Line Scan Diffusion Tensor MRI of the Cervical Spinal Cord in Preterm Infants

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Line scan diffusion tensor magnetic resonance imaging (DT-MRI) of the cervical spinal cord was demonstrated in vivo for unsedated preterm (gestational age 24–30 weeks at birth), very low birthweight (birthweight 620–1300 g) infants at postmenstrual ages from 29–40 weeks. Scalar invariant measures of diffusion [apparent diffusion coefficient (ADC) and relative anisotropy (RA)] determined from a cervical cord region of interest in each case are reported, characterizing the maturational status of the normal third trimester and newborn spinal cord. Mean ADC of 11 infants was $1.2 \pm 0.1 \mu m^2/msec$ and the mean RA was $24.3 \pm 4.9\%$. Normal infant cord neural fiber tract morphology was visualized using a mapping of the predominant diffusion tensor eigenvector. Potential clinical applications of line scan DT-MRI of the spinal cord of preterm and term newborns for assessment of spinal cord injury are discussed. J. Magn. Reson. Imaging 2001;13:949–953. © 2001 Wiley-Liss, Inc.

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NEUROIMAGING (NEURODEVELOPMENTAL) STUDIES of the preterm newborn brain using advanced magnetic resonance imaging (MRI) (1,2) techniques have shown that the description and appearance of local microstructure determined by diffusion tensor MRI (DT-MRI) (3) is feasible, provides valuable information regarding normal brain development, and can aid in early recognition of abnormalities leading to neurological deficits and functional disability (4–7).

DT-MRI, introduced by Basser et al (3,8), uses multiple samplings with diffusion-weighted pulsed-gradient pairs of differing directions and magnitudes to obtain the complete nine diffusion tensor components per voxel, from which the tensor eigenvectors and eigenvalues can be computed. Tensor eigenvectors represent the voxel-specific principal axes of diffusion, with the tensor eigenvalues equal to the diffusion coefficients characterizing diffusion of proton-bearing molecules along each respective orthogonal principal axis. Apparent diffusion can then be quantitatively analyzed, revealing intra-voxel information about the averaged local (intracellular and extracellular) environment.

In this study of the cervical spinal cord of unsedated preterm and near-term infants, DT-MRI was performed using the line scan diffusion imaging (LSDI) sequence of Maier and Gudbjartsson (9). Preliminary findings of this research have been reported previously (10). To analyze the microstructural tissue state of the cervical spinal cord in vivo, diffusion tensor eigenvalues, eigenvectors, and scalar invariant measures of anisotropy described by Basser (3) were calculated per voxel along with region of interest (ROI) statistics within the cord. Grayscale apparent diffusion coefficient (ADC) mappings and a diffusion tensor eigenvector map are displayed as examples of neural fiber tract visualization in infants with normal cord development.

The LSDI sequence is advantageous for imaging of infants since it is inherently insensitive to motion artifacts and able to produce diffusion maps without the use of restraints or cardiac gating (11,12). The LSDI sequence does not require high slew rate gradient hardware, and can be implemented on conventional clinical MR scanners (i.e., with slew rates < 20 mT/m/msec). Fast single-shot LSDI has recently been successfully developed and demonstrated in the adult brain by Fissterbusch and Frahm (13).

Recently, diffusion-weighted imaging of the normal adult cervical spinal cord was described by Clark et al (14) using a spin-echo sequence (15 minute acquisition, $256 \times 256$) with diffusion weighted pulsed-gradients requiring a navigator echo, peripheral pulse oximetry for gating, ECG triggering on every second R-wave, and fat saturation to eliminate ghost artifacts.
The spinal cord contains white matter (WM) composed of myelinated axons, neuroglia, and blood vessels that surrounds gray matter (GM) in the anterior (somatic efferent) and posterior horns (somatic afferent) composed of nerve cell bodies, dendrites, axons, neuroglia, and blood vessels. Caudal to cranial orientation of WM axonal bundles and GM lamina constituents supports spinal function, suggesting local DT eigenvalues consistent with cylindrical symmetry.

We demonstrate in this study that DT-MRI of the spinal cord using the LSDI sequence is feasible in newborns, can provide quantitative information and visualization in vivo regarding normal cord development, and may assist early recognition of abnormalities leading to functional disability.

METHODS

A convenience sample of eleven preterm (gestational ages 24–30 weeks at birth) very low birthweight (VLBW) infants (birthweight 620–1300 g), with no overt spinal cord abnormalities and no clinical indication to suspect spinal cord injury, were studied at post-menstrual age (PMA) 29–40 weeks. The age group studied represented stable, premature infants still in neonatal intensive care, at low risk of any acute life-threatening event at the time of the MR exam. The infants were selected as part of a larger prospective series of 108 VLBW infants born at the Brigham and Women’s Hospital during 1997–1999 who were recruited for MRI studies after informed parental consent. In addition, for a general comparison of maturational differences, two healthy normal adult volunteer subjects, 19- and 47-years old were also studied.

The hospital human subjects review board approved the study. Informed consent was obtained from the parents of each infant. No sedation was used, infants were fed immediately before the examination, ear/hearing protection (Natus Medical Inc, San Carlos, CA) was utilized, and a vacuum fixation pillow (S&K Xray Products, Inc., Brooklyn, NY) was utilized as a head cradle. Cardiorespiratory monitoring was used for all the examinations (Datascope Corp., Paramus, NJ). Infants were under the constant supervision of a neonatologist at all times throughout the examinations.

Preparing T1-weighted sagittal MRI localizer scans of the (typically sleeping) supine infant, DT-MRI data were acquired in the medial sagittal plane using a quadrature birdcage headcoil. The LSDI sequence was used (11). The LSDI sequence was adapted for neonatal neuroimaging using diffusion sensitivities $b = 5$ and 700 s/mm$^2$, where $b = 3(a\delta G)^2(D-\delta/3)$, $a$ is the proton gyromagnetic ratio, $G$ is the diffusion gradient magnitude, $\delta$ is the diffusion gradient duration (40.5 msec), and $\Delta$ is the gradient leading edge separation (50.0 msec). Other parameters were: TE = 105 msec and TR = 155 msec. employing seven measurements (16) with noncollinear gradient axes $[[1,0,0],[0,1,1],[1,0,1],[1,-1,0],[0,1,-1],[1,1,1]]$. The field of view (FOV) was $18 \times 13.5$ cm with a $128 \times 96$ matrix, 4.4-mm effective slice thickness (9). 1-minute acquisition per slice. A 1.5-T GE Signa MR scanner (GE Medical Systems, Milwaukuee, WI), initially with 10 mT/m maximum gradient amplitude, later upgraded to GE Signa LX scanner with 40 mT/m maximum gradient amplitude, was used. The bandwidth was $\pm 4$ KHz in order to avoid loss of signal-to-noise at higher bandwidth, and augmented image distortion caused by field inhomogeneities at lower bandwidth.

For each subject, an ROI was manually selected, composed of approximately 14 (range 5–60) voxels (each voxel 8.7 mm$^3$) in the C2–C7 cord region, defined specifically to exclude any cerebrospinal fluid (CSF) contribution. Analysis of ROI statistics was performed with XPhase image analysis software (S.E. Maier, unpublished software).

Apparent diffusion was measured according to the Stejskal and Tanner equation (16) with the diffusion tensor elements estimated for each voxel by non-linear regression, as suggested by Basser et al (17). Off-diagonal components of the diffusion encoding were ignored, as they have negligible magnitude with the LSDI sequence relative to diagonal tensor elements. Three eigenvalues (i.e., $\lambda_1$, $\lambda_2$, $\lambda_3$) and eigenvectors of the diffusion tensor $\mathbf{D}$ were computed per voxel, from which were also computed the apparent diffusion coefficient (ADC).

$$\text{ADC} = \frac{1}{3} \text{Trace } \mathbf{D} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad (1)$$

and relative anisotropy (RA) (10).

$$\text{RA} = \frac{1}{3} \left( \frac{1}{\text{ADC}} \cdot \lambda_1 \right) = \frac{1}{3} (\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2) / \text{ADC}. \quad (2)$$

The eigenvector corresponding to the maximum diffusivity describes the direction along which maximum rate of diffusion occurs, and is assumed to parallel the axonal fiber-tract axis in the spinal cord. The eigenvectors corresponding to the diffusivities of smaller magnitude represent directions with a lesser rate of diffusion, assumed to be in the transverse plane, perpendicular to the fiber-tract axis.

In each selected ROI for each infant studied, the ADC and RA were computed. The ADC represents the apparent rate of (isotropic) diffusion and the RA represents a measure of preferred directionality of water diffusion (8). In areas where diffusion is isotropic, the RA approaches zero, whereas in areas with a preferred direction of diffusion, the RA is increased, consistent with Eq. [2]. We deduced that the preferred direction of diffusion was parallel to the axonal fiber bundle direction, since the maximum rate of diffusion during the MRI encoding time was assumed to occur along the fiber-tract axis. Due to the predominant direction of diffusion being coincident with the major cord axis, we used the RA as an indirect measure of fiber tract development.

Vector maps of fiber orientation were also produced by drawing, per voxel, the projection of the eigenvector corresponding to the largest eigenvalue with magnitude scaled by the voxel RA overlaid on standard image data for reference. By this method, vectors indicating the
The direction of principal diffusion would appear longer in areas with relatively higher anisotropy (fiber tracts), and shorter in areas without a preferred diffusion direction (1), i.e., more isotropic diffusion.

RESULTS

Mean ADC for the infants was 1.2 ± 0.10 μm²/msec and was slightly greater than the mean adult ADC of 1.0 μm²/msec (Fig. 1). Mean RA values for the infants was 24.3 ± 4.9%, which was lower than the mean adult value of 42.5% (Fig. 2). Figure 3 (a–c) display, respectively, diffusion-weighted image (b = 700 s/mm²), ADC grayscale map, and T2-weighted MRI of a former 24 week gestation infant (extremely low birthweight, 620 g) at PMA 40 weeks. Motion artifact at the infant’s tongue due to sucking motion occurred independent of the infant’s stationary head position in the vacuum fixation pillow head cradle. Similar images from a 47-year-old adult scanned for comparison to the infants are displayed in Figure 4. The loss of signal at the lower cervical spine was due to the spatial extent of the head coil used, so optimal coverage was precluded here of the lower cervical and upper thoracic spine. A vector map of fiber orientation overlaid on a standard image data for reference is illustrated in Figure 5. These fiber tracts were not distinguishable with conventional T1- or T2-weighted MRI.

DISCUSSION AND CONCLUSIONS

DT-MRI of the cervical region of preterm infants provides objective quantitative measures of the developing intravoxel microstructure of the human cervical spinal cord. DT-MRI acquisition was successful in our study using the LSDI sequence, and benefited from its relative motion insensitivity compared to multi-shot echo planar-based diffusion-weighted imaging (DWI) methods. Single-shot echo planar imaging (EPI) of the cord is not practical because of susceptibility-related artifacts occurring when imaging close to bone structures. Furthermore, LSDI is very efficient, and complete coverage of the region can be achieved with reduction of the FOV, providing even greater reductions in overall scan acquisition time.

DT-MRI results obtained in this study from a small number of infants distributed throughout the PMA 29–40 weeks range illustrate the diffusive characteristics of the cervical spinal cord in infants. A study consisting of a greater number of subjects at each interim range is required in order to make more definitive statements regarding developmental (i.e., time-dependent) changes of cord architecture.

ADC values obtained from the cervical spinal cord, as shown in Fig. 1, corresponded closely with those found in the internal capsule (1.0 ± 0.1 μm²/msec) in this age group (1). Like the internal capsule, the cervical spinal cord during this maturational period is well-myelinated, and thus exhibits the relatively lower ADC values associated with myelinated regions. During the third trimester, cervical cord development substantially precedes the developmental changes in ADC observed in the cerebral central WM. In the central WM, myelination is still occurring, significantly altering the WM tissue diffusive environment (1,2). Cervical cord ADC val-
ues were relatively lower compared to the high-ADC (1.7 ± 0.1 μm²/msec) unmyelinated frontal lobe WM, which contains relatively freely diffusing water at this stage of development (1). Thus, the microstructural findings obtained by this in vivo technique are consistent with prior autopsy results (18).

Relatively unchanging RA values observed throughout the range of PMA 29–40 weeks reflect the previously matured fiber tract organization and myelination of the infant cervical cord consistent with immunohistochemical findings of myelination in the cord at this developmental stage (19). These ADC and RA results also are consistent with the mature fiber tract organization illustrated in Figure 5.

Spinal cord injury in the newborn infant presents major difficulties in diagnosis and management with significant long-term medical, legal, and ethical implication (20). Reports of improved prognosis in acute spinal cord injury related to early treatment with corticosteroids (21) serve to emphasize the need for methods for accurate and sensitive assessment of the spinal cord in newborns. Significant deviations in ADC have been recently observed in vitro in the injured rat spinal cord (22,23). In view of the feasibility of the measurements made in this study of normal infants and the developmental features defined, it is reasonable to suggest that significant deviations in ADC and RA values of the developing infant cervical spinal cord could serve as a measure of injury or abnormal development, though this requires demonstration in actual cord-injury cases. Visualization of perturbations in the cord fiber tracts compared to those seen in Fig. 5 could serve in the detection or confirmation of lesions not unequivocally apparent in standard T1- and T2-weighted imaging. We are currently studying additional sensitive measures for characterizing normal and abnormal cord development (24).

Figure 3. (a) Sagittal diffusion-weighted image (b = 700 s/mm²), (b) ADC grayscale map, and (c) T2-weighted MRI for former 24 week gestation (birthweight 620 g) at PMA 40 weeks.

Figure 4. (a) Sagittal diffusion-weighted image (b = 700 s/mm²), (b) ADC grayscale map, and (c) T2-weighted MRI for adult.
The eigenvector onto the image plane for each voxel, with the RA-scaled projection of the dominant sagittal diffusion-weighted scan (b = 700 s/mm²) overlaid, for each voxel, with the RA-scaled projection of the dominant eigenvector onto the image plane.

The results of our study indicate that advances in fast, relatively motion-insensitive linescan pulse sequences (9,11,13,25) for DT-MRI can provide information in vivo regarding normal cord development and may, in the future, offer the possibility of early detection and assessment of abnormal spinal cord development or injuries in this population of infant patients.

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