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Infratentorial gray matter atrophy and excess in primary craniocervical dystonia☆

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ABSTRACT

Background: Primary craniocervical dystonia (CCD) is generally attributed to functional abnormalities in the cortico–striato–pallido–thalamocortical loops, but cerebellar pathways have also been implicated in neuroimaging studies. Hence, our purpose was to perform a volumetric evaluation of the infratentorial structures in CCD.

Methods: We compared 35 DYT1/DYT6 negative patients with CCD and 35 healthy controls. Cerebellar volume was evaluated using manual volumetry (DISPLAY software) and infratentorial volume by voxel based morphometry of gray matter (GM) segments derived from T1 weighted 3 T MRI using the SUIT tool (SPM8/Dartel). We used *t*-tests to compare infratentorial volumes between groups.

Results: Cerebellar volume was $(1.14 \pm 0.17) \times 10^2$ cm^3 for controls and $(1.13 \pm 0.14) \times 10^2$ cm^3 for patients; $p = 0.74$. VBM demonstrated GM increase in the left I–IV cerebellar lobules and GM decrease in the left lobules VI and Crus I and in the right lobules VI, Crus I and VIIIb. In a secondary analysis, VBM demonstrated GM increase also in the brainstem, mostly in the pons.

Conclusion: While gray matter increase is observed in the anterior lobe of the cerebellum and in the brainstem, the atrophy is concentrated in the posterior lobe of the cerebellum, demonstrating a differential pattern of infratentorial involvement in CCD. This study shows subtle structural abnormalities of the cerebellum and brainstem in primary CCD.

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1. Introduction

Craniocervical dystonia (CCD) is the most common manifestation of adult-onset dystonia [1]. The term CCD encompasses blepharospasm, oromandibular, lingual, laryngeal and cervical dystonia or a combination of two or more of those. Based on prior studies, primary dystonia is thought to be a neurodevelopmental circuit disorder, which involves the cortico–striato–pallido–thalamo–cortical and cerebello–thalamo–cortical pathways [2]. Primary dystonia has been considered a manifestation of basal ganglia dysfunction; however, there is growing evidence that the cerebellum plays a crucial role in the pathophysiology of the disease. Nevertheless, there is still significant controversy as to whether these observed changes in cerebellar morphology and function are primary or secondary [3,4].

There are few studies addressing the structural changes in the whole brain of patients with CCD. VBM studies in cervical dystonia (CD) showed increased gray matter (GM) volume bilaterally in the motor cortex [5], the cerebellar flocculus [5], the right globus pallidus internus (GPi) [5,6]; bilateral orbitofrontal cortex, right medial frontal gyrus, left supplementary motor area and left cingulate gyrus [6]; superior left temporal lobe, thalamus, caudate head bilaterally and left cerebellum [7], as well as decreased GM in the right supplementary motor area, right prefrontal cortex, right visual cortex [5], and the putamen [7]. In primary blepharospasm the results have also been variable, revealing bilateral increased GM

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density in the caudate head, cerebellum [7], and putamen [8], but decreased GM in the putamen bilaterally, the thalamus [7], and the left inferior parietal lobule [8]. While some of these studies demonstrated cerebellar changes, none studied the infratentorial structures in detail.

There is also compelling evidence of cerebellar dysfunction in dystonia, which may represent a maladaptive response rather than a primary outcome of basal ganglia pathology [3,4]. Deep brain stimulation of the ventral posterior thalamus, the major recipient of cerebellar outflow, improves CCD [9]. Furthermore, surgical removal of the cerebellum in mutant tottering mice eliminates the dystonic movements [4]. Brainstem structures seem also to be involved in the pathophysiology of dystonia. For example, brainstem lesions, without basal ganglia or thalamic lesions may produce dystonia [10,11].

Hence, our main purpose was to perform a detailed analysis of the infratentorial structures in patients with primary CCD, using two different volumetric techniques of imaging analysis.

2. Methods

2.1. Subjects

The Institutional Review Board of our University Hospital approved the study and all subjects signed an informed consent prior to participation in any study related procedure. Patients were recruited from the Movement Disorders Outpatient Clinic, the Dystonia Outpatient Clinic and the Neurogenetic Outpatient Clinic at the University of Campinas (UNICAMP) University Hospital. We included 35 patients (mean age of 60.71 ± 12.47 years) with a clinical diagnosis of primary CCD. All tested negative for the DYT 1/DYT 6 gene mutation. We performed a detailed clinical evaluation, which included a review of the medical history, disease duration (mean duration of 9.94 ± 6.75 years), duration of botulinum toxin treatment (BoNT) (mean duration of 5.6 ± 5.25 years), Marsden–Fahn Scale (MFS) (mean score of 5.66 ± 2.90) and physical and neurological examination. We also included 35 healthy controls (mean age of 59.74 ± 12.21 years), matched for gender and age, with no history of neurological disorders; no family history of dystonia and a normal neurological examination.

The patients with CCD were classified according to the affected region: cervical, orbicular, oromandibular, laryngeal or a combination of two or more of those areas, as shown in Table 1. Nineteen patients had a focal presentation while 16 had a segmental one.

2.2. MRI acquisition

Images were acquired at a 3T MR unit (PHILIPS Achieva Intera®, release 2.6.1.0). In addition to the usual diagnostic sequences, we obtained volumetric T1-weighted images, with isotropic voxels of 1 mm, acquired in the sagittal plane (1 mm thick, flip angle, 8°,TR 7.1, TE 3.2,matrix 240 × 240, and FOV 240 × 240 mm).

Table 1
Classification of dystonia in the 35 subjects enrolled.

Range	Localization	Number of patients	%
Focal	Cervical (C)	13	37.14%
	Blepharospasm (B)	5	14.29%
	Oromandibular (O)	1	2.86%
Segmental	B + O	9	25.71%
	B + O + C	5	14.29%
	B + C	1	2.86%
	C + Lar	1	2.86%
Total	Total	35	100.00%

2.3. Image analysis and processing

Prior to any imaging processing, an experienced neuroradiologist evaluated all images in a blinded fashion for controls and patients, to assure image quality and the absence of significant brain pathology or artifacts.

2.3.1. Manual volumetric analysis

Images were converted from DICOM to MNC format. We used the Display software, which performs a tridimensional reconstruction of the image, voxel-by-voxel, for manual segmentation of the cerebellum. This allows individual segmentation of the brain structures and the transformation of data into standard spatial coordinates based on Talairach coordinates [12]. To perform a precise manual segmentation, 3 patients were excluded due to motion artifacts. The total intracranial volume (TIV) was calculated using SPM 8, after conversion to the Analyze format and determination of the anterior commissure in the MRIcro software. Corrected volume of each structure was equal to the measured volume × (mean TIV controls/TIV individual). We performed a *t*-test (p value < 0.05) to compare the mean cerebellar volume between groups (SPSS).

2.3.2. Pre-processing and voxel-based morphometry (VBM) analysis

The images were transformed from Dicom to the Nifti format using DCM2Nii (http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html). The pre-processing entails five main steps: isolation, segmentation in GM, spatial normalization of all images to the same stereotactic space, re-slicing into an atlas space (modulation) and smoothing. The Spatially Unbiased Infratentorial Atlas Template (SUIT) toolbox (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm) isolates the infratentorial structures from the surrounding tissue and generates segmentation maps, providing a more accurate intersubject-alignment than current whole-brain methods for these structures. The segmented GM images were then normalized to the SUIT template. We then re-sliced the segmentation map into a SUIT atlas space to correct the volume change induced by spatial normalization. We next performed homogeneity testing using the covariance of the images, which led to the exclusion of two patients. Finally, the GM probability images were smoothed with an 8 mm full-width half maximum (FWHM) isotropic Gaussian kernel filter in SPM8/DARTEL (http://www.fil.ion.ucl.ac.uk) to satisfy the Gaussian distribution assumption for statistical analysis of regional differences. This process minimizes effects due to residual differences in functional and gyral anatomy during inter-subject averaging and renders the data more normally distributed. Using SPM8, a two-sample test was created for voxel-by-voxel analysis and detection of GM differences between the groups. A statistical parametric map was generated, which identified the cerebellar regions with significant differences (height threshold: $T = 3.21$; $p = 0.001$; extent threshold: $k = 20$ voxels). Anatomical localizations of the cerebellar lobules and vermis were determined by the Probabilistic MR atlas of the human cerebellum by Diedrichsen et al. [13] which was developed by masking the cerebellar lobules of 20 healthy subjects MRI scans. It allows for a more accurate assignment of the cerebellar lobules as it preserves the anatomical details of these structures. However, this is a cerebellar atlas and, in order to access changes in other infratentorial structures such as medulla oblongata, pons and midbrain, we also report our results using the Automated Anatomical Labeling (AAL) [14].

We also attempted to correlate the identified GM changes with the following clinical data: age, disease duration, duration of BoNT and the MFS score. This analysis was performed in SPM8 using separated regression analyses. In the contrast manager, we could

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