SHORT REPORT

Diffusion tensor imaging in primary cervical dystonia

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Background: It is the traditional view that primary dystonia arises from abnormal basal ganglia function but causes no apparent morphological changes.

Objective: To determine whether cervical dystonia leads to ultrastructural changes in the brain, using diffusion tensor imaging to compare brain structure in 15 patients with cervical dystonia with 10 healthy controls.

Design: Fractional anisotropy (FA) and mean diffusivity (MD) were obtained in 17 brain regions of interest.

Results: Patients had higher FA values than controls in both putamina and lower FA values in the genu and in the body of the corpus callosum. Patients also had lower MD values in the left pallidum, the left putamen, and both caudati.

Conclusions: In patients with cervical dystonia, diffusion tensor imaging shows ultrastructural changes in specific brain areas, including the basal ganglia.

It is the traditional view that primary dystonia arises solely from abnormal basal ganglia function in the absence of apparent morphological changes.¹ This concept applies also to cervical dystonia,² one of the most common forms of focal dystonia, although a neuropathological report showed mild neuronal loss in some brain stem nuclei associated with neurofibrillary tangles.³ New non-conventional magnetic resonance imaging (MRI) techniques, such as diffusion weighted imaging, have been proposed as tools to improve diagnostic accuracy and achieve a better understanding of the pathophysiology of basal ganglia disorders.⁴ Among these, diffusion tensor imaging (DTI) has provided information not only about the random displacement or passive diffusion of water molecules, but also about fibre directionality and integrity. DTI has allowed visualisation of neuronal projections in the central nervous system,⁵ and estimation of the neuronal changes in the white matter of normal subjects and patients with various neurological diseases.⁶ A recent study using the DTI technique showed microstructural changes in the subgyral white matter of the sensorimotor cortex in carriers of the DYT1 gene.⁷

In the present study, we applied DTI in patients with cervical dystonia to determine whether this disorder leads to ultrastructural changes in the brain.

METHODS

Subjects

We studied 15 patients (four men, 11 women; mean (SD) age, 51.9 (11.0) years) with cervical dystonia and 10 age and sex matched healthy subjects using MRI. Cervical dystonia was diagnosed on the basis of published criteria.² Secondary or inherited dystonias and other disorders associated with dystonia were excluded. The mean duration of symptoms was 8.0 (4.0) years (range 1.5 to 23). The cervical dystonia severity score, assessed before the last botulinum toxin injection using the Tsui rating scale,⁸ ranged between 6 and 15 points (mean 9.9 (3.8)). Three patients had pure rotational

torticollis, one had mixed torticollis and anterocollis, four had mixed torticollis and laterocollis, and the remaining seven had a combination of torticollis, anterocollis, and laterocollis.

All patients with cervical dystonia received botulinum toxin injections following standard treatment regimens. The patients with cervical dystonia were scanned at the time of maximum therapeutic response relating to the treatment of their involuntary movements. None of the unaffected controls had a history of other neurological disorders.

All subjects gave their written informed consent before MRI examination and the study was approved by the local ethics committee of the University of Rome.

MRI acquisition

MRI was carried out using a 1.5 T scanner (Gyrosan NT 15, Philips Medical Systems, Best, Netherlands). To avoid the influence of motion, the subject's head was firmly fixed during acquisition by the use of foam padding and a restraining strap. Slice orientation parallel to the bicommissural (AC–PC) plane was assured by acquiring a multiplanar T1 weighted localiser at the start of each study. All patients had conventional spin echo proton density weighted, T2 weighted images (repetition time (TR) = 2000 ms; echo time (TE) = 30 ms, 120 ms) and T1 weighted images (TR = 550 ms; TE = 12 ms), acquired with a matrix size of 256 × 256 and a field of view (FOV) of 240 mm on 24 contiguous axial slices of 5 mm thickness, before DTI. DTI parameters were TR = 3694 ms, TE = 124 ms, matrix 128 × 128, FOV = 250 × 250 mm, and two b-values (0 and 1000 mm s⁻²) done in six directions. Amplitude images were averaged from 10 measurements. Data were processed to obtain maps of fractional anisotropy (FA) and mean diffusivity (MD).

Data analysis

Seventeen regions of interest (ROI) were located on specific cerebral structures of normal subjects and patients. Square ROIs of uniform size (nine pixels) were placed on white matter structures, including the genu, body, and splenium of the corpus callosum, the posterior limb of the internal capsule, and the subcortical white matter of the cerebellar hemispheres, as well as on grey matter structures including the caudate head, putamen, globus pallidum, thalamus, and supplementary motor area (SMA). The boundary of SMA was defined as the region between the vertical line perpendicular to the anterior commissure to posterior commissure (AC–PC) line, passing through the anterior commissure (VAC) and the vertical line perpendicular to the AC–PC line passing through the posterior commissure (VPC) above the cingulate sulcus.⁹ ROIs were located on the FA maps and then automatically transferred to the MD maps to ensure their correct location. Signal intensity differences and the schemes of the Talairach and Tournoux atlas¹⁰ were used for ROI positioning. The mean value of diffusion parameters for each ROI was then recorded.

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; SMA, supplementary motor area

Table 1 Diffusion tensor imaging: fractional anisotropy values

Regions	Patients (n = 15)	Controls (n = 10)	p Value
Genu of CC	750.13 (55.97)	814.00 (71.72)	0.02
Corpus of CC	693.40 (77.11)	800.50 (45.82)	0.01
Splenium of CC	845.27 (49.69)	843.30 (73.57)	NS
Caudate, L	219.93 (92.57)	233.20 (85.64)	NS
Caudate, R	205.93 (56.37)	222.00 (33.24)	NS
Putamen, L	220.60 (81.37)	147.60 (47.70)	0.01
Putamen, R	222.20 (94.11)	150.70 (46.47)	0.03
Pallidum, L	246.53 (56.59)	210.10 (42.87)	NS
Pallidum, R	273.73 (56.60)	237.60 (52.47)	NS
Thalamus, R	285.80 (44.64)	273.00 (48.24)	NS
Thalamus, L	286.73 (45.74)	321.50 (216.98)	NS
Internal capsule, R	673.00 (51.61)	704.30 (53.61)	NS
Internal capsule, L	668.87 (45.14)	671.50 (41.20)	NS
Cerebellar hemisphere, R	765.00 (53.09)	804.70 (55.28)	NS
Cerebellar hemisphere, L	759.71 (67.66)	806.50 (41.24)	NS
SMA, R	160.33 (41.04)	151.20 (28.68)	NS
SMA, L	161.73 (54.00)	146.20 (38.31)	NS

Values are mean (SD).

CC, corpus callosum; L, left; R, right; SMA, supplementary motor area.

Statistical analyses were done using SPSS 10.0 (SPSS Inc, Chicago, Illinois, USA) for Windows XP. Differences in FA and MD mean values between patients and control subjects in both hemispheres were assessed by one way analysis of variance (ANOVA). The relation between FA and MD values, cervical dystonia severity scores, and duration of symptoms was estimated using multiple regression analysis.

RESULTS

Conventional MRI was normal in all patients with cervical dystonia and in all the controls. The analysis of DTI data revealed multiple significant differences between patients with cervical dystonia and controls. Patients with cervical dystonia had higher FA values than controls in the left putamen ($p < 0.01$) and the right putamen ($p < 0.05$), and lower FA values in the genu ($p < 0.05$) and the body ($p < 0.001$) of the corpus callosum (table 1). Patients also had lower MD values than controls in the left pallidum ($p < 0.01$), the left putamen ($p < 0.05$), and the right ($p < 0.01$) and left caudate ($p < 0.05$) (table 2). Calculations of FA and MD in the splenium of the corpus callosum, the thalamus, the internal capsule, the cerebellum, and the SMA showed no significant differences between patients with cervical dystonia and controls. No asymmetries were observed in FA and MD indices calculated on homologous structures of the two

cerebral hemispheres in patients and controls. Furthermore, in patients with cervical dystonia, FA and MD values were not significantly correlated with disease duration or severity.

DISCUSSION

In this study we found that DTI can show changes in the striatum and the corpus callosum of patients with cervical dystonia, not otherwise evident on conventional MRI. Patients with cervical dystonia may therefore have ultra-structural changes in brain tissue.

Our results support previous MRI findings in patients with cervical dystonia. A previous MRI study showed abnormal T2 relaxation times within the basal ganglia in patients with this disorder.¹¹ A volumetric MRI study presented evidence that the putamen is about 10% larger in patients with cranial and limb dystonia than in healthy subjects,¹² while another morphometric MRI study, using voxel based morphometry, showed abnormalities in the grey matter of the pallidum as well as in the cerebral motor cortex and the cerebellar cortex.¹³

Our findings cannot be compared with those reported by Carbon *et al* in a DTI study in DYT1 mutation carriers,⁷ because those investigators analysed only white matter pathways.

Table 2 Diffusion tensor imaging: mean diffusivity values

Regions	Patients (n = 15)	Controls (n = 10)	p Value
Genu of CC	761.13 (72.23)	728.40 (84.53)	NS
Body of CC	803.67 (109.07)	787.30 (104.26)	NS
Splenium of CC	749.73 (88.30)	791.00 (26.26)	NS
Caudate, L	690.93 (146.61)	795.00 (61.42)	0.04
Caudate, R	663.53 (129.24)	781.20 (64.37)	0.01
Putamen, L	673.73 (53.33)	730.10 (56.70)	0.02
Putamen, R	669.00 (129.72)	732.00 (43.57)	NS
Pallidum, L	696.60 (36.79)	751.40 (49.31)	0.004
Pallidum, R	714.40 (41.68)	723.20 (29.26)	NS
Thalamus, R	760.53 (58.87)	789.20 (65.48)	NS
Thalamus, L	755.60 (62.58)	785.50 (54.97)	NS
Internal capsule, R	703.60 (64.55)	697.70 (35.36)	NS
Internal capsule, L	694.00 (39.82)	695.20 (43.23)	NS
Cerebellar hemisphere, R	715.43 (108.92)	728.30 (41.72)	NS
Cerebellar hemisphere, L	699.07 (101.39)	730.80 (42.04)	NS
SMA, R	735.29 (46.86)	753.90 (89.38)	NS
SMA, L	711.79 (92.05)	753.20 (60.24)	NS

Values are mean (SD).

CC, corpus callosum; L, left; R, right; SMA, supplementary motor area.

The pallidal and putaminal changes we documented with DTI may be of importance in the pathophysiology of cervical dystonia as these are the cerebral structures usually affected by secondary dystonias.¹⁴ In secondary dystonias, one would expect the pathological processes that affect the basal ganglia to produce a loss of tissue; a tissue loss apparently contrasts with findings of an increased FA in patients with primary cervical dystonia. A lesion or ultrastructural changes in basal ganglia structures might nevertheless induce similar clinical manifestations.¹⁵ The findings of abnormal changes at basal ganglia level are also consistent with the positive effect of internal pallidum ablation or high frequency stimulation in idiopathic dystonia.¹⁶

We found increased FA and decreased MD in the basal ganglia. Higher FA values indicate a more ordered tissue containing larger numbers of similarly aligned neurones; lower MD values indicate increased diffusion restriction owing to biological barriers.¹⁷ Hence our findings may be explained by an increased cellular density with increased fibre coherence in the basal ganglia of patients with cervical dystonia compared with healthy controls. In relation to the changes we report in the grey matter structures, spatial directionality is less pronounced in grey matter than in the high diffusion anisotropy of white matter, but it is still strong enough to be detected in normal¹⁸ as well as in pathological conditions.¹⁹

We also found a decreased FA in the genu and body of the corpus callosum. Ultrastructural abnormalities in the corpus callosum have not been reported in patients with cervical dystonia. The observed FA decrease in this structure might, however, be related to a decreased number of axons connecting cortical regions of the two cerebral hemispheres. Indeed, a decrease in grey matter density has been found in some cortical regions in cervical dystonia.¹³ Transcallosal connections have a mainly inhibitory function.^{20–21} A decrease in the number of callosal fibres could therefore change motor cortical excitability in dystonic patients. Thus a decrease in the number of callosal fibres may help to explain the changes in motor cortical excitability described in patients with focal dystonia.¹ In fact, a decrease in GABA levels in the sensorimotor cortex of patients with focal dystonia has been recently observed with MRI spectroscopy.²²

One difficulty in interpreting our structural data lies in the uncertainty over whether the DTI changes in the striatal grey matter density in idiopathic cervical dystonia are the primary cause or the consequence of a chronic disorder of the motor system.

Our results suggest that cervical dystonia may result from a dysfunction of the basal ganglia. These abnormalities cause altered thalamic control of cortical motor planning and executive areas, and abnormal regulation of brain stem and spinal cord inhibitory interneuronal mechanisms.¹

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