Uncomplicated Intraventricular Hemorrhage Is Followed by Reduced Cortical Volume at Near-Term Age

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ABSTRACT. Background. Intraventricular hemorrhage (IVH) is the most common brain injury among premature infants. Neonates with IVH are at greater risk of impaired neurodevelopmental outcomes, compared with those without IVH. IVH causes destruction of the germinal matrix and glial precursor cells, with possible effects on cortical development.

Objective. To investigate cortical development after uncomplicated IVH (with no parenchymal involvement and no posthemorrhagic hydrocephalus). We hypothesized that uncomplicated IVH would be followed by reduced cortical volume among premature infants at near-term age.

Methods. A prospective cohort study was conducted, with preset selection criteria. Infants with small-for-gestational age birth weight, congenital abnormalities or brain malformations, metabolic disorders, recurrent sepsis, or necrotizing enterocolitits were excluded. Also, infants with posthemorrhagic hydrocephalus, parenchymal involvement of hemorrhage, cystic periventricular leukomalacia, or persistent ventriculomegaly were excluded, on the basis of routine serial ultrasonographic assessments. Three-dimensional images were acquired for 23 infants at near-term age, with 3-T magnetic resonance imaging and a magnetization-prepared rapid gradient echo sequence. Image analysis and segmentation of the cerebral cortex were based on signal contrast and anatomic localization. The cortical gray matter (CGM), subcortical gray matter, white matter, and intraventricular cerebrospinal fluid volumes of 12 infants with uncomplicated IVH were compared with those of 11 infants without IVH, using multivariate analysis of variance.

Results. The multivariate analysis of variance for the regional brain volumes in the 2 groups indicated significance (Wilks’ Λ = 0.546). The CGM volume was significantly reduced in the IVH group (no-IVH group: 122 ± 12.9 mL; IVH group: 102 ± 14.6 mL; F = 13.218). This finding remained significant after testing for possible confounding factors and adjustment for size differences between the infants (F = 9.415). There was no difference in the volumes of subcortical gray matter, white matter, and cerebrospinal fluid.

Conclusions. This is the first study to document impaired cortical development after uncomplicated IVH. The impairment was demonstrated by a 16% reduction in cerebral CGM volume at near-term age. The finding supports concerns regarding possible glial precursor cell loss after germinal matrix IVH, but its clinical significance is still unclear.

Intraventricular hemorrhage (IVH) is the most common brain injury among premature infants and is the most common type of neonatal intracranial hemorrhage.1,2 The incidence is directly correlated with the degree of prematurity. As the survival rates for premature infants continue to increase, IVH will continue to be a major problem in modern neonatal intensive care units.1,2 It is known that IVH with associated ventriculomegaly or parenchymal involvement is associated with neurodevelopmental handicaps and disabilities.3–5 Furthermore, studies have indicated that even children with IVH but no ventriculomegaly or parenchymal involvement are at relatively higher risk for cognitive or motor disabilities, compared with those without IVH.6,7

The basic lesion in IVH is bleeding into the highly cellular, richly vascularized, primitive tissue of the subependymal germinal matrix. Bleeding into the germinal matrix causes destruction and possible loss of glial precursor cells, which are still in the process of migrating to the cortical layers.8,9 This may impede neural development, which may be manifested as reduced cortical volume. We therefore hypothesized that uncomplicated IVH (defined as IVH with no parenchymal involvement and no posthemorrhagic hydrocephalus) would be followed by reduced cortical gray matter (CGM) volume. To assess the effects of IVH on cortical volume, a cohort study was conducted. Serial ultrasonographic assessments were used for the diagnosis of brain pathologic conditions, and our specialized, neonatal, 3-T magnetic resonance imaging (MRI) system was used as the investigational tool for volumetric anal-
yses. Three-dimensional images of the cerebrum were segmented into CGM, subcortical gray matter (SGM), and white matter (WM), allowing quantitative volumetric analyses of these tissues.

METHODS

Subjects
Subjects were recruited from the neonatal intensive care unit of St. Joseph’s Hospital (London, Canada). Infants with birth weights of <1500 g, appropriate for gestational age, were eligible to enter the study. Exclusion criteria included congenital infections or malformations, metabolic diseases or hypoglycemia, central nervous system infections, brain malformations, seizures, hypoxic-ischemic injury, necrotizing enterocolitis, bowel perforation, and recurrent sepsis (defined as ≥2 episodes of positive blood cultures). Also, infants with cystic periventricular leukomalacia, persistent ventriculomegaly (ventriculomegaly present at near-term age), or any brain hemorrhage with parenchymal involvement and posthemorrhagic hydrocephalus were excluded, on the basis of clinical criteria and routine ultrasonographic findings. The infants entered the study when they completed their 34th week (postmenstrual age) and written informed consent was obtained from the parents (with ethics approval from the University of Western Ontario Health Sciences Research Ethics Board).

Routine Ultrasonography
Infants underwent serial routine cranial ultrasonographic assessments. All infants enrolled in the study underwent an ultrasonographic evaluation at the postnatal age of 7 days, all underwent assessments at least monthly, and all underwent ≥2 assessments before the corrected gestational age of 34 weeks. In all cases, there was no evidence of IVH at the postmenstrual age of 34 weeks. Evaluations were performed by qualified radiology technicians, with a HDI 3500 scanner (Advanced Technology Laboratories, Bothell, WA) with a broadband transducer of 5 to 8 MHz. Each scan received a formal clinical reading by a radiologist, who provided a diagnosis and grading of IVH, on the basis of the criteria described by Papile et al.11 For all neonates, the diagnosis and grading of IVH were consistent with assessments by a neonatologist.

MRI
The infants in our cohort underwent MRI at near-term postmenstrual age. The infants in our cohort underwent MRI at near-term postmenstrual age, when the contrast between gray matter and WM is still relatively low. The use of higher-than-conventional field strength (3 T) provides a greater signal-to-noise ratio.12 MRI studies were performed at 34.3 to 37.3 weeks postmenstrual age, with a dedicated, neonatal, 3-T MRI system (IMRIS, Winnipeg, Canada). To avoid the need for repeated sequences (because of motion) and to minimize the time that the infants spent in the MRI scanner, a single dose of chloral hydrate (50 mg/kg) was administered orally, for sedation, before scanning. A neonatal nurse and a neonatologist were present with the infant for the duration of the scanning. Infants were continuously monitored with pulse oximetry (8600 FO; Nonin Medical, Plymouth, MN). The heads of the infants were lightly cushioned with towels. To reduce acoustic noise, the head coil was lined with a layer of barium sulfate-loaded, vinyl-foam composite (type B-14C sound-proofing material; Wilrep Ltd, Mississauga, Ontario, Canada). In addition, the image sequences were optimized for low acoustic noise exposure (<85 dB), and ear shields (Ear Classic; Aearo Co, Indianapolis, IN) were used to reduce noise.

Three-dimensional images of the cerebrum were acquired in 6.5 minutes with a center-out acquisition, magnetization-prepared rapid gradient echo sequence, with timing parameters optimized for neonatal brain imaging.13 Imaging parameters were as follows: intersegment repeat time: 5200 milliseconds; inversion time: 2250 milliseconds; repeat time: 10 milliseconds; echo time: 5 milliseconds; image bandwidth: 33.3 kHz; flip angle: 10 degrees; matrix size: 120 × 120 × 75; field of view: 160 × 160 × 100 mm (giving an isotropic resolution of 1.3 mm).

Image Analysis
Three-dimensional images were analyzed by the same analyst, with Analyze 4.0 software (Biomedical Imaging Resources, Mayo

Fig 1. Segmentation of the CGM at the level of the body of the lateral ventricles.

Foundation, Rochester MN). The analyst was trained in neonatal brain anatomy and was blinded with respect to the subjects analyzed. The volumetric analysis included the cerebral hemispheres,
Subjects involved or posthemorrhagic hydrocephalus, 6 gestational age, 7 infants had IVH with parenchymal fants were excluded from the study, on the basis of to the neonatal intensive care unit. Forty-three in-

ture infants of very low birth weight were admitted overlapping variability with other covariates.18

ters (SPSS Inc, Chicago, IL), to test for differences in the regional multivariate analysis of (multiple tests of between-sub-

closed with positive blood cultures. Five infants re-
ned with positive blood cultures. Five infants re-

ted with positive blood cultures. Five infants re-

the lateral and third ventricles, the thalamus, and the basal gan-

Segmentation was based on the signal contrast between tissues and the anatomic localization, allowing grouping of voxels into regions and definition of the boundaries of different structures. Segmentation of regions within the cerebrum was performed on axial slices, by using signal intensity thresholds and tracing (combination of automated and manual functions; Figs 1 and 2). Images were segmented into CGM, WM, intraventricular cerebrospinal fluid (CSF), and SGM (basal ganglia and thalamus could not be differentiated from each another at the very young age of these subjects).

For each slice, the volumes of CGM, SGM, WM, and intraven-

tricsal CSF were calculated as the products of the total number of voxels in the segmented brain image, the dimensions of the voxels, and the thickness of the segmented brain slice. The total volumes of the different tissue types were calculated by adding the vol-

ues of all slices. The total cerebral volume represented the sum of the volumes of the different tissue types. The SD of the intraob-

server variability was <2.1%. The difference between 2 analysts was <2.5%.

Statistical Analyses

A power analysis was conducted first, to ensure an adequate sample size for hypothesis testing. We wished to have power of >0.8 with α ≤ .05, to detect a 15% reduction in CGM volume. The size of our sample met these criteria.16,17

Statistical analyses were performed with SPSS 11.5 for Win-

dows (SPSS Inc, Chicago, IL), to test for differences in the regional brain volumes between the 2 groups. Multivariate analysis of variance was conducted for the regional brain volumes (CGM, SGM, WM, and CSF), to minimize the family-wise type 1 error from multiple univariate analyses (multiple tests of between-sub-

jects effects). Potential confounding factors were tested for signif-

icance by using a multiple regression analysis and removing the overlapping variability with other covariates.10

RESULTS

Subjects

During the patient recruitment period, 77 prema-

ture infants of very low birth weight were admitted to the neonatal intensive care unit. Forty-three in-

fants were excluded from the study, on the basis of the preset selection criteria (18 infants were small for gestational age, 7 infants had IVH with parenchymal involvement or posthemorrhagic hydrocephalus, 6 infants had congenital abnormalities or brain malforma-

ions, 6 infants had >2 episodes of sepsis with positive blood cultures, 1 infant had necrotizing enterocolitis, 2 infants had cystic periventricular leu-

komalacia, diagnosed ultrasonographically, and 3 in-

fants had persistent ventriculomegaly, defined qualit-

atively).

Thirty-four infants were eligible to enter the study. After written informed consent was obtained, 25 pre-

mature infants of very low birth weight were en-

rolled. All infants were of white ethnicity. No preg-

nancy was a result of fertility treatment (including in vitro fertilization). No infant received repeated courses of prenatal corticosteroids, and in no case was chorioamnionitis clinically diagnosed. MRI scans obtained for 2 infants were marred by motion artifacts and were excluded from subsequent analyses. For 11 infants, no brain pathologic lesions were identified in routine ultrasonographic assessments; the infants were assigned to the no-IVH group. For 12 infants, IVH was demonstrated in routine cranial ultrasonographic assessments; these infants were as-

signed to the IVH group (7 infants had grade I IVH, 4 infants had grade II IVH, and 1 infant had grade III IVH, with no persistent ventriculomegaly; the IVH was bilateral for 8 infants). Thirteen infants had sep-

sies resulting from Gram-positive streptococci, as con-

firmed with positive blood cultures. Five infants re-

ceived 1 course of dexamethasone therapy for bronchopulmonary dysplasia (0.1 mg/kg per day for 3 days and 0.05 mg/kg per day for 2 days).

Demographic data (before and at birth) are shown in Table 1. The variations of neonatal clinical data are shown in Table 2.

Confounding Factors

Gestational age at birth, gender, sepsis, corrected gestational age, and weight at the time of MRI were tested as possible confounding factors for the cere-

bral volumes between the 2 groups. Tested sepa-

rately, gestational age at birth, gender, and sepsis were not significant confounding factors (all P > .2), whereas the corrected gestational age and weight at MRI were significant (P < .01). Similarly, in the multiple regression analysis (step-down model), ges-

tational age, gender, and sepsis were not significant covariates and were sequentially discarded. Also, there was overlapping variability between the re-

maining variables of corrected gestational age and

TABLE 1. Demographic Data (Prenatal and Birth)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No IVH (n = 11)</th>
<th>IVH (n = 12)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y*</td>
<td>28.3 ± 5.8 (19–39)</td>
<td>26.8 ± 5.5 (19–35)</td>
<td>t = 0.61, P = .55</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension (inf.)</td>
<td>1</td>
<td>1</td>
<td>X² = 0.01, P = .95</td>
</tr>
<tr>
<td>Prenatal corticosteroids (inf.)</td>
<td>9</td>
<td>8</td>
<td>X² = 0.68, P = .41</td>
</tr>
<tr>
<td>Chorioamnionitis (inf.)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cesarean section (inf.)</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Male (inf.)</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Twins (inf.)</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cord arterial pH*</td>
<td>7.27 ± 0.05 (7.20–7.33)</td>
<td>7.28 ± 0.07 (7.16–7.36)</td>
<td>t = -0.43, P = .67</td>
</tr>
<tr>
<td>Cord arterial base deficit*</td>
<td>5.4 ± 2.1 (1.4–7.9)</td>
<td>4.6 ± 2.5 (1.5–8.1)</td>
<td>t = 0.79, P = .44</td>
</tr>
<tr>
<td>Apgar score at 5 min†</td>
<td>8 (7–9)</td>
<td>8 (8–9)</td>
<td>Z = -1.4, P = .16‡</td>
</tr>
<tr>
<td>Gestational age at birth, wk*</td>
<td>27.9 ± 2.5 (24.6–31.7)</td>
<td>27.9 ± 2.2 (24.6–32)</td>
<td>t = 0.02, P = .99</td>
</tr>
<tr>
<td>Birth weight, g*</td>
<td>1106 ± 277 (645–1455)</td>
<td>1047 ± 257 (570–1470)</td>
<td>t = 0.53, P = .60</td>
</tr>
<tr>
<td>Birth head circumference, cm*</td>
<td>25.9 ± 2.3 (22–29)</td>
<td>25.5 ± 2.2 (21–28.5)</td>
<td>t = 0.37, P = .72</td>
</tr>
</tbody>
</table>

inf. indicates infant. All P values are 2-tailed.
* Mean ± SD (range).
† Median (range).
‡ Wilcoxon test.
TABLE 2. Neonatal Clinical Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No IVH (n = 11)</th>
<th>IVH (n = 12)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome (inf.)</td>
<td>10</td>
<td>9</td>
<td>$\chi^2 = 1.01, P = .32$</td>
</tr>
<tr>
<td>Inotropes (inf.)</td>
<td>6</td>
<td>6</td>
<td>$\chi^2 = 0.05, P = .83$</td>
</tr>
<tr>
<td>Postnatal indomethacin (inf.)</td>
<td>6</td>
<td>3</td>
<td>$\chi^2 = 2.10, P = .15$</td>
</tr>
<tr>
<td>Postnatal corticosteroids (inf.)</td>
<td>2</td>
<td>3</td>
<td>$\chi^2 = 0.16, P = .69$</td>
</tr>
<tr>
<td>Sepsis (inf.)</td>
<td>5</td>
<td>8</td>
<td>$\chi^2 = 1.05, P = .31$</td>
</tr>
<tr>
<td>Blood transfusion (inf./transfusions per inf.)*</td>
<td>8/2 (0–8)</td>
<td>9/3 (0–10)</td>
<td>$\chi^2 = 0.02, P = .90$</td>
</tr>
<tr>
<td>Caffeine (inf.)</td>
<td>5</td>
<td>4</td>
<td>$\chi^2 = 0.35, P = .55$</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia at 36 wk (inf.)</td>
<td>8</td>
<td>8</td>
<td>$\chi^2 = 0.10, P = .75$</td>
</tr>
<tr>
<td>Ventilation, d*</td>
<td>37 (0–70)</td>
<td>33 (0–61)</td>
<td>$Z = -0.7, P = .50^+$</td>
</tr>
<tr>
<td>Breast milk, d*</td>
<td>9</td>
<td>11</td>
<td>$\chi^2 = 0.49, P = .48$</td>
</tr>
<tr>
<td>Full feeds, d*</td>
<td>33 (12–50)</td>
<td>30 (8–51)</td>
<td>$Z = -0.7, P = .64^+$</td>
</tr>
<tr>
<td>Postmenstrual age at scan, wk‡</td>
<td>35.9 ± 0.8 (34.6–36.9)</td>
<td>35.7 ± 0.9 (34.3–37.3)</td>
<td>$t = 0.47, P = .65$</td>
</tr>
<tr>
<td>Weight at scan, g‡</td>
<td>2365 ± 291 (1960–2890)</td>
<td>2138 ± 294 (1760–2836)</td>
<td>$t = 1.85, P = .08$</td>
</tr>
</tbody>
</table>

inf. indicates infant. All P values are 2-tailed.
* Median (range).
† Wilcoxon test.
‡ Mean ± SD (range).

weight at MRI. The significant confounding factor was weight (Wilks’ $\lambda = 0.440, P < .01$, for weight; Wilks’ $\lambda = 0.645, P = $ not statistically significant, for the corrected gestational age), and the data on brain volumes were adjusted for the infants’ weight at the time of MRI.

Cerebral Volumes

The multivariate analysis of variance for the regional brain volumes (CGM, SGM, WM, and CSF) in the 2 groups indicated significance with raw data (Wilks’ $\lambda = 0.546, P < .05$) or adjusted data (Wilks’ $\lambda = 0.586, P < .05$). The tests of between-subjects effects showed that the volume of the CGM (hypothesis) was significantly reduced in the IVH group (Table 3; Figs 3 and 4). There was no difference in the SGM, WM, and CSF volumes (Table 3).

The total cerebral volume, as the sum of CGM, SGM (basal ganglia and thalami), WM, and intraventricular CSF volumes, was 274 mL (SD: 16.2 mL; 95% confidence interval [CI]: 263-285 mL) for the infants with IVH and 252 mL (SD: 28.7 mL; 95% CI: 235-271 mL) for the infants with IVH ($F = 4.851, P = .039$). The difference reflected the reduction in the CGM volume. The relative CGM volume (as a percentage of the total cerebral volume) was 44.7% (SD: 4.5%; 95% CI: 41.7-47.7%) for the infants with no IVH and 40.1% (SD: 2.6%; 95% CI: 38.4-41.7%) for the infants with IVH ($F = 9.281, P = .006$).

DISCUSSION

The germinal matrix represents the remains of the germinative zone; it becomes less prominent during the final 16 weeks of gestation and is essentially exhausted by term.19 Between 10 and 24 weeks of gestation, this cellular region is the source of cerebral neuronal precursors.20,21 After 24 weeks of gestation, the neuronal migration has been completed but the germinal matrix still provides glial precursors, which become cerebral oligodendroglia and astrocytes. At this late gliogenesis stage, astrocytes migrate to the upper cortical layers and are crucial for neuronal survival and normal development of the cerebral cortex.8 IVH and germinal matrix destruction may cause loss of astrocytic precursor cells and have effects on cortical development.9,22

To our knowledge, this is the first study to document impaired cortical development after uncompli-

TABLE 3. Regional Cerebral Volumes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No IVH (n = 11)</th>
<th>IVH (n = 12)</th>
<th>F</th>
<th>P</th>
<th>F*</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGM (mL)</td>
<td>122 ± 12.9 (114–131)</td>
<td>102 ± 14.6 (92–111)</td>
<td>13.218</td>
<td>.002</td>
<td>9.415</td>
<td>.006</td>
</tr>
<tr>
<td>SGM (mL)</td>
<td>14 ± 1 (13.4–14.7)</td>
<td>12.9 ± 1.6 (10.7–16.5)</td>
<td>4.123</td>
<td>NS</td>
<td>1.023</td>
<td>NS</td>
</tr>
<tr>
<td>WM (mL)</td>
<td>128 ± 19 (115–141)</td>
<td>128 ± 14 (120–137)</td>
<td>0.001</td>
<td>NS</td>
<td>0.235</td>
<td>NS</td>
</tr>
<tr>
<td>CSF (mL)</td>
<td>9.5 ± 5 (6.1–12.9)</td>
<td>9.5 ± 4.4 (6.7–12.3)</td>
<td>0.000</td>
<td>NS</td>
<td>0.231</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are displayed as mean ± SD (95% CI of mean). NS indicates not significant.
* Values corrected for infant’s weight at the time of MRI.
cated IVH. The impairment was demonstrated by a reduction in cerebral CGM volume in the IVH group, and this finding remained statistically significant even after correction for the significant confounding factor of weight at the time of MRI and removal of scaling effects and overall size differences between the infants in the 2 groups. Similarly, there was a statistically significant reduction in the relative CGM volume (as a percentage of total cerebral volume) in the IVH group.

The prospective design of our study, with strict preset selection criteria, was important because we excluded brain pathologic conditions and complications that are known to have or could potentially have effects on cortical development.23–25 However, there is a possibility that ultrasonography did not reveal subtle or diffuse global brain injuries, such as noncystic periventricular leukomalacia, which could have effects on cortical development.26–30 Also, we cannot exclude the possibility that brain injury other than IVH would be detectable only later in life.25

Despite the advantages of our having excluded several potential factors for brain injury other than uncomplicated IVH and having conducted a conservative statistical analysis, the small sample size is a limitation of this study. However, the size of our sample met the criteria for power analysis and had the level of sensitivity needed to detect group differences in CGM volumes (hypothesis).

The nature of a clinical cohort study introduced the question of confounding factors. Most epidemiologic and clinical data were similar for the 2 groups but, for accurate interpretation of the results, an analysis of possible covariates was performed and the results were corrected accordingly. However, there is evidence regarding the effects of factors such as prenatal or postnatal corticosteroid treatment on cerebral volumes.31,32 Although there were no repeated courses and no differences in administration between the 2 groups, the possibility of different effects among infants, alone or in combination with other parameters, cannot be excluded.

It is important to note that, even with the statistically significant reduction in CGM volume among infants with IVH, it is unclear whether the reduction is clinically significant. At this early age, the brain is still undergoing a process of dramatic growth and maturation.17 It is possible that compensatory mechanisms may support additional development at later times.

Our finding of reduced CGM volume in the IVH group is consistent with concerns raised in the literature regarding the possible effects of astrocytic loss on cortical development.8,9 Moreover, in view of developmental follow-up studies that reported that premature infants with low-grade IVH were at relatively greater risk of impaired outcomes, compared with those without IVH,6,7 our finding of reduced cortical volume may be of clinical significance and may be associated with impaired developmental outcomes.

This volumetric brain analysis, performed with advanced MRI techniques, provides insight into the pathologic features of uncomplicated IVH, which is the most common brain injury among premature infants. The alterations in brain development demonstrated in this report may be taken into consideration when parents are consulted, and closer developmental follow-up monitoring for infants with uncomplicated IVH may be considered. A follow-up study at older ages, incorporating volumetric MRI and neurodevelopmental outcome assessments, is required for full evaluation of the effects of uncomplicated IVH on brain development.

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We thank Dr Kevin Coughlin for assistance with patient recruitment.

REFERENCES

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