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Brain Biometry Reveals Impaired Brain Growth in Preterm Neonates with Intraventricular Hemorrhage

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Keywords

Biometry · Brain development · Brain growth · Brain injury · Intraventricular hemorrhage · Magnetic resonance imaging · Neonate · Neurodevelopmental outcome · Prematurity

Abstract

Introduction: Preterm birth and cerebral hemorrhage have adverse effects on brain development. Alterations in regional brain size on magnetic resonance imaging (MRI) can be assessed using 2D biometrical analysis, an easily applicable technique showing good correlation with 3D brain volumes. ***Methods:*** This retrospective study included 74 preterm neonates with intraventricular hemorrhage (IVH) born $<32^{+0}$ weeks of gestation between 2011 and 2019. Cerebral MRI was performed at term-equivalent age, and 2D measurement techniques were used for biometrical analysis and compared to normative data of two control groups. Finally, the correlation and association of brain parameters and patterns of impaired brain growth and outcome at 2 and 3 years of age were evaluated. ***Results:*** Interhemispheric distance (IHD), the 3rd ventricle, and lateral ventricles presented larger, in contrast, cerebral biparietal width (cBPW), fronto-occipital diameter (FOD), and the length of the corpus callosum were smaller in IVH patients compared to respective controls. The strongest correlations with outcome were observed for the parameters FOD, anteroposterior diameter of the vermis, transverse cerebellar diameter (tCD), corpus callosum, 3rd ventricle, and left ventricular index. Patients with the small FOD, small BPW, and increased IHD pattern reached overall lower outcome scores at follow-up. ***Discussion:*** Preterm neonates with IVH showed reduced total brain sizes and enlarged pericerebral spaces compared to neurologically healthy controls. Biometric analysis revealed that several 2D brain parameters as well as different patterns of impaired brain growth were associated with neurodevelopmental impairment in early childhood. These findings may support prediction of long-term outcome and parental counseling in patients with IVH.

Introduction

Improvements in perinatal and neonatal care have led to increased survival rates for extremely preterm infants. Nevertheless, the incidence of intraventricular hemorrhage (IVH) remains high, with 20–30% in infants born

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below 29^{+0} weeks gestational age (GA). IVH can be complicated by periventricular hemorrhagic infarction and/or posthemorrhagic ventricular dilatation and is associated with mortality as well as physical and mental disability [1].

Cranial ultrasound is the method of choice for detection and grading of IVH in preterm neonates. For detailed analysis, however, magnetic resonance imaging (MRI) provides more precise visualization and allows the identification of more subtle lesions as well as the full extent of brain injury [2]. A high correlation between abnormal findings on MRI and later adverse neurodevelopmental outcome has been demonstrated in several studies [3–5], as well as in patients with IVH [6]. Volumetric analysis of the neonatal brain has shown reduced cortical and deep nuclear gray matter and increased ventricular sizes in children with neurodevelopmental impairment [7–9]. Decreased cerebral volumes can persist up to adolescence [10], which demonstrates the importance of volumetric MRI in addition to the diagnosis of cerebral injury. As 3D volumetry requires complex postprocessing that is difficult to apply in the clinical setting, an alternative, easily applicable technique showing good correlation with 3D brain volumes has been introduced [11–13].

The purpose of the present study was to further investigate the value of these simple brain measurements in preterm infants with IVH. We evaluated differences in regional brain sizes identified on MRI in neonates with IVH compared to neurologically healthy controls, assessed the correlation of 2D brain parameters to later development, and finally determined those parameters particularly sensitive to neurodevelopmental outcome. To be able to distinguish between prematurity-based and IVH-induced alterations, patients were compared to the literature as well as local controls.

Materials and Methods

Study Group

Preterm neonates with IVH I-IV born $<32^{+0}$ weeks GA between January 2011 and July 2019 treated at the Medical University of Vienna were included. IVH was graded according to the maximum extension of the bleeding on sequential cranial ultrasound. Neonates with congenital malformations, central nervous system malformations, chromosomal anomalies, metabolic disorders, and deceased patients were excluded.

Magnetic Resonance Imaging and Brain Biometry

MRI was performed as part of routine clinical care on a 1.5-Tesla scanner (Philips Ingenia, Philips Healthcare, Best, the Netherlands) at term-equivalent age. T2-weighted Turbo Spin Echo sequences (slice thickness 2–3 mm) were evaluated for biometric analysis using the program IMPAX EE by two neonatologists (HS, KG) who were previously trained by a radiologist with >10 years of experience in fetal and neonatal neuroradiology (GK). Measurements were obtained based on Catherine Garel, MRI of the fetal brain [13] and included parameters described in Figure 1.

To compare brain parameters independently of GA, z transformations were performed. Z-scores were calculated by comparing the obtained measurement to normative data of respective controls (see below).

Patterns of impaired brain growth were adopted according to Kidokoro et al. [15] Each pattern was considered to be present if the obtained measurement deviated by more than two SDs from the norm. First, the increased interhemispheric distance (IHD) and the small cerebral biparietal width (cBPW) brain patterns were evaluated. Additional patterns, namely the small fronto-occipital diameter (FOD) and small transverse cerebellar diameter (tCD) patterns, were introduced and evaluated by similar criteria.

Neurodevelopmental Outcome

Neurodevelopmental follow-up assessment was obtained only for IVH patients and performed by trained clinical psychologists. Patients were tested with Bayley Scales of Infant Development 3rd edition (Bayley-III) at 2 and 3 years of age using German norms.

Control Groups

Literature Controls

Patients in the study group receiving MRI before discharge before 37^{+6} weeks of gestation were compared to controls published by Garel et al. (fetal MRI) [13], whereas those who received MRI at 38^{+0}–41^{+6} weeks were compared to a cohort published by Nguyen et al. (postnatal MRI) [12]. Published normative data were only available until term; MRIs $\geq 42^{+0}$ weeks GA were thus excluded from z-score calculations.

Local Controls

To ensure the best possible comparability and to account for the impact of prematurity, the study group was compared to a control group of GA-matched preterm infants receiving MRI at our department. Routine MRI at term-equivalent age was introduced for all infants born extremely preterm at our institution in November 2017 [16]. This control group consisted of 58 neurologically healthy neonates. Exclusion criteria were similar to the study group and the same methodology was applied.

Statistical Analysis and Ethics

Statistical analysis was performed using SPSS version 23 (IBM Corporation). A two-sided p value <0.05 was considered significant. Differences were compared using Mann-Whitney U test and χ^2 test. The correlation of z-scores with neurodevelopmental outcome was measured using the Pearson or Spearman's rank correlation coefficient as appropriate. Finally, multiple linear regression was applied to evaluate the association between significant parameters and neurodevelopmental outcome using a stepwise approach adjusted for GA, birth weight, and degree of IVH.

The intraclass correlation coefficient was used to test interobserver reliability. A 2-way random model was applied to assess absolute agreement and interpreted according to the strength of agreement scale of Brennan and Silman. This study was approved by the Ethics Committee of the Medical University of Vienna (EK 1968/2017).

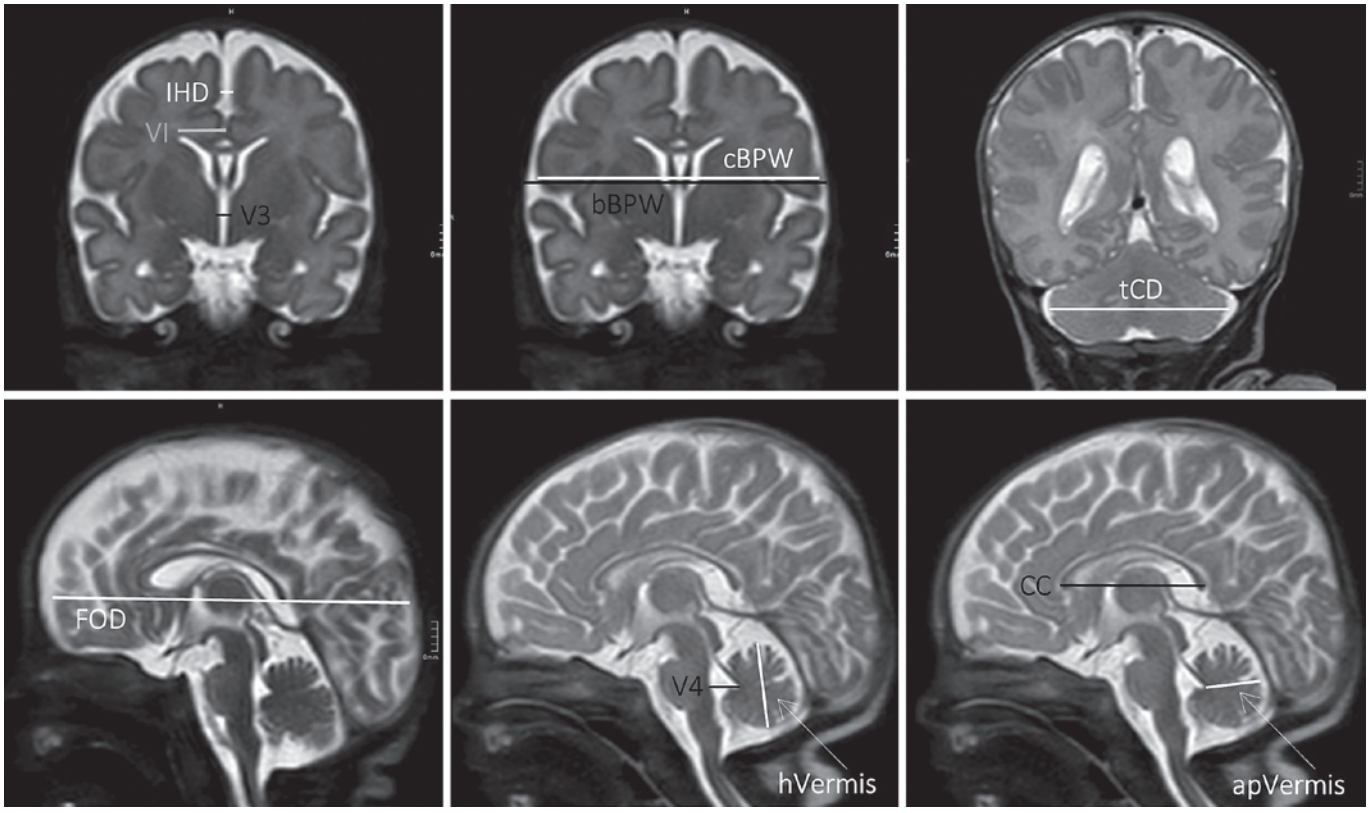

Fig. 1. 2D measurements in coronal and sagittal slices [14]. **Coronal view:** Measurements were taken at the level of the temporal horns of the lateral ventricles, cochlea, and arteria basilaris. Interhemispheric distance (IHD) was measured as the horizontal distance between the internal edges of the superior frontal gyri. Cerebral biparietal width (cBPW) was defined as the greatest transverse brain width and bone biparietal width (bBPW) as the maximum diameter between the internal margins of the skull. Ventricular index (VI) was defined as the distance between the falx cerebri and the lateral wall of the anterior horn; VI sum was calculated as right + left VI. The 3rd ventricle (V3) was measured at the level of this structure. Transverse cerebellar diameter (tCD) was obtained as the maximum diameter of the vermis at the level of the ventricular atria. **Sagittal view:** Fronto-occipital diameter (FOD) was defined as the distance between the extreme points of the frontal and occipital lobe. The 4th ventricle (V4) was evaluated between its floor and the median parts of its roof. The anteroposterior diameter (apVermis) corresponds to the greatest anteroposterior diameter of the vermis and the height of the vermis (hVermis) to its greatest height. Length of the corpus callosum (CC) was measured as the distance between genu and the posterior tip of the splenium.

Results

Study Group

During the 9-year study period, a total of 215 neonates born <32^{+0} weeks GA were diagnosed with IVH. Based on exclusion criteria, 141 were excluded: 71 death before follow-up, 25 no outcome data, 6 diagnosed with congenital anomalies, and 39 no MRI or >42^{+0} weeks GA at MRI. The final study cohort thus comprised a total of 74 patients with a median GA of 25^{+6} (24^{+4}–27^{+3}) weeks. Detailed descriptive data are summarized in Table 1. A total of 40 neonates (54.0%) developed posthemorrhagic ventricular dilatation; 36 (48.6%) required temporizing measures to decrease intracranial pressure, and of those, 27 (75.0%) required permanent decompression via ventriculoperitoneal shunt.

Brain Biometry

The reproducibility of measurements between observers was classified as very good (intraclass correlation coefficient >0.9). Therefore, mean values were used for further calculations. Z-score deviations of brain parameters in patients from controls are summarized in Table 2. cBPW, bBPW, FOD, and tCD were decreased by more than 2 SDs of the mean, IHD, and the 3rd ventricle by more than 1 SD in patients compared to literature controls. Compared to local controls, deviations above 1 SD

Table 1. Descriptive data of IVH patients and local controls

	IVH patients (n = 74)	Local controls (n = 58)	p value
Male	47 (63.5)	29 (50.0)	0.156
Inborn	**61 (82.4)**	**58 (100)**	**0.001****
Birth mode			**0.048***
Spontaneous delivery	**19 (25.7)**	**11 (19.0)**	
C-section	**44 (59.5)**	**45 (77.6)**	
Emergency C-section	**11 (14.9)**	**2 (3.4)**	
GA, weeks^{+days}	25^{+6} (24^{+4}–27^{+3})	26^{+2} (25^{+2}–27^{+4})	0.477
22^{+6}–25^{+6} weeks	37 (50.0)	23 (39.7)	0.880
26^{+0}–28^{+6} weeks	26 (35.1)	35 (60.3)	
29^{+0}–31^{+6} weeks	11 (14.9)	0 (0.0)	
Multiple birth	18 (24.3)	16 (27.6)	0.671
Measurements at birth			
Weight, g	843 (630–1000)	803 (686–985)	0.891
Weight percentile[1]	52 (32–69)	57 (36–75)	0.571
Length percentile[1]	54 (29–73)	53 (35–78)	0.829
Head circumference percentile[1]	60 (40–83)	56 (33–81)	0.475
APGAR score			
1 min	**7 (4–8)**	**8 (7–8)**	**<0.001****
5 min	**8 (7–9)**	**9 (8–9)**	**<0.001****
10 min	**9 (8–9)**	**9 (9–9)**	**0.037***
Umbilical cord pH	**7.31 (7.20–7.35)**	**7.34 (7.30–7.39)**	**0.003****
<7.0	**6 (10.0)**	**0 (0.0)**	**0.028***
First neonatal pH	7.15 (7.06–7.22)	7.16 (7.10–7.23)	0.127
<7.0	**12 (17.4)**	**1 (1.7)**	**0.004****
First neonatal lactate, mmol/L	**4.8 (3.5–7.7)**	**3.8 (2.7–4.8)**	**0.003****
≥10.0	**11 (16.2)**	**0 (0.0)**	**0.001****
Additional neonatal diagnoses			
Perinatal asphyxia	**17 (23.0)**	**3 (5.2)**	**0.005****
Blood-culture positive sepsis	**27 (36.5)**	**10 (17.2)**	**0.015***
Persistent ductus arteriosus[2]	8 (10.8)	4 (6.9)	0.438
Necrotizing enterocolitis[3]	6 (8.1)	5 (8.6)	1.000
Bronchopulmonary dysplasia[4]	26 (35.1)	17 (29.3)	0.479
Retinopathy of prematurity[5]	**14 (18.9)**	**3 (5.2)**	**0.019***
Periventricular leukomalacia or perinatal stroke	4 (5.4)	0 (0.0)	0.130
IVH grade (maximum)			
Grade I	4 (5.4)	–	–
Grade II	17 (23.0)	–	–
Grade III	31 (41.9)	–	–
Grade IV (periventricular hemorrhagic infarction)	22 (29.7)	–	–
Unilateral IVH	17 (23.0)	–	–
Bilateral IVH	57 (77.0)	–	–
Posthemorrhagic ventricular dilatation			
Yes, without intervention	4 (5.4)	–	–
Yes, with intervention	36 (48.6)	–	–
Temporizing intervention[6]	36 (48.6)	–	–
Permanent intervention (shunt)	27 (36.5)	–	–

Values are displayed as n (%) and median (IQR). Bold numbers indicate a statistically significant correlation (** $p < 0.01$ and * $p < 0.05$). GA, gestational age; IVH, intraventricular hemorrhage. [1] According to https://www.peditools.org/fenton2013/index.php. [2] Surgically treated. [3] Above Bell's stage 2. [4] Oxygen requirement at 36 weeks of postmenstrual age. [5] Stage 3 and above according to the International Classification. [6] Subcutaneously tunneled external ventricular drain or subcutaneous ventricular reservoir/Ommaya.

Table 2. *Z*-scores of brain parameters (*n* = 74)

	Compared to literature controls		Compared to local controls	
	Median	IQR	Median	IQR
IHD	+1.60	+0.30 to +2.51	+1.27	+0.06 to +2.72
cBPW	−2.16	−2.76 to −1.42	−0.27	−1.01 to +0.46
bBPW	−2.23	−2.91 to −1.52	−0.11	−0.81 to +0.54
FOD	−2.59	−3.96 to −1.07	−0.51	−1.26 to +0.35
hVermis	+0.36	−0.62 to +0.82	−0.19	−1.10 – +0.98
apVermis	−0.82	−1.63 to −0.03	−0.21	−1.47 to +0.51
tCD	−2.25	−3.54 to −1.16	−0.89	−2.17 to −0.02
Corpus callosum	−0.92	−1.84 to −0.11	−0.89	−2.14 to +0.52
3rd ventricle	+1.18	−0.31 to +3.02	+4.16	+0.73 to +8.18
4th ventricle	+0.79	−0.29 to +1.70	−0.10	−0.95 to +1.34
Right VI	[1]	[1]	+0.46	−0.06 to +1.47
Left VI	[1]	[1]	+1.08	+0.23 to +2.79
VI sum	[1]	[1]	+0.80	+0.19 to +2.68

[1] *Z*-score calculation was not possible due to lack of comparison values in the literature group. IHD, interhemispheric distance; cBPW, cerebral biparietal width; bBPW, bone biparietal width; FOD, fronto-occipital diameter; hVermis, height of the vermis; apVermis, anteroposterior diameter of the vermis; tCD, transverse cerebellar diameter; VI, ventricular index.

were only present for IHD, 3rd ventricle, as well as left ventricular index (VI).

A total of 67 (90.5%) neonates with IVH showed some form of impaired brain growth when compared to literature controls and 38 (51.4%) when compared to local controls. With regard to literature/local controls, the increased IHD pattern was observed in 28 (38.4%)/25 (34.2%), the small cBPW pattern in 46 (63.9%)/3 (4.2%), and both patterns first described by Kidokoro et al. [15] in 16 (21.6%)/2 (2.7%) neonates. Also, the small FOD pattern was present in 42 (56.8%)/10 (13.5%) and the small tCD pattern in 42 (56.8%)/20 (27.0%) neonates, respectively. No significant difference in the percentage of impaired brain growth was observed between groups of different IVH severity (IVH grade I+II vs. III+IV) as well as between uni- and bilateral IVH (online suppl. Table 1; see www.karger.com/doi/10.1159/000528981 for all online suppl. material). However, neonates with posthemorrhagic ventricular dilatation and neurosurgical intervention presented with the small FOD pattern four times more frequently than in the absence of ventricular dilatation (online suppl. Table 1).

Neurodevelopmental Outcome

Bayley-III values were available at 2 and/or 3 years of age in 73 patients (98.6%). Correlations of z-scores with cognitive, language, and motor outcomes at 2 and 3 years of age are summarized in Table 3. Several parameters showed significant correlations with cognitive, language, and motor composite scales, namely, FOD, anteroposterior diameter of the vermis (apVermis), tCD, corpus callosum, 3rd ventricle, as well as right and left VI. Significant results across all outcome domains were seen for the 3rd ventricle compared to literature controls and the apVermis, 3rd ventricle, and left VI compared to local controls.

Patients with the increased IHD pattern achieved significantly lower language scores at 3 years compared to local controls without any pattern of impaired brain growth and significantly lower outcome scores across all outcome domains at 3 years of age compared to local controls. Patients with the small FOD pattern reached significantly lower cognitive and motor scores at 2 and 3 years and significantly lower language scores at 2 years of age compared to literature controls. The same was true for cognitive and motor outcomes at 2 years, regarding local controls. Median outcome scores of patients presenting with different patterns of impaired brain growth are summarized in online supplementary Table 2.

Results of multivariable regression analysis, evaluating brain parameters and patterns of impaired brain growth in relation to neurodevelopmental outcome at 2 and 3 years of age, are shown in Table 4. Models were corrected for GA, birth weight, and degree of IVH; birth weight did not contribute to any model. Compared to literature controls, cognitive outcome was only associated with the degree of IVH

Table 3. Correlation of brain parameter *z*-scores (ZS) with neurodevelopmental outcome ($n = 74$)

	Correlation with Cognitive Composite Scale		Correlation with Language Composite Scale		Correlation with Motor Composite Scale	
	2 years	3 years	2 years	3 years	2 years	3 years
Literature controls						
IHD ZS	0.054	−0.135	−0.067	−0.255	0.044	−0.078
cBPW ZS	−0.182	−0.209	−0.077	−0.202	−0.159	−0.104
bBPW ZS	−0.099	−0.186	−0.043	−0.186	−0.052	−0.041
FOD ZS	**0.345****	**0.347***	**0.359****	0.253	**0.422****	**0.419****
hVermis ZS	0.304	0.191	0.192	0.431	0.317	0.128
apVermis ZS	0.318	0.106	0.257	0.146	**0.422***	**0.614***
tCD ZS	**0.311****	0.222	0.227	0.134	**0.331****	**0.274***
Corpus callosum ZS	**0.240***	**0.096**	0.147	−0.026	**0.326****	**0.368****
3rd ventricle ZS	**−0.277***	**−0.389****	**−0.264***	**−0.396****	**−0.293***	**0.346***
4th ventricle ZS	−0.297	−0.148	−0.334	−0.135	−0.135	−0.147
Local controls						
IHD ZS	0.060	−0.147	−0.068	−0.248	0.047	−0.078
cBPW ZS	−0.144	−0.196	−0.046	−0.144	−0.116	−0.110
bBPW ZS	−0.049	−0.130	−0.005	−0.064	0.006	−0.012
FOD ZS	**0.277***	**0.281***	**0.341****	0.262	**0.359****	**0.381****
hVermis ZS	0.004	−0.093	−0.025	0.000	−0.030	0.013
apVermis ZS	**0.301****	**0.298***	**0.334****	**0.347***	**0.339****	**0.444****
tCD ZS	0.207	0.032	0.180	0.122	0.218	0.181
Corpus callosum ZS	**0.243***	0.076	0.143	−0.018	**0.285***	**0.348***
3rd ventricle ZS	**−0.278***	**−0.403****	**−0.259***	**−0.415****	**−0.295***	**−0.356****
4th ventricle ZS	−0.223	**−0.289***	**−0.244***	**−0.344***	−0.042	−0.026
Right VI ZS	−0.224	**−0.320***	−0.154	−0.201	−0.225	−0.244
Left VI ZS	**−0.314****	**−0.304***	**−0.267***	**−0.319***	**−0.350****	**−0.367****
VI sum ZS	−0.160	−0.239	−0.157	−0.228	−0.195	−0.248

Correlation coefficients of *z*-scores of brain measurements with outcome at 2 and 3 years of age. Pearson correlation coefficient (PCC) or Spearman's rank correlation coefficient (Spearman's ρ) was applied as appropriate. Bold numbers indicate a statistically significant correlation (** $p < 0.01$ and * $p < 0.05$). IHD, interhemispheric distance; cBPW, cerebral biparietal width; bBPW, bone biparietal width; FOD, fronto-occipital diameter; hVermis, height of the vermis; apVermis, anteroposterior diameter of the vermis; tCD, transverse cerebral diameter; VI, ventricular index; ZS, *z*-score

at 2 years ($R^2 = 0.378$), whereas language performance was associated with the corpus callosum at 2 years ($R^2 = 0.163$), and tCD at 3 years of age ($R^2 = 0.440$). Motor outcome was related to the degree of IVH at 2 years ($R^2 = 0.212$), and additionally to GA and apVermis at 3 years of age ($R^2 = 0.726$). Compared to local controls, cognitive outcome was associated with the degree of IVH, FOD, and 4th ventricle at 2 years ($R^2 = 0.321$) and the 3rd ventricle at 3 years of age ($R^2 = 0.104$). Language outcome was related to the degree of IVH, FOD, and apVermis at 2 years ($R^2 = 0.238$) and 3rd ventricle and the presence of the increased IHD pattern at 3 years of age ($R^2 = 0.230$). Motor performance was associated with the degree of IVH, FOD, and 4th ventricle at 2 years ($R^2 = 0.376$) and with the degree of IVH, FOD, apVermis, and VI sum at 3 years of age ($R^2 = 0.473$).

Discussion

Our study expands the understanding of brain injury and impaired brain growth in very preterm infants with IVH using biometrical analysis based on conventional MRI at term-equivalent age. Preterm birth and cerebral hemorrhage are known to have adverse effects on brain development. Several studies investigated alterations in brain growth in patients with or without neurodevelopmental impairment as well as with or without brain injury [7, 15]. They have shown a decrease in total brain volume accompanied by increased ventricular sizes and cerebrospinal fluid volumes compared to neurologically healthy controls. These alterations appear to be prominent in most prematurely born infants [7–9, 12, 16–18].

Table 4. Multivariable linear regression (n = 74)

	B (95% CI)	SE	β	p value	Corrected R^2
Literature controls					
2 years					
Cognitive Composite Scale					
(Constant)	134.4 (103.2–165.6)	15.0			0.378
Maximum IVH grade	−19.5 (−30.2 to −8.8)	5.1	−0.64	**0.001****	
Language Composite Scale					
(Constant)	61.4 (48.8–74.0)	6.1			0.163
Corpus callosum ZS	−13.8 (−26.3 to −1.3)	6.0	−0.45	**0.032***	
Motor Composite Scale					
(Constant)	105.8 (79.1–132.4)	12.8			0.212
Maximum IVH grade	−11.6 (−20.7 to −2.4)	4.4	−0.50	**0.016***	
3 years					
Cognitive Composite Scale					
Language Composite Scale					
(Constant)	80.7 (69.1–92.3)	5.3			0.440
tCD ZS	11.9 (3.8–20.0)	3.7	0.70	**0.008****	
Motor Composite Scale					
(Constant)	−7.5 (−94.8 to 79.8)	39.2			0.726
GA	4.3 (0.6–7.9)	1.6	0.44	**0.026***	
Maximum IVH grade	−10.5 (−15.7 to −5.4)	2.3	−0.74	**0.001****	
apVermis ZS	11.2 (6.0–16.3)	2.3	0.75	**0.001****	
Local controls					
2 years					
Cognitive Composite Scale					
(Constant)	112.0 (96.0–128.1)	8.0			0.321
Maximum IVH grade	−12.3 (−17.5 to −7.0)	2.6	−0.48	**<0.001****	
FOD ZS	5.7 (2.0–9.3)	1.8	0.33	**0.003****	
4th ventricle ZS	−2.0 (−3.4 to −0.6)	0.7	−0.30	**0.005****	
Language Composite Scale					
(Constant)	99.9 (81.1–118.7)	9.4			0.238
Maximum IVH grade	−9.1 (−15.2 to −2.9)	3.1	−0.33	**0.005****	
FOD ZS	5.7 (1.4–10.1)	2.2	0.30	**0.011***	
apVermis ZS	3.6 (0.3–6.9)	1.7	0.25	**0.034***	
Motor Composite Scale					
(Constant)	104.5 (90.7–118.4)	6.9			0.376
Maximum IVH grade	−11.0 (−15.6 to −6.5)	2.3	−0.48	**<0.001****	
FOD ZS	6.5 (3.4–9.7)	1.6	0.42	**<0.001****	
4th ventricle ZS	−1.9 (−3.1 to −0.7)	0.6	−0.31	**0.003****	
3 years					
Cognitive Composite Scale					
(Constant)	79.1 (73.4–84.9)	2.9			0.104
3rd ventricle ZS	−0.6 (−1.1 to −0.1)	0.2	−0.35	**0.016***	
Language Composite Scale					
(Constant)	76.6 (69.9–83.2)	3.3			0.230
3rd ventricle ZS	−0.6 (−1.2 to −0.1)	0.3	−0.34	**0.015***	
Increased IHD pattern	−16.9 (−29.6 to −4.2)	6.3	−0.36	**0.010***	
Motor Composite Scale					
(Constant)	89.6 (77.5–101.7)	6.0			0.473
Maximum IVH grade	−7.0 (−11.0 to −3.0)	2.0	−0.41	**0.001****	
FOD Z	4.7 (1.8–7.6)	1.4	0.39	**0.002****	
apVermis ZS	3.5 (1.2–5.9)	1.2	0.35	**0.004****	
VI sum ZS	−1.9 (−3.5 to −0.4)	0.8	−0.29	**0.015***	

Stepwise multivariable linear regression analysis of brain parameters and patterns of impaired brain growth at 2 and 3 years of age after adjustment for gestational age, birth weight, and degree of IVH. B values are displayed as median (IQR). IVH, intraventricular hemorrhage; tCD, transverse cerebral diameter; GA, gestational age; apVermis, anteroposterior diameter of the vermis; FOD, fronto-occipital diameter; IHD, interhemispheric distance; VI, ventricular index; ZS, z-score.

Similarly to our study, IHD, the 3rd ventricle, and lateral ventricles presented larger, whereas cBPW, bBPW, FOD, and corpus callosum were smaller in IVH patients compared to controls, representing reduced total brain sizes and enlarged pericerebral spaces in extremely preterm neonates with IVH [15, 19, 20].

During the last decade, special attention was given to changes in the cerebellum regarding volume, signal abnormality, and water diffusion [7, 15, 20–22]. Our patients also presented with reduced cerebellar sizes, tCD showing the greatest decrease while apVermis and hVermis not distinctively differing from the mean of controls. As pointed out by Volpe, there is a particular vulnerability of the cerebellum in the extremely premature neonate, leading to cerebellar "underdevelopment" – a condition in which the cerebellum does not reach its full size due to disrupted growth or secondary to direct hemorrhagic lesions to the cerebellar parenchyma [23, 24]. The rapid growth in late gestation might make the cerebellum particularly susceptible in preterm infants [23, 25]. Tam et al. [21] used semi-automated tools and speculated that volume reduction following IVH may be caused by both simultaneous cerebellar injury and direct impact of subarachnoid blood on cerebellar growth and development.

Parameter differences represented by higher (both positive and negative) z-scores are overall more significant between our study group and literature controls, as the effect of prematurity is neglected/not taken into account in this comparison. This is in line with previously published data, suggesting compromised cerebral growth in preterm infants even in the absence of perinatal brain injury [7–9, 12, 16–18], and underlines the differing intrauterine and extrauterine cerebral growth rates.

IVH and subsequent white matter injury as well as alterations in cerebral and cerebellar growth have been recognized as a major cause of long-term neurodevelopmental delay [11, 18, 25]. The highest percentage of impairment can be observed in the most premature patients with the lowest GA and highest degree of IVH [6]. Global intellectual, language, and motor performance in our patients indicated a mild to moderate neurodevelopmental delay in early childhood with a strong correlation, especially for the parameters FOD, apVermis, tCD, corpus callosum, 3rd ventricle, and left VI.

Our multivariable linear regression analyses confirmed that cognitive, language, and motor outcomes are highly associated with the degree of IVH, reduced cerebral and cerebellar sizes, and increased ventricular sizes. Overall stronger correlations (higher R^2) values were observed for motor when compared to cognitive and language outcome scores. Interestingly, most of the measured structures are remote from the origin of the primary IVH lesion, namely, the thalamocaudate groove/germinal matrix of the lateral ventricles, emphasizing the global impact of IVH on neonatal brain development.

FOD, apVermis, the 3rd ventricle and left VI showed significant correlations with cognitive, language, and motor outcomes at both timepoints of testing compared to local controls. For the corpus callosum, significant correlations with motor outcomes were observed, while the 4th ventricle showed significant correlations with language outcomes at both timepoints.

Also, several brain patterns and their associations with neurodevelopmental outcomes were analyzed. The small BPW pattern as well as the small FOD pattern reflect reduced cerebral growth in total, whereas the small tCD pattern reflects a reduction in cerebellar growth. The increased IHD pattern represents insufficient cerebral growth in relation to the skull, resulting in increased extracerebral spaces. Compared to literature controls, different patterns of impaired brain growth were found in 38.4–63.9% of the study cohort. Using our local cohort of neurologically healthy preterm infants without IVH and subsequently taking prematurity into account, the respective percentages decreased to 4.2–34.2%.

The most common pattern of impaired brain growth compared to literature controls was the small cBPW pattern (63.9%), which was only present in 4.2% when compared to local controls. Hence, this pattern appears to be equally present in preterm neonates with and without brain injury and does not seem to be specifically related to IVH. In contrast, the increased IHD pattern showed quite similar percentages (38.4 and 34.2%) when compared to both literature and local controls, underlining the association with the diagnosis of IVH.

Patients with the small FOD pattern reached overall lower outcome scores at follow-up compared to those without any pattern of impaired brain growth (literature controls). This parameter could be additionally useful to better assess long-term neurodevelopmental impairments after IVH. Also, presence of the increased IHD pattern was associated with lower outcome scores across all outcome domains at 3 years of age (local controls). These results support the finding by Kidokoro et al. [15] that the existence of impaired brain growth leads to a poorer neurodevelopmental outcome in early childhood. The lack of association regarding the small BPW pattern has to be interpreted with caution as this pattern was only present in three patients when compared to local controls.

3D volumetric analysis is considered the gold standard to quantify cerebral volume. Therefore, the primary limitation of this work is the use of biometrical analyses. These 2D measurements of brain parameters have been chosen to circumvent complex postprocessing and have been proven to accurately correlate with 3D volumetry [12]. Most likely, automated super-resolution neonatal brain segmentation techniques will achieve a sufficiently elaborate clinical utility and practicability and, by that, an even more detailed and sensitive quantitative assessment of brain development. However, for now, we believe that the combination of simple and easily applicable 2D measurements, which can be performed in less than two minutes per case seems to provide sufficient prognostic information.

Even though there is no significant difference between GA at birth between groups, a skewed distribution can be appreciated in Table 1. This is due to our institutional policy with regard to routine MRI.

The comparison with different control groups is a strength of the present study, as it allows differentiation between the effects of prematurity and the effects of the bleeding itself. The neurologically healthy preterm cohort (local controls) has the advantage of minimizing confounding factors since patients were treated and followed up at the same department and MRI scans were acquired at the same scanner following the same protocol. Also, biometrical analysis was performed by the same raters. The evaluation of a large number of brain parameters as well as the introduction of new patterns of impaired brain growth represents another strength of the present study.

Conclusion

Neonatal brain injury has a major influence on the cerebral growth and neurodevelopment of preterm infants in early childhood. Biometric analysis revealed reduced total cerebral and cerebellar sizes accompanied by enlarged pericerebral spaces at term-equivalent age after IVH. The 2D data presented in the current study show a strong correlation between several brain parameters (FOD, apVermis, tCD, corpus callosum, 3rd ventricle, left VI) as well as a pattern of impaired brain growth (small FOD pattern) and neurodevelopmental impairment in early childhood. These findings need to be confirmed using 3D volumetric analysis and may thereafter support prognostication and parental counseling after IVH in clinical practice.

Statement of Ethics

This study was approved by the Ethics Commission of the Medical University of Vienna (EK 1968/2017) and conducted in accordance with the Declaration of Helsinki. Written informed consent from participants was not required in accordance with national guidelines (retrospective study).

Conflict of Interest Statement

The authors have no conflicts of interest relevant to this article to disclose. The authors have no financial relationships relevant to this article to disclose.

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Author Contributions

Conceptualization/design and methodology: Katharina Goeral, Gregor Kasprian, and Katrin Klebermass-Schrehof. Investigation: Mirjam Steiner, Hannah Schwarz, Gregor Kasprian, Victor Schmidbauer, and Renate Fuiko. Supervision/oversight: Monika Olischar, Katrin Klebermass-Schrehof, Angelika Berger, and Katharina Goeral. Data curation: Mirjam Steiner, Hannah Schwarz, Gregor Kasprian, Judith Rittenschober-Boehm, Victor Schmidbauer, Renate Fuiko, and Katharina Goeral. Formal analysis: Mirjam Steiner, Hannah Schwarz, Gregor Kasprian, Judith Rittenschober-Boehm, Victor Schmidbauer, Renate Fuiko, Monika Olischar, Katrin Klebermass-Schrehof, Angelika Berger, and Katharina Goeral. Resources: Angelika Berger.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Gilard V, Tebani A, Bekri S, Marret S. Intraventricular hemorrhage in very preterm infants: a comprehensive review. J Clin Med. 2020;9(8):2447.
2 Benders MJNL, Kersbergen KJ, de Vries LS. Neuroimaging of white matter injury, intraventricular and cerebellar hemorrhage. Clin Perinatol. 2014;41(1):69–82.
3 Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med. 2006;355(7):685–94.

4 Smyser CD, Kidokoro H, Inder TE. Magnetic resonance imaging of the brain at term equivalent age in extremely premature neonates: to scan or not to scan? J Paediatr Child Health. 2012;48(9):794–800.
5 Mirmiran M, Barnes PD, Keller K, Constantinou JC, Fleisher BE, Hintz SR, et al. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. Pediatrics. 2004;114(4):992–8.
6 Goeral K, Kasprian G, Hüning BM, Waldhoer T, Fuiko R, Schmidbauer V, et al. A novel magnetic resonance imaging-based scoring system to predict outcome in neonates born preterm with intraventricular haemorrhage. Dev Med Child Neurol. 2022;64(5):608–17.
7 Lind A, Parkkola R, Lehtonen L, Munck P, Maunu J, Lapinleimu H, et al. Associations between regional brain volumes at term-equivalent age and development at 2 years of age in preterm children. Pediatr Radiol. 2011;41(8):953–61.
8 Vasileiadis GT, Gelman N, Han VKM, Williams LA, Mann R, Bureau Y. Uncomplicated intraventricular hemorrhage is followed by reduced cortical volume at near-term age. Pediatrics. 2004;114(3):e367–72.
9 Setänen S, Lehtonen L, Parkkola R, Aho K, Haataja L; PIPARI Study Group. Prediction of neuromotor outcome in infants born preterm at 11 years of age using volumetric neonatal magnetic resonance imaging and neurological examinations. Dev Med Child Neurol. 2016;58(7):721–7.
10 Nosarti C, Al-Asady MHS, Frangou S, Stewart AL, Rifkin L, Murray RM. Adolescents who were born very preterm have decreased brain volumes. Brain. 2002;125(Pt 7):1616–23.
11 Tich SNT, Anderson PJ, Hunt RW, Lee KJ, Doyle LW, Inder TE. Neurodevelopmental and perinatal correlates of simple brain metrics in very preterm infants. Arch Pediatr Adolesc Med. 2011;165(3):216–22.
12 Nguyen The Tich S, Anderson PJ, Shimony JS, Hunt RW, Doyle LW, Inder TE. A novel quantitative simple brain metric using MR imaging for preterm infants. AJNR Am J Neuroradiol. 2009;30(1):125–31.
13 Garel C, Delezoide A, Guibaud L, Sebag G, Gressens P, Hassan M, et al. MRI of the fetal brain. Springer-Verlag Berlin Heidelberg; 2004.
14 Buchmayer J, Kasprian G, Giordano V, Schmidbauer V, Steinbauer P, Klebermass-Schrehof K, et al. Routine use of cerebral magnetic resonance imaging in preterm infants born <28 weeks. J Pediatr. 2022 Jun 20;(22):S002200485-34761. https://doi.org/10.1016/j.jpeds.2022.05.033.
15 Kidokoro H, Anderson PJ, Doyle LW, Woodward LJ, Neil JJ, Inder TE. Brain injury and altered brain growth in preterm infants: predictors and prognosis. Pediatrics. 2014;134(2):e444–53.
16 Woodward LJ, Clark CAC, Bora S, Inder TE. Neonatal white matter abnormalities an important predictor of neurocognitive outcome for very preterm children. PLoS One. 2012;7(12):e51879.
17 Graca AM, Cardoso KR, da Costa JM, Cowan FM. Cerebral volume at term age: comparison between preterm and term-born infants using cranial ultrasound. Early Hum Dev. 2013;89(9):643–8.
18 Keunen K, Kersbergen KJ, Groenendaal F, Isgum I, de Vries LS, Benders MJ. Brain tissue volumes in preterm infants: prematurity, perinatal risk factors and neurodevelopmental outcome: a systematic review. J Matern Fetal Neonatal Med. 2012;25(Suppl 1):89–100.
19 Roelants JA, Koning IV, Raets MM, Willemsen SP, Lequin MH, Steegers-Theunissen RP, et al. A new ultrasound marker for bedside monitoring of preterm brain growth. AJNR Am J Neuroradiol. 2016;37(8):1516–22.
20 Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol. 2013;34(11):2208–14.
21 Tam EWY, Miller SP, Studholme C, Chau V, Glidden D, Poskitt KJ, et al. Differential effects of intraventricular hemorrhage and white matter injury on preterm cerebellar growth. J Pediatr. 2011;158(3):366–71.
22 Sancak S, Gursoy T, Karatekin G, Ovali F. Effect of intraventricular hemorrhage on cerebellar growth in preterm neonates. Cerebellum. 2017;16(1):89–94.
23 Volpe JJ. Cerebellum of the premature infant: rapidly developing, vulnerable, clinically important. J Child Neurol. 2009;24(9):1085–104.
24 Messerschmidt A, Brugger PC, Boltshauser E, Zoder G, Sterniste W, Birnbacher R, et al. Disruption of cerebellar development: potential complication of extreme prematurity. AJNR Am J Neuroradiol. 2005;26(7):1659–67.
25 Tam EWY, Ferriero DM, Xu D, Berman JI, Vigneron DB, Barkovich AJ. Cerebellar development in the preterm neonate: effect of supratentorial brain injury. Pediatr Res. 2009;66(1):102–6.