Clinical characteristics and outcomes of the right congenital diaphragmatic hernia compared to the left: a 10-year single-center experience

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Abstract

Purpose: The features of right-sided congenital diaphragmatic hernias (RCDHs) are quite different from those of left-sided CDHs (LCDHs). We have summarized the features of RCDHs experienced in our institution.

Methods: This retrospective study analyzed the cases of patients with CDH registered at our institution between 2011 and 2020. Defects on each side were compared based on prenatal diagnosis, medical treatment, type of surgery, and outcomes.

Results: A total of 101 patients underwent surgery at our institution during the neonatal period, and 11 had RCDHs. RCDHs and LCDHs were significantly different in terms of extracorporeal membrane oxygenation (36% vs. 6%, $p = 0.002$), patch repair (81% vs. 28%, $p < 0.001$), recurrence rate (36% vs. 11%, $p = 0.022$), and length of hospital stay (117 days vs. 51 days, $p = 0.012$). The severity of the fetal diagnosis did not reflect postnatal severity. All patients with RCDH survived to discharge, and there was no significant difference in survival rate between the right and left sides.

Conclusion: Neonates with RCDH required more intensive treatments; however, the survival rate was comparable between RCDH and LCDH. RCDH was significantly different from LCDH and an optimal treatment strategy for RCDHs should be established.

Keywords: congenital diaphragmatic hernia, right congenital diaphragmatic hernia, neonate, prenatal diagnosis

Introduction

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly of the diaphragm. Perinatal and perioperative management, including prenatal diagnosis by ultrasonography, delivery in specialized facilities, administration of exogenous surfactant, high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO), have advanced over the past decades; thus, the overall survival rate of isolated CDH without severe cardiac malformations or fatal chromosomal abnormalities has improved to up to 75%–84% [1-7]. However, this result is mainly associated with left-sided CDH (LCDH), which accounts for most CDH cases. Studies on right-sided CDH (RCDH), accounting for 10%–20% of CDH [8-10], are few [8, 10-13]; thus, less is known about RCDH than LCDH. Fisher et al. compared the outcomes of 40 RCDH cases with those of LCDH from a single institution; the need for ECMO and a diaphragmatic patch was higher in the RCDH group than in the LCDH group [10]. A previously reported multicenter comparison of 84 cases of RCDH and 414 cases of LCDH also suggested that RCDH is associated with a greater likelihood of the need for patch repair and a higher short-term (and possibly long-term) risk of recurrence [8]. The survival rate of patients with RCDH is controversial because it is often different in each study. Compared to LCDH, there have been reports of lower survival rates [10, 14, 15], no difference in survival rate [8, 16], or higher survival rates associated with RCDH [17]. Since the features of RCDH are still unknown, this study aimed to clarify the perinatal status, clinical course, and postnatal outcomes of RCDH compared to those of LCDH at our hospital in the past decade.

Materials and Methods

We retrospectively reviewed neonates' clinical records who underwent radical surgery for CDH at our hospital between January 2011 and December 2020. They were divided into two groups according to the defect's location: the LCDH group and the RCDH group. Patient characteristics and outcomes, including the presence of prenatal diagnosis, mode of delivery, gestational age at delivery, birth weight, and the

presence of other anomalies, such as major or minor cardiac anomalies and severe chromosomal anomalies, were compared between the groups. As the prenatal variables, the value of the observed to expected fatal lung area-to-head circumference ratio (o/e LHR) was measured to determine the severity at the time of prenatal diagnosis. LHR was calculated by multiplying the longest diameter of the lung by its longest perpendicular diameter in the cross-sectional plane at the level of the four-chamber view of the heart, which was then divided by the appropriate normal mean for gestation and multiplied by 100 to derive the o/e LHR [18]. Severity was defined as severe (<26%), moderate (26%–45%), and mild (45%). The defect size was determined according to the schema provided by the CDH Study Group, which has been previously reported in the literature. The smallest defects are categorized as "A" defects and the largest as "D" defects [19]. The outcomes included survival to discharge from the birth hospitalization, length of hospital stay, need for ECMO, age at surgery, repair procedure, approach method (only open method in our hospital), complications, herniated organs, defect size, brain MRI findings at discharge, ventilator settings, pneumothorax morbidity, and recurrence. The need for home oxygen therapy (HOT), home mechanical ventilation (HMV), home parental nutrition (HPN), and home enteral nutrition (HEN) at discharge were also recorded.

Statistical analysis

Continuous variables are expressed as medians (interquartile ranges). The Mann–Whitney U-test was used to compare continuous variables. Fisher's exact probability test was used to analyze the differences between discrete variables. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using R software 3.5.0.

Results

A total of 101 neonates who underwent surgery for CDH were included in this study. Of the 101 patients, 11 (10%) had RCDH and 90 (90%) had LCDH. The characteristics and outcomes of RCDH are shown in

Tables 1 and 2, and a comparative analysis between the groups is shown in Table 3. Eight of the 11 patients (72%) with RCDH and 67 of the 90 patients (74%) with LCDH were prenatally diagnosed (p = 0.902), while the respiratory symptoms of other patients were evaluated using postnatal X-ray radiographs. The severity of pulmonary hypoplasia based on o/e LHR in the RCDH group was moderate in two patients and mild in six and did not reflect postnatal outcomes such as the need for ECMO and recurrence, as shown in Tables 1 and 2. No patient had severe pulmonary hypoplasia.

There was no significant difference in sex [male patients: 5(45%) vs. 52 (58%)], o/e LHR [46.8% (33–58) vs 30% (15–45)], mode of delivery [CS; 10 (90%) vs. 70 (77%), p = 0.311], gestational age [263 days (256–264) vs. 263 days (259–269), p = 0.616], operated age [3 days (2.5–4.5) vs. 2 days (1–4), p = 0.134], birth weight [2604 g (2240–2800) vs. 2770 g (2473–3078), p = 0.195], malformation [cardiac: 1 vs. 6, chromosomal: 0 vs. 5, major: 5 vs. 23, none: 6 vs. 59], and birth location [inborn: 9 (81%) vs. 66 (73%), p = 0.543]. ECMO was required in four patients (36%) in the RCDH group and six (6%) in the LCDH group (p = 0.002); the number of patients requiring repair using an artificial membrane was significantly higher in the RCDH group (n= 8, 73%) than in the LCDH group (n=25, 28%) (p = 0.003). The recurrence rate was significantly higher in the RCDH group than in the LCDH group (4 [36%] vs. 10 [11%], p = 0.022). Of the four patients with recurrence in the RCDH group, one required three reoperations due to infection of the artificial membrane. The other three patients had recurrence due to the fragile sutured tissue, and one of them required four reoperations. Ten patients had recurrence of LCDH. Of the five patients treated using a patch in the initial surgery, recurrence in four of the patients was caused by growth. The unexplained recurrence more than 6 months after the surgery was defined as growth-related recurrence. Recurrence in one patient was due to the involvement of the fragile pericardium within the suture line. Of the five patients who were treated using direct suture in the initial surgery, recurrence in two of the patients was caused by growth while in three patients, it was due to the fragile sutured tissue. Of the ten patients with recurrence of LCDH, one patient required two reoperations and had undergone direct suture repair in the initial surgery. There was no significant difference in recurrence rate between RCDH and LCDH (4/8

[50%] vs. 5/25 [20%], $p = 0.097$) among those who underwent diaphragm defect closure with an artificial patch; however, the re-recurrence rate was significantly higher in case of RCDH (2/8 [25%] vs. 0/25 [0%], $p = 0.021$) among these cases.

The median length of hospital stay was longer in the RCDH group than in the LCDH group (117 days [74–223 days] vs. 51 days [35–839 days], $p = 0.012$). RCDH did not influence HFOV usage in comparison to LCDH (7 [63%] vs. 44 [48%], p = 0.35); however, the median mean airway pressure (MAP) was higher in the patients with RCDH (18 cmH2O vs. 15 cmH2O, p = 0.01) than in those with LCDH. The incidence of pneumothorax was significantly higher in the RCDH group than in the LCDH group (3 [27%] vs. 4 [4%], $p = 0.005$).

All patients in the RCDH group survived to discharge, but in the LCDH group, six patients (7%) died due to severe pulmonary hypertension. ECMO could not be removed in two patients and pulmonary hypertension was exacerbated acutely due to pneumothorax on the healthy side in four patients.

Before discharge, tracheostomy was performed in one patient with RCDH and in five patients with LCDH; this finding was not significantly different between the groups ($p = 0.64$). There was no difference in the defect size [A: 0 vs. 6, B: 7 vs. 57, C: 4 vs. 17, D: 0 vs. 3] and brain MRI findings [WNL: 6 vs. 63, periventricular leukomalacia: 2 vs. 4, others: 7 vs. 8, none: 0 vs. 10]. While all surgical approaches for LCDH were transabdominal, only eight patients in the RCDH group underwent a transabdominal approach. All RCDH patients had intrathoracic herniation of the liver, which was noted in only 20 patients (22%) with LCDH ($p = 0$). In the RCDH groups, one patient needed HOT, and two patients needed HMV at discharge. None of the patients in either group needed HEN or HPN at discharge.

Discussion

This study demonstrated the prenatal status, clinical course, and postnatal outcome associated with RCDH when compared with those of LCDH in patients treated at our hospital during the last decade. The RCDH

cases accounted for 17.1% of all CDH cases in this study, similar to that in previous reports with an incidence of approximately 10% to 20% [8-10].

In this study, the need for ECMO, patch repair, and recurrence rate were all significantly higher in the RCDH group than in the LCDH group, similar to that in previous reports [8-10]; thus, the length of hospital stay was significantly longer in the RCDH group than in the LCDH. The length of hospital stay among patients with RCDH was longer for four patients with recurrence and four with persistent pulmonary hypertension (PPHN); three patients with RCDH were discharged early.

Since there was no significant difference in the recurrence rate between the patch closure groups, it is considered that the high rate of patch closure is related to the high recurrence rate in the RCDH group. Since, two of the four RCDH patients with recurrence required several reoperations and the re-recurrence rate was significantly higher in the RCDH group patients who underwent repair using a patch, patch closure for RCDH may pose complications, which can lead to a high re-recurrence rate. Although there was no difference in the defect size between the LCDH and RCDH cases, all RCDH patients had liver prolapse. In cases of RCDH, it may not be possible to replace the liver inferiorly, which can complicate the suturing and closure of the abdominal or thoracic cavity. Even if the liver can be replaced inferiorly, it interferes with the operating field, and it may be difficult to suture the innermost portions of the defect successfully. It is possible that the diaphragm margins were unclear and the patch was poorly secured to the chest wall. It is more complicated on the right side than on the left. There was also a risk of infection due to the need for a patch. Therefore, this study highlights the difficulty of treating patients with RCDH.

Since MAP is higher on the right side, pneumothorax is more likely to occur. Further, when a pneumothorax occurs, PPHN often worsens and ECMO is required [20]. We hypothesize that the reason for the high settings required for breathing in RCDH cases is that the liver, which is a parenchymal organ, is located more superiorly in RCDH patients. The resulting high pressure on the lungs may impede effective expansion. These series of events may be attributable to the requirement of ECMO in RCDH cases. The association between major malformations and prognosis is unclear owing to the relatively few subgroup

analyses conducted between CDH with major associated malformations and isolated CDH with a limited sample size and low statistical power [17, 21-24]. The predictors of poor prognosis for CDH include low LHR, ECMO use, and use of artificial membranes during surgery or malformation [25, 26-28]. In this study, the risk of these currently reported prognostic factors was significantly higher in the RCDH cases than in the LCDH cases, however, there was no difference in mortality between the two groups. In our study, 7% of the LCDH patients died during hospitalization due to severe pulmonary hypertension. A previous report stated that in LCDH, pulmonary hypertension resistant to therapeutic management, including ECMO, is more common and associated with a higher rate of neonatal demise [17]. This was similar to our findings. In contrast, RCDH patients were hospitalized for a long time due to pulmonary hypertension, except for when recurrence was noted; however, the survival rate of RCDH was as high as 100%. In LCDH, where many organs may prolapse into the thoracic cavity, the contractile function of the left ventricle (LV) deteriorates due to physical compression of the chamber and decreased pulmonary blood flow [29, 30]. After birth, the load increases, further diminishing the contractility of the LV [31, 32]. Five of the six patients with LCDH who were treated with ECMO experienced hypoplasia of the LV. However, the size and contractility of the LV was maintained in all 11 cases of RCDH. Since RCDH causes less compression of the heart from prolapsed organs and the resulting condition of the LV is good, cardiac function will eventually improve and recover. Consequently, although RCDH tends to predispose patients to PPHN, it is thought that good cardiac function contributes to the improvement of PPHN and fewer cases of death.

In this study, the prenatal o/e LHR did not predict postnatal outcomes in RCDH accurately, making the treatment of RCDH more difficult. Regarding LHR, because the error in the number of weeks of pregnancy is large, o/e LHR, corrected by the number of weeks of pregnancy, is used worldwide [18]. However, this predicted value was obtained in a single institution study in the United Kingdom, and LHR is based on LCDH [33]. Recently, studies on severity prediction based on the evaluation of total fatal lung volume by MRI have been reported [17, 34].

There are several limitations to our study. First, it was a single-center, retrospective, case-control study. Second, the sample size was small. Further, low statistical power owing to a small sample size potentially led to no statistical differences in some of the evaluation parameters.

In summary, patients with RCDH had a significantly higher need for ECMO and patch repair, significantly higher recurrence rate, and longer hospital stay than patients with LCDH, but there was no difference in mortality. Therefore, RCDH was significantly different from LCDH. An optimal treatment strategy for RCDHs should be established by conducting more studies in the future. Further studies with a large sample size are also warranted. An accurate approach for severity classification is also desired for both RCDH and LCDH.

Declarations

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The authors did not receive support from any organization for the submitted work.

Conflict of interest:

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethics approval:

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate/publish:

Informed consent was obtained from legal guardians.

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Table 1. RCDH characteristic

case	sex	PD	o/e LHR, %	MOD	GA, day	BW, g	malformation	BL
1	M	+	0.54	CS	266	2740	-	IB
2	F	-	unknown	CS	254	2459	-	OB
3	M	+	0.71	CS	263	3144	TM,BA,CO,SA	IB
4	M	+	0.43	CS	264	2604	SA	IB
5	F	+	0.48	CS	245	2150	-	IB
6	F	+	0.8	CS	265	2658	TM, PS	IB
7	F	+	0.7	CS	259	2860	-	IB
8	M	+	0.62	CS	263	1348	CP,MCA,IA,MR	IB
9	M	-	unknown	VD	285	3682	-	OB
10	F	-	unknown	CS	263	2338	SA	IB
11	F	+	0.33	CS	249	2010	-	IB

LHR: lung area to head circumference ratio, PD: prenatal diagnosis, MOD: mode of delivery, GA: gestational age, BW: birth weight, BL: birth location, M: male, F: female, CS: caesarean section, VD: virginal delivery, TM: tracheomalacia, BA: brain atrophy, CO: cryptorchidism, SA: spine anomaly, PS: pulmonary sequestration, CP: cleft palate, MCA: minor cardiac anomaly, IA: imperforate anus, MR: malrotation, IB: inborn, OB: outborn

Table 2. RCDH outcome

Case	ECMO	repair	AS, day	AP	HO	recurrence	DS, mm	CC	brain MRI
1	-	patch	4	TA	IT,LV	+	40*60	-	VM
2	+	patch	6	TA	LV	-	50*40	PE	PVL
3	+	patch	5	TT	IT, LV	+, 3 times	70*50	MI	PVL
4	-	patch	3	TA	SM,IT, LV	-	35*30	-	AC
5	-	patch	2	TA	IT, LV	-	50*40	-	WNL
6	-	patch	1	TA	LV	+	30*30	-	WNL
7	+	patch	3	TT	LV	+, 4 times	30*50		WNL
8	-	DST	3	TT	LV	-	20*20	-	WNL
9	-	DST	4	TA	LV	-	40*40	-	AC
10	-	DST	1	TA	LV	-	30*30	-	WNL
11	+	patch	7	TA	IT, LV	-	50*50	-	WNL

ECMO: Extracorporeal Membranous Oxygenation, DST: direct suture, AS: age at surgery, AP: approach, HO: Herniated Organ, DS: defect size, CC: complications, TA: trans-abdominal, TT: trans-thoracic, IT: intestines, LV: liver, SM: stomach, MI: membrane infection, PE: pleural effusion, VM: ventriculomegaly, PVL: periventricular leukomalacia, AC: Arachnoid cyst, WNL: within normal limits

Table3. compared RCDH to LCDH

	RCDH	LCDH	p.value
Total, n (%)	11 (10%)	90 (90%)	
characteristic			
Sex, male, n(%)	5 (45%)	52 (58%)	0.437
Prenatal diagnosis, n (%)	8 (72%)	90 (74%)	0.902
o/e LHR, %	46.8 [33-58]	30 [15-45]	0.060
severe, n (%)	0 (0%)	5 (6%)	0.423
moderate, n (%)	2 (18%)	28 (31%)	0.376
mild, n (%)	6 (55%)	24 (27%)	0.060
unknown, n (%)	3 (27%)	33 (37%)	
Caesarean section, n (%)	10 (90%)	70 (77%)	0.311
Gestational age,day [a]	263 [256-264]	263 [259-269]	0.616
Birth weight, g [a]	2604 [2244-2800]	2770 [2473-3078]	0.195
Malfomation, n (%)			
Cardiac	1 (9%)	6 (7%)	0.765
Chromosomal	0 (0%)	5 (6%)	0.423
Malrotation	1 (9%)	6 (7%)	0.765
Major	5 (45%)	23 (26%)	0.164
None	6 (7%)	59 (65%)	
Birth locate inborn, n (%)	9 (81%)	66 (73%)	0.543
outcome			
ECMO, n (%)	4 (36%)	6 (6%)	0.002*
Repair, patch, n (%)	8 (73%)	25 (28%)	0.003*
Age at surgery, day [a]	3 [2.5-4.5]	2 [1-4]	0.134
Approach abdominal, n(%)	8 (72%)	90 (100%)	<0.001*
Liver up, n (%)	11 (100%)	20 (22%)	<0.001*
Recurrence, n (%)	4 (36%)	10 (11%)	0.022*
Mortality, n (%)	0 (0%)	6 (7%)	0.377
Length of hospital stay, day [a]	117 [74-223]	51 [35-839]	0.012*
Tracheostomy, n (%)	1 (9%)	5 (6%)	0.640
Defect.size			
A, n (%)	0 (0%)	6 (7%)	0.377
B, n (%)	7 (63%)	57 (63%)	0.984
C, n (%)	4 (36%)	17 (19%)	0.178
D, n (%)	0 (0%)	3 (3%)	0.539

unknown	0 (0%)	7 (8%)	
Brain.MRI			
WNL, n (%)	6 (58%)	63 (70%)	0.079
PVL, n (%)	2 (18%)	4 (5%)	0.099
others, n (%)	7 (24%)	13 (14%)	
none, n (%)	0 (0%)	10 (11%)	

[a] Median (interquartile range).

* Significant difference.

WNL: within normal limits, PVL: periventricular leukomalacia