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Diagnostic value of diffusion tensor imaging derived metrics as biomarkers of cerebral changes in developmental delay

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Abstract

Context: Children with developmental delay (DD) can be rehabilitated if an early diagnosis and intervention is done. A negative magnetic resonance imaging (MRI) study utilizing routine sequences makes it difficult for the clinician to convince the family toward a long-term rehabilitation schedule. Diffusion tensor imaging (DTI) can demonstrate deranged myelination in developmentally delayed children having normal routine MRI. **Aim:** To evaluate the role of DTI-derived metrics for assessment of deranged myelination in developmentally delayed children having normal routine MRI. **Study Setting and Design:** Prospective case control observational study conducted over a cross-section of referrals at a university-based teaching institute over a period of 2 years. **Patients and Methods:** Fifty cases of DD and 15 age-sex matched controls (age group of 2-12 years) were included from those presenting voluntarily to the pediatric out-patient services. Routine MRI and DTI were performed in both the groups following a standard protocol. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were calculated in certain pre-defined regions. **Statistical Analysis:** Central tendency was measured for each of the metrics using mean. Inter- and intra-group comparisons were performed using *t*-test. **Results:** Twenty-three regions of interest with 46 variables were included in the final analysis. Nineteen (82.60%) regions of interest showed at least one statistically significant variable, while 24 out of 46 (54.34%) variables showed statistical significance for future consideration. The important regions to be evaluated in a case of DD are the corpus callosum, bilateral forceps minor and forceps major, bilateral parietal lobes, bilateral post-central gyrus, and bilateral posterior limb internal capsule (PLIC). The regions which did not show any significance are bilateral pars triangularis and right frontal lobe. Other regions remained indeterminate and need further evaluation. **Conclusion:** DTI demonstrates myelination abnormality in children with DD, having a normal routine MRI.

Key words: Apparent diffusion coefficient; developmental delay; diffusion tensor imaging; fractional anisotropy; magnetic resonance imaging

Introduction

Developmental delay (DD) is a common pediatric clinical syndrome affecting 10-15% of children.[1] The etiological insult leading to the embryological or fetal neuropathological changes that ultimately lead to DD can occur anywhere from pre-conception period till the time the child is born. These include varied causes like chromosomal anomalies, genetic mutations, toxic insults due to drugs and exogenous toxins, intrauterine infections, and feto-maternal endocrinal and metabolic imbalances.[2] Irrespective of the causative agent, the clinical manifestation remains common and stable, and mandates social counseling and physiotherapy to promote brain plasticity. Further, addition of certain neuroprotective and neurotonic drugs

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may hasten the process.[3] MRI is an important part of the comprehensive evaluation of children who receive a clinical diagnosis of DD. In the majority of cases, however, patients with DD have a "normal" MRI study, performed utilizing the routine sequences,[1] a fact which makes it very difficult for the treating physician to convince himself and the patient's family for making a long-term effort toward achieving developmental functionality for the child. Diffusion tensor imaging (DTI) is an emerging MRI-based technique that is often used in research and applied to the study of white matter fiber tracts. Quantitative DTI metrics like fractional anisotropy (FA) and apparent diffusion constant (ADC) have been shown to demonstrate progressive changes with age and cerebral white matter maturation.[4] Recent studies using DTI have shown detection of abnormalities in cerebral parenchyma of children showing DD.[5] Hence, DTI and related metrics can be used as non-invasive neuroimaging surrogates of DD. In light of emerging evidences, the present study intends to evaluate the cerebral morphology of patients diagnosed with DD using routine as well as DT-MRI to statistically validate the above notion. Further, inclusion of quantitative DT-metric in certain pre-designated regions would provide a numerical substantiation to the hypothesis.

Patients and Methods

The present study was a "prospective observational case control study" performed after obtaining due approval from the institutional review board and written informed consent from the legal guardians of patients. The study was conducted over 2 years duration, from June 2011 to July 2013. Cases were selected from the patients referred to the authors for MRI, as a part of routine clinical protocol during the course of their evidence-based management. Further, DTI was performed as an addition, over and above the routine sequences, without much increase in the time of imaging, after providing due information to and obtaining permission from the patients' legal guardians. No additional sedation or cost was incurred to the patient for additional sequences.

Cases and controls

Fifty consecutive cases [Table 1] of clinically diagnosed "global DD" were included in the study. These cases were diagnosed based on the established criteria.[1,2,6] Patients with other confounding factors like history of past or active cranio-spinal infection, systemic illness, and any ongoing chronic illness were, however, excluded. Patients having morphologically demonstrable abnormality on routine MRI sequences were also excluded. The mean age of the group was 4.76 years (range 2-12 years), with 30 male and 20 female patients having been included. Patients with age less than 2 years were not included, as normal myelination completes by 18-24 months of age.[7] Fifteen age- and gender-matched controls (mean age = 5.1 years) were selected for comparison. These included 10 male and 5 female controls. The controls were selected from those being referred for brain MRI for indications other than DD, such as incidental scalp lipoma ($n = 3$), scalp arteriovenous malformation ($n = 1$), superficial head injury ($n = 4$), conducting hearing deficits ($n = 3$), and reduced visual acuity ($n = 4$). All these patients were neurologically stable and revealed no signs of DD as per the established clinical criteria.

Table 1: Age distribution of five different age-groups, included in the study

Age (years)	Cases		Controls	
	No.	%	No.	%
2-4	27	54	4	26.6
4-6	12	24	4	26.6
6-8	3	6	6	40
8-10	6	12	0	0
10-12	2	4	1	6.6
Total	50	100	15	100

$P = 0.076$

Imaging

Routine (morphological/anatomical) MRI

Both groups underwent routine MRI on a 1.5 T Magnetom Avanto (Version BV-I7A; Siemens Medical System, Erlangen, Germany) system, equipped with an actively shielded whole body magnet. A quadrature bird-cage transmit receive coil (8 channel) was used for imaging. A pre-standardized protocol was followed for routine morphological imaging. This included high-resolution anatomical images acquired with a T1-weighted sagittal 3D MPRAGE sequence [repetition time (TR) 7.1 ms, echo time (TE) 3.45 ms, inversion time (TI) 1000 ms, flip angle 7°, field of view (FOV) 256 mm × 256 mm, and slab thickness 150 mm] for fusion of DTI data, along with T2, fluid attenuation inversion recovery (FLAIR) sequences as provided by the vendor propriety software. The acquisition matrix was 256 × 192 × 128, giving a reconstructed voxel resolution of 1.0 mm × 1.0 mm × 1.33 mm.

Diffusion tensor imaging

The DTI sequence utilized was a single-shot, balanced echo echoplannar imaging EPI sequence with timing parameters of TR 6000 ms and TE 97 ms. Twenty contiguous transverse slices with a slice thickness of 5 mm were aligned parallel to the anterior commissure and posterior commissure plane and covered all but the topmost part of the brain. The FOV was 128 × 128 mm, acquisition matrix 96 × 128, reconstructed to 128 × 128, giving a reconstructed in-plane resolution of 1.78 mm × 1.78 mm. For each slice, one image without diffusion weighting (b = 0 s/mm^2) and six images with diffusion weighting (b0 = 1000 s/mm^2) applied along six non-collinear directions were acquired. The six DTI acquisitions for each subject were registered using

a mutual information cost function and a 12-parameter transformation with the first b = 0 s/mm^2 volume reference.

Post-processing and analysis

Data post-processing was done using the automated Neuro-3D software (Siemens Medical System) on the offline workstation. The routine images were analyzed and reported initially by a junior radiologist (NCS) with three years experience, which was followed by repeat examination and validation by a senior radiologist (AV), with ten years experience. The senior radiologists, however, evaluated and reported the DTI data prior to viewing the routine MR imaging, to exclude any kind of observer bias. Another senior radiologist (AS), with twenty five years experience, evaluated all the sequences to ascertain the quality of imaging and validity of data collection. DTI data were evaluated in two steps: Firstly, a random eyeball evaluation of the DTI color maps (RGB maps) [Figure 1] and the tractographic fusion map [Figure 2] was done; secondly, a semi-quantitative evaluation of the same images was done to pre-identify areas of asymmetry of color saturation and hue. These were done for guiding and correlating with the quantitative analysis, which was the final aim of this study. Finally, quantitative analysis of FA and apparent diffusion coefficient (ADC) maps, generated automatically by the propriety software, was done by drawing region of interest (ROI) in the interactive maps, to include the white matter tracts emanating from the most functionally active areas in the brain (these included genu, body, and splenium of corpus callosum, bilateral forceps minor and major, bilateral frontal and parietal lobes, bilateral pre- and post-central gyrus, bilateral anterior and posterior limbs of internal capsule, bilateral temporal lobes, and pars triangularis). A diameter of 3 mm was used for each ROI and an average of three consecutive values at the same point was registered.

Statistical analysis

This includes the data charted while calculation of ROIs of various white matter areas. Mean ADC and FA values for each ROI were charted for each patient and then the algebraic mean of all values was calculated for each. This exercise was repeated for both cases and controls, so that the final numerics could be used for intergroup comparison of each of the anatomically significant areas, for both FA and ADC. Intergroup comparison of both variables, for each of the described areas, was done by using the non-parametric Mann-Whitney test using the SPSS software (SPSS version 17.0; SPSS, Chicago, IL, USA). $P < 0.05$ was used as an indicator of significance.

Results

Study population

No significant difference was noted between the case and control groups as far as the numerical adequacy and gender composition was concerned [Table 2] with a $\chi^2 = 0.217$ ($P = 0.642$). Although a male preponderance was noted amongst the cases in the present study, no statistical significance could be ascribed to the same. Majority of participants were in the age group of 2-4 years among cases as opposed to the controls where the majority was in the age group of 4-6 years; this again, however, failed to bear any statistical significance.

Imaging

Routine/morphological/anatomical imaging and semi-quantitative evaluation

Interestingly enough, the prospective evaluation of morphological imaging (without the color-coded RGB maps being available) of all cases was labeled as normal by all the radiologists. However, on a retrospective blinded evaluation of the same cases (RGB maps available, but without the availability of corresponding numerical data), about 47% of cases were labeled to have a "probably abnormal" morphological imaging. The areas identified as being "probably abnormal" coincided with the actual areas of

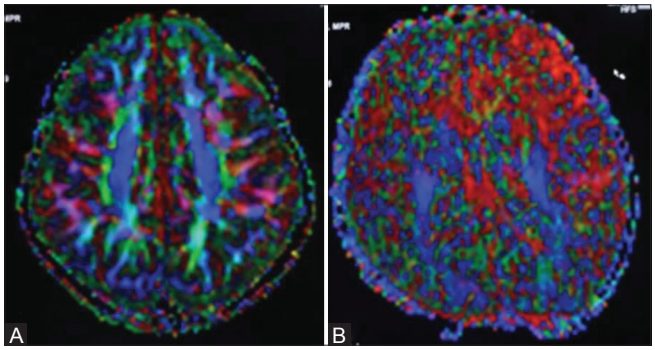

Figure 1 (A and B): Axial color-coded RGB maps (shown in gray scale here) of a control (A) and a case (B) at the level of parietal white matter. Note the loss of color-coded vectarity in the case in almost all regions, as compared to the control. The numerical values of this case were also abnormal in the areas depicted in RGB maps

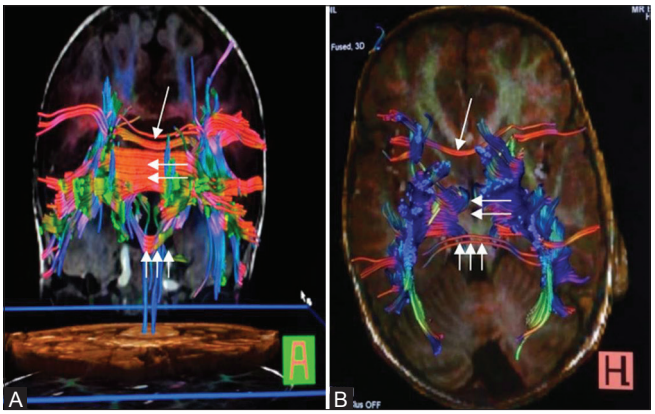

Figure 2 (A and B): Axial 3D color-coded diffusion tensor fiber tractography (shown in gray scale here) delineating the difference in the density of the fiber tracts between genu (single arrow), body (double arrow), and splenium (triple arrow) of corpus callosum. Note the difference in tract density in a case (B) in comparison to a control (A) This case also had a difference in quantitative measurements

abnormal numerical values in 78% of cases. Due to the latter fact, this phenomenon, which otherwise would have been called as an observer bias, was considered an observational improvisation due to availability of more refined data. This was especially true when the tractographic data was added to the color-coded RGB maps. However, since this was not one of the aims of the present study, we decided not to go forward with analysis of this data. This would have required a more elaborate and multi-parametric psycho-radiological assessment and was left to be carried over in another targeted study.

Quantitative evaluation

Global evaluation

The measured variables in 23 regions were analyzed and compared with the corresponding contralateral areas of same patient and with comparable areas of controls. The overall analysis included 23 ROIs with 46 variables, i.e. an ADC value and an FA value, for each region. This exercise was repeated both for cases as well as controls, and revealed the ROIs in 19 anatomically distinct areas (82.6%) to have at least one statistically significant variable. These 19 areas gave 25 (54.34%) statistically significant variables, of which 14 (30.43%) were FA values while 11 variables (23.91%) were ADC values [Tables 3 and 4].

Regional evaluation

Corpus callosum and forceps

The regions and variables that turned out to be of significance included FA in the genu (lower in cases than in controls), ADC in body and splenium (higher in cases than in controls), and both ADC and FA values in right forceps major and minor [Tables 3 and 4]. Forceps major and minor on the left was similar to the result noted on the right side, but ADC values failed to reach the level of significance.

Parietal white matter

Analysis of ADC values in parietal lobes showed statistically significant difference between cases and controls. However, FA showed no statistically significant difference between cases and controls in our study [Tables 3 and 4].

Frontal white matter

Statistical significance was noted in the difference between the FA values of cases versus controls; however, the ADC values did not reach the threshold of significance [Tables 3 and 4]. The variables in pars triangularis did not show any significance.

Internal capsule

Both FA and ADC showed statistically significant difference between cases and controls in both right and left posterior limbs of the internal capsule. Variables in the anterior limb, however, remained insignificant in the present study [Tables 3 and 4].

Table 2: Gender distribution in the study

Sex	Cases		Controls	
	No.	%	No.	%
Male	20	40	5	33.3
Female	30	60	10	66.7
Total	50	100	15	100

$X^2=0.217$, $P=0.642$

Table 3: Fractional anisotropy measurements

Region of measurement	Cases ($n=50$)	Control ($n=15$)	P value
Central genu	746.94±103.84	827.09±52	<.005
Central body	370.24±127.51	434.89±120.79	0.077
Central splenium	660.84±206.84	698.12±256.09	0.150
Forceps minor (right)	529.31±154.56	613.45±75.97	<0.048
Forceps minor (left)	501.66±115.70	596.88±98.72	<0.003
Forceps major (right)	550.54±199.13	667.19±131.30	<0.043
Forceps major (left)	582.61±192.59	724.56±150.55	<0.006
Frontal lobe (right)	404.17±97.67	448.47±67.72	0.109
Frontal lobe (left)	411.03±105.28	773.25±1172.79	<0.037
Parietal lobe (right)	430.19±134.53	482.29±81.78	0.141
Parietal lobe (left)	423.86±106.56	442.26±90.50	0.383
Pre-central gyrus (right)	257.19±146.32	332.76±86.39	<0.006
Post-central gyrus (right)	226.41±143.26	305.85±113.06	<0.004
Pre-central gyrus (left)	258.10±114.84	342.13±112.31	<0.014
Post-central gyrus (left)	229.63±146.56	317.96±115	<0.007
Alic (right)	469.89±96.14	507.15±84.51	0.181
Plic (right)	646.45±112.54	714.31±59.40	<0.027
Alic (left)	426.68±112.00	508.03±69.19	<0.012
Plic (left)	636.92±130.45	742.25±48.80	<0.001
Temporal lobe (right)	265.33±122.21	198.21±54.15	0.137
Partriangularis (right)	171.92±60.03	176.73±45.05	0.554
Temporal lobe (left)	248.68±124.40	177.44±60.20	<0.025
Pars triangularis (left)	164.77±67.10	178.45±59.57	0.256

Temporal lobe

Statistically significant difference was noted between the FA values of cases versus controls in the left temporal lobe [Tables 3 and 4].

Discussion

Myelination of the central nervous system is the key to maturation and hence a normal "development." This helps in acquiring different skills or milestones of a child for optimal functioning at the appropriate age range. Recently, DT-MRI–derived metrics have been used, with promising results, to assess normal myelination pattern in healthy children. These metrics, which chiefly include the ADC and FA, can be used as imaging biomarkers of normal brain maturation in children. This is due to the fact that as the age of the child increases, the organization of tracts and myelination of neurons increase the alignment and integrity of tracts and, hence, the anisotropy. The bulk

Table 4: Apparent diffusion coefficient measurements

Region of measurement	Cases (n=50)	Control (n=15)	P value
Central genu	873.65±108.3	835.75±84.5	0.276
Central body	1393.1±430.9	1129.6±256.8	<0.011
Central splenium	1069.1±409.3	845.9±101.2	<0.013
Forceps minor (right)	890.2±120.4	791.80±93.7	<0.002
Forceps minor (left)	862.97±141.86	831.58±84.06	0.157
Forceps major (right)	1056.8±364.52	851.79±69.27	<0.023
Forceps major (left)	1007.2±391.88	886.16±212.83	0.181
Frontal lobe (right)	877.64±98.14	857.65±48.38	0.570
Frontal lobe (left)	877.46±101.42	846.23±48.30	0.262
Parietal lobe (right)	1002.3±256.29	882.31±114.11	<0.011
Parietal lobe (left)	1004.0±257.66	848.19±80.87	<0.012
Pre-central gyrus (right)	882.37±140.37	870.59±111.09	0.327
Post-central gyrus (right)	890.94±101.68	837.34±48.16	<0.040
Pre-central gyrus (left)	901.73±153.54	880.27±202.62	<0.041
Post-central gyrus (left)	967.01±291.93	873.12±124.77	0.249
Alic (right)	825.11±50.78	794.81±48.69	<0.046
Plic (right)	816.92±65.44	753.87±47.89	<0.001
Alic (left)	797.16±90.28	781.44±49.80	0.150
Plic (left)	800.53±54.18	759.47±54.57	<0.004
Temporal lobe (right)	911.16±103.62	863.94±83.28	0.060
Partriangularis (right)	1019.3±285.29	1019.7±279.69	0.913
Temporal lobe (left)	929.51±165.17	900.48±86.03	0.840
Pars triangularis (left)	1033.2±310.31	1035.3±253.81	0.714

flow phenomenon acquires a specific directionality due to the above changes, a fact that has been exploited by DT-MRI. The present study does not intend to dwell into the complex details of physics of diffusion imaging, which can be found in focused texts.[8-18] We evaluated the role of these metrics in the selected case population and compared the validity of same by comparing it with children having normal development.

Routine/morphological/anatomical imaging and semi-quantitative evaluation

The morphological imaging was read as "normal" in all the patients by the two radiologists. This corresponds well with the results noted in previous studies on this issue, dealing with similar kind of population.[9-12,14,16] We would, however, like to submit that a re-evaluation of each case with correlation to the color-coded RGB map and tractographic data may improve upon the impression made on gray-scale images. Such results were seen in 47% of cases. Since this was not our primary aim, we would like to suggest or take up a separate study for the purpose.

Quantitative evaluation

Global evaluation

The data set expresses the impression that most areas evaluated on a random basis, with ADC and FA measurements, would give at least one useful measurement, which would enable one to give a tentative suggestion as to the need of further regional analysis. If a combination of at least three regions with a specified variable in each is included, the sensitivity for filtering out suspicious cases increases to 90%. This fact is important from the point of view that regional assessment is a time- and labor-intensive task and may need significant attention on the part of a dedicated neuroradiologist. This may disturb the workflow in a high-volume department if performed in each case.

Regional evaluation

Corpus callosum and forceps

FA in the genu, ADC in the body and splenium, and both ADC and FA values in the right forceps major and minor were the significant variables in the present study. Such results were noted in other studies as well.[1] We, however, did not find significance of both variables in all parts of corpus callosum. This may be primarily due to the fact that our data set consisted of younger children. Another fact that needs to be mentioned is the status of nutrition in Indian patients which leads to a slower myelination;[19] it is, therefore, easier to measure in regions with tightly packed fibers, such as genu and forceps, as compared to more loosely packed fibers in the body and splenium. Further ADC follows the same pattern and the absence of significance in genu may be due to smaller number of patients and controls. This needs further evaluation. A cut-off of 640 ± 103 (mean and SD) for FA and 846 ± 81 (mean and SD) for ADC is proposed for genu, while a cut-off value of 665 ± 123 (mean and SD) may be considered for FA for forceps minor.

Parietal white matter

ADC values in parietal lobes may be used in conjunction with the parameters noted in corpus callosum and forceps. In isolation, however, these do not seem to have any significance. To the best of our knowledge, no other study evaluated the role of DT metrics in this region.

Frontal white matter

FA values seem to be more important than ADC as far as the frontal white matter is concerned. Both the above facts may again be attributed to the compactness of fiber tracts in the relatively young children in our study. As compared to corpus callosum and forceps, these areas mature and attain directionality later, and hence the lesser level of significance than in the former areas. To our knowledge, no other study evaluated the role of DT metrics in this region.

Internal capsule

This remains an important region with both variables showing significance. Similar results have been noted in previous studies as well in the anterior and posterior limbs on both sides.[1] An FA value of 728 ± 53 (mean and SD) and an ADC value of 702 ± 53.5 (mean and SD) are proposed as the cut-off values.

Temporal lobe

This area appears insignificant as far as routine evaluation of FA and ADC parameters is concerned. They may, however, be included in cases where compound parametric maps of myelination are being formed.

Conclusion

A normal morphological (MRI) scan acts as a false-negative test and leads to unfortunate but frequent deferral in referring eligible children and their families for early intervention services (physiotherapy, language, occupational, etc.). Even more experienced clinicians have demonstrated difficulty in the identification of children with mild DDs, who are typically the children most amenable to early intervention.[15] Even if the clinician identifies such candidates, most families are misguided by false-negative results on imaging and fail to comply with the advice of clinicians. This study makes an attempt to bring out subtle objective parameters that would be convincing to such families and clinicians for considering early interventional services. The RGB maps and tractography may add to a visual confidence as well. It may be re-emphasized that most children who present with the mildest forms of DD typically have normal MR imaging results[1] with positive findings noted on DT-MRI. The important regions to be evaluated in a case of DD are the corpus callosum, bilateral forceps minor and forceps major, bilateral parietal lobes, bilateral post-central gyrus, and bilateral posterior limb of internal capsule. The regions which did not show any significance are bilateral pars triangularis and right frontal lobe. Other regions remained indeterminate and need further evaluation.

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