Thalamic Involvement in Paroxysmal Kinesigenic Dyskinesia: A Combined Structural and Diffusion Tensor MRI Analysis

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Abstract: Alteration of basal ganglia-thalamocortical circuit has been hypothesized to play a role in the pathophysiology underlying paroxysmal kinesigenic dyskinesia (PKD). We investigated macrostructural and microstructural changes in PKD patients using structural and diffusion tensor magnetic resonance imaging (MRI) analyses. Twenty-five patients with idiopathic PKD and 25 control subjects were prospectively studied on a 3T magnetic resonance (MR) scanner. Cortical thickness analysis was used to evaluate cortical gray matter (GM) changes, and automated volumetry and shape analysis were used to assess volume changes and shape deformation of the subcortical GM structures, respectively. Tract-based spatial statistics (TBSS) was used to evaluate white matter integrity changes in a whole-brain manner, and region-of-interest (ROI) analysis of diffusion tensor metrics was performed in subcortical GM structures. Compared to controls, PKD patients exhibited a reduction in volume of bilateral thalami and regional shape deformation mainly localized to the anterior and medial aspects of bilateral thalami. TBSS revealed an increase in fractional anisotropy (FA) of bilateral thalami and right anterior thalamic radiation in patients relative to controls. ROI analysis also showed an increase in FA of bilateral thalami in patients compared to controls. We have shown evidence for thalamic abnormalities of volume reduction, regional shape deformation, and increased FA in patients with PKD. Our novel findings of concomitant macrostructural and microstructural abnormalities in the thalamus lend further support to previous observations indicating causal relationship between a preferential lesion in the thalamus and development of PKD, thus providing neuroanatomical basis for the involvement of thalamus within the basal ganglia-thalamocortical pathway in PKD. *Hum Brain Mapp* 36:1429–1441, 2015. © 2014 Wiley Periodicals, Inc.

Key words: paroxysmal kinesigenic dyskinesia; thalamus; structural MRI; diffusion tensor imaging

Contract grant sponsor: Korean Government (National Research Foundation of Korea Grant); Contract grant number: NRF/2010–0004817; Contract grant sponsor: Korean Government (National Research Foundation of Korea Grant); Contract grant number: NRF/2012R1A1A1007757.

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Received for publication 6 June 2014; Revised 14 November 2014; Accepted 30 November 2014.

DOI: 10.1002/hbm.22713

Published online 11 December 2014 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Paroxysmal kinesigenic dyskinesia (PKD) is a rare neurological disorder, characterized by sudden, brief attacks of involuntary dyskinetic movements that are exclusively triggered by initiation of voluntary movements [Bhatia, 1999; Demirkiran and Jankovic, 1995]. The clinical manifestations of dyskinesia vary and include dystonia, chorea, athetosis, ballism, or any combination of these hyperkinetic movements. Family history is noted in an autosomal dominant trait, but sporadic cases are not uncommonly reported. Interictal and ictal electroencephalograms (EEG) are generally normal, and conventional neuroimaging does not reveal any structural abnormality of the brain in patients with idiopathic PKD. Consciousness is completely preserved during the attacks, and patients typically respond well to antiepileptic drugs.

The fundamental pathophysiology underlying PKD is still largely unknown. There has been some evidence suggesting dysfunctions of the subcortical gray matter (GM) structures, especially thalamus and basal ganglia, in the pathophysiologic basis in PKD [Joo et al., 2005; Shirane et al., 2001; Zhou et al., 2010a, 2010b]. Given an important role of the basal ganglia-thalamocortical circuit in control of normal voluntary movement, it seems plausible that abnormal neuronal activities of the basal ganglia or thalamus could be responsible for dyskinesias in PKD. Conversely, detailed electrophysiologic studies provided evidence for cortical involvement in PKD. Those studies have found a reduction of intracortical inhibition or spinal reciprocal inhibition in patients with idiopathic PKD, suggesting a dysfunction of cortical or spinal inhibition [Hsu et al., 2013a, 2013b; Kang et al., 2006; Mir et al., 2005]. Interestingly, some researchers believe that PKD is a kind of reflex epilepsy in which the epileptogenic focus may lie within the subcortical GM rather than the cortex [Depienne and Brice, 2011; Lombroso, 1995]. Recent genetic studies have identified mutations in the *PRRT2* (proline-rich transmembrane protein 2) gene as the major cause for both familial and sporadic PKD as well as PKD associated with infantile convulsion and choreoathetosis syndrome (ICCA), although the precise role of these mutations in the pathophysiology of PKD remains to be determined [Becker et al., 2013; Meneret et al., 2012; van Vliet et al., 2012].

To our knowledge, there is no currently available study that utilized a comprehensive evaluation of struc-

tural changes of the brain in patients with PKD. In the present study, we therefore used well-validated MRI analytic methods of structural MRI and diffusion tensor imaging (DTI) in order to determine whether PKD is associated with focal abnormalities of GM and/or white matter (WM). Specifically, whole-brain cortical thickness analysis [Fischl and Dale, 2000] was used to evaluate cortical GM changes, and automated volumetry [Fischl et al., 2002] and vertex-based shape analysis [Patenaude et al., 2011] were conducted to assess volume changes and regional shape deformation of the subcortical GM, respectively. Vertex-based shape analysis is another fully automated method that provides useful information about the location and pattern of morphological changes of the subcortical GM [Patenaude et al., 2011]. Because it can precisely localize regional shape deformation of the subcortical GM and detect changes that are not found in voxel-based morphometry, shape analysis is now increasingly used to study subcortical GM in a variety of neurological and psychiatric disorders. Tract-based spatial statistics (TBSS) [Smith et al., 2006] was used to evaluate microstructural WM changes in a whole-brain manner, and region-of-interest (ROI) analysis of the DTI metrics in subcortical GM was performed as well. We predicted that focal macrostructural and microstructural abnormalities of the basal ganglia or thalamus in conjunction with associative cortical regions may be present in patients with idiopathic PKD as compared to healthy controls.

MATERIALS AND METHODS

Subjects

We recruited 25 right-handed patients with idiopathic PKD (21 males, mean age = 23.3 ± 6.6 years, age range = 15–37 years, education years = 14.0 ± 2.3 years) who were followed in the outpatient clinic of the Department of Neurology at Korea University Guro Hospital from January 2011 to December 2013. Patients were eligible for inclusion if they met the following criteria proposed by Bruno et al. [2004]: (1) identified kinesigenic trigger for the attacks; (2) short duration (<1 min) of attacks; (3) no loss of consciousness or pain during the attacks; (4) exclusion of other organic diseases and normal neurologic examination; (5) control of attacks with antiepileptic drugs; and (6) age at onset between 1 and 20 years, if no family history of PKD. All patients underwent either routine EEG or long-term video-EEG monitoring to detect interictal or ictal EEG abnormalities. Exclusion criteria we used were the following: (1) claustrophobia or any MRI incompatibility; (2) hypertension, diabetes mellitus, ischemic heart disease, chronic liver disease, or other chronic systemic disorders; (3) traumatic brain injury, cerebrovascular disease, epilepsy, mental retardation, multiple sclerosis, or other proven neurological or psychiatric disorders;

Abbreviations

DTI	diffusion tensor imaging
EEG	electroencephalogram
FA	fractional anisotropy
FEW	Familywise error
MD	mean diffusivity
PKD	paroxysmal kinesigenic dyskinesia
TFCE	threshold-free cluster enhancement
TBSS	tract-based spatial statistics

and (4) chronic alcohol consumption and substance abuse. The following clinical characteristics were obtained through interviews with the patients and their parents and reviews of medical records: age of onset, disease duration, family history of PKD, history of infantile convulsion, type of dyskinesia, dominantly affected side and body parts, attack frequency, and response to an antiepileptic drug. None of the patients underwent genetic testing for the mutations of PRRT2 gene.

For group comparison, 25 right-handed control subjects matched for age and sex (19 males, mean age = 24.7 ± 5.9 years, age range = 16–37 years, education years = 14.9 ± 1.8 years) were recruited to serve as the control group. Patient and control groups did not differ in age ($P = 0.421$), sex ($P = 0.725$), and education years ($P = 0.150$). All control subjects underwent neurological examination and a detailed interview to ensure that they had (1) no neurological abnormality; (2) no history of neurological, psychiatric, or systemic disorders; (3) no family history of PKD or epilepsy; and (4) no history of severe head injury and substance abuse. This study was approved by the local ethics committee of the Korea University Guro Hospital, and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent prior to study inclusion.

MRI Data Acquisition

MRI data were acquired on a Siemens Trio 3T scanner (Erlangen, Germany) with a 12-channel phased array head coil. For volumetric analysis, a high-resolution three-dimensional (3D) MP-RAGE sequence was acquired with the following parameters: TR = 1,780 ms, TE = 2.34 ms, matrix = 256×256 , FOV = 256×256 mm, voxel size = 1 mm^3 . A single-shot spin-echo echoplanar imaging sequence was used for acquisition of DTI data with the following parameters: 30 noncollinear diffusion directions ($b\text{-value} = 1,000 \text{ s/mm}^2$) with two nondiffusion gradient ($b\text{-value} = 0 \text{ s/mm}^2$), TR = 6,500 ms, TE = 89 ms, matrix = 128×128 , FOV = 230×230 mm, voxel size = $1.8 \times 1.8 \times 3 \text{ mm}^3$. The acquisitions were repeated two times to improve the signal-to-noise ratio and to reproduce more diffusion directionalities. Particular attention was taken to center the subject in the head coil and to restrain head movements with cushions and adhesive medical tape. All patients remained on an antiepileptic drug at the time of MRI scanning.

For identification of structural abnormalities, the following MR images were acquired: axial T2-weighted and FLAIR images (4 mm thickness), oblique coronal T2-weighted and FLAIR images perpendicular to the long axis of the hippocampus (3 mm thickness). The MR images were reviewed by an experienced neuroradiologist (S.I.S.) for any structural abnormalities and reported as normal in all participants. Resting-state functional MRI data were acquired simultaneously but not included in the current analysis.

Cortical Thickness Analysis

Data preprocessing and subsequent cortical thickness analysis were performed using FreeSurfer image analysis suite (version 5.3, <http://surfer.nmr.mgh.harvard.edu/>). Automatic segmentation enables labeling cortical and subcortical tissue classes using an atlas-based Bayesian segmentation procedure [Fischl et al., 2002]. Briefly, the automated procedures included removal of nonbrain tissue, automated Talairach transformation, segmentation of the subcortical WM and deep GM volumetric structures, intensity normalization, tessellation of the GM-WM boundary, automated topology correction, and surface deformation. The last procedure is accomplished by following intensity gradients to optimally place the GM/WM and GM/cerebrospinal fluid (CSF) borders at the location where the greatest shift in intensity defines the transition to the other tissue class [Fischl and Dale, 2000]. All images were visually inspected for accuracy by an experienced neuroradiologist (S.I.S.) who was blinded to the subject's diagnosis. A first visual inspection was done after the skull stripping to detect skull tissues not successfully removed, and a second inspection was necessary after the GM/WM segmentation to visualize possible tissue misclassification. In three patients and four control subjects, minor manual corrections were performed by editing out the skull tissue and adding control points to correct topological defects, according to FreeSurfer guidelines (<http://surfer.nmr.mgh.harvard.edu/fswiki/>). The distance between the WM surface and pial surface yields an estimate of cortical thickness at each vertex. The reconstructed cortical surfaces for each participant were then aligned to produce an average cortical surface. A mapping was obtained between each vertex on the average surface and the corresponding vertex on the surface of each subject's cortical reconstruction. The cortical thickness maps for each subject were then resampled onto the average surface and smoothed with a 10-mm full width at half maximum Gaussian kernel to improve intersubject averaging.

A general linear model was used to test for cortical thickness differences between PKD patients and controls at each vertex while controlling for the effects of age and sex. The statistical surface maps were cluster-wise corrected for multiple comparisons using Monte Carlo simulation with 10,000 permutations. Only clusters that survived this correction were considered statistically significant (corrected $P < 0.05$). Linear correlation analysis was further performed between cortical thickness and disease duration in the patient group (corrected $P < 0.05$, controlling for age and sex as potential confounders).

Volumetry of Subcortical GM

The automated procedures for volumetric measurements of the subcortical GM were described in detail previously [Fischl et al., 2002]. Briefly, this procedure automatically provided segments and labels for up to 40 unique

structures, and assigned a neuroanatomical label to each voxel in an MRI volume based on probabilistic information estimated automatically from a manually labeled training set. A Bayesian segmentation procedure was then performed, and the maximum a posteriori estimate of the labeling was computed. All segmentations were visually inspected for accuracy prior to inclusion in the analysis.

Volumes of six GM structures (caudate, globus pallidus, putamen, thalamus, amygdala, and hippocampus) were automatically measured. The normalization was performed on each GM volume via a formula based on analysis of covariance (ANCOVA) approach: $\text{normalized volume} = \text{raw volume} - b \times (\text{TIV} - \text{mean TIV})$, where TIV stands for total intracranial volume and b is the slope of regression of a GM volume on TIV. Normalized volume data were first tested for normality of distribution and homogeneity of variance assumption using Kolmogorov-Smirnov test and Levene test, respectively. Prior to group comparison, interactions between the dependent variables and the covariate were checked using a custom model, which included group and age as main effects and the group $\times$ age interaction. When there was no significant age $\times$ group interaction ($P > 0.05$), a full factorial model was chosen. Group differences in normalized GM volumes were assessed using ANCOVA, adjusting for the effects of age and sex. Bonferroni correction was further applied and statistical significance was set at $P < 0.0042$ ($0.05/12$). The associations between the normalized GM volumes and disease duration were explored using partial correlations controlling for the effect of age (corrected $P < 0.05$). Statistical analyses were performed with the Statistical Package for Social Sciences (Version 19.0; IBM, Armonk, NY).

Shape Analysis of Subcortical GM

Automated segmentation of the subcortical GM was performed using FIRST, part of FMRIB's Software Library (FSL version 5.0.6, <http://www.fmrib.ox.ac.uk/fsl>), that uses Bayesian probabilistic approach [Patenaude et al., 2011]. Registration in FIRST comprises an affine transformation (12 degrees of freedom) of the volumetric T1-weighted images to MNI 152 standard space. After subcortical registration, a subcortical mask was applied to locate the different subcortical GM structures, followed by segmentation based on shape models and voxel intensities. The shape models used in FIRST are constructed from a library of manually segmented T1-weighted MRI datasets. FIRST then created a surface mesh for each subcortical GM using a deformable mesh model. The mesh is composed of a set of triangles and the apex of adjoining triangles is called a vertex. The number of vertices per mesh was fixed for a GM structure and the correspondence between vertices was enforced during the fitting so that corresponding vertices can be compared across individuals and between groups. The shape and appearance model is based on multivariate Gaussian assumptions, and shape is

then expressed as its mean and modes of variation. Default options were used for boundary correction allowing determination of whether boundary voxels belong to the structure or not (z -value = 3, corresponding to a 99.998% certainty that the voxel belonged to the respective structure).

Group comparisons of vertices were performed using F -statistics. The effects of TIV, age, and gender were regressed out. Group differences were tested against 5,000 random permutations and the statistical threshold was set at $P < 0.05$, corrected for multiple comparisons using familywise error (FWE). The relationship between regional shape changes of the subcortical GM and disease duration was explored in the patient group (FWE-corrected $P < 0.05$, controlling for age and sex as potential confounders).

Tract-Based Spatial Statistics

DTI data were preprocessed using the FMRIB's Diffusion Toolbox, part of FSL. First, DTI data were visually inspected for image quality, and then corrected for eddy current and head motion by registering each subject's 30 diffusion weighted images to their own nondiffusion-weighted image using FMRIB Linear Image Registration Tool. Brain extraction tool implemented in FSL was used to remove nonbrain structures and background noise by applying a fractional intensity threshold of 0.35. Next, a diffusion tensor model was fitted at each voxel using DTI-FIT to generate fractional anisotropy (FA) and mean diffusivity (MD) maps.

The resulting FA and MD maps were fed into TBSS to carry out whole-brain voxel-wise statistical analysis of FA and MD between patients and controls. The initial step of TBSS consisted of direct registration of individual FA images to the $1 \times 1 \times 1 \text{ mm}^3$ Montreal Neurological Institute (MNI152) standard space by normalization to the FMRIB58 FA template using the FMRIB's Nonlinear Registration Tool (FNIRT). The transformed FA images of all participants were averaged to create a mean FA image, and this mean FA image was then thinned to create the WM "skeleton" (a representation of WM tracts common to all subjects). A non-maximum suppression algorithm was applied afterward to search the image voxels with highest FA value along the direction perpendicular to the local tract surface to create a mean FA skeleton. An FA threshold of 0.2 was further applied to exclude the skeleton voxels, which may contain GM. Following thresholding of the mean FA skeleton, each participant's transformed FA map was projected onto the mean FA skeleton to create a skeletonized FA map. In a separate process using the FA image-derived skeleton, the maximum values along the direction perpendicular to the tract of MD image were also projected to a separate skeleton image using "tbss non-FA" script.

Each participant's skeletonized FA and MD images were used for voxel-wise analysis of group differences between

TABLE I. Clinical characteristics of 25 patients with idiopathic PKD

Patient No.	Sex/age, years	Onset age, years	Disease duration, years	Family history ^a	Type of dyskinesia	Affected side	Affected part	Attack frequency	Treatment	Outcome
1	F/16	11	5	Y	D	R > L	A, L	<3/day	OXC	Good
2	M/15	8	7	Y	D	B	A, L	<3/day	CBZ	Good
3	F/23	14	9	Y	D, C	R	A, L	<5/day	OXC	Good
4	M/25	18	7	Y	D, C	L > R	L	<2/day	OXC	Good
5	M/22	12	10	N	D	B	A	<10/day	CBZ	Good
6	M/21	16	5	N	D	B	A	<5/day	DPH	Good
7	M/29	16	13	N	D	L	A, L	<30/day	CBZ	Good
8	M/36	17	19	N	D	L > R	A, L, F	<10/day	OXC	Good
9	F/19	10	9	N	D	B	L	<40/day	CBZ	Good
10	M/22	14	8	Y	D	B	A, L, F	<30/day	CBZ	Good
11	M/30	8	22	N	C	B	A, L	<1/day	CBZ	Good
12	M/18	13	5	N	D	B	A, L	<15/day	CBZ	Good
13	M/19	7	12	Y	D	B	L	<5/day	OXC	Good
14	M/37	11	26	Y	D	B	A, L	<20/day	CBZ	Good
15	M/24	14	10	N	D, C	B	L	<10/day	CBZ	Good
16	F/20	12	8	Y	D	L > R	A, L	<20/day	CBZ	Good
17	M/16	14	2	N	D	L	A, L	<30/day	OXC	Good
18	M/20	10	10	Y	C	R	A, L	<10/day	DPH	Good
19	M/17	5	12	Y	D, C	L > R	A, L	<5/day	CBZ	Good
20	M/33	10	23	N	D, C	L	A, L	<30/day	CBZ	Good
21	M/20	11	9	N	C	R	A, L	<10/day	OXC	Good
22	M/21	12	9	N	D, C	L	A, L	<4/day	OXC	Good
23	M/30	18	12	N	D, C	B	A, F	<5/day	CBZ	Good
24	M/16	15	1	N	D, C	B	A, L	<50/day	OXC	Good
25	M/33	10	23	N	D	R > L	A, L, F	<1/day	CBZ	Good

^aFamily history of paroxysmal kinesigenic dyskinesia.

C, choreoathetosis; D, dystonia; L, left sided; R, right sided; B, bilateral or alternating sides; A, arm; L, leg; F, face; CBZ, carbamazepine; OXC, oxcarbazepine; DPH, phenytoin.

patients and control subjects. A nonparametric test with 5,000 random permutations was performed using "Randomise" program [Nichols and Holmes, 2002]. Two-sample *t*-test was used for between-group comparisons with age, sex, and education years [Teipel et al., 2009] treated as confounding covariates. Statistical significance was thresholded at $P < 0.05$, corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) [Smith and Nichols, 2009]. Linear correlation analyses were also performed to find relationships between disease duration and FA and MD in the patient group (TFCE-corrected $P < 0.05$).

ROI Analysis of FA and MD in Subcortical GM

As FA skeleton made from the TBSS pipeline does not include subcortical GM structures, except for the thalamus that contains layers of myelinated fibers commonly referred to as the medullary laminae of the thalamus, ROI approach was used to investigate FA and MD changes of the subcortical GM. First, all FA images were aligned to the FMRIB58_FA standard space template supplied with

FSL, using the nonlinear registration tool FNIRT. After the registration step, each subject's FA image was merged into a single four-dimensional (4D) image file and a mean FA mask was created. The same nonlinear registration was also applied to each subject's MD image and then merged into a 4D image file. Binary ROI masks were created for the bilateral caudate, globus pallidus, putamen, thalamus, amygdala, and hippocampus at $1 \times 1 \times 1 \text{ mm}^3$ resolution based on the 50% probability maps of the Harvard-Oxford subcortical structural atlas provided with FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases>). FA and MD values were retrieved from these 12 ROIs and then fed into statistical analysis. Data were first tested for normality of distribution and homogeneity of variance assumption using Kolmogorov-Smirnov test and Levene test, respectively. Prior to final analysis, interactions between the dependent variables and the covariate were checked using a custom model, which included group and age as main effects and the group $\times$ age interaction. When there was no significant age $\times$ group interaction ($P > 0.05$), a full factorial model was chosen. Group comparisons of FA and MD between patients and controls were made using ANCOVA, adjusting for the effects of age, sex, and

TABLE II. Normalized volume, fractional anisotropy, and mean diffusivity of the subcortical gray matter structures in controls and patients with PKD

	Volume (mm ³)	FA	MD (10 ⁻⁶ mm ² /s)	Volume (mm ³)	FA	MD (10 ⁻⁶ mm ² /s)
		L caudate			R caudate	
Controls	3966.5 ± 538.9	0.156 ± 0.015	780.3 ± 56.4	3631.3 ± 538.5	0.146 ± 0.019	774.2 ± 51.2
PKD	3788.1 ± 437.7	0.156 ± 0.015	770.3 ± 43.1	3517.9 ± 499.9	0.150 ± 0.019	774.2 ± 78.0
<i>P</i> -value	0.331	0.951	0.522	0.534	0.433	0.917
		L globus pallidus			R globus pallidus	
Controls	1436.7 ± 223.3	0.356 ± 0.019	661.6 ± 41.1	1507.1 ± 256.3	0.314 ± 0.026	660.1 ± 27.8
PKD	1475.5 ± 246.2	0.363 ± 0.018	647.7 ± 29.4	1493.0 ± 225.1	0.322 ± 0.015	656.8 ± 23.9
<i>P</i> -value	0.624	0.139	0.128	0.877	0.169	0.597
		L putamen			R putamen	
Controls	5839.9 ± 699.6	0.158 ± 0.012	718.8 ± 21.4	5570.6 ± 630.9	0.149 ± 0.012	708.5 ± 22.7
PKD	5869.3 ± 710.8	0.159 ± 0.014	714.0 ± 18.4	5570.8 ± 507.1	0.150 ± 0.013	703.6 ± 14.4
<i>P</i> -value	0.900	0.726	0.233	0.983	0.926	0.351
		L thalamus			R thalamus	
Controls	9378.9 ± 736.3	0.275 ± 0.009	802.4 ± 59.1	9183.0 ± 669.9	0.284 ± 0.009	767.2 ± 40.9
PKD	8680.8 ± 542.9	0.286 ± 0.016	775.1 ± 40.4	8592.3 ± 545.7	0.296 ± 0.015	750.5 ± 34.8
<i>P</i> -value	0.002*	0.001*	0.086	0.002*	0.001*	0.163
		L amygdala			R amygdala	
Controls	1827.2 ± 215.1	0.193 ± 0.014	805.9 ± 43.1	1841.3 ± 177.3	0.182 ± 0.016	804.0 ± 34.7
PKD	1814.1 ± 150.8	0.191 ± 0.018	797.4 ± 38.7	1818.4 ± 136.5	0.185 ± 0.014	785.0 ± 31.6
<i>P</i> -value	0.595	0.669	0.338	0.462	0.813	0.059
		L hippocampus			R hippocampus	
Controls	4906.3 ± 466.4	0.144 ± 0.013	1003.8 ± 80.5	5030.6 ± 444.2	0.150 ± 0.013	1031.6 ± 66.1
PKD	4660.6 ± 365.6	0.143 ± 0.013	1024.5 ± 90.5	4793.7 ± 381.3	0.149 ± 0.011	1025.4 ± 99.9
<i>P</i> -value	0.057	0.500	0.684	0.079	0.288	0.565

Values are reported as mean ± standard deviation. **P* < 0.05, ANCOVA adjusting for the effects of age and sex followed by Bonferroni correction. L, left; R, right; FA, fractional anisotropy; MD, mean diffusivity.

education years. Bonferroni correction was further applied and statistical significance was set at *P* < 0.0042 (0.05/12). The associations between FA and MD values of the subcortical GM and disease duration were explored using partial correlations controlling for the effect of age and education years (corrected *P* < 0.05).

RESULTS

Clinical Features

The clinical characteristics of the 25 patients are detailed in Table I. Mean age of PKD onset was 12.2 ± 3.4 years (range = 5–18 years) and mean disease duration was 11.0 ± 6.7 years (range = 1–26 years). Ten patients (40%) had a positive family history of PKD. Five patients (20%) reported a history of infantile convulsion or febrile seizure, but none of the patients had a history of epilepsy. All patients had paroxysmal, brief (usually less than 1 min) attacks of dystonia (14 patients), choreoathetosis (3 patients), or combination of both (8 patients), which was exclusively precipitated by sudden voluntary movements. Predominant attacks involved arm, leg, face, or any combinations of these body parts, and were bilateral or alternating sides in 18 patients, left sided in 4, and right sided in

3. Routine EEG showed no interictal abnormalities during wake and sleep in 17 patients. Long-term video-EEG monitoring was performed in eight patients and showed no abnormal ictal EEG changes before, during, or immediate after their typical PKD attacks. All patients showed good response to one of the antiepileptic drugs (carbamazepine, oxcarbazepine, and phenytoin).

Cortical Thickness Analysis

Cortical thickness analysis showed no significant cortical regions of either thickening or thinning in PKD patients compared to controls at the threshold of cluster-wise corrected *P* < 0.05. There was no cortical region of significant correlation with disease duration in the patient group at the same threshold.

Volumetry of Subcortical GM

Normalized volumes for the six subcortical GM and statistical results are summarized in Table II. Compared to controls, PKD patients had significant volume reductions in left thalamus (*F*[1,46] = 11.267, *P* = 0.002, partial eta squared = 0.197) and right thalamus (*F*[1,46] = 11.077, *P* = 0.002, partial eta squared = 0.194) (Bonferroni-corrected

Figure 1.

Mean (bars) and standard deviation (whiskers) for the normalized thalamic volumes (**A**) and thalamic fractional anisotropy (**B**) of controls and patients with idiopathic PKD. * $P < 0.05$ with Bonferroni correction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$P < 0.05$, Fig. 1). There was no significant interaction term of age $\times$ group in normalized volumes of the left thalamus ($P = 0.658$) and right thalamus ($P = 0.274$). There was no significant difference in normalized volumes of bilateral caudate, globus pallidus, putamen, amygdala, and hippocampus between patients and controls (all $P > 0.05$). There was no significant correlation between normalized volumes of all subcortical GM and disease duration in the patient group (all $P > 0.05$). Group comparison between PKD patients with a positive family history ($n = 10$) and those without ($n = 15$) revealed no differences in normalized volumes of the thalamus and the other subcortical GM structures (all $P > 0.05$).

(FWE-corrected $P < 0.05$). Regional shape deformation showed inward movement of vertices (regional atrophy) and primarily affected anterior and medial aspects of the thalami (Fig. 2). The other GM structures did not show significant regional shape changes in patients compared to controls. No significant correlations were found between shape changes of subcortical GM and disease duration in the patient group. Group comparison between PKD patients with a positive family history and those without revealed no shape differences in the subcortical GM structures.

Shape Analysis of Subcortical GM

Vertex-wise differences were identified between controls and PKD patients in the shape of the bilateral thalami

Figure 2.

Vertex-wise differences in thalamic shape between controls and patients with idiopathic PKD. Blue color indicates the 3D template mesh of the thalamus, and orange color indicates areas of significant shape difference between the groups. Results are corrected for multiple comparisons using familywise error (corrected $P < 0.05$). L, left; R, right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Tract-Based Spatial Statistics

After controlling for age, sex, and education years as confounding covariates, TBSS of FA identified several clusters of significant FA increases in PKD patients compared to controls (Fig. 3). These regions of FA increases involved right thalamus (MNI coordinate of local maxima = $6/-16/4$, TFCE-corrected $P < 0.024$), left thalamus (MNI coordinate of local maxima = $-11/-24/11$, TFCE-corrected $P < 0.020$), and right anterior thalamic radiation (MNI coordinate of local maxima = $16/5/8$, TFCE-corrected $P < 0.037$). No region of significant FA decrease was found in PKD patients compared to controls. TBSS of MD failed to show either increases or decreases of MD in patients compared to controls. There was no region of significant correlation between FA or MD and disease duration in the patient group. There were no significant differences in FA and MD between PKD patients with a positive family history and those without.

ROI Analysis of FA and MD in Subcortical GM

FA and MD values for the six subcortical GM and statistical results are summarized in Table II. Compared to controls, PKD patients exhibited significant FA increases in left thalamus ($F[1,45] = 12.167$, $P = 0.001$, partial eta squared = 0.213) and right thalamus ($F[1,45] = 11.446$,

Figure 3.

Tract-based spatial statistics analysis of fractional anisotropy (FA). Regions of significant FA increases (highlighted in red-yellow) in patients with idiopathic PKD compared to controls are superimposed on the axial (**A**) and coronal (**B**) T1 template image and white matter skeleton (green) across all subjects ($P < 0.05$,

corrected for multiple comparisons using threshold-free cluster enhancement). The left side of the image corresponds to the right hemisphere of the brain. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$P = 0.001$, partial eta squared = 0.203; Bonferroni-corrected $P < 0.05$, Fig. 1). There was no significant interaction term of age $\times$ group in FA of the left thalamus ($P = 0.899$) and right thalamus ($P = 0.478$). There were no significant differences in FA of bilateral caudate, globus pallidus, putamen, amygdala, and hippocampus between patients and controls (all $P > 0.05$). MD values of the six GM structures did not differ between controls and patients (all $P > 0.05$). There was no significant correlation between either FA or MD values of all subcortical GM and disease duration in the patient group (all $P > 0.05$). There were no significant differences in FA and MD of the subcortical GM structures between PKD patients with a positive family history and those without (all $P > 0.05$).

DISCUSSION

This study attempted to explore structural changes of the brain in patients with idiopathic PKD using a multimodal neuroimaging approach that took into account morphometric/volumetric GM changes and microstructural WM changes. We found that thalamic volumes are significantly reduced in PKD patients compared to controls, and that shape deformation is mainly localized to the anterior and medial aspects of the thalami. We also observed significant FA increases in bilateral thalami and right anterior thalamic radiation that interconnects anterior and medial thalamus and frontal cortex in PKD patients. No cortical GM change was found in patients relative to controls.

There has been much controversy regarding the pathophysiology and underlying neuroanatomical correlates of PKD. Specifically, over the decades there has been debate as to whether PKD is an epileptic or a nonepileptic parox-

ysmal disorder [Bhatia, 2011]. Some researchers regard PKD as a form of reflex epilepsy in which the epileptogenic focus may lie within the subcortical GM, especially basal ganglia or thalamus, rather than the cortex [Depienne and Brice, 2011; Lombroso, 1995]. This notion could be supported by the clinical observations that include paroxysmal nature of the dyskinetic attacks, nonprogressive and remitting character of the disorder, absence of interictal and ictal cortical EEG changes, and excellent response to antiepileptic drugs [Bhatia, 1999; Depienne and Brice, 2011]. Indeed, previous genetic studies have shown that the first locus for PKD, identified on chromosome 16p11.2-q12.1 [Tomita et al., 1999], overlaps with another locus identified for benign familial infantile convulsions (BFIC) [Caraballo et al., 2001] and ICCA [Szepietowski et al., 1997], suggesting that PKD, BFIC, and ICCA are to be different expressions of the same disorders or allelic disorders [Caraballo et al., 2001; Depienne and Brice, 2011]. It has therefore been proposed that PKD and some specific epilepsy syndromes could share common pathophysiological mechanisms and genetic factors, and that PKD, as with most genetic epilepsy syndromes [Mulley et al., 2003], could be regarded as an ion channel disorder [Guerrini, 2001; Margari et al., 2005]. In support of this hypothesis, there was a case series that illustrated co-occurrence of early-onset absence epilepsy and later-onset various forms of paroxysmal dyskinesia including PKD [Guerrini et al., 2002]. In addition to aforementioned genetic and clinical associations between PKD and epilepsy, our findings of thalamic morphometric and microstructural changes are also observed in some genetic epilepsy syndromes such as idiopathic generalized epilepsy [Seneviratne et al., 2014], suggesting a possibility that PKD might share a common neuroanatomical basis with a specific epilepsy syndrome with the primary abnormality in

the thalamus. However, there has been no currently available evidence that directly links these two conditions.

It is more widely accepted that PKD is a paroxysmal movement disorder caused by functional abnormalities of the basal ganglia-thalamocortical circuit. One traditional hypothesis is a loss of inhibitory control in the basal ganglia circuitry. The striatum (putamen and caudate) sends an inhibitory projection to the basal ganglia output nuclei (internal globus pallidus/substantia nigra pars reticulata, GPi/SNr) through two pathways: directly (direct pathway) and indirectly through the external globus pallidus and subthalamic nucleus (indirect pathway). The GPi/SNr sends inhibitory fibers to the thalamus (ventral anterior (VA) and ventrolateral nuclei), and the thalamus, in turn, projects excitatory fibers to the motor cortex and supplementary motor cortex, and finally to the spinal motor neurons, producing muscle contractions and movements [Breakefield et al., 2008; Peterson et al., 2010]. Loss of normal inhibitory control of basal ganglia output and resulting overexcitation of thalamocortical circuit are presumed to cause hyperkinetic movement disorders such as dystonia, chorea, and ballism [Mink, 2003; Quartarone and Hallett, 2013]. In support of this hypothesis, there is a large number of neuroimaging evidence that dystonia may be associated with structural and functional abnormalities in the basal ganglia, thalamus, or motor cortical regions [Neychev et al., 2011]. Involvement of basal ganglia in PKD has been suggested in recent studies using resting-state functional MRI and ictal SPECT [Ko et al., 2001; Zhou et al., 2010b]. However, at present there is no consensus on which subcortical GM is primarily responsible for this loss of inhibition within the basal ganglia-thalamocortical network [Quartarone and Hallett, 2013]. Based on our findings that both macrostructural and microstructural abnormalities were found only in the thalamus, but not in the basal ganglia nuclei (caudate, globus pallidus, and putamen), we speculate that basal ganglia dysfunction leading to loss of inhibition is not the primary cause of dyskinesias in PKD.

Conversely, there have been case reports providing convincing evidence for a causal relationship between a single lesion within the thalamus and the development of paroxysmal dyskinesia [Burguera et al., 1991; Camac et al., 1990; Lee and Marsden, 1994; Nijssen and Tijssen, 1992; Rollnik et al., 2003; Sunohara et al., 1984; Zittel et al., 2012]. The relatively frequent involvement of the thalamus in patients with secondary PKD suggests that as this subcortical structure is involved in sensory processing (proprioception), it may lead to characteristic dyskinesias that are kinesigenically induced in this disorder [Demirkiran and Jankovic, 1995]. An ictal-interictal SPECT subtraction study demonstrated a prominent increase in cerebral blood flow in the left posterolateral thalamus during the right-sided dyskinetic attacks in a patient with idiopathic PKD [Shirane et al., 2001]. Abnormal thalamic neuronal activity was recorded during stereotactic neurosurgery in patients with dystonia [Lenz et al., 1999]. Our findings are in line with previous observations, suggesting that thalamic dysfunction

may primarily contribute to abnormal involuntary movements in patients with PKD. Moreover, in our study thalamic shape deformation was mainly localized to the anterior and medial aspects, which seem to contain parts of the VA nucleus and centromedian nucleus (CM). As with ventral motor thalamic nuclei group, the role of CM in the motor circuit of basal ganglia-thalamostriatal loop is well documented in nonhuman primate model [Parent and Hazrati, 1995; Smith et al., 2004], and possible associations between lesions in the CM or ventral thalamus and occurrence of dystonia have also been suggested in human case reports [Cho and Samkoff, 2000; Deleu et al., 2000; Krystkowiak et al., 1998; Lehericy et al., 1996].

Given that most of our patients have a dystonia as a predominant symptom and that both PKD and primary dystonia are known to affect the basal ganglia-thalamocortical circuit, one central question that remains to be determined is whether the observed thalamic changes are specific to PKD or common to primary dystonia. A number of recent studies have used voxel-based morphometry to identify structural GM abnormalities associated with dystonia in patients with primary dystonia, but the main findings are not uniform across the studies. With regard to findings in the basal ganglia and thalamus, only a few studies reported a decrease in thalamic GM [Delmaire et al., 2007; Obermann et al., 2007], whereas most studies found a somewhat consistent finding of a change (either an increase or a decrease) in putaminal GM among patients with different forms of primary dystonia such as blepharospasm [Black et al., 1998; Etgen et al., 2006; Obermann et al., 2007; Ramdhani et al., 2014], cervical dystonia [Obermann et al., 2007; Pantano et al., 2011], and focal hand dystonia [Black et al., 1998; Granert et al., 2011]. In addition, changes in the sensorimotor cortex and/or cerebellum have been frequently described in patients with primary dystonia, although there is some variance across the studies in whether the observed abnormality is associated with an increase or a decrease in GM volume/density [Delmaire et al., 2007; Draganski et al., 2003; Garraux et al., 2004; Martino et al., 2011; Pantano et al., 2011; Ramdhani et al., 2014; Suzuki et al., 2011]. Similar to voxel-based morphometry studies, the results of a few DTI studies on patients with focal dystonia are also variable; however, alterations of FA and MD were mainly detected in the putamen, caudate, thalamus, and sensorimotor cortex [Bonilha et al., 2007; Colosimo et al., 2005; Delmaire et al., 2009; Fabbrini et al., 2008; Ramdhani et al., 2014]. Taken together, the results of the morphometric and DTI studies overall suggest the involvement of brain structures important for motor control and sensorimotor integration in the pathophysiology of primary dystonia. Conversely, in our study the morphometric and DTI metrics changes were confined to the thalamus without obvious changes in the basal ganglia nuclei and sensorimotor cortex, suggesting that the underlying neuroanatomical substrate of PKD may be different from that of primary dystonia. Based on these observations, we speculate that even though

PKD and primary dystonia have a similar symptom of dystonia, both conditions may not share a common pathophysiological mechanism. Future imaging studies comparing brain structures between PKD and primary dystonia should help clarify this unanswered question.

Our finding of increased thalamic FA in PKD patients relative to controls accords well with the previous DTI study recruiting a small number of patients, suggesting that PKD is associated with microstructural abnormality of the thalamus [Zhou et al., 2010a]. However, our demonstration of increased FA in conjunction with volume reduction of the thalamus is a new finding and requires careful interpretation. The observed thalamic volume reduction and increased FA are counterintuitive as the pathologic processes leading to macrostructural atrophy would have been thought to cause a reduction in FA within the brain tissue. One possible explanation may be that atrophic GM within the thalamus excessively constricts the space where numerous myelinated axons interperse. Myelinated axons have a much higher FA compared to GM, and the spatial constriction of myelinated axons may lead to a localized increased anisotropy of water diffusion [Keller et al., 2011]. This speculation could be supported by our TBSS result that demonstrated a significant increase of FA in the thalamic myelinated fibers, referred to as the medullary laminae of the thalamus, in PKD patients. Indeed, inverse relationship between volumetric and FA alterations (i.e., volume reduction in relation to increased FA) was also shown in the specific subcortical GM of the brain disorders such as putamen in idiopathic generalized epilepsy, caudate and thalamus in multiple sclerosis, and putamen and globus pallidus in Huntington's disease [Hannoun et al., 2012; Keller et al., 2011; Rosas et al., 2006]. Alternatively, other pathologic processes, including increased myelination and neuronal remodeling, increased intracellular pool of restricted water molecules associated with cell swelling, or changes in cell permeability, could also account for the increased FA in the thalamus [Beaulieu, 2002; Hannoun et al., 2012; Rosas et al., 2006]. In addition, it is of interest that increased FA in the thalamus was not accompanied by a significant change in MD. One explanation for our finding is that, although reduced rather than increased FA is considered the hallmark DTI correlate of microstructural WM damage, a more restricted intracellular (intraaxonal) water compartment associated with cytotoxic edema could result in increased FA with relatively low MD or no MD change, which supports the possibility that the observed DTI changes in the thalamus might primarily reflect WM injury [Cavallari et al., 2014]. A more plausible explanation is that extraaxonal degeneration in the thalamic nuclei might lead to increased FA with little or no MD change [Hannoun et al., 2012]. This notion suggests that increased FA in the thalamus may reflect microstructural damage within the thalamic GM nuclei rather than WM damage, as supported by our finding of thalamic GM atrophy [Cavallari et al., 2014]. Nevertheless, the biophysical basis of patho-

logically increased FA remains to be elucidated in human. Future studies using more advanced techniques to measure DTI metrics in the thalamic nuclei separately from the WM tracts may clarify the relative contribution of GM and WM damage to the observed finding of increased thalamic FA in PKD patients.

Some limitations of our study should be addressed. First, as the sample size was relatively small and our patients were recruited from an outpatient clinic of a university-affiliated hospital rather than from the community-based patient population, our novel findings may not be generalized to the entire PKD population. Second, the lack of investigation of the PRRT2 mutation in our study limits our ability to provide a more comprehensive evaluation of the role of PRRT2 mutation in the thalamic abnormalities in patients with PKD. Third, possible influence of antiepileptic drugs (e.g., carbamazepine, oxcarbazepine, and phenytoin) on brain structures could not be entirely discounted, although any robust evidence linking the relationship between these drugs and structural changes of the thalamus is currently lacking. Lastly, our study used a cross-sectional design, and therefore, interpretation of our findings with regard to causal relationship is limited. Given our findings of no significant relationships between disease duration and morphometric/volumetric and microstructural changes of the thalamus, the observed thalamic changes could be a reflection of an intrinsic pathology as the cause of PKD rather than a consequence of repeated dyskinesias in PKD. Future prospective studies incorporating a longitudinal design would provide a hint to disentangle causal relations between thalamic alterations and disease progression.

CONCLUSION

Using combined structural and diffusion tensor MRI analyses, we have, for the first time, shown evidence for thalamic abnormalities of volume reduction, regional shape deformation, and increased FA in patients with idiopathic PKD. Our findings of concomitant macrostructural and microstructural abnormalities of the thalamus lend further support to previous observations indicating causal relationship between a preferential lesion in the thalamus and development of PKD, thus providing neuroanatomical basis for the involvement of thalamus within the basal ganglia-thalamocortical pathway in PKD. Future longitudinal MRI studies investigating the same paradigm on a large, genetically homogenous patient cohort are required to corroborate our novel findings and to better understand the role of thalamic dysfunction in the pathophysiology underlying PKD.

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