新生兒期餵食困難對早產兒兩歲時不同神經發展預後的影響

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摘 要

有新生兒期餵食困難的早產兒，將來有高風險會發生神經發展障礙。不同類型的神經發展障礙所需要的治療策略不同，而且及早介入效果較佳。因此若能預測有餵食困難的早產兒將來較易發生的神經發展障礙類型，將有助於制定追蹤治療策略。本研究探討新生兒期餵食困難對早產兒兩歲時的認知、語言和動作發展預後的影響。我們回顧了在 2011 年至 2018 年出生、胎齡<34 週、出生後即住入奇美醫院新生兒加護病房早產兒的病歷，並排除有腦部病變的個案。有餵食困難的早產兒為病例組，而沒有餵食困難的早產兒為對照組，並依照胎齡、出生體重、性別和出生年份與病例組配對。我們記錄兩組在住院期間的基本資料及疾病，以及在兩歲追蹤時的貝氏嬰幼兒發展測驗評估結果。我們一共納入 102 名早產兒，病例組有 34 名，對照組有 68 名。與對照組相比，病例組有支氣管肺發育不良的發生率較高（61.8% vs. 33.8%），住院時間也更長（94.2 天 vs. 73.8 天）。在兩歲時，病例組的平均發展分數低於對照組，也有較高的比率發生認知（25.0% vs. 6.0%）、語言（28.1% vs. 13.4%）和動作（21.9% vs. 6.0%）發展遲緩。經校正其他可能會影響神經發展預後的因子後，新生兒期餵食困難對兩歲時發生認知發展遲緩有顯著影響。我們得到的結論是，有新生兒期餵食困難的早產兒在兩歲時出現神經發展障礙的風險很高，尤其是認知發展遲緩。針對此高風險的發展障礙類型早期制定介入策略，將有助於改善有餵食困難早產兒的神經發展預後。

關鍵詞：餵食困難、神經發展預後、早產兒

Effects of Neonatal Feeding Difficulties on Different Neurodevelopmental Outcomes of Preterm Infants at Age 2 Years

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Abstract

Preterm infants with neonatal feeding difficulties are at high risk of neurodevelopmental disabilities. Early predicting the major type of disability is critical for timely intervention strategies and follow-up programs. This retrospective study investigated the impact of neonatal feeding difficulties on cognitive, language and motor outcomes in preterm infants at age 2 years. The medical records of preterm infants born at gestational age < 34 weeks between 2011 and 2018 and admitted to a medical center after birth were reviewed, and infants with brain lesions were excluded. Infants with feeding difficulties were identified as the case group, while infants without feeding difficulties in the control group were matched with gestational age, birth weight, sex, and birth year. The neurodevelopmental outcomes at age 2 years were assessed with the Bayley Scales of Infant Development-III. A

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total of 102 infants were enrolled, including 34 case and 68 control infants. Compared to the control infants, the case infants had significantly higher rates of bronchopulmonary dysplasia (61.8% vs. 33.8%) and longer duration of hospital stay (94.2 vs. 73.8 days). At age 2 years, the case group had lower mean developmental scores than the control group, with higher rates of delay in cognitive (25.0% vs. 6.0%), language (28.1% vs. 13.4%) and motor (21.9% vs. 6.0%) development. After adjusting for confounders, neonatal feeding difficulties significantly contributed to cognitive delay at age 2 years. In conclusion, preterm infants with neonatal feeding difficulties are at high risk of neurodevelopmental impairment at age 2 years, particularly cognitive delay. Early intervention targeted at the specific deficit may help improve neurodevelopmental outcomes in preterm infants.

Keywords: Feeding difficulties, Neurodevelopmental outcomes, Preterm infants

I. Introduction

The survival of very-low-birth-weight (< 1500 gm) preterm infants has increased over the past decades as neonatal intensive care evolves, especially those born at gestational age (GA) < 32 weeks [1]. Infants with lower GA have higher risks of survival with neurodevelopmental disabilities in childhood, such as cognitive impairment, language delay or cerebral palsy [2]. Early prediction of neurodevelopmental outcomes is critical for starting intervention therapy at early ages to achieve better effects [3], and infants with disabilities in cognitive, language and motor development need different therapeutic strategies.

Feeding behavior is primary expression of brain function in newborn infants. Efficient and safe feeding requires the coordination of sucking, swallowing and respiration, and oral feeding function matures during an average gestation of 34-36 weeks [4]. Infants who fail to achieve the essential skills needed for full oral feeding by post-conceptional age (PCA) 37 weeks are regarded as having feeding difficulties, which require for professional evaluation and therapy [5]. Preterm infants have higher rates of feeding difficulties than term-birth infants [6], and several studies have found that preterm infants with neonatal feeding difficulties have increased risks of neurodevelopmental disabilities [7–13].

Although feeding difficulties may serve as an early predictor of adverse neurodevelopmental outcomes in preterm infants, there are some limitations or unresolved issues in previous studies. First, premature infants with feeding difficulties often have several co-morbidities such as brain injury and bronchopulmonary dysplasia (BPD), which may increase the risks of not only feeding difficulties in the neonatal period but also neurodevelopmental impairment in childhood [14–15]. Most studies did not exclude infants with brain lesions [7,11–12] or adjust co-morbidities of feeding difficulties [7–10], therefore it remains unclear whether feeding difficulties independently affect neurodevelopmental outcomes of preterm infants. Second, infants with neurodevelopmental disabilities may not appear developmentally delayed early in life until age 1.5-2 years [16–17], when more complex function and skills are required to meet daily demands or pass a developmental test, and developmental problems can be reliably diagnosed by age 2 years [18–20]. Most studies assessed neurodevelopmental outcomes at age 6-12 months [7–8,10–11], which might have changes with increased ages. Third, previous studies reported outcomes of developmental delay without classification of cognitive, language or motor development [7–10], or did not investigate what kind of development was mainly affected [11–13], which is crucial for developing intervention strategies. Cognitive programs focus on inspiring self-learning competence and supporting positive parent-child relationship; language programs create an interactive environment to promote linguistic communication through symbolic play; while motor training aims to facilitate self-initiated movements and postural control [21].

From retrospective review of the medical records in a medical center, this case-control study investigated the effects of neonatal feeding difficulties on cognitive, language and motor developmental outcomes at age 2 years

in preterm infants without brain lesions.

II. Patients and Methods

1. Study participants

This retrospective study reviewed the medical records of very-low-birth-weight preterm infants who were born at GA <34 weeks and admitted to the neonatal intensive care unit of Chi Mei Medical Center between 2011 and 2018. Infants who failed to achieve full oral feeding by PCA 37 weeks were evaluated by a speech-language pathologist, and received oral-motor interventions according to the patterns of feeding dysfunction. The infants with feeding difficulties were identified as the case group, and each case was matched with two control infants without feeding difficulties by GA, birth weights, sex and birth years. The medical complications during hospital stay and developmental scores at outpatient follow-up visits were collected. Infants with congenital brain anomalies, chromosomal abnormalities or severe brain injury were excluded. The Institutional Review Board in Chi Mei Medical Center approved this study.

2. Collection of potential predictors

In the prenatal period, low maternal education level was defined as less than high school, and antepartum complications such as preeclampsia and chorioamnionitis were identified. In the neonatal period, major neonatal morbidities which included severe brain injury [22], sepsis, necrotizing enterocolitis (NEC) [23], retinopathy of prematurity (ROP) [24], and BPD [25], were determined.

3. Neurodevelopmental outcome assessment

The outpatient records of follow-up visits at a mean corrected age of 2 years were reviewed. Neurodevelopmental outcomes were assessed using the Bayley Scales of Infant Development – Third Edition (BSID-III), which include 3 composite scores – cognitive, language, and motor scales, with a mean score of 100 points and one standard deviation of 15 points [26]. Significant (moderate or severe) delay in cognitive, language, and motor development were defined as a cognitive, language, and motor composite score < 85, respectively [27,28]. The BSID-III scores of the enrolled infants were collected.

4. Statistical analyses

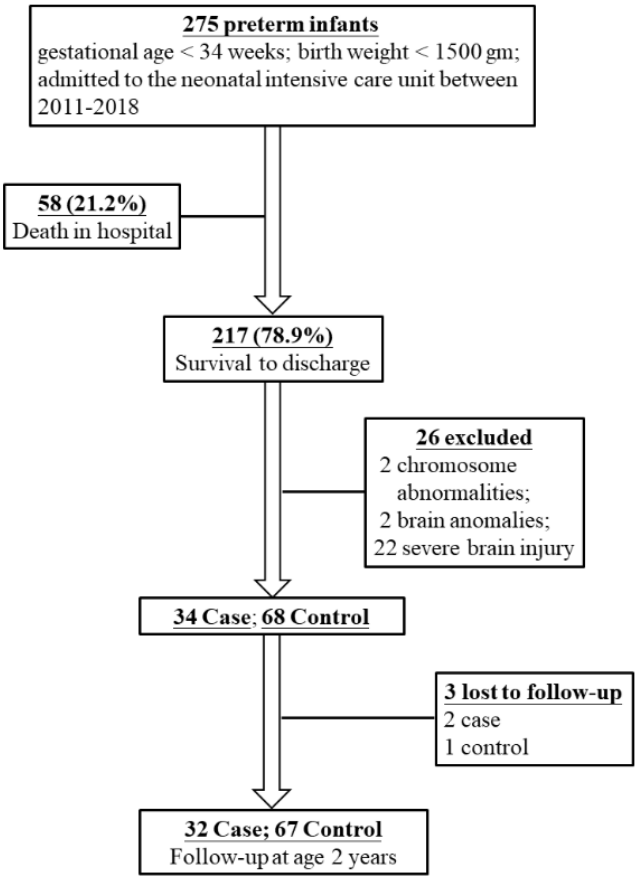
The differences in the medical complications and neurodevelopmental outcomes between the case and control group were compared by χ^2 analysis or t test. Binary logistic regression models were conducted to examine the relationship between feeding difficulties and significant delay in cognitive, language and motor development, respectively. Potential predictors of developmental delay in univariable analyses were fitted into a multivariable model, with computed odds ratios (OR) and 95% confidence intervals (CI). All analyses were performed using the SAS v9.4 statistical software.

III. Results

A total of 275 infants' medical records were reviewed, and 58 (21.2%) infants died during hospital stay. After excluding 26 infants with severe brain injury or congenital abnormalities, 34 cases with feeding difficulties and 68 controls were identified among the 217 infants who survived to discharge. One control and two case infants were lost to follow-up after discharge, and the remaining 99 infants had data of neurodevelopmental assessment at age 2 years **(Figure 1)**.

Figure 1

Flow chart illustrating the number of preterm infants recruited in this study.



In the perinatal period, there were no significant differences between the case and control group in the rates of low maternal education, preeclampsia, chorioamnionitis and delivery by cesarean section, and the two groups of infants did not differ in the mean GA and birth weights. In the neonatal period, the case and control infants had no significant differences in the occurrence of major neonatal morbidities, except for higher incidence of BPD in the case group (61.8% vs. 33.8%, p=0.009). Compared to the control infants, the case infants had longer duration of hospital stay (mean 94.2 vs. 73.8 days, p=0.035) with older PCA at discharge (mean 41.6 vs. 38.6 weeks, p=0.007) **(Table 1)**.

Table 1

Characteristics of the case and control group in the preterm infants

	Case group (n = 34)	Control group (n = 68)	χ 2 (df), p value	t, p value
Maternal characteristics				
Low maternal education, n (%)	19 (55.9)	29 (42.6)	3.143 (1), 0.076	-
Preeclampsia, n (%)	3 (8.8)	9 (13.2)	0.425 (1), 0.514	-
Chorioamnionitis, n (%)	4 (11.8)	6 (8.8)	0.222 (1), 0.638	-
Cesarean section, n (%)	20 (58.8)	44 (64.7)	0.336 (1), 0.562	-

(continued)

	Case group (n = 34)	Control group (n = 68)	χ 2 (df), p value	t, p value
Infant characteristics				
GA, mean (SD), week	28.1 (2.8)	28.0 (2.6)	-	-1.60, 0.873
Birth weight, mean (SD), gm	1067.4 (259.1)	1077.7 (256.4)	-	0.191, 0.849
Male, n (%)	18 (52.9)	36 (52.9)	0.327 (1), 1.000	-
Sepsis, n (%)	10 (29.4)	22 (32.4)	0.122 (1), 0.727	-
NEC, n (%)	13 (38.2)	17 (25.0)	1.787 (1), 0.181	-
ROP, n (%)	4 (11.8)	6 (8.8)	0.178 (1), 0.673	-
BPD, n (%)	21 (61.8)	23 (33.8)	6.906 (1), 0.009	-
Hospital stay, mean (SD), day	94.2 (50.6)	73.8 (28.9)	-	-2.178, 0.035
PCA at discharge, mean (SD), week	41.6 (6.0)	38.6 (2.5)	-	-2.836, 0.007

SD, standard deviation; GA, gestational age; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia; PCA, post-conceptional age

At the mean corrected age of 2 years, the case group had lower mean developmental scores than the control group in all the three domains, including cognitive (87.3 vs. 95.0), language (86.7 vs. 94.6) and motor (88.7 vs. 99.2), with higher rates of significant delay in cognitive (25.0 vs. 6.0%), language (28.1 vs. 13.4%) and motor (21.9 vs. 6.0%) development **(Table 2)**. We further examined potential predictors of significant developmental delay in univariable models which included maternal and infant factors. The results showed that feeding difficulties and BPD exerted prognostic contribution to cognitive, language and motor delay **(Table 3)**. Infants with feeding difficulties had the highest odds of cognitive delay (OR 6.20, 95% CI 2.67-9.79; $p < 0.01$), followed by motor delay (5.01, 1.34-8.78; $p < 0.05$) and language delay (3.22, 1.11-6.02; $p < 0.05$). The effects of feeding difficulties on different types of developmental delay were further determined in the multivariable models. After adjusting for social and medical factors, feeding difficulties significantly contributed to cognitive delay (adjusted OR 4.84, 95% CI 1.26-7.55, $p < 0.05$) rather than language (2.54, 0.83-5.79) and motor delay (3.68, 0.93-6.56) **(Table 4).**

Table 2

Neurodevelopmental outcomes of the case and control group at age 2 years

BSID-III	Case group (n = 32)	Control group (n = 67)	p value
Composite score, mean (SD)			
Cognitive	87.3 (12.7)	95.0 (9.3)	0.001
Language	86.7 (13.9)	94.6 (9.1)	0.008
Motor	88.7 (18.2)	99.2 (12.8)	0.002
Significant delay (<85), n (%)			
Cognitive	8 (25.0)	4 (6.0)	0.005
Language	9 (28.1)	9 (13.4)	0.041
Motor	7 (21.9)	4 (6.0)	0.016

BSID-III, Bayley Scales of Infant Development – Third Edition

Table 3

Potential predictors of significant developmental delay in the preterm infants at age 2 years

	Cognitive delay (n = 12)		Language delay (n = 18)		Motor delay (n = 11)	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Maternal factors						
Low maternal education	9 (75.0)	2.00 (0.50-4.96)	13 (72.2)	1.77 (0.57-5.49)	7 (63.6)	1.04 (0.28-3.85)
Preeclampsia	1 (8.3)	0.59 (0.07-5.00)	2 (11.1)	0.83 (0.16-4.14)	1 (9.1)	0.67 (0.08-5.78)
Chorioamnionitis	1 (8.3)	0.74 (0.09-6.40)	3 (16.7)	1.97 (0.46-8.52)	1 (9.1)	0.84 (0.10-7.39)
Infant factors						
Feeding difficulties	8 (66.7)	6.20 (2.67-9.79)[b]	9 (50.0)	3.22 (1.11-6.02)[a]	7 (63.6)	5.01 (1.34-8.78)[a]
Sepsis	4 (33.3)	1.06 (0.29-3.83)	8 (44.4)	2.06 (0.71-5.92)	4 (36.4)	1.21 (0.33-4.48)
NEC	5 (41.7)	1.92 (0.55-6.67)	8 (44.4)	2.53 (0.87-7.39)	6 (54.5)	3.60 (0.99-9.02)
ROP	3 (25.0)	2.78 (0.49-4.88)	3 (16.7)	3.00 (0.64-5.72)	2 (18.2)	2.85 (0.50-5.30)
BPD	9 (75.0)	5.38 (1.35-9.45)[a]	13 (72.2)	5.20 (1.67-8.22)[b]	9 (81.8)	7.69 (1.56-10.92)[a]

OR, odds ratio; CI, confidence interval; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia. [a]$p<0.05$; [b]$p<0.01$.

Table 4

Effect of neonatal feeding difficulties on different types of developmental delay at age 2 years in logistic regression models

	Odds ratio (95% confidence interval)		
Case vs. control	**Cognitive delay**	**Language delay**	**Motor delay**
Unadjusted	6.20 (2.67-9.79)[a]	3.22 (1.11-6.02)[a]	5.01 (1.34-8.78)[a]
Adjusted*	4.84 (1.26-7.55)[a]	2.54 (0.83-5.79)	3.68 (0.93-6.56)

*adjusted for low maternal education, preeclampsia, chorioamnionitis, sepsis, necrotizing enterocolitis, retinopathy of prematurity and bronchopulmonary dysplasia. [a]$p< 0.05$.

IV. Discussion

This case-control study investigated the impact of feeding difficulties on 2-year neurodevelopmental outcomes in preterm infants without congenital abnormalities or severe brain injury. We found that the case infants with feeding difficulties had higher rates of BPD and longer duration of hospital stay than the control infants. At age 2 years, the case infants had lower mean developmental scores than the control infants, with higher rates of delay in cognitive, language and motor development. Neonatal feeding difficulties significantly contributed to cognitive delay after adjusting for confounding factors.

Infants' and children's development is affected by medical and sociodemographic factors [16,29]. Preterm infants with feeding difficulties often suffered from several morbidities in neonatal intensive care units, such as severe brain injury, BPD and NEC [14], which not only adversely impact feeding endurance, swallowing abilities and tolerance to enteral nutrition, but also contribute to poor neurodevelopmental outcomes [15]. After discharge from hospital, the home environment and mother-infant interaction play increasingly crucial roles in infants' development, and preterm infants of high-educated mothers had better outcomes [16–17]. When evaluating the independent effect of oral feeding ability on neurodevelopmental outcomes, studies that did not exclude or adjust potential confounding factors of infants' development might lead to biases in results [7–12]. Our study excluded infants with brain lesions and matched the background data of the case and control infants by GA, birth weight

and sex, all of which were strongly related to neurodevelopmental outcomes [30]. After adjusting for confounding variables, we demonstrated that neonatal feeding difficulties remained significant on contribution to cognitive outcome at age 2 years in preterm infants.

Infants' behavioral organization reflects the function of the central nervous system which integrates the autonomic, motor, communication, attention or interactive, and regulatory systems [31]. Feeding and sucking behaviors in newborn infants are one of the earliest manifestations of neurological control, which may involve cognitive, language and motor development later in life [32]. Premature infants achieve full oral feeding ability approximately by PCA 36 weeks [4,6], and persistent feeding difficulties up to PCA 37-50 weeks were associated with adverse neurodevelopmental outcomes [7–13]. Among the previous studies investigating neonatal feeding difficulties, cognitive and psychomotor outcomes assessed with BSID-II were reported in studies recruiting preterm infants born in the 2000s [7–10], while studies in the 2010s added language outcomes assessed with BSID-III [11–13]. These studies did not explore the main type of disability associated with feeding difficulties. Another study reported that feeding dysfunction at age 18-22 months had concurrent correlations with lower cognitive and language scores in preterm infants [33]. Our study found neonatal feeding difficulties could serve as an early predictor for cognitive impairment rather than language or motor delay, which may help develop early intervention and follow-up programs for high-risk premature infants.

V. Strengths and limitations

Using a case-control design and adjusting for potential confounding variables, this study demonstrated the independent effects of neonatal feeding difficulties on cognitive, language and motor developmental outcomes in preterm infants without brain lesions. The small sample size in our study may cause less precise estimates of disability risks. Some factors that may affect cognitive development, such as home environment, parenting and family structure, were not available from medical records in this study. The generalizability of our findings may be validated by multi-center collaborative research involving a larger preterm cohort with long-term outcomes at preschool or school ages.

VI. Conclusions

Preterm infants with neonatal feeding difficulties have high risk of neurodevelopmental impairment at age 2 years, particularly cognitive delay. Early intervention targeted at the specific deficit may help improve neurodevelopmental outcomes of preterm infants with feeding difficulties.

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Abbreviations

BPD bronchopulmonary dysplasia
BSID Bayley Scales of Infant Development
CI confidence interval
GA gestational age
NEC necrotizing enterocolitis
OR odds ratio
PCA post-conceptional age
ROP retinopathy of prematurity