ORIGINAL ARTICLES

Brain Volumes at Term-Equivalent Age Are Associated with 2-Year Neurodevelopment in Moderate and Late Preterm Children

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Objective To explore the association between brain maturation, injury, and volumes at term-equivalent age with 2-year development in moderate and late preterm children.

Study design Moderate and late preterm infants were recruited at birth and assessed at age 2 years using the Bayley Scales of Infant and Toddler Development, Third Edition. Brain magnetic resonance imaging (MRI) was performed at term-equivalent age and qualitatively assessed for brain maturation (myelination of the posterior limb of the internal capsule and gyral folding) and injury. Brain volumes were measured using advanced segmentation techniques. The associations between brain MRI measures with developmental outcomes were explored using linear regression analyses.

Results A total of 197 children underwent MRI and assessed using the Bayley Scales of Infant and Toddler Development, Third Edition. Larger total brain tissue volumes were associated with higher cognitive and language scores (adjusted coefficients per 10% increase in brain size; 95% CI of 3.2 [0.4, 5.6] and 5.6 [2.4, 8.8], respectively). Similar relationships were documented for white matter volumes with cognitive and language scores, multiple cerebral structures with language scores, and cerebellar volumes with motor scores. Larger cerebellar volumes were independently associated with better language and motor scores, after adjustment for other perinatal factors. There was little evidence of relationships between myelination of the posterior limb of the internal capsule, gyral folding, or injury with 2-year development.

Conclusions Larger total brain tissue, white matter, and cerebellar volumes at term-equivalent age are associated with better neurodevelopment in moderate and late preterm children. Brain volumes may be an important marker for neurodevelopmental deficits described in moderate and late preterm children. *(J Pediatr 2016;174:91-7)*.

Children born between 32-36 weeks' gestational age (ie, moderate and late preterm) are at increased risk of developmental deficits in early childhood and school age.[1] As they comprise the majority of preterm births, developmental deficits in this group are likely to contribute significantly to the health burden associated with preterm birth.[1,2] Poorer cognitive performance in moderate and late preterm compared with term controls has been reported in infancy and early school age.[3-8]

Magnetic resonance imaging (MRI) has provided significant insights into the relationships between brain structure and neurodevelopment in very preterm (<32 weeks' gestational age) infants compared with those born at full term.[9] The presence of significant brain injury, such as major intraventricular hemorrhage or cystic periventricular leukomalacia, has been associated with cerebral palsy, major motor, and cognitive impairments.[10] In very preterm infants, brain volumes and white matter microstructure as early as term-equivalent age have been shown to correlate with developmental outcomes in childhood.[11] In contrast, little is known about brain-behavior relationships in children born moderate and late preterm. There are several factors that suggest that the pattern of brain-behavior associations observed after moderate and late preterm birth may be different compared with very preterm infants. Moderate and late preterm infants are exposed to postnatal environments and insults at a different stage of brain development than those born very preterm.[12] Furthermore, the prevalence of significant brain injury is much less in moderate and late preterm infants than in very preterm infants.[12,13] Therefore, the pattern of brain-behavior relationships cannot

Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
MRI	Magnetic resonance imaging

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be extrapolated from very preterm to moderate and late preterm children without caution.

The aims of this study were to explore the associations of brain volumes, maturation, and injury at term-equivalent age with 2-year cognitive, language, and motor development in moderate and late preterm children. We wanted to determine whether these relationships were similar in those born moderately preterm (32-33 weeks' gestation) and late preterm (34-36 weeks' gestation), given that the latter group has less morbidity compared with those born moderately preterm. In addition, we wanted to determine whether brain MRI measures were independently associated with development at 2 years, even after adjustment for previously reported perinatal factors that predict neurodevelopment in moderate and late preterm children.[5,14] We hypothesized that larger brain volumes, in particular white matter, subcortical gray, and cerebellar volumes, and a more mature brain would be associated with higher scores in cognitive, language, and motor domains.

Methods

Between November 2009 and November 2012, moderate and late preterm infants from the neonatal unit of the Royal Women's Hospital, Melbourne, were recruited at birth into a prospective longitudinal cohort study. Infants with congenital anomalies or syndromes known to affect development were excluded from the study. Perinatal and maternal details were collected by chart review at time of recruitment. Social risk was assessed using sociodemographic factors known to modulate outcomes in preterm infants, including family structure, education of primary caregiver, employment status of primary income earner, occupation of primary income earner, language spoken at home, and maternal age at birth of child. A composite score was calculated and dichotomized to higher and lower social risk.[15] The study was approved by the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, Melbourne, Australia, and written informed parental consent was obtained for all infants.

MRI

MRI brain scans were performed in natural sleep between 38 and 44 weeks' corrected age, using a Siemens 3T MAGNETOM TrioTim MRI system (Siemens, Erlangen, Germany) with a 12-channel circular polarized volume extremity coil. The following sequences were used as part of this study: 3-dimensional T1-weighted magnetization prepared rapid gradient echo; isotropic voxels $0.9 \times 0.9 \times 0.9$ mm, field of view 192 mm, repetition time 2100 ms, echo time 3.39 ms, and flip angle 9°. T2 datasets were obtained using T2 RESTORE (fast spin echo/turbo spin echo with 90° flip-back pulse); voxel size $1.0 \times 1.0 \times 1.0$ mm, field of view 192 mm, repetition time 8910 ms, echo time 152 ms, and flip angle 120°. The infants were fed, swaddled, had earplugs, and MiniMuffs (Natus, Pleasanton, California) noise attenuators, and were placed in a MedVac (CFI Medical Solutions Inc, Fenton, Michigan) immobilization device for the MRI scan. Throughout the scan, infants were monitored using an apnea monitor and oxygen saturation probe, and if required, oral sucrose was administered with parental consent.

MRI Assessment of Brain Maturation and Injury

Brain MRI scans were scored by 1 of 2 independent assessors (J.W., J.C.) for brain maturation (gyral folding and degree of myelination of the posterior limb of the internal capsule) and evidence of brain injury (intraventricular hemorrhage, periventricular cysts, and abnormal signal in brain tissue) (ie, hyperintense T1 and hypointense T2) using a validated MRI infant assessment.[13,16] Assessors were unaware of the clinical history or gestational age of the infant. Inter- and intrarater reliability for these assessments have previously been published and are high (kappa values ranging from 0.75-0.89).[13]

Brain Volumetric Segmentation

An in-house method of automated morphologically adaptive neonatal tissue segmentation (MANTiS) was used to classify a T2 structural MRI of the brain into white matter, cortical gray matter, cerebrospinal fluid, subcortical gray matter (including deep nuclear gray matter, hippocampus, and amygdala), brainstem, and cerebellum (**Figure 1**; available at www.jpeds.com). This technique extends the unified segmentation approach to tissue classification implemented in statistical parametric mapping software[17] to infant brain scans. MANTiS combines unified segmentation, template adaptation via morphologic segmentation tools and topological filtering. This method performs well in the presence of brain abnormalities common in preterm infants, including enlarged ventricles and white matter signal intensity abnormalities.

Two-Year Developmental Assessment

All participants were invited to attend a developmental assessment at 2 years' corrected age. Participants were assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)[18] by experienced accredited examiners who were unaware of the clinical history and gestational age of the child. The Bayley-III is a reliable standardized assessment of cognitive, language, and motor development, which is used extensively in clinical and research settings. Age-standardized cognitive, language, and motor composite scores have a normative mean of 100, with a SD of 15. Although there have been concerns about the Bayley-III underestimating developmental delay in the Australian population,[19] adjustments were not necessary for this study as results were not interpreted in terms of rates of delay.

Statistical Analyses

Data were analyzed using Stata v13.0 (StataCorp, College Station, Texas). Participant characteristics were compared