Parkinsonism and Related Disorders xxx (2012) 1–5

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Differentiating symptomatic Parkin mutations carriers from patients with idiopathic Parkinson's disease: Contribution of automated segmentation neuroimaging method

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ARTICLE INFO

Article history:
Received 16 November 2011
Received in revised form
16 February 2012
Accepted 20 February 2012

Keywords:
MRI
Automatic segmentation
Parkinson's disease
Parkin gene

ABSTRACT

Background: Parkin (PARK2) gene mutations are the predominant cause of autosomal recessive parkinsonism. Characteristic features include: early onset symptoms with slow clinical course, good response to low doses of levodopa, and frequently treatment-induced dyskinesia. Studies using a voxel-based morphometry approach showed a decrease in the gray matter volume of the basal ganglia in mutation carriers during the symptomatic stages. A bilateral, presumably compensatory increase of basal ganglia gray matter value was recently demonstrated in asymptomatic Parkin mutation carriers. Behavioral disorders including: anxiety, psychosis, panic attacks, depression, disturbed sexual, behavioral and obsessive–compulsive disorders have been reported in these patients.
Method: A total of 28 Parkinson's Disease (PD) patients consisting of 10 Young-Onset without Parkin mutations (YOPD), 9 Young-Onset with Parkin mutations (YOPD-p), 9 Late-Onset without Parkin mutations (LOPD) and 32 healthy control subjects were studied with an automated volumetric assessment method to quantify subcortical atrophy. Patients but not controls also underwent a neuropsychological and neuropsychiatric assessment.
Results: Results revealed a reduction of bilateral caudate nuclei volumes in YOPD-p patients compared to the YOPD patients while there were no statistically significant differences between other groups. YOPD-p patients showed similar results to other patient groups on neuropsychiatric and neuropsychological evaluation measures.
Conclusion: YOPD-p and YOPD patients showed a different pattern of volume changes in basal ganglia. Despite its relatively benign clinical course, carrying the Parkin mutation seems to be associated with greater atrophy in subcortical structures. Failure of compensatory mechanisms, different mutation types and pathophysiologic processes may underlie this diverse pattern of subcortical brain changes.

1. Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disorder affecting patients mostly over the age of 45. The etiology of PD remains unknown, only 2–3% of all cases can be explained by a monogenic cause [1]. Both autosomal recessive and autosomal dominant forms can cause PD. Mutations in the leucine-rich repeat kinase 2 (LRRK2) are the most frequent forms of autosomal dominant PD whereas mutations in the Parkin gene are the most frequent forms of autosomal recessive PD. Monogenic Parkin mutations are often implicated as the most common cause of young-onset PD (<45). While patients with this type of young-onset PD (YOPD-p) are clinically indistinguishable from other YOPD patients without Parkin mutations on an individual basis, Parkin mutation carriers tend to be younger at disease onset, have a slower disease progression and often have a better response to

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[1] The review of this paper was entirely handled by an Associate Editor, Prof. J. Carr.

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doi:10.1016/j.parkreldis.2012.02.017

levodopa [2–4]. Frequent neuropsychiatric symptoms such as anxiety, psychosis, obsessive–compulsive disorder and depression have been described in these patients [2,5–7] but there are also additional findings suggesting these problems are not unique to Parkin mutation carriers [4].

Previous studies using MRI-based volumetric analysis in PD revealed inconsistent findings: volume decrease in the basal ganglia structures was found by many authors [8–11] whereas others reported contrary results [12–14]. A study using a voxel-based morphometry (VBM) approach focusing on symptomatic Parkin mutation carriers found a decrease in the gray matter volume of the left caudate [14]. Another study described asymptomatic Parkin mutation carriers as having a bilateral increase in the volume of basal ganglia (BG) nuclei [15]. This finding has been interpreted as a compensatory increase which can be only partially maintained in the symptomatic stage of PD [14]. The majority of volumetry studies have used VBM, an automated voxel-wise whole-brain statistical comparison of MR images using the Statistical Parametric Mapping (SPM) software (Wellcome Department of Cognitive Neurology, London, UK). In the present study, FreeSurfer was chosen because of its high reproducibility and accuracy [16] (http://surfer.nmr.mgh.harvard.edu). This package provides completely automated parcellation of the cerebral cortex and subcortical structures. Several studies have validated the use of this technique to quantify subcortical volume in dementia [17], epilepsy [18,19], depressive disorders [20], essential tremor [21], and tracking volumetric changes associated with aging [22]. A recent study with FreeSurfer revealed a decrease in the volumes of bilateral putamen and right nucleus accumbens in late-onset idiopathic PD patients (LOPD) [23].

Using a reliable automated MRI segmentation technique, the aim of this study was to assess whether there are any differences in the volumes of subcortical structures and brainstem between patients with YOPD, YOPD-p and LOPD. Our secondary aim was to characterize the neuropsychiatric profile of these patients.

2. Methods

2.1. Subjects

Nine YOPD-p patients with homozygous ($n = 7$) or compound heterozygous Parkin mutation (6 women; mean age ± S.D., 42.2 ± 7.8 years) and 19 PD patients without Parkin mutation (7 women; mean age ± S.D., 50.6 ± 10.6 years) were selected for the study. As all YOPD-p patients had a disease onset before age 45, PD patients were also divided into young-onset (<45) and late-onset (≥45) groups. We screened YOPD patients for Parkin, DJ-1 and PINK1 mutations but no mutations were identified in this group. All patients were recruited from the outpatient clinic of the Behavioral Neurology and Movement Disorders Unit at the Department of Neurology, Istanbul Faculty of Medicine, Turkey. The diagnosis of PD was based on the UK Parkinson Society Brain Bank criteria for clinical diagnosis [24]. Exclusion criteria included diagnosis of dementia, current major depression or psychosis, presence of any neurodegenerative disorder other than PD, history of PD surgery history, or the presence of any unstable or untreated systemic disorder such as diabetes, cardiac failure, or renal failure.

All patients were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS), with and without treatment ("on" and "off" state), except UPDRS I and IV, which were evaluated only during "off" state. Thirty-two neurologically healthy individuals (12 women; mean age ± S.D., 48.9 ± 10.7 years) were included as control subjects for the imaging part of the study. All subjects gave written informed consent for participation in this study, which was approved by the institutional ethics committee.

2.2. Image acquisition and processing

Two successive high-resolution T1-weighted images were acquired for each subject by a Philips Achieva 1.5 T MR scanner with SENSE-Head-8 Coil. The pulse sequence parameters were: TR/TE = 8.6/4.0 s, flip angle = 8°, FOV = 240 mm, acquired voxel size = 1.25/1.25/1.2 mm (reconstructed = 0.94/0.94/1.2 mm), 150 coronal slices without gap, scan duration = 7.23 min (per volume).

The image files, acquired after the scans, were used for the morphometric analysis. FreeSurfer 4.05 was used to conduct subcortical volume analysis. This procedure, described previously [16], automatically segmented ≤40 unique structures and assigned a neuroanatomic label to each voxel in a given cranial volume on the basis of probabilistic information estimated automatically from a manually labeled training set. The segmentations were then visually inspected for accuracy. We focused on basal ganglia structures (caudate, pallidum, putamen), limbic structures (hippocampus, amygdala, nucleus accumbens), thalamus and brainstem. We excluded the nucleus accumbens from the analysis because of a known problem with accuracy due to the poor T1 contrast in this region.

2.3. Neuropsychiatric and neuropsychological evaluation

All patients underwent a standardized clinical neuropsychiatric assessment to evaluate obsessive–compulsive and depressive symptoms, impulsivity and personality traits with Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Beck Depression Inventory (BDI), 21-item Hamilton Rating Scale for Depression (HAM-D), The Montgomery Åsberg Depression Rating Scale (MADRS), Temperament and Character Inventory (TCI) and Barratt Impulsiveness Scale-11 (BIS-11).

Patients were also assessed with a comprehensive neuropsychological battery including MMSE, a 15-word Verbal Memory Process Test, Trail Making Test, Wisconsin Card Sorting Test, Stroop Test, Boston Naming Test, The Benton Facial Recognition Test, Judgment of Line Orientation Test, Digit Span Subtest of Wechsler Adult Intelligence Scale, phonemic and semantic fluency tests (KAS and animal naming) to evaluate cognitive domains comprising attention, memory, language, visuospatial, and executive functions. All tests have been validated in Turkish. Neuropsychiatric and neuropsychological data were available for 7 of 9 patients in the YOPD-p, 8 of 10 patients in the YOPD and 8 of 9 patients in the LOPD groups.

2.4. Statistical analysis

Behavioral and demographic data were compared between the YOPD, YOPD-p and LOPD groups with analysis of variance (ANOVA), and a post-hoc Tukey test was applied. Neural volumes were compared using analysis of covariance (ANCOVA) test, controlling for age at the time of the scan, gender and total intracranial volume followed by a post-hoc Tukey test to compare regional gray matter changes. A value of $p < 0.01$ was considered statistically significant for all tests.

3. Results

The demographic features are shown in Table 1. As expected, age at onset was significantly different between YOPD and YOPD-p patients when compared to LOPD patients. There were no significant differences including gender (not shown in table, $p = 0.244$) between YOPD and YOPD-p groups. In the volumetric part of the study, YOPD-p patients tended to be younger than the controls but this was not of statistical significance ($p = 0.039$). Disease duration, UPDRS scores, the daily levodopa dose equivalents and duration of treatment did not differ among the patient groups.

Univariate analysis corrected for total intracranial volume (ICV), gender and age at the time of the scan revealed that the presence of a mutation in the Parkin gene was associated with a bilateral decrease in gray matter volume in caudate nuclei when compared to YOPD patients. Even the p values of the model were significant only for bilateral caudate nuclei, post-hoc analyses revealed decrease in the volumes of bilateral putamen, right pallidum, right amygdala and brainstem of the YOPD-p patients when evaluated against to YOPD patients (Table 2).

The psychiatric profiles obtained with Y-BOCS, BDI, HAM-D, MADRS, TCI, BIS-11 and MADRS scale were similar and comparisons of the neuropsychological evaluation revealed no significant difference in both patient groups (Table 3).

4. Discussion

Using an automatic segmentation method, we found a decrease in the volumes of the basal ganglia structures of YOPD-p patients but not YOPD patients with similar clinical and demographic features. Thus, atrophy in the caudate nucleus seems to be specific for Parkin mutations. In accordance with our findings, another study including the same number of PD patients with Parkin mutations found unilateral caudate atrophy [14]. These results suggest a different pattern of volumetric changes among young-

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Table 1
Clinical characteristics of Parkinson's disease patients with Parkin and without Parkin mutations.

	I YOPD ($n = 10$)	II YOPD-p ($n = 9$)	III LOPD ($n = 9$)	*P*	Post-hoc comparison		
					I vs II	I vs III	II vs III
Age, y	46.0 ± 12.4 (20–72)	42.2 ± 7.8 (32–56)	55.7 ± 4.8 (50–62)	0.012	0.643	0.069	0.011
Age at onset, y	35.5 ± 7.5 (19–43)	32.0 ± 9.5 (19–48)	48.2 ± 2.3 (45–53)	0.0001*	0.546	0.002*	0.0001*
PD duration, y	10.5 ± 9.8 (1–32)	10.2 ± 1.9 (7–13)	7.7 ± 4.0 (3–15)	0.612	0.995	0.632	0.702
UPDRS I	3.1 ± 2.1 (1–8)	3.4 ± 1.9 (1–7)	3.1 ± 1.2 (1–5)	0.903	0.914	1.00	0.923
UPDRS II off	12.4 ± 11.0 (2–35)	14.3 ± 6.8 (7–25)	12.3 ± 6.8 (5–25)	0.853	0.877	1.00	0.875
UPDRS II on	4.3 ± 4.0 (1–13)	4.5 ± 4.1 (0–13)	4.7 ± 2.7 (1–9)	0.961	0.988	0.957	0.991
UPDRS III off	27.3 ± 16.2 (5–58)	30.1 ± 11.1 (14–44)	27.2 ± 11.4 (12–45)	0.869	0.890	1.00	0.889
UPDRS III on	10.5 ± 6.0 (3–24)	12.0 ± 7.0 (3–27)	15.0 ± 5.4 (8–25)	0.298	0.860	0.275	0.569
UPDRS IV off	4.3 ± 3.0 (0–9)	4.7 ± 3.3 (1–10)	3.5 ± 2.5 (0–7)	0.687	0.936	0.852	0.666
UPDRS V off	2.1 ± 1.2 (0.5–5.0)	2.3 ± 0.8 (1.0–4.0)	2.3 ± 1.1 (1.0–4.0)	0.917	0.932	0.932	1.00
UPDRS V on	0.9 ± 0.6 (0–2)	1.0 ± 0.8 (0–2.5)	1.2 ± 0.7 (0–2.5)	0.642	0.951	0.623	0.811
UPDRS VI off	74.5 ± 24.0 (20–95)	75.5 ± 14.2 (50–90)	71.6 ± 18.8 (40–90)	0.908	0.992	0.946	0.906
UPDRS VI on	93.5 ± 6.6 (80–100)	92.2 ± 6.6 (80–100)	88.8 ± 7.8 (80–100)	0.362	0.918	0.346	0.583
Daily doses of levodopa equivalent, mg/d	230.1 ± 239.4 (0–600)	238.8 ± 344.4 (0–950)	377.7 ± 299.0 (0–800)	0.495	0.995	0.632	0.702
Duration of treatment, months	83.4 ± 83.4 (0–252)	96.00 ± 62.9 (12–240)	76.0 ± 53.3 (12–168)	0.823	0.916	0.970	0.811

Data are expressed as the mean ± SD (range). *$p < 0.01$.
Analyses were performed by one-way analysis of variance with post-hoc Tukey test ($p < 0.01$).
PD: Parkinson's Disease, YOPD: Young-Onset PD patients without Parkin mutations, YOPD-p: Young-Onset PD patients with Parkin mutations, LOPD: Late-Onset Idiopathic PD patients, UPDRS = Unified Parkinson's Disease Rating Scale.

onset PD patients where Parkin mutations tend to accompany caudate atrophy. One explanation for this is the possible failure of the compensation process proposed by Reetz et al. [14] Hypertrophy of the basal ganglia, shown in asymptomatic Parkin carriers, has been suggested as a compensatory mechanism in response to dopaminergic dysfunction preceding the onset of the symptoms. In some studies, however, the caudate nucleus was not found to be as hypertrophic as the putamen and globus pallidus [15]. Thus, in the symptomatic stage, hypertrophic basal ganglia structures seem to revert to their normal range volumes, suggesting that the hypertrophy is transitory. Furthermore, hypertrophy occurs only in the presymptomatic stage and the progression of disease pathology is likely to reverse this increase. Disease progress may give rise to a significant atrophy in presymptomatically non-hypertrophic caudate nucleus but there are contradictory findings indicating a gray matter increase in caudate nucleus in asymptomatic Parkin carriers [25]. There is also evidence from positron emission tomography (PET), showing more severe loss of dopaminergic function in the caudate nuclei compared to putamen but only in the symptomatic stage in patients with Parkin mutations [26]. In LOPD patients, on the other hand, the decline of (18)F-dopa uptake was not found to be different between caudate and putamen nuclei [27]. These results are in-line with the more extensive involvement of the caudate nuclei in the symptomatic stage of the disease. Atrophy in the caudate nuclei in the symptomatic period, which is the main finding in our study, may reflect this more excessive involvement in YOPD-p patients compared to YOPD and LOPD patients.

Pathology in patients with Parkin mutation may show a different pattern than that in idiopathic PD. For instance, tau accumulation has been demonstrated in the basal ganglia of such patients but not in the idiopathic cases [28]. The type of the mutation may also have an important impact on the findings: many of the PD-linked point mutations, identified in only 2 out of 9 YOPD-p patients in our study, produce alterations in the solubility and intracellular localization of the wild-type Parkin where the mutation mediated-alteration in Parkin solubility is associated with

Table 2
Mean (standard deviation) volumes for various structures in YOPD, YOPD-p, LOPD patients and normal control subjects measured with an automated volumetric method (FreeSurfer).[a]

Data											
	I YOPD ($n = 10$)	II LOPD ($n = 9$)	III YOPD-p ($n = 9$)	IV Control ($n = 32$)	p[b]	Post-hoc comparison					
						I vs II	I vs III	I vs IV	II vs IV	III vs IV	II vs III
R Caudate	3.746 ± 0.306	3.289 ± 0.462	2.863 ± 0.410	3.502 ± 0.378	0.0001[b]	0.053	<0.0001[c]	0.381	0.357	<0.0001[c]	0.028
L Caudate	3.694 ± 0.348	3.156 ± 0.348	2.789 ± 0.474	3.404 ± 0.406	0.0001[b]	0.007[c]	<0.0001[c]	0.166	0.071	<0.0001[c]	0.161
R Pallidum	1.603 ± 0.231	1.217 ± 0.225	1.114 ± 0.282	1.354 ± 0.236	0.013	0.015	0.001[c]	0.078	0.480	0.056	0.788
L Pallidum	1.736 ± 0.432	1.236 ± 0.432	1.332 ± 0.444	1.463 ± 0.263	0.287	0.072	0.146	0.396	0.432	0.681	0.988
R Putamen	5.296 ± 0.698	4.695 ± 0.496	4.495 ± 0.631	5.064 ± 0.543	0.036	0.169	0.004[c]	0.902	0.244	0.003[c]	0.472
L Putamen	5.634 ± 0.705	4.946 ± 0.605	4.859 ± 0.659	5.431 ± 0.557	0.014	0.064	0.006[c]	0.973	0.045	0.002[c]	0.813
R Hippocampus	4.294 ± 0.426	4.300 ± 0.303	3.970 ± 0.302	4.245 ± 0.471	0.229	0.852	0.293	1.000	0.785	0.133	0.068
L Hippocampus	4.295 ± 0.473	4.208 ± 0.306	4.009 ± 0.258	4.124 ± 0.463	0.882	1.00	0.483	0.761	0.726	0.805	0.413
R Amygdala	1.683 ± 0.161	1.612 ± 0.113	1.463 ± 0.174	1.603 ± 0.173	0.109	0.872	0.006[c]	0.516	0.978	0.03	0.056
L Amygdala	1.638 ± 0.186	1.519 ± 0.167	1.424 ± 0.134	1.554 ± 0.153	0.238	0.503	0.017	0.582	0.963	0.067	0.368
R Thalamus	7.234 ± 0.868	6.577 ± 0.810	6.528 ± 0.671	6.864 ± 0.753	0.287	0.147	0.083	0.603	0.481	0.298	0.993
L Thalamus	7.406 ± 0.931	6.494 ± 0.798	6.676 ± 0.655	6.954 ± 0.858	0.303	0.100	0.183	0.580	0.369	0.587	0.991
Brainstem	22.362 ± 2.732	20.888 ± 2.021	19.651 ± 1.987	21.407 ± 2.225	0.384	0.053	0.006[c]	0.552	0.881	0.015	0.235

Volumes are in cubic millimeters. Data are expressed as the mean ± SD (range).
PD: Parkinson's Disease, YOPD: Young-Onset PD patients without Parkin mutations, YOPD-p: Young-Onset PD patients with Parkin mutations, LOPD: Late-Onset Idiopathic PD patients, Control: Control subjects.
[a] For each neuroanatomic volume, ANCOVA statistical test covariate with Intracranial Volume (ICV) and age is performed.
[b] p value of the ANCOVA ($p < 0.01$).
[c] Significant difference after post-hoc analysis between all groups, performed with Tukey test ($p < 0.01$).

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Table 3
Neuropsychological evaluations of YOPD, YOPD-p and LOPD patients.

	I YOPD ($N = 10$)	II YOPD-p ($N = 9$)	III LOPD ($N = 9$)	*P*	Post-hoc comparison		
					I vs III	I vs II	II vs III
MMSE (/30)	29.1 ± 1.4 $N = 8$ (26–30)	26.3 ± 2.4 $N = 7$ (22–30)	27.2 ± 3.2 $N = 8$ (22–30)	0.123	0.111	0.354	0.763
Digit span forward	6.9 ± 2.1 $N = 8$ (4–10)	5.0 ± 1.0 $N = 7$ (4–6)	5.7 ± 1.6 $N = 8$ (3–8)	0.055	0.230	0.051	0.649
Digit span backward	4.6 ± 1.6 $N = 8$ (2–7)	3.2 ± 1.1 $N = 7$ (2–5)	4.3 ± 1.5 $N = 8$ (2–7)	0.218	0.941	0.222	0.360
Verbal memory process test delayed spontaneous recall	11.81 ± 1.7 $N = 8$ (9–15)	11.7 ± 2.3 $N = 7$ (8–15)	10.2 ± 4.4 $N = 8$ (4–15)	0.525	0.525	0.994	0.635
Verbal memory process test delayed spontaneous + recognized recall	15.0 ± 0.0 $N = 8$ (15–15)	15.0 ± 0.0 $N = 7$ (15–15)	14.1 ± 2.1 $N = 8$ (9–15)	0.296	0.380	1.00	0.356
Stroop III (s)	48.1 ± 21.1 $N = 8$ (24–83)	63.4 ± 35.0 $N = 7$ (29–130)	60.3 ± 34.6 $N = 8$ (14–113)	0.594	0.709	0.609	0.980
BNT	26.1 ± 2.8 $N = 8$ (23–30)	24.5 ± 0.5 $N = 7$ (24–25)	25.7 ± 5.5 $N = 8$ (17–31)	0.708	0.978	0.701	0.814
JoLO	20.2 ± 5.7 $N = 8$ (9–26)	15.0 ± 6.0 $N = 7$ (7–21)	20.5 ± 3.4 $N = 8$ (15–25)	0.09	0.995	0.123	0.145
Benton facial recognition test	47.7 ± 4.9 $N = 8$ (36–52)	42.5 ± 4.1 $N = 7$ (37–50)	43.1 ± 3.6 $N = 8$ (37–50)	0.321	0.455	0.346	0.967
Lexical fluency – category	21.8 ± 5.7 $N = 8$ (11–31)	19.0 ± 4.5 $N = 7$ (15–28)	17.2 ± 2.8 $N = 8$ (8–29)	0.350	0.324	0.655	0.853
Lexical fluency – KAS	33.8 ± 11.9 $N = 8$ (21–55)	24.8 ± 4.5 $N = 7$ (19–32)	29.8 ± 17.5 $N = 8$ (14–62)	0.456	0.424	0.816	0.759
WCST % perseveration	18.1 ± 9.1 $N = 8$ (8.5–31.2)	22.0 ± 5.4 $N = 7$ (13.2–28.1)	25.4 ± 1.4 $N = 8$ (7.0–42.9)	0.326	0.294	0.770	0.711
Trail making part B – Part A (s)	29.12 ± 28.28 $N = 8$ (−20–62)	41.57 ± 37.30 $N = 7$ (12–113)	66.85 ± 48.31 $N = 8$ (29–167)	0.228	0.259	0.983	0.337

Data are expressed as the mean ± SD (range).
Analyses were performed by one-way analysis of variance with post-hoc Tukey test ($p < 0.01$).
PD: Parkinson's Disease, YOPD: Young-Onset PD patients without Parkin mutations, YOPD-p: Young-Onset PD patients with Parkin mutations, LOPD: Late-Onset Idiopathic PD patients, Control: Control subjects.
MMSE = Mini-Mental State Examination, WCST = Wisconsin Card Sorting Test, BNT = Boston Naming Test, JoLO = Judgment of Line Orientation, Stroop = Stroop Color Word Test.

its propensity to form intracellular, aggresome-like, protein aggregates [29]. On the other hand, mutations identified in the remaining 7 patients, including insertions and deletions, result in Parkin loss-of-function leading to an abnormal accumulation of non-ubiquitinated intracellular proteins and consequently loss of the dopaminergic neurons. There is also mounting evidence indicating that Parkin and PINK1 might function in concert to modulate mitochondrial degradation termed mitophagy [30,31]. The caudate nuclei may be more vulnerable to mitophagy than the other basal ganglia structures. Such pathological changes may underlie the atrophy in YOPD-p patients, but this remains speculative.

Despite the differences in atrophy in the basal ganglia structures, there were no clinical or neuropsychological differences between the groups. This suggests that subcortical volume loss had no significant effect on behavioral and cognitive function in YOPD-p patients.

These results are in agreement with another study using similar instruments but in a different cultural setting [5]. This suggests that the psychiatric comorbidity frequently ascribed to Parkin patients is not justified, despite the fact that subtle behavioral abnormalities and reduced numbers of noradrenergic neurons in the locus ceruleus have been reported in several lines of PARK2 knockout mice and not in others [32,33]. The respective identified mutation types might be the primary determinant of such symptoms.

In conclusion, our data suggest that volumetric analysis of MRI permits discrimination between YOPD-p and YOPD patients. In the future, with the advancement of simple and effective volumetric measurement tools, caudate atrophy may be used as an indicator of Parkin mutations as part of a clinical evaluation. Behavioral problems and cognitive deficits may accompany PD, but YOPD-p patients do not seem to exhibit more psychiatric features or cognitive deficits than other young-onset PD patients and late-onset idiopathic PD patients.

Author roles

Basar Bilgic – drafting and revising the manuscript, analysis and interpretation of data, acquisition of data. Ali Bayram and Ali Bilgin Arslan – analysis, interpretation and acquisition of data, Burcu Dursun – acquisition of data, Hasmet Hanagasi, Hakan Gurvit, Murat Emre, Ebba Lohmann – acquisition of data, revising the manuscript.

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Financial disclosure/Conflict of interest

Nothing to report.

Funding sources

This study was supported by Istanbul University Research Funds and Istanbul Neuropsychiatry Hospital Research Support Program.

Acknowledgement

The authors would like to thank all the patients their families and the normal volunteers for their contribution and Prof Nihan Unaltuna-Erginel for her help in DNA management. The authors also thank Sedat Aydın for his help in MRI acquisition, Huseyin Bulut, MD for the psychiatric advice, and Geetika Kalloo for the helpful suggestions on the manuscript.

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Please cite this article in press as: Bilgic B, et al., Differentiating symptomatic Parkin mutations carriers from patients with idiopathic Parkinson's disease: Contribution of automated segmentation neuroimaging method, Parkinsonism and Related Disorders (2012), doi:10.1016/j.parkreldis.2012.02.017