Genetic factors are important determinants of impaired growth after infant cardiac surgery

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Objectives: We sought to estimate the prevalence and identify the predictors of impaired growth after infant cardiac surgery.

Methods: We performed a secondary analysis of a prospective study of the role of apolipoprotein E gene polymorphisms on neurodevelopment in young children after infant cardiac surgery. Prevalence estimates for growth velocity were derived by using anthropometric measures (weight and head circumference) obtained at birth and at 4 years of age. Genetic evaluation was also performed. Growth measure *z* scores were calculated by using World Health Organization Child Growth Standards. Growth velocity was evaluated by using 2 different techniques: first by clustering the children into one of 3 growth velocity subgroups based on *z* scores (impaired growth, difference < –0.5 standard deviation; stable growth, difference of –0.5 to 0.5 standard deviation; and improving growth, difference > 0.5 SD) and second by using continuous difference scores. Statistical analyses were conducted with a combination of proportional odds models for the ordered categories and simple linear regression for the continuous outcomes.

Results: Three hundred nineteen full-term subjects had complete anthropometric measures for weight and head circumference at birth and 4 years. The cohort was 56% male. Genetic examinations were available for 97% (309/319) of the cohort (normal, 74%; definite or suspected genetic abnormality, 26%). Frequency counts for weight categories were as follows: impaired growth, 37%; stable growth, 31%; and improving growth, 32%. Frequency counts for head circumference categories were as follows: impaired growth, 39%; stable growth, 28%; and improving growth, 33%. The presence of a definite or suspected genetic syndrome ($P = .04$) was found to be a predictor of impaired growth for weight but not for head circumference. When growth *z* scores were used as continuous outcomes, the apolipoprotein E $\epsilon 2$ allele was found to be predictive of lower *z* scores for both weight ($P = .02$) and head circumference ($P = .03$).

Conclusions: Impaired growth for both weight and head circumference is common (both >30%) in this cohort of children after infant cardiac surgery. Both the apolipoprotein E $\epsilon 2$ allele and the presence of a definite or suspected genetic syndrome were associated with impaired weight growth velocity. The apolipoprotein E $\epsilon 2$ allele was also associated with impaired growth velocity for head circumference. Persistent poor growth might have long-term implications for the health and development of children with congenital heart defects. (J Thorac Cardiovasc Surg 2010;140:144-9)

CHD

Optimal growth during early childhood is important for normal development. Suboptimal growth can lead to decreased survival and poor cognitive outcomes. Chronic disease states increase the risk of growth impairment. Despite early neonatal repair and improved survival of children with congenital heart defects (CHDs), there is increasing evidence that children with CHDs are at an increased risk for both impaired growth and abnormal neurodevelopment.[1-5] Growth impairment in children with CHDs can begin before birth, as indicated by an increased prevalence of intrauterine growth retardation in several population-based studies.[6-8] During the perioperative period, altered energy intake and energy expenditure result in an ongoing risk of malnutrition.[9-14] The prevalence and cause of growth impairment in the CHD population is poorly understood. Simple cross-sectional analyses of growth using group means or simple thresholds for adequate growth are relatively insensitive and might fail to identify many children with impaired growth.[15] Assessment of growth patterns or velocity might be more appropriate in children with chronic diseases who are at an increased risk for

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Abbreviations and Acronyms
APOE = apolipoprotein E
CHD = congenital heart defect
DHCA = deep hypothermic circulatory arrest
HC = head circumference
HCZ = head circumference–for–age *z* score
SD = standard deviation
TOF = tetralogy of Fallot
VSD = ventricular septal defect
WAZ = weight-for-age *z* score
WHO = World Health Organization

poor growth.[16-18] Identification of children with impaired growth is important because inadequate nutritional intake and subsequent poor growth are potentially modifiable factors. Therapeutic interventions that lead to more optimal growth might result in improved outcomes.

In 1998, we initiated a prospective study evaluating the association between neurodevelopmental dysfunction and apolipoprotein E *(APOE)* genotype in 550 neonates and infants undergoing operations for CHDs. *APOE* is an important regulator of cholesterol metabolism and has an important role as a susceptibility gene that modifies outcome after central nervous system injury. The *APOE* $\epsilon 2$ allele was associated with significantly worse neurodevelopmental outcomes at 1 and 4 years of age.[19,20] Anthropometric growth measurements were obtained from labor and delivery records and at both these evaluations. The current study was undertaken to estimate the prevalence and identify predictors of impaired growth from birth to 4 years of age after infant cardiac surgery.

MATERIALS AND METHODS

Study Population

The study constitutes a secondary analysis of a subgroup of a prospective study of the role of *APOE* gene polymorphisms on neurodevelopment after cardiac surgery in infancy.[19,21] Patients 6 months of age or younger undergoing surgical intervention for CHDs with cardiopulmonary bypass with or without deep hypothermic circulatory arrest (DHCA) were eligible. Exclusion criteria were as follows: (1) multiple congenital anomalies, (2) recognizable genetic or phenotypic syndrome other than chromosome 22q11 microdeletion syndrome, and (3) language other than English spoken in the home. Patients underwent neurodevelopmental assessments at 1 and 4 years of age. The current study evaluated full-term infants (gestational age, $\geq$37 weeks) for whom complete birth and 4-year data on relevant anthropometric measures were available. Premature infants were excluded because the World Health Organization (WHO) growth chart normative data does not include premature infants. The study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia. Informed consent was obtained from the parent or guardian.

Operative Management

Surgical intervention was performed by 5 cardiac surgeons with a dedicated team of cardiac anesthesiologists. Alpha-stat blood gas management was used. Pump flow rates were not standardized for this study. DHCA was used at the surgeon's discretion. Before DHCA, patients underwent core cooling, with topical hypothermia of the head, to a nasopharyngeal temperature of 18°C. Modified ultrafiltration was performed in all patients.

Anthropometric Measurement and Growth Assessment

Anthropometric measurements (weight and head circumference [HC]] were obtained at birth and at a 4-year follow-up. Of note, both length and height were obtained at birth and the 4-year follow-up; however, the birth length measurement was considered not sufficiently accurate to use for an analysis in which the focus was on patterns of growth after cardiac surgery. Birth measurements were collected from labor and delivery records. Measurements at the 4-year follow-up were obtained by research nurses using standardized research protocols with digital scales and stadiometers. Weight-for-age *z* scores (WAZs) and HC-for-age *z* scores (HCZs) were calculated by using the WHO Child Growth Standards. The WHO Growth Standards were released in 2006 and are based on prospectively collected data from a population of ethnically diverse, singleton, term-born infants who were primarily breast-fed. This population was selected to represent optimal growth (ie, ''how children should grow'').[22] Use of the WHO standards provides adjustment for growth differences caused by sex and ethnicity.

Genetic Evaluations

Patients were evaluated at the 1-year evaluation, 4-year evaluation, or both by a genetic dysmorphologist. Chromosome analysis and testing for microdeletion of 22q11 were performed as indicated. Results of the genetic evaluations were classified as normal if no genetic or chromosomal abnormality was demonstrated, abnormal if a specific diagnosis was confirmed, and suspect if there was evidence of a genetic syndrome that could not be confirmed. For the analysis, the abnormal and suspect subgroups were combined.

APOE Genotype Determination

Whole blood or a buccal swab was obtained before the operation and stored at 4°C. Genomic DNA was prepared and used to determine *APOE* genotypes by using a previously published method. Subjects were grouped by *APOE* genotype into the $\epsilon 2$ group ($\epsilon 2\epsilon 2$ and $\epsilon 3\epsilon 2$), the $\epsilon 3$ group ($\epsilon 3\epsilon 3$), and the $\epsilon 4$ group ($\epsilon 3\epsilon 4$ and $\epsilon 4\epsilon 4$). The $\epsilon 2\epsilon 4$ subjects were excluded from the analyses because the $\epsilon 2$ and $\epsilon 4$ alleles are in opposition in their effects in some conditions, such as Alzheimer's disease.[19]

Cardiac Diagnosis

Cardiac diagnosis was coded according to a previously described classification incorporating anatomy and perioperative physiology that has been shown to be predictive of perioperative mortality.[23] Class I is 2 ventricles with no aortic arch obstruction, class II is 2 ventricles with aortic arch obstruction, class III is a single ventricle with no arch obstruction, and class IV is a single ventricle with arch obstruction. Patients with tetralogy of Fallot (TOF) and transposition of the great arteries are in class I, whereas patients with hypoplastic left heart syndrome or variants are in class IV.

Data Analysis and Statistical Methods

Data analysis proceeded in 3 discrete phases. First was a descriptive phase in which traditional descriptive statistics were computed for all variables in the data set, with a particular emphasis on growth status at birth and 4 years of age. Second and third were 2 separate prevalence phases, in which prevalence estimates for impaired growth were computed by using 2 different criteria: (1) a simple cross-sectional evaluation with a cutoff of –2 standard deviations (SDs) for weight and HC *z* scores at 4 years of age and (2) by using an estimate of growth velocity from birth to 4 years (*z* scores at

TABLE 1. Baseline and operative characteristics

	Entire group	Impaired growth	Stable growth	Improving growth
No.	319	117 (37%)	100 (31%)	102 (32%)
Sex				
Female	139 (44%)	47 (40%)	53 (53%)	39 (38%)
Male	180 (56%)	70 (60%)	47 (47%)	63 (62%)
Ethnicity				
Asian–Pacific, Hispanic, other	34 (11%)	13 (11%)	12 (12%)	9 (9%)
African American	68 (21%)	16 (14%)	20 (20%)	32 (31%)
White	217 (68%)	88 (75%)	68 (68%)	61 (60%)
Diagnostic class				
I: 2 ventricles/no arch obstruction	163 (51%)	53 (46%)	51 (51%)	59 (58%)
II: 2 ventricles/arch obstruction	43 (14%)	12 (10%)	18 (18%)	13 (13%)
III: 1 ventricle/no arch obstruction	29 (9%)	12 (10%)	5 (5%)	12 (12%)
IV: 1 ventricle/arch obstruction	84 (26%)	40 (34%)	26 (26%)	18 (17%)
Genetic evaluation				
Normal	237 (74%)	78 (67%)	79 (79%)	80 (78%)
Yes	82 (26%)	39 (33%)	21 (21%)	22 (22%)
APOE genotype				
$\epsilon 2$	30 (10%)	15 (13%)	9 (9%)	6 (6%)
$\epsilon 3$	187 (60%)	63 (55%)	57 (60%)	67 (67%)
$\epsilon 4$	92 (30%)	36 (32%)	29 (31%)	27 (27%)
Missing	10	3	5	2
DHCA at first operation				
No	135 (42%)	41 (35%)	43 (43%)	51 (50%)
Yes	184 (58%)	76 (65%)	57 (57%)	51 (50%)
Additional operations before 4-y evaluation				
None	189 (59%)	60 (51%)	63 (63%)	66 (65%)
1–2	122 (38%)	55 (47%)	35 (35%)	32 (31%)
>2	8 (3%)	2 (2%)	2 (2%)	4 (4%)

APOE, Apolipoprotein E; *DHCA*, deep hypothermic circulatory arrest.

birth − *z* scores at 4 years). Growth velocity categories were created by subdividing the *z* score difference values into 3 different velocity subgroups: impaired growth, difference less than –0.5 SD; stable growth, difference of –0.5 SD to 0.5 SD; and improving growth, difference greater than 0.5 SD. The importance of using both criteria is that the cross-sectional evaluation with a –2 SD threshold is a traditional screening criterion for growth failure in healthy populations. Use of growth velocities allows evaluation of the pattern and tempo of growth and will identify those children who have deviated substantially from their individual growth trajectories.

In the risk-modeling phase, a total of 14 separate single-covariate, proportional-odds, growth failure models were specified and tested by using the 3 velocity subgroups as the outcome and a selected set of patient-specific and perioperative variables as the testable covariates. Finally, 4 single-covariate linear regression models were also tested in which the original continuous measure of velocity (*z* score at birth − *z* score at 4 years) served as the outcome and genotype and duration of DHCA at the first operation were used as the testable covariates. In an effort to rule out the possibility of redundancy among predictors, the relationship between duration of DHCA and cardiac diagnosis was estimated by using a Spearman rho correlation coefficient. Because of the exploratory nature of the study, α was not adjusted beyond the traditional α level of 0.05. All data were analyzed with SAS version 9.1 software (SAS Institute, Inc, Cary, Inc).

RESULTS

Between September 1998 and April 2003, 675 eligible infants underwent cardiac surgery. Twenty-three infants died before consent, parents of 102 declined participation, and 550 (81%) were enrolled. There were 21 deaths during the initial hospitalization and an additional 43 before 5 years of age. Four hundred eighty-six patients were alive and eligible for the 4-year evaluation, which was completed by 381 patients (78% of the eligible population). Baseline characteristics have been previously reported for patients returning for the 4-year evaluation (n = 381), those who did not return (n = 105), and those who died before age 4 years (n = 64). The only significant difference in baseline characteristics between returning and nonreturning patients was underrepresentation of African Americans among the returning patients (21% vs 29%). Three hundred nineteen patients met the entry criteria for the current study. Baseline characteristics are shown in Table 1.

Prevalence of Impaired Growth

Cross-sectional evaluation. The mean WAZs at birth and 4 years of age were –0.14 (± 1.12) and 0.21 (± 1.17), respectively. The mean HCZs at birth and 4 years were –0.19 (± 1.37) and –0.28 (± 1.22), respectively. The prevalence of impaired growth as assessed by a WAZ of less than –2.0 was 5% at birth and 6% at 4 years. The prevalence of impaired growth as assessed by an HCZ of less than –2.0 at birth was 9% at birth and 8% at 4 years.

Growth velocity. Frequency counts for growth velocity groups for weight were as follows: impaired growth, 37% (117/319); stable growth, 31% (100/319); and improving growth, 32% (102/319). Frequency counts for growth velocity subgroups for HC were as follows: impaired growth, 39% (126/319); stable growth, 28% (88/319); and improving growth, 33% (105/319).

Risk models

Weight growth velocity categories. The presence of a definite or suspected genetic syndrome was a predictor of impaired growth for weight ($P = .04$, Table 2). Longer duration of DHCA was also associated with impaired weight growth ($P = .02$). Duration of DHCA was related to the cardiac diagnosis ($r = 0.57$, $P < .001$). Use and longer duration of DHCA were more common in class IV patients. Overall, cardiac diagnosis was not associated with weight growth. However, growth impairment for weight was more common in class IV patients compared with class I patients ($P = .01$). *APOE* genotype was not associated with weight growth.

HC growth velocity categories. Presence of a definite or suspected genetic syndrome, longer duration of DHCA, and cardiac diagnosis were not predictive of HC growth

TABLE 2. Risk models for weight growth velocity categories (logistic regression)

Parameter	Estimate	Standard error	*P* value
Confirmed or suspected genetic anomaly	**–0.242**	**0.121**	**.045**
Diagnostic class			.060
Class II vs class I	0.163	0.235	.489
Class III vs class I	0.110	0.273	.674
Class IV vs class I	**–0.475**	**0.193**	**.014**
APOE genotype			.12
APOE ϵ2 vs *APOE* ϵ3	–0.392	0.244	.107
APOE ϵ4 vs *APOE* ϵ3	0.064	0.178	.718
CPB duration, first Operation	0.001	0.003	.629
Duration of additional CPB	–0.002	0.002	.238
DHCA duration, first operation	**–0.011**	**0.005**	**.017**
Duration of additional DHCA	–0.005	0.004	.284

The statistically significant parameters are in bold. *APOE*, Apolipoprotein E; *CPB*, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest.

TABLE 3. Risk models for head circumference growth velocity categories (logistic regression)

Parameter	Estimate	Standard error	*P* value
Confirmed or suspected genetic anomaly	–0.095	0.120	.430
Diagnostic class			.40
Class II vs class I	–0.269	0.239	.260
Class III vs class I	0.250	0.274	.361
Class IV vs class I	-0.138	0.192	.471
APOE genotype			.099
***APOE* ϵ2 vs *APOE* ϵ3**	**-0.519**	**0.249**	**.037**
APOE ϵ4 vs *APOE* ϵ3	0.224	0.180	.213
CPB duration, first operation	0.001	0.003	.581
Duration of additional CPB	–0.001	0.002	.493
DHCA duration, first operation	–0.008	0.005	.092
Duration of additional DHCA	0.002	0.004	.648

The statistically significant parameters are in bold. *APOE*, Apolipoprotein E; *CPB*, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest.

(Table 3). Overall, *APOE* genotype was not associated with HC growth. However, growth impairment for HC was more common in patients with the *APOE* ϵ2 allele compared with those with the ϵ3 allele ($P = .037$).

Growth velocities as continuous outcomes. The *APOE* ϵ2 allele was predictive of lower growth velocity for both weight ($P = .02$) and HC ($P = .03$). Longer duration of DHCA at the first operation was also associated with lower growth velocity for both weight ($P = .01$) and HC ($P = .02$). However, the r^2 value for both was approximately 0.02, suggesting that most of the variance for both weight and HC, up to 98%, is not explained by these factors.

DISCUSSION

Growth patterns provide an important window into the overall well-being of healthy children and those with chronic diseases. In this study we show that growth impairment or faltering assessed as a decreasing growth velocity between birth and 4 years for both weight and HC is common (both >30%) after infant cardiac surgery. Evaluation of growth with more traditional criteria, such as group means, or use of cross-sectional assessment with a simple threshold was relatively insensitive and suggested a much lower prevalence of growth impairment (6% to 8%). Use of growth velocities identifies subnormal weight or HC rate of gain rather than merely subnormal weight or HC.[15] Defining growth impairment as decreasing to less than a predetermined percentile or *z* score is only an estimate of attained weight and not an estimate of growth because it will not identify children who fall from a high percentile or *z* score. Use of the growth velocities shows that children with CHDs are a heterogeneous population with differing patterns of growth. In addition to the impaired growth subgroup, there is a group with improving or increasing growth velocity. Although some of these children might be exhibiting ''catch-up'' growth, others might be at risk for childhood obesity.

In the current study we identified that both the *APOE* ϵ2 allele and the presence of a definite or suspected genetic syndrome were associated with impaired weight growth velocity. The *APOE* ϵ2 allele was also associated with impaired growth velocity for HC. In addition, longer duration of DHCA at the initial operation was associated with impaired growth, as assessed based on body weight. However, taken in combination, these factors explain only a very small portion (<2%) of the variability in growth for both weight and HC. No other factors were found to be predictive of either impaired or improving growth.

The large group of patients with impaired HC growth is particularly concerning. Neurodevelopmental dysfunction is now the most common and potentially disabling long-term complication of CHD and its treatment. Infancy and early childhood are critical periods for brain growth. Early postnatal malnutrition is associated with significantly retarded central nervous system growth, reduced brain weight, thinner cerebral cortex, and deficient myelinization.[24] The adverse effects of malnutrition on neurodevelopmental outcomes have been well described in other populations. Inadequate nutritional intake and subsequent poor growth are potentially modifiable factors. Early identification of patients at risk for poor growth could lead to therapeutic interventions, more optimal growth, and improved neurodevelopmental outcomes.

Impaired growth has long been recognized as a significant problem in children with CHDs. In 1962, Mehrizi and Drash[25] called attention to the common occurrence of growth disturbances in children with a wide variety of CHDs. Levy and associates[1] evaluated growth in patients with ventricular septal defects (VSDs) enrolled in the Joint Study on the Natural History of Congenital Heart Defects. Successful surgical intervention resulted in a significant increase in weight but not height. Medical therapy was associated with little change in the subnormal growth pattern. They

concluded that the severe growth disturbance in patients with VSDs is only in part caused by abnormal postnatal hemodynamics. Intrauterine and genetic factors and low birth weight were identified as risk factors and might explain the incomplete growth response after successful surgical intervention. A subsequent study of long-term growth of children with CHDs showed that growth in children with a large VSD or TOF was abnormal. Growth improved but did not normalize after surgical intervention.[4] More recently, Cheung and colleagues[26] demonstrated normalization of long-term growth after repair of TOF. There has been increased interest in growth patterns for patients with single-ventricle anatomy and physiology. Cohen and coworkers[27] found that children with functionally univentricular hearts who have been palliated with a Fontan operation are significantly underweight and shorter than the general population and their siblings. In a more recent study, Vogt and associates[28] found that impaired growth is common in children with single-ventricle physiology before completion of the superior cavopulmonary connection and that some catch-up growth occurred subsequently. However, even after the Fontan procedure, the median WAZ remained decreased at –0.7. The findings of these studies are consistent with the current study in identification of more complex CHDs and genetic factors as important risk factors for growth disturbance. Unlike the current study, these studies used group means to estimate the prevalence of growth failure. The current study demonstrates that group means and screening thresholds are insensitive measures that fail to identify many children with impaired growth.

The cause of growth failure in patients with CHDs is multifactorial and most likely includes a hypermetabolic state, inadequate caloric intake, malabsorption, genetic factors, or a consequence of fluid restriction as part of hemodynamic intervention.[10-13] Inadequate caloric intake is probably a major contributor to growth failure in neonates who require cardiac surgery.[13] Feeding difficulties are common in this population and might be due to congestive heart failure, vocal cord paresis, uncoordinated sucking and swallowing, fatigue, or feeding aversion.[12] In addition, digestion and absorption in the gastrointestinal tract can be impaired by gut edema. Patients with single-ventricle physiology and an aortopulmonary shunt might have relative splanchnic ischemia caused by diastolic runoff from the shunt and are at increased risk for necrotizing enterocolitis.[13]

APOE polymorphisms might have different roles during early development and aging.[29,30] In adults the *APOE* ϵ4 allele is associated with a risk of Alzheimer's disease and worse outcome after traumatic brain injury.[31] However, there is evidence that infants with the *APOE* ϵ4 allele might have advantages over those with the *APOE* ϵ2 and ϵ3 alleles with respect to early-life neuronal and brain development.[32] We have shown that the *APOE* ϵ2 allele was associated with significantly worse neurodevelopmental outcomes at 1 and 4 years of age.[19,20] In the current study we found that the *APOE* ϵ2 allele is also associated with a risk of impaired weight and HC growth. In addition, there is evidence that early cognitive development under the stresses of environmental factors, such as malnutrition and lead exposure, might be modulated by *APOE* genotype.[29,30,32] As in the current study, the *APOE* ϵ2 allele is associated with worse outcomes, whereas the *APOE* ϵ4 allele is protective. This finding is consistent with the concept of thrifty genotypes and thrifty phenotype, metabolic adaptations adopted as survival strategies by a malnourished fetus or infant that might be inappropriate to deal with a later life of affluence.[33] The *APOE* ϵ4 allele is a more lipid-thrifty variant that is more efficient in sequestering cholesterol and increasing serum lipid levels, which might have a critical role for brain development and maturation.[29,30,33] Although this phenomenon might be advantageous in an infant with marginal nutrition, it is associated with hyperlipidemia and coronary artery disease in adults.[31]

There are several limitations to this study. The birth data were collected from delivery room records, and thus measurements might not have been made in a standard fashion. Anthropometric data are available for only 2 time points. We did not collect parental anthropometric data to determine whether a small child is constitutionally small. However, use of growth velocity obviates some of this problem because a child who is small and has a decrease of 0.5 z score still exhibits poor growth. Finally, regression to the mean must always be considered as a potential influence when multiple measures are obtained over time. Yet regression to the mean is generally symmetric and is as likely to happen for low-scoring children as it is for high-scoring children. Even in the presence of regression to the mean, however, children tend to remain around their expectation (ie, their expected levels of performance), with some fluctuation both ways. Hence fluctuation associated with regression to the mean is not unidirectional. In the current sample of children undergoing operations for heart disease, we simply do not see the same proportion of children at the high ends of the distributions that we saw at the low ends, especially with respect to growth failure. We do, however, have a fairly high number of infants who scored low initially and then remained ''within their growth channel'' relative to the WHO standards at birth and 4 years of age.

In summary, impaired weight and HC growth, as assessed by decreasing growth velocities, is common after cardiac surgery in infancy. The significant prevalence of impaired head growth is particularly concerning because of the implications for neurodevelopmental outcomes. Growth velocities are more appropriate and sensitive measures of growth patterns than simple cross-sectional evaluations. Genetic factors are important determinants of impaired growth. However, the risk factors identified in this study explain only a small portion of the variability in outcomes,

suggesting that many thus far unidentified factors likely contribute to the risk of poor growth. Nutritional support of children with CHDs is a modifiable factor. Early identification of patients at risk for poor growth could lead to therapeutic interventions, more optimal growth, and improved neurodevelopmental outcomes. Further research is needed to assess risk factors for poor growth, evaluate the effect of poor growth on neurodevelopmental outcomes, and determine the role for therapies to improve nutrition and growth.

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