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Impact of feeding mode on neurodevelopmental outcome in infants and children with congenital heart disease

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Abstract

Objective: To investigate the impact of feeding mode on neurodevelopmental outcomes in children with congenital heart defects.

Design: A retrospective cohort study of 208 children with congenital heart disease (CHD), who had surgery from 1 January 2013 until 31 December 2016 at Texas Children's Hospital, Houston, TX, US.

Settings: University Hospital, Developmental Outcome Clinic.

Outcomes measures: Standardized cognitive scores were assessed with Capute Scales and motor development with Revised Gesell Developmental Schedules. We analyzed anthropometrics, mode of feeding, surgical complexity, syndrome, and gender as predictors of developmental outcomes at four time points: hospital discharge, and 6, 12, and 24 months of age.

Results: Mode of feeding is associated with neurodevelopmental outcome in children with CHD. Children on enteral feeding tubes had significantly lower developmental quotient (DQ) scores in cognition, communication, and motor function at 12 and 24 months compared to orally fed children. There were greater proportions of developmental delays (DQ < 70) in enteral tube fed children at the 6, 12, and 24 months visits. Further, there was a strong association between presence of enteral feeding tube, syndrome, and developmental outcome. Greater surgical complexity, weight gain and ethnicity were not associated with the developmental outcomes.

Conclusions: Our findings suggest that the presence of an enteral feeding tube following corrective congenital heart surgery are at increased risk of neurodevelopmental delays at 12 and 24 months.

KEYWORDS

cardiac, congenital heart defect, developmental impairment, feeding mode, heart surgery, infants, neurodevelopmental outcome

1 | INTRODUCTION

The overall outcomes for infants undergoing surgery for congenital heart disease (CHD) have improved significantly over the past two decades, with increased long-term survival and less major morbidity.[1] The focus has, therefore, shifted to defining outcomes according to the quality of survival rather than according to mortality alone. We, and others, have demonstrated that up to one half of the survivors of infant cardiac surgery have neurodevelopmental impairment, an incidence that is markedly higher than the healthy population without CHD.[2-4] Thus, developmental assessments are now performed more frequently to provide insight into the presence and magnitude of neurodevelopmental impairment, and to optimize the timing and quality of early interventions.[5,6] The etiology of neurodevelopmental impairment is multifactorial but is at least in part related to modifiable clinical risk factors.[1]

There is a known association between poor oral feeding and/or the need for enteral tube feeding, and neurodevelopmental impairment in preterm neonates.[7,8] Growth failure and poor weight gain affect up to 60% of children with CHD, and this can be due to a number of factors including ongoing heart failure, gastroesophageal reflux, impaired absorption or motility, poor oro-motor control, and swallowing dysfunction, as well as more significant neurological injury.[9] In order to optimize nutrition to overcome many of these potential risk factors for poor growth, enteral tube feeding with either a nasogastric (NG) or a gastric tube (GT) is often used as a short- or long-term solution.[9] Accordingly, there has been an increasing interest in the association between mode of feeding on nutrition-related factors such as growth trajectory and reduced neurodevelopmental performance during the first year of life.[5,10]

The aim of this study was to investigate the association between mode of feeding and growth and neurodevelopmental trajectories in a cohort of children who underwent surgery for CHD during early infancy and underwent routine neurodevelopmental assessments in our Cardiac Developmental Outcomes Program (CDOP) Clinic on two or more occasions during the first two years of life.

2 | METHODS

This was retrospective single center cohort study that was approved by the Institutional Review Board (IRB) of Baylor College of Medicine. The Texas Children's Hospital (TCH) CDOP Clinic was established in 2013 and offers routine serial neurodevelopmental assessments for all patients undergoing cardiac surgery during the first three months of life by a team of dedicated developmental pediatricians and neuropsychologists. Eligible patients are identified prior to hospital discharge after their index operation and are seen in clinic at around six months of age, and every six months for the first two years of life. Patient data including anthropometrics, mode of feeding, and neurodevelopmental assessments are recorded from each CDOP clinic visit in a prospective, IRB-approved research database.

To be eligible for inclusion in this study, patients had to fulfill all of the following criteria: surgery for CHD during the first three months of life between 1 January 2013 and 31 December 2016, two or more developmental assessments in the CDOP clinic during the first two years of life and weight and height documented at each visit. Patients were excluded from the analysis if they had major neurological injury. We identified 208 CDOP clinic attendees who fulfilled inclusion criteria.

Study data were collected from the Electronic Medical Record (EPIC) and the CDOP database. Gender, height, and weight at birth, gestational age, ethnicity, surgical complexity (STAT score), presence of a known syndrome, and hospital length of stay were collected from the index admission. Weight, height, and mode of feeding (oral, NG or GT) were recorded at hospital discharge and at CDOP clinic visits that were scheduled at approximately 6, 12, and 24 months of age. Actual ages at each clinic visit were variable (4 to 9 months for the first visit; 10-17 months for the 12-month visit; and 18-30 months for the 24- month visit), secondary to clinic availability, family circumstances, ill health, and/or hospitalization. Thus, all anthropometric measurements and developmental data were scaled and categorized according to the patient's actual age. Neurodevelopmental assessments were performed as follows: the Capute Scales and the Revised Gesell Developmental Schedules (for gross motor) were used as assessment tools for the 6-, 12-, and 24-months' visits. Three domains: Cognitive Adaptive Test (CAT), Clinical Linguistic and Auditory Milestone Scale (CLAMS), and Gross Motor skills were measured on two subscales and an overall developmental quotient (DQ) was calculated for each domain.[11,12] The CLAMS is used to assess receptive and expressive language, while the CAT assesses nonverbal visual-motor problem-solving and fine motor abilities. Anthropometric measures were used to calculate z-scores for weight, height, and age. Developmental outcomes were classified as "Normal" within 1 SD of the mean or higher (DQ ≥ 85), at "Risk" between 1 and 2 SD below the mean (DQ = 70-84) and as "Delayed" if their score was >2 SD below the mean (DQ < 70).[13]

Patients were stratified according to worst feeding mode from hospital discharge to the first clinic visit at around six months of age.

3 | STATISTICAL ANALYSES

Patient and clinical characteristics were summarized using means with standard deviation (SD) for normally distributed data and median with interquartile range (IQR) for non-normally distributed data. The summary statistics were stratified by feeding mode and compared using two-sample *t* test, Wilcoxon rank sum test, Fisher's exact test, or Chi-square test. Linear mixed models regression was used to assess growth over time and CAT, CLAMS, and Motor DQ's over time. Linear regression for the 6-, 12-, and 24-month visits with CAT, CLAMS, and motor DQ's as the outcome and the average change in weight *Z*-score for a six-month

TABLE 1 Demographics by feeding status at discharge/6 months

Variable		Oral (*n* = 173)	Tube (*n* = 35)	*P* value
Birth weight, kg Mean (SD)		3.06 (0.62)	2.94 (0.62)	.266
Hospital LOS, days Median (IQR)		23 (16.37)	52 (30.87)	<.001
Gestation, weeks Median (IQR)		38 (37.39)	38 (37.39)	.444
Gender, *N* (%)	Male	97 (56.1)	18 (51.4)	.710
	Female	76 (43.9)	17 (48.6)	
Ethnicity, *N* (%)	Hispanic/Latino	73 (42.2)	15 (42.9)	1.000
	Other	100 (57.8)	20 (57.1)	
STAT[a], *N* (%)	1-3	68 (41.0)	7 (21.2)	.048
	4-5	98 (59.0)	26 (78.8)	
Syndrome[a] *N* (%)	Yes	32 (19.3)	14 (42.4)	.006
	No	134 (80.7)	19 (57.6)	

Abbreviations: LOS, length of stay; STAT, **S**ociety of **T**horacic Surgeons—European **A**ssociation for Cardio-**T**horacic Surgery; Tube, NG or G-tube.
[a]Data available on 199 patients: 166 oral and 33 tube fed.

increase as the predictor. Multivariable analyses were performed using linear regression and included variables during the initial hospital stay. If data with discharge feeding method were missing, the worst route between discharge and six months was used with G-tube being the worst feeding method. All patients needed at least two visits at the CDOP clinic in the first two years of life. If a patient is missing a visit, the linear mixed models utilize all available visits. All other analyses only use complete data. A *P* value of <.05 was considered statistically significant. Analyses performed using Stata v 15.1 (Stata Corp, College Station, TX, USA).

4 | RESULTS

The two hundred and eight children were identified to have visited the CDOP clinic on at least two occasions during the two-year follow-up period. Of these, 193 infants were seen for a 6-month visit, 191 were seen for a 12-month visit, and 156 children were seen for a 24-month visit.

Of the 208 children included in this cohort, 35 (17%) had tube feeding within the first six months of hospital discharge. The remainder was fully orally fed. Infant characteristics (gender, ethnicity,

TABLE 2 DQ scores and growth measurements by feeding status (2 groups)

	Oral	Tube	
Variable	Median (IQR)	Median (IQR)	*P* value
Weight at birth	−0.63 (−1.27, −0.01)	−.88 (−1.37, −0.10)	.273
Change in weight per 6 mo (12 mo)	−0.02 (−0.20, 0.22)	−.17 (−0.41, −0.09)	.004
Change in weight per 6 mo (24 mo)	−0.01 (−0.27, 0.34)	−0.26 (−0.58, 0.08)	.003
Height (6 mo)	−0.28 (−1.24, 0.28)	−1.38 (−2.08,.0.73)	<.001
Height (12 mo)	−0.37 (−1.29, 0.37)	−1.1 (−1.85, −0.52)	.004
Height (24 mo)	−0.23 (−1.02, 0.41)	−1.27 (−1.95, 0.74)	<.001
CAT (6 mo)	114 (104, 127)	101 (87, 114)	.002
CAT (12 mo)	101.5 (95, 110)	91 (81, 102)	<.001
CAT (24 mo)	102 (89, 110)	79 (74, 97)	<.001
CLAMS (6 mo)	100 (89, 112)	96 (75, 104)	.197
CLAMS (12 mo)	93 (84, 102)	82 (66, 95)	.001
CLAMS (24 mo)	95 (75, 107)	68.1 (53, 88)	.002
Motor (6 mo)	83 (75, 94)	57 (43, 75)	<.001
Motor (12 mo)	87 (77.5, 96)	65 (55, 83)	<.001
Motor (24 mo)	91 (85, 97)	83.5 (63, 93.5)	.007

Note: Weight and height are presented in *z*-scores for age.

TABLE 3 DQ scores grouped into subgroups; delayed, at risk and normal by two feeding groups at 6, 12, and 24 months

Variable	Visit time (months)	Test result[a]	Oral *N* (%)	Tube *N* (%)	*P* value
CAT DQ	6	Delayed	5 (3.1)	5 (17.2)	.009
		At risk	7 (4.3)	2 (6.9)	
		Normal	151 (92.6)	22 (75.9)	
	12	Delayed	2 (1.3)	4 (13.8)	<.001
		At risk	11 (6.9)	7 (24.1)	
		Normal	147 (91.9)	18 (62.1)	
	24	Delayed	4 (4.6)	4 (21.1)	<.001
		At risk	12 (13.8)	8 (42.1)	
		Normal	71 (81.6)	7 (36.8)	
CLAMS DQ	6	Delayed	7 (4.3)	6 (20.7)	.013
		At risk	22 (13.5)	3 (10.3)	
		Normal	134 (82.2)	20 (69.0)	
	12	Delayed	8 (5.0)	10 (34.5)	<.001
		At risk	38 (23.6)	6 (20.7)	
		Normal	115 (71.4)	13 (44.8)	
	24	Delayed	16 (18.6)	10 (55.6)	.006
		At risk	15 (17.4)	2 (11.1)	
		Normal	55 (64.0)	6 (33.3)	
Motor DQ	6	Delayed	36 (22.4)	20 (69.0)	<.001
		At risk	61 (37.9)	7 (24.1)	
		Normal	64 (39.8)	2 (6.9)	
	12	Delayed	19 (11.9)	16 (53.3)	<.001
		At risk	52 (32.5)	8 (26.7)	
		Normal	89 (55.6)	6 (20.0)	
	24	Delayed	7 (7.7)	6 (30.0)	.005
		At risk	17 (18.7)	6 (30.0)	
		Normal	67 (73.6)	8 (40.0)	

[a]Normal scores (DQ > 85), Scores at risk (DQ 70-85), Delayed scores (DQ < 70).

and gestational age at birth) in the two groups were similar (Table 1). Tube-fed infants were more likely to have a syndrome (P = .006), higher STAT category of surgical complexity (P = .048), and a longer hospital length of stay (P < .001). Birth weight was similar in the two groups, but tube-fed infants had a significantly lower weight gain at 12 and 24 months of age (Table 2). Height was significantly lower in the tube-fed group compared to the orally fed group at 6, 12, and 24 months (Table 2).

Developmental outcomes were compared between two groups at 6, 12, and 24 months. Tube-fed infants had lower cognition (CAT) and Motor DQ scores at 6, 12, and 24 months and lower CLAMS scores at 12 and 24 months compared to orally fed children (Table 2).

Linear mixed models showed overall trends for all children (independent of feeding mode) that CAT and CLAMS DQ's decreased by 4.69 (−5.47, −3.91) and 2.93 (−3.86, −1.99), respectively, for every six months and Motor DQ's increased by 4.18 (2.93, 5.43) for every six months (data not shown). Having a NG or GT was associated with significantly lower CAT, CLAMS, and Motor DQ's[8,13,17] compared to the orally fed children (data not shown).

The distributions of DQ scores were grouped into three subcategories: delayed, at risk, and normal and according to mode of feeding. Tube-fed children were more frequently diagnosed with developmental delay in all domains at all visits compared to those who were orally fed (Table 3).

Multivariable linear regression identified a strong relationship between the need for tube feeds and lower DQ scores. Tube-fed children had significantly decreased scores in CAT (−11.96 points), CLAMS (−12.29 points) and Motor (−13.79 points) after adjusting for weight gain, gender, ethnicity, syndrome, and STAT category at 12 and 24 months (Table 4). The presence of a syndrome was associated with decreased DQ scores in all three developmental tests, whereas ethnicity and a high STAT category were not at 12 and 24 months. A change in weight was not associated with CAT, CLAMS, or MOTOR DQ scores at 12 months (Table 4), whereas a change in weight at 24

TABLE 4 Multivariable linear regression for CAT, CLAMS, and Motor-adjusted model at 12 (upper part) and 24 months (lower part).

	CAT (*n* = 172)			CLAMS (*n* = 173)			Motor (*n* = 174)		
Variables	***β***	**(95% CI)**	***P* value**	***β***	**(95%CI)**	***P* value**	***β***	**(95%CI)**	***P* value**
Change in weight for 6 mo Inc.	2.00	(−5.38, 9.38)	.593	−3.44	(−12.02, 5.15)	.430	7.66	(−0.32, 15.65)	.060
Tube	−11.96	(−18.34, −5.57)	<0.001	−12.29	(−19.72, −4.86)	.001	−13.79	(−20.63, −6.94)	<0.001
Female	5.42	(0.98, 9.85)	.017	4.20	(−0.95, 9.34)	.109	3.61	(−1.17, 8.38)	.138
Non-Hispanic	.73	(−3.71, 5.18)	.745	.41	(−4.75, 5.57)	.875	.92	(−3.86, 5.70)	.705
Syndrome	−11.16	(−16.68, −5.68)	<0.001	−13.59	(−20.00, −7.19)	<0.001	−9.41	(−15.32, −3.50)	.002
High STAT	−.64	(−5.28, 3.99)	.785	.66	(−4.72, 6.03)	.809	1.79	(−3.21, 6.79)	.480
Constant	101.62	(96.45, 106.78)	<0.001	94.81	(88.89, 100.74)	.000	84.71	(79.20, 90.22)	.001
	CAT (*n* = 101)			**CLAMS (*n* = 99)**			**Motor (*n* = 105)**		
	β	**(95% CI)**	***P* value**	***β***	**(95%CI)**	***P* value**	***β***	**(95%CI)**	***P* value**
Change in weight for 6 mo. Inc.	−9.53	(−17.43, −1.62)	.019	−10.0	(−20.69, 0.69)	.066	−0.81	(−9.63, 8.00)	.855
Tube	−18.40	(−28.00, −8.79)	<0.001	−21.29	(−34.52, −8.04)	.002	−12.77	(−23.73, −1.80)	.023
Female	10.20	(3.08, 17.32)	.005	9.06	(−0.55, 18.67)	.064	7.60	(−0.37, 15.58)	.062
Non-Hispanic	5.65	(−1.59, 12.89)	.125	9.55	(−0.23, 19.34)	.056	3.98	(−4.09, 12.04)	.331
Syndrome	−12.76	(−20.91, −4.61)	.002	−12.54	(−23.59, −1.49)	.027	−13.50	(−22.61, −4.38)	.004
High STAT	−.87	(−8.16, 6.43)	.814	−2.09	(−11.90, 7.73)	.674	.99	(−7.27, 9.26)	.812
Constant	94.80	(86.30, 103.29)	<0.001	87.34	(75.94, 98.74)	<0.001	88.85	(79.27, 98.43)	<0.001

months was associated with decreased CAT and CLAMS scores, but not Motor scores (Table 4).

5 | DISCUSSION

This is the first report analyzing the influence of feeding modes, growth trajectory, and neurodevelopment in children with CHD up to two years of age. This study identified that enteral tube feeding in infants and young children with early cardiac surgery is associated with impaired neurodevelopmental impairment in early childhood as evidenced by lower cognitive, linguistic, and motor scores at the two-year assessment compared to those exclusively orally fed. Our findings of better developmental scores at all visits in the orally fed group is consistent with a report by Mussatto et al that identified the ability to achieve full oral feeding is one of the most important factors associated with developmental outcome.[10]

Previous studies have shown that enteral tube feeding is associated with immature feeding skills and suboptimal brain development.[5,7] Distinguishing between these two factors in our study is challenging and is likely related. In fact, one might speculate that subtle pre-existing or perioperative neurologic impairment might be more commonly present in those discharged with tube feeds. The need for tube feeding is an indicator of the infant's health status including neurological status and a more complex medical history. Non-modifiable risk factors associated with neurologic impairment in children with complex CHD include prematurity (<37 weeks), gender, syndrome or genetic abnormality (up to 30%), and ethnicity.[1,14] In this study, we found a significant difference in the prevalence of syndromes between the oral- and tube-fed children, which can be related to neurological impairments. Furthermore, syndrome was an independently risk factor of worse neurodevelopmental scores at 12 and 24 months. However, we did not find any difference in prematurity, gender, or ethnicity between the groups.

Modifiable risk factors for neurologic impairment included prolonged LOS in the ICU, clinical seizures, and need for cardio-pulmonary resuscitation.[3] The ICU LOS in the tube-fed children had more than double the ICU LOS when compared to those who were orally fed. The tube fed children had more neurodevelopmental impairments, but likely incurred a more severe and complicated hospital course with coexisting operative, physiologic, and patient-specific variables that are not accounted for in this study.

Additionally, we are unable to account for non-neurologic indications for enteral tube feeding at discharge, specifically, those related to heart failure or respiratory insufficiency. Oral feeding is a complex process dependent on a combination of several skills including normal functioning cranial nerves (V, VII, IX-XII), neurosensory skills, and emotional states.[7] Each of these mechanisms is primarily stimulated by oral intake thus likely impaired by enteral tube dependence for nutrition. Thus, it is conceivable that children who are tube fed are predisposed to ongoing neurological impairments.

Interestingly, cognition and language skills decreased for every six months in all children, independent of feeding mode in contrast to motor skills, which increased for every six months. These findings are also similar to a previous report that identified that motor deficits were more common in the early clinically assessments and

that cognition and language impairments became more prevalent as the children became older,[13] suggesting that developmental testing becomes more sensitive with age due to the increased complexity of skills expected for age.[10] Not surprisingly we observed an association between the presence of a syndrome and decreased CAT, CLAMS and Motor DQs, whereas greater surgical complexity as measured by STAT score and ethnicity were not associated with decreased neurodevelopmental outcomes. The association between having a syndrome as well as CHD and impaired neurodevelopmental outcome has been observed in other studies.[2,13,15–17]

Height was significantly lower in the enteral tube fed children at 6, 12, and 24 months. This is particularly important, since a low height is an independent significant risk factor of neurodevelopmental disabilities in early childhood for those with single ventricle physiology.[5,18] Though weight-gain was significantly lower than the orally fed group in our cohort, it was not significantly associated with CAT, CLAMS, or Motor scores in the multivariable regression analysis. From these data, we would speculate that failure to thrive alone causes neurodevelopmental impairment, and though anthropometrics measurements are important, they cannot elucidate the specific neurodevelopmental issues and can, therefore, not be the only assessment tool. What we are unable to discern is whether the superior neurodevelopmental outcomes in the orally fed group is partly due to accumulated effects of stimulatory effort of oral feeding. Thus, emphasizing the importance on ensuring adequate caloric intake for somatic growth while simultaneously promoting oro-motor skills.

There are certain limitations to be considered. First, the retrospective nature of the study design was limited in our knowing the circumstances leading to enteral tube feeding at hospital discharge, specifically as it relates to the pre-existence of subtle neurologic deficits. This alone is an important confounder for which we cannot account. Second, though we intended to capture growth and neurodevelopment data at set ages, we recognized that the exact timing of assessments was not possible. Thus, we scaled and categorized data within predetermined windows around 6, 12, and 24 months of age according to the patient's actual age which may have influenced the classification of DQs particularly at the 24 months assessment which had a window of ±6 months. To account for this, the clinic assessments were consistently performed accounting for child's actual age. Due to the observational design, we cannot make any conclusions on whether the observed association is of causative nature. Furthermore, we recognize that single center study of a selected population cannot be generalized to all children with CHD. Further multicenter investigation is needed and may in fact be possible through emerging collaborative networks and registries.

6 | CONCLUSION

Infants and children who receive enteral tube feeds following hospital discharge after cardiac surgery are at increased risk for neurodevelopmental delays in cognition, language, and motor skills at 12 and 24 months. Oro-motor therapy and attention to neurodevelopment should occur in parallel with assessments of caloric intake and somatic growth. More studies are needed to understand the impaired neurodevelopment in children with CHD and enteral tube feeding as well as understand the influence of those variables on later childhood development.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Designed the study, collected data, prepared data for analysis, led interpretation of results, prepared and drafted the manuscript: Holst
Collected data, prepared data for analysis, advised on study design, contributed to drafting manuscript, critically reviewed and revised the manuscript: Serrano
Statistical analyses and contributed to interpretation and approved the final manuscript as submitted.: Guffey
Study design, data interpretation, critically reviewed and revised the manuscript: Ghanayem, Ravn, Shekerdemian
Conceptualized and designed the study, collected data, prepared data for analysis, led interpretation of results and revisedapproved the final manuscript as submitted.: Monteiro

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