Table 5 Comparison of the parameters in the patients who were unable to be treated with surgical intervention

Development of pneumothorax	No ($n = 21$)	Yes ($n = 18$)	p
Gestational age (d), mean ± SD	263 ± 18	260 ± 27	0.681
Birth weight (g), mean ± SD	2,645 ± 577	2,633 ± 690	0.952
Apgar score at 1 min, median (interquartile range)	2 (1–5)	2 (1–4)	0.871
Caesarean section at delivery, *n* (%)	12 (57)	11 (61)	1.000
Prenatal diagnosis, *n* (%)	17 (81)	12 (67)	0.465
Liver-up, *n*/*N* (%)	13/16 (81)	7/11 (64)	0.391
L/T ratio < 0.08, *n*/*N* (%)	6/11 (55)	3/5 (60)	1.000
Use of HFOV, *n*/*N* (%)	19/19 (100)	12/12 (100)	NA
Highest Pao_2 within 24 h after birth (Torr), mean ± SD	54 ± 43	44 ± 14	0.433
Lowest $Paco_2$ within 24 h after birth (Torr), mean ± SD	51 ± 18	61 ± 38	0.328
Best oxygenation index within 24 h after birth, mean ± SD	56 ± 46	38 ± 9	0.266
Mean airway pressure (cm H_2O), mean ± SD	17.8 ± 4.4	16.1 ± 2.4	0.290
Right-to-left shunting at ductus within 24 h after birth, *n*/*N* (%)	16/19 (84)	9/11 (82)	0.866
Use of iNO, *n*/*N* (%)	18/21 (86)	11/18 (61)	0.141
Use of ECMO, *n*/*N* (%)	3/21 (14)	5/18 (28)	0.432
Survival time (d), median (interquartile range)	2 (2–5.5)	2 (2–5.8)	0.920

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; L/T ratio, lung-to-thorax transverse area ratio; SD, standard deviation.

remains high,[11,13] even when HFOV, which is thought to be a protective method for minimizing ventilator-induced lung injury, is initially applied.[10,12] Moreover, Boloker et al and Migliazza et al have reported that the mortality rate considerably increases once a pneumothorax develops.[11,12]

Therefore, we analyzed the prevalence of pneumothorax based on the results of a nationwide Japanese survey of neonatal CDH. According to the questionnaire survey concerning the management strategy of each institution, which was conducted simultaneously with this survey and is described in detail elsewhere,[19] a gentle ventilation strategy was adopted in 87% of the institutions, and more than 80% of the institutions preferred to use HFOV initially or proactively. Although the tolerable levels of preductal $Paco_2$ and Pao_2 varied widely, almost all of the Japanese institutions treated CDH patients based on the concept of permissive hypercapnia and permissive hypoxia. Of the 510 isolated CDH neonates, 69 (13.5%) neonates developed a pneumothorax preoperatively and/or postoperatively, more than half of whom died, even under a gentle ventilation strategy.

We stratified the patients according to the disease severity represented by the diaphragmatic defect size, as the mortality of CDH is reported to be dependent on the defect size of diaphragm.[20,21] Although the inoperable patients could not be classified using the defect size as determined by the operative findings, we assumed that those patients were the most severe cases because they were too severe to be stabilized for surgical intervention. In fact, inoperable patients turned out to be more critical than the patients with 75% or more defects judging according to various parameters. The prevalence of pneumothorax was evidently dependent on the disease severity, as represented by diaphragmatic defect size and operability of the patient. The number of patients whose primary cause of death was a pneumothorax was also dependent on the severity of the disease. The survival to discharge rate and intact discharge rate decreased in association with the severity of the disease, and this trend was more significant in the patients who developed a pneumothorax, especially among those with a more severe condition. As the diaphragmatic defect size and operability status are assumed to express the degree of pulmonary hypoplasia, the high prevalence and mortality of pneumothorax are dependent on the degree of pulmonary hypoplasia.

We therefore attempted to identify other risk factors for the development of a pneumothorax with respect to the underlying condition or respiratory management by comparing several parameters between patients with the same level of disease severity. Among the patients with 25 to 75% defects, the best oxygenation index, mean airway pressure, incidence of right-to-left shunting at the ductus, use of iNO, and ECMO were higher in the patients who developed a pneumothorax. However, these differences were not thought to be the causes of pneumothorax occurrence, rather the underlying conditions representing the severity of the disease. In fact, no other risk factors for the development of pneumothorax were found in the 75% or more defects and inoperable groups. These results suggested that the cause of pneumothorax occurrence was the pulmonary hypoplasia itself, and it is inevitable that pneumothorax occurrence will likely be encountered at a constant rate when treating neonates with CDH associated with severe pulmonary hypoplasia. Namely, mortality was the only difference observed for

the patients in the severe condition with pneumothorax compared with those without pneumothorax. Therefore, clinicians must seek to use "more gentle ventilation" strategies and be prepared at any time to quickly treat sudden respiratory deterioration due to pneumothorax occurrence.

A single-center retrospective study revealed that the only statistically significant predictor of the need for ECMO in infants with left CDH and respiratory failure after 6 hours of iNO therapy is the presence of a pneumothorax requiring chest tube placement.[22] There is a current trend toward the significantly decreased use of ECMO in Japan because of advances in respiratory management,[14] and the incidence of ECMO in this series was only 37 cases (7.3%), with a survival rate of 41%. The more proactive and more rapid application of ECMO, which can allow the lung to rest and is considered to be the "ultimate gentle ventilation," in cases of acute deterioration due to pneumothorax occurrence may be helpful to improve both survival and intact discharge rates.

A major limitation of this study is that it was conducted in a retrospective manner using a questionnaire requesting details about the patients. Many of the institutions had a small number of cases, and the treatment strategies for neonates with CDH were determined according to the clinical decisions of each institution, although most of the institutions advocated a gentle ventilation strategy.[19] Unfortunately, more detailed information regarding pneumothorax occurrence, such as the time of pneumothorax recognition, whether the condition was ipsilateral or contralateral or preoperative or postoperative and whether a chest tube was required, was not included in the questionnaire. Because chest tubes are not currently placed routinely at the time of surgery in most Japanese institutions, a postoperative ipsilateral pneumothorax may also be a problem that can sometimes lead to mortality. More detailed prospective studies are therefore needed to analyze risk factors for the development of pneumothoraces and to establish a comprehensive strategy for treating pneumothorax occurrence in neonates with CDH in the era of gentle ventilation.

Conclusions

Pneumothoraces were found to more likely occur in neonates with CDH associated with a large defect of the diaphragm. The survival rate and intact discharge rate decreased as the severity of the disease worsened, especially among the patients who developed a pneumothorax accompanied by large diaphragmatic defects. No other risk factors related to pneumothorax occurrence were found, except for the severity of the disease itself, thus suggesting that pneumothorax was associated with a lethal outcome in neonates with CDH associated with a large defect of the diaphragm. It is necessary to establish a comprehensive strategy for treating pneumothorax occurrence in neonates with CDH in the era of gentle ventilation.

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Differences between periventricular hemorrhagic infarction and periventricular leukomalacia

Takeshi Tsuji [a], Akihisa Okumura [b,*], Hiroyuki Kidokoro [c], Fumio Hayakawa [a], Tetsuo Kubota [c], Koichi Maruyama [c], Toru Kato [a], Makoto Oshiro [d], Masahiro Hayakawa [e], Kazuyoshi Watanabe [f]

[a] *Department of Pediatrics, Okazaki City Hospital, Okazaki, Japan*
[b] *Department of Pediatrics, Juntendo University Faculty of Medicine, Tokyo, Japan*
[c] *Department of Pediatrics, Anjo Kosei Hospital, Anjo, Japan*
[d] *Department of Pediatrics, Ogaki Municipal Hospital, Ogaki, Japan*
[e] *Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[f] *Faculty of Medical Welfare, Aichi Shukutoku University, Nagoya, Japan*

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Abstract

Purpose: To clarify the differences between infants with periventricular hemorrhagic infarction (PVHI) and those with periventricular leukomalacia (PVL). *Methods:* We retrospectively evaluated the clinical features, ultrasonography, and electroencephalogram (EEG) findings in 22 preterm infants with PVHI and 49 with PVL. EEG and cranial ultrasonography were serially performed in all participants starting immediately after birth. Acute and chronic stage EEG abnormalities were evaluated separately. *Results:* Gestational age and birth weight were significantly lower in infants with PVHI than those with PVL. EEGs were normal in the majority of infants with PVHI on days 1–2. However, EEG abnormalities appeared after ultrasonography abnormalities. The majority of infants with PVL showed acute-stage EEG abnormalities on days 1–2. The rate of infants with acute-stage EEG abnormalities decreased with age, whereas the rate of infants with chronic-stage EEG abnormalities increased with age. Normal EEG before ultrasonography abnormalities was more common in infants with PVHI than in those with PVL. However, deterioration of acute-stage EEG abnormalities was more frequent in infants with PVHI than in those with PVL. *Conclusions:* PVHI was presumed to cause mostly postnatal injury, whereas PVL was presumed to cause mostly pre-or perinatal injury.

Keywords: Periventricular hemorrhagic infarction; Periventricular leukomalacia; Electroencephalography; Gestational age; Timing of brain injury

1. Introduction

Advances in perinatal medicine have succeeded in improving survival rates in preterm infants. However, neurological and/or behavioral problems are not uncommon in survivors. Several studies have revealed the relationship between white matter lesions and neurological sequelae in preterm infants [1–5]. Two types of well-defined white matter injury in preterm infants are closely related to neurological sequelae: periventricular hemorrhagic infarction (PVHI) and periventricular leukomalacia (PVL). The cranial ultrasonography (US) findings in patients with PVHI and PVL are quite different. Periventricular intraparenchymal echodensity (IPE) occurs mostly 1–3 days after birth in infants with PVHI,

* Corresponding author. Address: Department of Pediatrics, Juntendo University Faculty of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Tel.: +81 3 3813 3111; fax: +81 3 5800 1580.
E-mail address: okumura@juntendo.ac.jp (A. Okumura).

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whereas cystic changes in deep white matter are observed in infants with cystic PVL at 1–3 weeks following periventricular echodensities (PVEs) seen at 2–7 days of age. However, the differences in the pathogenesis of PVHI and PVL are incompletely understood.

Electroencephalography (EEG) is a powerful and sensitive tool for assessment of brain injury in preterm infants [6]. Several reports have shown that abnormal EEG findings are frequent in infants with PVHI and PVL [7–10]. Our previous studies showed that EEG abnormalities differ according to the time course of brain injury [6]; acute-stage EEG abnormalities (ASAs) reflect the suppression of EEG activities immediately after acute brain insults, and chronic-stage EEG abnormalities (CSAs) reflect irreversible brain lesions during the recovery phase [6]. Moreover, we investigated the timing of brain injury based on serial EEG findings beginning immediately after birth [11].

Although PVHI and PVL are both white matter injuries in preterm infants, differences in their pathogenesis can occur. We compared clinical and serial EEG findings between preterm infants with PVHI and PVL to clarify the differences between the two representative brain lesions, particularly in terms of the timing of brain injury.

2. Materials and methods

This study was approved by the ethical committee of the Nagoya University Graduate School of Medicine. From the parents of the infants, we obtained written informed consent for the clinical and research use of EEG, neuroimaging, and demographic data. We reviewed the hospital records of infants (gestational age, 23–32 weeks) with PVHI and cystic PVL who were admitted to Nagoya University Hospital and its four affiliated hospitals during 2000–2008. Because determination of the timing of brain injury was important, infants with PVHI were enrolled when at least one EEG had been recorded before the appearance of US abnormalities. Infants who had chromosomal abnormalities, multiple congenital anomalies, or both PVHI and cystic PVL were excluded. Finally, 22 infants with PVHI and 49 with cystic PVL were enrolled. Eighteen infants with PVL were included in our previous study [12].

PVHI and PVL were diagnosed based on US and MRI findings. PVHI was diagnosed when fan-shaped high echodensities continuing from an intraventricular hemorrhage were observed in the unilateral deep white matter. PVL was diagnosed when PVEs followed by cystic changes with a diameter $\geqslant$3 mm were observed in bilateral deep white matter. PVEs were judged to be present when white matter was brighter than or of equal brightness to that of the choroid plexus. We routinely performed cranial US at least every 3 days during the first 2 weeks of life, and then once per week until discharge. US was performed by attending neonatologists or neurologists blinded to EEG data. Coronal and sagittal sections through the anterior fontanelle were examined using 7.5 Hz sector transducer. Follow-up magnetic resonance imaging (MRI) was performed at 1–2 years of corrected age in all patients who survived. We obtained at least axial T1-weighted, T2-weighted and fluid-attenuated inversion recovery images, and sagittal T1-or T2-weighted images. MRI findings were interpreted in experienced pediatric neurologists blinded to US and EEG findings. Porencephalic changes continuing in the lateral ventricle were observed in infants with PVHI. Ventriculomegaly, with irregular ventricular walls and abnormal high intensities on T2-weighed images in the surrounding areas, was seen in infants with PVL.

We collected the following clinical data: gestational age, birth weight, singleton or twin, Apgar score, mode of delivery, premature rupture of membranes, clinical chorioamnionitis (maternal fever accompanied by elevated maternal C-reactive protein and/or fetal tachycardia), mechanical ventilation, pH and base excess on initial blood gas analysis, and early death. The clinical, ultrasonographic, and EEG data were collected anonymously. EEG confirmed neonatal seizures were observed in 1 infant with PVHI and in 2 with PVL. In these infants, phenobarbital was administered after the EEG recording. No infants had received antiepileptic drugs or sedatives at least few hours before EEG recordings.

EEG is routinely recorded in our hospitals to assess brain injury. We obtained informed consent for EEG examinations. EEG was recorded polygraphically at the bedside for 40–90 min using bipolar montage with eight surface electrodes (AF3, AF4, C3, C4, O1, O2, T3, and T4), according to the international 10–20 system. All EEGs were performed during spontaneous sleep. AF3 and AF4 were located halfway between Fp1 and F3 and between Fp2 and F4, respectively. Generally, the first EEG was recorded within 48 h of life. When an infant was born on a weekend day or a holiday, the first EEG was recorded on the third or fourth day of life. The second EEG was obtained between days 5 and 14, the third between days 15 and 28, and subsequent EEGs were obtained at 4-week intervals until discharge. When profound deterioration of general condition occurred, additional EEG recordings were performed at the request of the attending physician. All EEGs were independently interpreted by at least two of experienced pediatric neurologists (TT, AO, HK, FH, TKu, KM, and TKa) blinded to US findings. When the interpretations of raters differed, EEG findings were determined by consensus.

ASAs and CSAs [6,12] (Fig. 1), were the EEG abnormalities evaluated in this study. When an acute and strong brain insult has occurred, EEG activity shows

varying degrees of ASAs. ASAs were diagnosed when decreased continuity and/or lower amplitude of background activities were observed. ASAs were graded according to our previous study [13] (Table 1). EEG activity gradually recovers when an insult disappears, and ASAs are replaced by CSAs. CSAs in infants with PVHI or PVL were categorized into disorganized patterns [6], which were diagnosed as present when deformed delta waves were observed with or without abnormal sharp waves and abnormal brushes [9,10,12,14]. CSA severity was divided into two categories rather than the three described by us previously [12]. This was because the CSAs of some infants were interpreted before the CSA grading system was established. The CSAs of these infants were difficult to classify into three categories. Thus, classification into two categories was more appropriate for this study.

Statistical analysis was performed using Fisher's exact probability test for qualitative variables and the Mann–Whitney *U*-test for quantitative variables, using the SPSS Statistics ver. 17.0 computer software (SPSS Inc., Tokyo, Japan). Statistical significance was accepted at a level of $p < 0.05$.

3. Results

3.1. Patient characteristics

The clinical characteristics of the infants are shown in Table 2. Gestational age and birth weight were significantly lower in infants with PVHI than in those with PVL ($p < 0.001$, each). Apgar scores at 1 and 5 min were lower in infants with PVHI than in those with PVL ($p < 0.05$, each). Premature rupture of the membranes and cesarean section were significantly more frequent in infants with PVL ($p < 0.05$, each) than in those with PVHI. The initial blood pH value was significantly lower in infants with PVL than in those with PVHI ($p < 0.05$). Nine infants with PVHI died before discharge, whereas all but one infant with PVL survived ($p < 0.001$). All infants with PVHI who survived had spastic hemiplegia, and all infants with PVL had spastic diplegia.

3.2. US findings

The initial US was performed within the first 2 days of life in all infants. The median age at the first detection of IPE was 3 days (range, 0–37 days) in infants with PVHI. PVEs were first detected at a median age of 2 days (range, 0–38 days) in infants with PVL, and periventricular cysts were detected at a median age of 18 days (range, 8–46 days). The date of first appearance of US abnormalities in infants with PVHI and those with PVL was not different.

3.3. EEG findings

Serial changes in EEG findings are shown in Fig. 2 (top). EEGs were normal in 11 (65%) of 17 infants with PVHI on days 1–2, whereas EEG abnormalities were seen in 7 of 9 infants on days 3–4. ASAs with or without CSAs were observed in half of the infants until days 15–28. The EEG on days 1–2 showed ASAs with or without CSAs in 28 (85%) of 33 infants with PVL. Along with age, the number of infants with ASAs decreased, but that of infants with CSAs increased.

3.4. Acute-stage EEG abnormalities

ASA severity according to the timing of EEG recordings is shown in Fig. 2 (middle). ASAs were present in six (35%) of 17 infants with PVHI and 28 (85%) of 33 infants with PVL on days 1–2. ASAs were more frequent in infants with PVL than in those with PVHI ($p < 0.001$). In contrast, ASAs were more frequent in infants with PVHI than in those with PVL on days 5–14 ($p < 0.05$), 15–28 ($p < 0.005$), and 29–56 ($p < 0.05$). Moderate or severe ASAs were relatively infrequent on days 1–2 compared with days 3–4, 5–14,

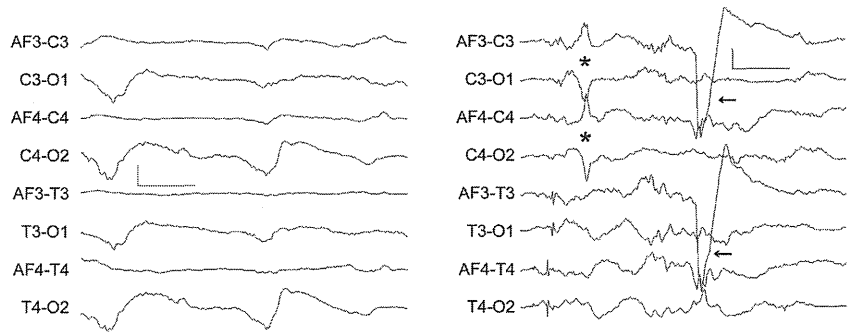

Fig. 1. Sample electroencephalograph (EEG) abnormalities. Left: Acute-stage EEG abnormalities (2 days of age, 29 weeks post-conceptional age). Relatively low voltage delta waves with amplitudes of 150–200 μV are observed, corresponding to mild acute-stage EEG abnormalities. Calibration 100 μV, 1 s. Right: Disorganized patterns (5 days of age, 32 weeks post-conceptional age). The delta wave shapes are deformed. Abnormal frontal sharp waves (arrows) and positive rolandic sharp waves (asterisks) are also evident; this corresponded to severe chronic-stage EEG abnormalities. Calibration 100 μV, 1 s.

Table 1
Grade of acute and chronic stage EEG abnormalities.

Acute stage EEG abnormalities	
Mild	Mildly decreased amplitudes [a] with preserved continuity
Moderate	Moderately decreased amplitudes [b] with decreased continuity [c]
Severe	No continuous patterns (burst suppression pattern)
Chronic stage EEG abnormalities	
Mild	Intermittent or continuous presence of disorganized patterns [d] without positive rolandic sharp waves
Severe	Continuous presence of disorganized patterns with positive rolandic sharp waves

[a] Mildly decreased amplitudes refer to delta waves of <200 microV before post-conceptional age of 30 weeks or <150 microV at post-conceptional age of 30–33 weeks.
[b] Moderately decreased amplitudes refer to delta waves of 20–50 microV.
[c] Decreased continuity refers to a continuous pattern occupying <10% of the entire record at post-conceptional age of < 30 weeks or < 30% of the entire record at post-conceptional age of 30–33 weeks.
[d] Disorganized patterns were diagnosed as present when deformed delta waves were observed with or without frontal and/or occipital sharp waves, positive rolandic sharp waves, and abnormal brushes.

Table 2
Clinical Characteristics of the infants.

	PVHI ($n = 22$)		PVL ($n = 49$)		
Gestational age (week)	26	(23–31)	29	(24–32)	$p < 0.001$
Birth weight (g)	787	(538–1240)	1428	(566–1992)	$p < 0.001$
Singleton	16	(73%)	37	(76%)	NS
Apgar score at 1 min	3	(1–7)	5	(1–9)	$p < 0.05$
Apgar score at 5 min	5	(1–9)	7	(1–10)	$p < 0.05$
Cesarean section	13	(59%)	42	(86%)	$p < 0.05$
PROM	3	(14%)	19	(39%)	$p < 0.05$
Clinical CAM	5	(23%)	6	(12%)	NS
Mechanical ventilation	22	(100.0%)	44	(90%)	NS
Initial pH	7.33	(7.09–7.52)	7.23	(7.10–7.56)	$p < 0.05$
Initial BE (mmol/l)	−6.0	(−12.8 to 0.9)	−6.5	(−13.6 to 0.8)	NS
Early neonatal death	9	(41%)	1	(2%)	$p < 0.001$

Numerical data are expressed by median (range).
PROM: premature rupture of membranes, CAM: chorioamnionitis, BE: base excess, NS: not significant.

and 15–28 in infants with PVHI. In contrast, moderate or severe ASAs were common on days 1–2 in infants with PVL.

3.5. Chronic-stage EEG abnormalities

CSA severity according to the timing of EEG recordings is shown in Fig. 2 (bottom). CSAs were uncommon in both groups on days 1–2. Thereafter, CSAs were frequent in infants with PVL; 20 (69%) of 29 on days 3–4, 45 (96%) of 47 on days 5–14, and 34 (97%) of 35 on days 15–28. In contrast, CSAs were infrequent in infants with PVHI; one (11%) of nine on days 3–4, five (28%) of 18 on days 5–14, and four (33%) of 12 on days 15–28. CSAs were more frequent in infants with PVL than in those with PVHI on days 3–4 ($p < 0.01$), 5–14 ($p < 0.001$), and 15–28 ($p < 0.001$). Severe CSAs were infrequent in infants with PVHI throughout the study period. In contrast, severe CSAs were seen in the majority of infants with PVL after days 3–4.

3.6. Comparison of PVHI and PVL

EEG before the first recognition of US abnormalities was normal in 13 (59%) infants with PVHI (Table 3). In contrast, the EEG was normal before the first recognition of US abnormalities only in 11 (22%) infants with PVL. Normal EEG before the first recognition of US abnormalities was more common in infants with PVHI than in those with PVL ($p < 0.01$). Deterioration of ASAs was observed in 11 (50%) of 22 infants with PVHI and in four (8%) of 49 infants with PVL. ASA deterioration was more frequent in infants with PVHI than in those with PVL ($p < 0.001$). The frequency of the most severe grade of ASA was not different between the two groups, whereas severe CSAs were more frequent in infants with PVL than in those with PVHI ($p < 0.001$). Early neonatal death was more frequent in infants with PVHI than in those with PVL. Severe ASA was recognized in all infants with PVHI who died during the neonatal period.

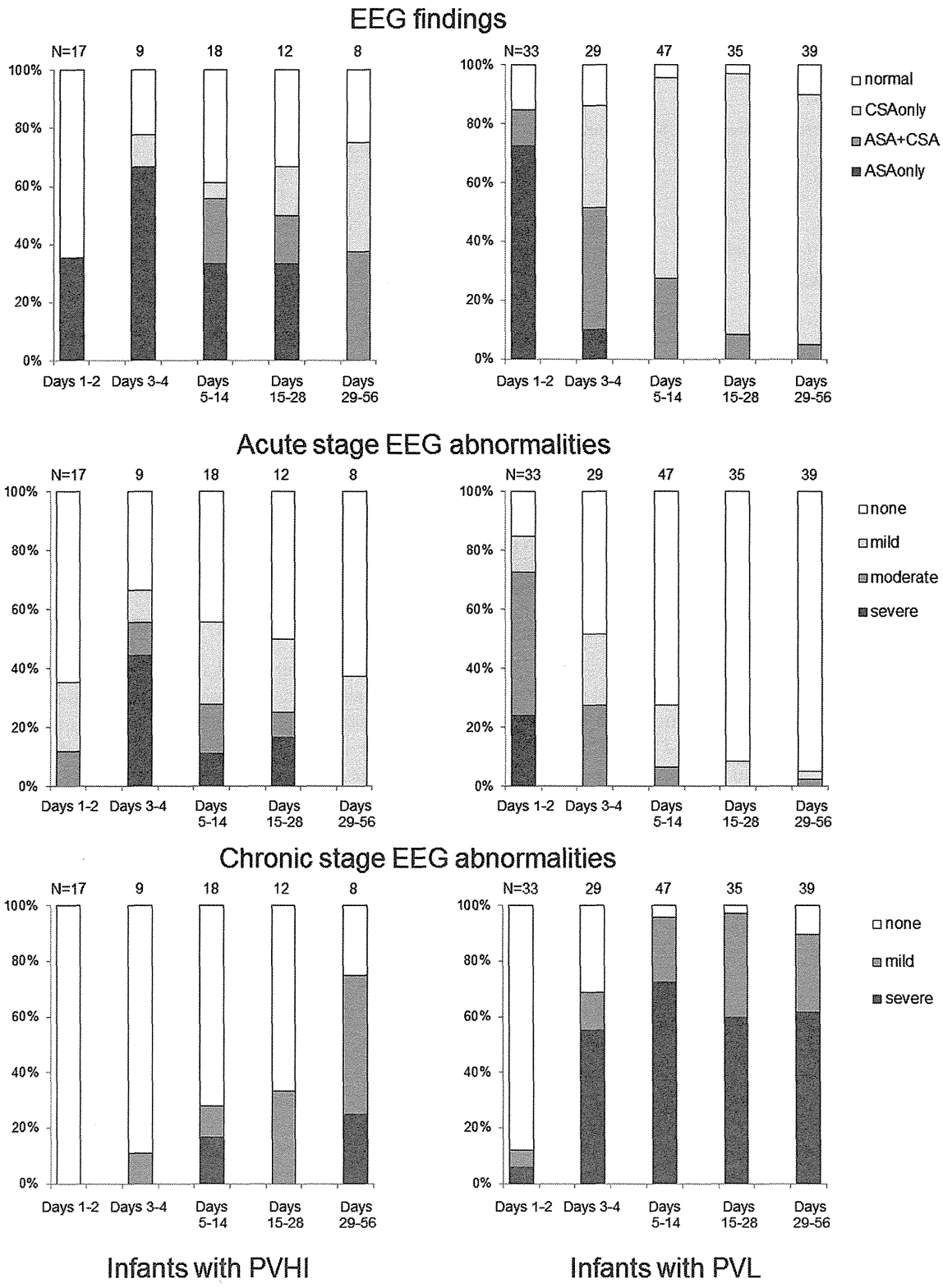

Fig. 2. Serial electroencephalograph (EEG) findings. The number above each bar indicates the number of infants in whom electroencephalogram was recorded during the period. The PVHI, periventricular hemorrhagic infarction; PVL, periventricular leukomalacia; ASA, acute stage EEG abnormality; CSA, chronic stage EEG abnormality.

Table 3
The comparison of EEG findings between PVHI and PVL.

	PVHI ($n = 22$)	PVL ($n = 49$)	
Date of the initial EEG (days)	1 (0–4)	1 (0–3)	NS
EEG findings before the first recognition of US abnormalities			
Normal	13 (59%)	11 (22%)	$p < 0.01$ [a]
ASAs only	8 (36%)	26 (53%)	
ASAs and CSAs	0	6 (12%)	
CSAs only	1 (5%)	6 (12%)	
Deterioration of ASAs after the initial EEG	11 (50%)	4 (8%)	$p < 0.001$
The most severe grade of ASAs			NS [b]
None	8 (36%)	13 (27%)	
Mild	3 (14%)	6 (12%)	
Moderate	4 (18%)	23 (47%)	
Severe	7 (32%)	7 (14%)	
The most severe grade of CSAs			
None	12 (54%)	0	$p < 0.001$ [c]
Mild	6 (27%)	14 (29%)	
Severe	4 (18%)	35 (71%)	

Data are expressed by median (range).
US: ultrasonographic, ASA: acute stage EEG abnormality, CSA: chronic stage EEG abnormality, NS: not significant.
[a] Comparing the rate of infants with normal EEG between two groups.
[b] Comparing the rate of infants with none or mild ASAs and those with moderate or severe ASAs.
[c] Comparing the rate of infants with none or mild CSAs and those with severe CSAs.

4. Discussion

This is the first report to compare neonatal EEG findings between infants with PVHI and those with PVL. The results clearly showed that serial EEG changes were different in infants with PVHI and those with PVL. In a majority of infants with PVHI, the EEG was normal before the first appearance of IPE. In contrast, the EEG before the first appearance of PVE was abnormal in most infants with PVL. These findings suggest that the timing of brain injury is quite different between infants with PVHI and those with PVL.

The timing of brain injury is presumed to be postnatal in the majority of infants with PVHI, based on serial EEG changes. This presumption is based on our results, as follows. EEGs before the appearance of IPE were normal in the majority of infants with PVHI. Even when EEG abnormalities were present, mild ASAs were common, and CSAs were not seen. These results strongly indicate that brain injury had not occurred in most infants with PVHI before the appearance of IPE. In contrast, ASA deterioration was recognized after the initial EEG in half of the infants with PVHI. On days 3–4 or later, ASAs was more frequent and severe in infants with PVHI than in those with PVL. These observations will suggest that brain injury occurred after the appearance of IPE.

The timing of brain injury is considered to be pre- or perinatal in most infants with PVL. EEGs were abnormal before the appearance of PVE in more than three-quarters of infants. EEGs on days 1–2 demonstrated moderate or severe ASAs in the majority of infants with PVL. Thereafter, the rate of ASAs was lower and their grade became milder with age. Deterioration of ASAs after the initial EEG was rare. These findings suggest that brain injury had occurred until birth in most infants with PVL. Several studies have indicated the contribution of prenatal factors to the development of PVL [15–18]. The results of our study are consistent with the hypothesis that PVL in preterm infants is closely related to several intrauterine factors, such as chorioamnionitis and premature rupture of the membranes.

The paucity of severe CSAs was remarkable in infants with PVHI throughout the study period, compared to those with PVL. This may be partly related to more frequent early neonatal deaths among infants with PVHI. All infants with PVHI who died during the neonatal period had severe ASAs. These infants may have died before CSAs appear on EEG. Among infants with PVL, the severity of CSAs correlates with that of ASAs [12]. The rate of CSAs in infants with PVHI may be underestimated by the lack of follow-up EEG in most severely affected ones.

The characteristics of infants with PVHI differed markedly from those of infants with PVL. Gestational age and birth weight were smaller in infants with PVHI than in those with PVL. The difference in gestational age between infants with PVHI and PVL was consistent with other reports [1], and was substantial. Therefore, comparisons of clinical variables between PVHI and PVL using gestational age-matched groups of infants will be difficult. The difference in gestational age

between infants with PVHI and PVL is related closely to the pathogenesis of brain injury. PVHI is closely related to prematurity, because more premature infants are more likely to have intraventricular hemorrhage, which often precedes PVHI, because of their less stable cardiorespiratory condition, itself a result of prematurity. The rate of infants treated with mechanical ventilation was not different between the groups, despite the higher Apgar scores in infants with PVL. This was consistent with our previous study, which revealed that infants with PVL often require mechanical ventilation, although their other physical condition parameters are not poor [19]. Respiratory distress in infants with PVL may be partly attributable to prenatal systemic stress. We also showed that infants with PVL have mild but significant oliguria and respiratory distress during the first 24 h of life [20].

The pathogenesis of brain injury in PVHI and PVL differs. PVHI is considered to be a venous infarction. A germinal matrix hemorrhage leads to obstruction of the terminal vein followed by impaired blood flow in the medullary veins. Periventricular venous congestion causes periventricular ischemia, which results in PVHI [21,22]. Although the pathogenesis of PVHI is complex, it is mainly attributed to the intrinsic fragility of the germinal matrix vasculature and a disturbance in the cerebral blood flow [23]. These problems are closely related to prematurity and can occur without antecedent brain insult. In contrast, PVL is related closely to arterial border zone infarction as well as the vulnerability of oligodendrocyte precursors. The arterial borders in the cerebral white matter are relatively distant from the periventricular region in preterm infants [24]. This region is vulnerable to injury in the presence of cerebral ischemia, resulting in PVL. Marked cerebral ischemia is presumed to have occurred before the appearance of US abnormalities. The difference in serial EEG findings between infants with PVHI and those with PVL is consistent with the different pathogenesis of these conditions.

The results of our study will provide insight into the prophylaxis of brain injury in preterm infants. Brain injury will be mild if present before the appearance of IPE in infants with PVHI. Thus, prophylaxis of intraventricular hemorrhage will be most important for the prevention of PVHI. Although the pathogenesis of intraventricular hemorrhage is multifactorial, stabilization of the cardiorespiratory state will be the key to prevention, whereas the timing of injury will be pre or perinatal in most infants with PVL. More attention should be paid to the general condition of the fetus, because postnatal treatment is less effective. Precise evaluation of fetal condition and determination of the appropriate time for delivery will facilitate a reduction in the number of infants with PVL.

In this study, we selected infants with relatively severe brain lesions to investigate typical clinical and serial EEG findings in PVHI and PVL. Eventually, the infants included in this study were biased towards a poor outcome, because all had spastic cerebral palsy. Thus, our results may not be applicable to infants with milder PVHI or PVL with no spastic cerebral palsy. For the same reason, infants with both PVHI and PVL were excluded, because the relationship between EEG findings and brain lesions in these patients is difficult to determine.

Some limitations to our study should be noted. First, the timing of EEG differed, although the date of the initial EEG was not different between infants with PVHI and those with PVL. We consider that the first EEG should be recorded within the first 24 h after birth to clarify the presence or absence of prenatal brain insult. However, this is not easy because the general condition of some infants who require intensive treatment is very poor, to the extent that EEG recording is not feasible. Secondly, some infants in our cohort showed no EEG abnormalities. There are two possible explanations. One is that ASA and/or CSA were missed, because the timing of EEG recordings was inappropriate. Continuous monitoring with amplitude-integrated EEG may solve this problem. The other reason may be that the brain insult was too mild to detect by EEG in such infants. This is a limitation of EEG interpretation. Thirdly, the subjects of this study excluded milder infants such as those with intraventricular hemorrhage without parenchymal involvement and those with noncystic PVL. The severity and timing of brain injury of infants with milder brain lesions may be different from those with PVHI or those with cystic PVL.

In conclusion, serial EEG changes and patient characteristics were different between infants with PVHI and those with PVL. PVHI brain injury is presumed to occur postnatally after the appearance of IPE among more premature infants. In contrast, PVL brain injury is presumed to occur *in utero* among less premature infants. Therefore, PVHI may be preventable with appropriate postnatal treatment, although PVL would likely not be preventable with similar measures. This information will reduce the occurrence of neurological sequelae in preterm infants.

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ORIGINAL ARTICLE

Prognostic factors of gastroesophageal reflux disease in congenital diaphragmatic hernia: a multicenter study

Keita Terui · Tomoaki Taguchi · Keiji Goishi · Masahiro Hayakawa · Yuko Tazuke · Akiko Yokoi · Hajime Takayasu · Hiroomi Okuyama · Hideo Yoshida · Noriaki Usui · The Japanese Congenital Diaphragmatic Hernia Study Group

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Abstract
Purpose Gastroesophageal reflux disease (GERD) is one of the concomitant problems in infants with congenital diaphragmatic hernia (CDH). We assessed risk factors of GERD in CDH patients.
Methods The retrospective observational study for CDH infants was conducted. Cases of CDH who were born between January 2006 and December 2010, were operated in the 9 participating institutions, and survived to discharge were included. Completion of medical therapy for GERD and incidence of surgery were primary outcomes. Kaplan–Meier survival analysis and Cox proportional hazards regression were used.
Results In 182 cases of CDH, the medical therapies for GERD were performed in 23.8 % (40/168), and were completed in 60.0 % (24/40). Prenatal detection of CDH (HR 5.87, CI 1.6–18.8, $p = 0.012$) and tube feeding at discharge (HR 5.04, 95 % CI 1.3–33.1, $p = 0.016$) were significantly correlated with unsuccessful weaning from medical therapy. Surgery for GERD was performed in 10.7 % (18/169). Gestational age (HR 4.78, 95 % CI 1.5–21.1, $p = 0.006$) and diaphragmatic defect of more than 75 % (HR 4.3, 95 % CI 1.6–12.9, $p = 0.005$) were significantly correlated with need for antireflux surgery.
Conclusion Diaphragmatic defect of more than 75 % was risk factor of future need for antireflux surgery.

Keywords Congenital diaphragmatic hernia · Gastroesophageal reflux · Diaphragm · Fundoplication · Long-term care

Introduction

Gastroesophageal reflux disease (GERD) is one of the concomitant problems in infants with congenital

K. Terui (✉) · H. Yoshida
Department of Pediatric Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuou-ku, Chiba 260-8677, Japan
e-mail: kta@cc.rim.or.jp

T. Taguchi
Department of Pediatric Surgery, Reproductive and Developmental Medicine, Graduate School of Medical Sciences, Kyushu University, Kyushu, Japan

K. Goishi
Division of Neonatology, Department of Maternal and Perinatal Medicine, National Center for Child Health and Development, Tokyo, Japan

M. Hayakawa
Division of Neonatology, Center for Maternal-Neonatal Care, Nagoya University Hospital, Nagoya, Japan

Y. Tazuke · N. Usui
Department of Pediatric Surgery, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

A. Yokoi
Department of Pediatric Surgery, Kobe Children's Hospital, Kobe, Japan

H. Takayasu
Department of Pediatric Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

H. Okuyama
Department of Pediatric Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

H. Okuyama
Department of Pediatric Surgery, Hyogo College of Medicine University, Hyogo, Japan

diaphragmatic hernia (CDH). Nearly 40 % of CDH survivors are thought to have symptomatic GERD [1]. Possible etiologies of GERD in CDH include abnormal hiatal anatomy at the gastro-esophageal junction, lack of an angle of His, herniation of the stomach into the chest and dilatation of the esophagus [2]. Treatment options for infantile GERD include lifestyle modifications, pharmacologic agents, and antireflux surgery. Surgical approaches are reserved for children who have intractable symptoms or who are at risk for life-threatening complications of GERD [3]. Historically, the risk of GERD in CDH is thought to have increased with improvement of the survival of severe CDH [4, 5]. Need for patch is one of risk factors of severe GERD which needs interventions [6–9], however, some have reported negative [10] or converse data [11] in pathological GERD. Indicators of severity of CDH, such as liver herniation [7], thoracic position of the stomach [9, 10], and time of diagnosis [10] were another risk factors reported to date. Meanwhile, Kamiyama et al. [11] reported that esophageal acid exposure was not influenced by severity of CDH based on detailed pH monitoring. Furthermore, Peetsold et al. [9] reported it was difficult to predict occurrence of GERD during long follow-up of CDH patients. Also, the natural history of GERD associated with CDH has not been clear yet. Bagolan and Morini reported that overall rate of surgery for GERD in CDH patients was 19 % based on the review of 21 literatures [12]. Abdullah et al. [13] reported 17 % of CDH cases underwent fundoplication according to the US database with a total of 2,173 cases of CDH. On the other hand, some reports have revealed that natural history of GERD associated with CDH has the tendency to resolve without surgery, as well as isolated GERD [9, 13, 14]. Hence, in CDH survivors, GERD cases who need antireflux surgery and the cases with the tendency to resolve without surgery are mixed. To choose appropriate treatments for infantile GERD, we have to know the characteristics of the cases which have no tendency to resolve without surgery. In this study, "the cases who have no tendency to resolve without surgery" was interpreted as "the cases with unsuccessful weaning from medical therapies" and "the cases with eventual need for surgery". By assessing these two factors, the natural history and the risk factors of GERD associated with CDH were discussed in the present study.

Materials and methods

Patient selection

This study was subsequent of a nationwide survey of neonatal CDH conducted by The Japanese Congenital Diaphragmatic Hernia Study Group in 2011 [15]. The subject of this retrospective cohort study was 674 CDH patients who were born between January 2006 and December 2010 in 109 institutions. In these, 444 CDH patients survived to discharge. Among these survivors, 182 cases who were treated in the 9 participating institutions were subject to this retrospective observational study. The 9 institutions were the high volume centers which belonged to The Japanese Congenital Diaphragmatic Hernia Study Group and declared intentions to participating in the study. Hence, inclusion criteria of this study were (1) CDH infants, (2) born between January 2006 and December 2010, (3) treated in 9 participating institutions, (4) survived to discharge. There were no exclusion criteria based on the side of hernia, associated anomalies, prenatally detection or ECMO use. Medical records during follow-up were retrospectively reviewed. The study was performed after being approved by the institutional ethics committee of Chiba University (No. 1647) and the independent ethics committees of 8 other participating institutions.

Data collection

We selected two primary outcomes; completion of medical therapy for GERD and incidence of antireflux surgery for GERD. In each institution, GERD was basically diagnosed by contrast study and pH monitoring with optional endoscopy. However, not the all patients underwent all these examinations mainly due to the policy of primary doctors. Operative indication of GERD was basically intractable symptoms including life-threatening complications of GERD, however, criterion of each case could not be confirmed. Furthermore, timing of surgery might be different between the participating institutions, and be on a case-by-case basis practically.

The patient demographics, including gender, gestational age, birth weight, Apgar score at 1 and 5 min, prenatal diagnosis, mode of delivery, and side of hernia were reviewed. Information about the severity of CDH including findings of liver herniation (prenatally detected herniation, occupying more than 1/3 of the thoracic space), position of the stomach, observed-to-expected lung area-to-head circumference ratio (o/e LHR), lung-to-thorax transverse area ratio (*L/T* ratio) [16], defect size of the diaphragm categorized into 4 groups (defect of <25 %, ≥ 25 and <75 %, ≥ 75 and <100 %, and agenesis), and the use of inhaled nitric oxide (iNO), extracorporeal membrane oxygenation (ECMO) or patch for closure were also reviewed. Home treatment including ventilatory support, oxygen administration, tracheotomy, tube feeding, or vasodilator administration at the time of hospital discharge, and evaluation of developmental delay at 1.5, 3 and 6 years of age were also reviewed.

Statistical analysis

The statistical analyses were performed using the JMP software program (v.9.02; SAS Inc., Cary, USA). The mean and standard deviation or median and interquartile range were used to describe continuous variables. Kaplan–Meier survival analysis and Cox proportional hazards regression were used for the analyses. Continuous data were divided in two groups by the median value. Chi-square test or Fisher's exact probability test were used for comparison. p values of <0.05 were considered statistically significant.

Results

Patient demographics

Table 1 shows patient demographics. In a total of 182 survivors, 156 cases (85.7 %) were diagnosed prenatally. Rate of left-sided herniation was 91.8 %. Cases with isolated CDH account for 92.9 %. Cases with liver-up, herniation of more than half of the stomach into the right chest, o/e LHR of less than 40, *L/T* ratio of less than 0.08, defect size of the diaphragm of more than 75 % were 27.0, 11.3, 70.9, 28.4 and 27.8 %, respectively. During therapies, iNO, ECMO, and patch for closure were used in 67.6, 5.5 and 37.8 %, respectively. Intact discharge which is defined as no home treatment including ventilatory support, oxygen administration, tracheotomy, tube feeding, or vasodilator administration at discharge, was seen in 144 cases (79.1 %). There was no death during the follow-up period.

Medical therapies for GERD

In 182 cases of CDH, the medical therapies for GERD were performed in 23.8 % (40/168) of CDH patients, and were completed in 60.0 % (24/40) during the period of survey (Fig. 1a). Median (range) age of completion was 288 (32–1,241) days of life. In the 40 cases with medical therapy for GERD, 13 cases (32.5 %) underwent antireflux surgery. In these, 7 cases (53.8 %) completed medical therapy after surgery. By the Kaplan–Meier survival analysis, the rate of unsuccessful weaning of medical therapies was significantly correlated with prenatal detection of CDH ($p < 0.0001$), diaphragmatic defect of more than 75 % ($p = 0.0270$), use of iNO ($p = 0.0101$), and tube feeding at discharge ($p = 0.0018$). In these factors, only prenatal detection of CDH [hazard ratio (HR) 5.87, 95 % confidence interval (CI) 1.6–18.8, $p = 0.0120$] and tube feeding (HR 5.04, 95 % CI 1.3–33.1, $p = 0.0164$) were significantly correlated with the rate of unsuccessful weaning of medical therapy by multivariable analysis (Table 2). Patients with prenatal detection tended to have worse indices about the severity of CDH compared to cases without prenatal detection; Apgar score at 5 min of <6 (48.7 vs 11.5 %, $p < 0.0001$), diaphragmatic defect of more than 75 % (31.4 vs 4.2 %, $p = 0.0055$) and patch closure (42.6 vs 8.0 %, $p < 0.0001$). These trends

Table 1 Patient demographics

Patient number	182
Gender (male)	99/182 (54.4 %)
Gestational age (day)	264.5 ± 12.2
Birth weight (g)	2,680 ± 473
Apgar score at 1 min	5 (1–9)
Apgar score at 5 min	6 (1–10)
Prenatal diagnosis	156/182 (85.7 %)
Cesarean section at delivery, (%)	111/182 (61.0 %)
Side of hernia (left)	167/182 (91.8 %)
Isolated CDH	169/182 (92.9 %)
Liver-up (%)	41/152 (27.0 %)
Herniation of more than half of the stomach into the right chest	17/150 (11.3 %)
o/e LHR <40	129/182 (70.9 %)
L/T ratio <0.08	29/102 (28.4 %)
Defect size of the diaphragm ≥75 %	50/180 (27.8 %)
Use of iNO	123/182 (67.6 %)
Use of ECMO	10/182 (5.5 %)
Use of patch for closure	68/180 (37.8 %)
Developmental delay, at 1.5 years of age	38/145 (26.2 %)
Developmental delay, at 3 years of age	28/127 (22.0 %)
Developmental delay, at 6 years of age	7/36 (19.4 %)
Ventilatory support at discharge	22/182 (12.1 %)
Oxygen administration at discharge	6/182 (3.3 %)
Tracheotomy at discharge	4/182 (2.2 %)
Tube feeding at discharge	21/182 (11.5 %)
Vasodilator administration at discharge	16/182 (8.8 %)

CDH congenital diaphragmatic hernia, *o/eLHR* observed-to-expected lung area-to-head circumference ratio, *L/T ratio* lung-to-thorax transverse area ratio, *iNO* inhaled nitric oxide, *ECMO* extracorporeal membrane oxygenation

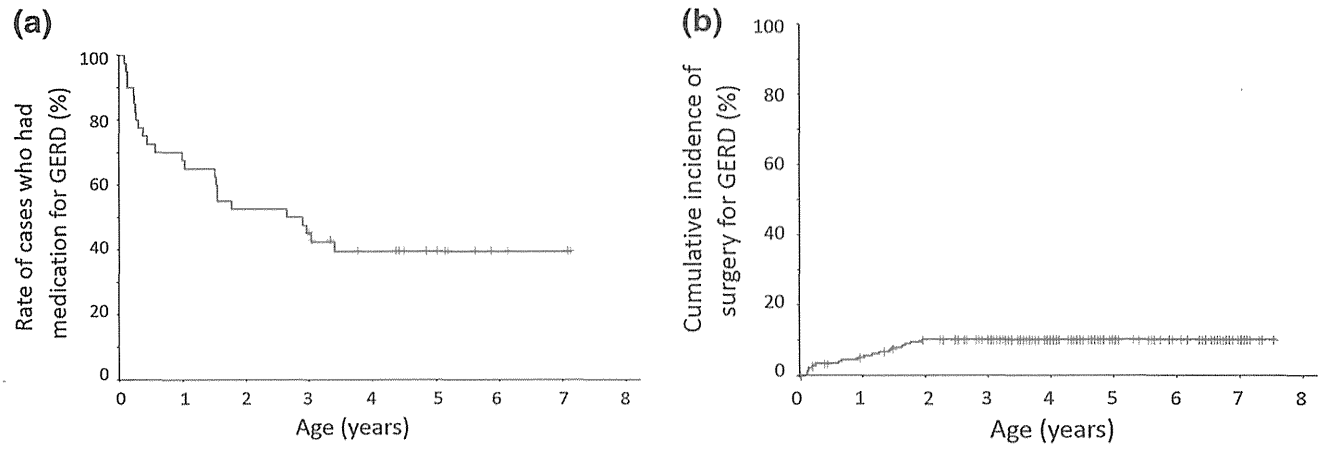

Fig. 1 **a** Kaplan–Meier curve of weaning from medical therapy for gastroesophageal reflux disease (GERD). *Longitudinal axis* represents the rate of the cases who had medication for GERD. In 40 cases, who had the medical therapies for GERD, 16 case (40.0 %) could not complete it during the period of survey. **b** Kaplan–Meier curve of incidence of antireflux surgery. *Longitudinal axis* represents the cumulative incidence of antireflux surgery. Antireflux surgery was performed eventually in 10.7 % of cases with congenital diaphragmatic hernia

Table 2 Univariate and multivariable analysis for the risk of unsuccessful weaning from medical therapy and the risk of future need of surgery for gastroesophageal reflux disease associated with congenital diaphragmatic hernia

	Univariate analysis	Multivariable analysis	
	p value	HR (95 % CI)	*p* value
The risk of unsuccessful weaning from medical therapy for GERD			
Prenatal diagnosis	<0.0001	5.9 (1.6–18.8)	0.0120
Diaphragmatic defect ≥75 %	0.0270	1.7 (0.6–5.3)	0.3104
Use of iNO	0.0101	2.5 (0.9–6.5)	0.0749
Tube feeding at discharge	0.0018	5.0 (1.3–33.1)	0.0164
The risk of future need of surgery for GERD			
GA, >265 day	0.0400	4.8 (1.5–21.1)	0.0063
Apgar score at 5 min, <6	0.0135	1.8 (0.6–6.1)	0.2818
Diaphragmatic defect ≥75 %	0.0006	4.3 (1.6–12.9)	0.0051

GERD gastroesophageal reflux disease, *iNO* inhaled nitric oxide, *HR* hazard ratio, *CI* confidence interval, *GA* gestational age

were not seen in patients with/without tube feeding at discharge. Instead, patients with tube feeding at discharge tended to have developmental delay during follow-up (at 3 years of age, 61.5 vs 17.5 %, $p = 0.0013$), while overall incidence of developmental delay was 26.2 %. Furthermore, the rate of antireflux surgery in patients with/without developmental delay was 25.0 and 6.1 %, respectively ($p = 0.008$).

The effects of the institutional biases on weaning from medical therapy for GERD were assessed. Rate of completion of the medical therapy in the institutions of high rate of prenatal diagnosis (94.4–100.0 %, in 4 institutions) and that of low rate (74.1–80.0 %, in 5) were 11.4 and 9.6 %, respectively ($p = 0.7002$). Similarly, rate of completion of the medical therapy in the institutions of high rate of tube feeding (20.8–30.8 %, in 3 institutions) and that of low rate (0–11.1 %, in 6) were 50.0 and 66.7 %, respectively ($p = 0.2918$).

Surgery for GERD

The rate of surgery for GERD was 10.7 % (18/169) of CDH survivors. Median (range) age at the surgery was 359 (42–710) days of life (Fig. 1b). By the Kaplan–Meier survival analysis, the rate of surgery was significantly correlated with gestational age over 265 days (median value) ($p = 0.0040$), liver herniation ($p = 0.0035$), herniation of more than half of the stomach into the right chest ($p < 0.0001$), the lung-to-thorax transverse area ratio less than 0.08 ($p = 0.0160$), Apgar score at 5 min less than 6 ($p = 0.0135$), diaphragmatic defect of more than 25 % ($p = 0.0359$), more than 75 % ($p = 0.0006$) (Fig. 2) and agenesis ($p = 0.0172$), and developmental delay at 3 years of age ($p = 0.0032$). Multivariable analysis was conducted for the only factors which satisfy both statistical significance ($p < 0.05$) and low missing value (<15 %), because too many factors had statistical significance. Accordingly, gestational age (HR 4.78, 95 % CI 1.5–21.1, $p = 0.0063$) and diaphragmatic defect of more than 75 % (HR 4.3, 95 % CI 1.6–12.9, $p = 0.0051$) were significantly correlated with the rate of surgery (Table 2). In the 50 cases with diaphragmatic defect of more than 75 %, 16 cases

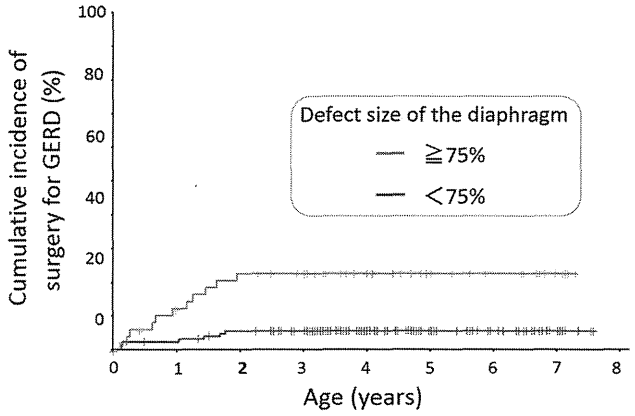

Fig. 2 Kaplan–Meier curve of incidence of antireflux surgery between the cases with diaphragmatic defect of ≥75 and <75 %. Longitudinal axis represents the cumulative incidence of antireflux surgery. Incidence of surgery was significantly higher in the cases with diaphragmatic defect of ≥75 % ($p = 0.0006$)

(32.0 %) actually had surgery (11 cases) or medication for longer than 3 years (9 cases, data overlap).

The institutional bias of gestational age was assessed, as follows. Median rate of patients with gestational age of >265 day in each institution was 48.1 %. Incidences of antireflux surgery in the institutions of extremely high rate of gestational age of >265 day (67.9 and 82.9 %, in 2 institutions) and that of extremely low rate (29.2 and 38.9 %, in 2) were 23.2 and 2.5 %, respectively ($p = 0.0046$).

Discussion

Gastroesophageal reflux disease associated with CDH is one of the considerable problems. Although the rate of GERD in CDH patients varies according to study designs, nearly 40 % of CDH survivors are thought to have symptomatic GERD, and half of them require antireflux surgery [1]. Meanwhile, some reports have revealed that natural history of GERD associated with CDH has the tendency to resolve without surgery, as well as isolated GERD [9, 14, 15]. In this study, 11 % of total cases underwent surgery by the age of 2 years, while 60 % of patients who had medical therapies for GERD completed it by the age of 3 years. In CDH survivors, GERD cases who need antireflux surgery and the cases with the tendency to resolve without surgery were mixed. Therefore, we purposed to know the natural history and the risk factors of GERD associated with CDH in the present study.

The multivariable analysis showed that the risk factors of unsuccessful weaning from medical therapies were prenatal detection of CDH and tube feeding at discharge. Because prenatal diagnosis was associated with severity of CDH including defect size of the diaphragm, patients with prenatal diagnosis might have severer GERD, resulting in long duration of medication for GERD. Tube feeding at discharge is usually used for not only the cases with severe GERD, but also the cases with difficulty in oral feeding due to developmental problems. Both of 2 factors might have influenced on long duration of medication for GERD, because patients with tube feeding at discharge actually tended to have developmental delay.

The other multivariable analysis shows that the risk factors of future need of antireflux surgery are gestational age of >265 day and diaphragmatic defect of more than 75 %. Institutional bias might be one of the possible interpretation that long gestational age is linked the necessity of antireflux surgery, because antireflux surgery was performed more frequently in the institutions which had higher rate of patients of gestational age of >265 day. Large diaphragmatic defect seems to be the reasonable and specific risk factor of future need for surgery, and consistent with the previous reports [7, 8]. And, it is basically consistent with the result that prenatal diagnosis is linked the duration of medical therapy for GERD, because patients with prenatal diagnosis tended to have large diaphragmatic defect. Meanwhile, tube feeding at discharge was the specific risk factor for medical therapy for GERD, possibly affected by the factor of developmental delay.

The merit of the present study is that we assessed the risk of severe GERD in CDH by the method which can evaluate the data on the time course using Cox regression model. By conducting this study, useful data for selecting the therapeutic strategies for GERD in CDH should be obtained. As a result, patients with the large diaphragmatic defect are associated with severe GERD. These data lead us to think of the additional antireflux surgery at the first operation for CDH. The same concept had been postulated since early 1990s [4], but is still controversial. The multicenter retrospective study conducted by French group showed a significant relationship between prophylactic fundoplication performed during initial diaphragmatic repair and survival without disordered growth [17]. They concluded that prophylactic fundoplication can prevent growth disorder in infants with CDH requiring a patch repair. However, randomized controlled study conducted by Maier et al. [18] revealed that there was no significant difference of GERD symptoms and development of body weight in the first 2 years between cases with regular hernia closure and cases with additional fundoplication at hernia repair. They concluded that simultaneous fundoplication at the time of primary CDH repair cannot be recommended in all patients with CDH. Because this prospective study involved all the left-sided CDH patients with various severities, usefulness of prophylactic fundoplication for limited cases with some risk factors is still

unclear. In the present study, the cases with diaphragmatic defect of more than 75 % were proposed as the risk factor of future need of antireflux surgery. But, only 32.0 % of patients with this risk factor actually had antireflux surgery or medication of longer than 3 years. Further studies are still needed to discuss about the pros and cons of prophylactic fundoplication.

The most considerable limitation of this study is that strategies for both CDH and GERD were not unified; all the factors including diagnostic method of GERD, severity of GERD, type of drugs used, the indication, and the procedure of antireflux surgery. This means that all the results were possibly influenced by each institutional policy. These limitations resulted from our study design to collect as much patients as possible by multicenter study. To elucidate the risk of GERD in CDH, the present study will need to be supported by further studies. However, the biases which this study contains should be avoided in the future. Hence, further studies should be designed to treat the patients prospectively. Otherwise, at least unifying the diagnostic criteria of GERD is needed in retrospective studies.

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Conflict of interest The authors declare that they have no conflicts of interest.

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Original Article

Outcome of congenital diaphragmatic hernia with indication for Fontan procedure

Nobuko Shiono,[1] Noboru Inamura,[1] Shigehiro Takahashi,[4] Kouji Nagata,[6] Yuji Fujino,[2] Masahiro Hayakawa,[7] Noriaki Usui,[3] Hiroomi Okuyama,[8] Yutaka Kanamori,[5] Tomoaki Taguchi[6] and Hisanori Minakami[9]

[1]*Department of Pediatric Cardiology, Osaka Medical Center and Research Institute for Maternal and Child Health,* [2]*Intensive Care Unit, Osaka University Hospital,* [3]*Department of Pediatric Surgery, Osaka University, Graduate School of Medicine, Osaka,* [4]*Division of Neonatology, Department of Maternal and Perinatal Medicine,* [5]*Division of Surgery, Department of Surgical Subspecialties, National Center for Child Health and Development, Tokyo,* [6]*Department of Pediatric Surgery, Reproductive and Developmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka,* [7]*Department of Maternal and Perinatal Care Center, Nagoya University Hospital, Nagoya,* [8]*Department of Pediatric Surgery, Hyogo College of Medicine University, Hyogo and* [9]*Department of Obstetrics and Gynecology Hokkaido University Graduate School of Medicine, Sapporo, Japan*

Abstract ***Background***: The aim of this study was to clarify the outcome of patients with cardiovascular malformation (CVM) among those with congenital diaphragmatic hernia (CDH) who are indicated for the Fontan procedure.

Methods: The subjects included 76 CDH patients with CVM recruited from a national survey of 614 CDH patients. The outcomes were evaluated between two groups divided according to indication for the Fontan procedure. Patients with functional univentricular disease were considered to be candidates for the Fontan procedure.

Results: Sixteen (21.1%) of the 76 patients were candidates for the Fontan procedure, accounting for 2.6% of all 614 patients with CDH. None of these patients, however, underwent the Fontan procedure. Among the 16 patients, the absence of obstruction of the left ventricular outflow tract (LVOTO) was significantly associated with better 90 day survival (71.4%, 5/7, for those without LVOTO vs 0.0%, 0/9, for those with LVOTO, $P = 0.0007$). After excluding 22 patients with chromosomal and/or genetic abnormalities or syndromes, the 90 day survival rate was significantly better in neonates without than with indication for the Fontan procedure (62.5%, 25/40 vs 28.6%, 4/14, $P = 0.0271$).

Conclusions: Patients with indications for the Fontan procedure are rare, and the outcome of patients with LVOTO among those with CDH is especially poor.

Key words cardiovascular malformation, congenital diaphragmatic hernia, Fontan procedure, national survey.

The Fontan procedure is a surgical procedure used to treat tricuspid atresia, devised by Fontan in 1971. It is a special technique that directly connects the pulmonary artery to the systemic venous system. Strict indications, called "Fontan's ten commandments", have been proposed to identify patients who are eligible to undergo this procedure.[1] The indications have been widened, however, to include patients with single ventricles (SV) and hypoplastic left hearts in addition to tricuspid atresia due to modifications of the procedure.[2]

Congenital diaphragmatic hernia (CDH) is a severe disease causing pulmonary hypoplasia due to impaction of the abdominal organs in the thoracic cavity, twisting of the heart to the intact side and compression of the lungs on both the intact and affected sides.[3] In Japan, the survival rate of patients with CDH alone surpasses 80%,[4] but the outcome of CDH patients with cardiovascular malformations (CVM) is poor.[5] Although it is generally thought that the outcome of patients with both CDH and CVM, such as functional SV, is especially poor, attempts to improve these outcomes have been made,[5–7] and Japanese physicians appear to be active in the treatment of such patients. The effects of treatment on the outcome of CDH patients with CVM who are potential candidates for the Fontan procedure, however, remain to be studied.

The aim of this study was therefore to clarify the prevalence and outcomes of patients with CVM among those with CDH who are indicated for the Fontan procedure.

Methods

This study was conducted after obtaining the approval of the independent ethics committees of our institution (approval number of 468) and five other institutions. The data obtained from 72 facilities that consented to a questionnaire survey targeted to 159 facilities, including facilities authorized by the

Correspondence: Nobuko Shiono, MD, Department of Pediatric Cardiology, Osaka Medical Center and Research Institute for Maternal and Child Health, 840 Murodo-cho, Izumi, Osaka 594-1101, Japan. Email: salt0226@yahoo.co.jp

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Japanese Society of Pediatric Surgeons, education-related facilities and Centers for Maternal, Fetal and Neonatal Medicine, in 2011 were retrospectively evaluated. There were 614 patients with CDH born between 2006 and 2010. The overall profiles of the 614 patients have been previously described.[4] A total of 108 (17.6%) of the 614 patients had CVM.[4] In this study, 76 CDH patients with CVM were evaluated after excluding 32 patients, including 21 patients with a patent ductus arteriosus (PDA) alone, six patients with both PDA and atrial septal defect (ASD), three patients with ASD alone, one patient with mild pulmonary valvular stenosis and ASD and one patient with a right-sided aortic arch.[5] Therefore, the 76 study subjects accounted for 12.5% of the 614 CDH patients.[5]

Type of cardiac disease, patient respiratory status, treatment(s) used for CDH and outcome were evaluated by dividing the 76 subjects into two groups: those with and those without indications for the Fontan procedure (Fontan and non-Fontan candidates, respectively). The primary indication for the Fontan procedure was univentricular disease. For example, patients with SV, hypoplastic left heart syndrome (HLHS) or pulmonary atresia, in addition to those with tricuspid atresia, were considered to be typical candidates for the Fontan procedure.

In an analysis of the association between type of cardiac disease and outcome, the patients were classified into four subgroups based on cardiac morphology: patients with left ventricular outflow tract obstruction (LVOTO), patients with right ventricular outflow obstruction (RVOTO), patients with pulmonary venous obstruction (PVO) and patients with PDA-dependent disease. The therapeutic strategy was classified as either positive or palliative.

Statistical analysis was done using chi-squared test, two-sample *t*-test and Wilcoxon test, as appropriate. The level of significance was set at $P < 0.05$.

Results

Of the 76 CDH patients with CVM, 16 and 60 were considered to be eligible or not eligible for the Fontan procedure, respectively (Table 1). None of the 16 patients, however, underwent the Fontan procedure. Among the patients with CVM in the Fontan candidate (FC) group, HLHS and SV were noted in seven (44%) and six (38%) patients, respectively (Fig. 1; Table 2). In the non-Fontan (non-FC) candidate group, the following CVM were noted: ventricular septal defect (VSD) in 25 patients (41%), tetralogy of Fallot/double outlet right ventricles accompanied by RVOTO (TOF/DORV with RVOTO) in 12 (20%) and DORV without RVOTO in eight patients (13%).

No significant differences were noted in Apgar score, number of patients with prenatal diagnosis of CDH, gestational age at birth, birthweight, side of CDH or the presence of chromosomal or genetic abnormalities between the FC and non-FC groups (Table 1). Surgery for CDH was performed in 63% of the patients in the non-FC group and in 38% of the patients in the FC group ($P = 0.064$). The frequency of postnatal use of extracorporeal membrane oxygenation (ECMO) did not differ significantly between the two groups. The highest PaO_2 was significantly lower and the lowest $PaCO_2$ and the lowest oxygen index (OI) were significantly higher in the FC group than in the non-FC group. Neither the rate of survival >90 days (31.3% in the FC group vs 46.7% in the non-FC group) or 2 years nor the rate of intact discharge differed between the two groups. After excluding 22 patients (two in the FC-group and 20 in the non-FC group) with chromosomal and/or genetic abnormalities or syndromes, however, the surgical rate of CDH in the non-FC group increased from 63.3% (38/60) to 75.0% (30/40), which was significantly higher than that of the 35.7% (5/14) observed in the FC group ($P = 0.0091$; Table 2). The rates of 90 day

Table 1 Subject clinical characteristics ($n = 76$)

		FC group ($n = 16$) n (%) or mean ± SD	Non-FC group ($n = 60$) n (%) or mean ± SD	P
Characteristics	Apgar score at 1 min (0–5)	12 (92.3)	46 (85.2)	0.4740
	Apgar score at 5 min (0–5)	9 (75.0)	34 (65.4)	0.5150
	Left-sided CDH	13 (81.2)	55 (91.7)	0.3150
	Prenatal diagnosis for CDH	14 (87.5)	48 (80.0)	0.4760
	Gestational age (weeks)	36.0 ± 0.5	36.7 ± 0.3	0.3020
	Birthweight (g)	2235 ± 149	2294 ± 77	0.7240
	Chromosomal or genetic abnormalities, syndromes	2 (12.5)	20 (33.3)	0.0820
Operation	Surgical repair of CDH	6 (37.5)	38 (63.3)	0.0640
Respiratory status after birth	Use of ECMO	2 (12.5)	3 (5)	0.3180
	Highest PaO_2 (mmHg)	53.0 ± 41.9	113.7 ± 101.3	0.0484*
	Lowest $PaCO_2$ (mmHg)	71.9 ± 11.4	43.5 ± 5.7	0.0291*
	Lowest OI	44.2 ± 6.4	23.6 ± 3.1	0.0056*
Outcome	90 day survival	5 (31.3)	28 (46.7)	0.2603
	2 year survival	2 (12.5)	12 (20.0)	0.4759
	Intact discharge rate	1 (6.3)	12 (20.0)	0.1550

*$P < 0.0.5$. CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; FC, candidates for the Fontan procedure; intact discharge, discharge without tracheostomy, oxygen, mechanical ventilation, parenteral nutrition or drugs (e.g. pulmonary vasculature dilators); non-FC, not candidates for the Fontan procedure; OI, oxygenation index.

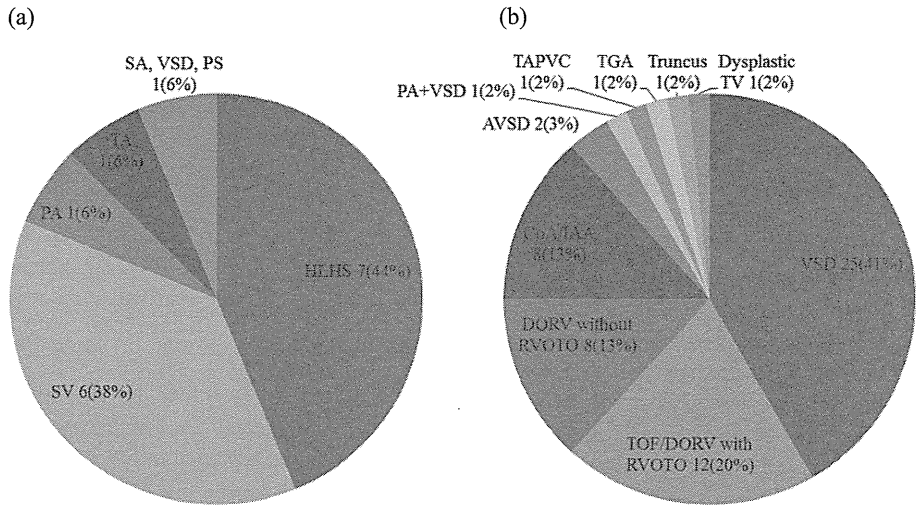

Fig. 1 Cardiovascular malformations in (a) 16 congenital diaphragmatic hernia (CDH) patients with indication for the Fontan procedure and (b) 60 CDH patients without indications for the Fontan procedure. AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; PA, pulmonary atresia; PS, pulmonary stenosis; RVOTO, right ventricle outlet obstruction; SA, single atrium; SV, single ventricle; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

survival, 2 year survival and intact discharge increased considerably to 62.5% (25/40), 27.5% (11/40) and 27.5% (11/40), respectively, in the non-FC group, although they did not change in the FC group (to 28.6%, 4/14; 14.3%, 2/14; and 7.1%, 1/14, respectively). Therefore, the differences in outcome with respect to 90 day survival rate (28.6%, 4/14 vs 62.5%, 25/40, $P = 0.0271$) became marked and significant after excluding 22 patients with chromosomal and/or genetic abnormalities or syndromes (Table 2).

The details of each patient in the FC group are given in Table 3. CDH was right-sided in three patients, one of whom had situs inversus viscerum. Complications other than CVM were noted in five patients: corpus callosum agenesis in two, Fryns syndrome in one, 18 trisomy in one and situs inversus viscerum in one. In these five patients, a positive therapeutic approach was chosen, except in the patient with Fryns syndrome. Two patients underwent ECMO without successful results. CDH was treated surgically in six patients, two of whom survived for 2 years. Palliative surgery for CVM was performed in four patients, including the use of the Glenn procedure in one patient (patient 14) who died 5 months after operation. The remaining three patients underwent shunting surgery only.

All of the five patients who survived >90 days underwent radical surgery for CDH, and the two patients who had long-term survival both underwent radical surgery for CDH and palliative surgery for CVM.

Table 2 Subjects without genetic abnormalities ($n = 54$)

		FC group ($n = 14$) n (%) or mean ± SD	Non-FC group ($n = 40$) n (%) or mean ± SD	P
Characteristics	Apgar score at 1 min (0–5)	10 (90.9)	28 (80.0)	0.3780
	Apgar score at 5 min (0–5)	7 (70.0)	20 (58.8)	0.5183
	Left sided CDH	12 (85.7)	38 (95.0)	0.2370
	Prenatal diagnosis for CDH	12 (85.7)	31 (77.5)	0.4990
	Gestational age (weeks)	35.8 ± 2.3	36.9 ± 2.5	0.1816
	Birthweight (g)	2234 ± 486	2434 ± 570	0.3742
Operation	Surgical repair of CDH	5 (35.7)	30 (75.0)	0.0091*
Respiratory status	Use of ECMO	2 (14.3)	2 (5)	0.2829
after birth	Highest PaO_2 (mmHg)	55.7 ± 42.8	138.0 ± 114.4	0.0276*
	Lowest $PaCO_2$ (mmHg)	61.1 ± 37.8	43.2 ± 41.7	0.0869
	Lowest OI	41.8 ± 24.1	19.5 ± 14.9	0.0047*
Outcome	90 day survival	4 (28.6)	25 (62.5)	0.0271*
	2 year survival	2 (14.3)	11 (27.5)	0.3005
	Intact discharge rate	1 (7.1)	12 (30.0)	0.0601

*$P < 0.0.5$. CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; FC, candidates for the Fontan procedure; intact discharge, discharge without tracheostomy, oxygen, mechanical ventilation, parenteral nutrition or drugs (e.g. pulmonary vasculature dilators); non-FC, not candidates for the Fontan procedure; OI, oxygenation index.