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Electrophysiological and structural MRI correlates of dystonic head rotation in drug-naïve patients with torticollis

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ABSTRACT

Introduction: We tested whether a change in head/neck position initiates head deviation in drug-naïve patients with cervical dystonia and to identify the electrophysiological and neuroanatomical correlates of dystonic head rotation.

Methods: Twenty-five consecutive drug-naïve patients with cervical dystonia and 25 healthy controls underwent the simultaneous surface electromyographic (EMG) recording of sternocleidomastoid (SCM) muscle contractions during head/neck position changes, blink reflex recovery cycle (BRrc), DAT-SPECT, and advanced structural neuroimaging analysis using voxel-based morphometry (VBM).

Results: Surface EMG recordings of SCM muscle activity during changes in head/neck position demonstrated an insignificant asymmetric low amplitude of the SCM muscle contractions in the horizontal position in both patients and controls, but an asymmetric high amplitude in SCM muscle contractions leading to abnormal head movements in vertical positions in patients with cervical dystonia.

All controls had a symmetric low increase in amplitude of SCM muscle contractions in response to changes in head/neck position. VBM analysis in 19 patients showed abnormal decreases of gray matter (GM) volume in the bilateral motor (localized in the homunculus of the head) and premotor cortices when compared to controls. In addition, the side of these neuroanatomical changes was asymmetrically related to abnormal head deviations in these patients. All subjects had normal results during BRrc and DAT-SPECT.

Conclusions: The passage from inactive horizontal position to active vertical head/neck posture initiates head deviation in drug-naïve patients with cervical dystonia, and the anatomical correlates of this dystonic head rotation is a restricted abnormal pattern of GM changes in the motor cortices.

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1. Introduction

Isolated cervical dystonia (CD) is the most common adult-onset focal dystonia in the general population [1], but the pathophysiological mechanism responsible for causing the excessive neck muscle contractions leading to abnormal head positions in CD is still unknown [2]. An electrophysiological study [3], suggests increased motor cortex excitability in patients with CD, but others

using blink reflex recovery cycle (BRrc) show an abnormal brainstem interneuron excitability in CD [4,5]. Neuroimaging studies detect abnormalities in many cerebral structures in patients with CD, and VBM-MRI studies of patients with CD reveal contradictory results. Some authors [6] found decreased gray matter (GM) volume in the bilateral premotor and primary sensory-motor cortices, caudate and putamen of treated patients with primary CD; while others [7,8] found increased GM volume of the globus pallidus internus, putamen bilateral motor cortex and cerebellar flocculus. In addition, results are also variable in craniocervical dystonias [9,10]. Recent studies [11,12] found abnormalities in the cerebellum and brainstem and failed to show abnormalities in the basal ganglia. Some authors [13,14] found abnormalities in the sensorimotor cortex, cerebellum and basal ganglia using functional imaging of regional blood flow with positron-emission tomography

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(PET) or metabolic mapping with fluorodeoxyglucose PET. Diffusion-tensor imaging (DTI) study [15] showed abnormalities in the cerebral cortex, particularly in the prefrontal cortex and supplementary motor area, corpus callosum and basal ganglia. However, the integrity of the nigro-striatal dopaminergic system is suggested by normal DAT-SPECT results in patients with dystonic tremor [16]. The more heterogeneous sample of patients used may explain the contradictory results obtained in the afore-mentioned studies. In sum, the results of the previous studies are inconclusive, and a further detailed study in drug-naïve patients with isolated CD is warranted to establish the electrophysiological and neuroanatomical correlates of CD.

As an abnormal sensorimotor integration has been found in focal dystonia [3], we theorize that CD may be due to altered brain postural control system [17] at the cortical level. We hypothesized, therefore, that isolated CD is a dynamic dystonic disorder due to altered sensorimotor integration during the head/neck position changes. To identify the electrophysiological and neuroanatomical correlates of dystonic head rotation and to address our hypothesis, we investigated 25 drug-naïve patients with CD by using both electrophysiological studies and morphologic MR measurements of the brain.

2. Methods

2.1. Subjects

In this case-control study, we enrolled 25 consecutive drug-naïve patients with isolated CD and 25 healthy controls matched for sex and age. Every subject underwent a complete history and neurological examination. The Tsui Scale was used to assess dystonic features. Diagnosis of isolated CD was according to clinical criteria [18]. Only patients with torticollis and laterocollis were included in this study. Exclusion criteria were: the presence of brain lesions (evidence of structural abnormalities as revealed by radiological examination), psychiatric disorders or drug treatment that could cause dystonia. In addition, 25 volunteers with no previous history of neurological or psychiatric diseases and with normal MRI of the brain were matched for demographic variables with the study patients. All participants underwent electrophysiological and neuroimaging studies. All patients were investigated at the time of diagnosis of CD and were treatment-naïve. All subjects provided informed consent for participation in the study, which was approved by the Ethical Committee of the University “Magna Graecia” of Catanzaro.

2.2. Electrophysiological studies

2.2.1. Surface electromyographic recording

We simultaneously investigated the electromyographic (EMG) activity bilaterally in the sternocleidomastoid (SCM) muscles. We placed self-adhesive surface EMG electrodes in the middle of SCM muscles and the “earth” electrode over the manubrium sterni or slightly above. Recruitment patterns induced by contractions of the appropriate muscles confirmed the electrode positions. The first channel recorded the right SCM muscle and the second channel recorded the left SCM, with a direct correlation between the EMG activity in the two channels and the clinical features that were video-recorded in patients and controls.

The EMG recording had a frequency of 3 Hz, duration of 800 ms and sensitivity of 0.05 mV and duration of 10 min of free maximal dystonic contractions during which patients were asked to not oppose dystonic neck spasms. All subjects were first evaluated at rest in the supine position with eyes lightly closed and with the head in the mid-position; they were then evaluated inactive (sitting

and standing) vertical positions. We measured the amplitude of muscle contraction as the maximum amplitude of the SCM muscles (peak to peak). We evaluated amplitude increases during SCM muscle contractions when the subject assumed the vertical positions. On EMG recordings, we considered a muscle active (dystonic) when the amplitude of the muscle contraction exceeded 250 μ V (peak-to-peak) and the difference between the amplitudes of SCM muscle contractions was greater than 100 μ V [19]. A muscle activity of less than 50 μ V was inactive (normal). The purpose of this EMG study was to detect an overall change in muscle contraction patterns through an evaluation of individual muscles during transition from horizontal to vertical head/neck positions.

2.2.2. Blink reflex recovery cycle

We recorded the blink reflex recovery cycle (BRrc) in all subjects while delivering stimuli of 0.2 ms duration to the supraorbital nerve of the right side. We recorded EMG responses of the ipsilateral and contralateral orbicularis oculi using surface electrodes below the eyelid and on the temple, using the method described by Kimura [20]. The EMG signals were amplified using D360 amplifiers, bandwidth filtered (20 Hz–10 KHz), analog-to-digital-converted using a 1401 AD converter at a sample rate of 5000 Hz, and recorded on a computer. We used stimuli intensities between 5 mA and 30 mA, choosing those that were three times the threshold of the BR responses. The threshold was determined as the lowest intensity of stimulation with an R2 response in at least 5 out of 10 trials. Subjects were studied at rest, with eyes lightly closed. We measured the intensity of each stimulus of the BR in response to paired stimulation at interstimuli of 100, 150, 200, 300, 400, 500 and 750 ms (where we would expect the R2 of the second stimulus to reappear in all healthy subjects). To rise above the variability of the responses, we applied each stimulus four times for each ISI, at intervals between trials ranging randomly from 20 to 50 s to minimize habituation. We calculated the area of the conditioned R2 over the same duration as the unconditioned; we then applied the same procedure to the left side. The R2 area ratio (R2 area of the conditioned response divided by the R2 area of the unconditioned response) defined the recovery cycle for each ISI.

2.3. MRI data acquisition

Brain MRI was performed according to our routine protocol by a 3 T scanner with an 8-channel head coil (Discovery MR-750, GE, Milwaukee, WI, USA). We acquired structural MRI data using a 3D T1-weighted spoiled gradient echo (SPGR) sequence with the following parameters: TR: 3.7 ms. TE: 9.2 ms, flip angle 12°, voxel-size 1 × 1 × 1 mm³; 368 sagittal slices. Subjects were positioned to lie comfortably in the scanner with a forehead-restraining strap and various foam pads ensuring head fixation. With respect to electrophysiological measurements, for neuroimaging analysis we excluded six CD patients due to motion artifacts during their MRI examination.

2.4. VBM data processing

We used SPM8 software to process and examine the data and the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>) with default parameters incorporating the DARTEL toolbox to obtain a high-dimensional normalization protocol for VBM. Images were bias-corrected, tissue classified and registered using linear and non-linear transformations, within a unified model [21]. Subsequently, the warped GM segments were affine transformed into Montreal Neurological Institute (MNI) space and were scaled by the Jacobian determinants of the deformations (modulated GM volumes). Finally, the modulated volumes were smoothed with a

Gaussian kernel of 8 mm.

2.5. ^{123}I -FP-CIT studies (DAT-SPECT)

All patients and control subjects received perchlorate (1000 mg) 30 min prior to scanning to block thyroid uptake of free radioactive iodine. Brain imaging was performed 3 h after the administration of 200 MBq of ^{123}I -FP-CIT (GE-Amersham, Eindhoven, The Netherlands) using a dual-headed gamma camera (Infinia Hawkeye, General Electric, Milwaukee, WI) equipped with a low-energy, high-resolution collimators (SPECT), as described elsewhere [22].

3. Statistical analysis

We used R Statistical Software (R for Unix/Linux, version 2.15.1, the R Software Foundation for Statistical Computing, 2012) to perform the statistical analysis. In order to choose between parametric and non-parametric tests, we used the Shapiro–Wilk test for normality checks. The Mann–Whitney U test assessed differences in age at examination. The χ^2 test checked for differences in sex distribution between groups. The paired t-test corrected according to Bonferroni compared the right and left amplitude of SCM muscle contractions within groups. The one-way Anova test compared the left-to-right variation in amplitude of muscle contraction for each head/neck position and between groups. All p values were two tailed, and α level was set at $p < 0.05$.

The general linear model based on Gaussian random field theory statistically analyzed the GM volume maps. An independent t-test analysis detected differences between CD patients and controls including age and total intracranial volume (ICV) in the model as covariates of no-interest. We applied a conservative approach with a whole-brain statistical threshold correction for multiple comparisons ($p < 0.05$, family-wise error (FWE)). Moreover, to evaluate co-variation between GM volume changes and clinical data, we performed a correlation analysis using the multiple regression function of SPM8. Specifically, we were interested in investigating the relationship between the electrophysiological measures to the detected anatomical changes.

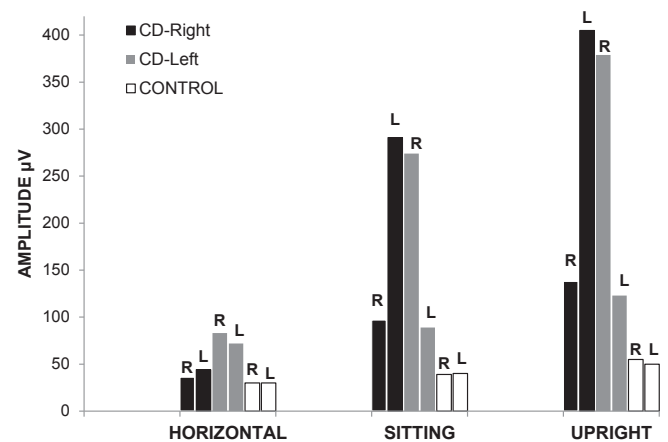
4. Results

4.1. Clinical data

The demographic and clinical features of all subjects are shown in Table 1. There were only three patients with a combination of torticollis to the right and mild laterocollis to the left. No significant

Table 1
Demographic and characteristics of drug-naïve patients with torticollis and controls.

	Torticollis n = 25	Controls n = 25
Men, n (%)	8 (32%)	8 (32%)
Age (years)	49.7 ± 14	42.2 ± 15
Age at onset (years)	41 ± 14.3	–
Disease duration (years)	8.6 ± 5.2	–
Affected side, Left/Right	17/8	–
TSUI scale	9 ± 4.7	–
Drug naïve	25 (100%)	25 (100%)
Botulinum toxin treatment	No	–
Tremor	No	–
Familiarity	No	–
Brain and cervical MRI	Normal	Normal
DAT-SPECT		
Left putamen	2.19 ± 0.31	2.20 ± 0.29
Right putamen	2.20 ± 0.35	2.21 ± 0.28
Blink reflex recovery cycle		
R2 recovery at ISI	400 ms	400 ms



CD, cervical dystonia; R, sternocleidomastoid right; L, sternocleidomastoid left.

Fig. 1. Amplitude of sternocleidomastoid muscles contraction in response to passage from inactive horizontal position to active vertical head/neck postures (sitting and upright) in patients with cervical dystonia and controls. CD, cervical dystonia; R, sternocleidomastoid right; L, sternocleidomastoid left.

differences were detected in demographical data between patients and controls.

4.2. Surface EMG recording data

There were no significant differences between patients and controls in the horizontal position. In both groups, surface EMG recordings revealed an asymmetric low amplitude of the SCM muscle contraction, the difference between the amplitude left to right of SCM muscle contraction was less than 100 μV (CD-R, $p = 0.44$; CD-L, $p = 0.27$), and the Anova test showed no significant differences in left-to-right amplitude variation (Δ_{RL}) ($p = 0.192$). When the patients with isolated CD assumed the vertical (sitting and standing) positions, we recorded a significant asymmetric higher increase in amplitude of SCM muscle contraction in both right and left CD. The amplitude was higher than 250 μV in the affected SCM muscle in vertical positions, while the amplitude of SCM muscle contraction in the controls remained below 100 μV (CD-R, $p < 0.0001$; CD-L, $p < 0.0001$) (Fig. 1).

We found a more interesting result when comparing the left-to-right amplitude of SCM muscle contraction variations between positions within groups. We observed highly significant differences in CD-R (sitting vs. supine, $p = 0.0003$; standing vs supine, $p = 0.0002$) and CD-L (sitting vs. supine, $p < 0.0001$; standing vs supine, $p < 0.0001$) patients, while observing no differences in control subjects (sitting vs. supine, $p = 1$; standing vs supine, $p = 0.3$). We also found slight significant differences between sitting and standing positions in patients with torticollis to the left (Table 2).

4.3. Blink reflex recovery cycle

BR responses to single supraorbital nerve electrical stimuli were present at a normal latency in all subjects; there were no differences between patients and controls. There were no significant differences in R2 area ratio between CD patients from ISI 150, 200, 300, 400 and 500 compared to controls, and the R2 recovery index was normal in all subjects. These revealed the integrity of the inhibitory circuits at the brainstem level in both patients and control subjects.

Table 2
Surface EMG recording data and head deviations during the passage from inactive horizontal position to active vertical head/neck postures in drug-naïve patients with torticollis and controls.

Body positions	Patients					Controls			
	Right HD		p	Left HD		p	Head in midposition		p
	SCM R	SCM L		SCM R	SCM L		SCM R	SCM L	
Horizontal	36 ± 20*	44 ± 20*	0.44†	83 ± 54*	72 ± 31*	0.27†	30 ± 11	30 ± 9	0.93‡
Sitting	97 ± 59	291 ± 84	<0.0001‡	274 ± 47	89 ± 18	<0.0001‡	39 ± 13	40 ± 14	0.84‡
Upright	138 ± 65	405 ± 96	<0.0001‡	379 ± 58	123 ± 66	<0.0001‡	55 ± 14	50 ± 16	0.26‡
Δ _{RL} sit. vs rec.	0.0003			<0.0001			1		
Δ _{RL} up. vs rec.	0.0002			<0.0001			0.3		

SCM, sternocleidomastoid; R, right; L, left; HD, head deviation; * Head in the Midposition; †paired t-test; ‡ Wilcoxon signed rank test.

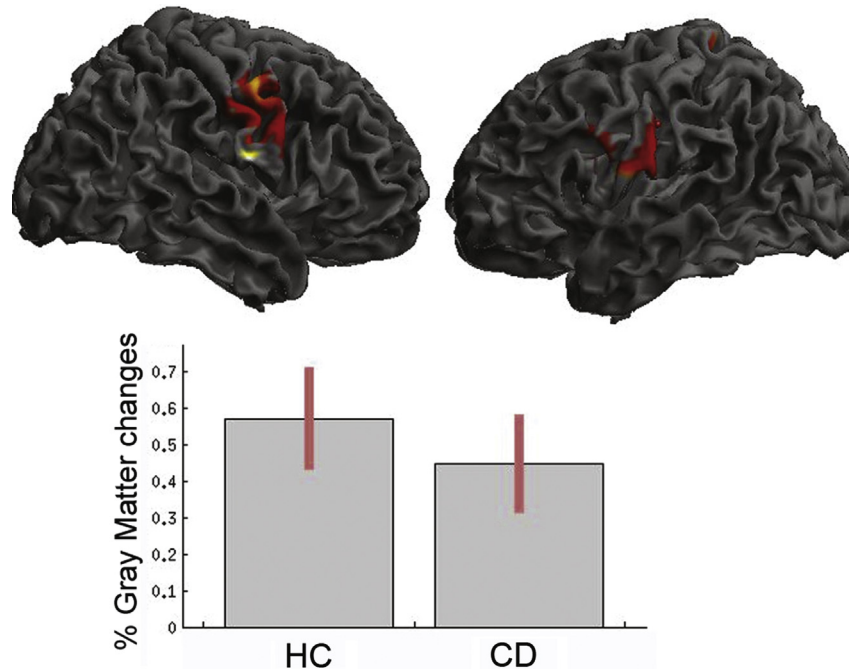


Fig. 2. VBM results. 3D surface render shows the significant cluster deriving from the main effect of group. Significant difference (**surviving correction for multiple comparisons at a whole brain level, FWE < 0.05) is found in the bilateral ventral motor and premotor cortices, where drug-naïve patients with CD display an abnormal decrease of the GM volume with respect to other groups. Mean differences (\pm SEM) between groups within regions of statistical significance have been plotted below. A statistical map is superimposed onto the T1-weighted standard template (MNI). Data analyses have been further corrected for age and intracranial volume. CD: cervical dystonia; HC: healthy controls.

4.4. 123I-FP-CIT studies

Both CD patients and control subjects had normal DAT-SPECT. The quantitative analysis of striatal uptake was equal to 2.19 ± 0.31 (PutL/Occ) and 2.20 ± 0.35 (PutR/Occ) in patients with CD and 2.20 ± 0.29 (PutL/Occ) and 2.21 ± 0.28 (PutR/Occ) in the control subjects.

4.5. VBM data

VBM analysis investigating the neuroanatomical changes occurring in CD patients compared to controls, revealed the presence of a very restricted pattern of difference surviving correction for multiple comparisons at a whole brain level (FWE < 0.05). As shown in Fig. 2, CD patients demonstrated an abnormal decrease of GM volume in the bilateral pre-/motor cortices. The local maxima of statistical changes was detected in the homunculus region of the head (T-value = 5.71, $P_{FWE} < 0.001$ for the right hemisphere and T-value = 5.42, $P_{FWE} = 0.02$ for the left hemisphere), and in the bilateral premotor cortex (T-value = 4.64, $P_{FWE} = 0.04$ for the right hemisphere and T-value = 5.1, $P_{FWE} = 0.03$ for the left

hemispheres).

We further performed regression analyses to investigate whether clinical variables influence the detected GM abnormalities in CD patients. There was a negative correlation between the TSUI scores in CD patients and GM volume in the right motor/premotor cortices (local maxima: $x = 38$, $y = 5$, $z = 49$, $P_{FWE} = 0.04$) (Figure esupp file), thus demonstrating that the detected abnormal neural loss characterizing patients with CD was dependent upon patients with high clinical disability. We did not find any significant correlation with other clinical or electrophysiological measures, such as age at onset, disease duration or surface EMG recording data.

5. Discussion

Our results demonstrate that the passage from inactive supine position to active vertical head/neck posture initiates the head deviation in drug-naïve patients with CD, and the anatomical correlation of this dystonic head rotation is a restricted abnormal pattern of GM changes in the motor cortices. These findings suggest that there is a dynamic dystonic disorder of the cervical muscles

produced by altered sensorimotor integration when patients with CD change head/neck posture from inactive to active.

Indeed, when the treatment-naïve patients with CD assumed the vertical positions, surface EMG recordings showed an asymmetrically high increase in amplitude of SCM muscle contraction leading to dystonic head rotations. This finding was not observed in the controls. In addition, EMG recordings in the supine position with the head in the mid-position displayed insignificant asymmetric low amplitude of SCM muscle contraction in patients as well as in controls, but this tonic muscle-activation pattern did not produce an abnormal movement of the head. All these results show the effect of an activated vertical head/neck posture upon the excessive phasic activation of the cervical muscles in CD patients. To explain this finding in drug-naïve patients with CD, we hypothesize that there is a misinterpretation of the input generating from muscle spindles; this is in response to a change inactive vertical position causing abnormal cervical muscles activation. This observation and given our earlier data support our hypothesis that CD is a dynamic dystonic disorder due to altered sensorimotor integration during the passage from inactive horizontal position to active vertical head/neck posture causing abnormal neck-muscle activation resulting in inappropriate head movement. There is evidence showing the presence of an altered sensorimotor integration in patients with CD [3]. Some authors [23] found an abnormal postural response to vibration of the neck muscles in CD, suggesting a brain misinterpretation of the input generating from these muscles.

Our findings also suggest that surface EMG recordings of the cervical muscles contraction during the passage from inactive horizontal position to active vertical head/neck posture may be a useful tool for detecting dystonic head rotation in drug-naïve patients suspected of having CD or in the differential diagnosis of subjects with functional movement disorders.

According to electrophysiological findings, neuroimaging structural analysis revealed a restricted pattern of anatomical changes within the motor and premotor cortices, which differentiated these drug-naïve patients with CD from healthy subjects. Interestingly, the detected volumetric loss in the motor cortex appears to be localized in the homunculus region of the head, thus providing further confirmation on the robustness of our findings. In addition, the negative correlation between the TSUI score and GM volume in the right motor/premotor cortices indicated that neural loss in these areas was more pronounced in those patients who were clinically more severely impaired. Our data are in agreement with previous neuroimaging studies [8] demonstrating that the pathophysiological pattern characterizing patients with CD specifically involved the striatal-frontal motor pathways. A previous VBM study [8] demonstrated the presence of GM atrophy in the sensorimotor network including the dorsal premotor cortex, which characterized patients affected by limb dystonia [24].

Functional neuroimaging studies confirmed that patients with focal dystonias were characterized by either abnormal activities of these cortical motor regions (detected by using functional MRI) [25,26] or disordered cortical representation of digits (detected by magnetoencephalography technique) [27]. This evidence supports our hypothesis that changes in the motor cortices represent the neural correlates of abnormal sensorimotor integration leading to abnormal activation of the neck muscles during the transition from inactive supine position to active vertical head/neck posture in patients with CD. The discrepancy between the numerous cerebral abnormalities found in previous neuroimaging studies and the isolated anatomical changes of the motor cortices detected in our series of patients may be explained by the more heterogeneous sample and the different brain MR imaging methods used [6,10,13,15].

Unlike previous studies, we performed brain MR with a 3 T scanner, and the imaging acquisition protocol, software, and choice of corrected and uncorrected imaging analysis were all different. Moreover, the patients did not have head tremor associated with CD and were treatment-naïve having never received botulinum toxin injections. Hence, potential confounders of morphologic MR measurement such as tremor [28] and botulinum toxin treatment [6] were avoided in our series of patients. The previous studies recruited a more heterogeneous sample of subjects, differing in treatment and disease duration, but those authors did not control these differences in their analysis. In short, these observations may explain the different image findings obtained in previous studies.

In the present study, both the controls and patients with isolated CD had both normal DAT-SPECT and BRrc. These data indicates an integrity of the pre-synaptic nigrostriatal dopaminergic system [29], and confirm the lack of alterations of inhibitory circuits at the brainstem level in CD [30]. These results further support the link between the motor pathway abnormalities revealed by VBM method and the inaccurate neck-muscle activation patterns shown by using EMG recordings during head/neck postural changes in patients with CD.

The strong feature of this study is the selection of drug-naïve patients evaluated at the time of CD diagnosis. A limitation is the lack of a significant relationship between the neuroimaging data and the amplitude of SCM muscles contraction. As well, the small number of patients with right torticollis made it difficult to create two significant groups of patients (e.g., torticollis to the right vs torticollis to the left). These limitations are clinical questions to address in the future.

Our multimodal electrophysiological and neuroimaging study indicates that drug-naïve patients with CD have a dynamic dystonic disorder of the cervical muscles due to altered brain postural control at the cortical level. Moreover, these data suggest that simultaneous surface EMG recordings of the cervical muscle contraction during the passage from inactive horizontal position to active vertical head/neck posture may be a useful electrophysiological tool in clinical practice for investigating patients suspected of having CD or functional movement disorders.

Disclosure

The authors report no disclosures. All authors have approved the final article.

Author roles

Francesco Bono: conception and design of the study, analysis and interpretation of data, drafting of article and revision for intellectual content, final approval of the version to be submitted; Dania Salvino: design of the study, acquisition/analysis and interpretation of data, drafting of article and revision for intellectual content, final approval of the version to be submitted; Antonio Cerasa and Salvatore Nigro: VBM data analysis and interpretation, article revision for content, final approval of the version to be submitted; Basilio Vescio: statistical analysis, article revision for content, final approval of the version to be submitted; Aldo Quattrone: data interpretation, article revision for content, final approval of the version to be submitted.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2015.09.050>.

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