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Cerebellar Hemorrhage: A 10-year Evaluation of Risk Factors

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Abstract

Background: While cerebellar hemorrhage (CH) has been linked with adverse neurodevelopmental outcome in preterm infants, it remains under-recognized and the underlying mechanisms are not fully understood.

Objective: To determine risk factors for CH in premature infants.

Methods: A retrospective cohort study included all inborn infants < 30 weeks EGA admitted to the NICU from 2007–2016. Comprehensive perinatal and clinical factors were collected. CH size, sidedness, and symmetry were noted. Factors associated with CH were evaluated using univariate and multivariate logistic regression.

Results: Of the 352 identified infants, 69 (20%) had CH. Those with CH were born at earlier EGA, received less antenatal steroids, more frequently had an admission temperature <36°C, had more severe lung disease, received more inotropes, and had higher rates of IVH.

In the regression model, low admission temperature (OR 3.5), inotrope exposure (OR 2.6), chorioamnionitis (OR 2.3), and increased ventilator days (OR 1.02) were associated with increased risk, while antenatal steroids (OR 0.3) and male sex (OR 0.5) were associated with decreased risk.

Imaging modality at first diagnosis was split between ultrasound and MRI (52 vs. 48%). Median age at diagnosis was 4d; 52% of cases were unilateral, and size was punctate, small, and large in 23, 45, and 32% of cases, respectively.

Conclusions: CH is common in premature infants and can be diagnosed using ultrasound or MRI. Clinically modifiable risk factors have been identified and should serve as the basis for improved clinical strategies in temperature, ventilator, and blood pressure management.

Keywords

cerebellar hemorrhage; premature infants; brain injury; risk factors

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Introduction

The two most common forms of brain injury in preterm infants, intraventricular hemorrhage (IVH) and white matter injury (WMI), have been extensively studied and have well-described risk factors [1]. In contrast, the risk factors and natural history of cerebellar hemorrhage (CH) are less well-known. Imaging through the anterior fontanelle limits the ability to examine the posterior fossa and greatly reduces the recognition of CH [2]. First suggested by Cramer et al. [3], the addition of imaging through the mastoid fontanelle has led to improved rates of diagnosis when compared to the conventional approach [1,4].

However, despite increased recognition of CH, risk factors remain undefined [5]. Although there are a number of small case series in the literature, there have only been four previous studies of relatively large sample size including those by Limperopoulos et al. (2005, n=35) [6], Steggerda et al. (2009, n=16) [7], Tam et al. (2011, n=9) [8], and Gano et al (2016, n=27) [9]. These and other studies have variably associated CH with early gestational age [10], emergent delivery [6], patent ductus arteriosus [6], hypotension [6,11], and low pH in the first 5 days of life [6]. In terms of outcome, CH has been associated with adverse neurodevelopmental outcome [8,11–14], autism spectrum disorder [9], and supratentorial injury, particularly white matter injury [5]. However, these studies are limited by small sample size, relatively mature cohorts, and inconsistent clinical variables.

In this study, we examine the timing and risk factors for cerebellar hemorrhage in a very preterm infant population, encompassing a 10-year study period (2007–2016). Extensive maternal, perinatal, and clinical factors are presented as well as detailed imaging results, permitting an in-depth evaluation of the risk and protective factors for CH with greater detail than previously described.

Patients and Methods

Patient selection

Cases of CH were selected using a searchable electronic medical record database (Clinical Investigation Data Exploration Repository, CIDER) maintained by our institution's Center for Biomedical Informatics. Inclusion criteria for the CH group were preterm birth (< 30 weeks EGA), CH noted on cranial ultrasound or term-equivalent brain MRI, delivery and admission to our NICU between 1 January 2007 and 31 December 2016, and lack of other known congenital anomalies. The control group was comprised of all other infants delivered and admitted to our NICU during the study period who met inclusion criteria (GA ≥ 30 weeks, complete clinical records, and cranial ultrasound and/or term-equivalent MRI) but did not have CH. Infants born at outside hospitals were excluded from study due to incomplete data (e.g. cord blood gas analysis and placental pathology not done), heterogeneous skill levels of resuscitating providers, and the unknown effects of transportation. Infants transferred to other hospitals prior to discharge were also excluded due to incomplete clinical records.

Data collection

Demographic and perinatal factors collected included estimated gestational age at birth (EGA), birth weight, intrauterine growth restriction (IUGR, defined as birth weight < 10th centile using the Fenton growth charts [15]), sex, race, mortality, post-menstrual age at hospital discharge, substance exposure during pregnancy (by maternal report and/or urine/meconium drug screen), pre-eclampsia, chorioamnionitis (diagnosed by histopathology), prolonged rupture of membranes (>18h), multiple gestation, mode of delivery, emergent delivery, administration of antenatal steroids and/or magnesium sulfate, need for CPR at delivery (defined as administration of chest compression and/or epinephrine), Apgar scores at 1 and 5 minutes, and arterial cord blood gas pH and base excess.

Clinical characteristics included admission temperature, pulmonary hemorrhage, pneumothorax, spontaneous intestinal perforation, number of ventilator days, need for high-frequency oscillatory ventilation in the first five days of life, mean blood gas pH and base excess at five days of life, diagnosis of bronchopulmonary dysplasia (BPD, defined as need for supplemental oxygen after 36 weeks corrected gestational age), presence of patent ductus arteriosus (PDA) requiring treatment (medical, surgical, or both), inotropic medication administration, hydrocortisone, dexamethasone, sepsis, necrotizing enterocolitis (defined as Bell stage IIA or worse), presence of clinically apparent seizures, retinopathy of prematurity requiring surgical treatment (ROP), and presence of IVH.

Although initial case selection was automated, manual review of all selected charts was performed by two authors (ZAV and MH) to ensure accuracy and completeness of abstracted data.

Imaging approach

The cranial ultrasound imaging was performed using a standardized institutional protocol, utilizing acoustic windows through the anterior fontanelle and the mastoid window. Ultrasound images were acquired using a GE Logiq S6 or S8 with a curvilinear 5 MHz transducer. All infants underwent a standardized exam including coronal, sagittal and mastoid views performed by licensed pediatric ultrasonographers.

Similarly, MR imaging was performed using a standardized institutional protocol, undertaken at term-equivalent age (38–42 weeks PMA). All studies were performed within sedation or contrast; infants were fed and bundled in a papoose before travelling to the MRI scanner [16]. Magnetic resonance images were acquired by using a 3-T TIM Trio system (Siemens, Erlangen, Germany). MRI scanning included anatomic images obtained with an axial magnetization-prepared rapid gradient echo T1-weighted sequence (TR/TE 1500/3 ms; voxel size: $1 \times 0.7 \times 1 \text{ mm}^3$), a turbo spin echo T2-weighted sequence (TR/TE 8600/160 ms; voxel size: $1 \times 1 \times 1 \text{ mm}^3$; echo train length: 17), and a susceptibility-weighted sequence (TR/TE 27/20 ms; flip angle 15° , section thickness 2.0 mm, in-plane resolution of $0.9 \times 0.9 \text{ mm}$).

Standard institutional guidelines call for ultrasound exams to be performed at least three times—3, 7–10, and 30 days of life for all infants born before 30 weeks gestation and/or weighing less than 1500 grams. Additional exams were performed at the discretion of the

primary medical team based on the clinical course. There are not similar institutional guidelines for term-equivalent MRI and it was performed at the discretion of the primary medical team. Imaging was generally performed in infants at risk for brain injury (born before 30 weeks gestation, history of injury noted on ultrasound, clinical risk factors [e.g. severe lung disease, necrotizing enterocolitis]). All imaging was interpreted by a clinical pediatric neuroradiologist at the time of scan and reviewed by two authors (ZAV and AMM) to confirm findings.

Collected imaging data included the postnatal age at CH diagnosis (ultrasound imaging only), percentage of cases with initial diagnosis by ultrasound vs. MRI, unilateral or bilateral injury, sidedness (if unilateral), injury of the vermis, and size—punctate, small (<50% of cerebellar hemisphere), large (>50% of cerebellar hemisphere).

Statistical approach

Demographic, perinatal, and clinical characteristics were compared between the CH and control groups using the Mann-Whitney U-test for continuous variables or Fisher's Exact Test (two-sided) for categorical variables. Selected variables were compared between infants with each of the three CH sizes (large, small, punctate). Post-hoc pairwise comparison for continuous variables was made using Dunn's test (adjusted with the Holm method) and pairwise Chi-square test for categorical variables (adjusted with Benjamini-Hochberg procedure).

A multivariate logistic regression model was constructed to identify factors most predictive of CH using backward stepwise selection by exact AIC (Akaike information criterion) with EGA and year of birth (to account for changes in clinical practice) forced into the model, based on the findings of prior studies and clinical experience. Although many clinical variables were collected in order to fully describe the clinical courses of the two cohorts, only variables which are clinically relevant during the time period in which CH occurs (first 10 days of life) were considered for the regression model.

Collinearity between predictors was assessed using the variance inflation factor (VIF), where variance inflation factor > 5 is indicative of highly correlated predictors. Results were considered significant where $p < 0.05$. Statistical analysis was conducted using R version 3.3.4 (R Foundation for Statistical Computing, Vienna, Austria).

Study procedures were reviewed and approved by our institution's Human Subjects Research Protection Office.

Results

Perinatal and clinical characteristics

A total of 360 infants meeting inclusion criteria during the study period were identified. Eight infants were excluded due to transfer of care to another facility prior to hospital discharge. Of the remaining 352 infants, 69 (20%) were noted to have CH.

When compared to the control group infants with CH were of lower mean gestational age (25.1 vs. 26.5 weeks, $p<0.01$) and birth weight (807 vs. 940 grams, $p<0.01$), had higher rates of acute chorioamnionitis (41% vs. 25%, $p<0.01$), were less likely to have received a complete course of antenatal steroids ($p<0.01$) or magnesium sulfate ($p<0.01$), were more likely to have been born in an emergent setting (55% vs. 39%, $p=0.02$), had lower median Apgar scores, and had worse metabolic acidosis (mean base excess -4.06 vs. -2.58 mEq/L, $p=0.04$) on arterial cord gas.

Infants with CH were more likely to have an admission temperature $<36^{\circ}\text{C}$ (30% vs. 10%, $p<0.01$), spontaneous intestinal perforation (17% vs. 7%, $p=0.02$), a greater median number of ventilator days (34 vs. 3, $p<0.01$), a higher rate of BPD (56% vs. 46%, $p<0.01$), a PDA which required treatment, to receive inotropic medications during hospitalization (64% vs. 32%, $p<0.01$), to receive hydrocortisone (stress- and lung-dosing), ROP (57% vs. 42%, $p<0.01$), and IVH of any grade (61% vs. 36%, $p<0.01$) or have a high-grade IVH (33% vs. 17%, $p<0.01$). A complete listing of patient characteristics is presented in Tables 1 and 2.

Comparison between hemorrhage sizes

Compared to those with punctate hemorrhage, infants with large and small hemorrhage were less mature (26.7 vs. 24.7 and 24.6 weeks, $p<0.01$), had lower birthweight (1067 vs. 741 and 730 grams, $p=0.03$), were more often male (13% vs. 65% and 48%, $p<0.01$) and had greater median ventilator days (5 vs. 37.5 and 46, $p=0.01$). Characteristics of infants with large and small hemorrhage were similar with the exception of increased rates of high-grade IVH for those with large hemorrhage (57% vs. 19%, $p=0.01$). The comparison between groups is shown in Table 3.

Imaging data

In this cohort, infants underwent a median of 4 ultrasound exams (interquartile range 3–6) during NICU hospitalization. The majority of infants (231/352, 66%) also underwent term-equivalent MRI, obtained at a mean corrected age of 38.9 ± 2.2 weeks, with no significant difference in scan PMA between the CH and control group ($p=0.99$). The primary medical reasons for not obtaining an MRI was death prior to term-equivalent age (45/352, 13%), or clinical instability precluding exam (3/352, 1%), thus 76% (231/304) of infants able to have term-equivalent MRI did so. The primary non-medical reason for not obtaining an MRI was lack of provider interest (73/352, 21%), particularly in an era where the utility of the term-equivalent MRI has been called into question [17].

Of the 69 infants diagnosed with CH, 35 (51%) were made by initially made by ultrasound, with a median postnatal age at diagnosis of 4 days (range 0–21 days). The remainder of the CH diagnoses were made (or confirmed) on term-equivalent MRI (Table 4a); these infants were excluded from the calculation of age at diagnosis, as imaging was performed at a time period remote from injury. Approximately half of infants had unilateral injury (36/69, 52%) with a slight right-sided predominance (58%). No infants with unilateral injury had vermis involvement while 4/33 (12%) of those with bilateral injury did. The preponderance of hemorrhages were small (45%), with punctate and large hemorrhages representing 23% and 32%, respectively. As noted in Table 4b, ultrasound imaging detected mostly small and large

hemorrhages, while MRI was more capable of detecting punctate hemorrhages, and was more sensitive at detecting CH overall. Examples of each of the three hemorrhage sizes on both imaging modalities is shown in Figure 1.

Regression model

Backwards stepwise regression resulted in strong and discriminatory models, providing insight into both protective and risk factors (adjusted $R^2=0.349$, $p < 0.01$, C-index=0.826). Protective factors included male sex (aOR 0.46, 95% CI 0.21–0.93), complete antenatal steroid exposure (aOR 0.29, 95% CI 0.13–0.62), and substance use during pregnancy (aOR 0.07, 95% CI 0.01–0.35). Risk factors included increased ventilator days (aOR 1.02, 95% CI 1.00–1.03), acute chorioamnionitis (aOR 2.26, 95% CI 1.05–4.85), inotrope exposure during hospitalization (aOR 2.64, 95% CI 1.16–6.08), and admission temperature $<36^\circ\text{C}$ (aOR 3.58, 95% CI 1.41–9.10). When controlling for other factors, EGA (aOR 0.95, 95% CI 0.74–1.22) and year of diagnosis (aOR 1.04, 95% CI 0.91–1.18) were not significant predictors of CH. VIF was <2 for all variables in the final model, thus no variables were rejected on the basis of collinearity. A forest plot of the regression model coefficients is shown in Figure 2. Unadjusted and adjusted odds ratios are listed in Table 5.

Discussion

Cerebellar hemorrhage is common in premature infants, affecting approximately 20% of all infants born before 30 completed weeks of gestation, a finding in line with previous estimates (10–37%). In this study we identified the most important contemporaneous risk factors (low admission temperature, inotrope exposure, chorioamnionitis, severity of lung disease) and protective (antenatal steroids, male sex). Additionally, the data provocatively suggest the additional modifier of maternal tobacco/cannabis use in reducing risk.

In this study, we found that the median postnatal age at CH diagnosis was 4 days, closely matching the timing for IVH, and somewhat earlier than that reported by Limperopoulos et al. in a smaller cohort [6]. Not surprisingly, many of the risk factors identified by this study are shared in common with IVH, namely chorioamnionitis [18], inotrope exposure [19], early hypothermia [20], as well as the protective effect of antenatal steroids [21]. As these factors are also linked with impaired cerebrovascular autoregulation, it is not unreasonable to conclude that both forms of injury share a common hemodynamically-driven cause. It is less clear why male sex would confer a protective effect, but may be the result of a higher mortality rate in males than female in this cohort (23 vs. 11%) resulting in a survival bias.

A surprising result was the protective effect of substance use (driven predominantly by tobacco and cannabis) for CH. In a recent multi-center study of maternal cannabis use and neonatal outcomes revealed no relationship with any form of neonatal brain injury (IVH and WMI) [22]. Maternal tobacco use is a well-established risk factor for preterm birth [23] but it is not linked to IVH directly. To the best of our knowledge, only one other study [9] has included data on maternal tobacco and/or cannabis use and CH and did not find a relationship, but sample sizes were much smaller in that study. At this point, these results can only be interpreted as provocative and should certainly not be viewed as an endorsement of cannabis and/or tobacco as a neuroprotective agent, although there are extensive pre-

clinical data which support the use of cannabinoids in a variety of neurologic disorders [24]. Future studies should examine this effect on CH (and IVH) in a more standardized fashion.

There are several limitations to this study. First, the long time period covered by the study is advantageous, as it permits evaluation of a larger number of infants. However, there is potential for practice variation over time to alter the underlying incidence. A plot of estimated incidence vs. time (Figure 3) demonstrates a widely-varying rate with no obvious pattern over time, and year of diagnosis was not a significant predictor of CH in the regression model. An unexpected peak in was noted in 2012. When examining the three-year period encompassing 2011, 2012, and 2013 to identify factors which might influence the outcome, most factors did not correlate with the change in incidence including antenatal magnesium administration (40%, 59%, and 83% respectively), inotrope use (40%, 32%, 63%), and male sex (53%, 41%, 54%). However, antenatal steroid administration (80%, 68%, 83%).and substance use (13%, 0%, 14%) were substantially lower in 2012, potentially explaining this surge of cases.

Second, neurodevelopmental follow-up was not reported as a part of this study. This was an intentional decision based on two factors: first, about 20% of the infants are not yet old enough to undergo testing, thus artificially reducing the cohort size and second, as the infants were not prospectively enrolled in a research study, follow-up was inconsistent and conducted at the discretion of clinical practitioners.

Third, while the mixed imaging modalities contributes to a degree of uncertainty about the true incidence of CH (given the different detection thresholds), it more accurately reflects real-world clinical practice, where the term-equivalent brain MRI is no longer routinely performed [17] and many infants have only ultrasound imaging. While the routine term-equivalent MRI has fallen out of favor, these results suggest that targeted MRI exams, in patients with significant risk factors predictive of CH, may yet have a role. Furthermore, the use of ultrasound for diagnosis permitted us to identify, for the first time, an estimate of the timeframe over which CH occurs, something not possible in prior studies which utilized only term-equivalent MR imaging. Future investigation should focus on earlier imaging, particularly during the first 24–48 hours, as this is the peak time period for intraventricular hemorrhage.[25]

The results of this study reinforce one of the major goals of the “Golden Hour” initiative, specifically the importance of thermoregulation. In this analysis, and as has been reported for IVH [20], hypothermia at NICU admission conferred the highest odds ratio for CH. Aggressive measures to maintain normothermia, by use of warming mattresses, polyethylene sheets, and warmed humidified transport incubators should be a major component of a CH prevention strategy in the preterm neonate. This study also provides further evidence about the risks of unstable circulation in the preterm neonate and further underscores the need for research into the mechanisms underlying blood pressure lability and impaired function of the cerebrovascular autoregulatory system.

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Abbreviations:

AIC	Akaike information criteria
BPD	bronchopulmonary dysplasia
CUS	cranial ultrasound
CH	cerebellar hemorrhage
EGA	estimated gestational age
IVH	intraventricular hemorrhage
OR	odds ratio
ROP	retinopathy of prematurity
SWI	susceptibility-weight imaging
VIF	variance inflation factor
WMI	white matter injury

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Figure 1.

Examples of cerebellar hemorrhage shown on cranial ultrasound (row A) and MRI (row B). All ultrasound imaging is through the mastoid window, all MR imaging is shown in the axial view, T2-weighted images. Punctate injury is shown in left column, small in the middle, and large in right column. Primary focus of injury shown by arrow.

Figure 2.

Forest plot of odds ratios for variables included in final regression model, arranged from most protective to greatest risk. OR is marked with a square and 95% CI is show with whiskers.

Figure 3.
Plot of estimated CH incidence by year of study period.

Table 1.

Demographic and perinatal characteristics

	Cerebellar Hemorrhage (n=69)	Control (n=283)	P value
EGA, mean (SD), weeks	25.1 (1.9)	26.5 (1.9)	<0.01 *
Birth weight, mean (SD), g	807 (327)	940 (277)	<0.01 *
Male sex, n(%)	32 (46)	148 (53)	0.42
IUGR, n (%)	5 (7)	28 (10)	0.65
Died, n (%)	14 (20)	39 (14)	0.19
Race/ethnicity			
White, n (%)	30 (45)	135 (48)	0.03 *
Black, n (%)	33 (46)	141 (50)	
Hispanic, n (%)	3 (4)	1 (1)	
Asian, n (%)	2 (3)	6 (2)	
Other, n (%)	1 (2)	0 (0)	
Substance exposure during pregnancy			
Tobacco, n (%)	0 (0)	28 (10)	<0.01 *
THC, n (%)	2 (3)	22 (8)	0.19
Opioids, n (%)	0 (0)	8 (3)	0.37
Cocaine, n (%)	0 (0)	2 (1)	1.00
Other, n (%)	0 (0)	8 (3)	0.37
Any, n (%)	2 (3)	46 (16)	<0.01 *
Pre-eclampsia, n (%)	12 (17)	83 (30)	0.05
Chorioamnionitis, n (%)	29 (41)	69 (25)	<0.01 *
PPROM, n (%)	10 (14)	62 (22)	0.19
Multiple gestation, n (%)	23 (33)	62 (22)	0.09
Abruption, n (%)	8 (12)	32 (11)	1.00
Any antenatal steroids, n (%)	54 (78)	243 (86)	0.14
Complete antenatal steroids, n (%)	21(30)	167 (59)	<0.01 *
Antenatal magnesium sulfate, n (%)	35 (51)	192 (68)	<0.01 *
Vaginal delivery, n (%)	23 (33)	82 (29)	0.47
Emergent delivery, n (%)	39 (55)	110 (39)	0.02 *
CPR at delivery, n (%)	14 (20)	37 (13)	0.19
1-min Apgar, median (range)	2 (0–9)	3.5 (0–9)	0.01 *
5-min Apgar, median (range)	5.5 (0–9)	6 (0–9)	0.01 *
Cord blood pH, mean (SD)	7.31 (0.11)	7.30 (0.09)	0.29
Cord blood base excess, mean (SD), mEq/L	−4.06 (4.39)	−2.58 (4.20)	0.04 *

Footnote:

* Denotes significance at $p < 0.05$. Comparisons were made using Mann–Whitney U-test for continuous variables or Fisher’s Exact Test (two-sided) for categorical variables.

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Table 2.

Clinical characteristics

	Cerebellar Hemorrhage (n=69)	Control (n=283)	P value
Admission temperature < 36C, n (%)	21 (30)	29 (10)	<0.01 *
Pulmonary hemorrhage, n (%)	6 (8)	26 (9)	1.00
Pneumothorax, n (%)	3 (4)	15 (5)	1.00
Spontaneous intestinal perforation, n (%)	12 (17)	21 (7)	0.02 *
Ventilator days, median (range)	34 (0–137)	3 (0–174)	<0.01 *
HFOV 5 days of life, n (%)	39 (55)	79 (28)	<0.01 *
Blood gas pH at 5 days of life, mean (SD)	7.26 (0.08)	7.28 (0.07)	0.04 *
Blood gas base excess at 5 days of life, mean (SD)	−5.0 (−3.5)	−4.1 (7.3)	0.66
BPD, n (%)	40 (56)	128 (46)	<0.01 *
PDA treatment			
No treatment, n (%)	27 (39)	183 (65)	<0.01 *
Medical treatment only, n (%)	22 (31)	72 (25)	
Surgical treatment only, n (%)	9 (11)	13 (5)	
Medical and surgical treatment, n (%)	11 (15)	15 (5)	
Inotropic medication during hospitalization, n (%)	44 (64)	89 (32)	<0.01 *
Inotropic medication 5 days of life, n (%)	34 (49)	68 (24)	<0.01 *
Stress-dose hydrocortisone, n (%)	21 (30)	42 (15)	<0.01 *
Lung-dose hydrocortisone, n (%)	31 (44)	55 (20)	<0.01 *
Lung-dose dexamethasone, n (%)	11 (15)	22 (8)	0.06
Culture-negative sepsis, n (%)	24 (35)	92 (33)	0.78
Culture-positive sepsis, n (%)	19 (27)	47 (17)	0.06
Necrotizing enterocolitis, n (%)	9 (13)	35 (12)	1.00
Clinically apparent seizures, n (%)	7 (10)	11 (4)	0.06
ROP any stage, n (%)	39 (57)	118 (42)	<0.01 *
ROP requiring surgery, n (%)	18 (39)	29 (10)	<0.01 *
Any IVH, n (%)	42 (61)	100 (36)	<0.01 *
Grade III/IV IVH, n (%)	23 (33)	48 (17)	<0.01 *

Footnote:

* Denotes significance at $p < 0.05$. Comparisons were made using Mann–Whitney U-test for continuous variables or Fisher’s Exact Test (two-sided) for categorical variables.

Table 3.

Comparison of Selected Variables Between Hemorrhage Size

	Post hoc analysis adjusted p values				
	Large vs. Small	Large vs. Punctate	Small vs. Punctate		
EGA, mean (SD), weeks	0.62	<0.01 *	<0.01 *		
Birth weight, mean (SD), g	0.69	0.04 *	0.04 *		
Male sex, n(%)	0.27	<0.01 *	0.04 *		
Any substance use, n (%)					
Died, n (%)	0.10	0.02 *	0.16		
Chorioamnionitis, n (%)					
Complete antenatal steroids, n (%)					
Antenatal magnesium sulfate, n (%)					
Emergent delivery, n (%)					
Cord blood base excess, mean (SD), mEq/L					
Admission temperature < 36°C, n (%)					
Ventilator days, median (range)	0.88	0.02 *	<0.01 *		
BPD, n (%)	1.00	0.07	0.05		
Inotropic medication during hospitalization, n (%)					
PDA requiring treatment, n (%)					
Spontaneous intestinal perforation, n (%)					
Stress-dose hydrocortisone, n (%)					
Lung-dose hydrocortisone, n (%)					
Any IVH, n (%)					
Grade III/IV IVH, n (%)	0.01 *	0.15	0.71		

Footnote:

* Denotes significance at $p < 0.05$. Comparisons were made using Mann-Whitney U-test for continuous variables or Fisher's Exact Test (two-sided) for categorical variables. Post-hoc pairwise comparison for continuous variables was made using Dunn's test (adjusted with the Holm method) and pairwise Chi-square test for categorical variables (adjusted with Benjamini-Hochberg procedure).

Table 4a.

Imaging characteristics

	N=69
Postnatal age at CH diagnosis, median (range), days	4 (0–21)
CH first seen on ultrasound, n (%)	36 (52)
Unilateral injury, (%)	36 (52)
Unilateral right-side injury, n (%)	21 (58)
Unilateral left-side injury, n (%)	15 (42)
Bilateral injury, (%)	33 (48)
Bilateral injury alone, n (%)	29 (88)
Bilateral and vermis injury, n (%)	4 (12)
Size	
Punctate, n (%)	15 (23)
Small, n (%)	31 (45)
Large, n (%)	23 (32)

Table 4b.

Hemorrhage size by initial diagnosis modality

	Infants with CUS only (n=20)	Infants with CUS and MRI (n=49)	
		Number on CUS	Number on MRI
Punctate	2	0	13
Small	9	5	22
Large	9	10	14

Table 5.

Unadjusted and adjusted odds ratios

	OR (95% CI)	P value	aOR^a (95% CI)	P value
Male sex	0.78 (0.46–1.33)	0.38	0.46 (0.21–0.93)	0.04 *
Complete antenatal steroid exposure	0.30 (0.17–0.53)	<0.01 *	0.29 (0.13–0.62)	<0.01 *
Substance use during pregnancy	0.15 (0.02–0.51)	<0.01 *	0.07 (0.01–0.35)	<0.01 *
Ventilator days	1.02 (1.01–1.03)	<0.01 *	1.02 (1.00–1.03)	0.01 *
Acute chorioamnionitis	2.29 (1.31–3.98)	<0.01 *	2.26 (1.05–4.85)	0.04 *
Inotrope exposure	3.83 (2.22–6.74)	<0.01 *	2.64 (1.16–6.08)	0.02 *
Admission temperature <36°C	3.82 (1.99–7.24)	<0.01 *	3.58 (1.41–9.10)	<0.01 *
Gestational age (completed weeks)	0.67 (0.56–0.78)	<0.01 *	0.95 (0.74–1.22)	0.68
Year of diagnosis	0.98 (0.89–1.07)	0.59	1.04 (0.91–1.18)	0.67

Footnote:

* Denotes significance at $p < 0.05$.^a adjusted odds ratio.