Assessment of Brain Injury and Brain Volumes after Posthemorrhagic Ventricular Dilatation: A Nested Substudy of the Randomized Controlled ELVIS Trial

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Objective To compare the effect of early and late intervention for posthemorrhagic ventricular dilatation on additional brain injury and ventricular volume using term-equivalent age-MRI.

Study design In the Early vs Late Ventricular Intervention Study (ELVIS) trial, 126 preterm infants ≤34 weeks of gestation with posthemorrhagic ventricular dilatation were randomized to low-threshold (ventricular index >p97 and anterior horn width >6 mm) or high-threshold (ventricular index >p97 + 4 mm and anterior horn width >10 mm) groups. In 88 of those (80%) with a term-equivalent age-MRI, the Kidokoro Global Brain Abnormality Score and the frontal and occipital horn ratio were measured. Automatic segmentation was used for volumetric analysis.

Results The total Kidokoro score of the infants in the low-threshold group (n = 44) was lower than in the high-threshold group (n = 44; median, 8 [IQR, 5-12] vs median 12 [IQR, 9-17], respectively; $P < .001$). More infants in the low-threshold group had a normal or mildly increased score vs more infants in the high-threshold group with a moderately or severely increased score (46% vs 11% and 89% vs 54%, respectively; $P = .002$). The frontal and occipital horn ratio was lower in the low-threshold group (median, 0.42 [IQR, 0.34-0.63]) than the high-threshold group (median 0.48 [IQR, 0.37-0.68], respectively; $P = .001$). Ventricular cerebrospinal fluid volumes could be calculated in 47 infants and were smaller in the low-threshold group ($P = .03$).

Conclusions More brain injury and larger ventricular volumes were demonstrated in the high vs the low-threshold group. These results support the positive effects of early intervention for posthemorrhagic ventricular dilatation. *(J Pediatr 2019;208:191-7)*.

Trial Registration ISRCTN43171322.

Substantial developments in obstetric and neonatal care have led to a significant increase in the survival of premature infants. Along with mortality, a further aim has been to reduce the major morbidities and improve neurodevelopmental outcome. However, germinal matrix-intraventricular hemorrhage continues to be a serious complication of preterm birth.[1,2] Posthemorrhagic ventricular dilatation (PHVD) occurs in approximately 30%-50% of the preterm infants after a severe hemorrhage and increases the risk of neurocognitive and motor impairments.[3]

Adverse effects of PHVD on the developing newborn brain include white matter injury and decreased volumes of deep gray matter and cerebellum. It is important to decrease these complications as much as possible with timely intervention.[4] After the use of temporizing methods, overall conversion to a permanent shunt varies from 20% to 65%, depending on the time of onset of the intervention.[5] Given the high rates of infection, dysfunction, and life-long dependence after ventriculoperitoneal (VP) shunt insertion, it would be beneficial if a treatment could reduce the risk of shunt requirement.[6,7] Removing the hemorrhagic cerebrospinal fluid (CSF) by lumbar punctures or taps from a ventricular reservoir may decrease the need for VP shunt placement, because the

AHW	Anterior horn width	MRI	Magnetic resonance imaging
BGT	Basal ganglia and thalami	PHVD	Posthemorrhagic ventricular dilatation
CSF	Cerebrospinal fluid	PVHI	Periventricular hemorrhagic infarct
ELVIS	Early vs Late Ventricular Intervention Study	TEA	Term-equivalent age
FOH	Frontal and occipital horn	VI	Ventricular index
ICC	Intraclass correlation coefficient	VP	Ventriculoperitoneal
MR	Magnetic resonance		

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The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2018.12.062

removal of CSF that contains blood components, protein, and cytokines might reestablish normal CSF circulation.[8] Although the optimum timing of intervention continues to be a matter of debate in the neonatal literature, there is accumulating evidence showing the beneficial effects of early intervention on ventricular dilatation and outcomes.[9,10]

In the Early vs Late Ventricular Intervention Study (ELVIS) randomized controlled trial, no significant difference was found for the need for VP shunt in those treated before or after crossing the 97th percentile +4 mm line of the graph of Levene.[11] However, only a small number of infants in both study arms had a VP shunt inserted, the lowest number reported in the literature so far (19%-23%).[5] The aim of the present nested substudy was to compare the extent of injury in different brain regions, and brain volumes on term-equivalent age (TEA) magnetic resonance imaging (MRI) in patients randomized to the early or late intervention group.

Methods

Patients

A total of 126 infants participated in the ELVIS trial, a randomized controlled trial (ISRCTN43171322) conducted between 2006 and 2016 to compare the effects of low- vs high-threshold treatment in preterm infants of ≤34 weeks' gestational age with progressive PHVD. Infants were eligible for the trial when they had an IVH grade III, with or without a periventricular hemorrhagic infarct (PVHI) according to Volpe.[12] They were randomly allocated to either low-threshold group (intervention when an increase in ventricular width according to Levene[11] above the p97 line showing an increase toward the p97 + 4 mm line, but without crossing the p97 + 4 mm line, and an increase in diagonal anterior horn width [AHW] according to Davies et al of >6 mm and toward 10 mm, but not >10 mm) or high-threshold group (intervention once the ventricular width crossed the p97 + 4 mm line and the AHW was >10 mm).[13]

Antenatal and perinatal factors including gestational age, birth weight, sex, the severity of hemorrhage, and timing and type of intervention, and postmenstrual age at MRI day were collected for each patient from the patient files and/or hospital database. Approval from the research ethics board at each center and informed written parental consent were obtained for all of the patients and for the control infants participating in the study before enrollment into the study.

MRI Acquisition

In all centers, MRIs were acquired around TEA. A 3.0 Tesla magnetic resonance (MR) system (Philips Healthcare, Best, The Netherlands) using a sense head coil was available at 3 centers (University Medical Center Utrecht, University Medical Center Leiden, and Isala Hospital, Zwolle) and from 2014 onward at Southmead Hospital, Bristol. Until April 2014, a 1.5-Tesla MR system (GE Signa Excite HD system, Boston, Massachusetts) was used in Bristol. University Medical Center Groningen (SonataVision, Siemens, Germany), University Hospital Puerta del Mar, Cadiz (Magnetom Symphony, Siemens), Radboud University Nijmegen Medical Centre (Magnetom Symphony, Siemens), University of Rotterdam (GE Signa Excite HD system), and University of Lisbon (Philips Healthcare) used a 1.5 Tesla MR system. All participating centers used conventional axial 3-dimensional T1-weighted imaging and T2-weighted imaging and followed a predefined MRI protocol according to their institutional guidelines during the study period. Only the high-quality images that were suitable for scoring and volumetric measurements were included in the study.

Assessment of Brain Injury

An investigator with >20 years of experience in reading neonatal MRIs who was blinded to the infant's clinical information, and the allocated arm of the trial, assessed the images. Ventricular measurements (ventricular index [VI] and AHW) were performed as described by Levene[11] and Davies et al.[13] The frontal and occipital horn (FOH) ratio was obtained by measuring the widest distances across the frontal horns and the occipital horns, and the average of these measurements was then divided by the largest biparietal diameter as defined by Kulkarni et al.[14] To evaluate the intraobserver reliability of the measurements, 15 studies from 15 random patients were assessed and the intraclass correlation coefficient (ICC) was calculated. For the assessment of brain injury, a validated scoring system for evaluating cerebral white matter, cortical gray matter, basal ganglia and thalami (BGT), and cerebellum abnormalities was used. The measurements were corrected for postmenstrual age, and a global brain abnormality score was calculated as the sum of the regional total scores and classified as normal (total score of 0-3), mild (total score of 4-7), moderate (total score of 8-11), and severe (total score of ≥12) as defined by Kidokoro et al.[15]

Assessment of Brain Volumes

Automatic segmentation of cerebral MRIs was applied on axial or coronal T2-weighted images for computerized volume analysis. The images were segmented into 8 regions: cerebellum, myelinated white matter, BGT, ventricular CSF, unmyelinated white matter, brain stem, cortical gray matter, and extracerebral CSF, as described by Moeskops et al.[16] The quality of the automatic segmentations was established by visual evaluation. Images with low-quality segmentations were excluded from further analysis, and high-quality images were manually edited when deemed necessary before further analysis. Subsequently, volumetric measurements of the segmented tissues were obtained by multiplying the number of segmented voxels per tissue by the voxel size. Thereafter, contours were drawn around the structure of interest on consecutive slices through the brain. Both porencephalic cysts and cysts after PVHI but not communicating with the lateral ventricles were included in ventricular volume measurements. The relative volumes of the brain regions were calculated by dividing the volume of the area of interest by total intracranial volume, which includes brain tissues and ventricular and extraventricular CSF spaces (Figure 1).

Statistical Analyses

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences v21.0 program (SPSS Inc, Chicago, Illinois). The continuous variables were presented as mean ± SD and median (IQR), depending on their distribution. The categorical values were presented as frequency and percentage. The Fisher exact and χ^2 tests were used to compare categorical variables among groups. The Mann-Whitney *U* test was used to compare nonparametric variables and the Student *t* test was used for the comparison of variables that showed normal distribution. Logarithmic transformation was used to obtain a Gaussian distribution of the non-normally distributed volumetric measurements. Observed associations controlled for the grade of IVH by using multiple regression. To evaluate the reliability of measurements, ICC was calculated and classified as good for an ICC between 0.8 and 0.9 and excellent for an ICC of >0.9. Statistical significance was set at $P < .05$.

Results

Study Population

During the 10-year study period, 126 infants were enrolled into the ELVIS cohort, of whom 38 were not eligible for inclusion in the present study. Of these ineligible infants, MRI was not available owing to death in 16 or was not performed around TEA in 22 infants. The main reasons for not obtaining an MRI were transfer back to the referring hospital where no MR device was present, and not being able to transfer the infant again to the study site exclusively for imaging reasons at TEA (n = 17). Two had a very early MRI only and 2 had an MRI well beyond the neonatal period, and 1 had an MRI in a level 2 hospital with insufficient quality. The final sample consisted of 88 infants; 44 were in the low-threshold group and 44 were in the high-threshold group (Figure 2; available at www.jpeds.com). No statistically significant differences between the low-threshold and high-threshold groups were observed in terms of gestational age, sex, birth weight, and postmenstrual age at the time of MRI. Infants who were not included in the present study due to not having MRI were similar to those included with respect to demographic

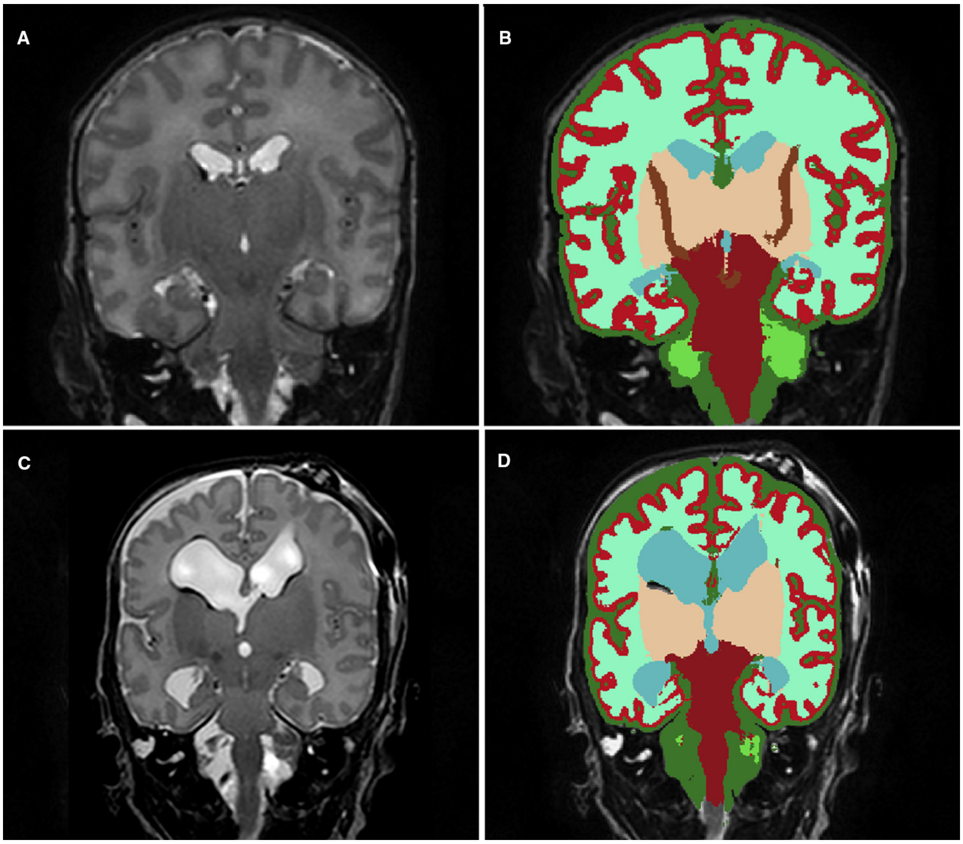

Figure 1. T2-weighted coronal MRIs obtained at TEA show **A**, mildly enlarged ventricular CSF volumes in a preterm infant in the low-threshold group, **B**, the same infant after automatic segmentation of the MRI into 8 regions for volumetric analysis, **C**, severely enlarged ventricular CSF volumes in a preterm infant in the high-threshold group, **D**, automatic segmentation of the image in **C**.

and clinical variables. Characteristics of the participants in whom MRI was completed are presented in Table I.

FOH Ratio and Kidokoro Score

The intra-observer reliability showed an excellent correlation for the measurements (ICC = 0.94). Median ventricular measurements, including VI and AHW ($P < .001$ for both), and the FOH ratio were lower in the low-threshold group ($P = .001$). The total Kidokoro score for the infants in the low-threshold group was also lower than that of the high-threshold group ($P < .001$). The subgroup analyses were performed after excluding infants with PVHI. Data regarding these measurements and comparisons are presented in Table I. When the groups were compared in terms of severity of the Kidokoro score, there were more infants in the low-threshold group with a normal or mildly increased score and more infants in the high-threshold group with a moderately or severely increased score ($P = .002$). The observed associations persisted after controlling for the grade of IVH. A linear correlation between the Kidokoro score and FOH ratio was found (r = 0.62; $P < .001$) and the average FOH ratio increased by 0.06 for every point increase in the Kidokoro score (95% CI, 0.05-0.08).

Table I. Clinical characteristics of the study population and MRI assessments

	Low-threshold group (n = 44)	High-threshold group (n = 44)	*P* value
Gestational age at birth, weeks	28.1 ± 2.4	27.8 ± 2.7	.6*
Birth weight, g	1176 ± 361	1175 ± 404	.9*
Sex			
Male	23 (52)	26 (59)	.5†
Female	21 (48)	18 (41)	
Day of enrollment	9 (6-10)	9 (6-12)	.9‡
Postmenstrual age at MRI, weeks	41.0 (40.4-42.7)	40.9 (40-41.7)	.3‡
GMH-IVH grade			
III	30 (68)	25 (57)	.3†
III + PVHI	14 (32)	19 (43)	
Reservoir inserted	28 (64)	23 (52)	.3†
VP-shunt inserted	9 (20)	12 (27)	.4†
Duration between VP shunt and TEA-MRI, days	4 (-1-28)	10 (-10-29)	.8‡
Ventricular measurements on MRI, mm			
Ventricular width	13.4 (12.6-15.1)	15.9 (14.5-18.8)	**<.001**‡
AHW	6.6 (5.3-10.3)	10.6 (8.4-13.5)	**<.001**‡
FOH ratio	0.42 (0.4-0.46)	0.48 (0.43-0.51)	**.001**‡
Total Kidokoro score	8 (5-12)	12 (9-17)	**<.001**‡
Infants with grade III	7 (5-9)	10 (8-12)	**<.001**‡
Infants with grade III + PVHI	13 (7-19)	16 (15-19)	**<.001**‡
Kidokoro score severity			**.002**‡
Normal	3 (7)	0 (0)	
Mild	17 (39)	5 (11)	
Moderate	12 (27)	13 (30)	
Severe	12 (27)	26 (59)	

GMH-IVH, Germinal matrix hemorrhage-intraventricular hemorrhage.
Significant values are given in bold.
Values are mean ± SD, median (IQR), or number (%).
**t* test.
†χ^2 test.
‡Mann–Whitney *U* test.

Kidokoro Subscores

In the cerebral white matter evaluation, statistically significant differences were observed between the groups in myelination delay, thinning of the corpus callosum, and dilatation of the lateral ventricles subscores. Furthermore, a trend toward biparietal volume reduction in the high-threshold group was seen ($P = .07$). The groups differed in cerebral white matter subscores ($P = .001$). In the cortical gray matter evaluation, infants in the high-threshold arm showed increased extracerebral spaces ($P < .001$) and a trend toward delayed gyral maturation ($P = .07$). The cortical and deep gray matter subscores were lower in the low-threshold group ($P < .001$). The groups were similar in terms of cerebellum signal abnormalities and volume reduction ($P = .8$ and $P = .4$, respectively). The subscore analysis of the infants are tabulated in Table II.

Brain and CSF Volumes on TEA-MRI

Brain and CSF volumes could be calculated in a total of 47 infants, of which 21 were in the low-threshold and 26 in the high-threshold group (Figure 2). No statistically significant differences in unadjusted brain and CSF volumes were observed in relation to PHVD (Table III). When the relative volumes of the brain regions were compared after normalization of the variables with logarithmic transformation, ventricular CSF volumes of the low-threshold group were lower than that of the high-threshold group ($P = .03$). Unmyelinated white matter volumes of the low-threshold and high-threshold groups were not significantly different ($P = .3$). Combination of the white matter and gray matter volumes showed a trend toward higher values in the low-threshold group when compared with the high-threshold group ($P = .06$). The analyses were performed after excluding infants with PVHI (n = 4 in the low-threshold and n = 11 in the high-threshold group), which resulted in a final sample of 17 infants in the low-threshold and 15 in the high-threshold group. Gray matter volume showed a trend toward a higher value ($P = .06$), and combination of the white matter and gray matter volumes was significantly higher in the low-threshold group ($P = .03$). There were no differences between groups in other regions of interest. The FOH ratio was positively associated with ventricular CSF volumes (β, +145; 95% CI, 72-218; $P < .001$).

Discussion

In this nested substudy of our randomized, controlled ELVIS trial[5] of preterm infants with PHVD, infants who were in the low-threshold group had lower global brain abnormality scores and had lower regional total subscores of the cerebral white matter, cortical gray matter, and BGT on TEA-MRI. When the total Kidokoro scores were stratified according to the severity, there were significantly more infants with normal or mildly increased scores in the low-threshold group, and significantly more infants with moderately or

Table II. Kidokoro subscore analysis of the study population

	Low-threshold group (n = 44)	High-threshold group (n = 44)	*P* value
Cystic lesions			.2*
None	27 (61)	18 (41)	
Focal unilateral	3 (7)	1 (2)	
Focal bilateral	2 (5)	3 (7)	
Extensive unilateral	11 (25)	20 (45)	
Extensive bilateral	1 (2)	2 (5)	
Focal signal abnormality			.6*
None	33 (75)	28 (63)	
Focal punctate	6 (14)	7 (16)	
Extensive punctate	3 (7)	6 (14)	
Linear	2 (4)	3 (7)	
Myelination delay			**.01***
PLIC and corona radiata	0 (0)	0 (0)	
Only PLIC	32 (73)	21 (48)	
Minimal—no PLIC	12 (27)	23 (52)	
Thinning of the corpus callosum			**.02***
None	39 (89)	27 (62)	
Partial	2 (4)	5 (12)	
Global	3 (7)	11 (26)	
Dilated lateral ventricles			**.01***
Both sides <7.5 mm	12 (27)	3 (7)	
7.5 mm ≤ 1 side < 10 mm	9 (20)	5 (11)	
7.5 mm ≤ both sides < 10 mm or 1 side ≥ 10 mm	13 (30)	13 (30)	
Both sides ≥ 10 mm	10 (23)	23 (52)	
Volume reduction			.07*
cBPW ≥ 77 mm	26 (59)	18 (41)	
77 mm > cBPW ≥ 72 mm	13 (29)	13 (29)	
72 mm > cBPW ≥ 67 mm	2 (5)	10 (23)	
67 mm > cBPW	3 (7)	3 (7)	
Cerebral white matter subscore			**.001**†
Median (min-max)	4 (1-13)	7 (1-14)	
Cortical gray matter signal abnormality			.5*
None	44 (100)	43 (98)	
Focal unilateral	0 (0)	0 (0)	
Focal bilateral	0 (0)	1 (2)	
Extensive unilateral	0 (0)	0 (0)	
Extensive bilateral	0 (0)	0 (0)	
Gyral maturation			.07*
Delay <2 weeks	4 (9)	1 (2)	
2 ≤ delay < 4 weeks	18 (41)	11 (25)	
Delay ≥ 4 weeks	22 (50)	32 (73)	
Increased extracerebral space			**<.001***
IHD < 4 mm	24 (55)	1 (2)	
4 mm ≤ IHD < 5 mm	8 (18)	8 (18)	
5 mm ≤ IHD < 6 mm	5 (11)	14 (32)	
IHD ≥ 6 mm	7 (16)	21 (48)	
Deep gray matter signal abnormality			.2*
None	40 (91)	38 (87)	
Focal unilateral	0 (0)	4 (9)	
Focal bilateral	1 (2)	1 (2)	
Extensive unilateral	3 (7)	1 (2)	
Extensive bilateral	0 (0)	0 (0)	
Deep gray matter volume reduction			.06*
cDGMA ≥ 9.5 mm^3	36 (82)	38 (86)	
9.5 mm^3 > cDGMA ≥ 8.5 mm^3	6 (14)	2 (5)	
8.5 mm^3 > cDGMA ≥ 7.5 mm^3	0 (0)	4 (9)	
7.5 mm^3 > cDGMA	2 (4)	0 (0)	
Cerebellum signal abnormality			.8*
None	26 (59)	24 (55)	
Punctate unilateral	7 (16)	9 (21)	
Punctate bilateral	6 (14)	8 (18)	
Extensive unilateral	2 (4)	2 (4)	
Extensive bilateral	3 (7)	1 (2)	

(*continued*)

Table II. Continued

	Low-threshold group (n = 44)	High-threshold group (n = 44)	*P* value
Cerebellum volume reduction			.4*
cTCD ≥ 50 mm	30 (68)	23 (52)	
50 mm > cTCD ≥ 47 mm	7 (16)	11 (25)	
47 mm > cTCD ≥ 44 mm	3 (7)	5 (11)	
44 mm > cTCD	4 (9)	5 (11)	
Cortical gray matter and deep gray matter subscore			**<.001**†
Median (min-max)	4 (0-14)	6 (2-14)	

cBPW, Biparietal width corrected for gestational age; *cDGMA*, deep gray matter area corrected for gestational age; *cTCD*, transcerebellar diameter corrected for gestational age; *IHD*, interhemispheric distance; *PLIC*, posterior limb of internal capsule.
Significant values are given in bold.
*Fisher exact test.
†Mann-Whitney *U* test.

severely increased scores in the high-threshold group, even though at the time of randomization the number of infants with a grade III hemorrhage or PVHI was similar in the study arms. Infants in the high-threshold group also demonstrated more delay in myelination and more often partial or global thinning of the corpus callosum. Moreover, lower FOH ratios, VI, and AHW at TEA and smaller ventricular CSF volumes were found in infants in the low-threshold group. In the subgroup analysis, after excluding infants with PVHI, combination of the white matter and gray matter volumes was significantly higher in the low-threshold group ($P = .03$). Using a structured scale assessment together with the quantification of the ventricular dilatation acquired at TEA, we were able to identify injury in specific regions of the brain, demonstrating the possible beneficial effects of early intervention after the onset of PHVD.

The pathogenesis of PHVD is a complex process determined by both direct injury and secondary inflammatory interactions.[17-21] To address the net effects of PHVD on brain lesions in different regions, an objective structured scale assessment was used in combination with volumetric analysis in the present study. This approach enabled us to determine the correlation between ventricular size and the extent of brain injury. The smaller ventricular CSF volumes together with the lower global brain abnormality scores as well as lower regional total subscores of the major regions of the brain in the low-threshold group indicates the possible beneficial effects of early intervention as we found that almost one-half (46%) of the infants in the low-threshold group had normal or mildly increased Kidokoro scores compared with only 11% in the high-threshold group. In infants with PHVD, expanding ventricles might cause atrophy of the adjacent brain tissue as a result of compression by CSF under pressure.[22,23] By using a manual segmentation technique, Jary et al calculated cerebral, thalamic and cerebellar volumes, and demonstrated that brain growth is significantly impaired in PHVD.[22] Ventricles were larger with a median volume of 48 mL (IQR, 27-145) than the ventricular volumes of both groups in our study (median volume, 18 mL and

Table III. Distribution of absolute and relative brain and CSF volumes between the groups

Volumes	Low-threshold group (n = 21)	High-threshold group (n = 26)	*P* value*
Ventricles			
Absolute	18 (11-30)	24 (17-37)	.07
Relative	0.05 (0.02-0.07)	0.06 (0.04-0.09)	**.03**
Absolute†	16 (12-27)	23 (15-31)	.4
Relative†	0.04 (0.03-0.06)	0.06 (0.04-0.07)	.1
Unmyelinated white matter			
Absolute	165 (136-186)	154 (128-184)	.5
Relative	0.3 (0.2-0.4)	0.3 (0.2-0.4)	.3
Absolute†	165 (140-186)	171 (129-185)	.7
Relative†	0.3 (0.2-0.4)	0.3 (0.2-0.4)	.6
Cortical gray matter			
Absolute	128 (119-166)	131 (117-155)	.8
Relative	0.3 (0.2-0.4)	0.3 (0.1-0.4)	.5
Absolute†	129 (119-173)	126 (114-152)	.3
Relative†	0.3 (0.2-0.3)	0.2 (0.2-0.3)	.06
Combined white and gray matter			
Absolute	304 (238-378)	302 (239-316)	.3
Relative	0.6 (0.5-0.7)	0.5 (0.5-0.6)	.06
Absolute†	307 (295-349)	302 (244-315)	.1
Relative†	0.6 (0.5-0.7)	0.5 (0.5-0.6)	**.03**
Basal ganglia and thalami			
Absolute	25 (21-27)	23 (19-25)	.4
Relative	0.04 (0.03-0.05)	0.04 (0.04-0.05)	.9
Absolute†	25 (22-27)	24 (22-25)	.5
Relative†	0.05 (0.04-0.06)	0.05 (0.04-0.06)	.8
Cerebellum			
Absolute	31 (25-41)	31 (23-41)	.8
Relative	0.06 (0.05-0.07)	0.06 (0.03-0.18)	.6
Absolute†	31 (25-41)	32 (25-47)	.5
Relative†	0.06 (0.05-0.07)	0.05 (0.04-0.07)	.5
Extracerebral CSF			
Absolute	127 (98-140)	116 (102-137)	.9
Relative	0.2 (0.2-0.3)	0.2 (0.2-0.3)	.5
Absolute†	113 (98-145)	119 (105-158)	.4
Relative†	0.2 (0.2-0.3)	0.2 (0.2-0.3)	.3

Data are presented as median (IQR). Absolute volumes are presented in milliliters. Significant values are given in bold.
**P* values are presented after logarithmic transformation of relative volumes.
†Volumes after excluding infants with periventricular hemorrhagic infarct (n = 17 in the low-threshold group and n = 15 in the high-threshold group).

24 mL in the low-threshold group and the high-threshold group, respectively). Brouwer et al reported data in a small group of infants and showed that PHVD was independently associated with decreased volumes of deep gray matter, cerebellum, and extracerebral CSF, despite early intervention.[4] They found a median ventricular volume of 18.3 mL (range, 8.6-64.5 mL) in infants with PHVD, which is lower than we report in the high-threshold group and overlaps considerably with values we found in the low-threshold group. It has been shown that, in infants with severe IVH who developed PHVD, ventricular size may be an important determinant of long-term neurodevelopmental outcome and infants with severe IVH who developed PHVD had worse neurodevelopmental scores compared with those who did not develop PHVD.[12,24,25] Recently, Leijser et al reported in their large cohort of preterm infants with PHVD that those who underwent intervention based on ventricular measurements, before the development of symptoms, even when eventually requiring a VP shunt, had outcomes indistinguishable from those without intervention, all being within the normal range.[10] Infants who first received the intervention once clinical symptoms had occurred had worse outcomes. The volumes of the ventricles, and combined volume of the unmyelinated white matter and gray matter regions were in favor of the low-threshold therapy in the present study. We also measured the VI and AHW on TEA-MRI, which revealed smaller lateral ventricles in the low-threshold group. Whether the smaller ventricular volumes and preserved unmyelinated white matter and gray matter volumes of infants who underwent low-threshold therapy will be associated with improved neurodevelopmental outcomes in the ELVIS trial is currently being assessed.

The higher Kidokoro scores in infants in the high-threshold group are in line with the accumulating literature, suggesting that progressive ventricular dilatation and prolonged pressure might be deleterious to the immature brain. A rapidly enlarging ventricular system could result in compression of adjacent brain parenchyma, and this has been used as an explanation for the MRI signal abnormalities in various regions of the brain.[26,27] Because infants in the high-threshold group had greater ventricular volumes than those of the low-threshold group, the Kidokoro scores of these infants, which increase directly with the presence of signal abnormalities could have increased. PHVD-induced microstructural white matter injury, as stated previously by Brouwer et al, might serve as another explanation for the signal abnormalities on TEA-MRI in our cohort.[4] It is also worth noting that FOH ratios showed good correlation with ventricular volumetric measurements, which can be used as a practical assessment tool for calculating the ventricular volumes in patients with PHVD.

The present study has several limitations. First, because this was a multicenter study, MRI protocols were not the same across centers, which could have led to varying image qualities. Second, a relatively large number of segmented MRIs could not be used for the volumetric analysis. This was due to the use of a convolutional neural network technique, which was trained on segmented images of preterm neonates without any pathology. As a consequence, the automatic segmentation had limitations in segmenting scans with PHVD. Furthermore, because the automatic segmentation method was trained with scans acquired in the main study site, it was not always able to provide optimal segmentation for images obtained with a different protocol. This technique also did not allow differentiation between the basal ganglia and thalamic volumes and could not demonstrate precise segmentation of myelinated white matter due to technical reasons. Third, because the present study was a nested substudy, it is possible that the lack of statistically significant differences in volumetric measurements was due to a limited sample size. Finally, there is the potential for selection bias arising from the excluded MRIs. However, we found that the excluded infants were similar with respect to demographic and clinical characteristics. The main strength of our study was the use of an objective scoring system enabling assessment of the extent of brain injury and reliable quantification of the ventricular and brain volumes in 80% of the surviving infants.

PHVD remains a serious complication of IVH, and control of PHVD using lumbar punctures as studied in the ELVIS trial before or just after the VI crossed the p97 + 4 mm line was associated with the lowest need for VP shunt reported in the literature.[5] This nested substudy of the ELVIS trial, designed to address parenchymal injury in different regions of the brain together with the quantification of the CSF and brain volumes, demonstrates beneficial effects of early intervention on the extent of brain injury and ventricular CSF volumes. Whether these findings translate into improved neurological development is being assessed and will be the subject of a later report. ■

We thank the MR technicians for their dedicated help to obtain the MRIs.

Submitted for publication Aug 31, 2018; last revision received Nov 26, 2018; accepted Dec 31, 2018.

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Appendix

ELVIS study group

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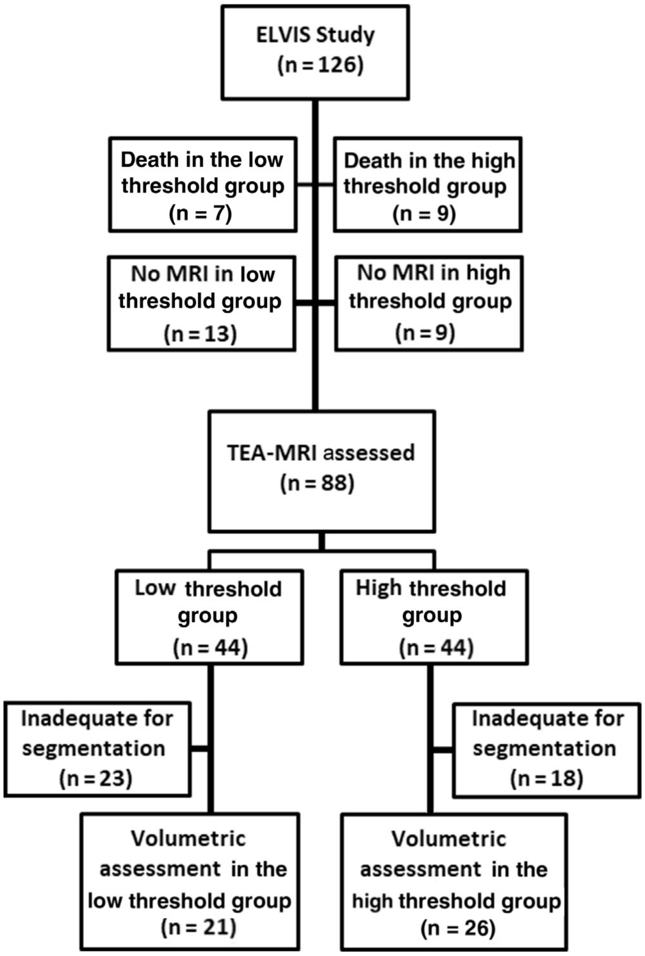

Figure 2. Flowchart of patient allocation and subsequent MRI assessments at TEA.