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Corpus callosum injury after neurosurgical intervention for posthemorrhagic ventricular dilatation and association with neurodevelopmental outcome at 2 years

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OBJECTIVE Direct injury to the corpus callosum (CC) due to neurosurgical interventions in infants with posthemorrhagic ventricular dilatation (PHVD) has not been reported in the literature. The authors observed a subset of infants who had suffered penetrating CC injury after neurosurgical interventions for PHVD and hypothesized that this pattern of injury may result in suboptimal CC maturation and neurodevelopmental impairment.

METHODS In this multicenter, retrospective, observational study, 100 preterm and 17 full-term infants with PHVD were included and compared with 23 preterm controls. Both neonatal and postneonatal brain MRI scans were assessed for injury, and measurements were performed on postneonatal MRI scans at 2 years' corrected age. Neurodevelopmental outcome was assessed at 2 years' corrected age.

RESULTS A total of 269 brain MRI scans of 140 infants were included. Of infants with PHVD, 48 (41%) had penetrating CC injury following neurosurgical interventions. The median (IQR) CC midsagittal surface area was smaller in infants with CC injury when compared with infants with PHVD who had intact CC and controls (190 mm^2 [149–262 mm^2] vs 268 mm^2 [206–318 mm^2] vs 289 mm^2 [246–320 mm^2], respectively; $p < 0.001$). In the univariate analysis, the area of the CC was associated with cognitive Z score (coefficient 0.009 [95% CI 0.005–0.012], $p < 0.001$) and motor Z score (coefficient 0.009 [95% CI 0.006–0.012], $p < 0.001$). In the multivariable model, CC injury was not independently associated with cognitive and motor Z score after adjusting for gestational age and presence of periventricular hemorrhagic infarction (coefficient 0.04 [95% CI −0.36 to 0.46] and −0.37 [95% CI −0.83 to 0.09], $p = 0.7$ and 0.1, respectively).

CONCLUSIONS CC injury was not uncommon following neurosurgical interventions for PHVD in both preterm and full-term infants. At the age of 2 years, the CC midsagittal surface area was smaller in infants with injury, but CC injury was not independently associated with cognitive and motor outcomes at 2 years' corrected age.

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KEYWORDS corpus callosum; hydrocephalus; newborn; preterm; posthemorrhagic ventricular dilatation

ABBREVIATIONS BSID-II = *Bayley Scales of Infant Development, Second Edition*; BSITD-III = *Bayley Scales of Infant and Toddler Development, Third Edition*; CC = corpus callosum; CP = cerebral palsy; GMDS = Griffiths Mental Development Scales; NDI = neurodevelopmental impairment; PHVD = posthemorrhagic ventricular dilatation; PVHI = periventricular hemorrhagic infarction; TEA = term-equivalent age; UMCU = University Medical Center Utrecht; VPS = ventriculoperitoneal shunt; VR = ventricular reservoir.

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Germinal matrix hemorrhage–intraventricular hemorrhage remains a common complication in preterm infants and is associated with increased risk of adverse neurodevelopmental outcomes—particularly when high-grade general matrix hemorrhage–intraventricular hemorrhage is complicated by posthemorrhagic ventricular dilatation (PHVD).[1,2] Although the question of when best to treat PHVD remains unanswered, recent studies and a meta-analysis showed that later timing of neurosurgical interventions predicted higher rates of ventriculoperitoneal shunt (VPS) placement and moderate to severe neurodevelopmental impairment (NDI), emphasizing the importance of timely intervention.[3–6] After documentation of enlargement of the ventricles beyond defined thresholds with the use of cranial ultrasonography, interventions for PHVD generally start with lumbar punctures to decompress the ventricles.[2] This relatively less invasive intervention is followed by more invasive temporizing neurosurgical measures if stabilization or regression of ventricular size does not occur.[4] For this purpose, placement of a ventricular reservoir (VR) as a ventricular access device with the aim to serially aspirate CSF is a commonly used technique.[2] Beyond the VR, VPS placement is considered in infants who require ongoing VR aspirations.[2,4]

The corpus callosum (CC) is the principal commissural pathway connecting the cerebral hemispheres and linking cortical and subcortical regions of the brain.[7] Complications of neurosurgical interventions for PHVD such as mechanical obstruction, hemorrhage, and infection are well documented; however, direct injury to the CC due to the insertion of a VR and VPS has not been reported in the neonatal population.[8] We observed a subset of infants who had penetrating CC injury after neurosurgical interventions for PHVD and hypothesized that this pattern of injury may result in suboptimal CC maturation and NDI. In this study, we assessed the neuroimaging features of penetrating CC injury, while also studying its relation to neurodevelopmental outcomes at 2 years' corrected age.

Methods

Study Participants

In this multicenter, retrospective, observational study, preterm and full-term neonates with PHVD who were admitted to the level III neonatal intensive care unit of the Wilhelmina Children's Hospital, University Medical Center Utrecht (UMCU), between January 2005 and December 2018 were eligible when they developed PHVD and required neurosurgical intervention. PHVD was diagnosed when infants had progressive measurements of the ventricular index > 97th percentile and anterior horn width > 6 mm on at least 2 cranial ultrasound scans using reference charts described by Levene[9] and Davies et al.,[10] respectively. Interventions for PHVD were initiated with lumbar punctures and followed by VR and VPS insertion when required. Treatment thresholds for neurosurgical interventions are described in detail in a previous article.[5] Neurosurgical interventions were performed using anatomical landmarks by experienced pediatric neurosurgeons without ultrasonography guidance. Catheters were inserted from the outermost lateral corner of the anterior fontanelle. The direction of the catheter was toward the midline, and the catheter tip was aimed to remain slightly above the level of the foramen of Monro. A database search of brain MRI of enrolled infants was conducted. Because brain MRI is not routinely performed at 2 years of age at UMCU in infants without brain injury and/or NDI, the control group was selected from a different cohort. The control group comprised preterm infants < 32 weeks' gestation without PHVD who were prospectively recruited at the level III neonatal intensive care unit of the Hospital for Sick Children, University of Toronto. These infants were recruited between January 2008 and December 2011 and were routinely scanned at 2 years' corrected age. Neonates with evidence of a chromosomal anomaly, congenital malformation of the CNS, hydrocephalus due to anatomical issues, and congenital infection were excluded. Demographic data were obtained from the patients' files and/or electronic hospital databases. Data on antenatal and perinatal factors including gestational age, birth weight, sex, hemorrhage severity, and comorbidities including the use of postnatal steroids, prolonged mechanical ventilation for > 7 days, sepsis, necrotizing enterocolitis, patent ductus arteriosus, and retinopathy of prematurity were collected. The study was approved by the research ethics boards at both centers, and a waiver of consent was provided for the study because of the use of anonymous data analysis.

Neuroimaging Protocol

Participating centers followed a predefined MRI protocol according to their institutional guidelines. At UMCU, until 2010, brain MRI was performed on a 1.5T system (Intera; Philips Healthcare) with an age-appropriate head coil, and the protocol included sagittal T1-weighted and axial T2-weighted images for both neonatal and 2-year scans. Between 2010 and 2018, a 3T system (Achieva; Philips Healthcare) was used and sagittal T1-weighted and axial T2-weighted images were obtained. The University of Toronto followed a similar brain MRI protocol according to the institutional guidelines using a 1.5T system (SIGNA; GE Healthcare) with an age-appropriate head coil for the neonatal and 2-year scans. In both centers, infants were sedated as per institutional protocols and received hearing protection for the procedure.

Assessment of the CC

MRI scans were acquired from infants in the study at two time points. Neonatal MRI scans were obtained in all infants who required a neurosurgical intervention at approximately 30 weeks' postmenstrual age and/or term-equivalent age (TEA). Both neonatal and postneonatal MR scans were used for the detection of injury to the CC. All assessments were performed by an investigator (M.N.C.) with formal training in neonatal neurology, who was blinded to the infants' clinical history and neuroimaging report. In equivocal cases, a senior investigator (L.S.D.V.) was consulted.

Postneonatal MRI scans were obtained routinely at 2 years of age in infants who required a VPS, and in infants with VR who developed NDI. Measurements were performed on postneonatal MRI scans obtained at 2 years

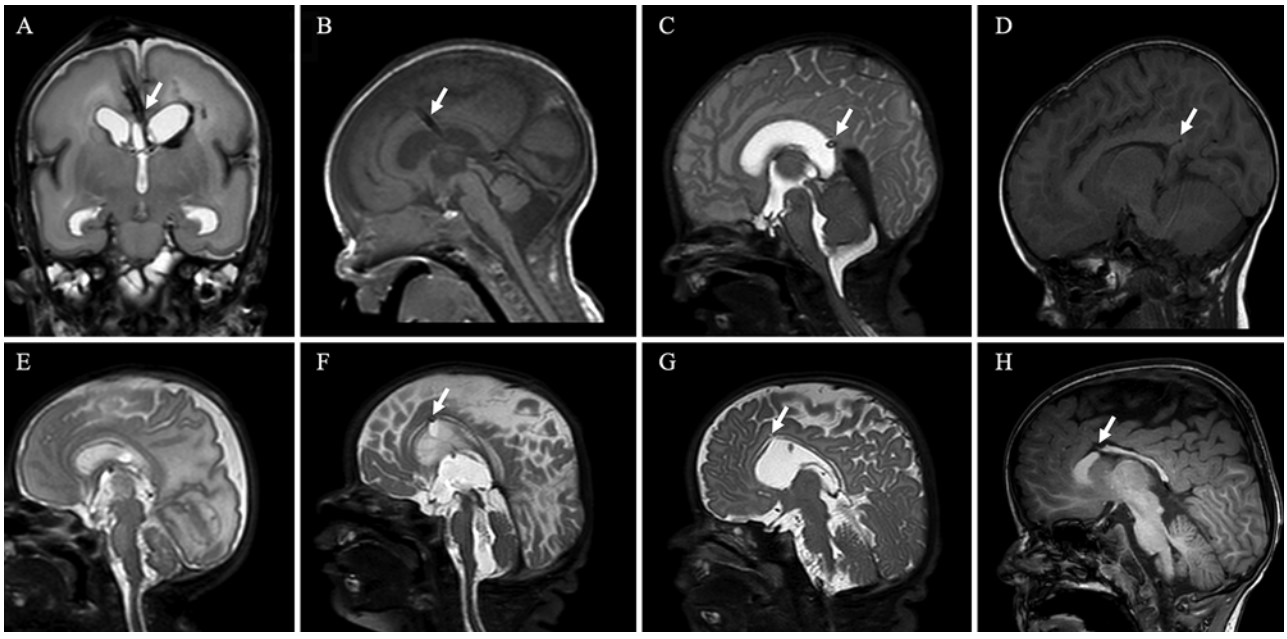

FIG. 1. MRI findings in 3 cases, with *arrows* pointing to the lesions in each image. **A and B:** A $30^{0/7}$ preterm infant with PHVD following VR insertion. Coronal T2-weighted MRI scan demonstrates CC injury (*arrow*) following VR insertion (A); and parasagittal T1-weighted image shows piercing injury to the CC (B). **C and D:** A $29^{3/7}$ preterm infant with PHVD following VPS insertion. Midsagittal T2-weighted image shows injury to the splenium of the CC (*arrow*, C); and midsagittal T1-weighted image shows the effect of injury to the splenium of the CC (*arrow*) at 2 years of age (D). **E–H:** A $26^{2/7}$ preterm infant with PHVD following 2 VR insertions. Parasagittal T2-weighted image shows the intact CC after the first VR insertion (E); midsagittal T2-weighted image demonstrates the piercing injury to the CC following the second VR insertion (*arrow*, F); parasagittal T2-weighted MRI scan shows apparent CC injury (*arrow*) at TEA (G); and midsagittal T1-weighted MRI scan demonstrates piercing injury with a significant gap in the body of the CC (*arrow*) at 2 years of age (H).

of age. The CC was manually traced on the midsagittal slice created from the 3D T1-weighted image at 2 years of age by using Osirix Lite for Macintosh software version 10.0.2 (Pixmeo). Linear measurements of the genu and splenium length were performed at their widest distance in the anteroposterior direction as described by Vannucci et al.[11] Midportion thickness was assessed by measuring the height of the CC body at its widest distance vertical to the CC axis. Total cross-sectional CC surface area was measured in the midsagittal plane. The CC was traced 3 times per MRI scan, and the mean values were used for each analysis. In infants with a penetrating injury to the CC, cross-sectional areas were measured separately and their sum was calculated. Patterns of injury are presented in Fig. 1. Intrarater reliability was tested in the first 15 scans to assess the consistency of measurements.

Neurodevelopmental Assessment

Neurodevelopmental outcomes were assessed at each center as part of the standard neurodevelopmental follow-up programs. Assessments were performed by developmental specialists, and cognitive and motor outcomes were assessed with either the *Bayley Scales of Infant Development, Second Edition* (BSID-II); the *Bayley Scales of Infant and Toddler Development, Third Edition* (BSITD-III); or Griffiths Mental Development Scales (GMDS). BSID-II and BSITD-III tests were routinely used to assess outcomes of infants who were born at < 28 weeks' gestation, and those born at > 28 weeks' gestation were tested with GMDS at UMCU, whereas at the University of Toronto, BSITD-III testing was the standard approach regardless of the gestational age. Cognitive and motor index or composite scores were corrected for prematurity. The conversion from the BSID-II mental developmental index to the BSITD-III composite cognitive score was calculated by the formula (59% of the BSID-II mental developmental index score plus 52) suggested by Lowe et al.[12] To include children who had an index score < 50 on the BSID-II or a cognitive or motor composite score < 55 or < 46, respectively, on the BSITD-III, developmental quotients were calculated (developmental age equivalent [in months, based on raw test scores] divided by the corrected test age and multiplied by 100).[13] The composite cognitive and motor scores at 24 months' corrected age were categorized as the normal range (mean ± 1 SD), subclinical range (< –1 SD), and clinical range (< –2 SD). Standardized Z scores were calculated for cognitive and motor scores for each infant to compare different test types. Cerebral palsy (CP), and type of CP if applicable, was defined based on the definition by Rosenbaum et al.[14] CP was classified as spastic, ataxic, or dyskinetic, and it was topographically categorized as unilateral or bilateral.[15] The gross motor function classification system was used to grade the severity of CP.[16]

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp.). Categorical variables were presented as numbers and percentages. The chi-

TABLE 1. Demographic and clinical characteristics of the study population

	PHVD w/ CC Injury, n = 48	PHVD w/ Intact CC, n = 69	Control Group, n = 23	p Value
Gestational age, wks	29.9 (26.6–33.9)	31.0 (27.7–35.1)	29.1 (27.3–30.3)	0.08
Gestational age category				0.1
Born <37$^{0/7}$ wks	41 (85)	59 (85)	23 (100)	
Born ≥37$^{1/7}$ wks	7 (15)	10 (15)	0 (0)	
Birth weight, g	1508 (968–2304)	1635 (1105–2725)	1100 (955–1390)	**0.005**
Sex				0.4
Male	32 (67)	38 (55)	15 (65)	
Female	16 (33)	31 (45)	8 (35)	
Accompanying PVHI	20 (41)	19 (28)	1 (4)	**0.003**
Reservoir placement	48 (100)	69 (100)	0 (0)	**<0.001**
VPS placement	30 (63)	30 (44)	0 (0)	**<0.001**
Mechanical ventilation >7 days	13 (27)	15 (22)	9 (39)	0.3
Culture-positive late-onset sepsis	5 (10)	6 (9)	6 (26)	0.08
Surgical treatment for NEC	0 (0)	3 (4)	0 (0)	0.2
Surgical treatment for PDA	3 (6)	2 (3)	0 (0)	0.4
Surgical treatment for ROP	0 (0)	2 (3)	0 (0)	0.3
Death	0 (0)	5 (7)	0 (0)	0.07

NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; ROP = retinopathy of prematurity.
Data are presented as the median (IQR) or number (%). Boldface type indicates statistical significance.

square and Fisher exact tests were used to compare categorical variables among groups. Continuous variables were presented as the mean (± SD) and the median (IQR) depending on their distribution. The Mann-Whitney U-test was used to compare nonparametric variables and the Student t-test for comparison between variables with gaussian distribution. The Kruskal-Wallis test and 1-way ANOVA test were used to determine the difference in subgroup analysis. A post hoc analysis was performed to determine the statistical differences in multigroup comparisons. Univariate linear regression was used to determine risk factors for an adverse neurodevelopmental outcome, and multiple linear regression and logistic regression were applied for the significant variables detected with the univariate analysis. Adjustment for gestational age, sex, and presence of periventricular hemorrhagic infarction (PVHI) was performed in the multivariable regression models. Statistical significance was set at $p < 0.05$.

Results

Study Participants

A total of 140 infants were included in the final analysis, of whom 117 had PHVD and 23 were controls. The median (IQR) gestational age and birth weight were similar between infants with CC injury and intact CC groups ($p = 0.3$ for both), whereas infants in the control group had a lower birth weight when compared to infants with PHVD ($p = 0.005$). Characteristics of included infants and distribution of the clinical factors and comorbidities are presented in Table 1.

Characteristics of CC Injury

A total of 269 brain MRI scans were assessed, of which 84 were obtained at 30 weeks' gestation, 112 at TEA, and 73 at 2 years of age. Of infants with PHVD, 48 (41%) had penetrating CC injury. Forty-six (94%) of the injuries were due to VR placement, and 3 (6%) occurred due to VPS insertion. All injuries due to VR insertion were observed in the body of the CC, whereas all injuries due to VPS placement were in the splenium. In infants with PHVD, all individuals had a VR insertion, and 60 (51%) of those with a VR required a VPS for permanent CSF diversion. The median (IQR) number of interventions including VR and/or VPS insertion was greater in infants with CC injury compared to the intact CC group (2 [1–2] interventions vs 1 [1–2] intervention, $p = 0.005$). Eleven (23%) with CC injury and 9 (13%) with intact CC had revision surgery for VPS or > 2 surgical interventions ($p = 0.1$). In 9 (19%) infants with CC injury and in 11 (16%) with intact CC, the VR tip was lying in the basal ganglia and thalamic region ($p = 0.6$). None of the infants showed ischemic findings of cystic white matter injury on cranial ultrasound or brain MRI scans.

Measurements of CC

The MRI scans were performed at a median age of 23.5 months in infants with CC injury and controls, and at 23.3 months in the intact CC group ($p = 0.9$). The intrarater reliability values for the linear measurements of the genu, midportion, splenium, and midsagittal CC surface area were 0.92, 0.86, 0.93, and 0.89, respectively. Genu length was similar across the groups ($p = 0.2$), whereas midportion thickness and splenium length were smaller in infants with PHVD when compared with controls ($p < 0.001$ for both). In the post hoc analysis, the median (IQR) midsagittal CC surface area was smaller in infants with CC injury when compared with infants with PHVD who had intact CC and controls (190 mm^2 [149–262 mm^2] vs 268 mm^2

TABLE 2. Characteristics of the CC injury

	PHVD w/ CC Injury, n = 48	PHVD w/ Intact CC, n = 69	Control Group, n = 23	p Value
Total no. of MRI scans	112	134	23	
No. of neonatal MRI scans	82	114	0	
No. of post-neonatal MRI scans	30	20	23	
Age at 2-yr MRI, mos	23.5 (20.9–27.0)	23.3 (20.9–27.3)	24.0 (24.0–24.2)	0.9
Genu length, mm	6.2 (5.4–7.4)	6.4 (5.3–8.2)	5.8 (5.0–6.4)	0.2
Midportion thickness, mm	1.4 (1.1–2.1)	3.0 (1.5–4.2)	4.2 (3.5–4.5)	**<0.001**
CC injury vs intact CC				**0.004**
CC injury vs controls				**<0.001**
Intact CC vs controls				**0.02**
Splenium length, mm	4.4 (2.6–4.8)	5.0 (3.9–5.8)	8.0 (7.1–8.5)	**<0.001**
CC injury vs intact CC				0.6
CC injury vs controls				**<0.001**
Intact CC vs controls				**<0.001**
Midsagittal CC area, mm^2	190 (149–262)	268 (206–318)	289 (246–320)	**<0.001**
CC injury vs intact CC				**0.04**
CC injury vs controls				**0.001**
Intact CC vs controls				0.9

All measurements are performed at 2-year MRI scans. Data are presented as median (IQR) or number (%). Boldface type indicates statistical significance.

[206–318 mm^2] vs 289 mm^2 [246–320 mm^2], respectively; $p < 0.001$). The results of the post hoc analysis are presented in Table 2.

Neurodevelopmental Outcomes

Five (4%) infants died in the neonatal period of causes unrelated to the neurosurgical intervention. Two (2%) were lost to follow-up, and 11 (9%) had incomplete follow-up data and were removed from the outcome analysis. Of the 122 (87%) infants who were included in the final neurodevelopmental outcome analysis, 60 (49%) were assessed with the GMDS, 17 (14%) with BSID-II, and 45 (37%) with BSITD-III. Details of the neurodevelopmental outcomes in the post hoc analyses are presented in Table 3. The mean ± SD cognitive Z score was −0.33 ± 0.9 in infants with PHVD and 0.90 ± 0.8 in the control group; the motor Z scores were −0.54 ± 1.2 and −0.26 ± 0.8, respectively. Cognitive Z scores were lower in infants with PHVD when compared with controls (mean difference −1.24 [95% CI −1.7 to −0.76], $p < 0.001$). In the univariate analysis, the midsagittal surface area of the CC was associated with cognitive Z score (coefficient 0.009 [95% CI 0.005–0.012], $p < 0.001$) and motor Z score (coefficient 0.009 [95% CI 0.006–0.012], $p < 0.001$). In the multivariable model, CC injury was not independently associated with cognitive and motor Z scores after adjusting for gestational age and presence of PVHI (coefficient 0.04 [95% CI −0.36 to 0.46] and −0.37 [95% CI −0.83 to 0.09], p = 0.7 and 0.1, respectively). PVHI was an independent risk factor associated with lower cognitive and motor Z scores after adjusting for gestational age (coefficient −0.53 [95% CI −0.96 to −0.09] and −0.84 [95% CI −1.34 to −0.35], p = 0.02 and 0.001, respectively). In infants with PHVD, 12 (29%) infants with CC injury and 6 (11%) with intact CC developed CP ($p = 0.02$). In the multivariable model, the presence of PVHI was the only independent risk factor for CP after adjusting for gestational age, CC injury, and sex (OR 7.7 [95% CI 2.2–27.3], $p < 0.002$).

Discussion

In this multicenter observational study, we assessed the effect of neurosurgical interventions in infants with PHVD, with a specific focus on macroscopic integrity and development of the CC. Our findings show that CC injury can occur due to neurosurgical interventions for PHVD in both preterm and full-term infants. The majority of these injuries were due to VR insertion; however, we also observed that a small proportion (6%) of the cases had injury to the posterior part of the CC following VPS insertion. In keeping with our hypothesis, the midsagittal surface area of the CC was smaller in infants with CC injury compared to that of infants whose CC remained intact after neurosurgical interventions and that of controls, reflecting underdevelopment of these essential commissural nerve fibers following the insult. Of note, infants with PHVD had smaller linear measurements and CC surface area when compared with controls regardless of injury to the CC. Although the CC surface area was positively associated with cognitive and motor outcomes at 2 years of age and CP was more common in infants with CC injury in the univariate analysis, these associations did not persist after adjusting for gestational age, sex, and the presence of PVHI. As expected, PVHI was found to be an independent risk factor that was negatively associated with both cognitive and motor outcomes; however, contrary to our hypothesis, CC injury was not independently associated with cognitive and motor outcomes at 2 years' corrected

TABLE 3. Subgroup analysis of the neurodevelopmental outcomes of the study infants

	PHVD w/ CC Injury, n = 42	PHVD w/ Intact CC, n = 57	Control Group, n = 23	p Value
Corrected age at FU, mos	24.2 (23.5–25.4)	24.1 (23.5–26.3)	27.2 (26.8–28.4)	**<0.001**
CC injury vs intact CC				>0.99
CC injury vs controls				**<0.001**
Intact CC vs controls				**<0.001**
Cognitive Z score	−0.36 ± 1.09	−0.33 ± 0.94	0.90 ± 0.88	**<0.001**
CC injury vs intact CC				0.9
CC injury vs controls				**<0.001**
Intact CC vs controls				**<0.001**
Motor Z score	−0.84 ± 1.3	−0.33 ± 1.1	−0.26 ± 0.9	0.09
CC injury vs intact CC				0.1
CC injury vs controls				0.2
Intact CC vs controls				0.9
Cognitive score category*				0.06
Normal range	30 (75)	41 (73)	21 (100)	
Subclinical range	4 (10)	10 (18)	0 (0)	
Clinical range	6 (15)	5 (9)	0 (0)	
Motor score category†				0.06
Normal range	24 (63)	36 (68)	16 (80)	
Subclinical range	4 (11)	11 (21)	4 (20)	
Clinical range	10 (26)	6 (11)	0 (0)	
CP	12 (29)	6 (11)	0 (0)	**0.004**
Type of CP				0.08
Unilat spastic CP	9 (75)	4 (66)	0 (0)	
Bilat spastic CP	3 (25)	1 (17)	0 (0)	
Ataxic	0 (0)	1 (17)	0 (0)	

FU = follow-up.
Data are presented as the median (IQR), mean ± SD, or number (%). Boldface type indicates statistical significance.
* Cognitive scores were available in 117/122 infants.
† Motor scores were available in 111/122 infants.

age. Although complications of neurosurgical interventions have been reported in the literature, to the best of our knowledge this is the first neonatal study to describe penetrating CC injury as a distinct entity following neurosurgical interventions for PHVD and to assess the association between metrics of CC development and neurodevelopmental outcomes.

Surgery for shunt placement is among the most common neurosurgical interventions in neonates, and most interventions are performed freehand using anatomical landmarks.[17] In the present study the interventions were performed without ultrasound guidance by pediatric neurosurgeons with many years of experience in performing this procedure. This intervention approach, which is performed without seeing the tip of the catheter during insertion, has been reported to have inaccuracy rates ranging between 15% and 40% in the pediatric literature, and may also explain the high rate of CC injury we observed in our cohort.[17] Of note, a proportion of infants in both groups (overall 17%) had their VR catheter tip positioned in the basal ganglia and thalamic region. To address this issue, Kellnar et al.[18] described the use of intraoperative cranial ultrasonography in newborns to optimize the position of the shunt catheter, and since the first description, multiple studies have shown the efficacy of neuronavigation, in which ultrasonography is used for real-time visualization of the ventricles.[17,19] A prospective controlled study by the Hydrocephalus Clinical Research Network investigated the use of ultrasound guidance in the pediatric population during neurosurgical interventions for hydrocephalus. Accurate placement was observed in 59% of the infants; however, this rate was well below the study goal of 80% and was only slightly better than the success rate (49%) in the control group.[20] We speculate that using ultrasonography for real-time visualization of the ventricles might be a promising technique to avoid CC injury during neurosurgical interventions for PHVD if supported by future well-designed studies. Our data also show that overall, 17% of infants with PHVD required either a revision surgery or > 2 surgical interventions due to VR/VPS dysfunction. Similar to our findings, in a population-based database, Donoho et al.[21] found that the 30-day readmission rate of pediatric patients undergoing ventricular shunting was 18%.

The blood supply of the CC derives from the branches of both anterior and posterior circulations that anastomose to form a pericallosal pial plexus, and in approximately 80%

of humans, additional blood supply comes from the anterior communicating artery.[22,23] Because of the dominance of the anterior circulation, anterior portions of the CC are more resilient to ischemia.[22,24,25] Several neonatal studies using Doppler examinations have demonstrated impairment of the cerebral circulation in infants with PHVD.[26,27] We observed thinning of the midportion and splenium regions of the CC in infants with PHVD compared to findings in controls. This probably reflects the fact that the circulation of the CC was impaired, leading to thinning in the middle and posterior parts, but not necessarily in the anterior part of the CC due to the aforementioned preserved circulation pattern. It has also been shown that white matter injury in the context of PHVD causes microstructural changes in the CC, which may also explain thinning in the CC found in the present study.[28,29] PVHI, which was the only independent risk factor for adverse cognitive and motor outcomes in the present study, may also have played a role in the underdevelopment of the CC. Additionally, we found that infants with CC injury had smaller CC body thickness than that of infants with intact CC, whereas splenium length was similar across these groups. This may be explained by the effect of penetrating injury leading to impaired circulation in the CC areas that are adjacent to the injury, but relatively preserved posterior circulation of the splenium. It is important to emphasize that we were not able to use volumetric analysis in the present study and applied 2D surface area and linear measurements instead. Although 2D measurements can be conducted with high reliability, further studies using volumetric analysis are warranted to confirm our findings.[30]

We were not able to document a negative effect of penetrating CC injury on cognitive and motor outcomes at 2 years in our study. The positive association between CC injury and cognitive and motor scores as well as CP did not persist after accounting for clinical factors. However, it is important to underline the fact that three different neurodevelopmental tests were used in the present study, given that the study infants were recruited over a 14-year period. Although we used Z scores to be able to compare scores obtained by different test types, ideally outcomes should have been compared using the same test for all infants. Also of note, unlike adults with CC injury and pediatric patients with developmental anomalies of the CC who commonly exhibit cognitive impairments, language delay, visuospatial integration issues, dyslexia, and behavioral issues, newborn infants with penetrating CC injury did not show impairments in the cognitive and motor domains.[7,22,31,32] We speculate that this may be reflective of the higher neuroplastic capacity of the developing human brain. It is also possible that cognitive impairments may first become apparent later in childhood when the cognitive demands increase at school age. It is important to reemphasize the fact that our follow-up data only represent neurodevelopmental outcomes during infancy, and it is not possible to draw firm conclusions about later childhood outcomes. Therefore, the effect of penetrating CC injury on the cognitive domain and higher cognitive functions should be further investigated in children at school age. Also of note, cognitive assessment at 2 years of age may not accurately measure cognitive functioning as compared with school-age testing.

The present study has several limitations. First, we were not able to use volumetric analysis to calculate the CC volume and instead used CC surface area and linear measurements. However, volumetric measurement of the CC is technically challenging, limiting its application in clinical practice—and it has been shown that measurement of the CC area does not require sophisticated image processing and can be conducted with high reliability.[30] Second, we used standard neurodevelopmental tests to assess cognitive and motor outcomes at 2 years' corrected age. However, we did not use neurodevelopmental tools specifically developed to assess cognitive domain and visuospatial integration that are commonly affected in CC injury, because these infants were not old enough to be assessed with these specific tests. Also of note, infants were evaluated with various neurodevelopmental tests, and comparisons could only be made by using standardized Z scores. Third, because this was a multicenter study, scanning protocols were not the same in the two centers, which could have led to varying image qualities. Fourth, the effect of noncystic white matter injury, which is a risk factor for adverse neurodevelopmental outcomes, was not taken into account in the present study. However, we did not observe major ischemic findings of cystic white matter injury in this cohort on cranial ultrasound or brain MRI scans. Finally, although their numbers are small, the inclusion of full-term infants adds heterogeneity to the present study. The major strength of this study is the inclusion of a considerable number of infants with PHVD with a high follow-up rate to document the neuroimaging aspects and neurodevelopmental consequences of this clinical entity.

Conclusions

Although timely neurosurgical interventions are required to prevent NDIs in infants with progressive PHVD, we report for the first time that CC injury can occur in neonates due to neurosurgical interventions for PHVD, and that this can potentially result in underdevelopment of these essential commissural nerve fibers. However, CC injury was not independently associated with cognitive and motor outcomes at 2 years of age in the present study. PVHI was the only independent risk factor for adverse cognitive and motor outcomes. Given that a wide range of NDIs due to CC injury may manifest later in childhood, further studies are warranted to investigate the impact of this pattern of injury on multiple neurodevelopmental outcome domains beyond infancy.

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References

1. Yeo KT, Thomas R, Chow SS, et al. Improving incidence trends of severe intraventricular haemorrhages in preterm infants <32 weeks gestation: a cohort study. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(2):145-150.
2. El-Dib M, Limbrick DD Jr, Inder T, et al. Management

of post-hemorrhagic ventricular dilatation in the infant born preterm. *J Pediatr*. 2020;226:16-27.e3.
3. Cizmeci MN, Groenendaal F, de Vries LS. Timing of intervention for posthemorrhagic ventricular dilatation: an ongoing debate. *J Pediatr*. 2021;234:14-16.
4. Lai GY, Chu-Kwan W, Westcott AB, Kulkarni AV, Drake JM, Lam SK. Timing of temporizing neurosurgical treatment in relation to shunting and neurodevelopmental outcomes in posthemorrhagic ventricular dilatation of prematurity: a meta-analysis. *J Pediatr*. 2021;234:54-64.e20.
5. de Vries LS, Groenendaal F, Liem KD, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2019;104(1):F70-F75.
6. Cizmeci MN, Groenendaal F, Liem KD, et al. Randomized controlled early versus late ventricular intervention study in posthemorrhagic ventricular dilatation: outcome at 2 years. *J Pediatr*. 2020;226:28-35.e3.
7. Andronikou S, Pillay T, Gabuza L, et al. Corpus callosum thickness in children: an MR pattern-recognition approach on the midsagittal image. *Pediatr Radiol*. 2015;45(2):258-272.
8. Badhiwala JH, Hong CJ, Nassiri F, Hong BY, Riva-Cambrin J, Kulkarni AV. Treatment of posthemorrhagic ventricular dilation in preterm infants: a systematic review and meta-analysis of outcomes and complications. *J Neurosurg Pediatr*. 2015;16(5):545-555.
9. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. *Arch Dis Child*. 1981;56(12):900-904.
10. Davies MW, Swaminathan M, Chuang SL, Betheras FR. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. *Arch Dis Child Fetal Neonatal Ed*. 2000;82(3):F218-F223.
11. Vannucci RC, Barron TF, Vannucci SJ. Development of the corpus callosum: an MRI study. *Dev Neurosci*. 2017;39(1-4):97-106.
12. Lowe JR, Erickson SJ, Schrader R, Duncan AF. Comparison of the Bayley II Mental Developmental Index and the Bayley III Cognitive Scale: are we measuring the same thing? *Acta Paediatr*. 2012;101(2):e55-e58.
13. Jary S, Kmita G, Whitelaw A. Differentiating developmental outcome between infants with severe disability in research studies: the role of Bayley Developmental Quotients. *J Pediatr*. 2011;159(2):211-214.e1.
14. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl*. 2007;109:8-14.
15. Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. *JAMA Pediatr*. 2017;171(9):897-907.
16. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther*. 2000;80(10):974-985.
17. Kullmann M, Khachatryan M, Schuhmann MU. Ultrasound-guided placement of ventricular catheters in first-time pediatric VP shunt surgery. *Childs Nerv Syst*. 2018;34(3):465-471.
18. Kellnar S, Ring-Mrozik E, Deindl C. Intraoperative sonographic diagnosis of the ventricular position of shunt systems in infants with hydrocephalus. Article in German. *Z Kinderchir*. 1989;44(3):131-134.
19. Babcock DS, Barr LL, Crone KR. Intraoperative uses of ultrasound in the pediatric neurosurgical patient. *Pediatr Neurosurg*. 1992;18(2):84-91.
20. Whitehead WE, Riva-Cambrin J, Wellons JC III, et al. No significant improvement in the rate of accurate ventricular catheter location using ultrasound-guided CSF shunt insertion: a prospective, controlled study by the Hydrocephalus Clinical Research Network. *J Neurosurg Pediatr*. 2013;12(6):565-574.
21. Donoho DA, Buchanan IA, Rangwala SD, et al. Readmissions after ventricular shunting in pediatric patients with hydrocephalus: a Nationwide Readmissions Database analysis. *J Neurosurg Pediatr*. 2021;28(5):553-562.
22. Blaauw J, Meiners LC. The splenium of the corpus callosum: embryology, anatomy, function and imaging with pathophysiological hypothesis. *Neuroradiology*. 2020;62(5):563-585.
23. Kahilogullari G, Comert A, Ozdemir M, et al. Arterial vascularization patterns of the splenium: an anatomical study. *Clin Anat*. 2013;26(6):675-681.
24. Türe U, Yaşargil MG, Krisht AF. The arteries of the corpus callosum: a microsurgical anatomic study. *Neurosurgery*. 1996;39(6):1075-1085.
25. Chrysikopoulos H, Andreou J, Roussakis A, Pappas J. Infarction of the corpus callosum: computed tomography and magnetic resonance imaging. *Eur J Radiol*. 1997;25(1):2-8.
26. Van Bel F, Van de Bor M, Baan J, Stijnen T, Ruys JH. Blood flow velocity pattern of the anterior cerebral arteries. Before and after drainage of posthemorrhagic hydrocephalus in the newborn. *J Ultrasound Med*. 1988;7(10):553-559.
27. Nishimaki S, Iwasaki Y, Akamatsu H. Cerebral blood flow velocity before and after cerebrospinal fluid drainage in infants with posthemorrhagic hydrocephalus. *J Ultrasound Med*. 2004;23(10):1315-1319.
28. Nieuwets A, Cizmeci MN, Groenendaal F, et al. Post-hemorrhagic ventricular dilatation affects white matter maturation in extremely preterm infants. *Pediatr Res*. Published online August 26, 2021. doi:10.1038/s41390-021-01704-2
29. Lean RE, Han RH, Smyser TA, et al. Altered neonatal white and gray matter microstructure is associated with neurodevelopmental impairments in very preterm infants with high-grade brain injury. *Pediatr Res*. 2019;86(3):365-374.
30. Malavolti AM, Chau V, Brown-Lum M, et al. Association between corpus callosum development on magnetic resonance imaging and diffusion tensor imaging, and neurodevelopmental outcome in neonates born very preterm. *Dev Med Child Neurol*. 2017;59(4):433-440.
31. Gao Y, Yan K, Yang L, Cheng G, Zhou W. Biometry reference range of the corpus callosum in neonates: an observational study. *Medicine (Baltimore)*. 2018;97(24):e11071.
32. Luders E, Thompson PM, Toga AW. The development of the corpus callosum in the healthy human brain. *J Neurosci*. 2010;30(33):10985-10990.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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