A LIMITED RANGE OF MEASURES OF 2-D ULTRASOUND CORRELATE WITH 3-D MRI CEREBRAL VOLUMES IN THE PREMATURE INFANT AT TERM

NIGEL G. ANDERSON,† SIMON K. WARFIELD,§ SCOTT WELLS,† CAROLE SPENCER,§ ADRIAN BALASINGHAM,† JOSEPH J. VOLPE† and TERRIE E. INDER* †

*Murdoch Children’s Research Institute, Royal Women’s and Royal Children’s Hospitals, Melbourne, Australia; †Howard Florey Institute, Melbourne, Australia; ‡Radiology; and §NICU, Christchurch Women’s Hospital, Christchurch, New Zealand; ‡Neurology, Children’s Hospital; and ¶Radiology, Brigham and Womens Hospital, Harvard Medical School, Boston, MA, USA

(Received 28 February 2003; revised 16 September 2003; in final form 2 October 2003)

Abstract—Two-dimensional (2-D) cranial ultrasound (US) is the principal method for the detection of cerebral injury in the newborn. The aim of this study was to compare 2-D sonographic methods with more advanced 3-D magnetic resonance imaging (MRI) for assessing brain structure. From July 1998 to November 2000, we conducted a prospective methodological study comparing 2-D cranial sonographic measurements with volumes of cerebrospinal fluid (CSF), white matter, grey matter and total volume of brain obtained using 3-D MRI. The study group comprised 63 infants (33 boys), mean gestational age 28 weeks (range 23 to 33 weeks), with imaging studies within 15 days of term equivalent. The highest correlations were between the occipital horn length and total brain volume (R² = 0.30), the subarachnoid space and both CSF volume (R² = 0.46) and relative intracranial space occupied by brain tissue (R² = 0.48). Only 8 (30%) of the 2-D cranial US measures demonstrated good reproducibility. 2-D sonographic measures are limited in reflecting variations in overall cerebral structure, although certain measures, such as subarachnoid space and occipital lobe measures, may be useful in better defining cerebral parenchymal and CSF volumes. (E-mail: nigel.anderson@cdhb.govt.nz). © 2004 World Federation for Ultrasound in Medicine & Biology.

Key Words: 2-D cranial sonography, 3-D magnetic resonance imaging, Prematurity, Cerebral structure, Posterior fontanelle, Very-low-birth weight infant.

INTRODUCTION

Surviving very-low-birth weight (VLBW) infants are at an increased risk for neurodevelopmental handicap and neurobehavioural deficits (Allan et al. 1997; Ment et al. 1999). Previous studies in the preterm infant have shown that parenchymal abnormalities on 3-D magnetic resonance imaging (MRI) performed at term equivalent have predictive value for the later development of cerebral palsy (Ajayi-Obe et al. 2000; Valkama et al. 2000; Maalouf et al. 2001; Panigrathy et al. 2001).

Current neuroradiological standards recommend one to two cranial ultrasound (US) examinations in the prematurely born infant (Ment et al. 2002). 2-D cranial US is routinely available as a bedside technique of low expense. However, the current practice and interpretation of 2-D cranial sonograms in the premature infant appear to be limited to the identification of haemorrhagic injury, and have a low predictive value for later adverse neurodevelopmental outcome. The sensitivity of 2-D US in predicting cerebral palsy in preterm infants ranges from 38 to 60%, and prediction of cognitive and behavioural difficulties appears even more limited (De Vries 2000; Valkama et al. 2000).

3-D US is as effective as 3-D MRI at estimating volumes of ventricles of the brain (Gilmore et al. 2001). However, US is less sensitive than MRI at delineating white matter injury (Inder et al. 2003). MRI provides a more sensitive assessment of both the nature and extent of cerebral injury and cerebral maturation. Advances in postacquisition analysis with 3-D MRI techniques of prematurely born children have allowed insights into the nature of structural cerebral alterations. Reductions in regional grey-matter volumes have correlated with im-
pairements in memory function (Isaacs et al. 2000), calculating ability (Isaacs et al. 2001) and intelligence quotient (IQ) (Peterson et al. 2000; Allin et al. 2001). Thus, the definition of structural cerebral alterations in the premature infant may allow better prediction of later neurodevelopmental outcome. If 2-D cranial US is to remain a mainstay of imaging the newborn brain in the future, new US signs of brain injury that is not cystic or haemorrhagic need to be identified. For these reasons, we elected to compare 2-D cranial US with 3-D MRI rather than 3-D cranial US.

The aim of this study was to develop a simple 2-D sonographic method for assessing cerebral structure at term equivalent in very-low-birth weight (VLBW) infants by comparing 2-D sonographic measurements with advanced 3-D MRI volumetric assessment.

MATERIALS AND METHODS

We recruited 100 VLBW infants admitted to the regional level III neonatal intensive care unit in Christchurch, New Zealand, from November 1998 to November 2000. This comprised 98% of infants eligible for recruitment. At 40 weeks corrected gestational age (term equivalent), a 2-D cranial sonogram was performed to obtain specific sonographic measurements for the purposes of this study. Infants also underwent 3-D MRI imaging of the brain to assess specific brain volumes.

Of the 100 infants, we excluded 34 because the 2-D sonogram and 3-D MRI were performed more than 24 days apart and, in 3, only hard copy images of the 2-D sonogram were available. The 2-D sonogram and 3-D MRI were performed on average 4 days apart (median 4 days, range 0 to 28 days). The study group comprised 63 infants (33 boys), mean gestational age 28 weeks (range 23 to 33 weeks). The mean birth weight was 1086 g, range 630 to 1475 g. There was no gender difference in gestational age or birth weight.

The Regional Ethics Committee approved all aspects of this study and informed parental consent was obtained from all parents.

2-D sonographic technique

2-D sonograms were performed with 7.5-MHz or 8.5-MHz probes using XP-10, Aspen, and Sequoia US machines (Acuson, Mountain View, CA). A standardised series of images were obtained. Six coronal and six sagittal/parasagittal views were obtained via the anterior fontanelle and three coronal and three sagittal/parasagittal images via the posterior fontanelle (Table 1, Fig. 1a–i). The 2-D sonogram was performed prospectively, specifically to obtain the multiple measurements, so that images were often optimised or repeated to allow clearly defined measurement end points. Images were stored on the hard disk of the US machine or on magneto-optical disk. Measurements from the stored images were made using the electronic calipers. We selected 22 pairs of measurements and 3 nonpaired measurements (Fig. 1a–i); the methodology for several of these measurements has been reported in previous studies (Levene 1981; Poland et al. 1985; McArdle et al. 1987; Lui et al. 1990; Allan et al. 1997; Ment et al. 1999; Davies et al. 2000; Valkama et al. 2000). We derived occipital horn length (measurement 5, Fig. 1c) by subtracting choroid plexus length from the thalamo-occipital length (measurements 3p and 4, Fig. 1b). We derived two ventricle-brain ratios in the occipital lobe: a medial occipital lobe ratio, measurement 6p (Fig. 1d), divided by measurement 22 (Fig. 1i).

3-D MRI technique

3-D MRI imaging was performed using the 1.5 T magnet (GE Medical Systems, Milwaukee, WI). After feeding, the infants were placed on a vacuum bean bag (S & S X-ray products, Brooklyn, NY). MRI sequences included sagittal T1 2-D spin echo, echo time (TE)15 ms, TR500, 4-mm slice, 1-mm gap, field-of-view (FOV) 20 cm × 20 cm, 256 × 192 matrix, 2 number of excitations (NEX); axial dual echo, 2-D fast spin echo, echo-train length (ETL) 16, TE1 30 ms, TE2 100 ms, TR 3000 ms, FOV 18 cm × 18 cm, 256 × 256 matrix, interleaved 3.0-mm slice thickness, 1 NEX; inversion recovery FSPGR coronal 3-D, flip angle 20°, TE minimum, T1 500 ms, FOV 18 cm × 13 cm, 256 × 256 matrix, slice thickness 1.5 mm, 124 locations, 1 NEX. All sequences used variable band width and autoshim.

We performed 3-D analysis by applying knn-segmentation algorithm after acquisition of the MRI data to generate volumes of unmyelinated white matter, cortical grey matter, total cerebrospinal fluid and total brain tissue volume, intracranial volume excluding cerebrospinal fluid (CSF) volume. The percentage brain within the intracranial cavity was calculated as the brain tissue volume/total intracranial volume (equivalent to brain tissue volume and CSF volume) (Huppi et al. 1998; Inder et al. 1999). White matter volumes were separately calculated for unmyelinated and myelinated white matter. CSF volume includes both extra-axial and intraventricular CSF. The brain volumes assessed at 3-D MRI were as follows: white matter (unmyelinated and myelinated) mean volume 199 mL (range 111 to 287 mL); cortical grey matter mean volume 188 mL (range 100 to 272 mL); CSF mean volume 41.6 mL (range 11.5 to 97.2 mL) and mean total brain tissue volume 406 mL (range 274 to 513 mL).
Each set of 2-D sonographic measurements was compared with the various brain volumes using univariate regression to generate correlation coefficients, correcting for repeated measures $R^2$. We have not reported individual correlations if $R^2$ was less than 0.07 ($r < 0.25$). Intra- and interobserver variation of the 2-D sonographic measurements was assessed for the two observers performing the 2-D sonograms. A complete set of measurements for 16 babies was remeasured twice from digitised images by both observers. The data were analysed using variance components to assign the magnitude of the measurement error according to inter- and intraobserver differences, compared with the biologic variability within the study group (De Vet 1998). Error results are reported as standard errors of measurement (SEM), and are in the same units as the measurements. The square root of the variance component is the SEM for that source. This indicates how best to reduce error; that is, by increasing the number of observers or increasing the number of observations per observer. The 95% confidence interval around a measurement is $1.96 \times \text{SEM}$.

### Table 1. Description of 2-D US measurements undertaken via the anterior (AF) or posterior fontanelle (PF) with mean (minimum, maximum) reproducibility and correlation with any 3-D MRI brain tissue volume

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Figure</th>
<th>Fontanelle</th>
<th>Reproducible*</th>
<th>n</th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
<th>Correlation with any 3-D brain tissue type ($r^2 =$ right/left)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Frontal horn long axis</td>
<td>1a</td>
<td>AF</td>
<td>No</td>
<td>63</td>
<td>2.2</td>
<td>0.3</td>
<td>16.6</td>
<td>WM ($r^2 = 0.09/0.10$) Brain tissue vol ($r^2 = 0.11/0.14$)</td>
</tr>
<tr>
<td>2 Frontal horn short axis</td>
<td>1b</td>
<td>PF</td>
<td>Yes</td>
<td>63</td>
<td>16.9</td>
<td>10.8</td>
<td>29.0</td>
<td>Brain tissue vol ($r^2 = 0.14/0.19$)</td>
</tr>
<tr>
<td>3a Thalamoocipital horn long axis</td>
<td>NS</td>
<td>AF</td>
<td>No</td>
<td>47</td>
<td>24.3</td>
<td>17.0</td>
<td>52.3</td>
<td>NS</td>
</tr>
<tr>
<td>3p Thalamoocipital horn short axis</td>
<td>1b</td>
<td>PF</td>
<td>Yes</td>
<td>58</td>
<td>8.4</td>
<td>5.5</td>
<td>13.0</td>
<td>NS</td>
</tr>
<tr>
<td>4 Choroid depth</td>
<td>1c</td>
<td>PF</td>
<td>NA</td>
<td>53</td>
<td>18.6</td>
<td>10.6</td>
<td>44.7</td>
<td>WM ($r^2 = 0.08/0.11$) Brain tissue ($r^2 = 0.22/0.30$)</td>
</tr>
<tr>
<td>5 Occipital horn long (3p–4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6a Occ horn vertical depth</td>
<td>1c</td>
<td>PF</td>
<td>Yes</td>
<td>60</td>
<td>3.9</td>
<td>0.3</td>
<td>32.4</td>
<td>NS</td>
</tr>
<tr>
<td>6b Occ horn vert-owl eye</td>
<td>1d</td>
<td>PF</td>
<td>Yes</td>
<td>60</td>
<td>5.5</td>
<td>0.7</td>
<td>36.4</td>
<td>NS</td>
</tr>
<tr>
<td>7 Occ horn horizontal-owl</td>
<td>1d</td>
<td>PF</td>
<td>No</td>
<td>60</td>
<td>3.4</td>
<td>0.6</td>
<td>19.6</td>
<td>NS</td>
</tr>
<tr>
<td>9 Vertical ventricle at splenium</td>
<td>1e</td>
<td>PF</td>
<td>Yes</td>
<td>54</td>
<td>7.2</td>
<td>3.8</td>
<td>21.2</td>
<td>NS</td>
</tr>
<tr>
<td>10 Horizontal vent at splenium</td>
<td>1e</td>
<td>PF</td>
<td>No</td>
<td>53</td>
<td>3.5</td>
<td>0.7</td>
<td>10.4</td>
<td>CSF ($r^2 = 0.10/0.08$)</td>
</tr>
<tr>
<td>Parenchymal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Frontal cortex med</td>
<td>1f</td>
<td>AF</td>
<td>Yes</td>
<td>57</td>
<td>12.7</td>
<td>9.0</td>
<td>24.1</td>
<td>NS</td>
</tr>
<tr>
<td>13 Frontal cortex lateral</td>
<td>1f</td>
<td>AF</td>
<td>Yes</td>
<td>60</td>
<td>25.1</td>
<td>17.1</td>
<td>31.3</td>
<td>NS</td>
</tr>
<tr>
<td>15 Parietal cortex</td>
<td>1f</td>
<td>AF</td>
<td>Yes</td>
<td>60</td>
<td>25.2</td>
<td>17.7</td>
<td>30.8</td>
<td>NS</td>
</tr>
<tr>
<td>16 Parietal cortex</td>
<td>1g</td>
<td>AF</td>
<td>No</td>
<td>60</td>
<td>13.1</td>
<td>7.7</td>
<td>19.2</td>
<td>NS</td>
</tr>
<tr>
<td>17 Gyrus depth</td>
<td>1g</td>
<td>AF</td>
<td>No</td>
<td>44</td>
<td>19.5</td>
<td>11.7</td>
<td>27.0</td>
<td>NS</td>
</tr>
<tr>
<td>18 Width of parenchyma</td>
<td>1g</td>
<td>AF</td>
<td>No</td>
<td>43</td>
<td>5.3</td>
<td>3.1</td>
<td>9.1</td>
<td>Brain tissue ($r^2 = 0.12/0.09$)</td>
</tr>
<tr>
<td>19 Parietal cortex</td>
<td>1h</td>
<td>PF</td>
<td>No</td>
<td>51</td>
<td>24.3</td>
<td>16.2</td>
<td>33.0</td>
<td>NS</td>
</tr>
<tr>
<td>20 Frontal cortex</td>
<td>1h</td>
<td>PF</td>
<td>No</td>
<td>51</td>
<td>23.0</td>
<td>10.6</td>
<td>29.9</td>
<td>NS</td>
</tr>
<tr>
<td>21 Occipital cortex medial</td>
<td>1i</td>
<td>PF</td>
<td>No</td>
<td>60</td>
<td>12.7</td>
<td>6.6</td>
<td>16.5</td>
<td>NS</td>
</tr>
<tr>
<td>22 Occipital cortex inferior</td>
<td>1i</td>
<td>PF</td>
<td>No</td>
<td>60</td>
<td>13.9</td>
<td>5.6</td>
<td>18.7</td>
<td>CSF ($r^2 = 0.16/0.18$)</td>
</tr>
<tr>
<td>23 Occipital cortex lat</td>
<td>1i</td>
<td>PF</td>
<td>No</td>
<td>60</td>
<td>23.1</td>
<td>9.6</td>
<td>23.2</td>
<td>NS</td>
</tr>
<tr>
<td>14 Subarachnoid space</td>
<td>1f</td>
<td>AF</td>
<td>Yes</td>
<td>48</td>
<td>2.7</td>
<td>0.5</td>
<td>8.2</td>
<td>CSF ($r^2 = 0.46$)</td>
</tr>
<tr>
<td>11 Corpus callosum</td>
<td>1e</td>
<td>PF</td>
<td>No</td>
<td>58</td>
<td>2.5</td>
<td>1.3</td>
<td>3.7</td>
<td>NS</td>
</tr>
<tr>
<td>8 Cerebellar body trans</td>
<td>1d</td>
<td>PF</td>
<td>Yes</td>
<td>56</td>
<td>51.5</td>
<td>40.0</td>
<td>60.6</td>
<td>NS</td>
</tr>
<tr>
<td>25 Cerebellar body sag</td>
<td>NS</td>
<td>PF</td>
<td>Yes</td>
<td>62</td>
<td>22.2</td>
<td>17.0</td>
<td>29.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Standard error of mean (SEM) for single observer making a single measurement negligible or small enough reliably to discriminate.

**Statistics**

Each set of 2-D sonographic measurements was compared with the various brain volumes using univariate regression to generate correlation coefficients, correcting for repeated measures $R^2$. We have not reported individual correlations if $R^2$ was less than 0.07 ($r < 0.25$). Intra- and interobserver variation of the 2-D sonographic measurements was assessed for the two observers performing the 2-D sonograms. A complete set of measurements for 16 babies was remeasured twice from digitised images by both observers. The data were analysed using variance components to assign the magnitude of the measurement error according to inter- and intraobserver differences, compared with the biologic variability within the study group (De Vet 1998). Error results are reported as standard errors of measurement (SEM), and are in the same units as the measurements. The square root of the variance component is the SEM for that source. This indicates how best to reduce error; that is, by increasing the number of observers or increasing the number of observations per observer. The 95% confidence interval around a measurement is $1.96 \times \text{SEM}$.
RESULTS

2-D sonographic ventricular measures

The 2-D US ventricular measurements showed a limited relationship to 3-D brain volumes (Table 1). The best 2-D sonographic measurement correlating with total brain volume was the distance between the choroid plexus edge and the tip of occipital horn measured on the posterior fontanelle longitudinal view (measurement 5, Fig. 1c) \((R^2 = 0.30)\) (Fig. 2). That is, the larger the ventricular measurements, the greater the overall brain tissue volume. Brain tissue volume was also correlated with the right horizontal trigone dimension (measurement 9, Table 1). There was a very poor correlation of ventricular measurements with CSF volume (Table 1).

Subarachnoid space measure

The size of the subarachnoid space (measurement 14, Fig. 1f) had a moderate strength positive correlation with CSF volume \((R^2 = 0.46, \text{Table 1, Fig. 3})\) and a moderate negative correlation with percentage brain within the intracranial cavity \((R^2 = 0.48)\).

Fig. 1. (a)–(i) Images from different babies demonstrating the end points for measuring, and the type of image obtained either at anterior fontanelle or posterior fontanelle, coronal or parasagittal views by 2-D US. Measurement 3a (not depicted) uses the same end points as those used for (b) 3p, but via the anterior fontanelle. Measurements 6a (c) and 6b (d) are similar, except for the different projection of the occipital horn.

Fig. 2. Correlation between the length of the occipital horn (mm) measured from posterior margin of choroid plexus to the tip of the occipital horn of the lateral ventricle on posterior fontanelle parasagittal image by 2-D US, plotted against total brain volume as assessed at MRI showing a moderately strong positive correlation.

Fig. 3. Subarachnoid space measurement (mm) at cranial 2-D sonogram compared with CSF volume assessed at 3-D MRI in 38 VLBW infants assessed at term equivalent, showing quite a strong positive correlation and the wide spread of measurements obtained.
2-D US brain vs. 3-D MRI ● N. G. ANDERSON et al.

Measurement error

Attempts to discriminate between babies based on US brain measurements is subject to observer error, which is negligible in some measurements and small in a number of others. The measurements that had good reproducibility included the frontal horn measurement in the short axis (measurement 2, Fig. 1a, 0.2 mm total error), subarachnoid space (measure 14, Fig. 1f, error = 0.4 mm), thalamo-occipital horn \textit{via} posterior fontanelle (measure 3p, Fig. 1b, error 0.9 mm), measures of the frontal cortex (measures 12 to 15, Figs. 1f, g, errors < 1.0 mm), and transverse cerebellar \textit{via} posterior fontanelle (measure 8, Fig. 1d, error 1.5 mm). For the remaining 14 measurements, the error was sufficiently large in the measures used to prevent reliably distinguishing between babies from a single measurement by a single observer. In these measures, the combined error variance due to observers was smaller than that from intraobserver error. The mean ratio of SEM for sources of error relative to the SD across babies was 0.71 for intraobserver error, compared with 0.03 and 0.24 for the two sources of interobserver error. This indicates that the major source of error was due to intraobserver variation. If these 14 measures with large errors are to be used at all, multiple measurements would be necessary to reduce the error to acceptable levels.

DISCUSSION

This is a methodological study comparing 2-D measurements obtained utilising 2-D cranial US with 3-D volumetric assessment of the CSF white matter, grey matter and total brain volume in premature infants at term. Our study demonstrated that 2-D US measurement of subarachnoid space (but not ventricular dimensions) correlated moderately well with total CSF volume. We could not predict white-matter volume using any of the 2-D US measurements. Ventricular measurements were surprisingly poorly correlated with total CSF and brain volumes. This is, in part, due to the poor reproducibility of measurements with a high intraobserver error rate in many of the measurements by an experienced radiologist.

Fig. 4. Coronal 2-D sonograms from three different infants; all images corrected for scale, pictorially demonstrating the complex interrelationships between volumes of white matter, grey matter, CSF and total brain. (a) 30 weeks of gestation, birth weight 1665 g. At 40 weeks corrected age, volume of WM = 227 mL, cortical grey matter = 218 mL, total brain = 467 mL, CSF = 52.8 mL. (b) 23 weeks of gestation, birth weight 440 g. At 40 weeks corrected age, volume of WM = 111 mL, cortical grey matter = 148 mL, total brain = 274 mL, CSF = 50.6 mL. (c) 26 weeks gestation, birth weight 960 g. At 40 weeks corrected age, volume of WM = 159 mL, cortical grey matter = 220 mL, total brain = 394 mL, CSF = 97.2 mL.

2-D sonographic parenchymal measures

The sonographic parenchymal measures correlated weakly with grey-matter volumes; the transverse dimensions of the panetal brain parenchyma were measured \textit{via} the anterior fontanelle (measurements 15 and 16, Fig. 1g) or \textit{via} the posterior fontanelle (measurement 20, Fig. 1h). The measurement of the inferior occipital cortex on the right (measurement 22, Fig. 1i, Table 1) was the only sonographic measurement to show a statistically significant correlation with white-matter volume. There was no significant relationship between any of the 2-D sonographic parenchymal measurements and total brain volume. However, three left-sided measurements, predominantly occipital (measurements 21, 22, Fig. 1g), showed mild positive correlation with percentage brain within the cranial cavity. Ventricle-brain ratios in the occipital lobe did not provide better correlation than the absolute measurement from which they were derived.

2-D sonographic assessment of corpus callosum

The measurement of the splenium of the corpus callosum at posterior fontanelle (measurement 11, Fig. 1e) did not correlate with any tissue volume measures.

Limits of 2-D sonographic qualitative assessment

Figure 4 illustrates the difficulty in qualitatively assessing absolute size from a single 2-D sonographic image. Figure 4a has the largest brain volume, 4b the smallest brain volume, and 4c the largest CSF volume. Part of the image optimisation involves altering the image scale to ensure that the image fills the screen. The observer is at risk of overestimating intraventricular volume and underestimating extra-axial CSF volume from a single image because of the shape and position of these spaces. Qualitative assessment of brain size is greatly enhanced by having side-by-side comparison images at a similar scale with known reference volume.
The 2-D US measurement of the extraaxial subarachnoid space was one of the strongest correlations found in our study, correlating with total CSF volume. Increased size of subarachnoid space when associated with ventriculomegaly and cystic white matter changes has been correlated with poor outcome; however, subarachnoid space enlargement alone may not predict adverse outcome (Lui et al. 1990; Valkama et al. 2000). In previous publications, subarachnoid space has been measured in the interhemispheric fissure (McArdle et al. 1987; Lui et al. 1990; Valkama et al. 2000) or over the convexity of the brain (Armstrong et al. 2002), with a normal measurement considered to be less than 4 mm (McArdle et al. 1987; Lui et al. 1990; Armstrong et al. 2002). The prognostic significance of enlarged subarachnoid space in our cohort will be assessed with later neurodevelopmental outcome.

A cranial 2-D sonogram appears reliably to detect cystic periventricular white-matter (WM) injury, but macrocystic WM injury is rare, occurring in only 4 to 5% premature infants (De Vries 2000; Maalouf et al. 2001). Cranial 2-D sonography is more limited in its detection of the common diffuse noncystic WM injury and, in particular, the cranial 2-D sonographic finding of periventricular WM echo-density appears to have limited sensitivity and specificity for pathologically defined white-matter injury (Maalouf et al. 2001). Ventriculomegaly in VLBW infants is strongly associated with WM disease (Kuban et al. 1999; Panigrahy et al. 2001) and ventriculomegaly is also associated with an increased risk of cognitive impairment (Whitaker et al. 1996), cerebral palsy (Whitaker et al. 1996; Valkama et al. 2000), reduced visual perception (Whitaker et al. 1996; Ment et al. 1999; SanGiovanni et al. 2000) and with neurobehavioral abnormalities (Stewart et al. 1999). Ventriculomegaly is frequently preceded by, or associated with, intraventricular haemorrhage (Kuban et al. 1999; Ment et al. 1999), and/or periventricular WM injury (Whitaker et al. 1996; Allan et al. 1997; Kuban et al. 1999; Valkama et al. 2000). Thus, in this study, we expected to find larger ventricle size in infants with increased CSF volume and reduced WM volumes. However, we found, instead, that larger absolute ventricular dimensions are most associated with larger absolute brain size and did not correlate with a reduced percentage of intracranial cerebral tissue.

The occipital horn is the first and the frontal horn is the last part of the ventricle to enlarge (Allan et al. 1982). The occipital horns are readily visible on sonography via the posterior fontanelle (Anderson et al. 1995). A variety of ventricular measurements have been described, both direct and indirect (Levene 1981; Allan et al. 1982, 1997; McArdle et al. 1987; Ment et al. 1999; Davies et al. 2000). We have included most of these in addition to our new occipital horn 2-D US measurement. We consider that our assessment of the thalamo-occipital dimension of the ventricle (Davies et al. 2000) more reliably measured via the posterior fontanelle, particularly at term equivalent because intra- and interobserver variation is much lower for posterior fontanelle measurements. This is because the end points are more easily imaged (Anderson et al. 1995), particularly in the nondilated ventricle.

If absolute ventricular size did not predict reduction in WM volume, perhaps relative ventricle size might. Other authors have found that ventricle-to-brain ratios correlate moderately well with clinical outcome, whether obtained at cranial 2-D sonography (Allan et al. 1997) or axial MRI (Valkama et al. 2000). In our study, ventricle-to-brain ratios in the occipital lobe did not provide better correlation with brain volumes than the absolute measurements from which they were derived. It is possible that 3-D US volumetric assessment of the lateral ventricles might be an advantage (Csutak et al. 2003; Gilmore et al. 2001); however, we did not assess this.

Thinning of the corpus callosum commonly accompanies WM atrophy (Stewart et al. 1999). However, we found no correlation between WM volume and corpus callosal thickness measured at the splenium. This may result from two key technical factors. The first factor relates to the small variation in measurable thickness of the corpus callosum (1.3 to 3.0 mm) and the second factor may relate to the site of our measurement and the projection from which it was obtained. We intend to further explore the relationship between WM volume and corpus callosal size by additional measurements, along the entire body of the corpus callosum.

We elected to compare 2-D cranial US with 3-D MRI for several reasons. First, MRI is more sensitive than 2-D US at detecting noncystic WM injury, the dominant form of brain injury in VLBW infants (Inder et al. 2003). Differentiation of gray and white matter is easier with MRI (Huppi 1998). The sector format of 2-D US precludes examining all of the subarachnoid space. We wished to assess CSF volumes because of the observation that CSF spaces around the brain are commonly increased in VLBW infants by term equivalent (McArdle et al. 1987; Lui et al. 1990; Armstrong et al. 2002). Perhaps more importantly, the role of 2-D cranial US in assessment of brain injury has diminished with the advent of MRI because US has been used to look for haemorrhage, ventricular enlargement and cystic changes in the WM. If US is to retain its usefulness, it is necessary to find US correlates of the more prevalent signs of brain injury visible on MRI. If that goal can be achieved, US can retain its preeminent role in assessing the newborn brain. It could be argued that, with advances in 3-D US, we ought to have compared 3-D US with 3-D.
MRI. 3-D US is not yet available to all neonatal intensive care units. We wished to find a method for assessing brain injury with 2-D US that was pragmatic and rapid and that could be incorporated into currently used cranial US applications. And we wished to compare 2-D cranial US with published definitions of brain injury. To our knowledge, there are no published reproducible cranial US findings of noncystic brain injury that match published MRI findings.

Why did our study not demonstrate closer correlations between 2-D sonographic measures and 3-D MRI cerebral volumes (e.g., larger ventricles and smaller white matter volumes, or thinner corpus callosum and thinner white matter volume)? There are a number of possible explanations. The first and most obvious is that our measurements selected the wrong place to reflect the true cerebral structural alteration. The very irregular volumetric shape of white matter and any structural alteration may limit the possibility of finding a useful 2-D linear correlative measurement for a total 3-D WM volume. The second explanation may relate to the fact that we have compared 2-D sonographic dimensions with 3-D MRI volumes over an entire cohort of infants. We have not selected out the subgroup with particularly small volumes. In this study, we have not attempted to determine, or even to distinguish between, normal and abnormal brain or CSF or WM or grey-matter volumes. Third, most of the measurements incorporating WM had large intraobserver errors. This large intraobserver variation in many of our measurements clearly confounds our ability to utilise these measures. Precision of any measurement can be improved substantially by increasing the number of times a measurement is sampled and, thus, we could obtain a more limited number of measures repeatedly to improve our accuracy in subsequent studies. The measurements we have described may also be more useful in the detection of abnormal brain structure in a selective sample of infants than is reflected in the correlation coefficients obtained from the brains of an entire population of VLBW infants.

Qualitatively, further difficulties with 2-D cranial US interpretation can be appreciated, because sonologists invariably modify the image scale to ensure that the image fills the screen. Thus, a relatively small brain will not be appreciated visually, unless side-by-side comparisons are made with other infant brain images to the same scale. Qualitative assessment of brain size and structure may be misleading; for instance, the brains with “normal-looking” ventricles have very different brain and CSF volumes (Fig. 4). These limitations of 2-D cranial US in reflecting cerebral structure in everyday practice are clearly illustrated in Fig. 4.

SUMMARY

In this methodological study, we have found limited correlation of linear 2-D sonographic measurements with 3-D MRI, tissue volumes of CSF, white matter or grey matter assessed by volumetric 3-D MRI techniques. Subarachnoid space 2-D US measurement correlated well with CSF volume, yet ventricular dimensions showed no correlation with CSF volume or WM volume. We found wide variations in measurements of the left occipital lobe, with thinner parenchyma and larger occipital horn showing negative correlation with global WM volume. The relationship of these measures to neurodevelopmental outcome of the infants remains to be evaluated and is critical in determining if these 2-D sonographic measurements have clinical utility. However, our findings still provide useful understanding of the strengths and limitations of the 2-D sonogram in the assessment of cerebral structure in the preterm infant.

Acknowledgments—This work was supported by grants from the Neurologic Foundation of New Zealand, Health Research Council of New Zealand and Lottery Health of New Zealand, and Whitaker Foundation, USA.

REFERENCES


