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Differential Effects of Intraventricular Hemorrhage and White Matter Injury on Preterm Cerebellar Growth

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Abstract

Objective—To hypothesize that detailed examination of early cerebellar volumes over time would distinguish differences in cerebellar growth associated with intraventricular hemorrhage (IVH) and white matter injury (WMI) in preterm infants.

Study design—Preterm newborns at the University of California San Francisco (n=57) and the University of British Columbia (n=115) were studied using serial MRI scans near birth and again at near term-equivalent age. Interactive semi-automated tools were used to determine volumes of the cerebellar hemispheres.

Results—Adjusting for supratentorial brain injury, cerebellar hemorrhage, and study site, cerebellar volume increased 1.7cm³/week postmenstrual age (95% CI 1.6–1.7, P<0.001). More severe supratentorial IVH was associated with slower growth of cerebellar volumes (P<0.001). Volumes by 40 weeks were 1.4 cm³ lower in premature infants with grade 1–2 IVH and 5.4 cm³ lower with grade 3–4 IVH. The same magnitude of decrease was found between ipsilateral and contralateral IVH. No association was found with severity of WMI (P=0.3).

Conclusions—Early effects of decreased cerebellar volume associated with supratentorial IVH in either hemisphere may be a result of concurrent cerebellar injury or direct effects of subarachnoid blood on cerebellar development.

Keywords

preterm; neuroimaging; cerebellum; intraventricular hemorrhage

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In 2005, 12.7% of all newborns were born prematurely in the US.[1] Premature birth is a significant risk factor for adverse motor, coordination, cognitive, and behavioural outcomes in survivors. Abnormal outcome is associated with increasing severity of white matter injury (WMI), intraventricular hemorrhage (IVH), and ventriculomegaly.[2]

The cerebellum helps to regulate motor tone, coordination, and cognitive function. Therefore, adverse outcomes from prematurity may also result from cerebellar dysfunction. Cerebellar development occurs from 4 weeks post-conception to 2 years postnatally, allowing for a large window for possible insults. The period of premature birth, from 24 to 37 weeks gestational age, is a period of dramatic growth and maturation for the cerebellum. [3,4] Isolated cerebellar hemorrhage in the preterm period was associated with disability in motor, language, and cognitive domains.[5]

Cerebellar injury during prematurity may be direct (including direct cerebellar infarct or hemorrhage) or indirect, reflecting abnormal growth.[6] Decreased cerebellar volumes described in follow-up of individuals born preterm.[7,8] Volumetric neuroimaging techniques at term-equivalent age or later have correlated decreased cerebellar volume with supratentorial WMI and IVH. Preterm neonates without supratentorial injury do not show reduced cerebellar volume.[9] Conversely, unilateral periventricular hemorrhagic infarction is associated with contralateral cerebellar volume loss, suggesting trophic interactions as a mechanism for the volumetric effects.[10] Diffusion tensor imaging studies during the preterm period show microstructural changes in the cerebellum associated with supratentorial IVH but not WMI, suggesting differential effects of supratentorial hemorrhage and hypoxia-ischemia on the cerebellum.[11]

Further study into the differential effects of supratentorial IVH and WMI will help to elucidate the different mechanisms of injury of the cerebellum in prematurity. The objective of this study is to characterize the growth and development of the cerebellum from the early postnatal period to term-equivalent age in a large cohort of premature newborns using advanced magnetic resonance brain imaging techniques in order to determine the relationship of this growth with supratentorial brain injury. It is hypothesized that, in the early preterm period, decreased cerebellar growth is more strongly associated with supratentorial IVH than with WMI.

Methods

A cohort of preterm neonates born between June 2006 and February 2009 admitted to the intensive care nurseries at the University of California San Francisco (UCSF, n=53) or the University of British Columbia (UBC, n=115) was studied. These patients were recruited under comparable ongoing research protocols at both institutions.[12,13] Parents of prematurely born neonates (<33 weeks gestational age) were approached for enrolment in a prospective cohort study evaluating the detection of brain injury by MRI. Exclusion criteria were (1) clinical evidence of a congenital malformation or syndrome, (2) congenital TORCH infection, and (3) newborns too clinically unstable for transport to the MRI scanner. Parental consent was obtained following a protocol approved by both institutional human research committees. Custom MR-compatible incubators with specialized neonatal head coils were used to provide a quiet, well-monitored environment for the neonate, minimizing patient movement and improving the signal-to-noise ratio.[14] Subjects were imaged as soon after birth as clinically stable and again near term-equivalent age.

Brain imaging techniques

MRI scans were acquired using a 1.5-T scanner (General Electric Sigma; GE Medical Systems, Milwaukee, WI or Siemens Avanto; Siemens Medical Solutions USA Inc,

Malvern, PA) and a specialized, high-sensitivity, neonatal head coil built into the MRI-compatible incubator (General Electric; GE Medical Systems, Milwaukee, WI or Lammers Medical Technologies; LMT Lammers Medical Technology, Luebeck, Germany). MRI scans at UCSF included axial spin-echo T2-weighted images (repetition time (TR), 3000ms; echo time (TE), 60,120ms; FOV, 240mm; gap, 2 mm) and sagittal volumetric 3-dimensional (3D) spoiled gradient echo T1-weighted images (TR, 36ms; TE, min; FOV, 180mm; slice thickness, 1.0mm; no gap). Scans at UBC included axial fast spin echo T2-weighted images (TR, 4610ms; TE, 107ms; FOV, 160mm; slice thickness, 4mm; gap, 0.2mm) and 3D coronal volumetric T1-weighted images (TR, 36ms; TE, 9.2ms; FOV, 200mm; slice thickness, 1mm; no gap). Volumetric data were reformatted for visualization in coronal, sagittal, and axial planes.

Cranial ultrasounds were performed as clinically indicated. Routine ultrasounds were obtained at 7 days of life and again at 4 weeks of life, or earlier if clinically indicated. Supratentorial injury, including IVH and WMI, was determined by a single pediatric neuroradiologist at each study site (AJB, KJP) blinded to patient history. All MRI sequences and head ultrasounds were evaluated for IVH using the grading system of Papile et al.[15] IVH was categorized as mild if there was subependymal germinal matrix hemorrhages or extension of hemorrhage into the ventricles without ventricular dilatation (grade 1 & 2). IVH was categorized as severe if associated with lateral ventricular dilatation or intraparenchymal hemorrhage (grade 3 & 4). MRI sequences were evaluated for WMI in each cerebral hemisphere using a clinically predictive scoring system previously shown to be associated with diffusion tensor imaging changes and spectroscopy on MRI[12,13] as well as neurodevelopmental outcomes at 12–18 months of age as assessed by the Mental Development Index of the Bayley Scales of Infant Development II and a verified neuromotor outcome.[2] WMI was categorized as mild if there were ≤ 3 areas of T1 abnormality measuring ≤ 2 mm. WMI was categorized as severe if there were > 3 areas of T1 abnormality or areas > 2 mm. Cerebellar hemorrhage was defined as any visible blood of any age in the cerebellum on ultrasound or MRI. High inter- and intra-rater reliability of the use of these MRI scoring systems was previously reported, demonstrating reliability in classification by this scoring system [2,13].

High-resolution T1-weighted SPGR sequences were used to perform 3D tracings of the cerebellar hemispheres using interactive semi-automated tools developed at UCSF (<http://rview.colin-studholme.net>). Tracings were performed by a single pediatric neurologist blinded to patient history (EWYT). Volumes were obtained by manual delineation of the cerebellum at each level using landmarks visualized in 3-dimensions (Figure 1). Cerebral spinal fluid spaces allowed delineation of the cerebellum from the surrounding structures. Each hemisphere was traced separately, divided midline at the vermis. This technique had excellent reproducibility when tested by performing 10 tracings in a blinded manner from five different scans, with an intraclass correlation coefficient of 0.99.

Statistical analysis

Statistical analysis was performed using Stata 10 (Stata Corporation, College Station, Texas). To investigate the association between supratentorial brain injury and cerebellar volume, a mixed random effects model with a random intercept for each child was used, permitting a multilevel correlation structure to account for the fact that serial MRI scans were performed on each subject.[16] The outcome variable was bilateral cerebellar volume, and the predictor variables were IVH and WMI. Adjustment was made for postmenstrual age at time of MRI, the presence of cerebellar hemorrhage, and study site. This model was used to determine the growth of the cerebellum over time, adjusting for supratentorial brain

injury, and to determine the effect of supratentorial brain injury on cerebellar growth. Histograms of the residuals for each model conformed to a normal distribution.

To investigate whether the association between supratentorial brain injury and cerebellar volume was ipsilateral or contralateral, a mixed random effects model with a random intercept for each child and cerebellar hemisphere was used, accounting for hierarchy in the dataset, where each subject had two MRI scans and each MRI scan imaged two hemispheres. The outcome variable was ipsilateral cerebellar hemispheric volume, and the predictor variables were contralateral and ipsilateral supratentorial brain injury. Adjustment was made for postmenstrual age at time of MRI, the presence of ipsilateral intracerebellar blood, and study site.

Results

At the two study centers, 398 MRI scans were performed on a total of 172 preterm subjects (Table I). Particular differences between the two centers include older age at second scan and lower incidences of severe IVH, mild WMI, and cerebellar hemorrhage at the UBC site.

Effect of gestational age

Mixed random effects models were used to adjust for the presence of supratentorial brain injury or cerebellar hemorrhage. Adjusting for the presence of supratentorial IVH or WMI, cerebellar hemorrhage, and study site, bilateral cerebellar volume increased at a rate of 1.68cm^3 per week over the range of ages studied (95% CI 1.62 to 1.74cm^3 , $P<0.001$, Figure 2). In this regression model, there was no association between cerebellar volume and study site ($P=0.95$).

Effect of supratentorial brain injury

Adjusting for postmenstrual age at time of MRI and cerebellar hemorrhage, there was a significant association between cerebellar volume and the severity of IVH (test for trend $P=0.0002$), but no significant trend for severity of WMI ($P=0.3$). Considering that the parenchymal involvement of grade 4 IVH might complicate the classification of WMI, excluding subjects with grade 4 IVH did not change the findings of no significant association between cerebellar volume and severity of WMI ($P=0.3$). Significant interaction exists between the gestational age at the time of MRI and the severity of IVH ($P=0.01$ for mild IVH, $P<0.001$ for severe IVH). When comparing those with severe IVH and those without IVH, cerebellar volumes were the same at a postmenstrual age of 29.7 weeks (95% CI 26.2 to 33.2 weeks). At 40 weeks postmenstrual age, compared with those with no IVH, cerebellar volume is 1.4cm^3 lower in those with mild IVH (95% CI -2.4 to -0.2cm^3 , $P=0.01$) and 5.4cm^3 lower in those with severe IVH (95% CI -7.3 to -3.4cm^3 , $P<0.001$, Figure 2). If subjects with cerebellar hemorrhage are excluded from the analysis, with the remaining 277 scans, the association with severity of IVH remains strong ($P=0.002$), with cerebellar volume 1.3cm^3 lower in those with mild IVH (95% CI -2.4 to -0.2cm^3 , $P=0.02$) and 5.3cm^3 lower in those with severe IVH (95% CI -7.5 to -3.0cm^3 , $P<0.001$).

When studying cerebellar hemispheric volumes using a mixed random effects model, there is a significant test for trend for the association between cerebellar hemispheric volume and the severity of both ipsilateral ($P=0.0001$) and contralateral ($P=0.001$) IVH. At 40 weeks postmenstrual age, decreased cerebellar hemispheric volume is significantly associated with both ipsilateral and contralateral IVH, with no difference in the cerebellar volume changes between ipsilateral and contralateral IVH (Table II).

Considering that 10 scans were associated with bilateral severe IVH, subgroup analysis was performed excluding these scans to investigate the effect of unilateral severe IVH. Repeating

the regression analysis on the remaining 288 scans, the test for trend was still significant for the association between cerebellar hemispheric volume and the severity of both ipsilateral ($P=0.0002$) and contralateral ($P=0.001$) IVH, with no difference in the cerebellar volume changes between ipsilateral and contralateral IVH.

Discussion

Cerebellar volume as measured by MRI increased at a constant rate from birth to term-equivalent age. However, in premature newborns with IVH, cerebellar growth was impaired. No association was found with WMI, suggesting novel mechanisms including the effects of blood products in the CSF and meningeal effects on cerebellar parenchymal development. Cerebellar volume increased at a constant rate after adjusting for brain injury, including IVH, WMI, and cerebellar hemorrhage. Of note, these results should only be used for prediction of cerebellar volumes during the preterm period, as this linear relationship may not continue later in development. These normative data are comparable with those previously reported at term equivalent age.[4] In addition, these results compare favorably to those reported for fetuses at the same gestational ages determined by ultrasound and MRI, suggesting that cerebellar growth in preterm newborns without significant supratentorial injury is similar to growth *in utero*. [17,18]

Severity of IVH was inversely associated with cerebellar volumes, but WMI was not associated with any adverse effect on growth. These findings contrast with previous studies, which found decreased cerebellar volumes associated with both severe IVH and WMI. [9,10,19] In contrast with previous reports where MRIs were analyzed at term-equivalent age or later in life, this study analyzed serial MRIs during the preterm period. The results in this study also are in concordance with a previous study of cerebellar diffusion tensor imaging in preterm neonates, where changes in mean diffusivity and fractional anisotropy were associated with IVH but not WMI during the early preterm period.[11] Taken together, these results suggest differential mechanisms for effects on brain microstructural maturation and cerebellar growth patterns associated with IVH and WMI.

This study highlights that cerebellar volume changes can be appreciated much earlier than previously reported for term equivalent brains. One explanation for these early changes may be that of concurrent injury to the cerebellum during the onset of IVH in the preterm period. Another explanation may invoke the toxicity of blood breakdown products such as heme or iron in the cerebrospinal fluid (CSF) as a result of supratentorial hemorrhage. Prior case series have associated superficial siderosis after subarachnoid hemorrhage with cerebellar atrophy or malformation.[20–22] In rodent models, the neurotoxicity of blood products, including heme and free iron, was reported after intraparenchymal or subarachnoid hemorrhage.[23–25] The absence of visible blood products in the basilar and pericerebellar cisterns on MRI in our study likely results from the size of the bleeds and the length of the interval between the hemorrhage and the time of imaging.

Because the germinal matrices of the cerebellum lie in the external granular layer (in close proximity to the subarachnoid space) and in the walls of the fourth ventricle, blood deposition in either location may affect generation of new cells and thereby slow the growth of the cerebellum or result in neuronal cell death. The external granular layer continues to be an active germinal zone through the first postnatal year.[26] Blood in the posterior fossa cisterns could affect cerebellar growth either by direct effects on these germinal matrices or on the surrounding mesenchyme.

The surrounding mesenchyme contributes to the development of the cerebellum. Early studies in newborn hamsters showed that destruction of the meningeal cells resulted in

disruption of lamination of the cerebellar cortex and decreased cerebellar volumes, supporting the influence of the leptomeninges on cerebellar growth.[27] A knock-out of the *Foxc1* gene, expressed only in the surrounding mesenchyme and not within the cerebellum, results in hypoplastic malformations in the cerebellum and anomalies of the surrounding cisterns in mice.[28] Cerebellar hemisphere volume reduction was equally associated with both ipsilateral and contralateral supratentorial IVH. This supports the possibility that blood in the CSF after IVH may be mediating the signals that result in decreased cerebellar volumes during the preterm period. Because CSF mixes in the third and fourth ventricles, exposing both cerebellar hemispheres to equivalent amounts of blood from each cerebral ventricle, it follows that both cerebellar hemispheres would come in contact with any blood in the CSF.

Because previous studies reported contralateral associations between severe IVH and decreased cerebellar volumes, we investigated whether or not subjects with bilateral severe IVH skewed the data. By performing a subgroup analysis excluding patients with bilateral severe IVH, associations were still not found to be contralateral. Excluding patients with bilateral severe IVH, cerebellar hemispheric volumes continued to be significantly associated with the severity of both ipsilateral and contralateral IVH.

Decreased contralateral cerebellar hemispheric volume was found to be associated with severe supratentorial parenchymal brain injury, resulting in contralateral associations that suggest diaschisis as a mechanism of volume loss.[10] In the current study examining cerebellar growth, bilateral impaired cerebellar growth was found in both mild and severe IVH, with more severe impairment seen with increasing severity of IVH. This supports three different mechanisms for impaired cerebellar growth with IVH – diaschisis after significant supratentorial parenchymal brain injury, bilateral cerebellar injury as a result of concurrent injury, or circulating blood products in the CSF. In addition, the finding of cerebellar involvement even in the face of mild IVH without significant supratentorial parenchymal involvement lends support to the hypothesis that blood products in the CSF impair cerebellar growth.

In contrast to IVH, WMI was not found to be associated with cerebellar volume changes in the early preterm period. As the postulated mechanisms of reduced cerebellar growth after IVH include both the effect of blood products in the CSF and diaschisis from supratentorial parenchymal brain injury, it is necessary to postulate a reason for the lack of association of cerebellar volume loss with WMI. One possible reason is milder WMI in our cohort compared with those previously reported[19]. Our scoring system is based upon detection of small, focal areas of mild T1 hyperintensity in the cerebral white matter on early postnatal MRI studies. These lesions are more difficult to detect on term-equivalent studies. Other studies at term have thus based the diagnosis of WMI on signal abnormalities as well as cerebral volume loss, which likely represent more severe injury. Thus, the milder degree of WMI in this cohort may explain the different findings regarding WMI and cerebellar growth compared with previous reports. This difference, however, has allowed better appreciation of the effects of IVH upon cerebellar growth.

Although our results highlight associations with IVH, further MRI studies on healthy term babies will help to determine if preterm birth itself affects cerebellar growth. In addition, long-term neurodevelopmental follow-up of these subjects is underway, which will help decide the clinical implications of impaired cerebellar growth.

By comparing the effects of IVH and WMI, this study demonstrates novel associations between supratentorial IVH without parenchymal injury and decreased cerebellar volumes. These novel mechanisms for impairment of cerebellar growth associated with supratentorial

brain injury, including the effects of blood products in the CSF on the developing cerebellum and meninges that may secondarily affect cerebellar parenchymal development, highlight previously unknown risk factors and potential targets for future therapies.

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Abbreviations

IVH	intraventricular hemorrhage
WMI	white matter injury

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Figure 1.
Volumetric tracings of left and right cerebellar hemispheres superimposed on 3D T1-weighted SPGR MR images. A. Left (red) and right (blue) cerebellar hemispheres are shown in axial, coronal, and mid-sagittal planes on this MRI scan performed at 38 weeks postmenstrual age. B. Resultant 3D rendered image.

Figure 2. Cerebellar volume as a function of postmenstrual age at time of MRI. A. Subjects with and without severe IVH. B. Subjects with and without severe WMI.

Table 1

Subject demographics at the two study sites – University of California San Francisco (UCSF) and University of British Columbia (UBC). Intraventricular hemorrhage (IVH) and white matter injury (WMI) are categorized as described in text. Means are compared using the t-test and proportions are compared using the Fisher exact test.

Site	UCSF	UBC	P-value
Subjects	57	115	
MRI scans	92	206	
Male sex	27/57 (47%)	55/115 (48%)	0.9
Gestational age at birth (weeks, mean $\pm$ SD)	28.1 $\pm$ 2.2	27.8 $\pm$ 2.1	0.5
Postmenstrual age at MRI (weeks, mean $\pm$ SD)			
First scan	31.7 $\pm$ 1.6	32.3 $\pm$ 3.3	0.3
Second scan	35.7 $\pm$ 2.2	40.5 $\pm$ 2.9	<0.001
Scans with IVH			
Mild IVH	27/92 (29%)	51/206 (25%)	0.5
Severe IVH	17/92 (18%)	10/206 (5%)	<0.001
Scans with WMI			
Mild WMI	16/92 (17%)	16/206 (8%)	0.02
Severe WMI	11/92 (12%)	39/206 (18%)	0.2
Scans with cerebellar hemorrhage	13/92 (14%)	8/206 (4%)	0.002

Table 2

Decrease in cerebellar volume is associated with both contralateral and ipsilateral IVH. Coefficients represent the decrease in cerebellar hemispheric volume associated with IVH in cm³ by 40 weeks postmenstrual age.

	Coefficient	95% CI	P-value
Contralateral mild IVH	−0.76	−1.14 to −0.37	<0.001
Contralateral severe IVH	−1.35	−2.02 to −0.68	<0.001
Ipsilateral mild IVH	−0.76	−1.15 to −0.38	<0.001
Ipsilateral severe IVH	−1.96	−2.62 to −1.29	<0.001