Brain MRI Measurements at a Term-Equivalent Age and Their Relationship to Neurodevelopmental Outcomes


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ABSTRACT

BACKGROUND AND PURPOSE: An increased prevalence of disabilities is being observed as more preterm infants survive. This study was conducted to evaluate correlations between brain MR imaging measurements taken at a term-equivalent age and neurodevelopmental outcome at 2 years’ corrected age among very low–birth-weight infants.

MATERIALS AND METHODS: Of the various brain MR imaging measurements obtained at term-equivalent ages, reproducible measurements of the transcerebellar diameter and anteroposterior length of the corpus callosum on sagittal images were compared with neurodevelopmental outcomes evaluated by the Bayley Scales of Infant Development (II) at 2 years’ corrected age (mean ± standard deviation, 16.1 ± 6.4 months of age).

RESULTS: Ninety infants were enrolled. The mean gestational age at birth was 27 weeks and the mean birth weight was 805.5 g. A short corpus callosal length was associated with a Mental Developmental Index <70 (P = .047) and high-risk or diagnosed cerebral palsy (P = .049). A small transcerebellar diameter was associated with a Psychomotor Developmental Index <70 (P = .003), Mental Developmental Index <70 (P = .004), and major neurologic disability (P = .006).

CONCLUSIONS: A small transcerebellar diameter and short corpus callosal length on brain MR imaging at a term-equivalent age are related to adverse neurodevelopmental outcomes at a corrected age of 2 years and could be a useful adjunctive tool for counseling parents about future developmental outcomes.

ABBREVIATIONS: AED = antiepileptic drug; NICU = neonatal intensive care unit; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index; TCD = transcerebellar diameter

The survival rate of preterm infants has increased with the advances in neonatal care in recent decades. However, a higher prevalence of disabilities has also been observed in survivors of preterm birth at infancy and in childhood. Factors such as intraventricular hemorrhage, hypoxia, prematurity, and neonatal care have been reported to affect the developing brain; the mechanism of injury during the development of the cerebellum and corpus callosum in surviving premature infants may be caused by primary destruction or underdevelopment and axonal injury, respectively. These factors in turn result in an altered brain volume or structure that can be seen as a reduced cerebral and/or cerebellar volume, subarachnoid space widening, corpus callosum thinning, and posthemorrhagic ventricular dilation on brain MR imaging. These findings have led to reports of various measurements of MR imaging as potential predictors of neurologic outcomes at infancy or in childhood.

We conducted a study in a single neonatal intensive care unit (NICU) to evaluate correlations between brain MR imaging measurements taken at term-equivalent age and the neurodevelopmental outcomes at 2 years’ corrected age.

MATERIALS AND METHODS

Patients and Perinatal Data

Infants admitted to the NICU of Asan Medical Center Children’s Hospital from January 2001 to December 2010 whose birth weight was <1 kg were included in the study cohort. Patients with a birth weight <1.5 kg who had clinical indications for brain MR imaging, such as a history of seizure or hypoxic events, or sus-
expected periventricular leukomalacia by head sonography were also included. The brain MR imaging was obtained at a term-equivalent age (37.0 to 41.6 weeks). All patients except for 2 (2.2%) underwent brain MR imaging before NICU discharge.

Exclusion criteria included infants who died before discharge and infants who had severe congenital anomalies such as chromosomal abnormalities or brain anomalies. The clinical charts of the subjects were retrospectively reviewed for various demographic and clinical data: antenatal steroids, necrotizing enterocolitis defined as modified Bell criteria greater than stage IIa, treatment of symptomatic patent ductus arteriosus either intravenously with indomethacin or by surgical ligation, laser operation for retinopathy of prematurity, Papile classification of intraventricular hemorrhage, bronchopulmonary dysplasia (defined as oxygen dependence at 36 weeks' postmenstrual age), and treatment with antiepileptic drugs (AEDs) for electrographic and clinical seizure.

Oxygen requirement was defined as the supplementation of oxygen during hospitalization to maintain the target range of 88–93% saturation for infants born with a birth weight of ≤1.5 kg with bronchopulmonary dysplasia and ≥90% for other infants.

**Brain MR Imaging**

The brain MR imaging was obtained with a 3T MR system (3T Achieva Nova Dual; Philips, Best, the Netherlands) around the term-equivalent age before discharge from the NICU. MR images reviewed for this study consisted of spin-echo T1-weighted sagittal, T1-weighted axial, and T2-weighted axial images with parameters of 450/10/2 (TR/TE/excitations), 500/10/2, and 3000/80/2, with a field of view of 15 or 18 cm and a 256 × 256 matrix. Section thickness was 4 mm, with a 1-mm gap. Infants wearing ear protection devices were sedated with choral hydrate (25–50 mg/kg orally) or morphine (0.05 mg/kg intravenously).

**Measurements of MR Imaging**

Brain MR imaging measurements were taken by 2 different neonatologists under the supervision of 1 certified pediatric radiologist. The axial view of the transverse diameter (TCD) and the anteroposterior length of the corpus callosum on sagittal view were measured (Fig 1) with the use of the entirely digital measuring system of the PACS of Asan Medical Center (PetaVision, version 2.1). The TCD was measured as the longest transverse diameter perpendicular to the cerebellar vermis on the axial view that showed both nasal septum and orbital area, and the corpus callosal length was measured as the anteroposterior length on the midline sagittal image in which the pituitary gland was seen (Fig 1).

**Neurologic Outcomes**

The neurodevelopmental outcomes were assessed at 2 years’ corrected age with the Bayley Scales of Infant Development II by a certified neonatologist. The Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) were obtained. MDI or PDI scores <70 were defined as significantly abnormal. Cerebral palsy was defined as a nonprogressive central nervous system disorder characterized by abnormal posture and abnormal muscular tone in at least 1 extremity; high-risk cerebral palsy was defined as the abnormal tone of extremities and delayed motor development during the first 2 years diagnosed by a certified medical doctor for pediatric rehabilitation. A major neurologic disability was defined as ≥1 of the following findings: MDI <70, PDI <70, cerebral palsy, sensorineural hearing loss, and/or seizure disorder.

**Data Analysis and Statistics**

Major neurologic disability was the primary outcome variable. A P value of <.05 was considered significant. Data were analyzed with the Student t test and logistic regression by use of SPSS 17.0 software (IBM, Armonk, New York). The intraclass correlation coefficients (ICC) for measurement consistency were calculated to analyze the intraobserver and interobserver agreement. In the multivariable regression, risk variables weakly associated with the outcomes in the univariate analysis (P < .1) were used as the candidate variables to identify independent predictors of adverse neurologic outcomes.
Table 1: General characteristics of the study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, wk</td>
<td>27.7 ± 2.3</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>805.5 ± 168.2</td>
</tr>
<tr>
<td>Sex, male</td>
<td>55.6% (M:F = 50:40)</td>
</tr>
<tr>
<td>Prenatal steroids</td>
<td>86 (95.6%)</td>
</tr>
<tr>
<td>PROM</td>
<td>38 (20%)</td>
</tr>
<tr>
<td>Delivery mode, C-section</td>
<td>67 (74.4%)</td>
</tr>
<tr>
<td>Presence of IUGR</td>
<td>36 (40%)</td>
</tr>
<tr>
<td>Apgar score, 1 min</td>
<td>4 ± 1.9</td>
</tr>
<tr>
<td>Apgar score, 5 min</td>
<td>7 ± 1.4</td>
</tr>
<tr>
<td>Duration of ventilator care, d</td>
<td>27 ± 25.3</td>
</tr>
<tr>
<td>Presence of BPD, O2 at 36 wk</td>
<td>22 (24.4%)</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>45 (50%)</td>
</tr>
<tr>
<td>History of sepsis, culture-proven</td>
<td>28 (31.1%)</td>
</tr>
<tr>
<td>Peak level of CRP, mg/dL</td>
<td>2.83 ± 4.84</td>
</tr>
<tr>
<td>NEC</td>
<td>8 (8.9%)</td>
</tr>
<tr>
<td>ROP</td>
<td>48 (53.3%)</td>
</tr>
<tr>
<td>IVH grade 3–4</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Laser operation for ROP</td>
<td>21 (23.3%)</td>
</tr>
<tr>
<td>AED medication</td>
<td>8 (8.9%)</td>
</tr>
</tbody>
</table>

Note: Data are reported as number (%) or as mean ± standard deviation. CRP indicates C-reactive protein; IUGR, intrauterine growth restriction; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PROM, premature rupture of membrane; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia.

RESULTS

General Characteristics of Patients
The general characteristics of the 90 infants are shown in Table 1. Of the 90 patients, 80 (88.9%) were extremely low–birth weight infants.

Perinatal Factors Associated with Adverse Neurologic Outcomes
In total, 15 of 90 infants (16.7%) and 24 of 90 (26.7%) infants showed MDI and PDI values <70, respectively. Another 8 patients (8.9%) were diagnosed with cerebral palsy, and 33 (36.7%) showed major neurologic disabilities. Risk variables found to be significantly correlated with the outcomes in the univariate analysis were entered into multivariate analysis: AED medication (OR, 7.687; P = .003) and the duration of O2 requirement (OR, 10.014; P = .055) were associated with a PDI <70.8 The rapid growth of the cerebellum that occurs from 28–40 weeks of gestation can be impeded by prematurity birth.7,32,33 Here, a smaller TCD, indicative of neuronal loss or impaired neuronal differentiation with a reduction in dendritic and axonal development that may be independent of immaturity,5 was associated with poor cognitive and psychomotor function. These results concur with those of the report of Tich et al14 in preterm infants born at a gestational age <30 weeks or a weight of <1.25 kg. The cerebellar injury, mainly occurring in the external granular layer, possibly related to a disturbance of cerebellar growth caused by hemosiderin on the cerebellar surface or postnatal factors such as hypoxia-ischemia, infection, and steroids as well as direct cerebellar destructive injury.7,8 Impaired neuronal connection between cerebrum and cerebellum as a remote effect can also contribute to cerebellar underdevelopment.7,8

We used phenobarbital as a primary medication in neonatal seizure when both clinical and electrical evidence of seizures was evident. Both the seizures and the AED medication may cause cerebellar atrophy—either synergistically35 or independently36—during the development of the cerebellum. Abnormalities of the cerebellum in mice after exposure to phenobarbital, such as a decrease in the number of Purkinje37 and granular cells,33 without...
an effect on the area of the cerebellum, have been reported. Sepsis, an independent risk factor for a poor neurologic outcome,
 could have exerted a detrimental effect on the growth of the cerebellum by diffuse white matter injury, bacterial products and cytokines, arterial hypotension, and combined cerebral ischemia. Bronchopulmonary dysplasia, a known risk factor for neurodevelopmental impairment, has also been reported to exert an effect on the granular cells of the cerebellum, as shown in a baboon model. In the present study, however, bronchopulmonary dysplasia alone was not associated with severe cognitive and motor deficits, though the duration of O2 requirement, which may have included a period of hypoxia and hypoxia, was associated with poor cognitive and motor outcomes. Reports have shown that the use of either a high oxygen concentration, which could have exerted a detrimental effect on the growth of the developing human cerebellum.

A premature transition from intrauterine to extrauterine life and stress or damage in the neonatal period could affect the development of the corpus callosum. The corpus callosum is known to have an intrinsic vulnerability to hypoxic-ischemic damage and hemorrhage. A decreased number or diameter of axons and myelin loss was observed in preterm infants with hypoxia or ischemia that could be explained with necrosis, apoptosis, astrogliosis, and microgliosis as well as injury of premylinating oligodendrocytes in white matter, including the corpus callosum. In the development of the corpus callosum, the corpus callosum expands in the craniocaudal direction: genu first and then body to splenium. Thus, the development of the posterior part is an ongoing process that continues through the neonatal period after preterm birth, and an altered development of the corpus callosum such as a shortening and/or thinning persists into childhood. We assumed that the underdevelopment of the posterior part of the corpus callosum would result in a shorter length of the corpus callosum as well as a thinning of the splenium. Our attempt to measure the thickness of the corpus callosum was hampered by a poor consistency in the measurements (ICC = 0.133–0.418 in interobserver variability, ICC = 0.003–0.367 in intraobserver variability). Reports have shown a positive relationship between both the corpus callosal size and total white matter volume and a decreased area of the posterior or midposterior region corresponding to the splenium and poor verbal skill in preterm males. In our study, a short corpus callosal length was associated in univariate analysis with high-risk or diagnosed cerebral palsy and an MDI <70.

In contrast to the study of Wood et al., which reported a relationship between the administration of antenatal steroids and a lower MDI, antenatal steroid showed a protective effect on the growth of the corpus callosum in our study (Table 4), in accordance with the protective effect of antenatal steroids on white matter injury in very low–birth-weight infants reported by Leviton et al and Agarwal et al.22 The effect of seizures, as evidenced by the use of AEDs in our study, might have caused the reduction in the corpus callosal volume, especially in the posterior region, as reported by Hermann et al. There are limitations that must be addressed regarding the present study. We did not examine the association of the white or gray matter abnormalities, such as hemorrhage or leukomalacia, and other signal changes with brain measurements. The other limitation includes the short-term follow-up period and a lack of control group. Further research is required to determine whether the changes in brain structures in very preterm infants would persist into later life.

CONCLUSIONS

In this study, we were able to elucidate the usefulness of the axial measurement of the TCD and the length of the corpus callosum taken from brain MR imaging at term-corrected ages in predicting long-term neurologic outcome. Various perinatal factors, such as a lower birth weight, use of AEDs, sepsis, bronchopulmonary dysplasia, and a smaller head circumference, some of which are independently associated with poor cognitive and motor skills later in life, could affect the development of the cerebellum and corpus callosum during the most vulnerable period in NICU hospitalization.
REFERENCES

Due to a print production error, Fig 1 in the article “Brain MRI Measurements at a Term-Equivalent Age and Their Relationship to Neurodevelopmental Outcomes” by H.W. Park, H.-K. Yoon, S.B. Han, B.S. Lee, I.Y. Sung, K.S. Kim, and E.A. Kim [AJNR Am J Neuroradiol 2014;35:599–603] did not contain tabular material that was part of the illustration. The correct image is displayed here.

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**FIG 1.** Linear measurements of anteroposterior length of corpus callosum (A and B) and transcerebellar diameter (C and D) and intraclass correlation coefficients (ICCs) for interobserver and intraobserver reliability. A, Short anteroposterior length of corpus callosum (34.1 mm); B, longer anteroposterior length of corpus callosum (44.4 mm); C, short transcerebellar diameter (36.2 mm); D, longer transcerebellar diameter (58.4 mm).