cases. We speculate that the outcome of ECMO was poor in the present study due to the fact that the treatment was used only in severe cases.

The outcome in the present CDH patients treated with ECMO was poor. The survival rate beyond 90 days was 37%, and the intact discharge rate was only 18%. In contrast, in the total of 614 cases, the intact discharge was 64.5%. Among the non-isolated CDH patients, ECMO was used in six cases. Cardiac anomalies were the most common complication, including severe cardiac anomalies, such as indication for the Fontan procedure.[13] Patients with indications for the Fontan procedure are rare, and the outcome of patients with indications for the Fontan procedure among those with CDH is especially poor.[14] Five of these six patients died. Given that non-isolated CDH is associated with many serious anomalies, such patients should be considered for ECMO. We observed, however, no improvement in the clinical outcome following ECMO for these cases.

Among the isolated CDH patients, ECMO was used in 37 cases. A total of 21 of the 37 isolated CDH patients treated with ECMO were able to be weaned from it. Only 15 of these 21 patients, however, survived, and intact discharge was achieved in eight cases. The outcome of ECMO, especially intact discharge, in the isolated CDH patients was poor. With regard to the type of ECMO utilized, VV ECMO was used significantly more often in the patients who survived ≥90 days than was VA ECMO. There were, however, 16 institutions using VV ECMO, while VA ECMO was used at only three institutions. It is therefore difficult to say that VA ECMO is contraindicated for severe CDH, because the indications for ECMO may have been affected by the differences between institutions.

Extracorporeal membrane oxygenation was initiated within 24 h after birth in 27 of the 43 patients (63%). Regarding the indications for ECMO, 31 of the 43 patients (72%) were treated with ECMO due to PPHN. Twenty-one of these 31 patients treated with ECMO due to PPHN died. In Japan, ECMO is most often used to treat PPNH, and is initiated within 24 h after birth. With regard to the other treatments for PPHN, nitric oxide inhalation was used in 96.2%, PGE_1 in 61.5%, prostacyclin in 42.3%, and phosphodiesterase III inhibitor in 53.8% of patients. Thus, vasodilator use was not effective for PPHN. We think that the

PPHN occurring within 24 h after birth was caused by pulmonary hypoplasia, which could not be effectively treated using these agents.

According to a previous report, the frequency of ECMO use was 30% of all CDH cases, and the survival rate of CDH patients treated with ECMO was approximately 50% in other countries.[14,15] Because the outcome of therapy without ECMO in Japan is similar to that in other countries, ECMO is usually used only in serious CDH cases, equivalent to 7% of all CDH patients, that is, in those unlikely to respond to other treatment. The medical cost of ECMO, however, is high (2.5–3.5-fold that of cases in which ECMO is not used).[16] In addition, in this study, the morbidity of the patients treated with ECMO was poor, at 18%. In Japan, the use of ECMO is not limited with regard to medical cost, but, considering the situation of ECMO use in Japan, it is necessary to determine the exclusion criteria for the use of ECMO in cases of CDH. The lowest OI observed within 24 h after birth can be used as an indicator of need for ECMO. On ROC analysis, the lowest OI that had the highest accuracy was 15. In this study, six CDH patients (28%) with the lowest OI > 15 survived ≥90 days. Intact discharge was possible in only one case (5%). This suggests that the probability of survival is low even when a patient with lowest OI within 24 h after birth >15 is treated with ECMO. In contrast, we believe that inhaled NO and PGE_1 for PPHN without pulmonary hypoplasia is effective, and that OI > 15 can be used to exclude patients with pulmonary hypoplasia from receiving ECMO.

Limitations

In this study, we demonstrated the present status of ECMO for the treatment of congenital CDH in Japan. The treatment outcomes for CDH in Japan are favorable, and the use of ECMO is decreasing. Management using a respirator and indication criteria for ECMO differed among institutions, however, and the number of subjects was limited. Although the study was restricted to institutions that use ECMO, these limitations may have influenced the present results.

Acknowledgment

A part of this study was supported by a grant from the Ministry of Health and Welfare of Japan (Health and Labour Science Research Grants for Research on Intractable Diseases). Funding source: Health Labour Sciences Research Grant, the Ministry of Health Labour and Welfare, Japan. The authors have no conflicts of interest to disclose.

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Clinical Features of Congenital Cystic Lung Diseases: A Report on a Nationwide Multicenter Study in Japan

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Eur J Pediatr Surg 2016;26:91–95.

Abstract

Aim The current study aimed to assess the perinatal risk of congenital cystic lung diseases (CCLD) and to establish a suitable surgical strategy in consideration of postoperative lung growth and problems during adulthood.

Methods Among 874 CCLD patients identified in a nationwide survey, 428 patients were born between 1992 and 2012 and treated at 10 high-volume centers were retrospectively reviewed with statistical analysis.

Results In the 194 patients who were prenatally diagnosed to have CCLD, 16.7% presented with fetal hydrops as observed using ultrasonography. The Apgar score (5 minutes) was lower than 5 in 5.4%. As of postnatal day 30, 14.0% of the neonatal patients required respiratory support, and 3.3% (8/243) had died because of pulmonary hypoplasia. Among those who were asymptomatic immediately after birth, 33.6% of the patients developed the respiratory infectious symptoms during their first year of life, and 22.1% did so between the age of 1 and 2 years. The postoperative percent vital capacity among the prenatally diagnosed patients was significantly higher than that among the postnatally diagnosed patients (98.3 ± 11.9 vs. 81.7 ± 9.7, $p < 0.0222$). Late complications included thoracic deformity in 30 patients and persistent lung cyst in 4 patients, whereas malignancy was not observed in the present series.

Conclusions Approximately 10 to 15% of prenatally diagnosed CCLD patients may carry a high risk of perinatal respiratory distress. Early operation before developing

Keywords
- congenital cystic lung disease
- congenital cystic adenomatoid malformation
- prenatal diagnosis
- lung development

received
May 11, 2015
accepted after revision
August 31, 2015
published online
October 27, 2015

DOI http://dx.doi.org/10.1055/s-0035-1566095.
ISSN 0939-7248.

episodes of lung infection, seem to be associated with a better development of the reserved lung during later life. The incidence of carcinogenesis among patients with CCLD may be extremely low.

Introduction

Although congenital cystic lung disease (CCLD) is a representative pediatric respiratory surgical disease, little is known regarding its suitable management. Although a certain population of patients with CCLD may develop a fatal feature during the perinatal period, the practical incidence of a critical pathophysiology has not yet been clarified. Most patients are asymptomatic immediately after birth, however, the natural clinical course of these asymptomatic patients and their late postoperative lung function have remained uncertain. To clarify the clinical features of CCLD from the perinatal period through the late postoperative period, the Japanese Study Group of Pediatric Chest Surgery conducted a nationwide survey on CCLD. This is the first report to provide an overview of the final results of this nationwide survey, and the present study also aimed to clarify when asymptomatic CCLD neonates first develop symptoms and to determine whether early surgery may improve later lung development.

Materials and Methods

A primary survey on CCLD was distributed to all 59 institutions registered with the Japan Study Group of Chest Surgery, and a total of 874 CCLD patients who were born between January, 1992 and December, 2012 were identified at 37 institutes. Of the 874 CCLD patients identified in the primary survey, 428 patients who were treated at the 10 high-volume centers (194 prenatally diagnosed and 234 postnatally diagnosed), were involved in a more precise review. The demographic data were summarized in ►Table 1. The medical records during the neonatal period were available for 243 patients, including both prenatally and postnatally diagnosed cases. The relevant clinical courses, pathological images, pre- and postnatal radiological images, late respiratory function were retrospectively reviewed after receiving institutional review board approval from each of the centers. Symptom-related respiratory system that required treatment with hospitalization, and complications that were rated grade III or higher in Clavien–Dindo classification,[1] and required management with hospitalization were also reviewed. Furthermore, the late postoperative respiratory function was assessed using spirometry in 22 patients after the age of 6 years in 22 patients, which corresponds to the age of the completion of rapid growth in lung development. The percent vital capacity (%VC; vital capacity/expected vital capacity) and FEV1/FVC (forced expiratory volume 1.0 second/forced vital capacity) were analyzed using statistical methods such as the Student *t*-test.

Results

Perinatal Clinical Features

Among the 194 prenatally diagnosed patients, lung lesions were first recognized at the 24 gestational week (median; range, 12–42 week) using fetal ultrasonography. Fetal hydrops, which is considered to be the most critical feature, was observed in 16.7% of the patients who were examined ultrasonographically.

Among the 243 neonatal patients, the Apgar score at 5 minutes was 9 to 10 in 68.0%, 8 in 17.0%, 7 in 5.4%, 5 to 6 in 4.1%, and 1 to 4 in 5.4%, thus 12.4% required tracheal intubation.

Postnatal examination revealed a lesion occupying the left lung in 55.6%, the right lung in 42.9%, and bilateral lungs in 1.5% according to the postnatal examination. Accompanying complications were recognized in 11.5% of the patients in the present series, including cardiac anomalies in 23 patients, thoracic deformities in 4, renal anomalies in 4, and congenital diaphragmatic hernia in 3.

On postnatal day 30, a total of 165 of the 243 neonatal patients (67.9%) were asymptomatic and living at home, 64

Table 1 Demographic data

	All	Prenatally diagnosed	Postnatally diagnosed	
Gender				
Male/female	224/204	103/91	121/113	N.S.
Gestational age (wk)	26–43 Median 38	26–41 Median 38	26–43 Median 38	N.S.
Birth weight (g)	472–4,300 Median 2,960	818–4,300 Median 2,965	472–4,266 Median 2,956	N.S.
Birth height (cm)	29.4–54.0 Median 48.8	30.0–54.0 Median 48.8	29.4–52.5 Median 48.8	N.S.

Abbreviation: N.S., not significant.

(26.3%) required hospitalization, 7 (2.9%) had been transferred to a regional hospital, and 8 (3.3%) expired. A total of 33 patients (13.6%) continue to require respiratory treatment, including 18 who required the use of a respirator and 6 who required a pulmonary vasodilator. One patient received a tracheotomy. Surgery had been performed in 137 patients and was scheduled for 60 patients, whereas 31 patients were being observed without surgery. In one patient, the lung lesion had become unrecognizable.

Late Onset of Clinical Symptoms in Asymptomatic Neonates

Among the patients who were asymptomatic immediately after birth, 140 patients were confirmed to have developed respiratory symptoms beyond the age of 1 month. Of them, 47 patients (33.6%) developed pulmonary symptoms within the first year of life. Thereafter, the onset of clinical symptoms was recognized between the age of 1 and 2 years in 31 patients (22.1%). As shown in ▸Fig. 1, the cumulated incidence of symptoms related to CCLD drastically increased before the age of 2 years, and was 74.3% at the age of 3 years. Only 10 patients (7.1%) developed symptoms after the age of 6 years.

Fever and coughing were the most common initial symptoms seen in 95 patients (67.9%) and 75 patients (53.6%), respectively. Other relatively common symptoms include continuous expectoration of sputum in nine (6.4%) and chest pain in eight (5.7%). In total of 74.0% of the patients exhibited infectious features of the lower airway.

Surgery, Complications, and Clinical Outcome

Among the 428 patients, 409 patients had undergone surgery as of the time of the survey. Among these patients, surgery was indicated because of respiratory symptoms requiring hospitalized management in 34.8%, because of infection requiring anti-infectious therapy in 29.8%, because of enlargement of the lung lesion in diagnostic images in 5.1%, and because of light tachypnea requiring no treatment in 1.3%, whereas 22.1% of the patients were operated prophylactically. The surgical procedure performed for CCLD was a monolobectomy in 292 patients (71.4%), a multiple lobectomy in 13 patients (3.2%), a segmentectomy in 32 patients (7.8%), a pneumonectomy in 13 patients (3.2%), and other procedures such as wedge resection and fenestration of the lung cyst in 59 (14.4%). Intraoperative complications were recorded in three patients (0.7%).

Fig. 1 Cumulative incidence of the congenital cystic lung diseases (CCLD) symptoms. The cumulated incidence of the symptoms related to CCLD drastically increased before the age of 2 years, and became 74.3% at the age of 3 years. Only 7.1% of the patients develop symptoms after the age of 6 years.

Among 78 patients, 91 early postoperative complications were identified in the present series, including pneumothorax in 19 patients, pneumonia in 15, respiratory distress in 11, pleural effusion in 8, a persisting cystic lesion in 7, thoracic deformity in 7, central nervous system complications in 5, and other unspecified complications in 20. Of these, 11 complications have not yet been cured. During the late postoperative period of more than 5 years after surgery, 40 complications were additionally identified, including thoracic deformity in 30 patients, persisting lung cyst in 4 patients, and others in 6 patients. However, none of the patients in the present series have developed pulmonary cancer.

In the present series, 14 patients died, mostly during the neonatal and early infantile period. The causes of death included pulmonary hypoplasia because of CCLD in nine patients, and uncontrollable pneumothorax, expanding CCLD lesion, pulmonary hypertension, massive intracranial hemorrhage, and accompanying major anomalies in one patient each.

Respiratory Function Measured during Late Postoperative Period

Data regarding the postoperative respiratory function beyond the age of 6 years were available in 22 patients (single lobectomy in 20 patients, dual lobectomy and partial lobectomy in 1 patient each). The %VC showed a gradual increase with age after the age of 7 years and finally reached around 90%. Interestingly, a few prenatally diagnosed patients who underwent single lobectomy similarly without preceding episodes of lung infection showed definitely higher %VC values even before the age of 7 years. The averaged achieved %VC finally was 98.3 ± 11.9% in the prenatally diagnosed cohort and 81.7 ± 9.7% in the postnatally diagnosed cohort (▸Fig. 2). On the other hand, FEV1/FVC showed no significant difference between the two cohorts (87.3 ± 13.7 in prenatally diagnosed cohort vs. 84.2 ± 8.3 in postnatally diagnosed cohort, $p > 0.34$) (▸Fig. 3).

Pathological Diagnosis

The pathological diagnoses of the resected lung specimens made by the local pathologists included congenital cystic adenomatoid malformation (CCAM) in 164 patients, intralobar bronchopulmonary sequestration in 63 patients, extralobar bronchopulmonary sequestration in 39 patients, bronchial atresia in 66 patients, bronchiogenic cyst in 15 patients, lobar emphysema in 9 patients, bulla/bleb in 2 patients, and the pathological diagnosis had not been established in 21 patients.

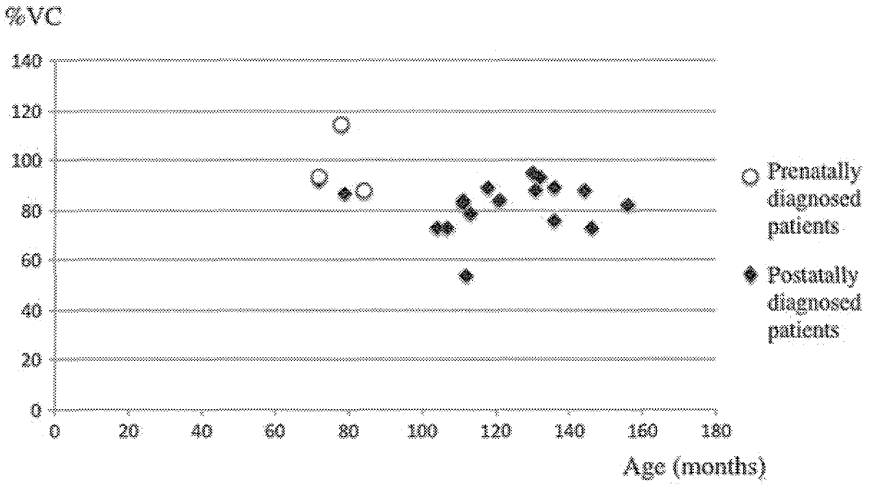

Fig. 2 Postoperative percent vital capacity (%VC) after grown-up. Averaged %VC at the age over 6 years was significantly higher in the prenatally diagnosed patients compared with the postnatally diagnosed patients (98.3 ± 11.9% vs. 81.7 ± 9.7%, $p < 0.0222$) (open circle: prenatally diagnosed patients, closed rhombus: postnatally diagnosed patients).

Discussion

The clinical entity of CCLD contains several concepts of pulmonary maldevelopment such as CCAM, bronchopulmonary sequestration, bronchial atresia, and bronchogenic cyst,[2–4] however, the embryological definition and the classification of these diseases have not been fully established, which disturbs standardization of surgical intervention for CCLD from the prenatal period through the puberty. Recently, more patients are diagnosed to have CCLD prenatally. Occupying fetal lung lesions may cause critical pathophysiologies such as fetal hydrops and neonatal respiratory distress, and an urgent surgical intervention is sometimes required during the perinatal period.[5–9] However, most patients are asymptomatic at birth and are found to have CCLD at a later life when they present with recurrent respiratory infection. Since the likelihood of encountering the patients who have been prenatally diagnosed as having CCLD but do not show any symptoms at the time of birth has been increased, identifying patients with a high risk of developing a critical pathophysiology during the perinatal period and determining the most suitable time to perform surgery in asymptomatic patients have become important issues. Furthermore, clinical outcome and lung growth after surgery for CCLD during the late postoperative period have also remained unknown. To address these problems, a nationwide multicenter study was performed to gather both prenatal and postnatal clinical information on CCLD patients. Among the clinical information collected by the survey, the present analysis focused on the perinatal risk and the postnatal clinical feature of CCLD.

Among the neonatal patients, approximately 70% of the patients were totally asymptomatic at birth in our current

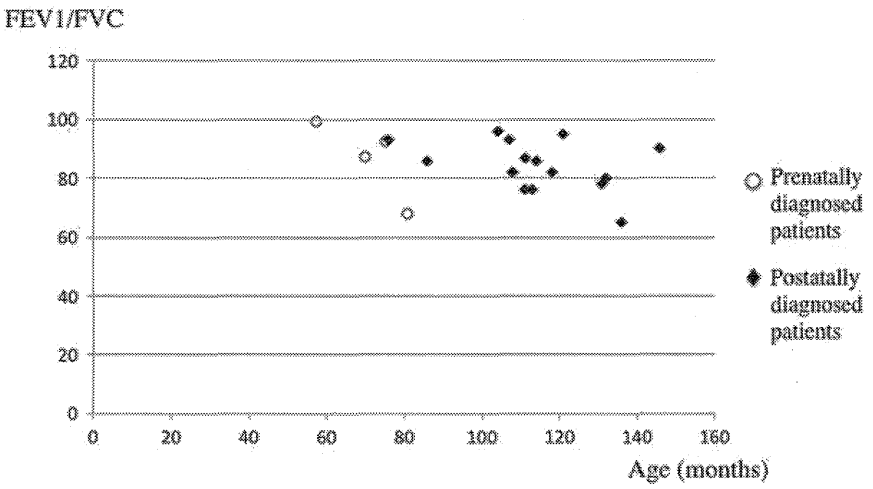

Fig. 3 Postoperative FEV1/FVC (forced expiratory volume 1.0 second/forced vital capacity) after grown-up. FEV1/FVC showed no significant difference between the prenatally and postnatally diagnosed patients (87.3 ± 13.7 in prenatally diagnosed patients vs. 84.2 ± 8.3 in postnatally diagnosed patients, $p > 0.34$) (open circle: prenatally diagnosed patients, closed rhombus: postnatally diagnosed patients)

series. In terms of the Apgar score, about 15% of the neonatal patients showed a score of less than 8. On postnatal day 30, approximately 15% of the neonatal patients required the assistance of a respirator, and almost all of the 14 patients who died did so during the early infantile period. These observations suggest that about 5 to 10% of neonatal cases, that is about half of symptomatic neonates, should be considered to have the highest risk of critical respiratory distress and may require urgent surgical intervention and intensive respiratory support during the neonatal period. Apparently, de novo respiratory distress was hardly seen after the early infantile period. On the other hand, infection involving a cystic lesion actually developed earlier in the present series than previously cited. Traditionally, infectious symptoms were considered to develop after the age of 1 year in CCAM, and after the age of 3 to 4 years in other CCLDs.[10,11] Nevertheless, in the present series, one-third of the patients showed symptoms during the 1st year of life. About 65% of the patients showed some symptoms before the age of 3 years in the present series. These observations have clarified the natural history of CCLD from the prenatal period.

The respiratory function of the completed lung was evaluated only in limited cases even in the current nationwide survey; however, the data obtained during the late postoperative period have provided very important information. In the present series, a single lobectomy was performed in most of the cases, and the average postoperative %VC after the age of 7 years (the age of nearly completed lung development) exceeded 90%, which is unbelievably high compared with that after adult chest surgery. Furthermore, a few prenatally diagnosed cases obtained a significantly higher % VC ($p < 0.022$) at an earlier age mathematically compared with the results for postnatally identified cases. Since these prenatally diagnosed patients had surgery without preceding episodes of lung infection, this observation suggests that patients who are diagnosed earlier and undergo surgery before developing a lung infection may achieve better development of the remaining lung, which strongly suggests the necessity of early surgery before the age of 1 or 2 years even in asymptomatic patients.

As for late complications, a persisting lung cyst was most commonly observed among patients with the involvement of multiples lung lobes. The conservation of less involved lung lobes appears to be a reasonable option to avoid a pneumonectomy and the postpneumonectomy syndrome in these cases. The persistence of cysts may be inevitable in the selected cases, which may require further resections in a second surgery performed later in life as seen in the present series. On the other hand, carcinogenesis from CCLD has not been identified in our series, which included data obtained over the past 20 years, although bronchioalveolar carcinomas that were believed to originate from CCLD, especially from CCAM, have been previously reported.[12–14] The incidence of carcinogenesis from lung cysts seems to be extremely low. Further observation should be continued in future studies.

Finally, the above late postoperative features clarified in the current survey should be taken into consideration at the time of the initial surgery for CCLD.

Conflict of Interest
None.

Acknowledgment
The authors are deeply grateful to Ms. Yuko Yamahara of the JCRAC data center for the data management and statistical analysis. This study received a grant from the Rare Diseases Study Project, Ministry of Health and Labor, Japan (no. H24-Rare diseases-general-034). The summary of this article was presented at the Annual Meeting of the European Pediatric Surgeons' Association in Ljubljana, Slovenia in June 2015.

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Pediatr Surg Int (2015) 31:943–947
DOI 10.1007/s00383-015-3773-1

ORIGINAL ARTICLE

Severe acquired subglottic stenosis in children: analysis of clinical features and surgical outcomes based on the range of stenosis

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Accepted: 6 August 2015 / Published online: 14 August 2015

Abstract
Purpose The present study analyzed the clinical features and surgical outcomes of laryngotracheal reconstruction (LTR) in pediatric patients with severe acquired subglottic stenosis (SGS) based on the range of stenosis. The aim was to clarify the indications for LTR in severe acquired SGS.
Methods The medical records of 33 pediatric patients with severe acquired SGS (Myer-Cotton grade III or IV) at our institution between January 1994 and December 2013 were retrospectively reviewed.
Results Nine patients had stenosis localized at the subglottis (localized SGS), and twenty-four patients had stenosis extending to the glottis or supraglottis from the subglottis (extended SGS). 66.7 % (6/9) of localized SGS patients were intubated after infancy, and 95.8 % (22/23) of extended SGS patients were intubated in the neonatal period. The duration of intubation was significantly shorter with localized than with extended SGS. Sixteen patients underwent LTR. The operation-specific decannulation rate was 80.0 % (4/5) in the localized SGS group and 14.3 % (1/7) in the extended SGS group.
Conclusion The range of stenosis was affected by the period and duration of endotracheal intubation. Surgical outcomes of LTR tended to differ between localized SGS and extended SGS. LTR can be effective for localized SGS.

Keywords Acquired subglottic stenosis · Laryngotracheal stenosis · Laryngotracheal reconstruction · Children

Introduction

Acquired subglottic stenosis (SGS) is defined as a narrowing of the subglottic larynx developing mainly after endotracheal intubation [1]. The management of severe acquired SGS in children remains a difficult challenge, and the appropriate surgical intervention strategies are still controversial. Laryngotracheal reconstruction (LTR) widening the subglottis has become a standard procedure for acquired SGS in most experienced centers. More recently, partial cricotracheal resection (PCTR), resection of the stenotic subglottic segment and an end-to-end thyrotracheal anastomosis, has been performed in a limited number of centers, and high success rates in patients with severe SGS have been reported [2, 3].

The present study investigated the range of stenosis in addition to the degree of stenosis in pediatric patients with severe acquired SGS, and it analyzed the clinical features and surgical outcomes of initial surgical intervention in a center where LTR has been performed. The aim of this study was to clarify the appropriate indications for LTR in severe acquired SGS.

Materials and methods

This study was performed with the approval of the institutional review board and complied with the Helsinki Declaration of 1964 (revised 2013). The medical records of patients who underwent medical treatment for severe

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