New Reference Values for the Neonatal Cerebral Ventricles

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Purpose:
To establish new cross-sectional reference values for the size of the lateral ventricles in a large cohort of neonates between 24 and 42 weeks’ gestational age (GA) as well as longitudinal reference values for the follow-up of very preterm infants born at less than 30 weeks’ gestation.

Materials and Methods:
Institutional review board approval and parental written informed consent were obtained for this prospective cohort study of 625 neonates (58% male patients) with a median GA of 33.4 weeks (range, 24.7–42.6 weeks). All infants underwent cranial ultrasonography (US) within 4 days after birth to evaluate the size of the lateral ventricles. Scanning was repeated in 30I preterm and term neonates within the 1st week of life to assess the presence of ventricular reopening. Seventy-nine very preterm infants (GA, <30 weeks) were prospectively included for cranial US at term-equivalent age (TEA). US measurements were performed of the ventricular index (VI), anterior horn width (AHW), and thalamo-occipital distance (TOD). Statistical analysis was conducted by using a paired t test, multilevel analysis, and analysis of covariance.

Results:
Cross-sectional reference values for the VI and TOD increased with maturity, whereas the AHW remained constant. Vaginal birth was independently associated with a slightly smaller AHW following birth and with an increase in AHW within the 1st week of life (P < .05). Preterm-born infants showed a larger ventricular size at TEA compared with term infants (P < .001).

Conclusion:
New cross-sectional and longitudinal reference curves were established for the size of the neonatal lateral ventricles, which may allow for early identification and quantification of ventriculomegaly due to either posthemorrhagic ventricular dilation or periventricular white matter loss.

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Posthemorrhagic ventricular dilation affects approximately 75% of preterm infants following a severe germinal matrix-intraventricular hemorrhage and represents a potential threat to the developing neonatal brain (1). In infants with progressive ventricular dilation, drainage of cerebrospinal fluid has been shown to improve cerebral hemodynamics and oxygenation and may prevent further brain injury (2,3). To diagnose posthemorrhagic ventricular dilation and evaluate the need for intervention, measurement of ventricular size by means of cranial ultrasonography (US) has been shown to be superior to measurement of head circumference or assessment of clinical symptoms of raised intracranial pressure (4,5). US measurement of the lateral ventricles offers, in addition, a sensitive tool to detect ex vacuo ventriculomegaly in preterm infants due to periventricular white matter loss.

In the early 1980s, Levene (6) was the first to publish reference values for the size of the neonatal lateral ventricles on cranial US images, and his curve is still widely used to decide whether an infant with progressive posthemorrhagic ventricular dilation needs treatment. Since then, others have also reported nomograms for the neonatal ventricles, among which the reference values by Davies et al are probably best known (4,7–10).

Recently, we reviewed available data on this topic and demonstrated considerable variation among reported reference curves, especially for the most immature infants, who face the greatest risk of developing ventricular dilation (11). A substantial number of studies were conducted more than a decade ago with less-sophisticated US equipment. Not all studies covered the entire neonatal period, and in general, only few extremely low birth weight infants were included in previous research. Furthermore, not all studies excluded neonates with small germinal matrix or intraventricular hemorrhages, which may have influenced reported measurements of ventricular size. In addition, to our knowledge, no longitudinal reference curves are currently available for sequential cranial US evaluation of ventricular size in preterm infants.

Accurate reference values are of importance for infants with posthemorrhagic ventricular dilation, as intervention is started on the basis of changes in ventricular size of only a few millimeters. Longitudinal reference data should enable improved identification of ex vacuo ventriculomegaly in preterm neonates. Therefore, the aims of this study were to establish new cross-sectional reference values for the size of the lateral ventricles in a large cohort of neonates between 24 and 42 weeks’ gestational age (GA) as well as longitudinal reference values for the follow-up of very preterm infants born at less than 30 weeks’ gestation.

### Materials and Methods

Institutional review board approval and written parental informed consent were obtained for this prospective observational cohort study.

### Patients

Between October 2005 and September 2010, 625 neonates were consecutively enrolled, including 217 term infants admitted with the mother on the maternity ward or to the medium care unit and 408 preterm infants admitted to either the medium or intensive care unit of the Wilhelmina Children’s Hospital. To acquire a representative sample size, a minimum of 25 neonates were included per week of gestation (except for 24 and 42 weeks’ GA). GA was determined as the time from the 1st day of the last menstrual period and confirmed with a crown–rump length measurement in the 1st trimester. If the US date differed by more than 6 days from the menstrual date, the US date was used.

### Advances in Knowledge

- Cross-sectional reference curves were established for the size of the neonatal lateral ventricles at cranial US, on the basis of a large cohort of neonates born between 24 and 42 weeks’ gestation.
- Longitudinal reference values were provided for the follow-up of very preterm infants (gestational age, <30 weeks) until term-equivalent age (TEA).
- Ventricular reopening following birth was shown to play only a minor role, with an estimated increase in anterior horn width of 0.7 mm or less within the 1st week of life.
- Preterm-born infants showed enlarged ventricular size at TEA compared with term-born infants (ventricular index: +0.5 mm; anterior horn width: +1.2 mm; thalamo-occipital distance: +3.5 mm).

### Implications for Patient Care

- Our reference values should enable early identification and accurate monitoring of posthemorrhagic ventricular dilation.
- The longitudinal reference curves for preterm-born infants should enable recognition of ex vacuo ventriculomegaly due to periven

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**Abbreviations:**

- AHW = anterior horn width
- GA = gestational age
- TEA = term-equivalent age
- TOD = thalamo-occipital distance
- VI = ventricular index

**Author contributions:**

Guarantors of integrity of entire study, M.J.B., L.S.d.V., F.G., M.J.N.L.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, M.J.B., L.R.P., M.J.N.L.B.; clinical studies, M.J.B., L.S.d.V., F.G., C.K., M.J.N.L.B.; statistical analysis, M.J.B., F.G., L.R.P., E.J.H.M.; and manuscript editing, M.J.B., L.S.d.V., F.G., L.R.P., E.J.H.M., M.J.N.L.B.

Potential conflicts of interest are listed at the end of this article.
Applied exclusion criteria for both preterm and term infants were congenital and chromosomal anomalies, metabolic disorders, perinatal asphyxia, seizures, central nervous system infections, cranial US abnormalities other than mild transient periventricular echogenicities, and an unknown GA.

A subgroup of 115 preterm-born infants (GA < 30 weeks), included between January 2007 and June 2009, was followed prospectively and included for cranial US at term-equivalent age (TEA) if no US abnormalities were observed at sequential examinations or around term. Neurodevelopmental outcome was assessed at 15 months corrected age by using the Griffiths Mental Development Scales. Infants with low scores according to Ivens and Martin (corrected developmental quotient, < 83) were excluded to ensure that the longitudinal reference values were based on a cohort of preterm infants with a favorable outcome (12). In total, one-third of the 115 infants had to be excluded and consequently, 79 preterm-born neonates were eligible for prospective inclusion at TEA (Fig 1)

Measurements

Maternal and neonatal charts were reviewed for demographic and clinical characteristics.

Perinatal and neonatal characteristics considered were maternal pregnancy-induced hypertension disease, prolonged rupture of membranes (> 24 hours), histologic diagnosis of chorioamnionitis, antenatal corticosteroids, multiple birth and monochorionicity, mode of delivery, GA, sex, birth weight, and head circumference.

Postnatal events recorded in the subgroup of preterm infants included mechanical ventilation, administration of hydrocortisone, bronchopulmonary dysplasia defined as need for supplemental oxygen at 36 weeks’ postmenstrual age, inotropic support, persistent ductus arteriosus requiring treatment with indomethacin or surgery, necrotizing enterocolitis, sepsis defined as a positive blood culture, and the infants’ postmenstrual age, weight, and head circumference at TEA.

**Figure 1:** Prospective inclusion of preterm-born neonates (GA < 30 weeks) between January 2007 and June 2009 (*). cUS = cranial US.

**Cranial US.**—The first cranial US scan (hereafter, US 1) was conducted within 4 days following birth. To assess the presence of ventricular reopening, cranial US scanning was repeated within the 1st week of life (hereafter, US 2) in those neonates that underwent US 1 within 48 hours after birth and were still admitted. Neonatal cranial US was performed as part of routine care at the neonatal medium or intensive care unit, whereas term newborns in the maternity ward were scanned for research purposes only. Cranial US at TEA (hereafter, TEA US) was part of the follow-up program of preterm neonates. Subsequent scans (US 2 and/or TEA US) in infants who developed cerebral abnormalities after US 1 were excluded from further analysis.

Cranial US was conducted by a team of experienced examiners including neonatologists (F.G., L.S.d.V. and M.J.N.L.B.) with more than 10 years’ experience in neonatal cranial US as well as medical doctors (M.J.B.) and fellow neonatologists with at least 3 months’ experience in neonatal cranial US, who performed cranial US under supervision of neonatologists (L.S.d.V. or M.J.N.L.B.). Scans were performed by using an Aplio (Toshiba Medical Systems, Zoetermeer, the Netherlands) or ATL 5000 (Philips Medical Systems, Best, the Netherlands) US machine (until 2010) and a Xario scanner (Toshiba Medical Systems) (from 2010 onwards) with a transducer frequency of 5–8 MHz. Scanning was performed at the bedside with the infant’s head in supine position. With the anterior fontanel used as an acoustic window, standard views were obtained in the coronal and sagittal planes. Ventricular measurements were performed offline with ImageJ (version 1.42q; http://rsb.info.nih.gov/ij) or DicomWorks (version 1.3.5; http://www.dicomworks.com) by one of the authors (M.J.B., with 3 years of experience in neonatal cranial US).

**Ventricular parameters.**—The ventricular index (VI) (defined as the distance between the falx and the lateral wall of the anterior horn in the coronal plane), anterior horn width (AHW) (defined as the diagonal width of the anterior horn measured at its widest point in the coronal plane), and thalamo-occipital distance (TOD) (defined as the distance between the outermost point of the thalamus at its junction with the choroid plexus and the outermost part of the occipital horn in the parasagittal plane) were evaluated (Fig 2).

**Intra- and interobserver reliability.**—The intra- and interobserver reliability were assessed in 10 infants. To evaluate the intraobserver variability, cranial US examination and ventricular measurements were repeated on the same day (with a 1–4 hour interval) by a single observer (M.J.B.). The interobserver reliability was evaluated by repeating the cranial US procedure and ventricular measurements in each infant by a second observer (M.J.N.L.B.), who was unaware of the first observers’ data.

The intraclass correlation coefficients were calculated by using the two-way random model for absolute agreement. The intraclass correlation coefficient for single measures was considered and interpreted according to the strength of agreement scale by Brennan and Silman (13).
The phenomenon of ventricular reopening following birth and its hypothesized relationship with a vaginal delivery were evaluated in a subcohort of term and preterm neonates that had undergone two US scans in the 1st week of life (15). The data of US 1 and US 2 were entered into a multilevel model, as well as the presence of prolonged ruptured membranes (>24 hours) and the mode of delivery (vaginal birth vs Caesarean section), while covarying for the GA and sex of the infants and the time intervals from birth to US 1 and from US 1 to US 2.

Longitudinal reference curves for the VI, AHW, and TOD were based on measurements at US 1 and TEA US in a subcohort of prospectively followed preterm infants (GA, <30 weeks). Estimates of the mean and 95% reference intervals were fitted to the data using multilevel modeling. The relationship between the previously described perinatal and postnatal events and the observed increase in ventricular size during the neonatal period was tested in a multilevel model, which was corrected for the infants’ postmenstrual age at birth and around TEA. Ventricular size of preterm born infants (GA, <30 weeks) at TEA and term neonates was compared by using analysis of covariance, with postmenstrual age and head circumference as final covariates.

Statistical analysis was performed with statistical software (SPSS 18.0 for Windows; SPSS, Chicago, Ill).

Results

Descriptive Results
A total of 625 neonates were enrolled (Table 1), of whom 79 preterm infants were eligible for prospective inclusion at TEA (Fig 1). US 1 was performed within 4 days after birth, mainly on day 1 \((n = 417 [67\%])\) or day 2 \((n = 130 [21\%])\). US 2 was performed in 55% (301 of 547) of the newborns in whom US 1 was conducted within 48 hours after birth. In the remaining neonates, it was not possible to repeat cranial US within the 1st week of life because of discharge from the hospital or subsequent exclusion after US 1.

Asymmetry
Asymmetry between the left and right ventricle was observed both following birth and at TEA. Absolute side-to-side differences ranged up to more than 3 mm for the VI and AHW and up to 7 mm for the TOD. Asymmetry of one parameter was not necessarily associated with larger (or smaller) measurements of the other ventricular dimensions in the ipsilateral hemisphere, and differences in left and right ventricular size were not consistent over time. On average, ventricular size appeared slightly larger on the left. Mean differences between lateral ventricles were, however, small and unlikely to be of clinical importance (Table 2).

Cross-sectional Reference Curves
Cross-sectional reference curves were designed for VI, AHW, and TOD according to measurements at US 1 (Fig 3). GA was associated with an increase in VI and TOD, but did not influence the AHW. Male neonates showed a slightly larger ventricular size than female neonates (Table 3). Birth weight, head circumference, multiple birth, and monochorionicity were not associated with ventricular size in multiple regression analysis.

Ventricular Reopening
The presence of ventricular reopening following birth was assessed in a subcohort of 301 neonates who had undergone two subsequent US scans within the 1st week (Table 1). Between US 1 and US 2, an increase in AHW was observed that was independent of the infants’ GA and the presence or duration of prolonged ruptured membranes. Vaginal birth was associated with a slightly smaller AHW following birth and a gradual, compensatory increase in the days thereafter (Table 3). No increase in VI and TOD could be demonstrated in the 1st week after birth.

Longitudinal Reference Curves
Longitudinal reference curves were designed for the VI, AHW, and TOD (Fig 4) on the basis of measurements at US 1 and TEA US in 79 prospectively included infants born at less than 30 weeks’ gestation (Table 1).
The infants’ postmenstrual age appeared to be most predictive for ventricular size. The most immature infants (GA, < 27 weeks) showed the largest increase in VI and TOD throughout the neonatal period. Male sex was associated with a larger AHW at birth but a smaller increase in AHW up until TEA (Table 3). No other perinatal and postnatal characteristics were associated with the increase in ventricular size from birth to TEA.

Compared with term-born infants \((n = 217)\), preterm infants \((n = 79)\) demonstrated larger ventricles around TEA, even after correction for differences in postmenstrual age and head circumference (Table 4, Fig E1 [online]).

### Intra- and Interobserver Reliability

The reproducibility of ventricular measurements by a single observer was considered very good \((\geq 0.81)\) for the AHW, TOD, and right VI and good \((0.61–0.80)\) for the left VI according to the classification by Brennan and Silman (13). Between observers, ventricular measurements appeared also to be consistent. Very good interobserver reliability was observed for the right AHW and good reliability was observed for the other ventricular dimensions (Table 5).

### Discussion

Sequential US measurements of the neonatal lateral ventricles enable recognition of ventriculomegaly and further differentiation between progressive,
pressure-driven dilation following a germinal matrix-intraventricular hemorrhage and ex vacuo dilation due to periventricular white matter loss.

In our study, new cross-sectional reference curves were established for the ventricular size of newborn infants between 24 and 42 weeks’ GA as well as longitudinal curves for the follow-up of very preterm infants until TEA.

Cross-sectional VI measurements showed a considerable increase with maturation, whereas the AHW remained constant and the occipital horns only slightly enlarged with GA. These observations are in line with prior reports (4,6–9), except for Sondhi et al (10), who demonstrated a marked increase in AHW and TOD with increasing GA.

The reference intervals for the VI presented in our study are consistent with the curve published by Levene (6) 30 years ago; however, in the study by Levene no preterm infants younger than 26 weeks’ GA were eligible. Liao et al (4) reported slightly higher values for the VI in preterm infants. The inclusion of fewer extremely premature infants in both studies and the lower transducer resolution in the 1980s may account for the small differences between the previous and present reference values. Reference intervals for the AHW (≤3 mm) are in line with earlier studies (4,7,8,10). Literature regarding the size of the occipital horns is inconclusive; previous reported upper limits for the TOD range from 7 mm for the most premature infants up to 24.7 mm (7,9,10). In our cohort, the 97th percentile for the TOD varied between approximately 19 mm for preterm infants and 21 mm for term infants.

Although measuring occipital horn size may be challenging due to obliquity of the transducer and difficulties in defining the occipital border in some infants, evaluation of TOD is of clinical value. The occipital horn may show the earliest and fastest increase in size in infants with posthemorrhagic ventricular dilation (16,17), and even isolated occipital horn dilation may be accompanied by signs of an increased
intracranial pressure and hence be an indication for intervention. Measurements of the AHW and TOD did not exceed 4 and 24 mm, respectively, in our cohort of neonates without brain abnormalities. Therefore, follow-up of infants with ventricular measurements exceeding these values is recommended, even though it is still unclear at what degree ventricular enlargement is associated with raised intracranial pressure.

Ventricular asymmetry was shown to play only a minor role. The lateral ventricles were, in general, slightly larger on the left and asymmetry appeared to be most pronounced in the occipital horns, which is in agreement with other neonatal (7,18–20) and fetal (21) US studies and with volumetric MR imaging studies in neonates (22), children, and adolescents (23).

Male sex was associated with a larger ventricular size after birth, but its effect was shown to diminish in preterm infants who were followed prospectively.

Sex-related differences in ventricular size have been reported previously for both fetuses (24) and neonates (7) and were also demonstrated to disappear with further growth (25).

After birth, a small increase in AHW was observed in term and preterm newborns. This confirms the concept of ventricular reopening proposed by Nelson et al (15), who subjectively assessed the amount of cerebrospinal fluid in the lateral ventricles of term infants who were born vaginally and observed a gradual

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VI (R²: 0.354)</th>
<th>AHW (R²: 0.430)</th>
<th>TOD (R²: 0.372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>11.22 (0.17)*</td>
<td>1.23 (0.07)*</td>
<td>15.84 (0.18)*</td>
</tr>
<tr>
<td>Preterm birth (&lt;30 weeks)</td>
<td>0.45 (0.18)*</td>
<td>1.20 (0.13)*</td>
<td>3.45 (0.31)*</td>
</tr>
<tr>
<td>Postmenstrual age, in weeks</td>
<td>0.19 (0.05)*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Head circumference, in centimeters</td>
<td>0.17 (0.05)*</td>
<td>0.08 (0.04)*</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note.—Data are the estimates in millimeters, with standard error of the estimate in parentheses. NS = not significant.

* P < .001.

† Centered at 37 weeks.

‡ Centered at 35 cm.

§ P < .05.

### Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VI (R²: 0.354)</th>
<th>AHW (R²: 0.430)</th>
<th>TOD (R²: 0.372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>8.03 (0.09)*</td>
<td>1.11 (0.04)*</td>
<td>15.09 (0.22)*</td>
</tr>
<tr>
<td>GA, in weeks</td>
<td>0.22 (0.01)*</td>
<td>NS</td>
<td>0.04 (0.02)‡</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.28 (0.07)*</td>
<td>0.12 (0.05)§</td>
<td>0.49 (0.19)‡</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.90 (0.11)*</td>
<td>0.22 (0.07)§</td>
<td>0.49 (0.19)‡</td>
</tr>
<tr>
<td>Interval birth-US 1, in hours</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Interval US 1–US 2, in hours</td>
<td>0.09 (0.03)*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>GA</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.16 (0.07)§</td>
<td>0.49 (0.19)‡</td>
<td>0.49 (0.19)‡</td>
</tr>
<tr>
<td>Vaginal birth</td>
<td>0.05 (0.02)§</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Vaginal birth by interval US 1–US 2, in hours</td>
<td>0.09 (0.03)*</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note.—Data are the estimates in millimeters, with standard error of the estimate in parentheses. NS = not significant.

* P < .001.

† Centered at 24 weeks.

‡ P < .01.

§ P < .05.

ll Natural logarithm.
increase in ventricular size in the first days following birth. Others also demonstrated a rapid increase in ventricular area (20,26) and volume (27) at the end of the 1st week and in the 2nd week after birth. We found that vaginal birth was associated with a slightly smaller AHW following birth and a gradual increase in AHW in the 1st week, which supports the hypothesis by Nelson et al that reopening of the cerebral ventricles may be related to the mechanical effect of a vaginal delivery (15). A correlation between the amount of cerebrospinal fluid in the lateral ventricles and the mode of delivery has been reported previously for term infants (28). The effect of ventricular reopening was small, however, and did not change the 97th percentile of the reference curve for the AHW, which was based on the first cranial US after birth.

For preterm infants born before 30 weeks' gestation, longitudinal reference curves were interpolated according to ventricular US measurements following birth and around TEA. At TEA, preterm-born infants had larger ventricles than term infants. Previous MR imaging studies have also demonstrated increased cerebrospinal fluid and ventricular volumes in preterm neonates at TEA compared with term-born control subjects (29-31). Differences in ventricular volume between preterm and term-born infants have been shown to persist throughout childhood and adolescence (32-34) and were also observed in infants (29) and adolescents (33) without a history of posthemorrhagic ventricular dilation. In the absence of major preceding brain disease, ventricular enlargement in preterm infants seems a consequence of more subtle brain injury with subsequent volume loss of the adjacent periventricular white matter and subcortical gray matter (32,34). Previous studies did not reveal any relationship between isolated ventriculomegaly and neurodevelopmental outcome in preterm-born infants. In the presence of other brain disease, however, ventricular dilation was shown to pose an additional risk for cognitive and motor impairments (35,36).

Our study is subject to several limitations that need to be addressed. The study period had to be extended
to 5 years to include the required minimum of 25 extremely low birth weight infants without US abnormalities per week GA. Although all images were reviewed and measured by a single researcher, some uniformity might have been lost due to the performance of cranial US by several examiners and with different US machines during this 5-year period. Measurements of third and fourth ventricular size as well as Doppler US measurements of cerebral blood flow velocities were beyond the scope of this study but should, however, be considered as a valuable additional tool to evaluate the pathophysiology of ventriculomegaly. The phenomenon of ventricular reopening was mainly studied in term neonates born by means of Caesarean section and preterm infants. Healthy term neonates born after a vaginal delivery were often discharged on the same or next day and had either no second cranial US or a shorter time interval between US 1 and US 2. Since the extent of reopening was shown to correlate with the time interval between US scans, the influence of vaginal birth on ventricular reopening in term infants may have been underestimated. The longitudinal reference values established in this study were based on premature infants with a favorable neurodevelopment at 15 months’ corrected age. These infants will be reassessed at later age to confirm their favorable outcome. Finally, no relationship was found between perinatal and postnatal events and the increase in ventricular size from birth to TEA in our cohort of preterm infants. Use of serial volumetric MR imaging measurements may, however, be a more sensitive method to identify risk factors for ex vacuo ventriculomegaly than two-dimensional measurements, and therefore caution has to be taken when interpreting these results.

In conclusion, new cross-sectional and longitudinal reference values were established for the neonatal lateral ventricles, which may allow early identification of posthemorrhagic and ex vacuo ventricular dilation and may offer the opportunity for accurate timing of intervention in infants with progressive posthemorrhagic ventricular dilation.

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