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Original contribution

Quantitative microstructural deficits in chronic phase of stroke with small volume infarcts: A diffusion tensor 3-D tractographic analysis

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ABSTRACT

Background: Non-infarct zone white matter wallerian degeneration is well-documented in large volume territorial infarctions. However to what extent these abnormalities exist in small volume infarction is not known, particularly since routine T2/FLAIR MR images show minimal changes in such cases. We therefore utilized DTI based quantitative 3D tractography for quantitative assessment of white matter integrity in chronic phase of small volume anterior circulation infarcts.

Methods: Eleven chronic stroke subjects with small anterior circulation large vessel infarcts (≤10 cm^3 volume of primary infarct) were compared with 8 age matched controls. These infarcts had negligible to mild gliosis and encephalomalacia in the primary infarct territory without obvious wallerian degeneration on conventional MRI. Quantitative Diffusion Tensor 3-D tractography was performed for CST, genu and splenium of corpus callosum. Tract based Trace and fractional anisotropy (FA) were compared with age matched controls.

Results: On univariate analysis, Chronic stroke subjects had significant elevation in Trace measurement in genu of corpus callosum (GCC), ipsilesional and contralesional CST, ($p < 0.05$), compared to controls. After adjusting for smoking, hypertension (HTN) and non-specific white matter hyperintensities, (WMHs), there was significant elevation in trace within the ipsilesional CST ($p = 0.05$). Contralesional CST FA correlated significantly with walking speed, $r = 0.67$, $p = 0.03$.

Conclusions: Stroke subjects with small volume infarcts demonstrate significant quantitative microstructural white matter abnormalities in chronic phase, which are otherwise subthreshold for detection on routine imaging. Ability to quantify these changes provides an important marker for assessing non-infarct zone neuroaxonal integrity in the chronic phase even in the setting of small infarction.

1. Introduction

Long-term functional and structural reorganization following ischemic stroke has been documented in animal and human studies [1,2]. In chronic phase of ischemic infarct, primarily two competing processes operate, namely, antegrade neuroaxonal degeneration [3,4], and counteracting reparative plasticity [5].

Vast majority of studies have investigated these processes in the context of large volume ischemic infarcts. Timely restoration of flow has become increasingly possible due to improved acute phase management leading to a growing number of patients with small infarcts. This has led to increasing interest in understanding the natural history of small volume infarcts in subsequent chronic phase. It is particularly essential to understand if these patients are also prone to progressive neuroaxonal degeneration in chronic phase of stroke. However, it is known that wallerian degeneration is proportionate to extent of primary infarct [6]. Therefore, the small volume of infarcted tissue, poses a particular challenge, such that the abnormalities in non-infarct zone may potentially be sub-threshold on conventional imaging techniques such as FLAIR and T2w images. Additionally, evidence suggests that lesion volume itself does not explain variance in functional recovery and it is plausible that the variability in the integrity of non-infarct zone white matter may have additive values in predicting functional profile [7].

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By virtue of small size, the extent of gliosis and encephalomalacia at the site of primary infarct is often minimal and there are virtually no overt stigmata of wallerian degeneration on routine imaging. However, advances in imaging techniques have improved ability to investigate abnormalities that are occult on routine imaging. Diffusion Tensor Imaging (DTI) is such a technique, which is particularly valuable in assessment of white matter integrity. DTI enables quantitative estimation of tissue microstructure based on diffusivity properties of water molecules, [8]. Schaeter et al. and Wang et al., used DTI in chronic stroke subjects to demonstrate microstructural abnormalities in corticospinal tracts and corpus callosum, which predicted motor function [9,10]. In this study we aim to investigate the extent and degree of these abnormalities in chronic stroke subjects with small volume primary infarcts and mild functional deficits. We hypothesized presence of microstructural deficit despite small volume infarcts that are subthreshold for detection using conventional techniques. We will utilize DTI based quantitative 3D tractography for targeted evaluation of corticospinal tracts and corpus callosum, which are the primary determinants of motor recovery in chronic stroke patients and likely to be involved in anterior circulation infarction, [9,10].

2. Methods

2.1. Participants

We analyzed data collected from 2005 to 2012. Community-dwelling men and women aged 50–85 years were recruited via advertisement at the Beth Israel Deaconess Medical Center. Individuals with stroke were at least 6 months post-infarct and had documented chronic large-vessel hemispheric infarcts affecting less than one-third of the MCA territory, as confirmed by clinical data/radiologic MRI or CT images/reports during the acute phase. The control group consisted of individuals recruited from the community to match the age characteristics of the stroke group. Exclusion criteria were intracranial hemorrhage on MRI or CT, bilateral infarction, any unstable medical condition, vertebrobasilar or carotid disease (not associated with stroke), diabetes mellitus, valvular heart disease or clinically significant arrhythmia, severe hypertension (systolic BP > 200 or diastolic BP > 110 mmHg or subjects taking three or more antihypertensive medications) and inability to walk unassisted, and significant functional impairment as evidenced by a total NIH Stroke Scale (NIHSS) score > 20. Additional MRI exclusion criteria included morbid obesity (body mass index >35) or any metallic bioimplants or claustrophobia. A total of 172 subjects were screened consecutively and taken consent; out of these 46 subjects completed the study protocol and DTI. Of these, 8 subjects did not have adequate quality DTI acquisition to enable fiber tracking. 16 of 38 subjects had large infarcts defined as infarct volume > 10 cm^3. 2 subjects had bilateral infarcts and 1 patient had two separate infarcts on the same side. Our final comparison group had 19 study subjects, 11 stroke subjects and 8 age matched healthy controls. One stroke subject did not complete walking speed. Two stroke subjects had significant artifact in the frontal lobes and genu of corpus callosum could not be reconstructed. Data from these subjects therefore did not account towards the specific sub-set analyses requiring these measurements.

2.2. Study protocol

The study protocol was approved by the Committee on Clinical Investigations at the Beth Israel Deaconess Medical Center. All subjects provided written informed consent. Studies were conducted at the Syncope and Falls in the Elderly Laboratory, the Center for Advanced MRI, and the Clinical Research Center (CRC) at the Beth Israel Deaconess Medical Center. An in-person screening visit was first completed to assess medical history and medication usage, vital signs, resting ECG, and anthropometrics. The NIHSS and modified Rankin Scale (mRS) were administered. Eligible subjects were then admitted to the CRC and completed a battery of assessments including a walk test and brain MRI.

2.3. Clinical functional assessment

Neurologic assessment was done with NIH Stroke Scale (NIHSS) and the modified Rankin Scale score (mRS) [11]. We also utilized measurement of walking speed in m/s. All subjects completed a 12-min walk along a 75-m course on an 80-m indoor hallway at their preferred speed. To minimize effects associated with turning and fatigue, we limited the analysis to the first 75 m of the walk.

2.4. MRI acquisition

MRIs were performed on a 3-T GE Signa Vhi scanner using a quadrature and phase array head coils (GE Medical Systems, Milwaukee, WI). High-resolution anatomic images included 3-dimensional magnetization prepared rapid gradient echo (MPRAGE), fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted images (DWI). DTI data were acquired using a single-shot echo planar imaging sequence, TE = 112 ms, TR = 1000 ms, FOV = 240 × 240 mm, thickness = 5 mm. Diffusion weighting was encoded along 25 independent orientations and the b value was 1000 s/mm^2. One additional image with minimal diffusion weighting was also acquired. Image data were saved offline on a CD-RW attached to the scanner.

2.4.1. Imaging data processing

2.4.1.1. Diffusion tensor imaging. DTI data were processed using the analysis software DTIstudio developed and distributed by this laboratory (H. Jiang and S. Mori, Johns Hopkins University and Kennedy Krieger Institute, http://godzilla.kennedykrieger.org). Diffusion-weighted images were visually inspected for apparent artifacts due to subject motion and instrumental malfunction by authors. The six elements of the diffusion tensor were calculated for each pixel using multivariate linear fitting. After tensor diagonalization, three eigenvalues and eigenvectors were obtained and fractional anisotropy (FA) maps were calculated. The eigenvector associated with the largest eigenvalue was used as an indicator for fiber orientation. In the DTI color maps, red, green, and blue colors were assigned to right–left, anterior–posterior, and superior–inferior orientations, respectively. For the 3-D tract reconstruction, the method of fiber assignment by means of continuous tracking was used [12]. The tracking fractional anisotropy (FA) threshold of 0.2 was used such that pixel to pixel fibers are tracked along the principal eigenvector, namely Fiber Assigned Continuous Tracking (FACT) approach. The angle threshold was set at 40°, preventing inclusion of fibers with sharper turning angles. To reconstruct tracts of interest, we used a two-region-of-interest approach, defining anatomic trajectories between proximal and distal ROIs. Three tracts of interest were chosen, namely genu and splenium of corpus callosum and bilateral corticospinal tracts. These were reconstructed using published protocols for manual delineation of tracts [13]; examples are shown in Fig. 1. To evaluate tract integrity, we ascertained average FA and trace (estimate of mean diffusivity) for each reconstructed tract, as previously demonstrated [14].

2.4.1.2. Infarct volume measurement. MRI images were analyzed on a Linux workstation using interactive data language tools (Research Systems, Boulder, CO). Infarct volumes were computed from manually delineated outlines on FLAIR images.

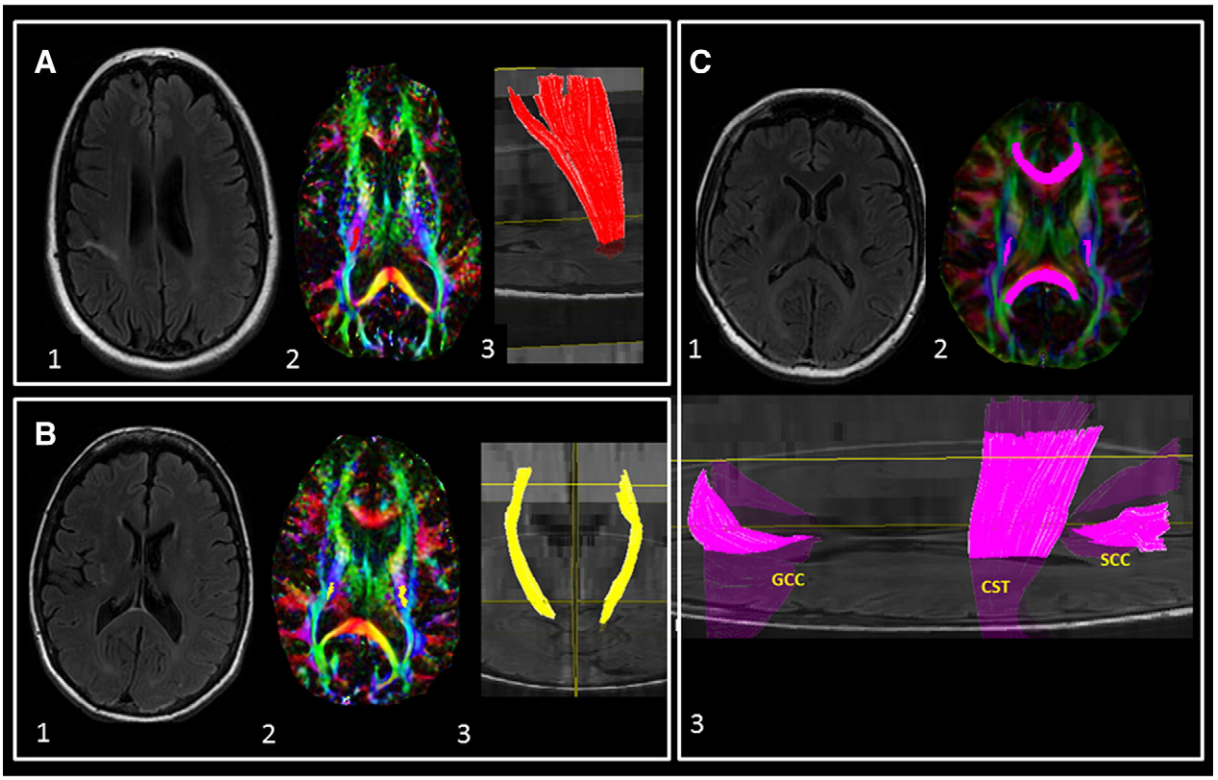

Fig. 1. Below are provided pictorial examples of subjects studied in this study with depictions of the 3D Tract Reconstructions for each subject. A) 50 year old female, with mRS and NIHSS of 2 in the setting of a small right parietal infarct seen on FLAIR (1) and A 54 year old female, with an mRS of 1, NIHSS of 2 in the setting of a small right corona radiate/internal capsule infarct seen on FLAIR. B) 54 yr. old female, with an mRS of 1, NIHSS of 2 in the setting of a small right corona radiate/internal capsule infarct seen on FLAIR. Both A and B depict typical subjects in this study with small infarcts and no visible abnormalities in the corticospinal tracts on color maps or on 3D reconstructions. C) A control subject, a healthy 66 year old female, normal FLAIR (1), normal appearing color map, (2), depicting the 3D-reconstructions of three major fiber bundles chosen for analyses (3), GCC: Genu of Corpus Callosum, SCC: Splenium of corpus callosum and CST: Bilateral corticospinal Tracts.

2.4.1.3. White matter hyperintensity (WMHs) grading. Due to relationship of non-specific white matter hyperintensity and stroke risk factors [15] we quantified the burden of white matter hyperintensities using previously described grading methodology [16]. FLAIR images were scored for WMHs using a semiquantitative scale from 0 to 3: 0 = no lesions; 1 = focal; 2 = beginning confluence; 3 = diffuse involvement on each slice and quantified as a sum of lesion grade for each region and for the whole brain. We generated punctate and confluent sum for total brain and used a sum of these two estimates to generate a unified estimate for total brain burden of WMHs.

2.5. Statistical methods

Student's T Test was performed to compare baseline demographics and tract specific diffusion estimates. In our group of controls there was no significant difference in right and left CST Trace or FA ($p = 0.4$ and $p = 0.6$, respectively). We therefore used average of right and left sided CST diffusion estimates in controls to compare with ipsilesional and contralesional CST based diffusion estimates in stroke subjects. Non-parametric chi-2 test was used to assess distribution of smoking and hypertension between controls and cases. Given small sample size, we perform robust non-parametric bootstrap median regression analyses with 20 repetitions of sampling to evaluate for effects adjusted smoking, hypertension and non-specific WMHs, all of which can impact the diffusion estimates within white matter tracts and were found to be differentially distributed in our stroke population compared to age matched controls. Relationship with functional/motor estimates was evaluated using Spearman rank correlation. A p value of 0.05 or less was considered statistically significant. Given our sample size was small we considered a p value between 0.05 and 0.1 as demonstrative of a trend of significance. All statistical analyses were done using STATA version 8.0 (STATA, College Station, TX).

3. Results

3.1. Baseline demographics

Our final comparison group had 19 subjects, 11 stroke subjects with very small chronic infarcts (>0.5 years after infarct, 6 (54%) female, 7 (63%) had R-sided infarcts) and 8 age matched healthy controls (62% women, $n = 5$). The clinical characteristics and baseline demographics are summarized in Table 1. Stroke participants had mild functional deficit (NIHSS ranged from 0 to 4, median: 1, mean 1.5 ± 1.03 and the mRS ranged from 0 to 2, median: 1, mean: 0.82 ± 0.87). There was a trend of increased prevalence of smoking and hypertension in the stroke group (72%, $n = 8$, smoking and hypertension in stroke group versus 27%, $n = 3$ in control group) ($p = 0.1$) (we adjusted for these in our final analyses).

3.2. Infarct location

There were 7 right sided and 4 left sided anterior circulations infarcts. On the right, 2 fronto-temporal, 1 basal ganglia, 1 parietal and 3 frontal lobe infarcts were seen. On the left, 2 temporal infarcts, 1 temporoparietal infarct and 1 posterior parietal infarct were seen.

3.3. Group comparison of tract specific diffusion estimates

3.3.1. Univariate analyses

Stroke subjects had significant abnormalities in genu of corpus callosum, ipsilesional and contralesional corticospinal tracts

Table 1
Demographic and imaging characteristics.

	Controls N = 8	Stroke N = 11	p value
Group Demographics			
Age	63 ± 7	66 ± 9	0.5
Sex (f/m)	5/3	6/5	0.7
Hypertension (%)	37%	72%	0.1
Smoking (%)	37%	72%	0.1
Clinical Characteristics			
Time since acute event infarct	n/a	4.2 ± 3.3	n/a
NIHSS	n/a	1.5 ± 1.0	n/a
mRS	n/a	0.8 ± 0.9	n/a
Walking Speed (m/s)	1.2 ± 0.08	1 ± 0.2	0.02
Imaging Characteristics			
Infarct Volume	n/a	4.5 ± 3.6	
Infarct Site, (R/L)*	n/a	7/4	
WMHs Whole Brain Continuous Sum (a)	11.2 ± 7.5	28 ± 17.1	0.02
WMHs Whole Brain Punctate Sum (b)	9 ± 22.6	51.5 ± 58.8	0.07
Total WMHs Whole Brain (a + b)	20.2 ± 28.4	79.5 ± 63.7	0.04

P values for t test (reported as mean ± sd) and chi^2 test (%).
* On right, 2 fronto-temporal, 1 basal ganglia, 1 parietal, and 3 frontal lobe infarcts. On left, 2 temporal infarcts, 1 temporoparietal infarct and 1 posterior parietal infarct.

($p < 0.05$, Table 2) compared to controls. The splenium of corpus callosum showed no significant abnormalities in diffusion estimates. We found no correlation between volume of infarction and tract based diffusion estimates.

3.3.2. Multivariate adjusted analyses

Non-parametric bootstrap median regression with 20 repetitions adjusting for smoking, hypertension and WMHs demonstrated significant abnormalities in ipsilesional CST trace ($p = 0.05$), axial diffusivity (0.01) and radial diffusivity ($p = 0.04$). There were no significant abnormalities in the contralesional CST diffusivity metrics after adjusting for smoking, hypertension and WMH's. Comparative predictive capacity of these diffusivity metrics assessed with Receiver operating characteristic, (ROC) curves, demonstrated no significant differences in total predictive capacity with Ipislesional CST Trace having the greatest area under curve, measuring 89% (Fig. 2).

3.4. Relationship to walking speed

Correlation of tract based diffusion estimates was performed with walking speed (m/s), NIHSS and mRS in stroke subjects. In stroke subjects, the contralesional CST FA demonstrated a significant correlation with walking speed ($r = 0.67$, $p = 0.03$) and trend of correlation with NIHSS ($r = 0.51$, $p = 0.1$) and mRS ($r = 0.52$, $p = 0.09$). Ipsilesional CST FA, ipsilesional and contralesional CST Trace did not show any correlation with walking speed, NIHSS or mRS.

Table 2
Summary of tract specific diffusion estimates between stroke patients and controls.

Tract Specific Diffusion Parameter	Stroke Patients mean ± sd	Controls mean ± sd	p Value
Genu Trace	3.1 ± 0.27	2.8 ± 0.19	0.02
Genu FA	0.45 ± 0.03	0.49 ± 0.06	0.2
Ipsilesional CST Trace[a]	2.4 ± 0.13	2.2 ± 0.12	0.002
Ipsilesional CST FA[a]	0.57 ± 0.03	0.58 ± 0.03	0.5
Contralesional CST Trace[a]	2.4 ± 0.16	2.2 ± 0.12	0.01
Contralesional CST FA[a]	0.56 ± 0.02	0.58 ± 0.03	0.1
Splenium Trace	2.6 ± 0.24	2.5 ± 0.3	0.6
Splenium FA	0.7 ± 0.04	0.7 ± 0.04	0.6

[a] Average of right and left CST Trace and FA measurement was computed in the control group for comparison with ipsilesional and contralesional CST Trace and FA measurements in the stroke group.

4. Discussion

In this study, we investigated non-infarct zone white matter in chronic stroke subjects who had small volume anterior circulation primary infarcts and mild functional deficit (infarct volume ≤ 10 cm^3 and mRS ≤ 2). These subjects did not have overt wallerian degeneration on routine imaging and sustained very little gliosis and encephalomalacia in the primary infarct territory making this a relatively homogenous mildly affected subgroup. Using Diffusion Tensor 3D tractography, we saw significant quantitative abnormalities in tract based diffusivity metrics in ipsilesional and contralesional corticospinal tracts and genus of corpus callosum. The ipsilesional CST abnormalities persisted after adjustment for smoking, hypertension and white matter hyperintensities. This suggests presence of non-infarct zone white matter microstructural alterations that are occult on routine FLAIR and T2-weighted MRI commonly used in clinical practice.

Whether these changes are stroke related white matter microstructural alterations or pre-existing changes due to stroke associated vascular risk factors remains unclear. The lack of pre-stroke baseline DTI hinders our ability to adequately assess discriminate potential contribution from these factors. However, changes in the ipsilesional CST persisted after adjusting for vascular risk factors such as smoking, HTN and WMHs, suggesting that part of the changes can be attributed to direct impact of the infarct itself. Our patient population did not have severe hypertension or diabetes.

The dominant neurodegenerative pathology in chronic infarction is due to wallerian degeneration, propagating distal to the site of primary ischemic insult, [3,4]. It is known that the extent and severity of wallerian degeneration are proportionate to the volume of initial infarction [6]. Therefore, it is plausible that we are detecting wallerian degeneration related microstructural abnormalities that are subthreshold for conventional techniques due to small size of the primary infarct in our study population. Nevertheless, due to potentially progressive nature of this degenerative process, ability to detect and quantify these alterations will allow an objective marker for neuroaxonal integrity during recovery and rehabilitation phase of stroke.

Alternatively, it is conceivable that other factors such as post-ischemia altered cerebral vasoregulation [17], oligodendroglial dysfunction [18] or simply wider zone of ischemia not resulting in infarction, may be contributing factors. However, all of these explanations assume changes did not precede the incident cerebrovascular event. In the absence of pre-infarct MRI, this assumption cannot be entirely confirmed. However, presence of most significant changes ipsilateral to the side of infarct that persist after adjusting for vascular risk factors makes it highly probable that at-least some of these changes are indeed secondary to the cerebrovascular event itself.

In terms of tract based diffusion estimate, we found that contralesional CST FA showed significant correlation with walking speed and trend of correlation with NIHSS and mRS. Our results agree in part with a prior study demonstrating similar findings [9]. Our results now also extend these findings in patients with small volume primary infarctions. However, we noted that ipsilesional CST FA did not correlate significantly with motor measures in our study. We hypothesize that this is related to fiber tracking thresholding effect, where a severely diseased fiber is excluded from tract 3D reconstruction due to subthreshold FA (FA lower than tracking threshold of 0.2), thereby elevating the ipsilesional FA and mitigating the effect on motor estimates, causing us to be underpowered to detect significant association ($r = 0.43$. $p = 0.2$).

At this time, baseline grade of paresis is the best prognostic marker for functional recovery, and has been found to be superior to final infarct volume in predicting functional prognosis [19]. We know that baseline grade of paresis in anterior circulation large vessel infarction is determined primarily by the extent of initial ischemia. Therefore possibility of white matter abnormalities within

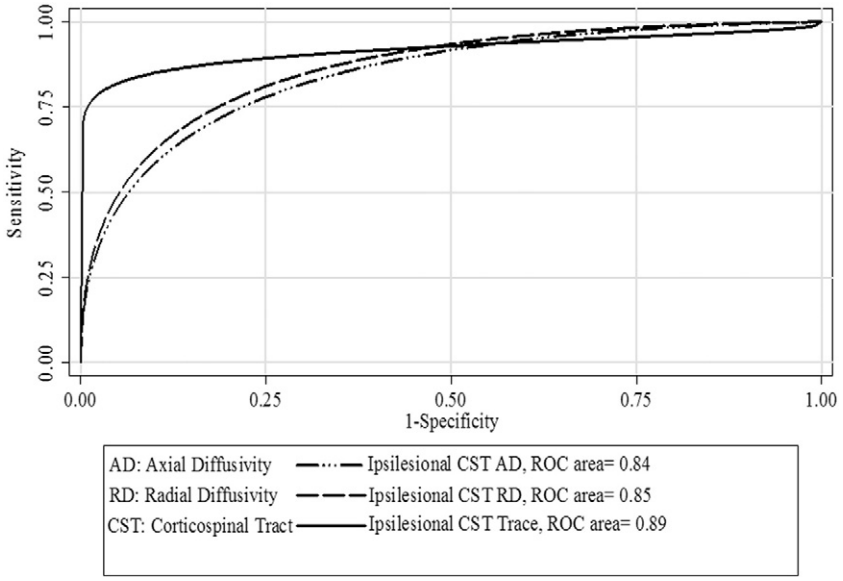

Fig. 2. Comparative ROC curve for ipsilesional CST diffusivity estimates showing relatively similar predictive capacity in discriminating stroke versus controls. There was no significant difference between the predictive capacity of the three curves, $p = 0.2$.

the revascularized territory warrants consideration as a factor determining downstream functional deficit. Diffusion Tensor Imaging provides such a quantitative tool for assessment of white matter changes in non-infarcted ischemic zone, which be applied in both acute and chronic phases of stroke.

Our study had limitations. Primarily, our sample size was small, which limits the power to detect smaller changes and to account for infarct location. Secondly, study design was cross-sectional, and we did not have pre-stroke baseline MRI, thereby limiting assessment of temporality of these changes. Lastly, we did not have information on baseline neurologic parameters such as NIHSS at the time of the acute cerebrovascular event. This factor is likely to be related to the extent of ischemia not resulting in infarction, and therefore might impact the white matter microstructural abnormalities detected in our study. However, given that our chronic stroke group has very mild functional deficit, they are likely to have presented with a favorable NIHSS and relatively smaller ischemic territory during the acute phase as well.

5. Conclusion

In this study, using Diffusion Tensor Imaging 3D tractography we were able to detect quantitative microstructural abnormalities in ipsilesional and contralesional corticospinal tracts and genu of corpus callosum in chronic stroke patients with small volume anterior circulation infarcts and mild functional deficits (infarct volume ≤ 10 cm^3 and mRS ≤ 2). These abnormalities were otherwise occult on routine FLAIR and T2 weighted sequences. Additionally, the changes seen in the ipsilesional corticospinal tract persisted after adjusting for smoking, hypertension and white matter hyperintensities.

This suggests that significant post-infarct wallerian degeneration is present even in the setting of very small infarcts, which leaves minimal stigmata of overt tissue damage on routine imaging. Due to the potentially progressive nature of this neurodegenerative process, the ability to detect and quantify these microstructural abnormalities provides an essential tool for assessment of neuroaxonal integrity during the recovery phase of stroke, independent of infarct size.

Disclosures

There are no disclosures for any of the authors.

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