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Neurodevelopmental Outcomes and Brain Volumetric Analysis of Low-Grade Intraventricular Hemorrhage

Seul Gi Park, MD, Hyo Ju Yang, MD, Soo Yeon Lim, MD, Seh Hyun Kim, MD, PhD, Seung Han Shin, MD, PhD, Ee-Kyung Kim, MD, PhD, and Han-Suk Kim, MD, PhD

Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, Korea

ABSTRACT

Purpose: Extremely preterm infants are prone to brain injury and underdevelopment. Intraventricular hemorrhage (IVH) is the most common cause of brain injury and a significant risk factor for neurodevelopmental delay in preterm infants. Severe IVH is known to have a poor outcome; however, the outcomes of low-grade IVH remain controversial. This study aimed to evaluate neurodevelopmental outcomes and brain segmental volumes of preterm infants with low-grade IVH.

Methods: This retrospective cohort study included 109 extremely preterm infants who underwent term equivalent age-magnetic resonance imaging and neurodevelopmental evaluation at a corrected age of 18 to 24 months. We compared infants with and without low-grade IVH.

Results: Among the 109 extremely preterm infants, 25 had low-grade IVH and 84 had no IVH. There were no significant differences in the neurodevelopmental outcomes between the low-grade and no IVH groups. In multivariate analysis, low-grade IVH was associated with a smaller medullary volume (adjusted odds ratio, 0.575; 95% confidence interval, 0.346 to 0.957; *P*=0.034).

Conclusion: We found no significant differences in the neurodevelopmental outcomes of extremely preterm infants at a corrected age of 18 to 24 months between those with low-grade IVH and those without IVH. Low-grade IVH was associated with a smaller medullary volume.

Key Words: Prematurity; Intraventricular hemorrhage; Brain regions; Neurodevelopmental disorders

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Correspondence to: Seh Hyun Kim, MD, PhD
Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-0083
Fax: +82-2-2072-0590
E-mail: drcorkim@gmail.com

INTRODUCTION

Improvements in obstetric and neonatal care have significantly altered the spectrum of neonatal diseases. Decreasing mortality rates in neonatal intensive care units (NICUs) have led to the recognition of new neurological disorders and treatments. Among these neurological disorders, brain injury, including intraventricular hemorrhage (IVH), is the major

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cause of neurodevelopmental impairment (NDI)[1]. Although numerous centers have used standard techniques to improve neurocritical care in NICUs, such as amplitude-integrated electroencephalography, near-infrared spectroscopy, cranial ultrasonography, and magnetic resonance imaging (MRI), IVH still contributes to neonatal morbidity and mortality. Neonatal brain injury increases the risk of mortality and adverse neurodevelopmental outcomes, including cerebral palsy and epilepsy [1]. The incidence of low-grade IVH (grades 1 to 2) is 11% and that of severe IVH (grades 3 to 4) is 3% to 5% in preterm infants[2,3]. Numerous studies have addressed the adverse outcomes of severe IVH; however, the neurodevelopmental outcomes of low-grade IVH remain controversial[4,5]. Acute destructive brain injuries, such as IVH, are not the only factors that influence neurodevelopmental outcomes; reduced brain volume also affects outcomes in preterm infants[1,6]. Underdevelopment of brain segmental structures, including the hippocampus, cortical gray matter, white matter, and cerebellum, is also known to adversely affect neurodevelopment[7]. The association between segmental brain volumes on brain MRI at a term equivalent age (TEA-MRI) and low-grade IVH is poorly understood. As even low-grade IVH can induce other brain injuries, including white matter injury, we hypothesized that low-grade IVH might affect the underdevelopment of specific brain segments[8]. The current study aimed to explore the association between neurodevelopmental outcomes and brain volumes of extremely preterm infants with low-grade IVH at a corrected age (CA) of 18 to 24 months.

MATERIALS AND METHODS

1. Participants

We retrospectively reviewed the previously collected data of extremely preterm infants (<28 weeks of gestation) at a single NICU from January 1, 2009 to December 31, 2019. Extremely preterm infants who underwent TEA-MRI at a postmenstrual age (PMA) of 36 to 40 weeks and Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) assessment at a CA of 18 to 24 months were enrolled. To diagnose IVH, cranial ultrasound was performed within 24 hours of birth, on postpartum days 3 and 7, and then weekly till discharge. IVH grade was classified according to Papile et al.[9] Infants with significant brain lesions on TEA-MRI, including severe IVH (grades 3 to 4), periventricular leukomalacia, and cerebellar hemorrhage were excluded. Infants who were small for gestational age and with congenital anomalies were also excluded.

2. Data collection and NDI definition

We collected the medical records, including demographic, clinical, and follow-up data of the enrolled participants. Development was classified using standardized scores, with a normal score defined as within one standard deviation (SD) of the mean (≥85)[10]. Thus, we defined NDI as cases with BSID-III scores in the cognitive, language, or motor domains of less than 85 (<–1 SD)[10] or having cerebral palsy, hearing loss, or blindness.

3. MRI assessment

T1-weighted MRI images were acquired using a 1.5T MRI scanner (Siemens Healthcare). TEA-MRI is a routine clinical practice for preterm infants born at less than 29 weeks of gestation or with a birthweight of less than 1,000 g. Brain segmental volumes were analyzed using an automated segmentation pipeline for T1-weighted images, Infant FreeSurfer software v7.1.1 (www.freesurfer.net)[11]. Regional volumes of each infant's brain (ventricle, midbrain, pons, medulla, cerebellum, thalamus, caudate nucleus, putamen, pallidum, hippocampus, amygdala, accumbens area, cerebral white matter volume, subcortical gray matter volume, cortical gray matter volume, total gray matter, supratentorium, and total intracranial volume) were measured automatically. The extracted volumetric data were processed by a single researcher.

4. Statistical analysis

Statistical analyses were performed using R statistical software v4.1.2 (www.r-project.org). Student's *t*-test, Wilcoxon's rank-sum test, chi-square test, or Fisher's exact test were performed to compare neurodevelopmental outcome and brain volume data. Multivariate regression analysis adjusted for gestational age, birth weight, and PMA on TEA-MRI was performed to examine the association between low-grade IVH and segmental brain volume. Statistical significance was set at $P<0.05$.

RESULTS

A total of 295 extremely preterm infants were born in the NICU during the study period. Among them, 186 infants were excluded because of congenital anomalies (n=6), small for gestational age

(n=17), significant brain lesions on TEA-MRI at PMA 36 to 40 weeks (n=68), no TEA-MRI at PMA 36 to 40 weeks (n=46), or no BSID-III assessment at CA 18 to 24 months (n=54). Ultimately, 109 infants were included in this study, 25 of whom had low-grade IVH and 84 had no IVH (Figure 1).

1. Neurodevelopmental outcomes

BSID-III cognitive scores (95.0 vs. 90.0, *P*=0.974), language scores (91.8 vs. 91.8, *P*=0.998), and motor scores (94.0 vs. 91.0, *P*=0.380) were comparable between the no IVH and low-grade IVH groups. Additionally, there was no significant difference in NDI between the two groups (20.2% vs. 32.0%, *P*=0.339) (Table 1).

2. Brain volume analysis

The medulla was smaller (0.6 mL vs. 0.7 mL, *P*=0.023) and the thalamus (8.6 mL vs. 8.1 mL, *P*=0.034), caudate nucleus (3.3 mL vs. 2.8 mL, *P*=0.023), amygdala (1.1 mL vs. 1.0 mL, *P*=0.029), accumbens area (0.5 mL vs 0.4 mL, *P*=0.014), and subcortical gray matter (22.8 mL vs. 21.5 mL, *P*=0.034) were larger in the low-grade IVH group than in the no IVH group (Table 2). However, multivariate logistic regression analysis adjusted for gestational age, birth weight, and PMA at MRI showed that only the medulla was negatively associated with low-grade IVH (adjusted odds ratio, 0.575; 95% confidence interval, 0.346 to 0.957; *P*=0.034) (Table 3).

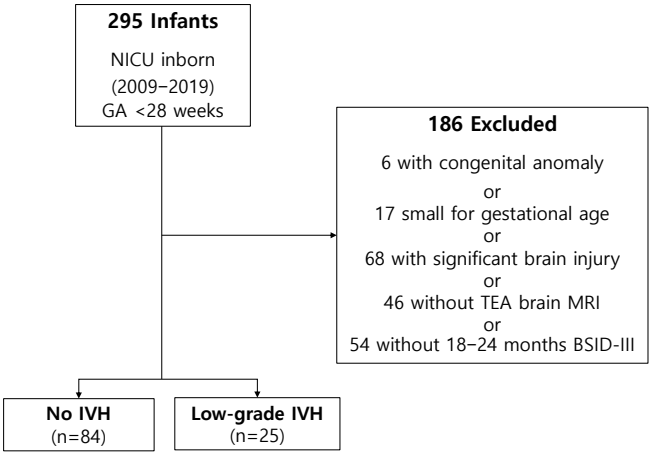

Figure 1. Study cohort. Abbreviations: NICU, neonatal intensive care unit; GA, gestational age; TEA, term equivalent age; MRI, magnetic resonance imaging; BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; IVH, intraventricular hemorrhage.

DISCUSSION

This study evaluated the association between low-grade IVH, long-term neurodevelopmental outcomes and segmental brain volume. Low-grade IVH did not have a significant effect on BSID-III scores or NDI at 18 to 24 months CA in preterm infants born at <28 weeks of gestation. In addition, low-grade IVH was associated with a smaller medullary volume.

Adverse neurodevelopmental outcomes are significant morbidities among preterm infants that are still common, although mortality rates in preterm infants have dramatically decreased[12]. IVH is a major morbidity of prematurity and is known to be related to negative neurodevelopmental outcomes[13,14]. IVH can be identified by cranial ultrasonography during NICU admission. The incidence of severe IVH is 15%, and that of any grade of IVH was 34% before 28 weeks of gestation[15]. The impact of severe IVH on neurodevelopmental outcomes has been extensively studied, and severe IVH reportedly has a significant contribution to adverse neurodevelopmental outcomes at 2 years of CA[14]. In addition, a meta-analysis by Mukerji et al.[16] showed that there was a higher risk of moderate-to-severe NDI in the severe IVH group than in the no IVH group. However, the effect of low-grade IVH on long-term developmental outcomes is not yet clearly understood. Brain injury associated with low-grade IVH could involve two key sites: the cerebral white matter and the germinal matrix [17]. The developing cerebral white matter may be injured by hypoxic-ischemic insults related to IVH and free radical-mediated

Table 1. Demographic, BSID-III Scores, and NDI

Variable	No IVH (n=84)	Low-grade IVH (n=25)	*P*-value
GA (wk)	26.6 (25.6–27.3)	26.0 (25.4–27.1)	0.434
Birth weight (g)	854.8±166.7	872.0±185.9	0.659
Cesarean section	41 (48.8)	16 (64.0)	0.268
Female sex	48 (57.1)	13 (52.0)	0.822
1 minute Apgar score	4.0 (2.0–5.0)	2.5 (1.0–4.0)	0.022
5 minutes Apgar score	7.0 (5.0–7.0)	6.0 (4.0–7.0)	0.089
BSID-III cognitive score	95.0 (87.5–100.0)	90.0 (90.0–105.0)	0.974
BSID-III language score	91.8±15.3	91.8±13.7	0.998
BSID-III motor score	94.0 (88.0–100.0)	91.0 (88.0–100.0)	0.380
NDI	17 (20.2)	8 (32.0)	0.339

Values are expressed as median (interquartile range), mean±standard deviation, or number (%).
Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; NDI, neurodevelopmental impairment; IVH, intraventricular hemorrhage; GA, gestational age.

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Table 2. Association between Brain Volume and Low-Grade IVH

Variable	No IVH (n=84)	Low-grade IVH (n=25)	*P*-value
PMA at MRI (wk)	36.4 (35.9–37.5)	37.3 (36.7–38.3)	0.012
Weight at MRI (g)	2,165.0 (1,975.0–2,415.0)	2,200.0 (2,050.0–2,630.0)	0.330
Head circumference on MRI (cm)	30.5 (29.9–32.0)	31.3 (30.5–32.5)	0.244
Ventricle (mL)	5.0 (4.1–6.1)	5.5 (4.0–6.9)	0.555
Midbrain (mL)	1.6±0.2	1.7±0.2	0.112
Pons (mL)	1.7±0.3	1.8±0.3	0.131
Medulla (mL)	0.7 (0.6–0.8)	0.6 (0.6–0.7)	0.023
Cerebellum (mL)	13.9 (12.4–16.6)	14.8 (13.2–17.2)	0.118
Thalamus (mL)	8.1±1.0	8.6±1.0	0.034
Caudate (mL)	2.8 (2.4–3.3)	3.3 (2.8–3.5)	0.023
Putamen (mL)	3.5±0.6	3.8±0.5	0.063
Pallidum (mL)	1.9±0.3	1.9±0.3	0.481
Hippocampus (mL)	1.9±0.2	2.0±0.3	0.071
Amygdala (mL)	1.0±0.2	1.1±0.2	0.029
Accumbens area (mL)	0.4 (0.4–0.5)	0.5 (0.5–0.6)	0.014
Cerebral white matter (mL)	92.9 (86.6–101.5)	98.0 (91.7–105.4)	0.100
Subcortical gray matter (mL)	21.5±2.8	22.8±2.6	0.034
Cortical gray matter (mL)	100.1 (90.2–109.0)	104.8 (95.2–117.0)	0.170
Total gray matter (mL)	133.7 (120.8–145.6)	141.8 (128.2–154.6)	0.126
Supratentorium (mL)	217.1 (202.4–238.3)	227.5 (218.8–254.1)	0.108
Total intracranial volume (mL)	253.3 (233.7–278.8)	265.4 (235.0–289.1)	0.567

Values are expressed as median (interquartile range) or mean±standard deviation.
Abbreviations: IVH, intraventricular hemorrhage; PMA, postmenstrual age; MRI, magnetic resonance imaging.

insults resulting from elevated iron-producing highly-reactive hydroxyl radicals[17]. Since the germinal matrix contains glial precursor cells, direct injury to it in IVH can result in impaired myelination and cortical organization[17]. Thus, it can be assumed that even low-grade IVH might result in poor neurodevelopmental outcomes. Recent studies have revealed conflicting results, as shown by a few reports that grade 1 and 2 IVH was associated with higher rates of cerebral palsy, visual impairments, and NDI at 2 years of CA[18], with other reports showing that low-grade IVH does not affect cognitive, motor, and academic outcomes at school age[19]. Patra et al.[8] showed that the risk of adverse neurodevelopmental outcomes at 20 months CA was higher in extremely low-birth-weight infants with low-grade IVH than in the control group. Low-grade IVH was associated with an approximately ≥2-fold greater risk of lower cognitive and motor outcomes[8,17]. However, our data showed no significant association between low-grade IVH, BSID-III scores, and NDI development at 2 years of CA among extremely preterm infants.

The period between 28 weeks of PMA and TEA is important for the functional and structural development of the brain, and TEA-MRI can be a powerful tool for assessing the effects of IVH. Prematurity and cerebral hemorrhage adversely affect brain development[20]. Moreover, it has been reported that premature infants have smaller brain volumes, including that of the cerebral cortex and deep gray matter, as well as increased cerebrospinal fluid volume at TEA[21]. Preterm infants with IVH also have been found to have reduced total brain sizes and enlarged pericerebral spaces relative to those without IVH[20]. Several studies have demonstrated the association between low-grade IVH and segmental brain volumes, including reduced cortical and cerebellar volumes[22-24]. To observe the effect of low-grade IVH on brain volume, we excluded preterm infants who had high-grade IVH on TEA-MRI. Compared with the no IVH group, the low-grade IVH group had a smaller medullary volume. To the best of our knowledge, this is the first study to report impaired medullary development after low-grade IVH. The medulla oblongata has respiratory, cardiac, and digestive centers, and is an important regulator of blood pressure, respiration, and heart rate[25]. Since low-grade IVH is associated with decreased cerebral blood flow in the cortical and subcortical regions in preterm infants, these

Table 3. Multivariate Logistic Regression Analyses for Low-Grade IVH

Variable	aOR*	95% CI	*P*-value
Ventricle (mL)	0.985	0.942–1.030	0.508
Midbrain (mL)	1.266	0.807–1.986	0.302
Pons (mL)	1.063	0.809–1.398	0.657
Medulla (mL)	0.575	0.346–0.957	0.034
Cerebellum (mL)	0.991	0.960–1.023	0.583
Thalamus (mL)	1.054	0.960–1.158	0.268
Caudate (mL)	1.023	0.873–1.198	0.780
Putamen (mL)	1.024	0.848–1.237	0.802
Pallidum (mL)	1.051	0.814–1.358	0.700
Hippocampus (mL)	1.201	0.869–1.659	0.264
Amygdala (mL)	1.402	0.860–2.287	0.174
Accumbens area (mL)	1.263	0.522–3.056	0.601
Cerebral white matter (mL)	1.001	0.993–1.001	0.823
Subcortical gray matter (mL)	1.019	0.982–1.058	0.320
Cortical gray matter (mL)	0.996	0.988–1.003	0.222
Total gray matter (mL)	0.997	0.991–1.003	0.341
Supratentorium (mL)	0.999	0.996–1.003	0.654
Total intracranial volume (mL)	1.086	0.996–1.001	0.243

*Adjusted for gestational age, birthweight, and postmenstrual age at magnetic resonance image.
Abbreviations: IVH, intraventricular hemorrhage; aOR, adjusted odds ratio; CI, confidence interval.

brain lesions, such as those in the medulla, are vulnerable to structural changes[26]. In extremely preterm infants, disruptive effects on subsequent brain development in parts adjacent to and remote from the first brain injury can affect neurodevelopmental outcomes[27]. Although the pathways are unclear, injury of the germinal matrix may triggered the underdevelopment of brain stem regions, including the medulla. An autopsy study in autistic patients showed a shortening of the brainstem between the trapezoid body and inferior olive, a part of the medulla oblongata at birth, suggesting an association between a smaller medullary area and autism spectrum disorders[28]. Therefore, preterm infants with a reduced medullary volume might be at a higher risk of autism spectrum disorders. The association found between a smaller medulla and low-grade IVH in our study population might be an incidental finding, and the fact that there was no difference in the BSID-III scores and NDI incidence between the two groups makes the finding of a smaller medulla in the low-grade IVH group less important. However, further investigation is needed to better understand the pathological mechanisms involved in low-grade IVH and medullary volumes.

This study had a few limitations that should be considered when interpreting the results. First, data were collected solely from a single NICU. More data from multiple NICUs would improve the reliability of the subsequent findings. Second, not all images were acquired using the same MRI scanning parameters, possibly leading to differences in image quality, which may have influenced the automated segmentation pipeline of the brain regions. Third, our team evaluated only the association between low-grade IVH and neurodevelopmental outcomes 2 years after CA. However, it has been reported that low-grade IVH affects neurodevelopment at school age. Thus, further investigation of the relationship between low-grade IVH and the neurodevelopment status of preterm infants at school age should be considered.

In conclusion, no significant difference in BSID-III scores and the incidence of NDI was found between extremely preterm infants with low-grade IVH and those without IVH at a CA of 18 to 24 months. However, the low-grade IVH group had a smaller medullary volume on TEA-MRI.

ARTICLE INFORMATION

Ethical statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 2206-135-1335). The requirement of informed consent requirement was waived because of the retrospective nature of the study design.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conception or design: S.G.P., H.J.Y., S.Y.L., S.H.K., S.H.S., E.K.K., H.S.K.

Acquisition, analysis, or interpretation of data: S.G.P., S.H.K., S.H.S.

Drafting the work or revising: S.G.P., H.J.Y., S.Y.L., S.H.K., S.H.S., E.K.K., H.S.K.

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ORCID

Seul Gi Park https://orcid.org/0000-0002-3862-5263
Hyo Ju Yang https://orcid.org/0000-0003-1208-6887
Soo Yeon Lim https://orcid.org/0009-0009-4536-7109
Seh Hyun Kim https://orcid.org/0000-0001-8686-1909
Seung Han Shin https://orcid.org/0000-0002-7008-4073
Ee-Kyung Kim https://orcid.org/0000-0002-7063-168X
Han-Suk Kim https://orcid.org/0000-0002-9777-3231

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