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Corpus callosum alterations in very preterm infants: Perinatal correlates and 2 year neurodevelopmental outcomes

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ABSTRACT

The aim of this study was to relate altered corpus callosum (CC) integrity in 106 very preterm (VPT) infants (<30 weeks' gestational age or <1250 g birth weight) at term equivalent to perinatal predictors and neurodevelopmental outcomes at two years. T1 and diffusion magnetic resonance images were obtained. The CC was traced, and divided into six sub-regions for cross-sectional area and shape analyses. Fractional anisotropy, mean, axial and radial diffusivity were sampled within the CC, and probabilistic tractography was performed. Perinatal predictors were explored. The Bayley Scales of Infant Development (BSID-II) was administered at two years. Intraventricular hemorrhage was associated with a smaller genu and altered diffusion values within the anterior and posterior CC of VPT infants. White matter injury was associated with widespread alterations to callosal diffusion values, especially posteriorly, and radial diffusivity was particularly elevated, indicating altered myelination. Reduced CC tract volume related to lower gestational age, particularly posteriorly. Reduced posterior callosal skew was associated with postnatal corticosteroid exposure. This more circular CC was associated with delayed cognitive development. Higher diffusivity, particularly in splenium tracts, was associated with impaired motor development. This study elucidates perinatal predictors and adverse neurodevelopmental outcomes associated with altered callosal integrity in VPT infants.

Introduction

Very preterm (VPT) infants born <30 weeks' gestational age (GA) or weighing <1250 g at birth are at risk for adverse neurodevelopmental outcome, which is mediated by alterations in cerebral development in the neonatal period. Perinatal variables related to alterations in cerebral development are not fully understood but may include the following: respiratory disease such as bronchopulmonary dysplasia (BPD) (Anjari et al., 2009); exposure to postnatal corticosteroids (PCS), which are used to treat BPD (Halliday et al., 2009a); infection, such as necrotizing enterocolitis and sepsis (Shah et al., 2008); immaturity at birth; low birth weight; and cerebral injury such as white matter injury (WMI) and intraventricular hemorrhage (IVH).

VPT infants are born during a sensitive time of brain development, and are vulnerable to hypoxia–ischemia and infection. Periventricular leukomalacia (PVL) is the most common form of brain injury in the VPT infant, and pre-oligodendrocytes are particularly vulnerable (Volpe, 2009). Importantly, VPT infants have high rates of adverse long term neurodevelopmental outcomes with up to 15% of VPT infants being diagnosed with cerebral palsy (CP) and a further 50% having significant deficits including visual-motor problems, attention difficulties, impaired memory, delayed language skills and executive dysfunction (Holsti et al., 2002). Such neurodevelopmental delays lead to considerable educational burden, with both economic and social implications (Doyle, 2004).

The corpus callosum (CC) is the major inter-hemispheric commissure that connects the majority of the neocortical areas (Schmahmann and

Abbreviations: AC–PC, anterior commissure to posterior commissure line; BPD, bronchopulmonary dysplasia; CC, corpus callosum; DTI, diffusion tensor imaging; FA, fractional anisotropy; FOV, field of view; FSL, Oxford centre for functional magnetic resonance imaging of the brain software library; FT, full-term; GA, gestational age; IVH, intraventricular hemorrhage; MD, mean diffusivity; MDI, mental developmental index; PCS, postnatal corticosteroids; PDI, psychomotor developmental index; VPT, very preterm; PVL, periventricular leukomalacia; ROI, region of interest; TE, echo time; TR, repetition time; WM, white matter; WMI, white matter injury; $\lambda_{\parallel}$, axial diffusivity; $\lambda_{\perp}$, radial diffusivity.

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Pandya, 2006) and is the largest WM fiber bundle in the human brain. The CC is important for inter-hemispheric communication of sensory, motor and higher-order information. Deficits in the CC have been previously implicated in delayed motor functioning (Rademaker et al., 2004), and reduced intelligence quotient (Caldu et al., 2006), which are problems VPT infants often display. Therefore, alterations to the CC in VPT infants may contribute to later adverse neurodevelopmental outcomes.

Magnetic resonance imaging (MRI) is a safe and non-invasive tool to study the development of the VPT brain in vivo. MR image analysis techniques can detect and quantify the size and morphological characteristics of WM structures within VPT infants. In conjunction with structural MRI, diffusion tensor imaging (DTI) provides insight into the micro-structure and connectivity of WM tracts (Pierpaoli et al., 1996). The literature is consistent in confirming that WM anisotropy increases, and overall diffusivity decreases with increasing age and maturation (Huppi et al., 1998; Schneider et al., 2004). Furthermore, both axial diffusivity ($\lambda_{||}$) and radial diffusivity ($\lambda_{\perp}$) decrease with age and maturation as water content decreases and myelination increases (Partridge et al., 2004). Thus, higher $\lambda_{||}$ and $\lambda_{\perp}$ in infants likely represents immaturity of the WM.

It has previously been shown in children, adolescents and adults that prematurity is associated with a smaller CC size (Caldu et al., 2006; Lawrence et al., 2010; Narberhaus et al., 2007; Nosarti et al., 2004; Peterson et al., 2000), and altered diffusion characteristics (Andrews et al., 2010; Constable et al., 2008; Kontis et al., 2009; Nagy et al., 2009, 2003). A few studies have reported altered CC diffusion in VPT infants (Anjari et al., 2007; Rose et al., 2008; Skiold et al., 2010). One study found that VPT males had delayed splenium development on diffusion imaging (Rose et al., 2009). We recently reported that VPT infants had smaller corpora callosa, particularly for the mid-body and posterior sub-regions, and the shape was more circular compared with full-term infants. Further, we found that fractional anisotropy (FA) was lower, mean diffusivity (MD), $\lambda_{||}$, and $\lambda_{\perp}$ were higher, particularly posteriorly, and CC connectivity was reduced (Thompson et al., 2011). However no study to date has assessed associations between altered callosal measures obtained from structural MRI and DTI at term-equivalent, perinatal variables and neurodevelopmental outcomes. Thus, the aims of this study were to determine the perinatal correlates for changes to VPT CC development, and to associate alterations in CC development at term with functional outcomes at 2 years of age. It was hypothesized that CC size reductions and shape alterations would be associated with younger GA and WMI, and that males would have smaller posterior CC sub-regions. It was also hypothesized that reduced FA values, increased MD, $\lambda_{||}$, and $\lambda_{\perp}$ within the VPT CC and callosal tracts, and reduced interhemispheric tract volume would relate to WMI. Regarding neurodevelopmental outcomes, the hypotheses were that altered CC area, shape, diffusion and tractography measures would relate to adverse cognitive and motor functioning at 2 years, where anterior regions of the CC would relate to cognitive measures, while posterior regions would relate to motor scores.

Materials and methods

Subjects and scanning

A prospective observational cohort study was conducted at the Royal Women's Hospitals in Melbourne, Australia between July 2001 and December 2003. Of 348 eligible VPT infants (<30 weeks' GA and/or <1250 g at birth), 227 VPT infants (65% of those eligible) were recruited, as described previously (Thompson et al., 2011). Infants with congenital anomalies were excluded (3%). There were no significant differences between infants recruited or not included for sex, GA at birth, BPD (defined as requirement for oxygen at 36 weeks' GA), grade III or IV IVH, or cystic PVL. Informed parental consent was obtained and the study was approved by the Research and Ethics Committee at the Royal Women's Hospital, Melbourne. A total of 106 stable VPT infants were able to be analyzed for the current study (47% of those recruited). The reasons for non-inclusion were that DTI was not attempted (34%), DTI was unsuccessful or of insufficient quality for further analysis (17%), or structural MRI was unsuccessful or of insufficient quality (2%) largely due to movement or imaging artifact. There were no significant differences between infants included or not included for sex, GA at birth, BPD, grade III or IV IVH, or cystic PVL.

MRI acquisition and pre-processing

All infants were scanned at term equivalent (median 40, range 38–42 weeks' GA) in a 1.5 T General Electric MRI scanner. Infants were fed and tightly swaddled, immobilized in a vacuum fixation bean-bag and scanned during natural sleep, without sedation. Whole brain structural 3D T1 spoiled gradient recalled images (0.8–1.6 mm coronal slices; flip angle 45°; repetition time (TR) 35 ms; echo time (TE) 9 ms; field of view (FOV) 210×157 mm; matrix 256×192; in plane voxel dimensions 0.82 mm^2), T2 dual echo fast spin echo images with interleaved acquisition (1.7–3 mm coronal slices; TR 4000 ms; TE 60/160 ms; FOV 220×165 mm; matrix 256×192, interpolated 512×512; in plane voxel dimensions 0.43 mm^2), and linescan diffusion images (4–6 mm axial slices; 2 baselines, b = 5 s/mm^2; six non-collinear gradient directions, b = 700 s/mm^2; in plane voxel dimensions 0.86 mm^2) were acquired.

Post-acquisition MRI analyses were undertaken on sun Microsystems workstations (Palo Alto, CA). T1-weighted and diffusion images were pre-processed and aligned as previously described (Thompson et al., 2011). In short, T1 images were aligned to the anterior commissure to posterior commissure line (AC–PC) (Talairach and Tournoux, 1988) and brain extraction was achieved by creating an intracranial cavity mask (Kikinis et al., 1992). Diffusion weighted images were pre-processed using the Oxford centre for functional magnetic resonance imaging of the brain software library (FSL), correcting for eddy current distortions (Jenkinson and Smith, 2001), creating a binary brain mask (Smith, 2002), fitting the diffusion tensor model (Behrens et al., 2003), and estimating probabilistic diffusion orientation and diffusion parameters (Behrens et al., 2003). The diffusion images were co-registered with the AC–PC aligned T1 structural images using FSL's linear registration tool (Jenkinson and Smith, 2001).

Corpus callosum structural measures

Corpora callosa were manually delineated on the mid-sagittal slice of the AC–PC aligned T1-weighted image using 3D slicer software (www.slicer.org). The operator (D.K.T.) was blind to all perinatal data, and neurodevelopmental test results. Each CC was delineated twice, and the overlap of the two delineations was obtained and used as the final mask. Reliability, as measured by intraclass correlation coefficient, was 0.84 (95% CI 0.45, 0.95; p = 0.003), and the Dice overlap score (Pfefferbaum et al., 2006) was 0.89 (range 0.82 to 0.96, SD 0.04). The CC mask was sub-divided at intervals of one sixth, one third, one half, two thirds, and four fifths the distance from the most anterior to most posterior points, creating regions representing the genu, rostral body, anterior mid-body, posterior mid-body, isthmus and splenium, based on well established schemes (Hofer and Frahm, 2006; Witelson, 1989) as previously described (Thompson et al., 2011). The cross-sectional area of the whole CC and all sub-regions were corrected for the cross-sectional area of the intracranial cavity measured on the mid-sagittal slice from which the CC was delineated, as previously described (Thompson et al., 2011).

Measures of CC shape for this cohort have been previously described in detail (Thompson et al., 2011). In brief, CC eccentricity was measured by fitting an ellipse to each CC mask and calculating the ratio between the semi and major axes. CC skew was calculated by dividing the CC