Does ventricle size contribute to cognitive outcomes in posthemorrhagic hydrocephalus? Role of early definitive intervention

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OBJECTIVE Posthemorrhagic hydrocephalus (PHH) is associated with significant morbidity, smaller hippocampal volumes, and impaired neurodevelopment in preterm infants. The timing of temporary CSF (tCSF) diversion has been studied; however, the optimal time for permanent CSF (pCSF) diversion is unknown. The objective of this study was to determine whether cumulative ventricle size or timing of pCSF diversion is associated with neurodevelopmental outcome and hippocampal size in preterm infants with PHH.

METHODS Twenty-five very preterm neonates (born at ≤ 32 weeks' gestational age) with high-grade intraventricular hemorrhage (IVH), subsequent PHH, and pCSF diversion with a ventriculoperitoneal shunt ($n = 20$) or endoscopic third ventriculostomy ($n = 5$) were followed until 2 years of age. Infants underwent serial cranial ultrasounds from birth until 1 year after pCSF diversion, brain MRI at term-equivalent age, and assessment based on the Bayley Scales of Infant and Toddler Development, Third Edition, at 2 years of age. Frontooccipital horn ratio (FOHR) measurements were derived from cranial ultrasounds and term-equivalent brain MRI. Hippocampal volumes were segmented and calculated from term-equivalent brain MRI. Cumulative ventricle size until the time of pCSF diversion was estimated using FOHR measurements from each cranial ultrasound performed prior to permanent intervention.

RESULTS The average gestational ages at tCSF and pCSF diversion were 28.9 and 39.0 weeks, respectively. An earlier chronological age at the time of pCSF diversion was associated with larger right hippocampal volumes on term-equivalent MRI (Pearson's $r = -0.403$, $p = 0.046$) and improved cognitive ($r = -0.554$, $p = 0.047$), motor ($r = -0.487$, $p = 0.048$), and language ($r = -0.414$, $p = 0.021$) outcomes at 2 years of age. Additionally, a smaller cumulative ventricle size from birth to pCSF diversion was associated with larger right hippocampal volumes ($r = -0.483$, $p = 0.014$) and improved cognitive ($r = -0.711$, $p = 0.001$), motor ($r = -0.675$, $p = 0.003$), and language ($r = -0.618$, $p = 0.011$) outcomes. There was no relationship between time to tCSF diversion or cumulative ventricle size prior to tCSF diversion and neurodevelopmental outcome or hippocampal size. Finally, a smaller cumulative ventricular size prior to either tCSF diversion or pCSF diversion was associated with a smaller ventricular size 1 year after pCSF diversion ($r = 0.422$, $p = 0.040$, $R^2 = 0.178$ and $r = 0.519$, $p = 0.009$, $R^2 = 0.269$, respectively).

CONCLUSIONS In infants with PHH, a smaller cumulative ventricular size and shorter time to pCSF diversion were associated with larger right hippocampal volumes, improved neurocognitive outcomes, and reduced long-term ventriculomegaly. Future prospective randomized studies are needed to confirm these findings.

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KEYWORDS posthemorrhagic hydrocephalus; intraventricular hemorrhage; ventriculoperitoneal shunt; endoscopic third ventriculostomy; ETV

ABBREVIATIONS AUC = area under the curve; cUS = cranial ultrasound; ETV = endoscopic third ventriculostomy; FOHR = frontooccipital horn ratio; GA = gestational age; IGV = intracranial volume; IUGR = intrauterine growth restriction; IVH = intraventricular hemorrhage; pCSF = permanent CSF; PDA = patent ductus arteriosus; PHH = posthemorrhagic hydrocephalus; tCSF = temporary CSF; VP = ventriculoperitoneal.

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DESPITE advances in obstetric, perinatal, and neonatal care, preterm intraventricular hemorrhage (IVH) remains the most common cause of acquired hydrocephalus in the United States, with a reported incidence of approximately 20%–30% in preterm very-low-birth-weight infants (< 1500 g).¹ Furthermore, these infants have the worst neurocognitive outcomes among infants born preterm.² Because of their small size, preterm infants who develop posthemorrhagic hydrocephalus (PHH) usually require temporary CSF (tCSF) diversion with ventricular reservoirs, subgaleal shunts, external ventricular drainage, or serial lumbar punctures,³ and more than 60% ultimately require some form of permanent CSF (pCSF) diversion with ventriculoperitoneal (VP) shunt placement, endoscopic third ventriculostomy (ETV), or ETV with choroid plexus cauterization.⁴

The timing of and thresholds for tCSF diversion have been evaluated in both retrospective and prospective randomized studies. While the initial results of the ELVIS (Early vs Late Ventricular Intervention Study) showed no difference in the composite outcome of death and the need for a VP shunt based on ventricular size treatment thresholds for tCSF diversion, post hoc analysis demonstrated that lower thresholds for tCSF diversion were associated with lower brain abnormality scores.³⁷ After controlling for gestational age (GA), IVH severity, and cerebellar hemorrhage, lower treatment thresholds for tCSF diversion were associated with an improved composite outcome of death and neurodevelopmental outcome at 2 years.^{5,42} This trial also revealed that a smaller frontooccipital horn ratio (FOHR) at term-equivalent age was associated with more favorable cognitive and motor outcomes.⁵ These findings were similar to those in retrospective studies showing improved neurodevelopmental outcomes; however, they did not demonstrate a decreased need for pCSF diversion with lower tCSF diversion treatment thresholds.^{6–8} Nonetheless, other investigations have reported more revisions, externalizations, and removal procedures with earlier tCSF intervention, which may contribute to altered cognitive and motor outcomes.^{7,12,13,34}

While studies have evaluated postsurgical outcomes in the timing of pCSF diversion for the treatment of PHH, the impact of the timing of pCSF diversion or cumulative ventricle size on neurodevelopmental outcomes has not been studied.^{7,11–13} Furthermore, as hippocampal function is integral to learning and memory, we previously evaluated preterm infants with PHH and found significantly smaller hippocampal volumes in this population, which were associated with worse cognitive outcomes compared to those of preterm infants with other forms of brain injury and without brain injury.² However, it is unknown how potentially modifiable variables in patients with PHH, such as cumulative ventricle size and the timing of pCSF diversion, relate to hippocampal volumes and neurocognitive outcomes.

Here, we present a cohort of preterm infants with PHH and evaluate 1) the timing of pCSF diversion and 2) the impact of cumulative ventricle size prior to pCSF diversion on hippocampal development and neurodevelopmental outcomes. To the best of our knowledge, this is the first study to address these two potentially modifiable factors in the neurodevelopmental outcome of patients with PHH.

Methods

Study Participants

In this longitudinal observational study, very preterm infants were prospectively recruited from the St. Louis Children's Hospital Neonatal Intensive Care Unit from 2007 to 2015. Subjects were initially identified based on evidence of high-grade (grade III or IV) IVH on cranial ultrasound (cUS) within the 1st month of life.¹⁴ Infants with a subsequent diagnosis of PHH who underwent tCSF and pCSF diversion were included in the study. In general, a diagnosis of PHH was based on an FOHR > 0.55, a full anterior fontanelle, and/or 2-mm split sutures in the parietal region.⁹ Infants were excluded for congenital infections, chromosomal aberrations, or systemic infections and positive CSF cultures immediately prior to intervention. The study was approved by the Human Research Protection Office of the study site. Parental informed consent was obtained for each subject prior to study participation.

Clinical variables shown to have significant effects on PHH susceptibility or hippocampal development and neurodevelopmental outcomes in prior studies, including patent ductus arteriosus (PDA), exposure to antenatal and postnatal steroids, indomethacin use, necrotizing enterocolitis, confirmed sepsis, chorioamnionitis, and sex, were noted among the patient characteristics.^{16,18,19} As described previously,² this clinical information was combined to create an infant medical index score for each patient.¹⁸ The components of the infant medical risk score are a composite of intrauterine growth restriction (IUGR), prolonged oxygen supplementation, lack of antenatal steroids, dexamethasone use, necrotizing enterocolitis, sepsis, PDA, retinopathy of prematurity, ≥ 3 SD change in weight-for-height/length, and > 75th percentile for duration of parental nutrition.¹⁹ Each variable was presented in a dichotomized manner in which those that met the criteria were assigned a 1 and those that did not were assigned a 0. The risk score was then calculated on a scale of 1–10, where 10 is the highest risk.

pCSF Diversion

The timing of pCSF diversion was left up to the discretion of the treating neurosurgeon. At our institution, a patient weight of at least 1800 g, clinical stability, and visibly clear CSF were used to make the decision about when to transition to pCSF diversion. More recently, some have intervened at lower patient weights.

MRI and Hippocampal Volumetric Measurements

As described previously,² subjects underwent MRI on a 3-T scanner at term-equivalent age with an infant-specific head coil. Imaging was completed during infant sleep or quiet rest without sedation. T2-weighted data were acquired with the following sequence parameters: TR 8600 msec, TE 161 msec, voxel size $1 \times 1 \times 1$ mm³. High-quality T2-weighted data were available for all infants.²

For calculating hippocampal volumes, Morphologically Adaptive Neonatal Tissue Segmentation (MANTiS) was utilized to first identify intracranial volume (ICV), which is volume within the cranium, including the brain, meninges, and CSF.^{2,20,43} Hippocampal volumes were gen-

FIG. 1. FOHRs assessed from serial cUSs were charted over time from birth to tCSF diversion and from birth to pCSF diversion. AUC analysis from birth to procedural time points represents cumulative ventricular size.

erated through anatomical outlining of boundaries on T2-weighted MR images. These hippocampal volumes were then divided by the ICV to provide corrected hippocampal volumes with no units of measurement.^{2,20}

cUS Reporting

One to 2 times weekly, as part of routine clinical care for all preterm infants with high-grade IVH within the first month of life, cUS was performed using a Zonare.one UltraSmartCart diagnostic system. These serial ultrasounds were monitored for the development and evolution of IVH, PHH, and any other neurological changes. The highest IVH grade was determined from the board-certified pediatric radiologist assessment of the cUSs for each patient.

Ventricle Size on cUS

For each patient, ventricle size was determined on cUSs performed from the time of birth until pCSF diversion and then at 1 year after pCSF diversion. Measurements of bi-frontal horn width (a), bi-occipital horn width (b), along with interparietal diameter (c), were determined. Estimations of ventricle size were calculated using the FOHR ($(a + b)/2c$; Supplementary Fig. 1).²¹ The FOHR area under the curve (AUC) was calculated mathematically via right-endpoint approximation (Fig. 1) and utilized in order to determine cumulative ventricle size over time.

Neurodevelopmental and Behavioral Testing

Seventeen of 25 patients returned for standardized developmental testing at age 2 years, corrected for prematurity. A blinded psychometrician assessed subjects using the Bayley Scales of Infant and Toddler Development, Third Edition, generating composite scores in motor, lan-

guage, and cognitive performance.²² Parents also provided standardized sociodemographic information, which was used to define sociodemographic risk by applying a composite index consisting of the presence or absence of high school graduation, African American race, public health insurance, maternal age at birth < 18 years, and single-parent household.^{23,24} If three or more items were missing, social risk was not calculated, and for fewer than 3 missing components, the mean of the remaining components was substituted to determine score.²⁴

Statistical Analysis

Analyses were performed using SPSS version 26 (IBM Corp.). The FOHR AUC was used to approximate cumulative ventricle size until tCSF or pCSF neurosurgical intervention. The coefficient of determination (R^2) and Pearson's correlation coefficient (r) were reported when appropriate. A p value < 0.05 was considered statistically significant.

Results

Clinical Characteristics

Twenty-five patients met study inclusion criteria, all of whom underwent tCSF diversion with a subgaleal shunt ($n = 2$) or ventricular reservoir ($n = 23$) and later pCSF diversion with a VP shunt ($n = 20$) or ETV ($n = 5$). The mean estimated GA at birth was 25.0 ± 1.8 weeks (mean $\pm$ standard deviation), 80% of the patients were male, and the mean birth weight was 828.9 ± 192.2 g. All patients had bilateral IVH. The mean infant medical risk index was 3.6 ± 1.9 for this cohort. The mean social risk score at 2 years' follow-up of patient and family demographics was $2.2 \pm$

TABLE 1. Clinical characteristics of 25 very preterm infants with PHH

Characteristic	Value
Mean GA in wks (SD)	25 (1.8)
Mean PMA at time of MRI in wks (SD)	39.2 (2.3)
Mean birth weight in g (SD)	828.9 (192.2)
Right IVH grade, no. (%)	
I	0
II	2 (8)
III	6 (24)
IV	17 (68)
Left IVH grade, no. (%)	
I	1 (4)
II	1 (4)
III	11 (44)
IV	12 (48)
Male, no. (%)	20 (80)
African American, no. (%)	16 (64)
Mean social risk score (SD), n = 14 patients	2.2 (1.4)
Mean clinical medical risk index (SD)	3.6 (1.9)
IUGR, no. (%)	1 (4)
Oxygen at 36 wks, no. (%)	24 (96)
No antenatal steroids, no. (%)	12 (48)
Postnatal dexamethasone, no. (%)	10 (40)
Necrotizing enterocolitis, no. (%)	10 (40)
PDA, no. (%)	9 (36)
Retinopathy of prematurity, no. (%)	7 (28)
Sepsis, no. (%)	16 (64)
Mean no. days on TPN (SD), n = 25 patients	53.5 (46.5)
Chorioamnionitis, no. (%)	9 (36)
Mean no. hrs on ventilator (SD)	867.6 (550.9)

PMA = postmenstrual age; TPN = total parenteral nutrition.

1.4. The average age at first IVH diagnosis was 2.9 days for 22 patients. Three patients were transferred from an outside hospital (all ≤ 22 days at age of transfer) with the presence of IVH on cUS at transfer. The average postmenstrual age at the time of tCSF and pCSF diversion were 28.9 and 39.0 weeks, respectively. The timing of tCSF or pCSF diversion was calculated as the number of days from birth to the day/time of the intervention; the average numbers of days from birth to tCSF and pCSF diversion were 27.5 and 98.1 days, respectively. The average weights at the time of tCSF and pCSF diversion were 958 and 2259 g, respectively. Additional clinical characteristics are summarized in Table 1.

Bayley composite scores are summarized in Table 2. Seventeen patients were assessed at approximately 2 years (24–39 months), and median Bayley cognitive, motor, and language scores were 70, 67, and 75.5, respectively. There was no association between GA at birth and any of the three outcome measures or hippocampal volumes. Of the 25 patients who underwent pCSF diversion, 64% (n = 16) underwent shunt revision prior to 2 years of age, whereas

TABLE 2. Neurodevelopmental outcomes

Bayley Composite Scores	No. of Patients	Median Score
Cognitive composite	17	70
Language composite	16	75.5
Motor composite	17	67

all patients who underwent initial ETV had eventual VP shunt placement (n = 5). The average time of first shunt revision from primary shunt placement was 210 days. Three patients underwent revision for an abdominal pseudocyst and 1 underwent revision for local wound breakdown with exposed hardware prior to 2 years of age. These cases were not associated with CSF infection. There was no significant difference in average postmenstrual age at pCSF diversion between the cohort with complications and the cohort without (p = 0.31). Furthermore, there was no significant difference in average postmenstrual age at pCSF diversion in infants who required 2 or more revisions by 2 years of age versus infants who had fewer revisions (p = 0.57).

Ventricle size was measured on serial cUSs using the FOHR. Cumulative ventricle size was determined using time and FOHR AUC for the following time periods: days from birth to tCSF diversion and days from birth to pCSF diversion, as depicted in Fig. 1.

tCSF Diversion and Neurodevelopmental Outcome

There was no relationship between time to tCSF diversion and Bayley motor scores (Pearson's $r = -0.344$, $p = 0.177$, R^2 linear = 0.118), cognitive scores ($r = -0.178$, $p = 0.494$, R^2 linear = 0.032), or language scores ($r = -0.161$, $p = 0.551$, R^2 linear = 0.026; Fig. 2A). Maximum ventricle size, measured by the largest FOHR value recorded on cUSs prior to tCSF diversion, was not associated with cognitive ($r = -0.283$, $p = 0.272$, R^2 linear = 0.102), motor ($r = -0.473$, $p = 0.055$, R^2 linear = 0.222), or language ($r = -0.202$, $p = 0.454$, R^2 linear = 0.031) scores (Fig. 2B). Cumulative ventricle size (FOHR AUC) prior to tCSF diversion was not associated with Bayley motor ($r = -0.244$, $p = 0.345$, R^2 linear = 0.060), language ($r = -0.250$, $p = 0.350$, R^2 linear = 0.063), or cognitive ($r = -0.188$, $p = 0.471$, R^2 linear = 0.035) scores (Fig. 2C).

pCSF Diversion and Neurodevelopmental Outcome

An earlier time to pCSF diversion was significantly correlated with higher cognitive ($r = -0.554$, $p = 0.047$, R^2 linear = 0.206), motor ($r = -0.487$, $p = 0.048$, R^2 linear = 0.237), and language ($r = -0.414$, $p = 0.012$, R^2 linear = 0.207) scores at 2 years of age (Fig. 3A). Maximum FOHR prior to pCSF diversion was not associated with cognitive (Pearson's $r = -0.403$, $p = 0.109$, R^2 linear = 0.162), motor ($r = -0.158$, $p = 0.544$, R^2 linear = 0.025), or language (Pearson's $r = 0.016$, $p = 0.953$, R^2 linear < 0.01) scores (Fig. 3B). However, a larger cumulative ventricular size (FOHR AUC) prior to pCSF diversion was associated with lower cognitive (Pearson's $r = -0.711$, $p = 0.001$, R^2 linear = 0.505), motor (Pearson's $r = -0.675$, $p = 0.003$, R^2

FIG. 2. Correlation of days to tCSF diversion (A), maximum FOHR (B), and cumulative ventricular size as an integrated AUC of FOHR values (C) with Bayley motor and cognitive outcomes ($n = 17$) and language outcomes ($n = 16$).

linear = 0.456), and language ($r = -0.618$, $p = 0.011$, $R^2 = 0.382$) scores at 2 years of age (Fig. 3C).

Long-Term Ventricle Size: After pCSF Diversion

Maximum FOHR in the year following pCSF diversion was not associated with Bayley motor ($r = -0.158$, $p = 0.544$, $R^2 = 0.046$), cognitive ($r = -0.403$, $p = 0.109$, $R^2 < 0.01$), or language ($r = -0.162$, $p = 0.564$, $R^2 = 0.026$) scores at 2 years of age (Fig. 4A). A larger ventricle size (FOHR) 1 year after pCSF diversion (assessed from cUS, head CT, or MRI) was associated with worse motor ($r = -0.308$, $p = 0.046$, $R^2 = 0.095$) and language ($r = -0.231$, $p = 0.048$, $R^2 = 0.054$) scores but not with cognitive scores ($r = -0.001$, $p = 0.997$, $R^2 < 0.001$; Fig. 4B). An earlier time to tCSF diversion ($r = 0.402$, $p = 0.045$, $R^2 = 0.146$) and a smaller cumulative ventricle size before tCSF diversion ($r = 0.422$, $p = 0.040$, $R^2 = 0.178$) were associated with a smaller FOHR 1 year after pCSF diversion (Fig. 5A). A shorter time to pCSF diversion ($r = 0.428$, $p = 0.037$, $R^2 = 0.183$) and smaller cumulative ventricle size prior to pCSF diversion were significantly associated with a smaller ventricle size 1 year after pCSF diversion ($r = 0.519$, $p = 0.009$, $R^2 = 0.269$; Fig. 5B).

Hippocampal Volumes

There was no significant association between time to tCSF diversion and corrected right hippocampal volumes on term-equivalent MRI ($r = -0.185$, $p = 0.375$, R^2 linear = 0.142; Fig. 6A). Neither maximal FOHR values ($r = -0.256$, $p = 0.217$, R^2 linear = 0.024) nor cumulative ventricular sizes prior to tCSF diversion ($r = -0.250$, $p = 0.240$, R^2 linear = 0.138) were correlated with corrected right hippocampal volumes. A longer time to pCSF diversion in days from birth was significantly correlated with smaller right corrected hippocampal volumes ($r = -0.403$, $p = 0.046$, R^2 linear = 0.244; Fig. 6B). Maximum FOHR prior to pCSF diversion was not associated with corrected right hippocampal volumes ($r = -0.305$, $p = 0.139$, R^2 linear = 0.059); however, total cumulative ventricular size corrected prior to pCSF diversion was significantly associated with right corrected hippocampal volumes, where the greater the cumulative ventricular size, the smaller the right corrected hippocampal volume on term-equivalent MRI ($r = -0.483$, $p = 0.014$, R^2 linear = 0.233). Left hippocampal volumes were not significantly associated with maximal ventricle size or cumulative ventricle size prior to temporary or permanent interventions. The time to either

FIG. 3. Correlation of days to pCSF diversion (A), maximum FOHR (B), and cumulative ventricular size as an integrated AUC of FOHR values (C) with Bayley motor and cognitive outcomes ($n = 17$) and language outcomes ($n = 16$).

temporary or permanent intervention was not correlated with left corrected hippocampal volumes. There was no significant association between the timing of tCSF diversion ($p = 0.252$) or pCSF diversion and total hippocampal volume ($p = 0.211$).

Discussion

Summary

In our single-center observational study, we evaluated the role of 1) the timing of pCSF diversion and 2) cumulative ventricle size on neurodevelopmental outcomes and hippocampal development in PHH. We found that a younger chronological age at the time of pCSF diversion (but not tCSF diversion) and a smaller cumulative ventricle size prior to pCSF diversion are associated with larger right hippocampal size at term-equivalent age and improved motor, language, and cognitive outcomes at 2 years of age.

Neurodevelopmental Outcome in PHH

We show for the first time that a smaller cumulative ventricle size and an earlier time to pCSF diversion are

associated with improved cognitive, motor, and language outcomes at 2 years in preterm infants with PHH. It is likely that the injury mechanisms involved in PHH overlap with those related to poor neurodevelopmental outcomes in preterm infants. Low-birth-weight preterm infants without IVH have been shown to have worse motor and cognitive outcomes than full-term infants,¹⁵ highlighting the background rate of brain injury and abnormal functioning in preterm birth. The long-term cognitive outcome of infants who survive with IVH-PHH worsens with increasing severity of IVH and male sex.^{25,26} Furthermore, males at low birth weights are at greater risk for developing IVH and severe IVH than females.²⁷ Other papers evaluating infants with PHH have had predominantly male representation ranging from 56% to 65%.^{28–30} Notably, 80% of our patient population was male, providing further evidence that males are perhaps more vulnerable to severe presentations and subsequent neurological injury burden. Our patients had severe bilateral grade III/IV IVH with a GA averaging 25 weeks and low birth weights (Table 1), consistent with prior studies demonstrating an increased risk of IVH and subsequent PHH with a decreased GA and birth weight.³¹ We and others have shown baseline differ-

FIG. 4. Correlation of maximum FOHR in the year after pCSF diversion (A) and FOHR 1 year after pCSF diversion (B) with Bayley language ($n = 16$) and motor and cognitive ($n = 17$) outcomes.

ences in hippocampal size during development, with right larger than left hippocampal volumes.^{2,20,32} In our cohort, more patients had right grade IV IVH than left grade IV IVH; however, after combining grades III and IV IVH, our cohort had similar hemorrhage rates on the right and left. The relative contributions to potential hippocampal growth of intraventricular blood, which may have more direct contact with the ependyma overlying the hippocampus versus a parenchymal injury (grade IV), are not known. Given the baseline differences in hippocampal size between right and left in other cohorts of full-term or preterm infants without brain injury, we may have been able to detect a difference with this small cohort given the potential for larger variations in right hippocampal size.

Prenatal infections, specifically chorioamnionitis, and maternal healthcare disparities including lower family socioeconomic status, low maternal education, and prenatal abnormalities are all associated with IVH.^{18–20,23,24,33} Similarly, our preterm infant population included significant proportions of risk factors such as chorioamnionitis,

IUGR, and sepsis, with many patients in the upper quartile of sociodemographic and medical risk scores. Complications after pCSF diversion and the need for revision were similar to reported outcomes.³⁴ Our patient population had risk factors that not only contributed to the development of progressive PHH, but also likely compounded their burden of neurological impairment beyond the detrimental impact of pCSF diversion procedures alone. This cohort is representative of preterm infants with IVH-PHH in the literature with respective comorbidities and provides a basis for understanding the impact of the timing of pCSF diversion on neurodevelopmental outcomes.

tCSF Diversion

Prior studies evaluating the relationship between timing of intervention in IVH-PHH and outcome have focused entirely on tCSF diversion, in which early intervention with tCSF diversion in preterm infants with IVH is based on ventricular size thresholds or within 3 to 4 weeks

FIG. 5. Correlation of days to tCSF (A) or pCSF (B) diversion and cumulative ventricular sizes (FOHR AUC) before each intervention with ventricle size (FOHR) 1 year after pCSF diversion.

FIG. 6. Scatterplots of FOHR representing correlations of days to tCSF diversion, maximum ventricular size, and cumulative ventricular size as an integrated AUC prior to tCSF diversion with right hippocampal ratio ($n = 25$, A) and correlations of days to pCSF diversion, maximum ventricular size, and cumulative ventricular size as an integrated AUC of FOHR prior to pCSF diversion with right hippocampal ratios (B).

of birth.^{5,7,35,36,42} A large retrospective study showed that 2-year outcomes were better in preterm infants with earlier tCSF diversion;⁷ however, a follow-up randomized study (ELVIS) did not show any difference in the primary composite outcome of death or VP shunt with early versus late ventricular size thresholds for tCSF diversion in posthemorrhagic ventricular dilation.⁴² At the 2-year follow-up, although there was no overall difference in neurodevelopmental outcome between early and late intervention, after controlling for GA, IVH severity, and cerebellar hemorrhage, lower thresholds for tCSF diversion were associated with an improved composite outcome of death and neurodevelopmental outcome.⁵ However, higher thresholds for tCSF diversion may provide more time for the infant to gain weight and result in fewer surgical complications including infection, which may alter neurodevelopmental outcomes.^{35,44}

Our study, in contrast, was not designed to evaluate rates of permanent shunt placement, as all patients were selected based on their need for eventual pCSF diversion; therefore, these patient cohorts have baseline differences.^{7,31} We found that time to tCSF diversion was not associated with improved outcomes, and a time point balancing earlier protective brain measures with sufficient infant growth for reducing complications for temporary intervention may underlie these findings. Our results of cognitive improvement with timing of pCSF, but not tCSF diversion, are supported by results of the DRIFT (Drainage, Irrigation and Fibrinolytic Therapy) trial, which showed that infants who had drainage, irrigation, and fibrinolytic therapy had an improved cognitive ability at 10 years.¹⁰ Mechanistically, the persistent drainage of CSF in the setting of pCSF diversion compared to that of tCSF intervention may be neuroprotective. Understanding the impact of the transition time point from tCSF diversion to pCSF diversion on long-term neurocognitive development deserves further study.

pCSF Diversion

This is the first study specifically evaluating the relationship of the timing of pCSF diversion and modulation of ventricle size prior to pCSF diversion with neurodevelopmental outcome. We observed that maximal ventricular size before and after pCSF diversion was not associated with motor, cognitive, or language scores (Figs. 3B and 4A); however, cumulative ventricular size before pCSF intervention was strongly associated with all neurodevelopmental outcomes evaluated at 2 years of age (Fig. 3C). Similarly, a shorter time to pCSF diversion was associated with improved neurodevelopmental outcomes. Our findings implicate duration and severity of ventricle enlargement as factors in neurodevelopmental outcome. While this is an area that deserves further study, potential explanations include enhanced removal of blood products from the CSF^{17,39} and facilitation of ependymal (and subventricular zone) development. This may prevent long-term ventricular expansion and mitigate downstream consequences on white matter damage related to pressure and interference of perfusion, distortion of periventricular white matter, ischemia, free radical formation, and inflammation.³⁸

Prior studies have shown that persistent ventricular di-

lation in IVH is associated with poor neurodevelopmental outcomes.^{35,37,45} In our analysis, smaller cumulative ventricle size prior to either permanent or temporary intervention was significantly correlated with smaller ventricular size 1 year after pCSF diversion (Fig. 5A and B). Larger cumulative ventricular sizes may indicate more blood and blood product-related CSF ependymal injury prior to progenitor cell proliferation, migration, and differentiation.³⁸ This may, in turn, affect long-term ventricle size through altered brain development; however, further study of the mechanisms of this relationship is needed.

Impact of pCSF Diversion on Hippocampal Size

As the hippocampus is subjacent to the ventricle, we evaluated hippocampal injury in our preclinical neonatal IVH model and showed an iron-mediated injury pattern in the hippocampus after IVH.⁴⁰ Following that, in preterm infants with brain injury, we found that infants with IVH-PHH have the smallest hippocampi, compared to infants with IVH alone and cystic PVL, and that larger ventricles were associated with significantly smaller hippocampi.² Given this finding, we then asked the question of whether modulation of ventricle size over time could impact hippocampal development. Here we show that, similar to neurodevelopmental outcomes, a smaller cumulative ventricle size and shorter time to pCSF diversion were associated with significantly larger right hippocampal volumes at term-equivalent age. Though there was no significant association between left hippocampal volumes and smaller cumulative ventricular size, possibly because of the small sample size, this finding supports the idea that ventricle size is a potentially modifiable factor and not simply a result of the primary injury. With a shorter time to pCSF diversion, prolonged ventriculomegaly, which may be associated with injury to periventricular brain structures such as the hippocampus, can be minimized.⁴⁰ The interplay between ongoing removal of blood products from the ventricle and ventricle size deserves further study in relation to long-term hippocampal development.

Limitations

Given the nonstandardization of ventricular tapping regimens among physicians and the inclusion of both reservoir and ventriculosubgaleal shunts, we used FOHR measurements and the time from birth until tCSF or pCSF diversion as estimates of cumulative ventricle size. The AUC calculation was based on each specific cUS FOHR measurement, and infants who had more frequent cUSs had more time points to assess changes in their ventricle size. There may also be important differences in the relative contributions of time to definitive CSF diversion versus the degree of ventricular enlargement prior to CSF diversion. Another potential confounder that can contribute to ventricle size is an increased burden of IVH. Given the size of the cohort, we grouped all high-grade IVH patients together ($n = 3$ grade III and $n = 22$ grade IV). The long-term parenchymal damage seen in patients with grade IV IVH may contribute to ventricular size, which will be evaluated in a future study. However, in the majority of the time points addressed in this study, parenchymal damage and *ex vacuo* changes are unlikely to be significant

contributors to ventricle size because of the still evolving hemorrhagic infarction. We did not find any significant associations with key covariates on our stepwise analysis, and it is unlikely that there are significant measurable factors that account for the changes we saw in outcome. However, future randomized cohorts with larger numbers will be needed to confirm this. We are unable to draw conclusions about recommendations for or against the use of ETV in this patient population. However, ETV is not routinely performed for the treatment of PHH given its poor efficacy in recent reports.⁴¹ Finally, as has been shown previously,^{7,12,13,34} an earlier time to pCSF diversion may be associated with additional surgical complications, and this may be an important factor to consider when interpreting our results.

Conclusions

A younger chronological age at pCSF diversion, but not tCSF diversion, in preterm infants with IVH-PHH is associated with improved hippocampal development as well as improved motor, cognitive, and language outcomes. Furthermore, a smaller cumulative ventricular size prior to definitive pCSF diversion is associated with improved neurodevelopmental outcomes and a larger right hippocampal size. Randomized studies addressing the timing of definitive CSF diversion and modulation of ventricle size are needed to confirm these findings.

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Author Contributions

Conception and design: Strahle, Triplett, Paturu. Acquisition of data: Paturu, Triplett. Analysis and interpretation of data: Paturu, Triplett. Drafting the article: Strahle, Paturu. Critically revising the article: all authors. Reviewed submitted version of manuscript: Strahle, Paturu, Triplett, Alexopoulos, Smyser, Limbrick. Approved the final version of the manuscript on behalf of all authors: Strahle. Statistical analysis: Paturu, Triplett, Thukral. Administrative/technical/material support: Strahle, Paturu, Alexopoulos, Smyser. Study supervision: Strahle.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Figure 1. <https://thejns.org/doi/suppl/10.3171/2021.4.PEDS212>.

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