

Diffusion Tensor Scalars Vary with Age and Across Spinal Levels in Children

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Abstract

Purpose: 1) To evaluate the maturational evolution of the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) of the normal pediatric cervical as well as upper thoracic cord, 2) to evaluate whether ADC and FA values vary at different levels within the spinal cord [upper cervical (UC), lower cervical (LC) and upper thoracic (UT)].

Methods: Normal pediatric MRI and diffusion tensor imaging (DTI) studies of the spinal cord obtained with a 1.5 Tesla MR scanner were retrospectively analyzed. ADC and FA maps were reconstructed from the DTI data. Regions of interest were manually placed at the center of the cervical and upper thoracic cord at the intervertebral disk levels in mid-sagittal plane. The ADC and FA values were analyzed by linear regression and a general linear model with repeated measures.

Results: Forty-seven subjects ranged in age from 2 months-17.5 years (mean \pm standard deviation: 74.3 \pm 61.1 months) were included in the study. At all spinal cord levels a statistically significant decrease in ADC and increase in FA with increasing child's age was evident. The ADC values of the UC/LC levels were higher than those of UT while the FA values did not show significant differences.

Conclusion: DTI scalars vary with age, likely due to ongoing maturational processes, and ADC values vary across levels of the spinal cord. Consequently when quantitative DTI of the spinal cord is undertaken in children; an age and level-matched normative data should be used to accurately interpret the quantitative results.

Keywords: Apparent Diffusion Coefficient (ADC), Fractional Anisotropy (FA), Diffusion Tensor Imaging (DTI)

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Introduction


Diffusion tensor imaging (DTI) is a non-invasive, advanced imaging modality that has helped in understanding the pathophysiology of white matter diseases at a microstructure level in the brain and might be an important additional tool for the quantitative evaluation of the spinal cord. The spinal cord DTI studies in the literature are limited in number compared to brain DTI studies and mostly are performed in adults and focused on the cervical spinal cord [1-10]. This is due to inherent technical challenges of the spinal cord DTI; related to small cord volume, susceptibility artifacts created by different tissue interfaces such as bone, soft tissue, CSF; as well as CSF pulsation, respiratory and cardiac

motion artifacts. These artifacts affect the thoracic cord the most at mid thoracic level, therefore the majority of the prior studies focused on cervical spine or even upper cervical spine.

There are even less studies in children and hardly any normative data [5,6,11,12]. Age-specific normative data are necessary to identify and grade spinal cord pathology in developing children. Similar to the brain, many ongoing maturational processes

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(myelination, fiber packing, networking, sprouting of synapses, etc.) are expected to alter the DTI scalars of the spinal cord [13,14]. Another aspect of spinal cord is potential differences across spinal levels [15]. Only recently Barakat et al. in 25 normal children aged 7 to 21 years showed a variation in DTI metrics between C1 and T1 levels [5].

The goals of this study were two-fold. 1) To evaluate the age-dependent evolution of the ADC and FA values of the normal pediatric cervical spinal cord as well as upper thoracic cord, and 2) to evaluate whether there are statistically significant differences of ADC and FA values between upper cervical, lower cervical and upper thoracic levels in developing children.

Materials and Methods

Subjects

All children studied by MRI and DTI of the cervical and upper thoracic cord were retrospectively evaluated. Children 0 to 21 years old with good quality spinal MRI and DTI images were included in this study. Exclusion criteria were 1) clinically confirmed pathology or disease of the spinal cord or central nervous system, 2) positive MRI and DTI findings for disease of the spinal cord, 3) non-diagnostic image quality and 4) incomplete clinical and imaging information. The cut-off age of 2 (30 months to be precise) was chosen as it is a widely-accepted milestone for early maturation including myelination in the corticospinal tracts which neurodevelopmentally correlates to independent walking and effective hand control (reaching and grasping). The study was approved by the institutional review board of our hospital with permission to access the patients' database.

Imaging Techniques

All MRI studies were performed on a clinical 1.5 Tesla MR scanner (Avanto, Siemens Healthcare, Erlangen, Germany) using a standard 4-element neck matrix coil and a standard 24-element spine matrix coil. Routine conventional sequences of the spine were performed including axial and sagittal T1- and T2- weighted turbo spin echo imaging and sagittal short [inversion time (TI)] inversion recovery (STIR) sequences.

We obtained sagittal DTI of the cervical and upper thoracic spinal cord using a single-shot, interleaved, multi-slice, spin-echo EPI pulse sequence in combination with parallel imaging with an acceleration (iPAT) factor of two. Cervical and upper thoracic cord could be included in a single FOV with minimal artifacts as detailed above. DTI images were acquired using the following parameters: TR: 2400 ms; TE: 100 ms; field-of-view: 220 mm; slice thickness: 1.9 mm; imaging matrix: 192x192 with an in-plane resolution of 1.1x1.1 mm. Balanced pairs of diffusion gradients were used, centered around the 180° pulse, to minimize eddy current effects. The tensor of the diffusion was sampled by diffusion gradients oriented in 20 non-collinear directions in space using two b-values (0 and 750 mm²/s). No respiratory or cardiac gating was performed. Diffusion weighted images, as well as ADC, FA and color-coded FA maps, were created using the standard vendor-

specific software (Siemens Neuro3D).

Data analysis

The conventional MRI images and post-processed DTI maps (ADC and FA maps) were visually evaluated for quality and for any incidental pathology by 2 experienced pediatric neuroradiologists. Any spinal cord level which showed distortion, artifacts or inhomogeneity of the signal intensities was excluded. Regions of interest (ROI) were manually placed at the center of the cervical and upper thoracic spinal cord at every intervertebral disk level defined on a sagittally reconstructed trace-image. Meticulous ROI-placement to avoid the partial volume averaging effect with the CSF was performed at mid-sagittal images. Sizes of the ROIs ranged between 2-9 mm² to include the maximum cord area while avoiding the CSF averaging (**Figure 1**). Average ADC and FA values were collected over the selected ROIs at every intervertebral disc level concurrently with the minimum and maximum values and standard deviations. Any measurement which showed more than 30% standard deviation was not included in the analyses. The upper cervical level (UC) was defined from the cranio-cervical junction to C3/4 intervertebral disc level. The spinal cord ROIs at C4/5-C7/T1 were classified as lower cervical level (LC) and T1/2-T4/5 were classified as upper thoracic level (UT). Each of UC, LC, UT levels was comprised of up to 4 measurements and for that reason there were up to 12 measurements per child.

Statistical analysis

Statistical analysis was performed with STATA version 11.1 (STATA Corporation, 2010; College Station, Texas). Linear regression was used to evaluate the relationship between age and ADC and FA. The subjects were also classified into two groups by age less than or greater than 2 years (specifically 30 months). The ADC and FA values were compared between the two age groups across the

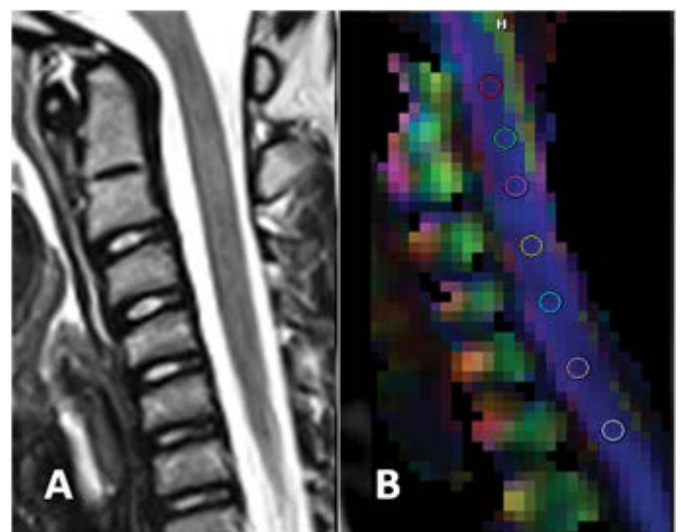


Figure 1 T2 weighted sagittal (A) color coded FA map of sagittal DTI (B) showing ROI placements in the spinal cord

levels UC, LC, and UT using a general linear model with repeated measures. Up to 12 measurements (excluding those with more than 30% standard deviation) were used for each child in a mixed effects model with fixed effects of area (LC, UC, UT) and level (4). This general linear model used the available measurements as repeated measures for each child to compare the three areas for FA and ADC individually. A two-tailed p-value ≤ 0.05 was considered statistically significant.

Results

Forty-seven subjects were included (23 male, 24 female) with mean \pm standard deviation (SD) age of 74.3 ± 61.1 months (range 2 months-17.5 years). Using a cut-off age of 2 years (30 months), there were 16 subjects ≤ 2 years of age (34%) and 31 subjects older than 2 years (66%).

Across the 47 scans, after exclusion of the levels with significant artifacts; there were 176 ADC measurements (mean \pm SD: 3.7 ± 0.6 per scan) at the UC level, 180 ADC measurements (3.8 ± 0.4 per scan) at the LC level, and 139 measurements (3.0 ± 1.2 per scan) at the UT level. Across the 47 scans, there were 178 FA measurements (mean \pm SD: 3.8 ± 0.5 per scan) at the UC level, 179 FA measurements (3.8 ± 0.4 per scan) at the LC level, and 142 measurements (3.0 ± 1.2 per scan) at the UT level.

ADC and FA demonstrated statistically significant relationships with age for all three spinal levels, decreasing and increasing, respectively (Table 1 and Figure 2). The mean ADC values for ages ≤ 2 years were significantly greater than for ages >2 years at each of the three levels (Table 2 and Figure 3). The mean FA values for ages ≤ 2 years were significantly less than for ages >2 years at all three levels (Table 3 and Figure 4). When comparing levels within each age category, UT has significantly lower ADC values than either UC or LC (Table 4 and Figure 3). No significant differences between levels were found for FA values within each age category (Figure 4).

Discussion

MRI diffusion tensor metrics; ADC and FA in this study; at cervical and upper thoracic cord; showed relationships with age in children of ages from 2 months to 17.5 years. ADC values decreased and FA values increased with increasing age. This result correlates with the previous DTI studies which showed an age-related ADC decrease and FA increase in the brain [14,16,17]. Recently Singhi et al. showed age-related ADC decrease and FA increase in the

Table 1 Slope and 95% confidence intervals (CI) for apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values with age for three spinal cord levels

Level ^b	ADC ^a	FA
	Slope ^c (95%CI)	Slope (95%CI)
UC	-12.8 (-19.1, -6.4)	0.012 (0.007, 0.016)
LC	-12.4 (-12.9, -3.0)	0.010 (0.006, 0.014)
UT	-15.1 (-22.8, -7.3)	0.008 (0.003, 0.012)

^a $10^{-6}\text{mm}^2/\text{s}$; ^bUC-Upper Cervical, LC-Lower Cervical, UT-Upper Thoracic; ^cSlope represent change in ADC/FA for each year increase in age

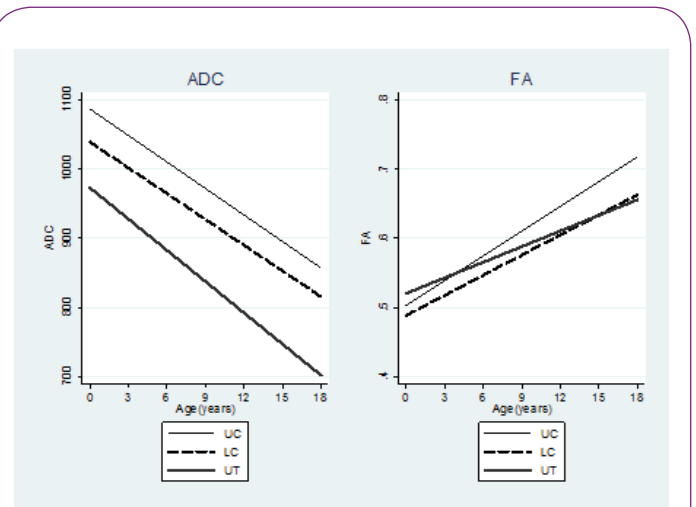


Figure 2 Association of apparent diffusion coefficient (ADC) ($\times 10^{-6}\text{mm}^2/\text{s}$) and fractional anisotropy (FA) with age by spinal cord level (UC-upper cervical, LC-lower cervical, UT-upper thoracic).

Table 2 Comparison of the ADC^a values by age categories split at two years (30 months) for three spinal cord levels.

Level ^b	ADC value $\times 10^{-6}\text{mm}^2/\text{s}$ (95% CI ^c)		p-value
	≤ 2 years (n=16)	> 2 years (n=31)	
UC	1085.8 (1021, 1150)	970.4 (923, 1018)	0.005
LC	1052.8 (988, 1117)	919.0 (872, 966)	0.001
UT	980.0 (914, 1046)	836.0 (785, 887)	0.001

^aADC-Apparent Diffusion Coefficient; ^bUC-Upper Cervical, LC-Lower Cervical, UT-Upper Thoracic; ^cCI-Confidence Interval

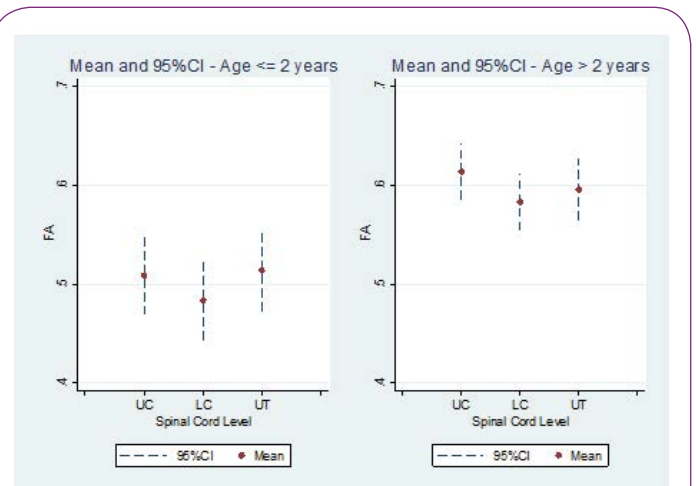


Figure 3 Mean and 95% confidence interval (CI) of fractional anisotropy (FA) values by spinal cord level (UC – upper cervical, LC – lower cervical, UT – upper thoracic) and age category (where two years represent 30 months of age).

UC spinal cord in 41 normal children [11]. Otherwise there are no previous studies, to our knowledge, that investigated the normal diffusion metrics of the spinal cord in children from infancy to adulthood. A gradual decrease in ADC and gradual increase in

Table 3 Comparison of the FA^a value by age categories split at two years (30 months) for three spinal cord levels.

Level ^b	FA value (95% CI ^c)		p-value
	≤ 2 years (n=16)	> 2 years (n=31)	
UC	0.509 (0.469,0.548)	0.613 (0.585, 0.642)	< 0.001
LC	0.484 (0.444,0.524)	0.583 (0.554, 0.611)	< 0.001
UT	0.514 (0.473,0.554)	0.595 (0.564, 0.626)	0.002

^aFA-Fractional Anisotropy; ^bUC-Upper Cervical, LC-Lower Cervical, UT-Upper Thoracic; ^cCI-Confidence Interval

developmental process from fetal life to the 2nd year of life by macroscopic and microscopic analysis of preserved human spinal cord specimens [13]. The authors showed an orthograde (craniocaudal) maturation of the lateral and ventral corticospinal tracts in the first 2 years of life. A larger normal population between 0 to 2 years of age and axial DTI acquisition with high resolution can enable measurements of specific corticospinal tracts and would probably demonstrate the same orthogonal maturation by using DTI.

The UT cord showed significantly lower ADC values than either the UC or LC in both age groups in our study. A recent cervical spinal cord DTI study in developing children also showed a gradual decrease in mean diffusivity (MD) (synonymous to ADC) in craniocaudal direction (C1 to T1) [5]. This is attributed to the decreasing number of axons in the spinal cord from cervical to thoracic direction, which was also mentioned in adult DTI studies [2,18]. Interestingly the same study showed a gradual decrease in FA from superior to inferior direction whereas in our study FA did not show statistically significant differences across spinal cord levels. Major white matter tracts are highly ordered and course in a single direction (craniocaudal or caudocranial) in the human spinal cord. Even without myelination of the axons there is high anisotropy along the longitudinal axis of the cord; on the contrary to the brain where there are innumerable crossing fibers. We think the decreasing number of axons craniocaudally result in decreased diffusion in both axial and radial diffusion keeping the FA constant [14]. Secondly, the previously published data represents the age range from 7 years to 85 years whereas our cohort includes 31 children between 2 months and 6 years of age which might have affected the FA results differently. The potential effect of gray matter inclusion on sagittal DTI makes understanding the simultaneously ongoing maturational processes and changes in FA and ADC metrics more difficult.

There are some limitations of our study. First, cardiac or respiratory gating was not used during MR scanning. The thoracic levels are the most sensitive to respiratory and cardiac motion. Therefore some cardiac and respiratory artifacts may have biased our results. This might be reflected on smaller number of measurements of good quality DTI data in UT compared to cervical cord. However gating increases the scanning time and our goal was to keep scanning time to a reasonable minimum for a clinical MRI in this pediatric population (the used DTI sequence takes approximately five minutes). Secondly, by measuring ADC and FA at mid-sagittal plane we have most likely included both gray and white matter in the voxel, however this is an inherent limitation of a sagittal DTI technique and the measured values represent an overall diffusion characteristics at the individual cord levels. Sagittal DTI acquisition was chosen as it took shorter scan time compared to axial acquisition and allowed scanning of the entire cervical and upper thoracic cord in a single acquisition. Thirdly, due to limitations of DTI technique in applying to the spinal cord especially at the upper thoracic cord level as listed before; we had to exclude data with artifacts and this resulted in varying numbers of samples for each three spinal cord levels.

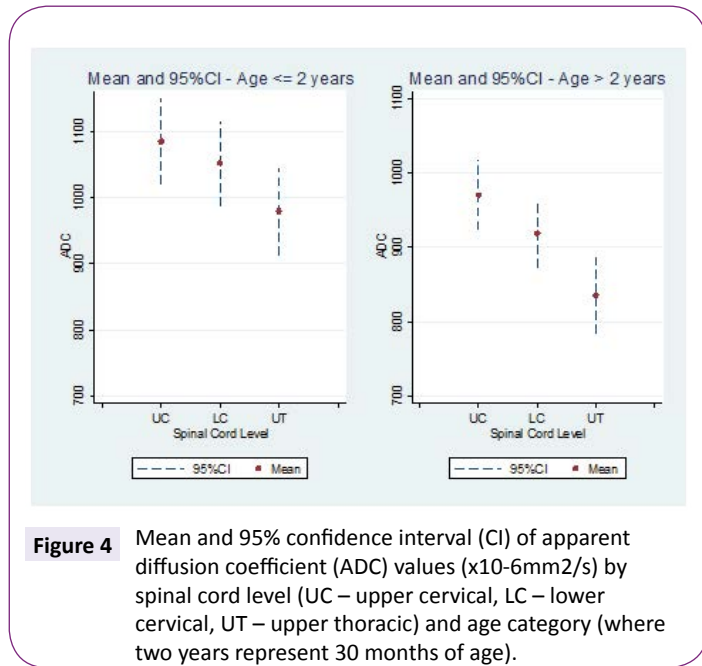


Figure 4 Mean and 95% confidence interval (CI) of apparent diffusion coefficient (ADC) values ($\times 10^{-6} \text{mm}^2/\text{s}$) by spinal cord level (UC – upper cervical, LC – lower cervical, UT – upper thoracic) and age category (where two years represent 30 months of age).

Table 4 Comparison of the ADC^a values between levels for each age group.

Level ^b	Mean difference of the ADC value $\times 10^{-6} \text{mm}^2/\text{s}$ (95% CI ^c)			
	≤ 2 years (n=16)	p-value	> 2 years (n=31)	p-value
LC-UC	-33.0 (-108, 42)	0.391	-51.5 (-106, 3)	0.066
UT-UC	-105.8 (-182, -30)	0.006	-134.5 (-193, -76)	< 0.001
UT-LC	-72.9 (-149, 3)	0.061	-83.0 (-141, -25)	0.005

^aADC-Apparent Diffusion Coefficient; ^bUC-Upper Cervical, LC-lower Cervical, UT-Upper Thoracic; ^cCI-Confidence Interval

FA with increasing age reflects CNS maturation process in the spinal cord which includes myelination of the axons, membrane proliferation, decreasing extra axonal space and decreasing overall water content among other things that are not yet well known [14].

When the study cohort was divided into two groups, the ADC values were significantly lower and FA values were significantly higher at all levels in children older than 2 years of age compared to children equal to or younger than 2 years of age. The cut-off age of 2 (30 months to be precise) was chosen as a widely-accepted milestone for early maturation including myelination in the corticospinal tracts which neurodevelopmentally correlates to independent walking and effective hand control (reaching and grasping). Altman J and Bayer S.A. demonstrated this

Lastly, this is a retrospective study and prospective larger multi institutional population based studies would be the ideal study design.

Conclusion

Our study shows that developmental differences in maturing pediatric spinal cord exist and it should be taken into account when MR imaging with DTI is undertaken in children. We

recommend having an age and level-matched normative data for more accurate interpretation of the DTI results. A quantitative in vivo method of spinal cord imaging is important in young children with spinal cord injury.

Conflicts of Interest and Source of Funding Related to the Study

No conflicts of interest and no funding was received for this study.

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