Quantitative cranial ultrasound prediction of severity of disability in premature infants with post-haemorrhagic ventricular dilatation

Sally Jary, 1 Grazyna Kmita, 2 Jolanta Wroblewska, 3 Andrew Whitelaw 1

ABSTRACT

Background Infants with post-haemorrhagic ventricular dilatation (PHVD) have a high risk of severe disability and parenchymal infarction increases this risk. Existing cranial ultrasound (CUS) markers of neurodevelopmental outcome are based on categorical features.

Objective To investigate to what extent quantitative CUS measurements correlated with severity of developmental outcome and the need for ventriculoperitoneal (VP) shunt at 2 years of age.

Design 69 premature infants with PHVD had lateral ventricle area, intraventricular echodensity and parenchymal lesion dimensions measured at the start of treatment for PHVD. Outcome measures were the Bayley Scales of Infant Development-II and functional ability at 2 years of age. Bayley developmental quotients (DQ) were used in preference to index scores to enable inclusion of severely disabled children.

Results Quantitative CUS measurements of parenchymal lesion area correlated significantly with later mental and motor DQ. Intraventricular echodensity area correlated with motor DQ in infants with grade 4 intraventricular haemorrhage (IVH). Neither ventricular area nor ventricular width correlated with DQ in grade 3 IVH. Infants who ultimately required a VP shunt had a significantly larger intraventricular echodensity area.

Conclusions CUS measurement of parenchymal lesions in infants with PHVD can increase the precision of predicting severe mental and motor disability, but ventricular size at the start of treatment is not predictive of outcome in infants with PHVD following grade 3 IVH.

INTRODUCTION

Despite advances in perinatal medicine and improved survival, intraventricular haemorrhage (IVH) and post-haemorrhagic ventricular dilatation (PHVD) continue to be serious complications of very preterm birth. While the overall incidence of PHVD has decreased, a more aggressive clinical course has been noted1 and an increasing incidence in those born at <28 weeks.2 PHVD is associated with a high risk of serious cognitive disability, cerebral palsy (CP), and visual and hearing impairment.3–6 However, the range of outcomes can be wide7 and 14% infants with large IVH and a ventriculoperitoneal (VP) shunt were found to have normal development at 18–22 months.8 These findings underline the need for improved predictors of outcome in PHVD.

The presence of haemorrhagic parenchymal infarction (grade 4 IVH) is thought to be the main predictor, especially for motor outcome, in neonates with progressive PHVD.5–6 Around 45–60% of infants with PHVD have marked cognitive impairment (DQ or equivalent of <70).3–4 Some studies have found serious disability in infants with PHVD without apparent parenchymal infarction,4–9 while others have not.6 PHVD is thought to cause secondary widespread white matter damage (WMD) over time as a consequence of increasing pressure interfering with cerebral perfusion,10–11 distortion, inflammation12 and free radical generation facilitated by free iron.13 Around 20% of infants with grade 3 IVH14 will consequently need a permanent VP shunt3–6 and 30–40% of those with grade 4 IVH.3–6 The requirement for a VP shunt is associated with the severity of neurodisability in infants with and without parenchymal lesions.3–16 While the need for a VP shunt is known to increase with the grade of IVH,1 there are no other known indicators of which infants will progress to a VP shunt.

Serial cranial ultrasound scanning (CUS) is the clinical tool of choice for the diagnosis and monitoring of progressive ventricular dilatation in PHVD. While MRI is more sensitive in identifying subtle WMD associated with prematurity, CUS is much more useful during the first few weeks of...
life for the unstable preterm infant. Categorical features such as the site, shape, bilaterality and lobar involvement of parenchymal echodensities as well as CUS indicators of impaired brain growth have been associated with poor developmental outcome, but there has been no study correlating quantitative variables for CUS and the neurodevelopmental outcome of infants with PHVD.

Most modern CUS machines can record area measurements. Saliba et al. used lateral ventricle area measurements to relate ventricle area growth velocity to later overall developmental outcome in a cohort of preterm infants of <35 weeks gestation, but this approach has not been used to investigate the precision of prediction.

Previous outcome studies of infants with PHVD have included significant numbers of children who have not reached the basal threshold for allocating an individual developmental score. This may have limited study of the full range of disability at the severe end of the spectrum.

The aim of this research was to examine the correlation of quantitative area measurements on early CUS in infants with PHVD with all degrees of neurodevelopmental outcome at 2 years corrected age.

**METHODS**

Seventy-seven infants of <34 weeks gestational age born between January 2003 and December 2006 were enrolled into the Drainage, Irrigation and Fibrinolytic Therapy (DRIFT) trial. All infants underwent CUS scanning showing IVH and PHVD defined as (a) both lateral ventricles' width (ventricular index) exceeding the 97th centile + 4 mm or (b) frontal diagonal, third ventricle width and thalamo-occipital dimension all exceeding the 97th centile + 1 mm or (c) one lateral ventricle width exceeding the 97th centile + 4 mm with a marked midline shift. The study was approved by the research ethics board of each institution that took part: Southmead Hospital (Bristol, UK), the Royal Hospital for Sick Children (Glasgow, UK), the Medical University of Silesia (Katowice, Poland) and Haukeland Hospital (Bergen, Norway). Written informed consent was obtained from the mother of each infant to take part. Infants were randomised to either DRIFT or standard treatment (ST) (lumbar puncture (LP) with excessive head enlargement (2 mm/day) or suspected raised intracranial pressure followed by tapping and reservoir). If more than two LPs were required or if LP failed, a ventricular reservoir was indicated. A volume of 10–20 ml/kg was tapped at a frequency sufficient to limit head growth to <2 mm/day. If DRIFT was followed by persistent enlargement of ventricles and excessive head growth, ST with LP and ventricular reservoir was used. If expansion was persistent at term in either group, a VP shunt was inserted. As the DRIFT Trial found no significant differences in the primary short term or long term outcomes, for the purposes of this study the two treatment groups were combined; however, treatment group was included when regression was adjusted.

**CUS screening**

In all four centres, preterm infants who were born at <32 weeks or showed neurological abnormalities had daily CUS scans for the first 3 days and then had scans at least twice weekly for 4 weeks or until resolution of ventricular enlargement.

**Quantification of CUS**

The scans used in this study were taken at the start of treatment for PHVD. Cross-sectional areas of the lateral ventricles and intraventricular echodensities in the mid coronal plane were measured using 7–8 MHz sector scan heads. Because treatment aimed to reduce, or at the very least stabilise ventricular expansion, measurements were assumed to be at the point of maximum ventricular size. If parenchymal lesion(s) were present, the optimal parasagittal view was used to measure the area of the lesion(s) in preference to the coronal view because the fronto-occipital extent of the lesion has been shown to be important prognostically. Ventricular area and width measurements were excluded for infants with grade 4 IVH due to difficulty visualising the ventricular border on the side of the lesion.

Area measurements were made using the software on the ultrasound machine or using ImageJ (http://rsbweb.nih.gov/ij/) if only paper copies were available (figure 1). Intra-observer variability was assessed by one observer measuring the ventricular cross-sectional area 10 times in each of 23 different infants. The coefficient of variation for ventricular area for each infant varied from 1.52% to 5.54% with a mean of 2.5%. One observer measured the parenchymal lesion area 10 times in each of seven infants. The coefficient of variation for each infant varied from 2.5% to 10.2% with a mean of 6.9%. Inter-observer variability was assessed by two observers measuring independently and the mean difference in ventricular cross-sectional area in 14 infants was 5.2% of the mean area. Mean inter-observer difference for parenchymal lesion area in seven infants was 7.5% of the mean area. For the purposes of this study, left and right area measurements were combined.

**Developmental evaluation**

Sixty-nine surviving preterm infants with PHVD had neurodevelopmental evaluation at a mean corrected age of 2 years 1 month (SD 1.7 month) by developmental assessors blind to treatment allocation and imaging. Functional ability was classified according to the scheme proposed by Wood et al. and, for the purposes of this study, each infant was graded as ambulant or non-ambulant and as having speech or no speech at 2 years corrected age. Developmental delay was quantified using the Bayley Scales of Infant Development (second edition). In order to include infants of all abilities, developmental age equivalent (DAE) scores were derived from raw scores. DAE scores were converted to mental and motor developmental quotients (DQ) to adjust for corrected age at assessment, which we have shown to correlate with measures of functional ability. A DQ of 100 represents appropriate development for corrected age. CP was diagnosed according to the criteria of Hagberg et al. The Gross Motor Function Classification System (GMFCS) was used to assign a severity to CP. Mild CP corresponded to a GMFCS score of 1–2, moderate CP to a score of 3, and severe CP to a score of 4–5.

**Statistical analysis**

The Mann–Whitney U test was used to compare mental and motor DQ in different grades of IVH and to compare intraventricular echodensity area in infants with and without a VP shunt at 2 years of age. Fisher’s exact test was used to compare the frequency of VP shunts, rates of CP and the severity and laterality of CP in different grades of IVH. Simple and multivariate linear regressions were calculated between CUS measurements and motor and mental DQ with adjustment for treatment group,
RESULTS

The demographic details of the cohort are shown in table 1. CUS area measurements were taken for all 69 survivors (table 2) and all had follow-up at 2 years corrected age.

Two children were assessed on functional ability only, and one child was assessed with the Bayley mental scale but not the motor scale. Infants with grade 4 IVH had significantly worse mental and motor DQ scores and higher rates of CP and VP shunts (table 3).

In infants with grade 3 IVH, neither ventricular width, ventricular area or intraventricular echodensity correlated with mental and motor DQ (table 4 and figure 2).

In infants with grade 4 IVH, parenchymal lesion area correlated with motor and mental DQ and intraventricular echodensity correlated with motor DQ following unadjusted as well as adjusted regression analysis (table 4). Twelve of the 14 infants with parenchymal lesions ≥500 mm\(^2\) had a motor DQ of < 50 and were non-ambulatory. Nine of the 14 had a mental DQ of < 50 and 6/14 had no speech.

Significantly larger intraventricular echodensities at the start of treatment were found in infants who subsequently required a VP shunt (median echodensity area 161.5 mm\(^2\)) compared to those who did not (median echodensity area 87 mm\(^2\)) (p=0.01) (figure 3).

CUS lesion characteristics and CP

All 10 infants diagnosed with grade 3 IVH who later developed CP, had bilateral signs of CP but the majority were mild in severity (table 5).

The mean motor and mental DQ of the 22 infants with PHVD following grade 3 IVH who did not go on to develop CP, were 97 (SD 15) and 90 (SD 18), respectively. In infants with grade 4 IVH, parenchymal lesions were bilateral in 8/37 (22%). Six of these eight had bilateral CP and two had no CP at 2 years of age. Of the 29 infants with unilateral lesions at trial entry, 14 had signs of bilateral CP, 12 had unilateral CP and three had no CP at 2 years of age. It is noteworthy that 14% of infants with grade 4 IVH had no CP and had Bayley Index scores within 1 SD of the mean.

DISCUSSION

In common with previous studies of PHVD, our cohort had high levels of developmental mental and motor delay, CP (61%) and a VP shunt (45%) at 2 years of age.

Table 1  Cohort demographics (n=69)

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Size (mm(^2)), median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 IVH</td>
<td></td>
</tr>
<tr>
<td>Sum of ventricular width</td>
<td>37 (28–52)</td>
</tr>
<tr>
<td>Sum of ventricular area</td>
<td>516.5 (215–1048)</td>
</tr>
<tr>
<td>Intraventricular echodensity</td>
<td>68 (20–327)</td>
</tr>
<tr>
<td>Grade 4 IVH</td>
<td></td>
</tr>
<tr>
<td>Parenchymal lesion area</td>
<td>308 (38–1775)</td>
</tr>
<tr>
<td>Intraventricular echodensity</td>
<td>177 (20–335)</td>
</tr>
</tbody>
</table>

DRIFT, Drainage, Irrigation and Fibrinolytic Therapy Trial; VP, ventriculoperitoneal.
A strength of this study is the prospective collection of outcome data of a relatively large cohort of infants with well defined PHVD at the start of treatment. A limitation is the lack of CUS sensitivity for diagnosing the diffuse non-cystic form of periventricular leukomalacia (PVL). Half of the infants with CUS evidence of unilateral lesions had bilateral signs of CP at 2 years of age. In addition, 10 of the infants with grade 3 IVH showed later CP. These findings are likely to result from underestimation of associated PVL. In addition, we cannot exclude the influence of cerebellar infarcts on later developmental outcome. A further limitation is that we were not able to include socio-economic status in our analysis.

In infants with grade 4 IVH, lesion size correlated strongly with all grades of later developmental outcome, which remained statistically significant after adjustment for gender, birth weight and treatment group. Our finding of a significant correlation between motor DQ and intraventricular echodensity area only in infants with grade 4 IVH suggests that intraventricular echodensity size most likely reflects debris from periventricular infarction as well as old blood clots. In the case of grade 3 IVH, intraventricular echodensity is assumed to indicate blood clot and this did not correlate with DQ. However, we did find that a larger intraventricular echodensity size was associated with a later VP shunt when infants with grade 3 and 4 IVH were combined. Thus, cerebral debris and blood clots appeared to combine to interfere with cerebrospinal fluid absorption.

Despite the limitation of excluding analysis of ventricular measurements and developmental outcome in infants with grade 4 IVH, the lack of an association between ventricular measurements at the start of treatment with later developmental outcome in infants with grade 3 IVH is noteworthy. Beyond the initial enlargement exceeding the 97th centile + 4 mm, sonographic measurements of ventricular area at diagnosis of PHVD were not associated with worse developmental outcome and therefore, while essential in determining the point of intervention, were of limited value in predicting outcome in PHVD in infants with grade 3 IVH. Secondary damage to white matter as a result of the hydrocephalic process may have already occurred by the time ventricular width exceeds 4 mm over the 97th centile. This supports the concept of adopting a lower threshold for intervention and ventricular measurements earlier in the hydrocephalic process may show associations with later outcome. However, if severe enlargement does not worsen developmental outcome, our findings also suggest mechanisms (such as free iron and pro-inflammatory cytokines) other than pressure and distortion as a cause of secondary WMD. Our results refer to the start of treatment and do not exclude the possibility that changes in ventricular size after treatment, as well as complications such as infection and necrotising enterocolitis, may influence developmental outcome.

### Table 3 Cohort characteristics at 2 years of age according to IVH grade (n=69)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Grade 3 IVH (n=32)</th>
<th>Grade 4 IVH (n=37)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental DQ, median (range)</td>
<td>89 (20–111)</td>
<td>57 (4–100)</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Motor DQ, median (range)</td>
<td>77.5 (8–117)</td>
<td>42 (4–89)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>VP shunt, n (%)</td>
<td>9/32 (28)</td>
<td>21/37 (56)</td>
<td>0.031</td>
</tr>
<tr>
<td>CP, n (%)</td>
<td>10/32 (31)</td>
<td>32/37 (87)</td>
<td>&lt;0.00011</td>
</tr>
</tbody>
</table>

*Adjusted for gender, treatment group and birth weight.

### Table 4 Regression analysis of cranial ultrasound measurements and Bayley mental and motor DQ in infants with PHVD

<table>
<thead>
<tr>
<th>Area of interest</th>
<th>Unadjusted R</th>
<th>p Value</th>
<th>Adjusted* R</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental DQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 IVH (n=36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal lesion area</td>
<td>−0.45</td>
<td>0.005</td>
<td>−0.49</td>
<td>0.003</td>
</tr>
<tr>
<td>Intraventricular echodensity</td>
<td>−0.31 NS</td>
<td>NS</td>
<td>−0.18 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Grade 3 IVH (n=30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular width</td>
<td>0.07 NS</td>
<td>NS</td>
<td>0.12 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular area</td>
<td>0.05 NS</td>
<td>NS</td>
<td>0.14 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Intraventricular echodensity</td>
<td>−0.06 NS</td>
<td>NS</td>
<td>0.15 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Motor DQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 IVH (n=36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal lesion area</td>
<td>−0.5</td>
<td>0.002</td>
<td>−0.58</td>
<td>0.0004</td>
</tr>
<tr>
<td>Intraventricular echodensity</td>
<td>−0.46 0.005</td>
<td>NS</td>
<td>−0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Grade 3 IVH (n=30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular width</td>
<td>0.04 NS</td>
<td>NS</td>
<td>−0.1 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular area</td>
<td>0.02 NS</td>
<td>NS</td>
<td>−0.06 NS</td>
<td>NS</td>
</tr>
<tr>
<td>Intraventricular echodensity</td>
<td>−0.21 NS</td>
<td>NS</td>
<td>−0.07 NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Adjusted for gender, treatment group and birth weight.

DQ, developmental quotients; IVH, intraventricular haemorrhage; PHVD, post-haemorrhagic ventricular dilatation.
The ease of taking area measurements at the costide during the early clinical management of PHVD may assist clinicians in providing more tangible information to parents concerning the neurodevelopmental outcome of infants with large parenchymal lesions. Infants with lesions >500 mm<sup>2</sup> had an 86% risk for non-ambulation at 2 years and a 45% risk for no speech at 2 years. Quantitative CUS measurements can enhance the precision of predicting outcome in infants with PHVD following parenchymal lesions, but have limited prognostic value following grade 5 IVH.

Contributors SJ carried out developmental assessments, wrote the first draft of the manuscript and contributed to the planning, analysis and editing of the paper. GK carried out developmental assessments and contributed to editing the paper. JW helped initiate the study, carried out CUS scanning in Poland, and contributed to data processing and drafting of the manuscript.

Competing interests None.

Ethics approval The study was approved by the research ethics board of each institution that took part: Southmead Hospital (Bristol, UK), the Royal Hospital for Sick Children (Glasgow, UK), the Medical University of Silesia (Katowice, Poland) and Haukeland Hospital (Bergen, Norway).

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