Risk Factors for Developing Hydrocephalus in Neonatal Intraventricular Hemorrhage

Gabriel Flores, MD*†; Natalie Amaral-Nieves, MS*; Orlando De Jesús, MD*†; Juan Vigo, MD*†

Objective: More than 50% of the premature infant survivors of intraventricular hemorrhage (IVH) develop serious neurological sequelae, including progressive post-hemorrhagic hydrocephalus (PPHH) requiring a ventriculo-peritoneal (VP) shunt. Little is known about the risk factors associated with the development of PPHH in the neonatal population of Puerto Rico and thus the purpose of this study was to learn more about those risk factors.

Methods: We performed a retrospective analysis on neonates born from 2013 through 2017 who had been diagnosed with IVH. The data extracted included gender, gestational age at birth, birth weight, IVH grade, and whether the child had required a VP shunt.

Results: Two hundred and sixty-one survivors of neonatal IVH were included in the study. The overall mortality rate was 19.4%, and the incidence of PPHH was 7.7% (N = 20). The results from the Fisher's exact test for the association between the development of PPHH and the independent variables of gender (p = 0.06), birth weight (p = 0.18), and gestational age (p = 0.21) were not statistically significant. Binomial logistic regression showed that subjects with IVH (grades 3 and 4) were 20 times more likely to exhibit PPHH.

Conclusion: The incidence of PPHH secondary to IVH was slightly lower in our population compared to such incidence in other populations reported in the literature; however, the overall mortality rate was similar. The only statistically significant associated risk factor for PPHH was the severity of the IVH. [*P R Health Sci J 2020;39:55-57*]

Key words: Intraventricular hemorrhage, Hydrocephalus, Neonatal

Approximately 12,000 premature infants are affected by intraventricular hemorrhage (IVH), also called germinal matrix hemorrhage, every year in the United States (1). The fragile sub-ependymal germinal matrix, prominently located at the head of the caudate nucleus during normal neurodevelopment, progressively disappears at 36 to 37 weeks of gestation (2). The inherent fragility of the germinal matrix vasculature and fluctuations in the cerebral blood flow set the ground for IVH in premature neonates. IVH is a major health issue in premature infants, since more than 50% of the survivors develop neurological sequelae, such as cognitive deficits, cerebral palsy, developmental delay, or hydrocephalus (3,4,5). The neurosurgical management of IVH involves different invasive measures, ranging from serial lumbar puncture and temporary drainage to permanent diversion with a ventriculo-peritoneal (VP) shunt. Post-hemorrhagic ventricular dilatation after neonatal IVH may respond to less-invasive treatments, but sometimes a permanent shunt is required. If a patient develops symptomatic progressive ventricular dilatation and needs a permanent shunt to be placed, the term progressive post-hemorrhagic hydrocephalus (PPHH) is applied. Of these patients, approximately 76% exhibit marked disability and 56% may develop numerous impairments (6).

A good understanding of the risk factors involved in the development of PPHH may be helpful in its management and in the prevention of its neurological sequelae in this vulnerable population. These risk factors have not been well described for the Puerto Rican population. However, a study realized in 1994 in Puerto Rico reported that the overall incidence (in Puerto Rico) of IVH was 43%—30% for severe IVH. Mean blood-pressure fluctuations were the only significant factor associated with neonates with severe IVH and not with patients with mild IVH (7). The objective of our study was to investigate the incidence of PPHH arising from neonatal IVH at the Dr.

*University of Puerto Rico Medical Sciences Campus, San Juan, PR; †Section of Neurosurgery, University of Puerto Rico Medical Sciences Campus, San Juan, PR

The author/s has/have no conflict/s of interest to disclose.

Address correspoendence to: Gabriel Flores, MD, University of Puerto Rico Medical Science Campus, Neurosurgery Section, PO Box 365067, San Juan, PR 00936. Email: gabriel.a.flores@upr.edu

Antonio Ortiz University Pediatric Hospital from 2013 to 2017 and to evaluate how gender, gestational age at birth, birth weight, and IVH grade affect the development of PPHH.

Material and Methods

We retrospectively analyzed neonates born from January 2013 through December 2017 who had been diagnosed with IVH at the Dr. Antonio Ortiz University Pediatric Hospital Three hundred twenty-four IVH neonate patients were identified; of these, 63 patients were excluded due to their having died prior to day 30. Consequently, 261 neonatal IVH survivors were included in the study. The data extracted from the medical records and the Vermont Oxford Network database in the hospital's neonatal intensive care unit included gender, gestational age at birth, birth weight, IVH grade, and whether the child had required a VP shunt. The World Health Organization's guidelines were used to classify gestational age and birth weight. The radiologist at our institution used the IVH grading system of Papile et al. (8), which was later adapted for use with sonography by Bowerman et al. (9). The Papile grading system for IVH defines grade 1 as the presence of blood in the periventricular germinal matrix region and grade 2 as the presence of blood within the lateral ventricular system, without ventricular dilation. The more severe grades, 3 and 4, are classified as blood acutely distending the lateral ventricles and blood that extends into the brain parenchyma, respectively.

Follow-up was done during the first 90 days postpartum. In our institution, we followed preterm infants with evidence of IVH with weekly ultrasounds and fronto-occipital diameter measurements because of the possibility of that they might develop hydrocephalus. All the patients with progressive ventricular dilation that was not responsive to conservative or less-invasive procedures were considered to have PPHH and were treated with a VP shunt, when they weighed at least 1,500 g and were clinically stable with no signs of cardiovascular compromise or infection. The decisions regarding the surgical treatment of these patients were based on the criteria of the senior pediatric neurosurgeon.

Univariate analysis was performed using Fisher's exact test. Binomial logistic regression analysis was performed to determine the association between categorical variables and PPHH. Statistical significance was defined as a 2-tailed p value lower than 0.05, and odds ratios were reported, with a 95% CI for each independent variable. The University Institutional Review Board of the University of Puerto Rico Medical Sciences Campus approved the protocol.

Results

The population consisted of 153 males (58.6%) and 108 females (41.1%). The means for gestational age and birth weight were 32 (±4) weeks and 1802 (±861) grams, respectively. In terms of gestational age, the sample was composed of 62 (23.8%) term neonates (38 weeks or older) and 199 (76.2%) preterm neonates. Regarding weight, 22.2% (n = 58) of the patients presented normal birth weights (more than 2,500 grams), and 77.8% (n = 203) had low birth weights. The incidence of PPHH in neonatal IVH survivors was 7.7% (n = 20), of which survivors 15 were males and 5 were females. The overall mortality up to 90 days after birth was 19.4%.

Fisher's exact test revealed that the association between gender and PPHH was not statistically significant (p = 0.06). No statistically significant differences were found between gestational age (p = 0.21) and birth weight (p = 0.18) with PPHH presence. As there were no instances of PPHH and IVH grade 1 or 2, we compared IVH grade 4 with IVH grade 3. We found statistically significant evidence (Fisher's exact test; p<0.001) of an association between the severity of IVH an development of PPHH. The incidence of PPHH in extremely preterm babies was 16.3% (n = 8); for extremely low weight babies, the incidence was 13.3% (n = 6). Summaries of PPHH distribution by gestational age and birth weight in neonatal IVH survivors are shown in Tables 1 and 2, respectively.

Table 1. Descriptive statistics of the number of cases of progressive post-hemorrhagic hydrocephalus in each gestational age classification (per the World Health Organization guidelines)

Gestational age	PPHH	Percent (%)	No PPHH	Total
Term	4	8.5	43	47
Moderate preterm	5	5.0	96	101
Very preterm	3	4.7	61	64
Extremely preterm	8	16.3	41	49
Total	20	7.7	241	261

Table 2. Descriptive statistics of the number of cases of progressive post-hemorrhagic hydrocephalus in each birth weight classification (per the World Health Organization guidelines)

Birth weight	PPHH	Percent (%)	No PPHH	Total
Normal weight	3	5.2	55	58
Low weight	6	7.3	76	82
Very low weight	5	6.6	71	76
Extremely low weight	6	13.3	39	45
Total	20	7.7	241	261

No occurrences of PPHH in patients with IVH grades 1 or 2 were recorded in this cohort. In subjects with severe IVH (grades 3 and 4), the incidence of PPHH treated with a VP shunt was 51.3% (n = 20). Of this 51.3%, 38.1% (n = 8) of the children had grade 3 IVH and 66.7% (n = 12), grade 4. The remaining 48.7% with severe IVH did not develop PPHH. Logistic regression was performed to establish the effects of gender, gestational age, birth weight, and IVH grade on the likelihood that participants would develop PPHH. The logistic regression model was statistically significant ($\chi 2(4) = 85.726$; p<0.001). The model explained 67.0% (Nagelkerke's R squared) of the variance in PPHH and correctly classified 94.6% of cases. Subjects with severe IVH grade were 20 times more likely to exhibit PPHH.

Independent variables such as gender, gestational age, and birth weight showed no statistical significance. Summaries of p values, odds ratios, and 95% confidence intervals are shown in Table 3.

Table 3. Logistic regression performed to establish the effects of gender, gestational age, birth weight, and IVH grade on the likelihood that patients would develop PPHH (95% CI for odds ratios in the lower and upper margins are shown)

Independent variable	p value	odds ratio	95% CI Lower	95% CI Upper
Gender	0.15	3.2	0.6	16.4
Gestational age	0.07	1.3	1.0	1.8
Birth weight	0.10	1.0	1.0	1.0
IVH grade	<0.001	20.3	7.3	56.6

Discussion

The incidence of PPHH in our cohort was 7.7%. The incidence of PPHH in the literature ranges from 8.5% to 9.0% (7,10,11). The overall mortality rate of 19.4% in our study compares with the mortality rate of 20% reported in the literature (11). No statistically significant association was found between PPHH and the variables of birth weight (OR = 1.00; p = 0.10) or gestational age (OR = 1.31; 95% CI: 0.978-1.76). However, the literature has reported that with lower gestational age and birth weight, the risk of IVH and post-hemorrhagic hydrocephalus increases due to the fragility of the microvasculature of the germinal matrix (1). Although not statistically significant, the risk of shunt-dependent hydrocephalus was higher in males (OR = 3.25; 95% CI: 0.65-16.38) than in females, which is consistent with reports in the literature (11,12).

Our analysis demonstrated that the severity of the IVH was the only independent variable that showed a statistically significant association with PPHH. We consider this variable as the principal risk factor for the development of PPHH. Christian et al. (13) showed that 25% of patients with IVH grade 3 and 28% of patients with IVH grade 4 developed PPHH, compared with 1% of patients with IVH grade 1 and 4% of patients with IVH grade 2, who did not. Vassilyadi et al. (11) found that 44% of patients with IVH grade 3 and 39% of patients with IVH grade 4 developed PPHH. Our study showed that 38.1% of the patients with IVH grade 3 and 66.7% of the patients with IVH grade 4 developed PPHH. However, none of the patients with IVH grade 1 or 2 developed PPHH. As a result, the incidence of PPHH in patients with IVH grade 4 was significantly higher in our study compared to others. These findings merit further research in terms of determining how patient management may affect these statistics. In our study the confidence interval for the IVH grade was extremely wide (7.3 to 56.6), which suggests that our sample size may have been so small because of the lower incidence of PPHH in our population.

In our cohort, the incidence of PPHH in neonatal IVH was lower compared to that reported previously; however, the overall mortality rate was similar. The effects of gender, gestational age, and birth weight did not appear to significantly influence the risk of developing PPHH. Within the clinical parameters of our study, once neonatal IVH was established, the only statistically significant associated risk factor for PPHH was the severity of the IVH. We hope this information will help in the management of this vulnerable population in Puerto Rico. In the future, further studies that include a greater number of risk factors for PPHH should be developed to acquire an even better understanding of this condition in this population.

Acknowledgments

We would like to thank Aixa De Jesús Espinosa for all her help in the preparation of this manuscript.

References

1. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res 2010;67:1-8.
2. Ballabh P. Pathogenesis and prevention of intraventricular hemorrhage. Clin Perinatol 2014;41:47-67.
3. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R; NICHD Research Network. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 2008;121:e1167-e1177.
4. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. Pediatrics 2009;123:1037-1044.
5. Vohr BR, Allan WC, Westerveld M, et al. School-age outcomes of very low birth weight infants with indomethacin intraventricular hemorrhage prevention trial. Pediatrics 2003;111:e340-e346.
6. Murphy BP, Inder TE, Rooks V, et al. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. Arch Dis Child Fetal Neonatal Ed 2002;87:F37-F41.
7. Alvarez MD, Villamil M, Reyes G. Predictive factors in the genesis of intraventricular hemorrhage in premature infants. P R Health Sci J 1994;13:251-254.
8. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-534.
9. Bowerman RA, Donn SM, Silver TM, Jaffe MH. Natural history of neonatal periventricular/intraventricular hemorrhage and its complications: sonographic observations. Am J Roentgenol 1984;143:1041-1052.
10. Klinger G, Osovsky M, Boyko V, et al. Risk factors associated with post-hemorrhagic hydrocephalus among very low birth weight infants of 24-28 weeks gestation. J Perinatol 2016;36:557-563.
11. Vassilyadi M, Tataryn Z, Shamji MF, Ventureyra EC. Functional outcomes among premature infants with intraventricular hemorrhage. Pediatr Neurosurg 2009;45:247-255.
12. Cuestas E, Bas J, Pautasso J. Sex differences in intraventricular hemorrhage rates among very low birth weight newborns. Gend Med 2009;6: 376-382.
13. Christian EA, Jin DL, Attenello F, et al. Trends in hospitalization of preterm infants with intraventricular hemorrhage and hydrocephalus in the United States, 2000–2010. J Neurosurg Pediatr 2016;17:260–269.