Effects of Gestational Age and Birth Weight on Brain Volumes in Healthy 9 Year-Old Children

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Objective To assess the effects of gestational age and birth weight on brain volumes in a population-based sample of normal developing children at the age of 9 years.

Study design A total of 192 children from twin births were included in the analyses. Data on gestational age and birth weight were reported shortly after birth. Total brain, cerebellum, cerebrum, gray and white matter, and lateral ventricle volumes were assessed with structural magnetic resonance imaging. The Wechsler Intelligence Scale for Children-III was administered to assess general cognitive abilities. Structural equation modeling was used to analyze the effects of gestational age and birth weight on brain volumes.

Results Shorter gestational age was associated with a relatively smaller cerebellar volume ($P = .002$). This effect was independent of IQ scores. Lower birth weight was associated with lower IQ score ($P = .03$). Birth weight was not associated with brain volumes.

Conclusion The effect of gestational age on cerebellar volume is not limited to children with very premature birth or very low birth weight, but is also present in children born >32 weeks of gestation and with birth weight >1500 g. *(J Pediatr 2010;156:896-901)*.

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Several studies have indicated that children born very preterm (VPT; <32 weeks) or with a very low birth weight (VLBW; <1500 g) have a higher risk for the development of cognitive, motor, and behavioral problems at a later age.[1-4] Most studies focus on long-term outcome in this high-risk group of infants born VPT. However, infants born between 32 and 37 weeks (also referred as late-preterm or low-risk infants) have an increased risk of deficits in neurological development, development delay, and school-related problems at the age of 5 years.[5-7] Earlier studies also indicated that the influence of preterm birth on intelligence is not limited to infants with VLBW. Within the normal range of birth weight (BW), childhood IQ scores showed an increase with higher BW.[8-10] The results of several magnetic resonance imaging (MRI) studies have revealed morphological brain abnormalities associated with preterm birth.[11]

Overall, reduction of cerebral tissue and enlargement of the lateral ventricles has been reported in infants with VLBW compared with term infants (≥37 weeks) who underwent scanning at approximately the 39th and 41st week of gestation.[12,13] Furthermore, cerebellar volume reduction has been associated with VPT birth when compared with full-term control subjects at term.[14] Other studies only found a decrease in cerebellar volume that was related to the presence of white matter injury in preterm infants compared with control subjects.[15,16]

In individuals with a history of preterm birth, brain tissue differences are still present in early adolescence and adulthood.[17-22] At 15 years of age, reduction of cerebellar volume was observed when comparing VPT born adolescents with full-term control subjects.[23] Cerebellar volume was reduced with time in the VPT individuals when they were scanned again at age 18 years, and cerebellar volume remained stable in term-born control subjects.[24] Thus, these studies show an association between preterm birth and disturbed cerebellar development, not only shortly after birth but also in later life.

Most of these studies focussed on infants with VLBW without taking gestational age (GA) into account or vice versa. As a result, these studies also include

BW	Birth weight
DZ	Dizygotic
GA	Gestational age
IC	Intracranial
MRI	Magnetic resonance imaging
NTR	Netherlands Twin Register
PT	Preterm
VLBW	Very low birth weight
VPT	Very preterm

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infants who are small for GA. These infants have an increased risk for impaired developmental outcome at later age.[25] Furthermore, other medical complications at birth and brain injuries are more often present in infants who are VPT and small for GA. These infants could present a specific high-risk group within the larger group of all premature births. Although infants born after 32 weeks of gestation and within the normal range of birth weight (>1500 g) are considered to be a low-risk group, recent research observed increased deficits in developmental trajectories.[5-7] We explored the association among brain volumes at 9 years of age and gestational age and birth weight in a sample of 192 preterm and term children. All children were born with a birth weight >1500 g and without major medical complications.

Methods

Subjects

A total of 224 children from monozygotic and dizygotic (DZ) twin pairs were recruited from the Netherlands Twin Register (NTR[26]) at the age of 9 years. The twin pairs all participated in a larger ongoing study to explore the genetic and environmental influences on individual differences in brain maturation around puberty.[27,28] Data on GA and BW were obtained with a survey sent to the mothers shortly after birth. Exclusion criteria for participating in the MRI study consisted of having a pacemaker, any metal materials in the head (including dental braces), chronic use of medication, a known major medical problem (eg, known neurologic problems, physical or sensory disabilities) or psychiatric history (parents or children), and participation in special education.

A total of 207 individuals completed the MRI protocol. One monozygotic twin pair was excluded from analysis because of being VPT on the basis of short pregnancy duration (<32 weeks). Children with VLBW were excluded (<1500 g; n = 3). The Wechsler Intelligence Scale for Children-III was administered, and children with an IQ <70 were excluded (n = 3).

A total of 192 children were included in the analyses (98 female and 94 male). The mean GA of the children was 36.8 weeks (SD, 1.6 weeks), with a range of 32.5 to 40 weeks. Seventy-eight children were born preterm, and 114 children were born at 37 weeks gestation or later. The mean birth weight was 2614.6 g (SD, 438.6 g), with a range of 1525 to 3820 g. After birth, 91 children remained in an incubator (for an average of 6 days). The mean age of the children at the time of the scan was 9.2 years (SD, 0.1 years), with a range of 9.0 to 9.7 years. The mean (SD) of full-scale IQ score was 101.1 (SD, 12.9), with a range of 71 to 143. Parents gave written informed consent to participate in the study. The study was approved by the Central Committee on Research involving Human Subjects of the Netherlands, and experiments were performed in accordance with the Declaration of Helsinki.

Scan Acquisition

Structural MRI of the whole brain was performed on a 1.5-T Achieva scanner (Philips, Eindhoven, the Netherlands). All children had a practice session in a dummy scanner in advance. During this session, children could familiarize themselves with the scan procedure, small space, and the sounds of the MRI machine. Children were able to watch a movie or listen to music during the scan protocol, which took approximately 35 minutes per child. Image-sequences of the whole head were acquired, including a short scout scan for immediate verification of optimal head positioning, a clinical scan that was used for neurodiagnostic evaluation, and a 3-dimensional T1-weighted coronal spoiled-gradient echo scan of the whole head (256 × 256 matrix, TE = 4.6 ms, TR = 30 ms, flip angle = 30°, 160-180 contiguous slices; 1 × 1 × 1.2 mm^3 voxels, field-of-view = 256 mm / 70%), which was conducted for volumetric analysis. Additionally, a diffusion tensor image (DTI-B0: transverse; 15-64 directions; SENSE factor 2.5; flip angle 90°; 60 slices of 2.5 mm; no gap; 128 × 96 acquisition matrix; field-of-view = 240 mm; TE = 78 ms) and a magnetization transfer image scan (transverse; 60 transverse slices of 2.5 mm; no gap; 128 × 96 acquisition matrix; field-of-view = 240 mm; flip angle 8°; TE = 4.5 ms; TR = 37.5 ms) were used for segmentation of the intracranial volume.[29]

Volumetric Measurements

Scans were put in Talairach frame (no scaling) for alignment of brain images and were corrected for inhomogeneities in the magnetic field.[30] Quantitative assessments of the intracranial (IC) volume and brain volumes of total brain, cerebellum, cerebrum, gray and white matter of the cerebrum, and lateral ventricle volumes were performed on the basis of histogram analyses and a series of mathematical morphology operations to connect all voxels of interest, as validated[31,32] and reported.[28] Because of motion artifacts, it was not possible to separate gray and white matter tissue in 11 children. For 10 of these 11 children, it was also not possible to calculate lateral ventricle volumes. In addition, in 2 children only the segmentation of lateral ventricles was missing. As a result, the analyses on gray and white matter volumes included data from 181 children, and the analyses on lateral ventricles included data from 180 children.

Statistical Analyses

The effects of GA and BW on brain volumes and IQ were tested with regression analyses. To control for familial dependency, data were analyzed with a structural equation modeling approach. The covariance structure in twin pairs was simultaneously modeled with the fixed effects of BW and GA on mean brain volumes and IQ.[33] For all analyses, the software package Mx (Myricom; www.myri.com/scs/download-mx10g.html) was used.[34]

GA was tested in 2 ways. First, GA was modeled as a continuous variable (in weeks). Second, with dichotomizing GA with a threshold at 37 weeks, group differences on brain volumes and cognitive abilities were explored in children born preterm (ie, 32.0-36.5 weeks) or at term (ie, 37-40 weeks). In all tests for brain volumes, IC volume, age at time of scan, and sex were included as co-variates. The full regression

model to describe the observed variance in brain volumes is given by this equation:

$$\text{Brain volume} = \text{Intercept} + (\beta_{ga} * \text{GA}) + (\beta_{bw} * \text{BW}) + (\beta_{age} * \text{age}) + (\beta_{sex} * \text{sex}) + (\beta_{ic} * \text{IC})$$

All parameters were estimated with maximum likelihood. The effects of GA and BW were tested by constraining the regression coefficient at 0 (ie, the effect of GA was tested while correcting for effects of BW and vice versa). Comparison of the models was done with likelihood ratio χ^2 tests. These tests compare the differences between –2*log likelihood (which is χ^2 distributed) of the full model with that of the restricted nested model against the corresponding degrees of freedom.

Results

Means (SD) of GA, BW, absolute brain volumes, and intelligence scores are presented in Table I. Brain measures and IQ were all normally distributed, except for lateral ventricle volume. After a logarithmic transformation, the lateral ventricle volumes were normally distributed.

GA and age at the time the MRI was performed were not correlated with each other (ie, children who were scanned at a younger age were not the children with shorter pregnancy duration; r = .01, P = .94). Absolute brain volumes were significantly larger for boys than for girls for all measures. Children born preterm did not differ in IQ compared with children born ≥37 weeks (P = .08).

Results of structural equation model fitting are presented in Table II. First, effect of GA was tested on mean brain volumes and IQ scores. GA had a significant effect on cerebellar volume (P = .002), indicating that children who were born at a later GA had a larger cerebellar volume at 9 years of age (β = 1.98 mL/week). The Figure depicts the association between GA and relative cerebellar volume (ie, corrected for BW, IC volume, age at time of scan, and sex). By dichotomizing GA, cerebellum volume was smaller for children born preterm (estimated value for deviation between groups was 5.7 mL; P = .006), while correcting for differences in BW, sex, age, and IC volume. No significance effects of GA were found for the other brain volumes. To explore whether this effect could be explained with differences in general cognitive abilities, intelligence scores were included as a co-variate. GA still had a significant effect on cerebellar volume (P = .002). Thus, the association between GA and cerebellar volume could not be explained by differences in intelligence scores. GA had no significant effect on the other brain measures (ie, total brain, total cerebral and cerebral gray and white matter, and lateral ventricle volumes).

Second, the effect of BW on brain volumes was tested, while correcting for GA, IC volume, age at scan, and sex.

Table I. Mean gestational age, birth weight, and age at time of scan, standardized IQ scores, and absolute brain measurements of the children included in the analyses

	Mean (SD)	Range	n
GA (weeks)	36.8 (1.6)	32.5-40.0	192
BW (g)	2614.6 (439.6)	1525-3820	192
Age at time of scan (years)	9.2 (0.1)	9.0-9.7	192
Full scale IQ	101.1 (12.9)	71-143	192
Intracranial volume (mL)	1468.3 (127.0)	1213.2-1813.2	192
Total brain volume (mL)	1357.4 (115.4)	1120.5-1641.7	192
Cerebrum (mL)	1193.7 (105.6)	966.3-1458.3	192
Cerebellum (mL)	153.2 (13.8)	126.3-191.9	192
Cerebral gray matter (mL)	742.2 (66.9)	592.8-905.4	181
Cerebral white matter (mL)	451.5 (48.2)	340.5-579.7	181
Lateral ventricles (mL)	9.2 (6.6)	2.1-55.0	180

No significant effects were observed for BW on any of the brain volumes. Children born with lower BW had lower scores on the IQ test (β = .49 points/per 100 g; P = .03). When IC volume was included as a co-variate, the effect of BW on IQ score no longer reached significance (P = .30). To gain a more comprehensive view of this relationship, BW was tested for its effect on IC volume. Higher BW was associated with larger IC volume (P < .01), corrected for GA, sex, and age at scanning.

Discussion

We explored volumetric brain measurements at 9 years of age in normally developing children with a GA between 32 and 40 weeks and within the normal range of birth weight, from 1525 to 3820 g. Children born preterm had a smaller cerebellar volume compared with children born ≥37 weeks. We found that shorter GA was associated with a relatively smaller cerebellar volume at 9 years. These analyses were corrected for BW, IC volume, age at time of scan, and sex. Thus, the reported effects were to a large extent independent of overall head size differences. GA had no significant effect on the other brain volumes or on IQ. We found that lower BW was associated with lower IQ score at age 9 years. When IC volume was included as a co-variate, the effect of BW on IQ score did not reach significance anymore. BW had no effect on any of the brain volumes.

Because of the number of tests that we performed, false-positive results were possible. Therefore, an adapted significance threshold was calculated to control for the possible presence of multiple testing effects (http://gump.qimr.edu.au/general/daleN/matSpD/). On the basis of the correlation matrix of the variables tested (ie, brain volumes, IQ), the experiment-wide significance threshold required to keep the type I error rate at 5% should be P = .006. As a result, the effect of GA on cerebellar volume (P = .002) is still significant after a stringent correction for multiple comparisons. The effect of BW on IQ (P = .03) must be interpreted with caution.

The results of the effect of GA on cerebellar volume are in agreement with earlier studies. Reduced cerebellar volume

Table II. Results of the model fit analyses on the mean volumetric measures at age 9 years

	Estimated β (unstandardized)	95% CI	*P* value
Total brain			
GA	0.822	−1.24-2.87	NS
BW	0.003	−0.004-0.010	NS
Cerebellum			
GA	1.98	0.741-3.18	.002
BW	−0.002	−0.005-0.001	NS
Cerebrum			
GA	−1.59	−3.98-0.804	NS
BW	0.005	−0.001-0.012	NS
Gray matter			
GA	−1.76	−4.91-1.38	NS
BW	0.003	−0.007-0.013	NS
White matter			
GA	−0.004	−2.96-2.96	NS
BW	0.004	−0.005-0.013	NS
Lateral ventricle			
GA	0.362	−5.68-6.37	NS
BW	0.002	−0.017-0.021	NS
Total IQ			
GA	−1.45	−3.04-0.0133	NS
BW	0.005	0.001-0.009	.030

The estimated β value of GA and BW on brain volumes and total IQ are given with the 95% CI, while correcting for sex, IC volume, age at scanning, and BW or GA, respectively.
NS, Not significant.

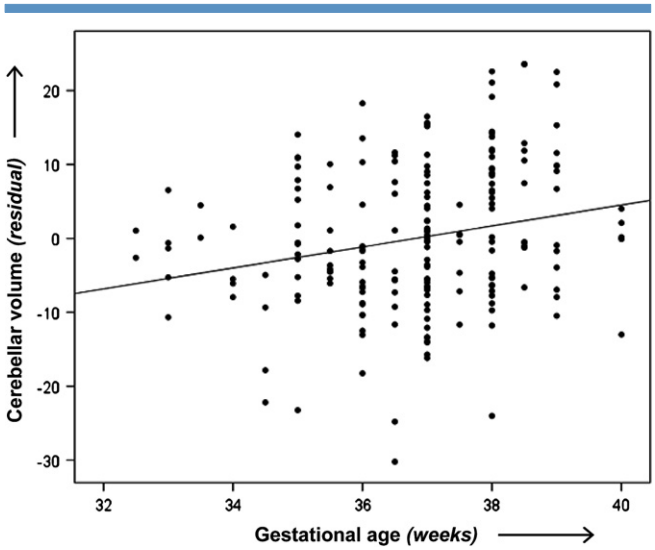

Figure. Association between gestational age (weeks) and relative cerebellar volume. For each individual the unstandardized residual was calculated (ie, corrected for birth weight, IC volume, sex, age at time of scan). Children who were born at a later gestational age had a relatively larger cerebellar volume at 9 years of age (β = 1.98 mL/week; *P* = .002).

was previously found in preterm and VPT infants (range, 23-37 weeks gestation; mean BW, 1341 g) scanned at term compared with full-term infants.[14] In contrast, other studies only found a decrease in cerebellar volume that was related to the presence of white matter injury in preterm infants compared with control subjects.[15,16]

In adolescence, reduction of cerebellar volume was also observed at approximately the age of 15 years, when young adults born VPT (<32 weeks of gestation) were compared with full-term control subjects.[23] In VPT children, the cerebellar volume decreased in the period from age 15 to 18 years, while cerebellar volume remained stable in term-born control subjects.[24] Our results illustrate that the relationship between preterm birth and disturbed cerebellar development is not limited to VPT children, but is also present in preterm children with BW >1500 g.

Furthermore, our findings support the notion that during the last trimester of pregnancy the cerebellum undergoes a very active state of development.[14] It is known that the cerebellum reaches maturity late, comparable with the prefrontal cortex.[35] Recently, the role of the cerebellum has been acknowledged in cognitive and emotional functioning.[36-38] Moreover, the cerebellum has been implicated in the pathology of several neuropsychiatric disorders.[39]

A lower BW was associated with lower IQ, while correcting for GA, sex, and age. This result is in line with earlier studies reporting that childhood IQ measures are influenced by BW.[8-10] The effect of BW on IQ disappeared when differences in IC volumes were taken into account. Additional analyses showed that BW had an effect on absolute IC volume, suggesting that the association found between BW and childhood IQ is mediated by individual differences in head size.

There was no effect of BW on any of the brain volumes at age 9 years. These findings are partly consistent with other MRI studies. Some of these studies report smaller brain volumes in VLBW infants compared with normal BW infants,[13,21] but other studies found no effects of BW on total cerebral brain volume.[17,19,23] Although most of these studies did not find effects on total cerebral volume, they do report differences in local gray matter and white matter differences. An important difference compared with this study is that other studies have included VPT infants of <32 weeks of gestation. Disruption of development or severe injuries within the cerebellum are most prominent in infants who were born at <32 weeks of gestation[40] and have been associated with poor neurological outcome at a later age.[41]

Infants born after 32 weeks of gestation or with BW >1500 g are, in general, considered to be a late-preterm or low-risk group. However, recent research noted that this group of infants has an increased risk of deficits in neurologic development and a higher risk for developmental delay and school-related problems at later age.[5-7] This present sample included a wide GA range (32-40 weeks) and BW >1500 g. These birth parameters are within the normal range for average twin pregnancies.[42,43] More important, although the mean BW of twins is lower compared with that of singletons, there were no children included in this sample who had a VLBW. This study can help to get a better understanding of the developmental trajectory in this group of children.

Data on possible birth complication, pregnancy duration, and BW of the twins were based on questionnaires filled in by the mothers shortly after birth, a method found to be highly

accurate.[44-46] The mothers also reported the number of days twins spent in an incubator after birth. The average period of being in an incubator was 6 days, and this is not uncommon for multiple birth and infants who are born preterm.

A limitation of this study is whether or not these findings in twins can be generalized to the general population, consisting of mostly singletons. Although for most multiple pregnancies, children are delivered preterm and with lower BW compared with singletons, the mechanisms that initiate preterm labor are still not fully understood. Associations are found with maternal factors (eg, age, weight, socioeconomic status), fetal factors (eg, sex), and environmental factors (eg, substance abuse, infection, traumatic life events).[47,48] Genetic susceptibility and interactions between factors also may play a role.[49] Twins undergo catch-up growth during childhood, and by the age of 5 years, growth differences between twins and singletons have disappeared.[50] In adulthood, cognitive performances and brain volumes are comparable between singletons and twins.[51,52] Thus, it might be argued that these results in twins can be generalized to the singleton population.

Another limitation of this study might be the exclusion criteria. Because deficits in cognitive functioning are associated with deficits in brain structure and volumes, it is possible that some of the subjects with the most prominent sequelae of cerebellar volumetric loss are not included in this study. However, this study still exhibits a wide range of individual differences in general cognitive abilities and is a good representation of healthy developing children. It is likely that the observed effect might be even more pronounced if children with known developmental, cognitive, or brain developmental deficits would be included in the analyses.

All children were 9 years old at time of the scan, and age was not associated with GA. The association between GA and cerebellar volumes was not moderated by age at the time of scan, but appears to be very specific for the duration of pregnancy. Recently, GA was found to be decreasing in a linear fashion in twin birth in the last 2 decades, at an average of 0.25 days per year.[43] Furthermore, BW appeared to decrease for infants born before 32 weeks of gestation and increase after 32 weeks of gestation.[43] Therefore, it is important not to ignore this low-risk group, and future research should focus on their long-term developmental trajectories.

This study showed that younger GA was associated with a relatively smaller cerebellar volume at the age of 9 years while correcting for effects of sex, age at time of scan, BW, and IC volume. Our results extend the relationship between preterm birth and disturbed cerebellar development at birth and later life in VPT children to the group of preterm children. Children with lower BW scored lower on intelligence tests, but this effect disappeared when IC volume differences were taken into account. This study contributes to the understanding of the long-term effects of preterm birth and shows that effects of GA and BW on brain volumes and IQ is not limited to the group of VPT infants or infants born with VLBW. Further research should focus on the long-term outcomes of the developmental trajectories of late-preterm children. ■

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