Published in final edited form as:

Mov Disord. 2014 August ; 29(9): 1197–1201. doi:10.1002/mds.25893.

***In vivo* dopaminergic and serotonergic dysfunction in *DCTN1* gene mutation carriers**

Andre C. Felicio, MD, PhD¹, Katherine Dinelle, MSc¹, Pankaj A. Agarwal, MD, DNB, DM¹, Jessamyn McKenzie, LPN¹, Nicole Heffernan, RN¹, Jeremy D. Road, MD², Silke Appel-Cresswell, MD¹, Zbigniew K. Wszolek, MD³, Matthew J. Farrer, PhD¹, Michael Schulzer, MD, PhD¹, Vesna Sossi, PhD¹, and A. Jon Stoessl, CM, MD, FRCPC^{1,*}

Pacific Parkinson's Research Centre, University of British Columbia, 2221 Wesbrook Mall, Vancouver, BC, Canada

Division of Respiratory Medicine, Department of Medicine, University of British Columbia, 2775 Laurel Street, Vancouver, BC, Canada

Department of Neurology, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL, USA

Abstract

Introduction—We have used positron emission tomography (PET) to assess dopaminergic and serotonergic terminal density in three subjects carrying a mutation in the *DCTN1* gene, two clinically affected with Perry syndrome.

Methods—All subjects had brain imaging using 18F-6-fluoro-L-dopa (FDOPA, dopamine synthesis and storage), (+)-11C-dihydrotetrabenazine (DTBZ, vesicular monoamine transporter type 2), and 11C-raclopride (RAC, dopamine D2/D3 receptors). One subject also underwent PET

* **Correspondence to:** Dr. A. Jon Stoessl Correspondence at Pacific Parkinson's Research Centre, University of British Columbia, 2221 Wesbrook Mall, Vancouver, BC, Canada Tel.: +1 604 8227967; fax: +1 604 8227866. jstoessl@mail.ubc.ca.

Financial disclosure/conflict of interest concerning the research related to the manuscript: none

Author roles

Andre C. Felicio (Principal author) – 1C, 2C, 3A, 3B.

Katherine Dinelle – 2B, 2C, 3B.

Pankaj A. Agarwal – 2C, 3B.

Jessamyn McKenzie – 1B, 1C, 3B.

Nicole Heffernan – 1B, 1C, 3B.

Jeremy D. Road – 2C, 3B.

Silke Appel-Cresswell – 2C, 3B.

Zbigniew K. Wszolek – 1C, 2C, 3B.

Matthew J. Farrer – 1C, 2C, 3B.

Michael Schulzer – 2A, 2B, 2C, 3B.

Vesna Sossi – 1A, 2C, 3B.

A. Jon Stoessl (Corresponding author) – 1A, 1B, 2C, 3B.

Financial Disclosures

§ **Financial disclosure related to research covered in this article:**

§ **Full financial disclosure for the previous 12 months:**

Katherine Dinelle reports no disclosures.

Pankaj A. Agarwal reports no disclosures.

Jessamyn McKenzie reports no disclosures.

Nicole Heffernan reports no disclosures.

Michael Schulzer reports no disclosures.

with 11C-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB, serotonin transporter).

Results—FDOPA-PET and DTBZ-PET in the affected individuals showed a reduction of striatal tracer uptake. Also, RAC-PET showed higher uptake in these area. DASB-PET showed significant uptake changes in left orbitofrontal cortex, bilateral anterior insula, left dorsolateral prefrontal cortex, left orbitofrontal cortex, left posterior cingulate cortex, left caudate and left ventral striatum.

Conclusions—Our data showed evidence of both striatal dopaminergic and widespread cortical/subcortical serotonergic dysfunctions in individuals carrying a mutation in the *DCTN1* gene.

Keywords

Perry syndrome; dynactin gene; positron emission tomography; dopaminergic dysfunction; serotonergic dysfunction

Introduction

Perry syndrome is a rare genetic disorder characterized by autosomal dominantly inherited parkinsonism, depression, weight loss and hypoventilation. The genetic cause of Perry syndrome was recently identified as a dynactin gene (*DCTN1*) mutation.[1] To the best of our knowledge there are only two previous functional brain imaging studies reported in Perry syndrome. A ¹⁸F-6-fluoro-L-dopa (FDOPA) positron emission tomography (PET) study, which showed reduced striatal tracer uptake in one case.[2] Second, a ¹⁸F-fluorodeoxyglucose (FDG) PET study showing reduced metabolic rate in the prefrontal and temporal regions.[3]

We have used PET to assess dopaminergic and serotonergic dysfunction in three subjects with confirmed *DCTN1* mutation, one clinically unaffected and two with Perry syndrome.

Methods

Study population

Subject 1, clinically affected, was seen at the age of 56 with a two-year history of anxiety and depression, and an eight-month history of rest tremor and weight loss. Family history was positive for Perry syndrome. Actually, this patient comes from the original Canadian family early described [2], and it was found a G71R mutation in *DCTN1*. Clinical exam showed predominantly right-sided rigid-akinetic parkinsonism. Breathing was irregular, and Beck Depression Inventory was 23. Levodopa and antidepressants were prescribed with partial benefit. A multitracer PET study was performed at age 57. Two years after the first consultation the patient died due to respiratory failure.

Subject 2, the cousin of Subject 1, was clinically affected, and was seen at the age of 48 with a one-year history of slowness, social withdrawal, and sleep problems. Clinical exam showed predominantly right-sided rigid-akinetic parkinsonism. The patient's respiration seemed to be shallow and somewhat rapid, but pulmonary function tests did not disclose

significant abnormalities. Beck Depression Inventory was 9. A G71R mutation in *DCT1* was found. A multitracer PET study was carried out at the age of 49.

Subject 3, unrelated to Subjects 1 and 2, is an unaffected mutation carrier. This subject has a family history with several affected relatives who had died due to Perry syndrome. A T72P mutation in *DCT1* gene was found. A multitracer PET study was carried out at the age of 38.

PET studies

Imaging was carried out using ^{18}F -6-fluoro-L-dopa (FDOPA, a measure of dopamine synthesis and storage), (+)- ^{11}C -dihydrotetrabenazine (DTBZ, marker for the vesicular monoamine transporter type 2), and ^{11}C -raclopride (RAC, marker of dopamine D2/D3 receptors), and ^{11}C -3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB, marker of the serotonin transporter). Imaging with dopaminergic tracers was performed on the GE Advance tomograph (4.2 mm resolution FWHM), while DASB scanning took place on the Siemens ECAT high resolution research tomograph (HRRT, 2.3 mm resolution FWHM). Emission data were collected for 60 (DTBZ, RAC), 90 (FDOPA), or 100 minutes (DASB) following bolus injection of the PET tracer. This study was approved by the University of British Columbia Ethics Committee.

Imaging Analysis

For the dopaminergic tracers striatal regions were defined on an average image of 4 consecutive transaxial slices. Time activity curves were extracted for each region of interest. From the FDOPA images the uptake rate constant (k_{occ}) was determined using the Patlak tissue input graphical method, and from the RAC and DTBZ images the binding potential values were determined using the Logan tissue input graphical method. Occipital cortex (FDOPA, DTBZ) or cerebellum (RAC) were used as the reference regions. The age matched normal values derived from our database.[4]

The DASB data were analyzed using an ROI template defined on a dataset comprised of DASB images and corresponding T1-weighted MRI images acquired on healthy volunteers. All images were normalized to the same space through the MRI data using SPM8. Time activity curves were extracted for each region of interest and binding potential values were calculated using the Logan method with the cerebellum as a reference region.

Statistical Analysis

For FDOPA, DTBZ and RAC uptake, values were compared to age-expected normal control values from our database. Age-correction was based on linear regression. Independent 2-sided Student t-test was used to compare means. For DASB uptake, we compared values obtained from Patient 2 against values obtained in 6 healthy control subjects ($n=6$, mean age $\pm$ standard deviation = 56 $\pm$ 18) using 2-sample t-tests with 5 degrees of freedom.

Results

FDOPA-PET and DTBZ-PET in the affected individuals showed a reduction of striatal tracer uptake compared to age-matched healthy subjects, to a similar degree in both caudate

and putamen. RAC-PET, on the other hand, showed normal to increased striatal uptake, also affecting the caudate and putamen to a similar degree. The unaffected gene carrier displayed slight and statistically non-significant reductions of FDOPA uptake while RAC binding was slightly but significantly reduced in bilateral putamen (Table 1).

In the affected carrier Perry subject 2 who underwent a DASB-PET study, tracer uptake reductions were outside more than 2 standard deviations compared to healthy controls in the bilateral dorsolateral prefrontal cortex and orbitofrontal cortex, left posterior cingulate cortex, bilateral anterior insula, left caudate, and left ventral striatum (Figure 1). An illustrative panel of dopaminergic and serotonergic brain images is presented in Figure 2.

A 2-sample t-test confirmed a statistically significant reduction for all regions except for the right dorsolateral prefrontal cortex and right orbitofrontal cortex. *P*-values/corresponding regions were: 0.0173/left dorsolateral prefrontal cortex, 0.0041/left orbitofrontal cortex, 0.0338/left posterior cingulate cortex, 0.0269/left anterior insula, 0.0173/right anterior insula, 0.0140/left caudate, and 0.0004/left ventral striatum.

Discussion

In this multitracer PET study we found that striatal pre-synaptic dopaminergic dysfunction was relatively symmetric in clinically affected patients with Perry syndrome, with normal to slightly up-regulated post-synaptic tracer uptake. The unaffected carrier also displayed abnormal post-synaptic dopaminergic changes in bilateral putamen. Also, a considerable widespread cortical and subcortical serotonergic dysfunction was also seen in the one Perry affected patient.

Parkinsonism is a universal finding in Perry syndrome patients. We found that there was a striking reduction in DTBZ uptake and moderate reduction in FDOPA uptake in the 2 clinically affected patients, despite both individuals being symptomatic for only a year. This suggests a much faster rate of striatal dopaminergic function decline than seen in sporadic Parkinson's disease.[5]

In the two clinically symptomatic subjects RAC binding was normal to increased, in keeping with early sporadic Parkinson's disease,[6] although increases were if anything more apparent in the caudate, in contrast to Parkinson's disease, where they are more prominent in the putamen. [4] In the clinically unaffected subject, however, we found decreased RAC binding in the putamen. Previous evidence in asymptomatic MPTP-treated monkeys showed slight reductions in RAC binding,[7] possibly reflecting loss of pre-synaptic terminal autoreceptors.

Perry syndrome is also characterized by depression. By means of neuroreceptor imaging, several serotonergic brain regions have been implicated in depression. Our findings in the left dorsolateral prefrontal cortex, left orbitofrontal cortex, left posterior cingulate cortex, bilateral anterior insula, left caudate and left ventral striatum demonstrated reduced 5-HTT binding, in contrast to the increased uptake seen in Parkinson's disease.[8]

Also, the hypothalamus plays a major role in appetite regulation. As weight loss is typical in Perry syndrome [9] we were interested to evaluate the hypothalamus, but despite increased 5HTT binding these values did not reach significance in the single patient studied.

Finally, previous neuropathologic evidence in a Perry patient who died of respiratory failure showed serotonergic neuronal loss in the medullary raphe,[10] a finding we were unable to confirm in our patient using DASB PET, who actually had normal respiratory function at the time of the PET studies.

Notwithstanding the limitations of our study, mainly the understandably small sample size, this is the first multi-tracer PET study in three individuals (2 clinically affected with Perry syndrome) carrying a mutation in the DCTN1 gene. Our data showed evidence of both striatal dopaminergic and widespread cortical/subcortical serotonergic dysfunctions. Such studies may provide further insights into the basis of this devastating illness.

Acknowledgments

We would also like to thanks A. Strongoski in making travel arrangements, and the gift from Carl Edward Bolch, Jr. and Susan Bass Bolch.

Funding sources for this study: The research leading to these results has received funding from NIH/NINDS grant P50 NS072187, Mayo Clinic Florida Research Committee, and the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch.

The research leading to these results has received funding from NIH/NINDS grant P50 NS072187, Mayo Clinic Florida Research Committee, and the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch.

Andre C. Felicio is supported by a Clinical Research Fellowship fund from Parkinson Society Canada.

Jeremy D. Road is supported by the Canadian Institutes of Health Research. He has served as a paid advisor and has received speaker honoraria from Takeda, Novartis, Grifols and Boehringer Ingelheim.

Silke Appel-Cresswell has received speaker fees from Teva, and the Dystonia Medical Research Foundation Canada, travel support from Merz, Novartis and Teva, has served as a consultant for Novartis, Merz, and Actelion and has received research support from Novartis and Allergan. She has received research grant support from the Pacific Parkinson's Research Institute, the Pacific Alzheimer Research Foundation, the National Parkinson Foundation, the Parkinson Society Canada, and the Parkinson Society British Columbia.

Zbigniew K. Wszolek serves as Co-Editor-in-Chief of Parkinsonism and Related Disorders, Regional Editor of the European Journal of Neurology, and on the editorial boards of Neurologia i Neurochirurgia Polska, Advances in Rehabilitation, the Medical Journal of the Rzeszow University, and Clinical and Experimental Medical Letters; holds and has contractual rights for receipt of future royalty payments from patents re: A novel polynucleotide involved in heritable Parkinson's disease; receives royalties from publishing Parkinsonism and Related Disorders (Elsevier, 2011, 2012,2013) and the European Journal of Neurology (Wiley- Blackwell, 2011, 2012, 2013); and received educational grant support from Allergan, Inc. (2012), and research support from the NIH/NINDS P50 NS072187, the Mayo Clinic Center for Regenerative Medicine, the Dystonia Medical Research Foundation, the Michael J. Fox Foundation for Parkinson's Research, and the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch.

Matthew J. Farrer received honoraria for consulting advice with Bristol-Myers-Squibb and Genetech. Dr. Farrer also serves on the Executive Scientific Advisory Board of the Michael J. Fox Foundation, and the Scientific Advisory Board Parkinson's Society Canada. He receives research support as a Canada Research Excellence Chair, through a Leading Edge Endowment from British Columbia, genome BC and Life Labs, as well as the Canadian Institutes of Health Research.

Vesna Sossi is supported by the Canadian Institutes of Health Research, the Michael J. Fox Foundation and the Natural Science and Engineering Research Council of Canada.

A. Jon Stoessl is supported by the Canadian Institutes of Health Research, the Pacific Alzheimer Research Foundation, Canada Research Chairs program, and Michael J. Fox Foundation. He has served as a paid advisor or consultant for Abbott, Biogen-Idec, Kyowa, Ono Pharma and UCB and has received speaker honoraria from Abbott, Medscape and Teva.

References

1. Farrer MJ, Hulihan MM, Kachergus JM, et al. DCTN1 mutations in Perry syndrome. *Nat Genet.* 2009; 41:163–165. [PubMed: 19136952]
2. Perry TL, Wright JM, Berry K, Hansen S, Perry TL Jr. Dominantly inherited apathy, central hypoventilation, and Parkinson's syndrome: clinical, biochemical, and neuropathologic studies of 2 new cases. *Neurology.* 1990; 40:1882–1887. [PubMed: 2247238]
3. Lechevalier B, Chapon F, Defer G, et al. Perry and Purdy's syndrome (familial and fatal parkinsonism with hypoventilation and athymhormia). *Bull Acad Natl Med.* 2005; 189:481–490. [PubMed: 16149212]
4. Nandhagopal R, Kuramoto L, Schlzer M, et al. Longitudinal evolution of compensatory changes in striatal dopamine processing in Parkinson's disease. *Brain.* 2011; 134:3290–3298. [PubMed: 22075521]
5. Vingerhoets FJ, Snow BJ, Lee CS, Schulzer M, Mak E, Calne DB. Longitudinal fluorodopa positron emission tomographic studies of the evolution of idiopathic parkinsonism. *Ann Neurol.* 1994; 36:759–764. [PubMed: 7979222]
6. Kaasinen V, Ruottinen HM, Någren K, Lehtikainen P, Oikonen V, Rinne JO. Upregulation of putaminal dopamine D2 receptors in early Parkinson's disease: a comparative PET study with [11C] raclopride and [11C]N-methylspiperone. *J Nucl Med.* 2000; 41:65–70. [PubMed: 10647606]
7. Doudet DJ, Jivan S, Ruth TJ, Holden JE. Density and affinity of the dopamine D2 receptors in aged symptomatic and asymptomatic MPTP-treated monkeys: PET studies with [11C]raclopride. *Synapse.* 2002; 44:198–202. [PubMed: 11954052]
8. Boileau I, Warsh JJ, Guttman M, et al. Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [11C]DASB. *Mov Disord.* 2008; 23:1776–1780. [PubMed: 18661545]
9. Wider C, Dickson DW, Stoessl AJ, et al. Pallidonigral TDP-43 pathology in Perry syndrome. *Parkinsonism Relat Disord.* 2009; 15:281–286. [PubMed: 18723384]
10. Tsuboi Y, Dickson DW, Nabeshima K, et al. Neurodegeneration involving putative respiratory neurons in Perry syndrome. *Acta Neuropathol.* 2008; 115:263–268. [PubMed: 17576579]

Figure 1.

Figure 1. [^{11}C]-DASB positron emission tomography study in an affected subject with genetically-proven Perry syndrome compared to healthy control subjects (n=6). Bar charts represent (A) Cortical areas, (B) Subcortical areas, and (C) Brainstem.

Legend: Amyg = amygdala; AntCing = anterior cingulate; AntIns = anterior insula; Caud = caudate; DLPFC = dorsolateral prefrontal cortex; HypTh = hypothalamus; MidBr = midbrain; OFC = orbitofrontal cortex; PostCing = posterior cingulate; Put = putamen; SN = substantia nigra; Thal = thalamus; VS = ventral striatum. An asterisk (*) denotes values

outside 2 standard deviations compared to control values. *For midline structures (pons/midbrain/medulla) only a single value is reported.*

Figure 2.

^{18}F -6-fluoro-L-dopa (FDOPA), (+)- ^{11}C -dihydrotetrabenazine (DTBZ), ^{11}C -raclopride (RAC), and ^{11}C -3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB) imaging panel showing a genetically-proven Perry syndrome subject (right) as compared to an approximately age-matched control (left). FDOPA uptake (A) and DTBZ binding (B) are reduced in the Perry subject compared to the control subject (left). In contrast, RAC binding is normal in the Perry subject (C). There are widespread reductions in DASB binding in the Perry subject (D). (A) through (C) are axial images, (D) is sagittal.

Table 1

Dopaminergic multitracers PET studies in three individuals with mutation in the *DCTN1* gene, two clinically affected with Perry syndrome

PET tracer	Site			
	<i>Right Caudate</i>	<i>Left Caudate</i>	<i>Right Putamen</i>	<i>Left Putamen</i>
FDOPA	Kocc (% of age matched normal value)			
S1-a	0.0037 (33%) **	0.0035 (30%) **	0.0024 (26%) **	0.0023 (23%) **
S2-a	0.0051 (45%) **	0.0038 (34%) **	0.0035 (37%) **	0.0036 (36%) **
S3-u	0.0096 (87%)	0.0093 (86%)	0.0091 (97%)	0.0082 (85%)
DTBZ	BP _{ND} (% of age matched normal value)			
S1-a	0.24 (11%) **	0.23 (11%) **	0.32 (15%) **	0.38 (18%) **
S2-a	0.34 (15%) **	0.37 (16%) **	0.38 (17%) **	0.39 (17%) **
S3-u	NA	NA	NA	NA
RAC	BP _{ND} (% of age matched normal value)			
S1-a	2.25 (101%)	2.65 (119%) *	2.06 (95%)	2.18 (102%)
S2-a	2.68 (115%) *	2.68 (114%)	2.44 (106%)	2.54 (110%)
S3-u	2.34 (93%)	2.25 (88%)	2.08 (84%) *	2.03 (81%) *

Legend: a = clinically affected; BP_{ND} = Binding potential; FDOPA = ¹⁸F-6-fluoro-L-dopa; NA = not available; PET = Positron emission tomography; RAC = ¹¹C-raclopride; DTBZ = (+)-¹¹C-dihydrotetrabenazine; S1-3 = Subjects with *DCTN1* mutation 1–3; u = clinically unaffected (asymptomatic gene carrier); % = means % of age-matched healthy control subjects;

(*) denotes 2-sided significant *p* values <0.05 or (**) <0.001, as compared to age-matched healthy control subjects.