Published in final edited form as:

J Neural Transm. 2013 October ; 120(10): 1421–1424. doi:10.1007/s00702-013-1013-1.

Gender Differences in Cholinergic and Dopaminergic Deficits in Parkinson Disease

Vikas Kotagal, MD¹, Roger L. Albin, MD^{1,2}, Martijn L.T.M. Müller, PhD³, Robert A. Koeppe, PhD³, Kirk A. Frey, MD, PhD^{1,3}, and Nicolaas I. Bohnen, MD, PhD^{1,2,3}

¹Department of Neurology, University of Michigan, Ann Arbor, MI

²Neurology Service and GRECC, VAAAHS, Ann Arbor, MI

³Department of Radiology, Division of Nuclear Medicine, University of Michigan, Ann Arbor, MI

Abstract

Background & Methods—As Parkinson disease (PD) may affect men and women differentially, we investigated gender differences in regional projection system integrity in 148 PD subjects (36 women, 112 men) using monoaminergic [¹¹C]dihydrotetrabenazine and acetylcholinesterase [¹¹C]PMP positron emission tomography.

Results—After controlling for age, disease duration, and Hoehn and Yahr score, men showed 5.9% greater caudate dopaminergic denervation (p=0.0018) and 5.8 % greater neocortical cholinergic denervation (p=0.0097). No significant gender differences were seen in putaminal dopaminergic or thalamic cholinergic denervation.

Keywords

Gender; Women; Acetylcholine; Dopamine; Parkinson disease

Corresponding Author: Vikas Kotagal, 2301 Commonwealth Blvd, Suite 1013, Ann Arbor MI, 48105, Phone: 734-764-6831, Fax: 734-647-8535, vikaskot@med.umich.edu.

Potential conflicts of interest regarding this specific study for all authors are as follows:

V.K. none

R.A.L. none

M.L.M. none

R.A.K. none

K.A.F. none

N.I.B. none

Author Disclosures

Dr. Kotagal: Research support from National Institutes of Health T32 training grant (NS007222) and from the American Academy of Neurology Clinical Research Training Fellowship.

Dr. Albin: Research support from the NIH and the Department of Veterans Affairs. Dr. Albin has received compensation for expert witness testimony in litigation regarding dopamine agonist induced impulse control disorders. Dr. Albin serves on the editorial boards of Neurology, Experimental Neurology, and Neurobiology of Disease and has served on the Data Safety and Monitoring Boards for the QE3 and HORIZON trials.

Dr. Müller: Research support from the NIH and the Department of Veteran Affairs.

Dr. Koeppe: Research support from NIH. Dr. Koeppe has served as a consultant for Johnson & Johnson and Merck and serves on the board of the International Society of Cerebral Blood Flow and Metabolism.

Dr. Frey: Research support from the NIH, GE Healthcare and AVID Radiopharmaceuticals (Eli Lilly subsidiary). Dr. Frey serves as a consultant for AVID Radiopharmaceuticals, MIMVista, Inc, Bayer-Schering and GE healthcare. He holds equity (common stock) in GE, Bristol-Myers, Merck and Novo-Nordisk.

Dr. Bohnen: Research support from the NIH, Michael J. Fox Foundation and the Department of Veteran Affairs.

Introduction

Parkinson disease (PD) is a multisystem neurodegenerative disorder with significant heterogeneity of clinical disease characteristics. Men develop PD more frequently than women (de Lau et al. 2004) and may differ from women in their risk for developing certain motor and non-motor features of PD. (Miller and Cronin-Golomb 2010) The specific factors that contribute to gender disparities are not known.

To explore gender-related differences in regional dopaminergic and cholinergic denervation in PD, we evaluated a cohort of non-demented men and women with PD. Dopaminergic and cholinergic projection systems were evaluated with PET imaging.

Subjects and methods

Subjects and clinical battery

We performed a cross-sectional study of 36 women and 112 men (N total =148) with mild-to-moderate PD. Subjects were recruited from Movement Disorder clinics at the University of Michigan Medical Center and the Veterans Affairs (VA) Ann Arbor Health System. All subjects met UK Brain Bank clinical diagnostic criteria for PD. (Hughes et al. 1992) Subjects were excluded if they met criteria for dementia outlined in our previous studies. (Kotagal et al. 2012; Emre et al. 2007) The diagnosis of PD was confirmed in all subjects by typical patterns of nigrostriatal dopaminergic denervation as visualized by monoaminergic [¹¹C]dihydrotetrabenazine (DTBZ) PET imaging. No subjects were using anticholinergic or cholinesterase inhibitor medications. A subset of subjects (n=99; 71 men & 28 women) answered a depression rating scale score and underwent motor exam scoring in the pharmacological “off-state” with the Movement Disorders Society-Unified Parkinson Disease Rating Scale. (Goetz et al. 2007)

Standard Protocol Approvals and Patient Consent

The study was approved by the Institutional Review Boards of the University of Michigan and Ann Arbor VA Hospital. Written informed consent was obtained from all subjects.

Imaging techniques

DTBZ and PMP PET imaging were performed in 3D imaging mode using an ECAT HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum (FWHM) over a 15.2 cm axial field-of-view. A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/shielding unit was attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field-of-view. Before radioligand injections began, a 5-minute transmission scan was acquired using rotating ⁶⁸Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and re-projection routines.

DTBZ PET imaging

No-carrier-added (+)-[¹¹C]DTBZ (250 to 1000 Ci/mmol at the time of injection) was prepared as reported previously. (Jewett et al. 1997) Dynamic PET scanning was performed for 60 minutes immediately following a bolus injection of 55% of 555 MBq (15 mCi) of (+)-[¹¹C]DTBZ dose, while the remaining 45% of the dose was continuously infused over the next 60 minutes. (Innis et al. 2007)

PMP PET imaging

[^{11}C]PMP was prepared using a previously described method.(Snyder et al. 1998) Dynamic PET scanning was performed for 70 minutes immediately following a bolus intravenous injection of 666 MBq (18 mCi) of [^{11}C]PMP.

MRI Imaging

All subjects underwent brain magnetic resonance imaging on a 3T Philips Achieva system (Philips, Best, The Netherlands) as previously described.(Kotagal et al. 2012)

Data Analysis

Interactive Data Language image analysis software (Research systems, Inc., Boulder, CO) was used to manually trace volumes of interest (VOIs) on MRI images including the thalamus, caudate nucleus, and putamen of each hemisphere. Right and left hemisphere values were averaged together within subjects to create a composite score for each region. Total neocortical VOI were defined using semi-automated threshold delineation of the cortical gray matter signal.

All image frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session. These motion-corrected PET frames were spatially co-registered to the T1-weighted MR using standard co-registration procedures in SPM8b implemented in Matlab 2010b (The Mathworks, Natick, MA). Time activity curves for each VOI were generated from the spatially aligned PET frames. ^{11}C -DTBZ distribution volume ratio (DVR) was then estimated by using the Logan plot graphical analysis method(Logan et al. 1996) with the time activity curves as the input function and the neocortex as reference tissue for ^{11}C -DTBZ.(Logan et al. 1996; Innis et al. 2007; Koeppe et al. 1999) AChE hydrolysis rates (k_3) were estimated using a method using the striatum as the reference input tissue.(Nagatsuka Si et al. 2001)

Multivariable linear regression (SAS version 9.3, Cary, NC) was used to explore the effect of gender on four different PET imaging measures including caudate and putamen DTBZ DVR as well as neocortical and thalamic PMP k_3 . Age, duration of motor symptoms, and Hoehn and Yahr score were used as covariates along with gender in each of these models. Bonferroni correction was used to adjust for multiple comparisons. Duncan's post-hoc testing was used to compare the percent difference between gender groups in each of the regions of interest studied in the regression models.

Results

Clinical and demographic factors for both genders are listed in table 1. There were no significant differences between genders in any of these factors. Using multivariable linear regression, we compared differences in caudate and putamen DTBZ DVR as well as neocortex and thalamic PMP k_3 , controlling for the effects of age, duration of motor symptoms, and Hoehn and Yahr (HY) score. Compared to women, men showed lower caudate DTBZ DVR (Overall model $F=13.89$; $p<0.0001$; Gender t value = 3.19, $p=0.0018$; 5.9% lower binding in men) and lower PMP k_3 in the neocortex (Overall model $F=3.47$, $p=0.0098$; Gender t value = 2.62; $p=0.0097$; 5.8% lower activity in men). Duration of parkinsonian motor symptoms showed an association with caudate DTBZ DVR ($t=5.17$, $p<0.0001$). There were otherwise no significant effects of age or HY staging on caudate DTBZ or neocortex PMP. Regression analyses showed no differences between genders in putamen DTBZ DVR (Model F -value = 11.83, $p<0.0001$; Gender t -value = 1.30, $p=0.1955$) or thalamic PMP k_3 (Model F -value = 2.29, $p=0.0626$).

Discussion

We report gender differences in caudate nucleus dopaminergic and neocortical cholinergic denervation in PD with males having greater deficits than females. The majority of epidemiological data suggest a higher PD incidence rate in men compared to women with incidence risk being anywhere from 1.1 to 2.6 times greater in men.(de Lau et al. 2004) Others have suggested that these observed gender differences may be more pronounced in individuals who develop PD after the age of 70 and amongst those living in western populations.(Lees et al. 2009) Haaxma et al. found evidence of about 16% higher overall striatal dopamine transporter binding in female compared to male PD patients.(Haaxma et al. 2007) These authors postulated that the known gender difference in PD prevalence might relate to higher physiological levels of striatal dopamine in women and hypothesized a possible link to estrogen hormonal status. These findings are compatible with our recent report of approximately 8% higher total striatal dopamine transporter expression in younger normal women compared to men, with these same gender differences receding in healthy adults after age 60.(Wong et al. 2012) The relatively delayed age of onset and lower disease prevalence of PD in women compared to men may reflect basal differences between genders in overall striatal dopamine terminal density.(Haaxma et al. 2007)

An alternative explanation is that these gender-specific differences in PD prevalence may be better explained by a temporal gradient (putamen-then-caudate) of regional striatal denervation whose pace early in life is quickened in men or whose finish line (marking the onset of symptomatic PD) is pushed back in women. Prior cross-sectional DTBZ PET findings from our study of normal elderly controls indicates a roughly 0.5% annual-rate-of-loss in striatal dopaminergic terminals, similar in all striatal regions and similar between both genders.(Bohnen et al. 2006) Measurements of putaminal dopaminergic terminal denervation in PD patients may suffer from “floor” effects that would limit the identification of gender differences in dopaminergic terminal degeneration. The 5.9% greater magnitude of caudate denervation found in men, if generalized to and projected back in time to the putamen, would be consistent with male PD subjects crossing the symptomatic “threshold” earlier, potentially accounting for both earlier clinical expression of parkinsonism in men compared to women and lower incidence rates of PD in women compared to men.(Haaxma et al. 2007; de Lau et al. 2004) A ‘putaminal floor’ denervation effect in PD subjects also explains the absence of differences in motor severity between genders in our cohort. Differences in caudate dopaminergic terminal density could potential account for gender variations in non-motor features as well. Although our subgroup analysis of 99 subjects showed no significant differences between men and women in UPDRS-I depression scoring, more detailed clinical testing is required to thoroughly explore this possibility.

Our findings of greater cortical cholinergic denervation in male PD patients may provide a potential pathophysiological explanation for gender differences in some PD clinical features. Neocortical cholinergic denervation reflects loss of terminals originating from the basal forebrain and associates with cognitive impairment in PD, while thalamic cholinergic denervation associates more closely with gait difficulties and reflects loss of cholinergic terminals originating in the pontine tegmentum.(Bohnen et al. 2012) It is possible that the differential neocortical PMP k_3 values seen between genders in our cohort might associate with gender-specific variability in non-motor PD features. Further studies with detailed clinical testing will be required to assess this possibility.

Limitations of our study include over-representation of men relative to women. This is likely due to the male predominance of PD and the fact that we recruited subjects from a Veterans hospital. The two gender groups, however, were well matched for age, duration of disease, and Hoehn and Yahr staging. Further studies are needed to determine whether gender-

specific differences in dopaminergic and cholinergic projection systems associate with specific disease features or are brought about by gender-specific factors including endogenous differences in hormones or in genetic or environmental risk factors.

Acknowledgments

We would like to thank Jamie Miller, Christine Minderovic, Cyrus Sarosh, and Virginia Rogers for their help with study subject coordination. We would also like to express our sincere gratitude to all subjects for their participation.

Source of Funding

Supported by the Michael J. Fox Foundation, the Department of Veterans Affairs, NIH grants P01 NS015655 & R01 NS070856.

References

- Bohnen NI, Albin RL, Koeppe RA, Wernette KA, Kilbourn MR, Minoshima S, Frey KA. Positron emission tomography of monoaminergic vesicular binding in aging and Parkinson disease. *J Cereb Blood Flow Metab.* 2006; 26(9):1198–1212. doi:10.1038/sj.jcbfm.9600276. [PubMed: 16421508]
- Bohnen NI, Muller ML, Kotagal V, Koeppe RA, Kilbourn MR, Gilman S, Albin RL, Frey KA. Heterogeneity of cholinergic denervation in Parkinson's disease without dementia. *J Cereb Blood Flow Metab.* 2012; 32(8):1609–1617. doi:10.1038/jcbfm.2012.60. [PubMed: 22569194]
- de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. *Neurology.* 2004; 63(7):1240–1244. [PubMed: 15477545]
- Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, Goldman J, Goetz C, Korczyn A, Lees A, Levy R, Litvan I, McKeith I, Olanow W, Poewe W, Quinn N, Sampaio C, Tolosa E, Dubois B. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord.* 2007; 22(12):1689–1707. quiz 1837. doi:10.1002/mds.21507. [PubMed: 17542011]
- Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, Stern MB, Tilley BC, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, Lewitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, Van Hilten JJ, Lapelle N. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Mov Disord.* 2007; 22:41–47. [PubMed: 17115387]
- Haaxma CA, Bloem BR, Borm GF, Oyen WJ, Leenders KL, Eshuis S, Booij J, Dluzen DE, Horstink MW. Gender differences in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2007; 78(8):819–824. doi:10.1136/jnnp.2006.103788. [PubMed: 17098842]
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathologic study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992; 55:181–184. [PubMed: 1564476]
- Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab.* 2007; 27(9) doi:9600493 [pii] 10.1038/sj.jcbfm.9600493.
- Jewett DM, Kilbourn MR, Lee LC. A simple synthesis of [11C]dihydrotetrabenazine (DTBZ). *Nucl Med Biol.* 1997; 24(2):197–199. doi:S0969-8051(96)00213-2 [pii]. [PubMed: 9089713]
- Koeppe RA, Frey KA, Kuhl DE, Kilbourn MR. Assessment of extrastriatal vesicular monoamine transporter binding site density using stereoisomers of [11C]dihydrotetrabenazine. *J Cereb Blood Flow Metab.* 1999; 19(12):1376–1384. [PubMed: 10598942]
- Kotagal V, Albin RL, Muller ML, Koeppe RA, Chervin RD, Frey KA, Bohnen NI. Symptoms of rapid eye movement sleep behavior disorder are associated with cholinergic denervation in Parkinson disease. *Ann Neurol.* 2012; 71(4):560–568. doi:10.1002/ana.22691. [PubMed: 22522445]

- Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet*. 2009; 373(9680):2055–2066. doi:10.1016/S0140-6736(09)60492-x. [PubMed: 19524782]
- Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL. Distribution volume ratios without blood sampling from graphical analysis of PET data. *J Cereb Blood Flow Metab*. 1996; 16(5):834–840. [PubMed: 8784228]
- Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: clinical characteristics and cognition. *Mov Disord*. 2010; 25(16):2695–2703. doi:10.1002/mds.23388. [PubMed: 20925068]
- Nagatsuka Si S, Fukushi K, Shinotoh H, Namba H, Iyo M, Tanaka N, Aotsuka A, Ota T, Tanada S, Irie T. Kinetic analysis of [(11)C]MP4A using a high-radioactivity brain region that represents an integrated input function for measurement of cerebral acetylcholinesterase activity without arterial blood sampling. *J Cereb Blood Flow Metab*. 2001; 21(11):1354–1366. doi: 10.1097/00004647-200111000-00011. [PubMed: 11702050]
- Snyder SE, Thuczek L, Jewett DM, Nguyen TB, Kuhl DE, Kilbourn MR. Synthesis of 1-[¹¹C]methylpiperidin-4-yl propionate ([¹¹C]PMP) for in vivo measurements of acetylcholinesterase activity. *Nucl Med Biol*. 1998; 25:751–754. [PubMed: 9863562]
- Wong KK, Muller ML, Kuwabara H, Studenski SA, Bohnen NI. Gender differences in nigrostriatal dopaminergic innervation are present at young-to-middle but not at older age in normal adults. *J Clin Neurosci*. 2012; 19(1):183–184. doi:10.1016/j.jocn.2011.05.013. [PubMed: 22030267]

Gender Comparisons**Table 1**

	Women (n=36) <i>Mean (SD)</i>	Men (n=112) <i>Mean (SD)</i>
Age	64.78 (9.48)	66.84 (8.09)
Disease duration	6.51 (4.98)	5.88 (3.82)
Hoehn and Yahr score	2.58 (0.47)	2.41 (0.52)
MDS-UPDRS-III	(n=28) 37.16 (16.66)	(n=78) 36.24 (13.61)
MDS UPDRS-I Depression score	(n=28) 0.32 (0.55)	(n=78) 0.25 (0.58)

MDS-UPDRS-III = Movement Disorders Society-Unified Parkinson Disease Rating Scale Motor Examination