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ORIGINAL ARTICLE

Associations between regional brain volumes at term-equivalent age and development at 2 years of age in preterm children

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Abstract
Background Altered brain volumes and associations between volumes and developmental outcomes have been reported in prematurely born children.
Objectives To assess which regional brain volumes are different in very low birth weight (VLBW) children without neurodevelopmental impairments ([NDI] cerebral palsy, hearing loss, blindness and significantly delayed cognitive performance) compared with VLBW children with NDI, and to evaluate the association between regional brain volumes at term-equivalent age and cognitive development and neurological performance at a corrected age of 2 years.
Materials and methods The study group consisted of a regional cohort of 164 VLBW children, divided into one group of children without NDI (n=148) and one group of children with NDI (n=16). Brain (MRI) was performed at term-equivalent age, from which brain volumes were manually analysed. Cognitive development was assessed with the Bayley Scales of Infant Development II (BSID-II), and neurological performance with the Hammersmith Infant Neurological Examination at the corrected age of 2 years.
Results The volumes of total brain tissue, cerebrum, frontal lobes, basal ganglia and thalami, and cerebellum were significantly smaller, and the volume of the ventricles significantly larger, in the children with NDI than in those without NDI. Even in children without NDI, a smaller cerebellar volume was significantly correlated with poor neurological performance at 2 years of corrected age.
Conclusion Volumetric analysis at brain MRI can provide an additional parameter for early prediction of outcome in VLBW children.

Keywords Prematurity · Brain volumes · Developmental outcome · MRI

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Introduction

It is well documented that prematurity increases the risk of brain abnormality and developmental problems. Alongside discrete brain lesions, there is growing interest in the significance of altered regional brain volumes in preterm infants. There are several reports of associations between altered volumes and developmental outcome [1–5].

In studies of the associations between altered brain volumes at term-equivalent age and later developmental outcome in prematurely born infants, reduced cortical and deep nuclear gray matter, and increased cerebrospinal fluid (CSF) volumes have shown to be associated with neurodevelopmental disability at 1 year of corrected age [1]. Reductions of white matter volumes of the sensorimotor and midtemporal regions have in turn been linked to low mental developmental indices at a corrected age of 18-20 months [2]. Further, a reduced cerebellar volume has been suggested to correlate with abnormal cognitive and motor development at 2 years of age [3], and reduced inferior occipital regional volumes have appeared to be associated with impaired visual function at 2 years of corrected age [4]. It has also been reported that the volumes of several regions at term-equivalent age are related to memory functions at the age of 2 years [5].

Correlations between volumes and developmental state have also been found later in childhood and in adolescence, when volumetric analysis and developmental assessment have been performed simultaneously [6–16]. However, other studies have failed to demonstrate statistically significant relationships between volumes and outcome [17].

Our aim was to evaluate whether volumetric analysis at brain (MRI) may be used as an additional predictive tool. Specifically, we assessed the differences in regional brain volumes of very low birth weight (VLBW) children with and without neurodevelopmental impairments (NDI). Secondly, we analysed the relationship between total and regional brain volumes at term-equivalent age, and cognitive development and neurological performance at 2 years of corrected age in the VLBW children without NDI. We hypothesised a correlation between smaller volumes and poorer development in VLBW infants.

Materials and methods

Participants

This study is part of a multidisciplinary, longitudinal research project PIPARI (Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age). The study sample consisted of VLBW children born 2001–2006 in Turku University Hospital, Turku, Finland. Inclusion criteria for this study were: (1) infant weight <1,501 g and gestational age <37 weeks at birth, (2) the family spoke Finnish, Swedish or both, and (3) the family lived within the hospital catchment area. Exclusion criteria were: (1) the infant died in the neonatal period (n=42), and (2) major congenital anomalies, recognised syndromes or known chromosomal abnormalities (n=2). Of the 195 children who were eligible for the study, 12 families refused to take part or dropped out, and 19 children did not have complete datasets for this study. The final study population consisted of 164 VLBW children.

Written consent was obtained from the parents after oral and written information. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of the South-West Finland in December 2000.

Serial cranial ultrasound

Brain pathology was classified based on serial cranial ultrasound for later use as an independent variable. Ultrasound examinations were performed for all preterm infants at 3-5 days, at 7-10 days, at 1 month old, monthly thereafter until discharge from hospital and at term-equivalent age. A 7-MHz vector transducer (Sonos 5500 Hewlett-Packard, Andover, MA, USA) was used for the examinations before term-equivalent age. The cranial ultrasound examination at term-equivalent age was performed with a 7.5-MHz vector transducer (Aloka SSD 2000, Aloca Co., Tokyo, Japan) in the period January 2001 to August 2002, and with an 8-MHz vector transducer (General Electric Logic 9) thereafter by a paediatric radiologist.

The classification of intraventricular haemorrhage (IVH; grades I to IV) was done according to Papile et al. [18]. Multiple cysts with typical location were classified as cystic periventricular leukomalacia (PVL) [19]. Ventriculomegaly was defined according to the reference values for VLBW infants at term introduced by Virkola [20]. The infants were categorised into three groups according to the most pathological finding at brain ultrasound: (1) normal (no, or minor, abnormalities such as germinal layer/plexus cysts, subependymal pseudocysts or calcifications only), (2) mildly abnormal (IVH grade I/II, PVL I, germinal layer necrosis or a combination of these features), and (3) severely abnormal (IVH grade III/IV, cystic PVL II/III, thalamic lesion, focal infarction, convexity haemorrhage or a combination of these). This classification was used as an independent variable in regression analysis. The division into these groups was done according to Rademaker et al. [21].

MRI

An MRI study of the brain was performed at term-equivalent age on the same day as the ultrasound examination. The imaging took place during postprandial sleep without pharmacological sedation or anaesthesia. Ear protection was used (3M Disposable Ear Plugs 1100, 3M, Brazil and Würth Hearing protector, Würth, Austria). The first 111 infants were scanned with an open 0.23-Tesla Outlook GP scanner (Philips Medical, Vantaa, Finland) and the following 53 infants with a 1.5-Tesla Philips Intera

scanner (Philips Medical Systems, Best, The Netherlands). Any information regarding brain lesions found at MRI was not used for further analysis as the upgrading of the equipment might have resulted in noncomparable findings between the first and the last included patients.

For volume measurements, at 0.23 T we obtained a T1-weighted field echo sequence with the following parameters: repetition time (TR), 30 ms; echo time (TE), 10 ms; flip angle, 45° degrees; slice thickness, 5 mm; field of view (FOV), 220×220 mm^2; matrix, 256×256; and 24 slices covering the whole brain in the coronal plane. At 1.5 T, we acquired a coronal inversion recovery (IR) sequence with the following parameters: TR/TE, 3,500/15 ms; inversion time (TI), 400 ms; flip angle, 90°; slice thickness, 4.8 mm; FOV, 180×180 mm^2; matrix, 256×256; and 24 slices covering the whole brain. The sequences were optimised relative to the age of the infants and the field strength of the equipment used.

The volume measurements were performed on a GE workstation (GE AW1.0, GE Medical Systems, Milwaukee, WI USA) by one neuroradiologist (R.P.). The coronal T1-weighted images were loaded into Functool 1.0 post-processing software (GE Medical Systems, Milwaukee, WI USA). Volume measurement was performed manually, separating cerebrospinal fluid and the skull from the brain tissue image by image (Fig. 1). Anatomical differentiation of the brain areas was based both on anatomical landmarks and on signal intensity differences of the brain structures. In addition to total brain volume (total brain volume minus ventricle volume), the regional brain volumes measured were cerebral volume, cerebellar volume, frontal lobe volume, the combined volume of the medulla oblongata and the pons, and the combined volume of the basal ganglia and thalami. These areas were chosen because they were clearly definable. The cerebellar volume included the cerebellar hemispheres, the vermis and the cerebellar peduncles. The frontal lobes included the area anterior to the central sulcus. The pons and medulla oblongata were delineated together with the upper border of this area being the lower border of mesencephalon, and the lower border the junction between the medulla oblongata and cervical spinal cord. The basal ganglia and thalami were measured as a block and the anatomical border between these basal gray matter nuclei and unmyelinated deep white matter was easily delineated by visual inspection. The medial border of the basal ganglia and thalami was formed by the third

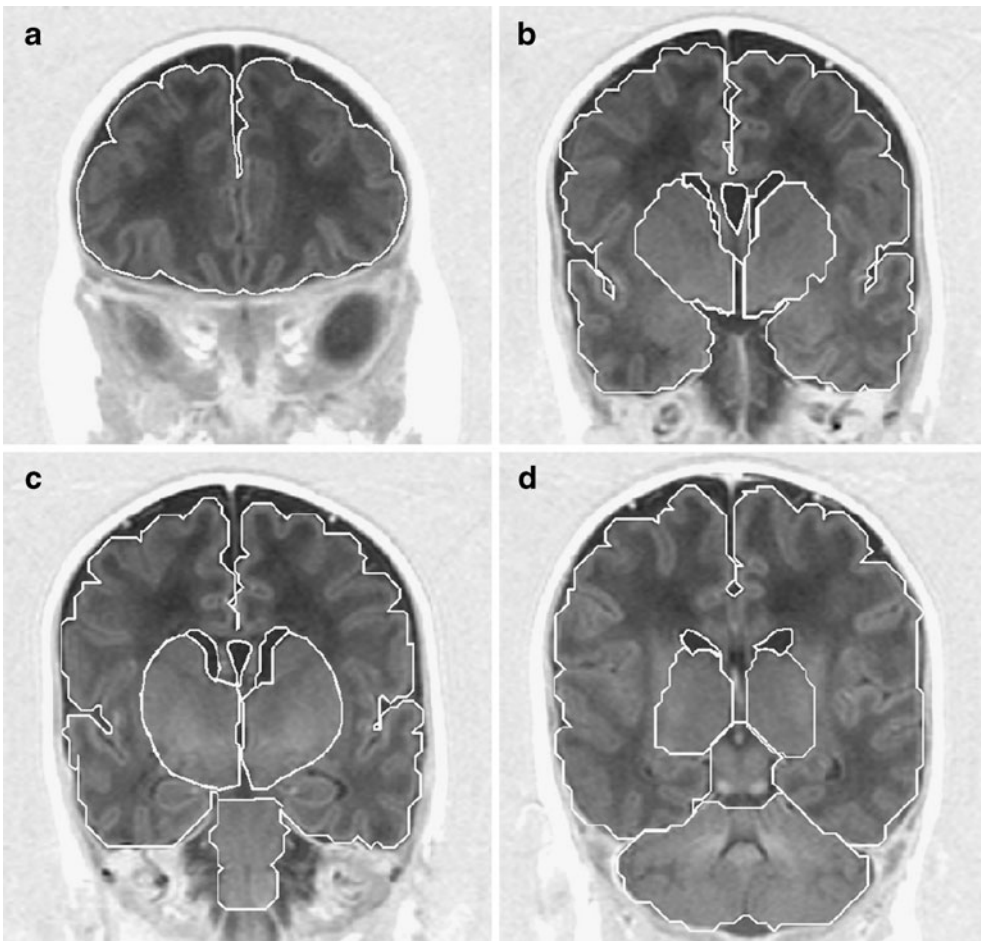

Fig. 1 Coronal section at 1.5-Tesla MRI with manual delineation of different brain structures based on anatomical landmarks. **a** The total brain volume included the gray and white matter, excluding the ventricles and the extra-axial fluid spaces. Frontal lobes included the area anterior to central sulcus. **b-d** The basal ganglia and thalami and the pons and medulla oblongata were measured as one block

ventricle, the lateral border by the external capsule and the inferior border by the upper border of the mesencephalon.

One neuroradiologist performed the brain volume measurements in all the children in this study. The reproducibility of these measurements was assessed by repeated brain volume measurement in 20 children performed by a second neuroradiologist who was masked to the prior measurement.

Bayley Scales of Infant Development II

Cognitive development was assessed using the Bayley Scales of Infant Development, 2nd edition (BSID-II) [22]. The mental developmental index (MDI) was determined. A psychologist performed the examination at a corrected age of 2 years (range, 1 year 51 weeks to 2 years 1 month). The psychologist was masked to the results of the volumetric analyses. In accordance with the BSID-II norms, an MDI ≥85 or above was considered normal, 70-84 mildly delayed and ≤69 (−2 SD) significantly delayed cognitive performance.

Neurological examination

Neurological status was assessed with the Hammersmith Infant Neurological Examination [23], which is a reliable method for assessing neurological findings in preterm and term infants [24–27]. It includes 37 items in three sections. The first section assesses neurological signs; the second, development of motor functions; and the third, the state of behaviour. Each item can be scored separately, and a global score (0—78) is the sum of all individual items. The optimal score is based on the frequency distribution of the scores in a normal low-risk, term-born population at 12 and 18 months of age. Optimal score at 12 months is a global score ≥73, and at 18 months and onwards ≥74; lower scores are regarded as suboptimal in term-born infants [23]. Because the optimal scores for preterm infants at 2 years of age have not been published, we used the total scores as a continuous variable in this study. Two physicians or one physiotherapist trained to use the examination performed the neurological assessment at 2 years of corrected age in all infants. The scorers were masked to the results from the volumetric analyses. A paediatric neurologist confirmed all diagnoses of cerebral palsy (CP), blindness and hearing loss (defined by the use of a hearing aid). CP, when present, was defined using the classification proposed by Himmelmann et al. [28, 29]. NDI included CP, cognitive impairment (MDI <70), hearing loss and blindness.

Statistical analysis

Statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, N.C.). A p value<0.05 was considered statistically significant. The intraclass correlation coefficient [1, 2] was calculated to describe the interobserver reliability [30] between two neuroradiologists for volume measurements. Before data analysis, positively skewed variables (ventricle and brain stem volumes) were log-transformed. Associations between brain volumes and the categorical outcome variable (presence or absence of NDI) were studied using univariate logistic regression. Continuous demographic variables were compared between infants with or without NDI using independent samples t-tests. Comparisons between two categorical variables were done using chi-square tests.

The following analyses were done only for children without NDI, as the group of children with NDI was too small for meaningful multiple regression analysis. The demographic variables included in the statistical analysis were birth weight, gestational age, small for gestational age ([SGA] ≤−2.0 SD from mean weight according to the age and gender specific Finnish growth charts; yes/no), gender, parents' education (in three categories: ≤9 years, 10-12 years, >12 years), respectively, and the severity level of brain pathology based on cranial US findings (three groups: normal, mildly abnormal and severely abnormal). Univariate associations between categorically scaled variables and continuously scaled outcome variables were examined using nonparametric Mann-Whitney U and Kruskal-Wallis tests for shift in location. The strength and direction of relationships between continuously scaled predictor variables and continuous outcome variables were examined using Pearson's correlation coefficient. Variables found to be associated from these univariate procedures were then selected for entry as covariates into a series of multiple linear regression procedures, in which associations between brain volumes and outcome variables were studied, controlling for previously specified demographic variables. The following brain volumes were entered into the regression model as independent variables one at a time: total brain tissue, ventricles, cerebrum, frontal lobes, cerebellum, brainstem, and the combined volume of the basal ganglia and thalami. Regression coefficients, 95% confidence intervals (CIs) of the coefficient and p values are reported. Bootstrap methods were used to validate our regression analysis. Analyses were rerun omitting children with major brain pathology.

Results

Demographic variables are presented in Table 1. Nine children had CP, one had hearing loss, two had cognitive impairment, two had both CP and cognitive impairment, one had both hearing loss and cognitive impairment, and one had CP, hearing loss and cognitive impairment. There were no blind children in the study population.

Table 1 Demographic variables in very low birth weight (*VLBW*) children without and with neurodevelopmental impairments (*NDI*)

	VLBW children without NDI $n=148$	VLBW children with NDI $n=16$	p
Birth weight (g),			0.03
mean (SD) [min, max]	1,106 (274) [400, 1,500]	942 (284) [520, 1,500]	
Gestational age (weeks + days),			<0.001
mean (SD) [min, max]	29+1 (2+4) [23+0, 35+6]	27+0 (2+6) [23+2, 35+1]	
Small for gestational age			0.36
yes (%)	54 (36%)	4 (25%)	
no (%)	94 (64%)	12 (75%)	
Sex			0.68
male (%)	82 (55%)	8 (50%)	
female (%)	66 (45%)	8 (50%)	
Mother's education			0.90
≤9 years (%)	15 (10%)	2 (13%)	
10-12 years (%)	41 (28%)	5 (31%)	
>12 years, *n* (%)	91 (62%)	9 (56%)	
Father's education			0.58
≤9 years (%)	14 (9%)	1 (7%)	
10–12 years (%)	88 (59%)	11 (73%)	
>12 years (%)	46 (31%)	3 (20%)	
Brain ultrasound			<0.001
normal (%)	78 (53%)	2 (13%)	
mildly abnormal (%)	64 (43%)	7 (44%)	
severely abnormal (%)	6 (4%)	7 (44%)	
Head circumference at birth (cm)			0.08
mean (SD) [min, max]	26 (2) [20, 31]	25 (3) [20, 30]	
Weight at term (g),			0.01
mean (SD) [min, max]	2,758 (505) [1,588, 3995]	2,406 (467) [2,000, 3,815]	
Height at term (cm)			0.33
mean (SD) [min ,max]	48 (3) [40, 55]	47 (2) [42, 52]	
Head circumference at term (cm)			0.48
mean (SD) [min, max]	35 (1) [31, 40]	34 (2) [32, 38]	

Intraclass correlation coefficients for the volume measurements ranged from 0.93 to 0.99, except for the volume of brainstem for which the intraclass correlation coefficient was 0.78.

Brain volumetric findings, MDI and scores for the Hammersmith Infant Neurological Examination are shown in Table 2. Children with larger volumes of total brain tissue (OR, 1.03; 95% CI, 1.01-1.04), cerebrum (OR, 1.03; 95% CI, 1.01-1.05), frontal lobes (OR, 1.05; 95% CI, 1.02-1.08), basal ganglia and thalami (OR, 1.30; 95% CI, 1.12-1.51), and cerebellum (OR, 1.18; 95% CI, 1.07-1.31) were less likely to have NDI than children with smaller volumes. These results were unchanged after omitting children with severe brain pathology. Children with smaller ventricular volumes (OR, 0.36; 95% CI, 0.18-0.72) were less likely to have NDI than the children with larger ventricular volumes. This association was not found when the children with severe brain pathology were omitted. In the group of children without NDI, the MDI was normal (≥85) in 139 (94%), mildly delayed (70-84) in nine (6%) and significantly delayed (≤69) in none of the children. In the 16 children with NDI, MDI was normal in ten (63%), and significantly delayed in six (38%). The global score for the Hammersmith Infant Neurological Examination was ≥74 in 95 (64%) and <74 in 53 (36%) of the children without NDI, while the score was ≥74 in two (13%) and <74 in 14 (88%) of the children with NDI.

The analysis of associations between brain volumetric findings and outcome measures, controlling for the demographic variables, showed that a smaller cerebellar volume was significantly associated with poorer scores in the Hammersmith Infant Neurological Examination ($p=0.01$) in VLBW children without NDI. All associations between brain volumes and outcome variables are presented in Table 3. Figure 2 shows the associations between the cerebellar volume and the scores in the Hammersmith Infant Neurological Examination for VLBW children with and without NDI. We repeated the analysis of the association between cerebellar volume and the score of the Hammersmith Infant Neurological Examination using the proportion of cerebellar volume to total brain tissue volume (instead of the absolute volume) and using the total brain tissue volume as an additional covariate. Even after this adjustment, the association remained significant ($p=0.049$; estimated regression coefficient, 0.428; standard error, 0.215). Table 3 shows associations between all regional brain volumes and outcome variables in children without NDI.

Discussion

To our knowledge, this is the largest prospective cohort study of the relationship between several regional brain volumes at term-equivalent age and developmental outcome at 2 years of corrected age in preterm infants with a low attrition rate. We found that the volumes of total brain tissue, cerebrum, frontal lobes, basal ganglia and thalami, and cerebellum were significantly smaller, and the volume of ventricles significantly larger in the children with NDI. In addition, even after excluding the children with NDI from the analyses, a smaller cerebellar volume at term-equivalent age was significantly associated with poorer neurological performance at 2 years of corrected age.

It is well recognised that the cerebellum is important in motor control. In addition, several studies have reported associations between the cerebellum and cognitive functions, such as language. Shah et al. [3], whose study

Table 2 Mean values (SD) [min, max] of brain volumes (ml), mental developmental index (*MDI*), and scores at the Hammersmith Infant Neurological Examination in very low birth weight children without and with neurodevelopmental impairments (*NDI*). The *p* values are based on logistic regression analysis

	Without NDI *n*=148	With NDI *n*=16	*p*
Total brain parenchyma	400 (46) [280, 510]	353 (33) [292, 424]	<0.001
Ventricles	13 (8) [2, 44]	42 (61) [4, 223]	0.004
Cerebrum	369 (44) [259, 473]	327 (28) [268, 387]	0.001
Frontal lobes	130 (23) [83, 194]	111 (18) [81, 141]	0.002
Basal ganglia and thalami	26 (5) [13, 43]	22 (3) [16, 27]	0.001
Cerebellum	25 (5) [8, 38]	20 (6) [6, 31]	0.002
Brain stem	7 (3) [3, 15]	6 (2) [3, 12]	0.246
MDI	105 (12) [72, 128]	82 (24) [50, 118]	
Score at the Hammersmith Infant Neurological Examination	74 (3) [67,78]	59 (11) [38,76]	

focused on cerebellar volumes, suggested a correlation between cerebellar volume at term-equivalent age and cognitive and motor development at 2 years of age. The importance of cerebellar volume in cognitive functioning has also been documented in studies of brain volumes later in childhood and in adolescence [6–8]. As the cerebellum is a structure that is developing extraordinarily rapidly during the premature period, it is vulnerable in the preterm baby [31]. Accordingly, it has been suggested that cerebellar abnormality is a relatively under-recognised but important cause of neurodevelopmental disability in prematurely born children, and more data on the relationship between cerebellar damage and development in preterms have been requested [31]. However, as brain pathology in one brain region, for example white matter injuries, can cause changes in volumes in other parts of the brain [1, 13, 32, 33], we found it important to broaden the focus from one single to multiple regions, and simultaneously control the overt brain pathology as a background factor in multiple regression analyses when studying connections between volumes and outcome. Associations between volumes of different brain regions and cognitive development have previously been reported [2, 5]; and likewise in our study, most of the volumes of children with NDI were smaller than in children without.

It has been reported that one third of the very premature infants at a mean corrected age of 12 months have suboptimal scores (64–72) in the Hammersmith Infant Neurological Examination despite normal gross motor function at 2 years of age [24]. Our results are in agreement with this. It has been proposed that the subgroup of preterm infants with relatively low scores, but without disability at an early age, could be the same children recognised as having minor motor or perceptual motor problems later on [24]. Therefore, the association between brain volumes and early motor performance is of major interest. One can also speculate that very mild hemiplegia or diplegia can be missed clinically at 2 years of age, but nevertheless would contribute to reducing the scores in a quantitative neurological examination. However, it has been shown that CP

Table 3 Associations (95% CI) between brain volumes and outcome measures in very low birth weight children without neurodevelopmental impairment, controlling for demographic variables that were significantly associated with outcome in univariate analyses

	MDI[a]		Hammersmith Infant Neurological Examination[b]	
		p		*p*
Total brain parenchyma	0.02 (−0.03, 0.08)	0.35	0.01 (−0.01, 0.02)	0.13
Ventricles	−1.42 (−4.50, 1.66)	0.36	-0.21 (−0.90, 0.48)	0.55
Cerebrum	0.02 (−0.03, 0.08)	0.38	0.01 (−0.00, 0.02)	0.19
Frontal lobes	0.03 (−0.05, 0.11)	0.47	0.01 (−0.01, 0.03)	0.18
Basal ganglia and thalami	0.31 (−0.13, 0.74)	0.16	0.04 (−0.05, 0.14)	0.37
Cerebellum	0.19 (−0.24, 0.62)	0.38	0.12 (0.03, 0.20)	0.01
Brainstem	−0.73 (−6.10, 4.63)	0.78	-0.27 (−1.46, 0.92)	0.66

[a] Adjusted for birth weight, gestational age, mother's education and father's education

[b] Unadjusted estimates

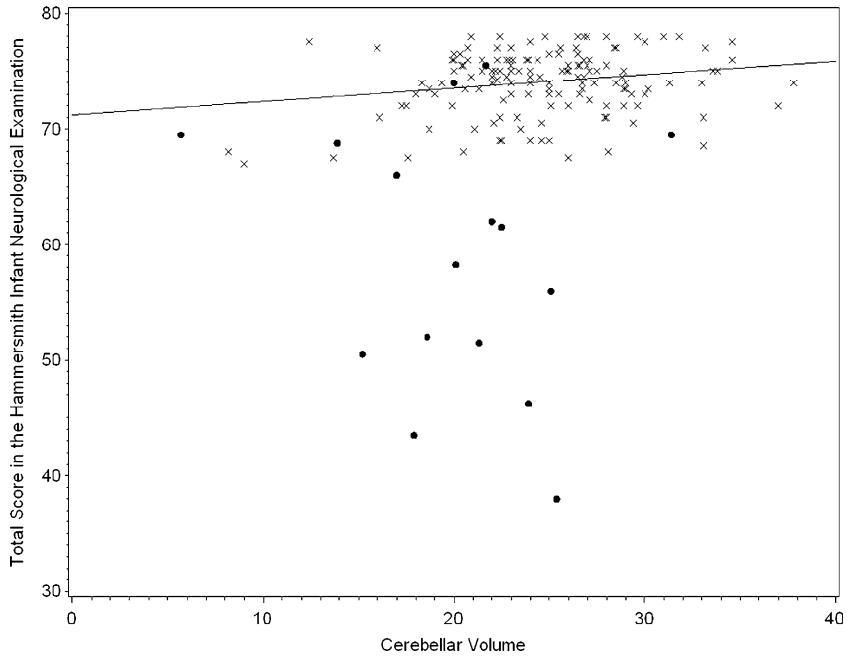

Fig. 2 Scatterplot of cerebellar volume (*x*-axis) and scores at the Hammersmith infant neurological examination (*y*-axis) in very low birth weight children without (*crosses*) and with (*dots*) neurodevelopmental impairments. Regression line for the children without NDI

can be diagnosed with sufficient reliability in most cases by 2 years of age [34].

The normal findings or minor lesions, either at cranial ultrasound or in MRI, is associated with optimal scores at the Hammersmith infant neurological examination; and severe lesions with suboptimal scores relate to disability [24, 26]. In our study, even when controlling brain pathology as a background factor and excluding children with NDI from the analyses, a significant association remained between the volume of the cerebellum and neurological abnormalities. This result supports the evidence that the less optimal neurological scores in preterm infants without neurosensory disability also reflect earlier brain pathology [35, 36]. Further, one can speculate that the minor neurological findings resulting in relatively low global scores in our cohort correlate with white matter injuries, either in cerebellum or cerebrum, that cannot be detected at ultrasound but nevertheless affect brain growth, which in turn manifests as reduced brain volumes at MRI. In this respect, it is of major interest that Spittle et al. [37] reported a significant relationship between the quality of general movements at 1 and 3 months and cerebral white matter abnormalities at MRI in very preterm infants (<30 weeks' gestation).

A limitation of our study is the relatively short follow-up and small number of children with NDI. Two years is not a sufficient follow-up period when the goal is to define a detailed developmental profile [33, 38–40]. MDI of BSID-II summarises many areas of mental development and provides a broad picture of the cognitive outcome at group-level in preterm infants [22]. Therefore, MDI does not give detailed information on specific areas of infant cognitive development, such as language development. It can be speculated that significant associations between brain volumes and cognitive development may have been found were it possible to assess visuomotor skills, executive functioning, memory and language functions separately. However, it should also be recognised that there would be a larger influence of environmental factors when outcomes are measured later.

Another possible limitation of our study is the upgrading of the MRI equipment during the data collection period, since this might have affected image contrast. To minimise the effect of this, easily definable anatomical landmarks were selected for volume measurements. Voxel-based morphometry (VBM) is a widely used method for volume measurements in adults for research purposes. In the infant brain, automatic segmentation is a technically demanding task because of the changing white and gray matter contrast on T1- and T2-weighted images of the growing brain. The manual volume measurement performed by an experienced radiologist has been regarded as a gold standard for volume measurement. In our work, we tested the reproducibility of the manual volume measurement, and the intraclass correlation coefficient was good.

In many centres, brain MRI is performed at term-equivalent age in prematurely born infants. To gain full clinical advantage of neonatal MRI, more studies are needed of associations between volumetric findings and development of preterm children beyond 2 years of age. Moreover, as brain volumes change relative to general growth during childhood [41], the course of volumetric

changes should be studied. In addition, the volumetric normative values for term infants, and for preterm infants term-equivalent age, are mandatory for future research.

Conclusion

We found that the volumes of the total brain tissue, the cerebrum, frontal lobes, basal ganglia and thalami, and the cerebellum were significantly smaller, and the volume of ventricles significantly larger, in VLBW children with NDI compared with those without. Smaller cerebellar volumes were significantly associated with poorer neurological performance at 2 years of corrected age in children without NDI. Knowledge of this may help clinicians in early prediction of outcome in premature infants. Automated segmentation methods would facilitate the use of this knowledge in clinical practice.

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