Asymmetrical Ventricular Enlargement in Parkinson's Disease

Xuemei Huang, MD, PhD,[1]* Yueh Z. Lee, MD, PhD,[2] Martin McKeown, MD, PhD,[3] Guido Gerig, PhD,[4,5] Hongbin Gu, PhD,[4] Weili Lin, PhD,[2] Mechelle M. Lewis, PhD,[1] Sutapa Ford, PhD,[1] Alexander I. Tröster, PhD,[1] Daniel R. Weinberger, MD,[6] and Martin Styner, PhD[4,5]

[1]*Department of Neurology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA;* [2]*Department of Radiology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA;* [3]*Department of Medicine (Neurology), Pacific Parkinson's Research Centre, University of British Columbia (UBC), University Hospital, Vancouver, British Columbia, Canada;* [4]*Department of Psychiatry, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA;* [5]*Department of Computer Science, University of North Carolina, Chapel Hill, North Carolina, USA;* [6]*Clinical Brain Disorder Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA*

Abstract: **Parkinson's disease (PD) typically manifests with asymmetric motor symptom onset. Ventricular enlargement, a nonspecific measure of brain atrophy, has been associated with cognitive decline in PD, but not with motor symptom asymmetry. Asymmetrical ventricular enlargement on magnetic resonance images was explored in a monozygotic twin pair discordant for PD and in nine healthy monozygotic twin pairs. The left–right lateral ventricular volumetric difference of the PD-twin was greater than that of his twin and all other healthy twins, with the larger ventricle observed contralateral to the more symptomatic side. Moreover, the lateral ventricle asymmetry difference between twin pairs was significantly higher for the discordant PD-twin pair than for the healthy twin pairs. This is the first report to suggest the presence of asymmetrical ventricular enlargement in PD, findings that may be worthy of further study.** © 2007 Movement Disorder Society

Key words: Parkinson's disease; ventricle; volume asymmetry; motor impairment.

*Correspondence to: Dr. Xuemei Huang, Department of Neurology, CB 7025, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27599-7025
E-mail: xuemei@med.unc.edu

Received 1 March 2007; Revised 30 March 2007; Accepted 16 May 2007

Published online 22 June 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21626

BACKGROUND

Parkinson's disease (PD) typically has an asymmetric onset of motor symptoms (tremor, bradykinesia, rigidity), and this asymmetry, which persists throughout the disease,[1] may reflect asymmetrical nigrostriatal dysfunction.[2] Lateralized cognitive deficits,[3,4] in contrast, are postulated to reflect an asymmetrically decreased cortical dopaminergic tone.[5]

Brain atrophy and ventricular enlargement consequent to neurodegenerative cell loss is associated with cognitive deficits in PD.[6,7] The extent to which lateral ventricular enlargement and asymmetries relate to motor symptom asymmetries is unknown, but such a relationship might reasonably be hypothesized, given that the lateral ventricles are surrounded by basal ganglia and downstream structures (thalamus and frontal lobe) affected by PD. To address the potential relationship of ventricular size and symptomatic asymmetries, we compared the lateral ventricular volumetric difference between each hemisphere in both members of a monozygotic twin (MZ) pair discordant for PD and in nine pairs of healthy MZ twin pairs from a prior study.[7]

PATIENTS AND METHODS

Study Subjects

A 37-year-old identical MZ twin pair discordant for PD was identified through a tertiary-care movement disorders clinic. Zygosity was confirmed for the twins by DNA profiles of 14 genetic markers (GeneTree DNA testing center, Salt Lake City, UT). The pre- and perinatal histories were unremarkable except for premature birth at 32 weeks (PD-twin first, 6.4 pounds; non-PD-twin second, 4.4 pounds). The life histories of the twins were remarkably similar in terms of upbringing, education, and occupation. Neither had smoked, they both drank coffee (regularly for the non-PD-twin, occasionally for the PD-twin), and both drank alcohol occasionally.

The PD-twin developed right-hand postural tremor at 35 years, 2 years prior to the baseline study. He was diagnosed with PD at 36 years after presenting with right hand resting tremor and rigidity, both attenuated by pramipexole. At baseline, single-photon emission computed tomography (SPECT) neuroimaging using [^{123}I](−)-2-β-carboxymethoxy-3-β-(4-iodophenyl)-tropane confirmed the twin's disease-discordant status. The PD-twin had severe asymmetric loss of transporter binding (left greater than right), whereas the non-PD-twin was symmetrical and healthy (Fig. 1A,B). At follow-up study, the PD-twin (then 39 years old) noticed mildly reduced dexterity on the left hand. The non-PD-

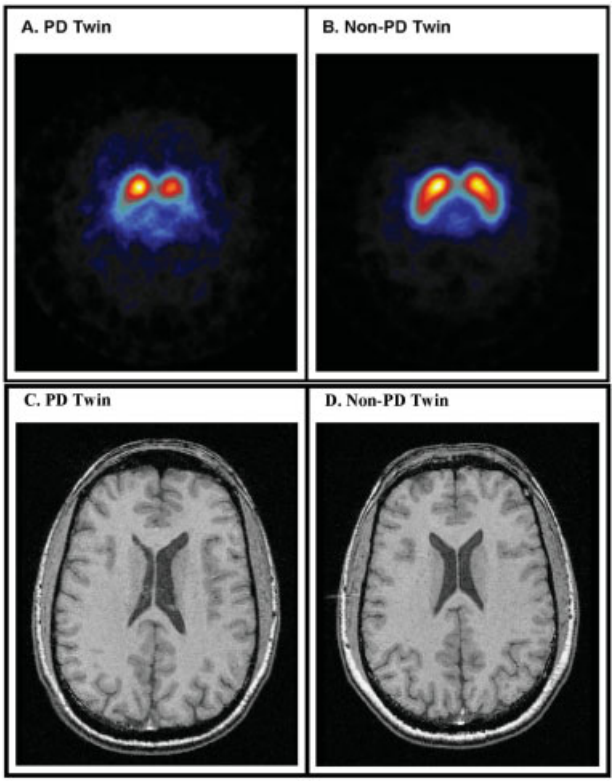

FIG. 1. SPECT images of [^{123}I](−)-2-β-carboxymethoxy-3-β-(4-iodophenyl)-tropane binding (**A** and **B**) and MRI images showing ventricular asymmetry (**C** and **D**) in the PD-twin and the non-PD-twin.

twin was perceived as clinically healthy, was not taking any medication, and showed no motor signs of PD. No other family members had been diagnosed with PD. The twin pair had normal Mini Mental Status Examination scores (PD-twin 28/30, non-PD-twin 29/30) at baseline, and detailed neuropsychological testing revealed mild executive and recall decrements in the affected twin but not in the nonaffected twin. Executive and memory changes, though not specific to PD, have recently been reported to be observable in about one-third of PD patients at the time of diagnosis.[8,9]

Nine healthy twin pairs (four women, mean age 31 years, range 19–54) were volunteers from a previous study,[7] and free of neurological, psychiatric, and major medical illnesses. Zygosity was confirmed by matching on 19 red blood cell antigens that predicts monozygosity at a minimum 97% confidence level for healthy twin pairs. The study had Institutional Review Board approval, and written informed consent was obtained from all subjects.

Structural MRI

Structural magnetic resonance images (MRIs) for the discordant PD-twins were acquired on a 3.0 T Siemens scanner (Siemens, Erlangern, Germany) with a birdcage type standard quadrature head coil, and high-resolution T1-weighted anatomical images (3D MP-RAGE, TR = 14 millisecond, TE = 7,700 millisecond, flip angle = 25°, voxel dimensions $1.0 \times 1.0 \times 1.0$ mm^3, 176×256 voxels, 160 slices) were obtained on an advanced nuclear magnetic resonance echoplanar system. The twins were scanned with the same protocol at baseline and 27 months later.

MRI datasets for healthy twins were acquired using a 1.5-T scanner (Signa, General Electric) with a T1-weighted spoiled gradient-recalled acquisition in the steady-state sequence (TR = 24 millisecond, TE = 5 millisecond) for a previous study,[7] in which a single sagittal series of 124 contiguous 1.5-mm-thick slices with an in-plane field of view of 240 mm across a 256×256 pixel matrix ($0.9375 \times 0.9375 \times 1.5$ mm^3) was collected.

All image sets were first processed by a rater-independent, automatic tissue-segmentation method[10] that generates detailed maps of gray matter, white matter, and cerebrospinal fluid (CSF). This processing includes a bias field correction that adjusts for intensity inhomogeneities. A semiautomatic, rater-initialized method was employed to segment the lateral ventricles based on the probabilistic CSF segmentation.[11]

Finally, all segmentations were inspected by an expert, and judged adequate for ventricular body, occipital horn, and lateral horn. Ventricular volume consisted of the lateral ventricles excluding the temporal horn, and the third and fourth ventricles. A single rater generated the segmentations for the discordant PD-twin images, whereas another rater performed the segmentations of all the healthy twins for a previous study.[7] Both the intrarater and interrater reliabilities of our semiautomatic ventricular measurements were above 99%.[11]

The main hypotheses of this study were related to the asymmetry features of each twin, and the concordance of each twin-pair, not the absolute volume of the ventricles of each individual. This approach minimizes the impact of using two different scan systems and rating approaches for PD-discordant and healthy twin pairs.

Statistical Analysis

Lateral ventricular asymmetry [expressed by an asymmetry score (AS)] was measured by the relative volumetric differences between right and left lateral ventricles:

$$\mathrm{AS} = \mathrm{abs}\frac{(V_{\mathrm{left}} - V_{\mathrm{right}})}{(V_{\mathrm{left}} + V_{\mathrm{right}})} \times 100$$

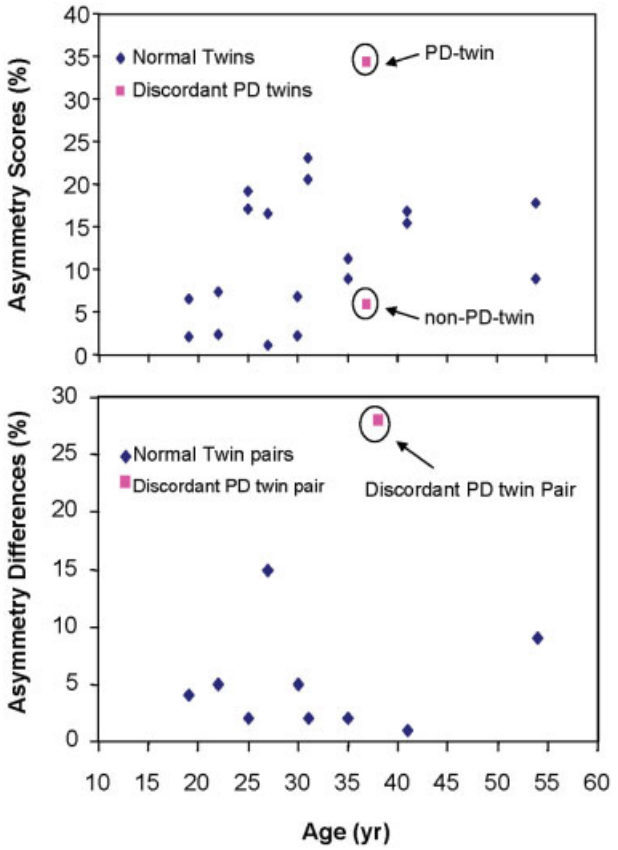

FIG. 2. Scatter plot of asymmetry scores (AS) and asymmetry score differences (ASD) of healthy and discordant PD twin pairs. AS and ASD scores were calculated as detailed in the Methods.

Asymmetrical score differences (ASD) between MZ twin pairs were calculated as the difference of AS between MZ twin pairs:

$$\text{ASD} = \text{abs}(AS_{\text{twin A}} - AS_{\text{twin B}})$$

We compared AS and ASD scores of the PD-twin pair to the reference population of healthy twins by calculating the standardized z scores using the mean and SD of the healthy sample.

RESULTS

There was obvious lateral ventricular asymmetry in the PD-twin, but not in the non-PD-twin (Fig. 1C,D), with larger ventricles observed on the side contralateral to the more symptomatic side. There was a high intrapair correlation for AS in the control twins (Pearson correlation coefficient = 0.69, $P = 0.04$) that was not significantly affected by gender. The scatterplots of AS and ASD for the healthy and discordant PD-twin pairs are shown in Figure 2. For healthy twins, the mean (±SD) of AS was 11.3% (7.2%) and the mean ASD was 5.6% (4.8%). The AS was within the normal range for the non-PD-twin (4.2%), but significantly higher for the PD-twin (32%, z-score of 2.82, $P < 0.001$). The ASD between the discordant twins (28%, z-score 4.54, $P < 0.001$) was significantly greater than that for healthy twins. During the 27-month follow-up, the size of the larger ventricle contralateral to the more symptomatic side increased 11.4% in the PD-twin and 5.5% in the non-PD-twin, whereas the size of the smaller ventricle increased 4% in the PD-twin and 1.1% in the non-PD-twin.

DISCUSSION

To our knowledge, this is the first report to suggest the presence of asymmetric ventricular enlargement in PD. Further study of this observation may offer insight into the pathogenesis of PD and symptom asymmetry, and the possibility of using lateral ventricular volumetric measurement as a possible marker of disease progression.

This study has several limitations that potentially restrict the generalizability of the findings to others with PD, principally the young age of the discordant PD-twins, and the availability of only a single discordant PD-twin pair. Clearly, replication of our findings is necessary before ventricular enlargement can be considered even a nonspecific marker for neurodegeneration in PD. Nonetheless, our proposal that ventricular asymmetry might represent a marker of disease progression is consistent with the view that radiographic measures of regional atrophy may be useful in assessing disease progression in other forms of parkinsonism.[12]

Although the lateral ventricular asymmetry difference between the discordant PD-twin pair is large, one cannot exclude the possibility that it is not PD-related. Although the available pre-, peri-, and postnatal history suggests that this is not the case, the affected twin may have suffered an unknown insult that initiated or accelerated the ventricular asymmetry. Alternately, other postnatal environmental factors (e.g., a "second hit") ultimately may have caused the PD. The faster lateral ventricle enlargement in the more affected side, however, argues that the asymmetrical ventricular enlargement may possibly be part of the process of PD progression.

Volumetric measures that could reflect specific information may have utility in following disease progression in vivo. First, volumetric measurement may reveal directly the consequence of cell loss that is not easily modulated by symptomatic treatments. Second, PD is known to have diffuse cell loss beyond the nigrostriatal dopamine system that cannot be reflected adequately by limited clinical evaluation focused on one or a few as-

pects of the disease, or by the simple measurement of nigrostriatal dopaminergic terminal integrity. Third, because there are many "silent" areas/cells in the brain that provide functional resilience (compensatory mechanisms) after insult, a fundamental understanding of the PD process, in terms of cell death, needs to account for the loss of silent cells, both within and outside the dopaminergic system. For these reasons, future ventricular volumetric studies involving more discordant PD-twin pairs, larger case–control studies with genetically unmatched subjects, and/or longitudinal cohort studies of PD subjects (all with correlation to PD-specific functional measurements) may appear warranted.

Acknowledgments: This work was supported in part by NIH grants AG21491 (XH), RR00046 (GCRC). We are thankful to the discordant PD-twin pair who participated in the studies. We also thank Dr. Douglas W. Jones for providing MRI data on the nine pairs of healthy twins and Drs. Ken Marek and Danna Jennings for performing the SPECT studies.

REFERENCES

1. Lee CS, Schulzer M, Mak E, Hammerstad JP, Calne S, Calne DB. Patterns of asymmetry do not change over the course of idiopathic parkinsonism: implications for pathogenesis. Neurology 1995;45(3, Part 1):435-439.
2. Kumar A, Mann S, Sossi V, et al. [11C]DTBZ-PET correlates of levodopa responses in asymmetric Parkinson's disease. Brain 2003;126 (Part 12):2648-2655.
3. Huber SJ, Miller H, Bohaska L, Christy JA, Bornstein RA. Asymmetrical cognitive differences associated with hemiparkinsonism. Arch Clin Neuropsychol 1992;7:471-480.
4. Tomer R, Sharon-Peretz J, Tsitrinbaum Z. Dopamine asymmetry interacts with medication to affect cognition in Parkinson's disease. Neuropsychologia 2007;45:357–367.
5. Marie RM, Barre L, Rioux P, Allain P, Lechevalier B, Baron JC. PET imaging of neocortical monoaminergic terminals in Parkinson's disease. J Neural Transm Park Dis Dement Sect 1995;9:55-71.
6. Hu MT, White SJ, Chaudhuri KR, Morris RG, Bydder GM, Brooks DJ. Correlating rates of cerebral atrophy in Parkinson's disease with measures of cognitive decline. J Neural Transm 2001;108: 571-580.
7. Styner M, Lieberman JA, McClure RK, Weinberger DR, Jones DW, Gerig G. Morphometric analysis of lateral ventricles in schizophrenia and healthy controls regarding genetic and disease-specific factors. Proc Natl Acad Sci USA 2005;102:4872-4877.
8. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004;127 (Part 3):550-560.
9. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005;65:1239-1245.
10. Van LK, Maes F, Vandermeulen D, Suetens P. Automated model-based bias field correction of MR images of the brain. IEEE Trans Med Imaging 1999;18:885-896.
11. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 2006;31:1116-1128.
12. Paviour DC, Price SL, Jahanshahi M, Lees AJ, Fox NC. Longitudinal MRI in progressive supranuclear palsy and multiple system atrophy: rates and regions of atrophy. Brain 2006;129 (Part 4): 1040-1049.

A Pilot, Double-Blind, Placebo-Controlled Trial of Pregabalin (Lyrica) in the Treatment of Essential Tremor

Theresa A. Zesiewicz, MD,[1,2,3,4,5]* Christopher L. Ward, LMT,[1,2,4] Robert A. Hauser, MD,[1,2,3,4] Jason L. Salemi, MPH,[6] Shaila Siraj, BS,[1,2,4] Maria-Carmen Wilson, MD,[2] and Kelly L. Sullivan, MSPH[1,2,4]

[1]Parkinson's Disease and Movement Disorders Center, University of South Florida, Tampa, Florida, USA; [2]Department of Neurology, University of South Florida, Tampa, Florida, USA; [3]Department of Pharmacology and Experimental Therapeutics, University of South Florida, Tampa, Florida, USA; [4]National Parkinson Foundation Center of Excellence, University of South Florida, Tampa, Florida, USA; [5]James A. Haley Veterans Administration Hospital, University of South Florida, Tampa, Florida, USA; [6]Birth Defects Surveillance Program, Department of Pediatrics, University of South Florida, Tampa, Florida, USA

Video 

Abstract: **We performed a pilot, double-blind, placebo-controlled, randomized trial to evaluate the efficacy and tolerability of pregabalin (PGB, Lyrica), an antiepileptic agent, in treating essential tremor (ET). Twenty two patients with ET were randomly assigned to receive PGB or placebo. PGB was initiated at 50 mg/day and was escalated by 75 mg/day every 4 days to a maximum dose of 600 mg/day. Patients were evaluated by accelerometry and the Fahn–Tolosa–Marin (FTM) rating scale. There was a significant reduction in tremor amplitude in the PGB group compared with the placebo group, as measured by accelerometry, at a mean dose of 286.76 ± 100.05 mg/day. Action tremor limb scores on the FTM also improved in the PGB group compared with the placebo group (*P*-value for multilevel modeling = 0.04). PGB was fairly well tolerated, with about one-third of patients dropping out of the study because of adverse events. PGB provided significant improvements in accelerometry and in action tremor limb scores on the FTM. However, larger studies are needed to further**

The authors have confirmed with the Editor that their work complies with the Journal's Editorial policy on ghost writing [Mov Disord 2005;20(12):1536].

This article includes supplementary video clips, available online at http://www.interscience.wiley.com/jpages/0885-3185/suppmat.

*Correspondence to: Dr. Theresa A. Zesiewicz, University of South Florida, 12901 Bruce B. Downs Blvd, MDC Box 55, Tampa, Florida 33612. E-mail: tzesiewi@hsc.usf.edu

Received 16 February 2007; Revised 26 March 2007; Accepted 18 May 2007

Published online 19 June 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21629