Deficit of Fat Free Mass in Very Preterm Infants at Discharge is Associated with Neurological Impairment at Age 2 Years

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Preterm infants have a deficit of fat-free mass accretion during hospitalization. This study suggests that z score of fat-free mass at discharge is associated with neurologic outcome ($P = .003$) at 2 years of age, independent of sex, gestational age, and birth weight z score. Interventions to promote quality of growth should be considered. *(J Pediatr 2017;■■:■■-■■).*

Ehrenkranz et al described an association between growth velocity between birth and hospital discharge and neurologic outcome at 2 years in very preterm infants.[1] As a consequence, early growth is monitored more closely in the neonatal intensive care unit, and prevention of extra-uterine growth restriction is now among the top priorities in neonatal care.[2]

Body weight gain can result from gains in fat mass fat-free mass (FFM), or a combination of both. In addition, whole body weight gain does not necessarily reflect organ growth, particularly brain growth, which presumably determines neurodevelopmental outcome. We hypothesized that lean body mass accretion would reflect organ growth (including brain growth) more adequately than weight gain alone.[3] In earlier studies, we found that preterm infants, particularly male infants, experience insufficient FFM accretion during hospitalization.[4] This finding leads to consideration of whether lack of lean body mass, rather than poor weight gain, influences long-term outcome. Monitoring not only weight gain but the quality of growth during hospitalization along with assessment of body composition has, thus, become more common among neonatologists.[5] Our study aimed to determine whether the neurologic outcome of preterm infants at 2 years of age was associated with the deficit in FFM accretion during their initial hospital stay.

Methods

Eligible subjects were preterm infants admitted to the neonatal intensive care unit of Nantes Hospital between September 2008 and November 2013, participating in the prospective observational study, EPIPOD (NCT01450436).[4,5] Inclusion criteria were as follows: gestational age less than 33 weeks and enrollment discharge into our regional follow-up cohort, the Loire Infant Follow-up Team cohort at discharge.[6] Exclusion criteria were the presence of severe malformation, the use of supplemental oxygen or intravenous infusion at discharge, which did not allow placing the infant into the air-displacement plethysmography device, a transfer to another hospital before discharge, or the parents' refusal to participate.

This study is a part of the EPIPOD Study, approved by the Nantes Ethics Committee.[4,5] Written parental consent was obtained for each patient enrollment into the Loire Infant Follow-up Team cohort.[6]

Body Composition Assessment

In this prospective, observational study, each subject's characteristics (ie, birth weight, gestational age, and sex) were recorded at birth. The week before discharge, body composition was assessed on each child by using air-displacement plethysmography (PEA POD Infant Body Composition System; COSMED, Rome, Italy).

Air-displacement plethysmography is a densitometric technique in which body density (d) is determined from the ratio of body mass (m) to body volume (v) as d = m/v. Body mass is measured by weighing the infant on a high-precision electronic scale; body volume is measured by placing the infant in the enclosed chamber of the PEA-POD device, and by applying gas laws that relate pressure changes to air volume. The proportion of body fat is then deduced from body density.[7] In earlier work on the same cohort of preterm infants,[5] we demonstrated that absolute FFM at discharge was better associated than the fat mass percentage with classic clinical variables reflecting perinatal growth and the severity of illness. We, therefore, focused on FFM in the current study. We assumed a normal distribution of FFM in the data published by Hawkes et al for each range of gestational age according to sex, and calculated z score of FFM from the mean FFM and SD in their article as follows: z score of FFM = (FFM − mean of FFM)/SD.[8]

Neurodevelopmental Assessment

Neurodevelopment was assessed at age 24 months corrected, using the Ages and Stages Questionnaire (ASQ). ASQ is a

ASQ	Ages and Stages Questionnaire
FFM	Fat-free mass

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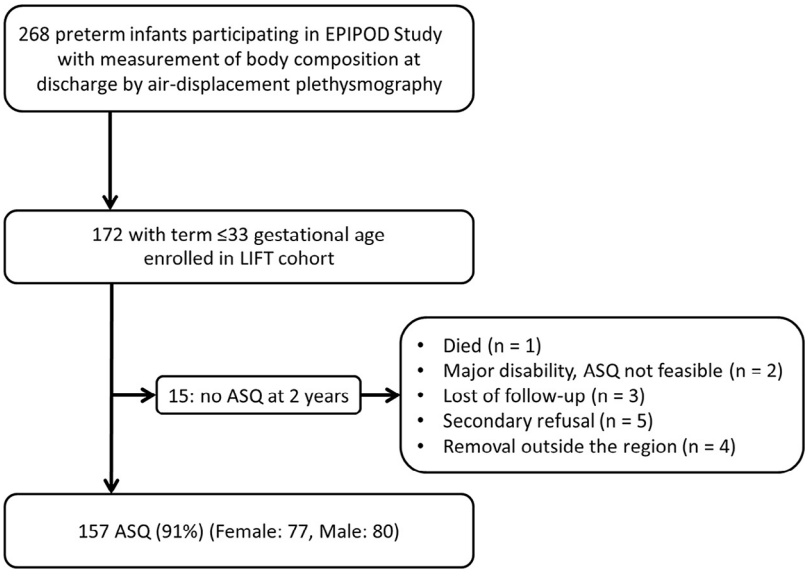

Figure. Flow chart of subjects. *LIFT*, Loire Infant Follow-up Team.

parent-completed questionnaire that assesses development in 5 areas (communication, overall and fine motor skills, problem solving, and personal-social skills). Parents were asked to complete the ASQ while in the waiting room before the child's physical examination. The maximal overall ASQ score is 300.

Statistical Analyses

First, to assess the relation between body composition at discharge and neurodevelopment at 2 years of age, we calculated correlations between z score of FFM, percentage of fat mass at discharge, and ASQ score as a continuous variable without and with adjustment for gestational age, sex, birth weight z score, and postconceptional age at discharge.

Second, to assess the risk of suboptimal neurodevelopment at 2 years of age, we ranked children into 3 classes depending on their global ASQ score (suboptimal ASQ score <186; intermediate ASQ score between 186 and 220, and optimal ASQ score >220). In earlier studies, we showed that an ASQ score <186 had a specificity of 0.92 and a positive likelihood ratio of 8 to predict a developmental quotient below 85.[9] An ASQ score >220 had a specificity of 0.96 and a positive likelihood ratio of 16 to predict a developmental quotient above 85.[10] We compared main perinatal characteristics in relation to body composition at discharge (sex, gestational age, birth weight z score, postmenstrual age)[5] between the 3 classes of ASQ score using χ^2 test for categorical values or ANOVA for continuous ones. We also compared weight at discharge, fat mass, FFM, percentage of fat mass, and z score of FFM.

Third, a stepwise logistic regression approach was performed involving forward inclusion and backward elimination of risk factors to determine whether sex, gestational age, birth weight z score, percentage of fat mass, and z score of FFM could be significant predictors of suboptimal ASQ. Inclusion (or exclusion) of a variable was deemed to be statistically significant at $P < .05$ ($P > .10$).[11] With the final model, we estimated the aOR of significant predictors for 24- month suboptimal ASQ score. All statistical analyzes were performed with SPSS software v 24 (SPSS Inc, Chicago, Illinois).

Results

Body composition measurement was performed on 172 preterm newborns (**Figure**). Mean gestational age was 29.9 weeks (±2.2), birth-weight z score: −0.28 (±1.02) and z score of FFM at discharge −2.29 (±1.18). Among those 172 infants, 157 were assessed at 2 years of age using the ASQ.

ASQ score correlated significantly with the z score of FFM ($R^2 = 0.10$, n = 157) before ($P = .001$) and after adjustment for gestational age, sex, birth weight z score, and postmenstrual age at discharge ($P = .003$). ASQ score also correlated significantly with the percentage of fat mass ($R^2 = 0.04$, n = 157) before ($P = .015$) but not after adjustment ($P = .46$).

Suboptimal ASQ score was associated with lower gestational age ($P = .003$), higher postmenstrual age at discharge ($P = .007$), higher fat mass percentage ($P = .02$), and lower z score of FFM ($P = .002$) (**Table**). Forward and backward stepwise logistic regression selected 2 risk factors for suboptimal ASQ score: gestational age and z score of FFM. Risk of suboptimal ASQ score decreased when gestational age increased (aOR 0.7, 95% CI 0.5-0.9, $P = .006$) and when z score of FFM increased (aOR 0.6, 95% CI 0.4-0.9, $P = .014$).

Discussion

In contrast to prior approaches, our study identified an association between z score of FFM at discharge and ASQ score at 2 years of age. Earlier studies addressing the neurologic outcome of preterm born infants at 2 years of age focused on a relationship between change in weight and weight z score

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