Motor and non-motor symptoms in cervical dystonia

Smit, Marenka

CHAPTER 7

7

Indications of an altered regional cerebral blood flow in cervical dystonia and its relation with motor and non-motor symptoms

M Smit
D Vállez García
BM de Jong
RA Dierckx
AT Willemsen
EF de Vries
AL Bartels
MA Tijssen

In preparation.

ABSTRACT

Relative cerebral blood flow (rCBF) was studied in cervical dystonia (CD) patients relating to motor and non-motor symptoms (NMS).

Fourteen CD patients and 12 healthy volunteers underwent MRI and serotonin transporter PET ([^{11}C]DASB) scans. The obtained PET data enabled calculation of initial tracer distribution as surrogate of rCBF, using a nonlinear reference tissue model (SRTM2). Motor and NMS (i.e. depression, anxiety, fatigue and sleep disturbances) were assessed. A decreased rCBF in temporal and frontal areas and the insula was found in CD patients compared to controls. A negative correlation was observed between the rCBF in temporal lobes and depression and anxiety scores, and between a decreased rCBF in the basal ganglia and motor symptoms.

Our results indicate an altered rCBF in CD, representing dysfunction of networks involved in head-motion registration and sensory-motor integration. Current pathophysiological hypotheses in CD are supported and motivate the design of larger studies towards involvement of temporal and frontal lobe regions and the insula in dystonia.

INTRODUCTION

Cervical dystonia (CD) is the most prevalent form of adult-onset focal dystonia, affecting 28-183 cases per million people [1]. The definition of CD is based on the abnormal motor movements of the cervical musculature, but in 95% of all cases CD is also accompanied by non-motor symptoms (NMS) like psychiatric co-morbidity, fatigue and sleep disturbances [2].

Alterations in the regional cerebral blood flow (rCBF) have been implicated in the pathophysiology of dystonia [3]. In primary dystonia, using [^{15}O]H_2O PET a prefrontal increase in relative cerebral blood flow (rCBF) has been demonstrated, which could be reversed by effective deep brain stimulation [4]. Moreover, [^{15}O]H_2O PET activation studies in idiopathic torsion dystonia have shown overactivity of striatofrontal projections and impaired activity of motor executive areas [5]. It was hypothesized that alterations in rCBF in motor and sensory areas suggest dysfunction in interconnecting circuits, causing defective sensorimotor integration [6].

In general, PET rCBF studies with [^{15}O]H_2O concern activation experiments aimed to explore distinct regional cerebral functions by task-evoked responses, requiring repeated rCBF measurements in each participating subject. In the current PET study, we calculated rCBF by using the initial distribution curve of the [^{11}C]DASB receptor tracer. In this way, a single rCBF measurement in each subject provides a robust index of regional neuronal activity comparable with the information obtained by [^{18}F]fluorodeoxyglucose (FDG).

The method of [^{11}C]DASB-based rCBF measurements was employed in CD patients and controls to assess whether changes in rCBF were related to motor and NMS.

METHODS

Subjects

Patients (*n*=14, 56yr [46-70]) with a clinically diagnosed idiopathic CD and age- and sex-matched controls (*n*=12, 54yr [39-70]) were included in the study (Supplementary table 1). The same patients have been described in a previous paper (Smit et al., in preparation) reporting the use of [^{11}C]DASB to study the cerebral distribution of serotonin transporter sites with PET in patients with CD and controls. By using the Simplified Reference Tissue Model (SRTM2) model [7], we now additionally calculated the relative tracer delivery to a preselected series of brain regions as compared to the reference region (R_1) [8]. This model has proved to generate a reliable measure of the relative rCBF [8]. The use of R_1 as a robust apparent index of rCBF has also been validated for [^{11}C]PiB [9].

Supplementary table 1
Demographic and clinical characteristics

	CD (*n*=14)	Controls (*n*=12)	Maximum value	Cut-off value	*p*-value
Age	56±9 y	53±8 y			Ns
Female	12 (86%)	10 (83%)			Ns
Dystonia duration	12±13 y				
TWSTRS					
- Motor severity	17.5±5.7		35		
- Disability	11.6±5.7		30		
- Pain	7.2±6.4		20		
- Total	36.4±15.9		85		
CGI-S tremor/jerks	1.9±0.8		7		
Beck Depression Inventory	12.6±6.6	3.6±3.9	63	≥ 10	0.01
Beck Anxiety Inventory	8.9±5.6	3.9±3.6	63	≥ 10	<0.01
Fatigue Severity Scale	38.8±14.3	22.9±6.6	63	≥ 36	<0.01
Pittsburgh Sleep Quality Index	8.3±3.8	5.3±4.3	21	≥ 5	ns

Demographic and clinical characteristics of cervical dystonia patients (CD) and controls, including the maximum values of the different motor and non-motor scales and cut-off values. Data shown as mean ± standard deviation or number (%). Y = years. TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale. CGI-S = Clinical Global Impression Scale.

An exclusion criterion for the CD patients was onset of CD before the age 18 and severe tremor and/or jerks obstructing accurate brain imaging. Additional exclusion criteria for all subjects included other relevant neurological co-morbidity and the use of serotonergic medication or antidepressants. Informed consent was obtained from all participants and the study was approved by the local ethics committee (2014/034).

Clinical measures

Motor assessments, including dystonia severity (TWSTRS) [10] and the severity of jerks and tremor (CGI-S jerks/tremor) [11], were performed using a systematic video protocol and scored by two experts (MS, VH). In addition, depression (BDI) [12], anxiety (BAI) [13], fatigue (FSS) [14], and sleep disturbances (PSQI) [15] were examined in all the subjects.

Brain imaging

Image data acquisition, reconstruction, and processing are described in detail elsewhere (Smit et al., in preparation). In brief, all subjects underwent a dynamic 60-min PET scan simultaneously to an intravenous bolus injection of [^{11}C]DASB (379±44 MBq), in addition to a T1-weighted gradient-echo magnetic resonance imaging (MRI). Image processing and pharmacokinetic analysis was performed with PMOD v3.7 software (PMOD Technologies Ltd, Switzerland). After registration of individual PET to the individual MRI, the images were spatially normalized into the Montreal Neurological Institute (MNI) standard space.

Predefined volumes of interest (VOIs) were defined based on the Hammers atlas [16] and limited to the grey matter tissue of cortical regions. With the VOI analysis, we focused only on hemispheric regions. We did not define brainstem VOI's because rCBF did not demarcate a distinct subregion in this small structure, in contrast to the local spot of specific binding sites for the serotonin transporter in the dorsal midbrain. For the additional voxel-based analysis, the whole brain was assessed.
Pharmacokinetic modelling was performed for using the Simplified Reference Tissue Model 2 (SRTM2) [17] with the cerebellum (excluding vermis) as the reference region. The ratio of tracer delivery ($R_1=K_1/K_1'$ [17]) was used as the apparent index of the rCBF and further referred to as rCBF.

Statistics
Statistical analysis was performed using SPSS Statistics 22 (IBM SPSS Statistics, USA). Demographics, clinical data and VOI-based data were compared between groups using the Pearson $\chi 2$ test, Fisher's exact test, and the Mann-Whitney U test. Correlation analysis between the rCBF values and clinical characteristics were explored with Spearman's rho test. Differences were considered statistically significant at $p<0.05$, without correction for multiple comparisons.

Additionally, voxel-based analysis of rCBF images was performed using SPM12 (Wellcome Trust Centre for Neuroimaging, UK) between dystonia patients and healthy volunteers. T-maps data were interrogated at $p=0.005$ (uncorrected) and only clusters with $p<0.05$ corrected for family-wise error were considered significant. Moreover, effect sizes were calculated using the Cohen's *d* test.

RESULTS

VOI-based analysis
A decreased rCBF was found in several brain regions in CD patients when compared with controls, including bilaterally the temporal lobe (right 7.6%, $d=1.2$, $p=0.01$; left 6.4%, $d=1$, $p=0.02$), and unilaterally in the left anterior cingulate cortex (7%, $d=0.8$, $p=0.046$), right middle/inferior frontal gyrus (6.3%, $d=0.77$, $p=0.04$), right orbital gyrus (7.8%, $d=1.14$, $p=0.02$) and right insula (6.5%, $d=0.92$, $p=0.046$) (Table 1).

Voxel-based analysis
The mean rCBF image derived from the control subjects is shown in supplementary figure 1.

In the voxel-based analysis, a statistically significant decrease in the rCBF values was found in CD patients when compared with controls, namely bilaterally in the superior temporal gyrus pars anterior (left, T=3.6 (SD ± 0.6); right T=3.1 (SD ± 0.3)) and pars

posterior (left T=3.5 (SD ± 0.6); right T=3.2 (SD ± 0.3)), the posterior part of the temporal lobe (left T=3.2 (SD ± 0.3); right T=3.3 (SD ± 0.4)), and in the left thalamus (T=3.4 (SD ± 0.4)) (Figure 1, supplementary table 2).

Correlations between clinical variables and the rCBF.

In the CD patients, the severity of jerks and tremor was negatively correlated with the rCBF in the right caudate nucleus (r*s*=-0.69, *p*<0.01), the right putamen (r*s*=-0.54, *p*=0.046), and the right insula (r*s*=-0.56, *p*=0.04).

No statistically significant correlation between the rCBF values and the NMS was observed within the CD patients. However, when both CD patients and controls were included in the analysis, a significant negative correlation was found between the rCBF in the superior temporal posterior (STP) and anterior (STA) areas and depression (STP right: r*s*=-0.50, *p*<0.01, STP left: r*s*=-0.45, *p*=0.02, STA left r*s*=-0.48, *p*=0.01), anxiety (STP right: r*s*=-0.43, *p*=0.03, STP left: r*s*=-0.44, *p*=0.03, STA left r*s*=-0.45, *p*=0.02), and fatigue (STP right: r*s*=-0.43, *p*=0.03, STP left: r*s*=-0.62 *p*=0.047).

Table 1
Relative cerebral blood flow

	CD (n=14)		HC (n=12)	
	Right	*left*	*right*	*left*
Thalamus	1.02±0.06	0.99±0.06	1.04±0.08	1.02±0.08
Putamen	1.02±0.06	1.02±0.06	1.03±0.08	1.03±0.09
Nucleus Caudatus	0.69±0.11	0.69±0.12	0.68±0.12	0.68±0.14
Globus Pallidus	0.74±0.06	0.74±0.03	0.75±0.05	0.78±0.07
Substantia Nigra	0.80±0.05	0.80±0.07	0.79±0.07	0.79±0.06
Hippocampus	0.75±0.05	0.76±0.05	0.81±0.06*	0.83±0.07*
Amygdala	0.67±0.04	0.66±0.05	0.67±0.03	0.69±0.02
Anterior cingulate cortex	0.96±0.10	0.93±0.10	1.00±0.08	1.00±0.07*
Frontal cortex - Middle- and inferior frontal gyrus	1.04±0.08	1.04±0.09	1.11±0.10*	1.10±0.09
- Superior frontal gyrus	0.96±0.08	0.96±0.09	1.02±0.07	1.01±0.09
- Anterior-, medial-, lateral- and posterior orbital gyrus	0.95±0.07	0.96±0.07	1.03±0.07*	1.02±0.07
- Subgenual frontal cortex, subcallosal area and pre-subgenual frontal cortex	0.78±0.08	0.84±0.09	0.85±0.09	0.89±0.07
Cuneus + lingual gyrus	1.03±0.07	1.01±0.06	1.06±0.08	1.03±0.07
Insula	0.86±0.06	0.87±0.06	0.92±0.07*	0.93±0.08
Temporal lobe	0.73±0.05	0.73±0.05	0.79±0.05*	0.78±0.05*

The rCBF in cervical dystonia patients (CD) and controls. Data concerning pre-defined volumes of interest (VOI) are shown as mean ± standard deviation.CD=cervical dystonia. HC= healthy control. * p<0.05

Supplementary figure 1
Mean rCBF image derived from the control subjects.

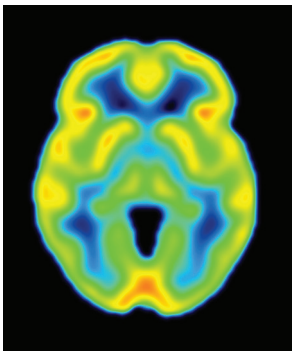
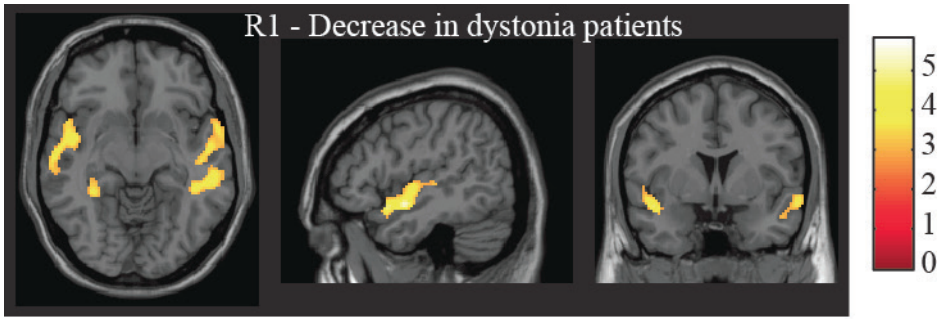


Figure 1
Areas with decreased rCBF in CD patients, when compared with the controls



Voxel-based analysis based on decreased rCBF, based on initial tracer distribution (R1), in CD compared to control subjects. Only significant clusters are represented (p-voxel<0.005 uncorrected, and p-cluster<0.05family-wise error corrected).

Supplementary table 2
Decreased rCBF in CD patients compared with controls.

Region	Voxels	T	±	SD	Cohen's *d*
Superior temporal gyrus anterior part left	213	3.63	±	0.57	1.48
Superior temporal gyrus anterior part right	128	3.14	±	0.28	1.28
Superior temporal gyrus posterior part left	425	3.53	±	0.58	1.44
Superior temporal gyrus posterior part right	448	3.25	±	0.34	1.33
Posterior temporal lobe left	175	3.21	±	0.27	1.31
Posterior temporal lobe right	335	3.33	±	0.44	1.36
Thalamus left	111	3.43	±	0.45	1.40

Functional regions (>100 voxels) showing decreased rCBF, obtained from significant clusters (p-voxel<0.005 uncorrected, and p-cluster<0.05family-wise error corrected). For each functional region, the mean T-value, standard deviation (SD), effect size (Cohen's d) and voxel size are reported.

DISCUSSION

In this brain imaging study, a significantly decreased rCBF was observed in CD patients when compared with controls, particularly comprising temporal lobe regions, the thalamus, frontal and orbital gyrus, insula and anterior cingulate. These results emerged from both VOI-based and voxel-based analysis. Moreover, the decreased rCBF in the temporal lobe was significantly correlated with the NMS anxiety, depression and fatigue. In CD patients, the severity of jerks and tremor was negatively correlated with the rCBF in the caudate nucleus, putamen and insula. Our results indicate impairment of distinct circuitries for motor and NMS in CD patients.

The observed CD-related decreases in temporal lobe regions, the thalamus, frontal and orbital gyrus and cingulate regions point at functional impairment of circuitries serving integration of limbic and sensorimotor information, indeed likely associated with motor and NMS in CD.

Of special interest was the observed decreased rCBF in the insula. This region serves as a primary reception area for interoceptive sensory information, including head-motion registration [18,19]. In Parkinson's disease, NMS have also been associated with insula dysfunction, thus supporting our results [18,19]. Disturbed integration and altered head motion registration is compatible with the pathophysiological hypotheses in dystonia [20]. In CD, dysfunction of the insula has not been described before, but might thus be an interesting region at the interface of CD motor symptoms.

We found a correlation between decreased temporal cortex rCBF and both depression and anxiety. This is consistent with a pattern of decreased rCBF in the temporal and frontal areas in a SPECT study in a patient with myoclonus dystonia [21], explained as a consequence of psychiatric comorbidity. Involvement of the temporal cortex in idiopathic dystonia is also supported by human pallidum recordings in combination with magnetoencephalography (MEG). In that study a coherent pallido-temporal theta frequency band and pallidum coherence with sensorimotor regions was detected [22]. This network, considered to reflect learning and integration of limbic information in sensorimotor output, support a likely role of the temporal lobe in CD. With FDG PET, involvement of the temporal cortex in CD has also been described, although both decreased and increased regional metabolism has been found [23].

In conclusion, by employing the initial distribution of [^{11}C]DASB as an apparent index of relative rCBF we were able to identify changes in the limbic circuitry. Together with decreases in the spatially adjacent insula, the involvement of these regions point at functional impairment of circuitry serving integration of limbic and sensorimotor information likely associated with CD. Indeed, we found a relationship between a decreased rCBF in the temporal lobe and psychiatric co-morbidity, and a relationship between the basal

ganglia and motor symptoms. A challenge for future functional brain imaging in CD research is to identify crucial nodes in cerebral circuitry that may be initially affected and how network dysfunction subsequently expands in the brain.

REFERENCES

[1] G. Defazio, J. Jankovic, J.L. Giel, S. Papapetropoulos, Descriptive epidemiology of cervical dystonia, Tremor Other Hyperkinet. Mov. (N. Y). 3 (2013) tre-03-193-4374-2. eCollection 2013. doi:tre-03-193-4374-2 [pii].

[2] L. Klingelhoefer, D. Martino, P. Martinez-Martin, A. Sauerbier, A. Rizos, W. Jost, et al., Non-motor symptoms and focal cervical dystonia: observations from 102 patients, 4(3-4):117-120. (2014). doi:10.1016/j.baga.2014.10.002.

[3] E. Zoons, J. Booij, A.J. Nederveen, J.M. Dijk, M.A. Tijssen, Structural, functional and molecular imaging of the brain in primary focal dystonia--a review, Neuroimage. 56 (2011) 1011–1020. doi:10.1016/j.neuroimage.2011.02.045 [doi].

[4] O. Detante, L. Vercueil, S. Thobois, E. Broussolle, N. Costes, F. Lavenne, et al., Globus pallidus internus stimulation in primary generalized dystonia: a H215O PET study., Brain. 127 (2004) 1899–1908. doi:10.1093/brain/awh213.

[5] A.O. Ceballos-Baumann, R.E. Passingham, T. Warner, E.D. Playford, C.D. Marsden, D.J. Brooks, Overactive prefrontal and underactive motor cortical areas in idiopathic dystonia, Ann. Neurol. 37 (1995) 363–372. doi:10.1002/ana.410370313.

[6] A. Lerner, H. Shill, T. Hanakawa, K. Bushara, A. Goldfine, M. Hallett, Regional cerebral blood flow correlates of the severity of writer's cramp symptoms, Neuroimage. 21 (2004) 904–913. doi:10.1016/j.neuroimage.2003.10.019 [doi].

[7] Y. Wu, R.E. Carson, Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging, J. Cereb. Blood Flow Metab. 22 (2002) 1440–1452. doi:10.1097/00004647-200212000-00004 [doi].

[8] M. Ichise, J.S. Liow, J.Q. Lu, A. Takano, K. Model, H. Toyama, et al., Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain, J. Cereb. Blood Flow Metab. 23 (2003) 1096–1112. doi:10.1097/01.WCB.0000085441.37552.CA [doi].

[9] Y.J. Chen, B.L. Rosario, W. Mowrey, C.M. Laymon, X. Lu, O.L. Lopez, et al., Relative 11C-PiB Delivery as a Proxy of Relative CBF: Quantitative Evaluation Using Single-Session 15O-Water and 11C-PiB PET, J. Nucl. Med. 56 (2015) 1199–1205. doi:10.2967/jnumed.114.152405 [doi].

[10] E.S. Consky, A.E. Lang, Clinical assessments of patients with cervical dystonia. In: Jankovic J, Hallett M, editors. Therapy with botulinum toxin. New York, NY: Marcel Dekker, (1994) 211–237.

[11] W. Guy, The Clinical Global Impression scale. In: ECDEU Assessment Manual for Psychopharmacology-Revised. Rockville, MD: US Dept. of Health, Education and Welfare, ADAMHA, NIMH Psychopharmacology Research Branch, (1976) 218. doi:222.

[12] A.T. BECK, A systematic investigation of depression, Compr. Psychiatry. 2 (1961) 163–170.

[13] A.T. Beck, N. Epstein, G. Brown, R.A. Steer, An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (1988) 893–897.

[14] L.B. Krupp, N.G. LaRocca, J. Muir-Nash, A.D. Steinberg, The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus, Arch. Neurol. 46 (1989) 1121–1123.

[15] D.J. Buysse, C.F. Reynolds 3rd, T.H. Monk, S.R. Berman, D.J. Kupfer, The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research, Psychiatry Res. 28 (1989) 193–213. doi:0165-1781(89)90047-4 [pii].

[16] A. Hammers, R. Allom, M.J. Koepp, S.L. Free, R. Myers, L. Lemieux, et al., Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe, Hum. Brain Mapp. 19 (2003) 224–247. doi:10.1002/hbm.10123 [doi].

[17] SRTM2, (n.d.). http://doc.pmod.com/pkin/pmclass.lib.pmkin.models.PKSRTM2.htm.

[18] P.G. Gasquoine, Contributions of the insula to cognition and emotion, Neuropsychol. Rev. 24 (2014) 77–87. doi:10.1007/s11065-014-9246-9 [doi].

[19] L. Christopher, Y. Koshimori, A.E. Lang, M. Criaud, A.P. Strafella, Uncovering the role of the insula in non-motor symptoms of Parkinson's disease, Brain. 137 (2014) 2143–2154. doi:10.1093/brain/awu084 [doi].

[20] A. Quartarone, M. Hallett, Emerging concepts in the physiological basis of

dystonia, Mov. Disord. 28 (2013) 958–967. doi:10.1002/mds.25532 [doi].

[21] S. Papapetropoulos, A.A. Argyriou, P. Polychronopoulos, T. Spyridonidis, P. Gourzis, E. Chroni, Frontotemporal and striatal SPECT abnormalities in myoclonus-dystonia: phenotypic and pathogenetic considerations, Neurodegener. Dis. 5 (2008) 355–358. doi:10.1159/000119458 [doi].

[22] W.J. Neumann, A. Jha, A. Bock, J. Huebl, A. Horn, G.H. Schneider, et al., Cortico-pallidal oscillatory connectivity in patients with dystonia, Brain. (2015). doi:awv109 [pii].

[23] M. Carbon, S. Su, V. Dhawan, D. Raymond, S. Bressman, D. Eidelberg, Regional metabolism in primary torsion dystonia: effects of penetrance and genotype., Neurology. 62 (2004) 1384–1390. doi:10.1212/01.WNL.0000120541.97467.FE.