ORIGINAL ARTICLE



Intraventricular hemorrhage in term infants: a single institutional experience between 2016 and 2020

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Abstract

Purpose Intraventricular hemorrhage (IVH) of prematurity is a known complication of preterm birth. Intraventricular hemorrhage in term infants is much less commonly encountered. To address the lack of information in the current literature concerning this demographic, we offer demographic and image findings that demonstrate etiology and predict the need for permanent cerebrospinal fluid (CSF) diversion.

Methods A prospectively maintained database was queried for all patients with intraventricular hemorrhage from 2016 to 2020 treated at our institution. Demographic data and etiology were collected, along with need for and timing of surgical intervention.

Results A total of 150 IVH patients were identified. Of these patients, 138 were excluded due to prematurity. Twelve patients were born at term with IVH. All patients were followed for at least 8 months. Seven patients (58.3%) underwent ventriculoperitoneal (VP) shunt placement, performed between 4 days and 4 months of age. Superficial siderosis detected by MRI during in-patient stay or follow-up showed a sensitivity of 100% and specificity of 60% for the future development of posthemorrhagic hydrocephalus (PHH) (p < 0.05). All full-term infants who developed PHH (n=7, 58.3%) obtained a VP shunt. **Conclusion** IVH in term infants occurs infrequently when compared to IVH of prematurity. Etiology of IVH in term infants remains difficult to ascertain, but the majority of patients did demonstrate risk factors. The presence of superficial siderosis on MRI significantly predicted the development of PHH and eventual need for CSF diversion.

Keywords Superficial siderosis · Ventriculoperitoneal shunt · Post-hemorrhagic hydrocephalus

Introduction

While intraventricular hemorrhage (IVH) is typically described in the premature infant with a well-understood pathophysiology and management protocols, IVH in the term infant is not. IVH of prematurity occurs in approximately 3

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live births per 1000, has a mortality of 20-30%, and is the cause of death in 1.7% of infants in the USA [1]. Evolving ventriculomegaly can cause cognitive sequelae if neurosurgical intervention is delayed [2]. A common sequela of IVH is post-hemorrhagic hydrocephalus (PHH) which causes premature IVH patients to need cerebrospinal fluid (CSF) diversion at rates ranging from 6-40%, with an average of 15% [3]. By definition, PHH is the progressive dilation of the ventricles following IVH [4, 5]. For infants with IVH of prematurity, CSF diversion is first undertaken when the frontooccipital horn ratio (FOHR) is greater or equal to 0.55, and at least two of the following three are present: splayed cranial sutures, bulging anterior fontanelle or apneic or bradycardic events. This is often initially a temporizing procedure and subsequently converted to a permanent VP shunt when their weight is > 1.8-2 kg and CSF diversion is still required [6].

While some studies have made attempts, the true incidence of IVH in term infants is unknown, as term infants

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are usually asymptomatic [7]. In a study that involved 505 healthy, asymptomatic term infants undergoing ultrasonography within 72 h of life, the incidence of IVH was 4% [8]. In a retrospective study that included 35,939 full-term newborns, grades III and IV IVH comprised an incidence rate of 5.5 per 100,000 (or 0.0055%) live term births [9].

Known risk factors of IVH in term infants include birth asphyxia with requirement of resuscitation at birth [10–13], hypoxic ischemic encephalopathy [14], instrumental deliveries [15, 16], and severe congenital heart disease (causing altered hemodynamics or use of anticoagulant pharmacotherapy) [11]. Less commonly, thrombocytopenia and coagulation factor deficiencies are associated with IVH in term infants [12, 17, 18].

In this study, we present our institutional experience with intraventricular hemorrhage (IVH) of the full-term newborn. This serves to show that symptomatic IVH at term is an event that does occur, there are often associated risk factors, imaging can aid in predicting patients who will need CSF diversion, and CSF diversion may be necessary in general.

Methods

Database and demographics

A prospectively maintained database at Riley Hospital for Children (Indianapolis, IN, USA) was queried for patients with the diagnosis of IVH who were consulted on by the pediatric neurosurgical service from the years 2016 to 2020. Included patients had IVH, a gestational age of more than 36 weeks and 6 days (>36+6), and IVH presenting after delivery on imaging. At our institution, any pediatric patient with the diagnosis of IVH grade III or IV in the preterm population or any IVH in the term population receives a pediatric neurosurgery consult regardless of the primary treating service or whether the IVH was detected while inpatient or outpatient. It also includes all referred patients with IVH grades III and IV from outside hospitals that do not have a pediatric neurosurgery service. Our study only included term infants diagnosed with IVH from the time after delivery to 28 days of age. Patients not meeting said criteria were excluded.

A protocol is in place for screening premature infants. Term infants who had signs of distress, including apnea, bradycardia, seizure, or signs of external trauma concerning for intracranial pathology underwent cranial imaging, and if positive imaging findings were identified, patients were referred to the pediatric neurological surgery service. Included infants underwent further imaging with MRI. MR angiogram and MR venogram were performed if a vascular etiology was suspected. Evaluation for coagulopathy (e.g., PTT, PT/INR, CBC, genetic screens), congenital infection screening (including STORCH), maternal and infantile drug screens, child abuse screen, and thorough review of maternal, delivery, and prenatal history was completed. The study was approved by the Institutional Review Board.

IVH location was confirmed with MRI. The following imaging findings were obtained: IVH grade, laterality, presence or absence of superficial siderosis, and hemorrhage location. Information regarding the IVH location was obtained from cranial ultrasounds or MRI that were interpreted by pediatric neuroradiologists in conjunction with our pediatric neurosurgery team. Location of hemorrhage included the caudothalamic groove (the area composed of the residual germinal matrix, the thalamus, and the watershed area of the foramen of Monro near the caudate nucleus), choroid plexus (posterior tufts of glomus), and intraparenchymal. When a patient had different graded IVHs on either side, the higher overall grade was used. All patients' IVHs were diagnosed post-natally. In our set of patients, superficial siderosis is defined as the slow accumulation of hemosiderin on the pial surfaces of the brain. This was detected by susceptibility weighted imaging (SWI) and T2* gradient echo (GRE) sequences [19].

Conservative management consisted of evaluation by the pediatric neurosurgery service including fontanelle, suture, and head circumference assessment, tracking of apneic or bradycardic events on a daily basis and weekly cranial ultrasounds with tracking of the FOHR. The shunting outcomes of post-hemorrhagic hydrocephalus, or SOPHH criteria [20], albeit an extrapolation for non-premature infants, served as the institutional guideline in terms of which patients to intervene upon and when. The interventions included in this study were either temporary CSF diversion in the form of a tapping reservoir or ventriculosubgaleal shunt or permanent diversion with either an endoscopic third ventriculostomy or ventriculoperitoneal shunt placement. As ventricular lavage and fibrinolytic therapy were not included in the treatment pathway as described by SOPHH, the patients in our study, when intervened upon, only received CSF diversion. In term patients of which index hospitalization did not necessitate surgical intervention, patients were discharged with planned neurosurgical follow up. Those who underwent CSF diversion during index hospitalization met SOPHH criteria [20].

Statistical analysis

The study data wasmanaged using REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA). Descriptive statistical analyses were performed using SASstatistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA). One-wayANOVA followed by Tukey's multiple comparisons tests, ordinal regression, and contingencyfollowed by Fisher's exact test was performed using GraphPad Prism version8.2.1 for Windows (GraphPad Software, San Diego, CA, USA).

Results

Demographics

A total of 150 patients diagnosed with IVH were identified. Out of 150 patients, 12 (8.00%) met the criteria for a term pregnancy and presented after the time of delivery. Most patients were male (75.0%). Table 1 contains descriptive information of the study population. Table 2 shows superficial siderosis findings, the development of PHH and whether patients received a VP shunt (VPS) or were conservatively managed (CM).

All 150 patients had gestational age information, and records included information regarding IVH etiology and grade. Of the 12 term infants with IVH, the median gestational age was 38.4 weeks (range: 37.1-40.0 weeks). The median age at IVH presentation was day 0 (range: 0-18 days). We observed that as gestational age increased, so did the severity of the hemorrhage grade (Nagelkerke $R^2 = 0.827$, model of fitting p < 0.001). All patients received a head MRI; 10 (83.3%) were additionally imaged by head ultrasound (hUS), 8 (66.7%) obtained a MRV, 7 (58.3%) obtained a MRA, and 5 (41.7%) had a head CT scan (these were exclusively obtained from the referring institutions). Five (41.7%) of the 12 of patients did not require surgical intervention and were followed with serial imaging. Seven patients (58.3%) underwent a VP shunt placement, and 1 of those seven patients had an external ventricular drain placed before the shunt as a temporizing measure. Patients who were managed conservatively had a median follow-up period of 18 months (range: 8.0-28.0 months). Of those requiring surgical intervention, the median age was 20.0 days (mean: 33.0 days, range: 4.0-120 days). Patients who had a VP shunt placed had a median follow-up period of 18.0 months (range: 8.0-48.0 months). Eleven patients (91.7%) were discharged home, and 1 (8.3%) died while inpatient secondary to high-output heart failure due to an arteriovenous fistula (AVF).

Etiology

Nine were determined to be idiopathic but had other congenital anomalies or some perinatal stressor effecting the infant or mother. Two had underlying vascular causes, and one had both an intraventricular tumor as well as traumatic delivery.

Imaging findings

MRI findings of superficial siderosis (Fig. 1), development of PHH, and clinical management (surgical or conservative) are noted in Table 2. Of the seven that received a VP shunt, six (85.7%) were alive by the 8-month follow-up period, and one mortality was identified secondary to complications of an AVF. An additional patient died at the 48-month timepoint secondary to glioma metastases. In retrospect, the ventricular glioma is the likely cause of the patient's IVH; however, MRI findings at presentation did not show clear evidence of a neoplastic etiology. The MRI finding of superficial siderosis subsequently requiring VP shunt had a sensitivity of 100% and a specificity of 60.0% (p=0.046).

Discussion

In this study, we present our institutional experience with IVH in the term infant. Literature has frequently focused on IVH in the premature infant. Albeit a minority of IVH, our database revealed that when IVH is present, 8% of the time, the infants have achieved a term delivery. These infants are not without other factors. While most (75%) of our population had no clear cause of IVH, risk factors were present (Table 1). In addition, intracranial hemorrhage is a known complication of forceps- and vacuum-assisted delivery, and the intraventricular location seems to be rare [21, 22]. Three patients did have clear causes of intraventricular hemorrhage, reinforcing the need for advanced imaging acquisition to determine an etiology.

Full MRI acquisition (as opposed to limited sequence, or "fast spin") was critical in this patient population. In our limited cohort of patients, superficial siderosis identified on MRI was predictive of the need for permanent CSF diversion. The decision to treat an infant was based on SOPHH criteria [20]. Prior to VPS placement, CSF analysis obtained through ventricular tap or lumbar puncture affirmed the presence of low-protein CSF without markers of pathogenic microorganisms.

Experimental models have provided fundamental insights into the iron-regulated pathophysiological sequela of PHH that underpin GMH and choroid plexus involvement in IVH [1, 23–28]. An emerging mechanism explaining PHH pathogenesis after IVH is the lysis of red blood cells and subsequent release of hemoglobin and iron into surrounding cerebral parenchyma causing iron toxicity. Termed as "superficial siderosis," blood products and extracellular matrix (ECM) proliferation (an indication of gliosis) have been hypothesized to cause PHH by disrupting CSF flow [29]. In our study, we observed that seven patients with radiographic superficial siderosis progressed to permanent CSF diversion. In a recent study by Mahaney et al., CSF hemoglobin, ferritin, bilirubin, and iron-scavenging protein levels were measured in PHH and high-grade IVH of premature neonates. They found that there was a significantly higher level of hemoglobin

2										
A	GA	Maternal presenting factor(s)	Delivery type	Infant presenting & IVH risk factor(s)	IVH etiology	Grade	Laterality	Age at presentation (days)	Age at intervention (days)	Management
-	40 + 0	Obesity	Vacuum-assisted	Asphyxia; hypoglycemia; seizures; congenital heart disease: PDA with AR, MR, & TR	Idiopathic	2	Bilateral	1	06	Surgical
7	39 + 5	Fever, HSV IgG+	Cesarean section	Asphyxia	Idiopathic	V	Bilateral	1	20	Surgical
З	39 + 3	None	Spontaneous vaginal	Asphyxia; seizures	Idiopathic	V	Bilateral	0	17	Surgical
4	39+1	1q21.1 duplications 6q duplications	Spontaneous vaginal	IUGR; HIE; multiple con- genital abnormalities: low lying conus medullaris, respiratory distress syn- drome, PDA, retrognathia, PFO, bicuspid aortic valve, biliary abnormalities; chromosomal abnormali- ties: 1q21.1 duplication (pathogenic), 6q24.2q27 copy (pathogenic) HYMAI gene duplication	Idiopathic	2	Left	4	n/a	Conservative
5	39 + 0	None	Spontaneous vaginal	AVF	Vascular: dural sinovenous thrombosis	III	Bilateral	0	4	Surgical
9	38+5	None	Spontaneous vaginal	783.4 kb interstitial duplica- tion at 10q26.16 (VUS)	Vascular: congenital sino- venous hypoplasia	III	Bilateral	0	n/a	Conservative
2	38 + 1	None	Spontaneous vaginal	Open lip schizencephaly	Idiopathic	Ш	Bilateral	18	28	Surgical
8	38 + 0	None	Forceps-assisted	Left shoulder dystocia; asphyxia; seizures	Idiopathic	III	Bilateral	б	13	Surgical
6	37+4	None	Forceps-assisted	IUGR; HIE; epilepsy	Idiopathic	Π	Left	0	n/a	Conservative
10	37+3	Pre-eclampsia, no prenatal care	Cesarean section	Subdural hematoma; sei- zures; external signs of trauma: neck swelling, subgaleal hematomas	Idiopathic	П	Bilateral	0	n/a	Conservative
11	37+1	None	Forceps-assisted	HIE; external signs of trauma: subgaleal hematoma	Multifactorial: ventricular gliomas	Π	Bilateral	0	120	Surgical
12	37+1	Gestational HTN, DM type 2 (treated), pre-eclampsia	Cesarean section	Breech presentation; asphyxia; hypoglycemia	Idiopathic	Ш	Right	0	n/a	Conservative
Patis PDA	ent den Patent	nographics, presenting and risk t ductus arteriosus, AR aortic n	factors, etiology and lc	cation of IVH, and manageme regurgitation, <i>TR</i> tricuspid reg	nt. Patient reference number (nuroitation. <i>III/GR</i> intrauterine	(ID); gest	ational age (6	GA) in "weeks - SV hernes simr	-days" dex virus <i>PFO</i>	patent foramen

Fig. 1 Three patients' axial cross-sections of susceptibility weighted \blacktriangleright imaging (SWI) MRI sequences. The presence of iron susceptibility products (superficial siderosis) is denoted with white arrows in preoperative patients who later underwent ventriculoperitoneal shunt placement. (A) Axial SWI of patient 11 (grade II IVH, 37+0 gestational age). Arrows display the presence of bilateral superficial siderosis lining the lateral ventricles. (B) Axial SWI of patient 5 (grade III IVH, 39+0 gestational age). Arrows point bilaterally to superficial siderosis of markedly dilated lateral ventricles. (C) Axial SWI of patient 2 (grade IV IVH, 39+5 gestational age). Right arrow displays iron susceptibility products of the intraparenchymal cerebral tissue. Left arrow displays superficial siderosis of the left lateral ventricle

in PHH compared to high-grade IVH without subsequent hydrocephalus development. Additionally, hemoglobin, ferritin, and bilirubin correlated with increased ventricular size. The lack of elevation of CSF iron-scavenging proteins indicated that endogenous iron clearance mechanisms were overwhelmed [30]. While this data does not encompass the granularity of CSF hemoglobin, ferritin, and bilirubin, imaging further supports the hypothesis that there is a role of iron accumulation toward development of PHH, as shown by our findings of superficial siderosis on MRI (Table 2).

In our study, all IVH term infants were born between a gestational age of 37 + 1 and 40 + 0. Precursors of arachnoid villi develop as small indurations in the venous wall of the dura at 26 weeks of gestation. Within those indurations, arachnoid cells are found sub-endothelially [31]. Then, complete formation of arachnoid villi and granulations occur by 35 and 39 weeks of gestation, respectively [32]. In context of premature infants with IVH, the

 Table 2
 MRI detection of superficial siderosis, development of posthemorrhagic hydrocephalus, and clinical course

Patient umber	Superficial siderosis (MRI)	РНН	Clinical course
1	Yes	Yes	VPS
2	Yes	Yes	VPS
3	Yes	Yes	VPS
4	No	No	СМ
5	Yes	Yes	VPS
6	No	No	СМ
7	Yes	Yes	VPS
8	Yes	Yes	VPS
9	Yes	No	СМ
10	No	No	СМ
11	Yes	Yes	VPS
12	Yes	No	СМ

Patient's number (1–12) corresponds to the same patient in Table 1 *PHH* post-hemorrhagic hydrocephalus, *VPS* ventriculoperitoneal shunt, *CM* conservative management



theory that CSF outflow is obstructed through arachnoid villi and granulations by blood or its breakdown products has largely been dismissed since they do not have arachnoid granulations [31]. While a significantly larger cohort is required than is presented in the current study, the dismissal of this theory based on a lack of anatomical development cannot be completely ruled out, as term infants by definition are at least 37 weeks old; thus, some may have complete formation of arachnoid granulations. Future clinical studies could yield insight into the outcome of PHH by comparing the gestational age of premature and full-term infants.

Limitations

This is a retrospective cohort study looking at term infants with symptomatic intraventricular hemorrhage. It is limited by selection bias as well as a small target population given the rarity of the occurrence of intraventricular hemorrhage in a term infant. Mild or asymptomatic patients were not included in the review, and conclusions here cannot be applied to a more general population.

Conclusion

In this study, we report our institutional experience from a large quaternary care pediatric institution of term infants with intraventricular hemorrhage. To our knowledge, this is the first study to find a significant association between superficial siderosis on MRI and the eventual need for CSF diversion secondary to PHH. It also serves to demonstrate intraventricular hemorrhage that can occur in the term infant population, but additional factors are often present. Comprehensive work up of this population is critical to identify risk factors and etiology. Future prospective studies are necessary to allow a more inclusive population and for better prediction of the need for surgical intervention.

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Author contribution K.D. and B.A. conceptualized and designed the study. B.A. gathered the data; prepared Tables 1 and 2, and Fig. 1; and wrote the main manuscript text. B.A. and G.X. performed the statistical analysis. M.Z. and K.D. revised and edited the manuscript. B.A. made final revisions. All authors reviewed the final manuscript.

Availability of data and material De-identified data can be made available upon reasonable request with the corresponding author.

Declarations

Ethical approval This project was granted approval by the Indiana University Institutional Review Board. Due to the retrospective nature of this study, the need for consent was waived.

Consent to participate No subjects are identifiable from this manuscript.

Consent for publication No subjects are identifiable from this manuscript. Consent to use imaging was approved by the Indiana University Institutional Review Board.

Conflict of interest No disclosures nor conflicts of interest.

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